COMPLEX MOLECULAR SYNTHESIS

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CHAPTER OVERVIEW

1: Some Principles of Synthetic Planning

1.1: Introduction

The challenge of synthetic planning is the identification of a set of available precursors that can be combined and manipulated by a series of chemical reactions to provide the synthetic target. Analysis does not *a priori* have to proceed from target to starting materials along the exact reverse of the actual synthesis (i.e. **retrosynthetic analysis**), but this protocol is highly effective for the analysis of structurally complex molecules because it provides a logical basis for the systematic recognition of potential synthetic pathways. For example, recognizable characteristics of the precursors predispose them toward chemical reactions that generate the target. These characteristics are the result of certain structural features of the precursors (e.g. functionality), the residue of which is often apparent in the target and from which the precursor can be inferred. The ⇒ symbol is used to indicate one or more backward steps, often referred to as **dislocations** or **transforms** of the target to a precursor. Bonds severed in a dislocation (i.e. generated during the synthesis) are indicated by drawing wavy lines through the appropriate bonds. Furthermore, the target will generally be shown to the left of the ⇒ symbol and the precursor(s) to the right.The dislocation may correspond to a single known chemical reaction, or a hypothetical reaction, or may be the result of a multistep retrosynthetic process. For example, the hydroxyl group in a secondary alcohol may be viewed as the residue of the carbonyl functional group that predisposes a precursor aldehyde toward reaction with a Grignard reagent to deliver the synthetic target. The C=C bond in a cyclohexene may be viewed as the residue of the pi system in 1,3-butadienediene that predisposes this precursor toward a Diels-Alder cycloaddition with methyl acrylate to deliver the synthetic target.

The following dislocations of some molecules that we will consider more thoroughly in subsequent chapters show only the targets and a set of **starting materials**, precursors that are readily available organic chemicals. Thus, the overall strategy of each total synthesis is summarized in a single dislocation of the target. The molecular numbering system of the synthetic target is adopted to designate the corresponding atoms of synthetic precursors. The examples in Charts 1-3 provide a glimpse of the diversity of solutions possible for a particular synthetic problem. The systematic procedures which guide the invention of such strategies are the focus of this book.

Three overall strategies are presented in Chart 1 for the total synthesis of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) a fatty acid derivative. These examples constitute a tiny sample of the numerous strategies that have been applied to the total synthesis of this important natural product.[1] These and other syntheses of prostaglandins will be considered in detail in chapter 3. Each strategy in chart 1 uses the same starting material **1** for carbons 1-5 of the upper side chain and similar starting materials **2** or **3** for carbons 14-20 of the lower side chain. But very different precursors are employed for the C6-7 and C8-13 portions of the target. Thus, the Woodward strategy involves ring contraction of a six- membered ring to generate the cyclopentane of C8-12 with C13 appended and glyoxalic acid to provide carbons 7 and 8.[2] The Brown strategy[3] uses α-chloroacrylonitrile for these carbons and acetoxyfulvene as precursor for the portion of the target which is provided by cyclohexanetriol in the Woodward synthesis. Turner's strategy carves the cyclopentane nucleus, C8-12, from the readily available Diels-Alder dimer of cyclopentadiene.[4] Thus, carbons 9-11 are derived from one molecule of cyclopentadiene while carbons 6-8 and 12-13 are derived from a second molecule of cyclopentadiene.

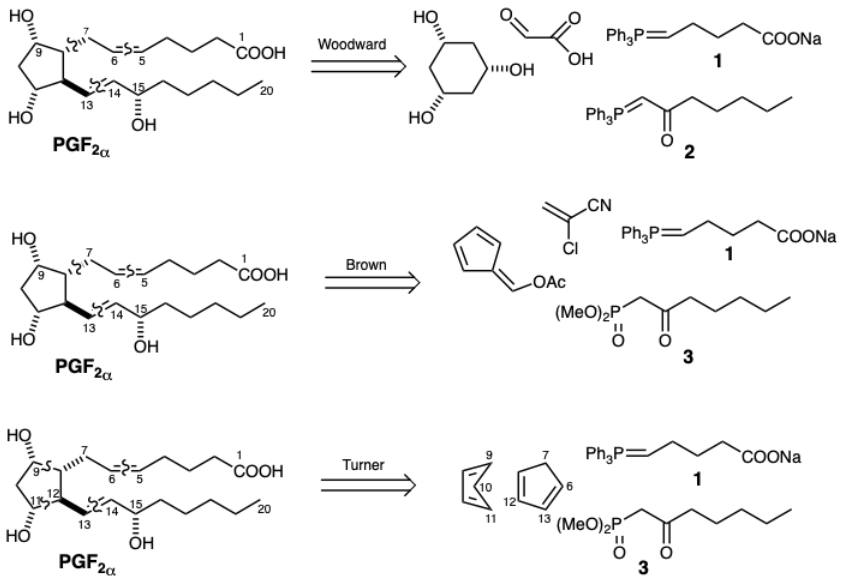


Chart 1. Three Overall Strategies for Prostaglandin $F_{2\alpha}$

Two strategies for total synthesis of the sesquiterpene longifolene are presented in Chart 2. The Corey synthesis[5] builds the tetracyclic skeleton from a cyclohexan-1,3-dione precursor that provides carbons 1 and 7-11. The Johnson strategy[6] builds the same carbon network from a cyclopentane precursor that provides carbons 1-3 and 9-11 of the target. The bonds formed in the two approaches are completely different.

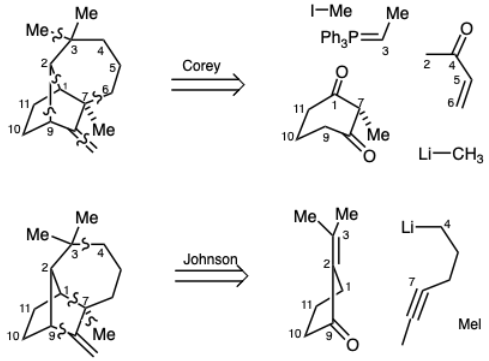


Chart 2. Two Overall Synthetic Strategies for Longifolene

While the choices of starting materials in the above examples may seem mysterious, consider the even more remarkable strategy for synthesis of these molecules in nature. As summarized in Chart 3, all of the carbon atoms of all natural products are derived from the same starting material, carbon dioxide. The biosynthesis of more complex biosynthetic building blocks, e. g., 3-phospho-D-glyceric acid and D-glucose from CO_2 will be our starting point for examining the logic that can be applied to designing total syntheses of organic molecules. The biosynthesis of natural products is a convenient framework for a systematic overview of the total synthesis of a variety of organic structural types. The logic of each biosynthesis will be considered and then compared with strategies employed in laboratory total syntheses of the same natural product.

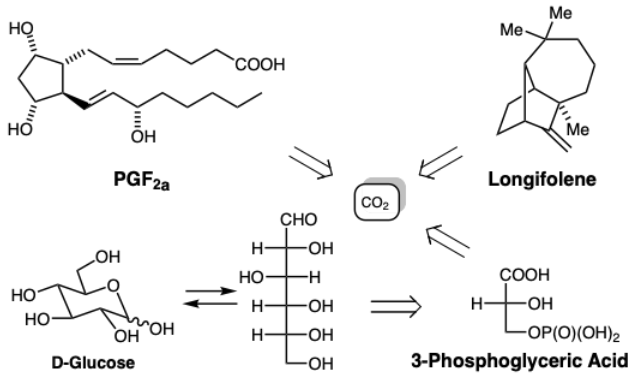


Chart 3. The Common Feature of Biosynthetic Strategies: Start with CO_2

First, however, in the remaining sections of this chapter, some basic principals of synthetic planning will be presented. The biosynthesis of glucose and other sugars from carbon dioxide in the dark reactions of photosynthesis will be examined in chapter 2. Sugars are not skeletally complex synthetic targets, but their functional and stereochemical complexity is a significant challenge for synthetic design. Chapter 2 concludes with a brief consideration of enantioselective total synthesis of sugars. Ensuing chapters examine the logic of biosyntheses and corresponding total syntheses of structurally complex natural products of the fatty acid, terpenoid, polyketide, and alkaloid families. An important feature of the discussion is the inclusion of unsuccessful plans that emerged from the work of leading practitioners of the art and science of organic total synthesis. These examples emphasize the practical limits of synthetic planning even by experts in the field.

Some previous books on the principles, logic, strategies, and tactics of synthesis design and surveys of total syntheses of complex organic molecules are described briefly in the following list.

A. A. Akhrem, A. A. Titov, A. Yu, *Total Steroid Synthesis* (Plenum, New York, NY, 1970): briefly discusses some principles of total synthesis and then exhaustively outlines total syntheses of steroids oganized according to topological categories of skeletal construction.

N. Anand, J. S. Bindra, and S. Ranganathan, *Art in Organic Synthesis* (Holden-Day, Inc., San Francisco, first edition, 1970): flow chart presentations of syntheses of complex organic molecules occaisionaly accompanied by brief discussions of strategic highlights.

N. Anand, J. S. Bindra, and S. Ranganathan, *Art in Organic Synthesis* (John Wiley, New York, second edition, 1987): updated flow chart presentations of syntheses of complex organic molecules occaisionaly accompanied by brief discussions of strategic highlights.

John ApSimon, Ed., *The Total Synthesis of Natural Products*, Vols. 1-9 (John Wiley & Sons, New York, 1973-1992): A collection of graphical surveys organized by biosynthetic families.

J. S. Bindra and R. Bindra, *Creativity in Organic Synthesis* (Academic Press, Inc., New York, 1975):

R. T. Blickenstaff, A. C. Gosh, G. C. Wolf, *Organic Chemistry Vol. 30: Total Synthesis of Steroids* (Academic Press, New York, 1974): exhaustively outlines total syntheses of steroids oganized according to topological categories of skeletal construction.

E. J. Corey and Xue-Min Cheng, *The Logic of Chemical Synthesis* (John Wiley & Sons, New York, 1989): duscusses the principles of synthetic design then provides specific examples by an exhaustive presentation of Corey's successful syntheses in outline format with little or no discussion.

Samuel E. Danishefsky and S. Danishefsky, *Progress in Total Synthesis* (Appleton-Century-Crofts, New York, 1971): graphical outlines of total syntheses of natural products organized by biogenetic families accompanied by a discussion of strategic highlights.

Ian Fleming, *Selected Organic Syntheses* (Wiley-Interscience, New York, 1973): discusses the key reactions in the total syntheses of more than two dozen complex organic molecules, the majority being natural products. It features multiple syntheses of several molecules, i. e. Cecropia Juvenile Hormone and Colchicine, providing an opportunity for comparison of different approaches.

J. Furhop, G. Penzlin, *Organic Synthesis. Concepts, Methods, Starting Materials* (Verlag Chemie: Weinheim, Fed. Rep. Ger., 1983): exhaustive systematic discussion of synthetic methods organized by synthons, difunctional relationships, and functional

group interconversions followed by a consideration of the principles of retrosynthetic analysis and graphical summaries for syntheses of a wide variety of complex organic molecules.

S. Hanessian, *Total Synthesis of Natural Products: The 'Chiron' Approach* (Pergamon Press, London, 1983): concepts for designing total syntheses of natural products using readily available chiral nonracemic natural products as starting materials are discussed and extensively illustrated with examples.

Robert E. Ireland, *Organic Synthesis* (Prentice-Hall, Englewood Cliffs, New Jersy, 1969): A discussion of the principles of synthetic design is followed by a detailed consideration of specific examples of successful syntheses.

Thomas Lindberg, Ed., *Strategies and Tactics in Orgainc Synthesis*, Vols. 1-3 (Academic Press, Inc., New York, 1984-1991): anecdotal case histories of specific total syntheses illustrating the design and execution of synthetic plans and revealing the obstacles and failures commonly encountered even by experts.

Bradford P. Mundy, *Concepts of Organic Synthesis* (Marcel Dekker, New York, 1979): a review of synthetic methods organized according to specific goals or reaction types such as ring formation or rearrangements respectively. Also discussed are the biosynthesis of terpenes, concepts of stereocontrol and synthetic planning, and examples of complex syntheses.

Koji Nakanishi, Toshio Goto, Shô Itô, Shinsaku Natori, Shigeo Nozoe, Eds., *Natural Products Chemistry*, Vols 1-3 (Academic Press, Inc., New York, 1974-1983): information on the structural characterization and outlines of total syntheses organized by biogenetic families.

Fèlix Serrratosa, *Studies in Organic Chemistry 41*, *Organic Chemistry in Action The Design of Organic Synthesis* (Elsevier, Amsterdam, 1990): a textbook on the principles of synthesis design including the use of computers that concludes with several examples including several strategically different syntheses of twistane and lucidulene.

Stephen Turner, *The Design of Organic Synthesis* (Elsevier, New York, 1976): systematically discusses principles of synthesis planning with examples of considerable complexity. The focus is on concepts, and thorough discussion of specific total syntheses is not provided.

Stuart Warren, *Organic Synthesis: The Disconnection Approach* (John Wiley & Sons, New York, 1982): presents principles of synthesis planning on a very simple level. Concepts, especially retrosynthetic analysis, are defined and their applications systematically exemplified by the design of short syntheses of simple targets.

1. For a recent monograph, see: "New Synthetic Routes to Prostaglandins and Thromboxanes", Roberts, S.M.; Scheinmann, F., Academic Press, New York (1982).

2. Woodward, R.B.; Gosteli, J.; Ernest, I.; Friary, R.J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, C.; Whitesell, J.K. *J. Am. Chem. Soc.* **1973**, *95*, 6853.

3. Brown, E.D.; Lilley, T.J. *Chem. Commun.* **1975**, *39*.

4. Brewster, D.; Myers, M.; Ormerod, J.; Other, P.; Smith, A.C.B.; Spinner, M.E.; Turner, S. *J. Chem. Soc. Perkin I*, **1973**, 2796.

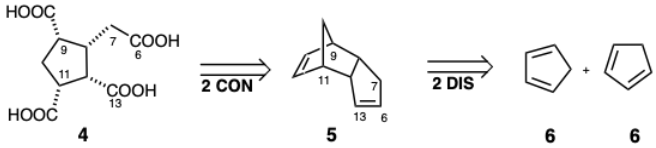
5. Corey, E.J.; Ohno, M.; Vatakencherry, P.A.; Mitra, R.B. *J. Am. Chem. Soc.* **1964**, *86*, 478.

6. Volkmann, R.A.; Andrews, G.C.; Johnson, W.S. *J. Am. Chem. Soc.* **1973**, *97*, 4777.

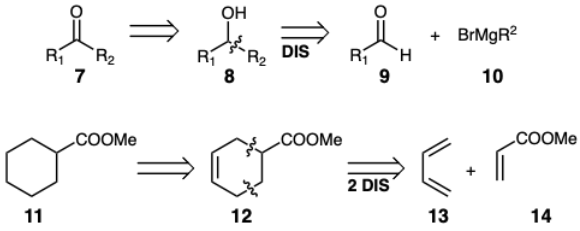
1.2: Logic Centered Analysis

Exhaustive Retrosynthetic Analysis

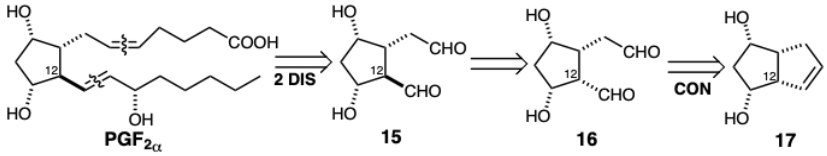
Three things must be established to accomplish the total synthesis of an organic molecule. These are the appropriate (1) carbon network, (2) functionality, and (3) stereochemistry. The **carbon network** consists of carbon atoms and a set of connections between them. An exhaustive retrosynthetic analysis of the problem of synthesizing a complex organic molecule would include consideration of all possible strategies involving each C-C bond as the hypothetical last connection in the skeletal construction, a disconnection (**DIS**) in the retrosynthetic analysis. Furthermore, it may be advantageous to generate intermediates that contain bonds not present in the final target. These bonds must be severed at some stage in the synthesis. For example, consider a synthesis of the tetracarboxylic acid **4**. This target could be obtained readily by oxidative cleavage of *endo*-dicyclopentadiene (**5**), itself readily available by dimerization of cyclopentadiene (**6**). In planning such a synthesis, these bond cleavages correspond to *dislocations which generate connections* (**CON**). Thus, an exhaustive analysis must also consider all possible bond cleavages that could generate the desired skeleton from a more highly connected precursor.



Besides establishing the requisite carbon skeleton from available precursors by the formation or cleavage of C-C bonds, the generation of a synthetic target may require manipulation of functional groups. Thus, synthetic targets may contain functionality that is different than that in a readily available precursor. For example, a well known synthesis of ketones **7** involves oxidation of alcohol precursors **8** that are, in turn, often assembled by the union of aldehydes **9** with Grignard reagents **10**. Another example is provided by a strategy for the synthesis of cyclohexane **11**. Cyclohexene **12**, that is readily available from **13** and **14**, is an excellent precursor that would deliver the cyclohexane **11** upon saturation of the C=C bond.



Finally, some reactions neither change the carbon network nor modify functionality, but merely alter stereochemistry. For example, a possible dislocation of the precursor **15** for $PGF_{2\alpha}$ is epimerization of the stereocenter at position 12 since this allows generation of **16** from a readily available cis fused bicyclic precursor **17**.



An exhaustive logic centered retrosynthetic analysis would consider every possible disconnection, connection, functional group modification, and stereochemical modification as a potential last step of the synthesis. In so doing, a set of **subtarget** structures (e.g. T_1, T_2, T_3 . . . T_i) is generated, which may be converted in a single synthetic operation, that is, chemical step, to the synthetic target. The same process is applied to each subtarget and so on until the molecule is reduced to several sets of readily available starting materials, and a complete **tree** of synthetic intermediates (sometimes referred to as a **synthetic tree**) is generated (Figure 1). It is often convenient during the planning process to generalize potential intermediates of a particular type. Such generalized intermediates or **synthons** may correspond to stable organic molecules or to hypothetical reactive fragments such as a "methyl cation", "acyl carbanion" or “α-keto carbocation”. The actual organic intermediates corresponding to various synthons are called **synthetic equivalents**. Thus, methyl iodide, methyl bromide, methyl chloride, methyl trifluoromethanesulfonate or methyl p-toluenesulfonate are all synthetic equivalents of the "methyl electrophile" synthon. Synthetic equivalents of acyl carbanions and α-keto carbocations will be discussed on page 17. Usually a synthetic tree of synthons is generated and possible synthetic equivalents

are noted, but the final choice of a suitable synthetic equivalent for each synthon is often determined by experiment during the execution of the synthesis.

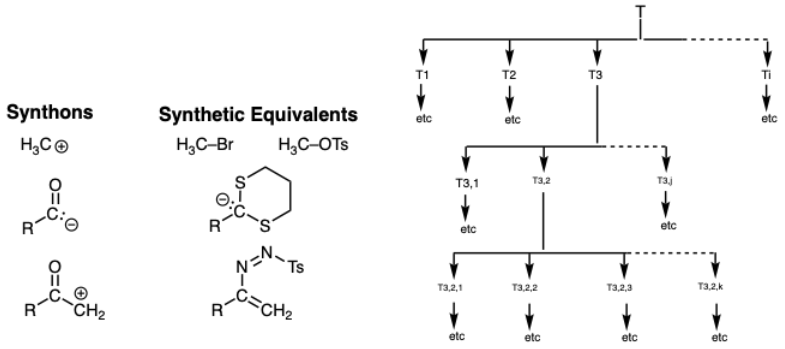
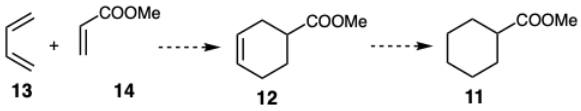


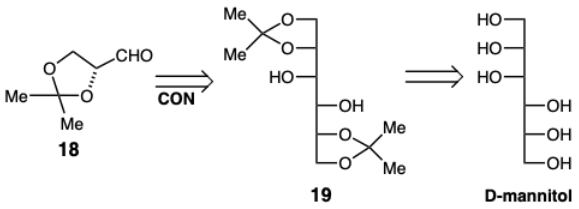
Figure 1. A synthetic tree.

Boundary Conditions

Logic centered retrosynthetic analysis generating a tree of synthons[7] is the basis of computer-assisted synthetic analysis.[8] Even with the help of a computer, however, an indiscriminately exhaustive analysis would be impossibly cumbersome and of little use because much effort would be expended exploring pathways that have little or no likelihood of being useful. Rather, it is desirable to identify dislocations that are unlikely to be fruitful and abandon them, to prune the synthetic tree as it grows. The goals of reterosynthetic analysis are: (1) the identification of readily available starting materials and (2) an efficient pathway for their conversion into the synthetic target. Since the starting materials will usually have simple structures, dislocations that reduce molecular complexity are likely to lead to them. This recommends seven boundary conditions for the selection of desirable dislocations. Thus, a desirable dislocation (or transform) must **(i)** ***reduce internal connectivity by scission of rings***, **(ii)** ***reduce molecular size by disconnection of chains or appendages***, **(iii)** ***remove functionality***, and/or **(iv)** ***simplify stereochemistry***, for example, by removal of asymmetric centers. The synthetic pathways that emerge under the guidance of these boundary conditions will rapidly generate the requisite molecular complexity of the target and will, thus, involve a minimum number of steps. However, some dislocations that **(v)** ***increase molecular complexity*** may also be desirable ***if they facilitate a simplifying dislocation***. For example, increasing the molecular complexity of **11** by adding unsaturation suggests a subtarget **12** that should be readily available by a 2π + 4π cycloaddition that generates two C-C bonds in a single step from the readily available starting materials **13** and **14**. If the C=C bond in the subtarget **12** can be selectively hydrogenated in the presence of a C=O bond, then the final target **11** could be obtained from **12**. Note that a hypothetical synthesis will be designated with dashed arrows in this book.

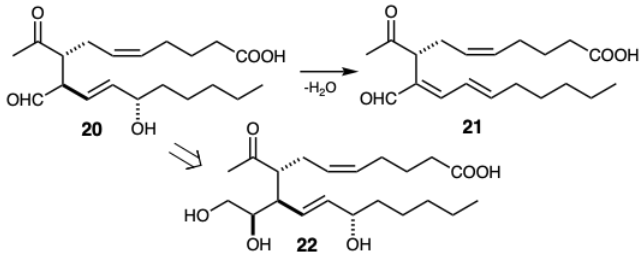


Another example of a potentially desirable dislocation that increases molecular complexity is provided by a strategy for preparing glyceraldehyde ketal **18**. Thus, a dimeric subtarget **19** should provide **18** by oxidative cleavage of the vicinal diol functional array. Although **19** is structurally and functionally more complex than **18**, it would be an excellent precursor if a method can be found to selectively ketalize the terminal vicinal diol arrays in D-mannitol, because the hexitol starting material is an inexpensive naturally derived product.



Another boundary condition is suggested by the need to **(vi)** ***avoid undesirable side reactions*** during the early stages of the total synthesis of a functionally complex target. Thus, side reactions are less likely if a sensitive functional array in the target is generated near the end of the synthesis. Reterosynthetically, this means that dislocations that modify (e. g. hide) or remove sites of unusually high chemical reactivity or instability are especially desirable. For example, the δ-hydroxy- β,γ-unsaturated aldehyde

functional array in **20** is especially prone toward dehydration to give the dieneal **21**. The aldehyde functional group can promote the dehydration. Therefore, generation of the aldehyde group in the last step of the synthesis is recommended. One possibility is to use a vicinal diol functional array in a subtarget **22** as a hidden aldehyde. Of course, the success of this strategy depends upon the feasibility of achieving oxidative cleavage of the structurally and functionally more complex subtarget **22** under suitably mild reaction conditions. This may be considered a risky strategy because the entire scheme would fail if the last step cannot be accomplished. However, the stability of the target to reaction conditions that are required to oxidatively cleave vicinal diols can be tested. However, other potential pitfalls can probably only be tested on the subtarget **22** itself. For example, will **22** tend to undergo intramolecular ketalization that cannot be easily and cleanly reversed? On the other hand, the benefits of finding a method of achieving the **22** to **20** conversion justify attempting the synthesis through this subtarget.

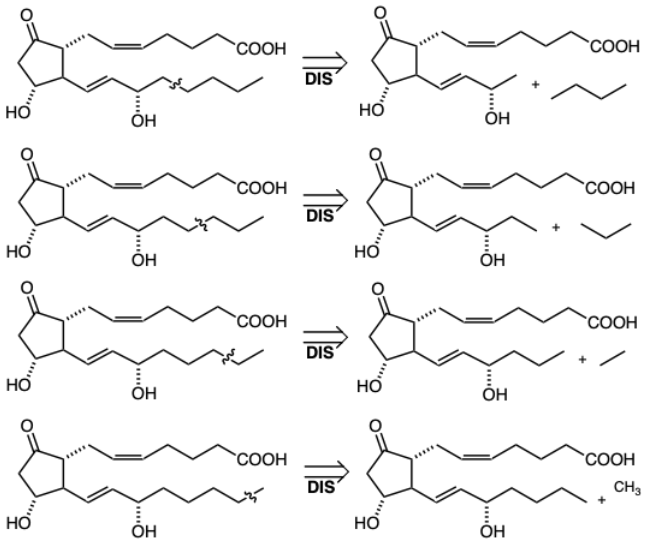


The ultimate goal of synthetic planning is to devise the most economical synthesis of the target. The suitability of a particular strategy must inevitably depend upon the state of the art (science?). As the availability of starting materials or methods (new or more effective) for uniting and manipulating them vary, so will the relative merits of different pathways. Put another way, a poor synthesis can become the method of choice if a method for improving a bad step can be discovered. Even a "logic centered" approach cannot produce absolute answers. What it can do is *systematically* generate a large number of alternative strategies for consideration in light of existing chemical knowledge.

Another concept that can guide the fruitful growth of a synthetic tree is the identification of target characteristics that direct special attention to a particular synthetic method or starting material and, thus, channel the choice of dislocations. For example, a six-membered ring invites consideration of a Diels-Alder cycloaddition as we have seen above in a strategy for the synthesis of **11** from **13** plus **14**. Similarly, because of the stability associated with aromaticity, the presence of an aromatic ring in a synthetic target recommends consideration of aromatic precursors because: (1) their stability may prevent undesirable side reactions and (2) a great variety of aromatic compounds are readily available.

The facts that: (1) chemical reactions are the means of achieving skeletal construction, and (2) functionality facilitates chemical reactions, recommends a boundary condition that favors synthetic strategies that make **(vii) *maximum use of target-related functionality*** in precursors to pro- mote skeletal construction. "Target-related" refers to functionality in precursors that may be identical with or closely related to functionality in the final synthetic target.

The imposition of boundary conditions during the generation of a synthetic tree may eliminate the need for considering a large fraction of potential synthetic pathways. For example, in devising a synthesis of prostaglandin $F_2\alpha$ we would disfavor all pathways involving a final connection between any of the carbons 16-20 which constitute an n-pentyl group. This group of atoms is an unreactive nonfunctionalized moiety. Joining two synthons at any of these bonds would require extensive functional manipulation with no obvious justification. Such strategies do not make maximum utilization of functionality.



Direct Associative Strategies

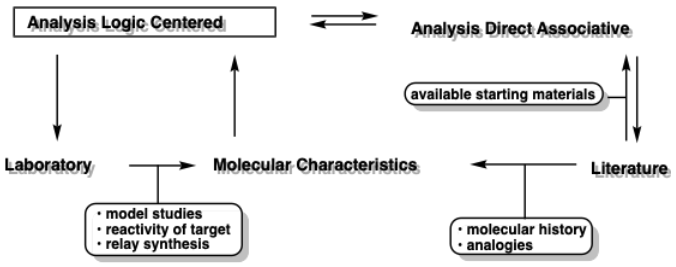
Syntheses of some target molecules or subtargets do not require the logic centered rigorous analytical approach since the molecules may be recognized as arising from the union of a number of readily available undisguised subunits which can be brought together in the proper way using standard reactions. This is known as a **direct associative** approach to synthetic planning. Thus, for example, strategies for the synthesis of polypeptides, almost without exception, involve the union of amino acids or suitable derivatives by the creation of amide bonds.

Generally, synthetic planning for complex molecules is intermediate between a direct associative and a logic centered approach. The initial recognition process may use logic centered analysis until a number of potentially readily available subunits or **key intermediates** become apparent. The choice of a particular key intermediate as a starting point channels and simplifies the analysis. This is followed by careful, usually logic centered analysis of detailed sequences that lead to the desired subunits and from them to the synthetic target.

Thus, the practical goal of logic centered analysis is to reduce a complex molecule to a set of "readily available" or "recognizable" synthons. That is, to simplify the synthetic objective to the extent that a direct associative approach becomes feasible. A knowledge of what is readily available need not precede the logic centered simplification of the problem. The simplified structures generated by such analysis may, on the contrary, become the subject of a thorough search of the chemical literature. This search might begin with a computer database such as Chemical Abstracts Online or one of the following general references:

(a) H.O. House, "Modern Synthetic Reactions", 2nd ed, Benjamin, 1972.
(b) R.B. Wagner and H.D. Zook, "Synthetic Organic Chemistry", Wiley, 1953.
(c) C.A. Buehler and D.E. Pearson, "Survey of Organic Syntheses", Wiley, 1970.
(d) A.I. Vogel, "Practical Organic Chemistry", 3red ed, Wiley, 1956.
(e) I.T. Harrison and S. Harrison, "Compendium of Organic Sythetic Methods", Wiley, 1971.
(f) L.F. Fierser and M. Fierser, "Reagents for Organic Synthesis", Wiley.
(g) "Organic Reactions", Wiley.
(h) "Organic Syntheses", Wiley.
(i) "Newer Methods of Preparative Organic Chemistry", Academic Press.

Information gleaned from the literature on established synthetic approaches to similar structures may then be used to generate further refinements of the synthetic plan by logic centered analysis. This general procedure for synthetic planning is an interactive approach. Furthermore, synthetic planning generally does not end when work in the laboratory begins. Information on molecular reactivity gleaned in the laboratory may be exploited to modify or generate new strategies. The interactions between modes of analysis and sources of relevant information are summarized below.



1.3: Perception of Structure-Functionality Relationships

Exploitation of functionality in synthetic planning requires an understanding of the *interrelationships between chemical reactions and functionality*. This is most effectively achieved in terms of basic electronic reaction mechanisms that allow a very compact and systematic classification of hundreds of synthetic reactions. For example, let us systematically consider the relationships which inhere between molecular structure and functionality with respect to polar reactions.

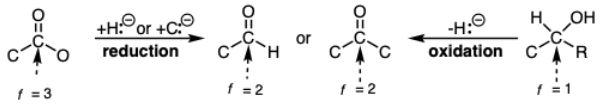
Functionality Level Changes

For organic synthetic analysis it is often assumed that all carbon centers in a hydrocarbon are not activated toward polar C-C bond forming reactions, hence, the name paraffin (from the Latin parum affinis = little affinity) denotes relative unreactivity. The hydrocarbon skeleton of organic molecules is considered to be a homogeneous conglomeration of unreactive carbon atoms. It is useful to define the **functionality level**[9] of an atom as *f = the number of valence electrons in the neutral atom minus the number of electrons assigned to the atom by the following protocol:* all bonding electrons are divided equally between C-C, C=C, C≡C, C-H, M-M or X-X, but all bonding electrons are given to the better nucleofuge (often but not always the more electronegative atom, *vide infra*) for C-X, C-M, or X-Y bonds, where X and Y are hetero atoms, and M is a metal. Thus, for example, the electrons taken or given to carbon when breaking the following bonds to carbon are assigned as follows: RO-, RS- (-1); O= (-2); F-, Cl-, Br-, or I- (-1); R_2N-, R_2P- (-1); RN= (-2); N≡ (-3); Li-, Na-, K-, R_2Al-, R_3Si- (+1).

The functionality level approximation emphasizes the similarity between similarly functionalized carbons. Thus, the functionality level of all carbons in a hydrocarbon is zero. That is, in a hydrocarbon all carbon atoms whether quaternary, tertiary, secondary, or primary, share a common functionality level (f = 0). Likewise, all carbinol carbon atoms share a common functionality level (f = +1) regardless of whether they are primary, secondary or tertiary. Aldehydes and ketones share a common functionality level (f = +2). To organic chemists these conclusions of similarity are tacitly accepted. The functionality level approximations differ from those made for defining the **oxidation state** *x = the number of valence electrons in the neutral atom minus the number of electrons assigned to the atom by the following protocol:* all bonding electrons are divided equally between C-C, C=C, C≡C, M-M or X-X, but all bonding electrons are given to the more electronegative element for bonds between different elements.[10] It is of little significance to an organic chemist that the oxidation states of the carbonyl carbon in formaldehyde (x = 0), other aldehydes (x = +1), and ketones (x = +2) differ as do the oxidation states of primary (x = -1), secondary (x = 0), or tertiary (x = +1) carbinol carbons. The abovementioned contrasts between the oxidation state and functionality level approximations result from the fact that in effect, the functionality level approximation assigns an oxidation number of 0 for hydrogen when bound to carbon in contrast with the oxidation state approximation that assigns an oxidation number of +1.

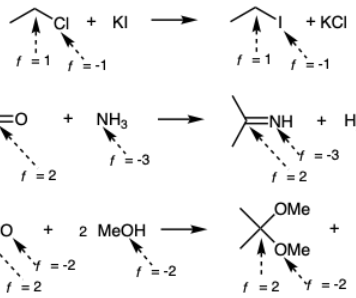
As we shall see, the functionality level concept is useful in the context of **polar reactions** which are those that result in *bond formation by electron pair donation from an electron rich synthon (nucleophile) to an electron deficient synthon (electrophile)*. In this context, for example, organic chemists generally consider all methyl halides, i. e. fluoride, chloride, bromide, iodide, to be similarly functionalized, and thus it is appropriate that they all share f = +1. It is of little significance (and probably not widely known) that the oxidation states of the carbons in methyl iodide (x = -4) and methyl bromide (x = -2) are different.

Interconversions of functional groups of different functionality level correspond to oxidations or reductions:

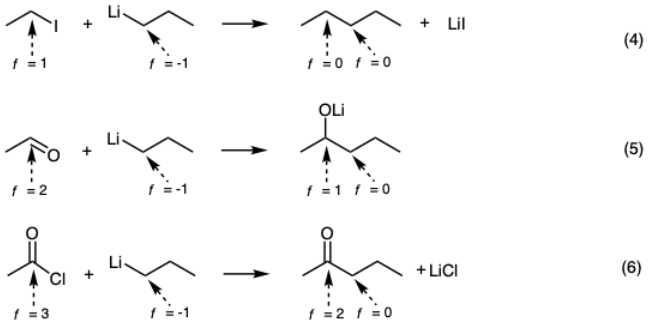


Heterolysis of the C-H bond is viewed as a special mode of C-H reaction that results in functionalization of a hydrocarbon. If hydride is abstracted the reaction is considered oxidation whereas proton abstraction is considered reduction.

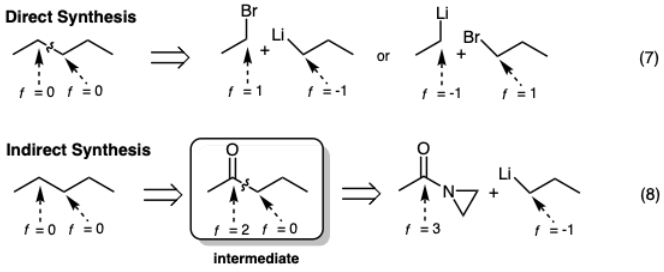
All functional groups of the same functionality level are, in principle, interconvertable by metatheses or polar addition and elimination reactions such as in equations 1-3.



For organic synthetic analysis, it is important to recognize that *polar carbon-carbon bond forming reactions are redox processes*. The carbon nucleophile is oxidized, and the carbon electrophile is reduced. In terms of functionality levels of carbon in representative hypothetical polar reactions; nucleophilic substitution, nucleophilic addition, and nucleophilic acyl substitution are indicated in equations 4-6 respectively.

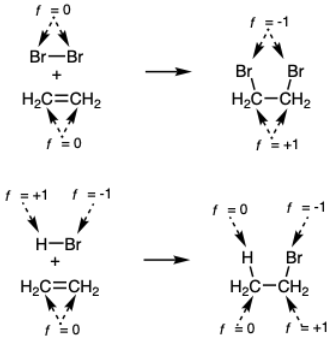


Thus, if we desire a product without functionality ($f = 0$) we must plan to react a (+1) electrophile with a (-1) nucleophile (equation 7). Alternatively, we may use reactants of other functionality level, but the functionality level of the initial product will have to be changed (oxidation or reduction) after C-C bond formation (e.g. equation 8).



Unsaturation Level Changes

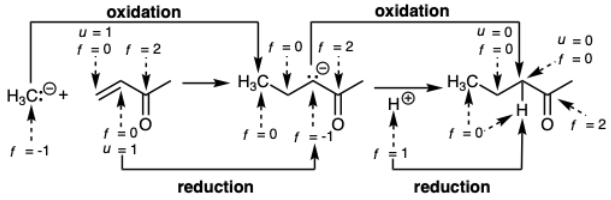
If carbon functionality is defined as carbon for which $f \neq 0$, then C=C and C≡C bonds are not considered to be functionality. Clearly, then, functionality is not the only molecular characteristic (structural feature) that facilitates bond forming reactions. In order to systematically consider the relationships which inhere between molecular structure and polar reactions, it is useful to define the **unsaturation level** of a specific atom as *u = 0 for all singly bonded atoms, as u = 1 for all atoms involved in homonuclear double bonding, and as u = 2 for all atoms involved in homonuclear triple bonding*. Thus, carbon-carbon and homonuclear multiple bonding in general does not change functionality levels. Introduction of C-C unsaturation is viewed as activation rather than oxidation (increased functionality level). Hydrogenation of C-C unsaturation is viewed as **saturation** rather than reduction of functionality level. These conventions find analogy in the concepts of coordinative unsaturation in organometallic chemistry. Thus, reactivity depends of *f* and *u*. Changes in *f* during chemical reactions are always balanced, i.e. an increase of f for one atom requires a decrease of f for another atom. For example, addition of bromine to C=C results in oxidation of both C's and reduction of both Br's (from $f = 0$ to $f = -1$).



Addition of HBr to C=C results in oxidation of one C (the one receiving Br) while $H\oplus$ is reduced to H•. The functionality level concept corresponds well with experience for the most

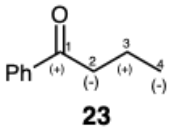
part. Although synthetically valuable differences in chemical reactivity are achievable for 1°, 2°, and 3° C-H bonds of hydrocarbons, it is useful to view these as different proclivities towards oxidation (hydride abstraction) or reduction (proton abstraction).

An increase of the functionality level of the carbon nucleophile also accompanies nucleophilic conjugate addition. But the carbon electrophile is not reduced. Rather, $H\oplus$ is reduced to H• and the unsaturation level of the carbon electrophile is decreased.



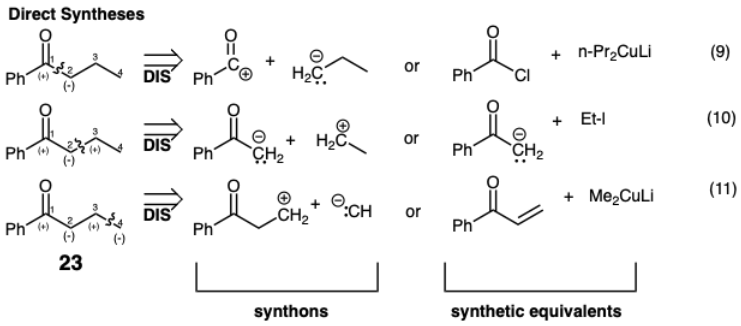
1.4: Polar Reactivity Analysis

The π-electron pair in a C=C bond may be unevenly distributed if the π-bond bears or is conjugated with a functional group. It is reasonable to approximate the electron pair distribution in, for example, the enol or enolate π-bond as having electron abundance on the β-carbon since a hydroxyl substituent activates the β-carbon toward bond formation with a carbon electrophile. Thus, functional groups stabilize neighboring centers of electron abundance (nucleophilic centers) and centers of electron deficiency (electrophilic centers). For example, the carbonyl carbon of a ketone is electrophilic while the carbon α- to a carbonyl is *potentially* nucleophilic. Actual nucleophilicity at this carbon is obtained when this carbon is conjugated with the carbonyl carbon as the corresponding enol or enolate. Similarly, the enone C-C π-bond is electrophilic at the β-carbon while the γ-carbon is *potentially* nucleophilic, actual nucleophilicity being available by conversion to the corresponding enol or enolate. Thus, the polar activation afforded by a functional group may be extended to remote carbon centers by conjugation. This possibility is indicated for **23**. In the ensuing discussion, centers of actual or potential **electrophilic or nucleophilic reactivity** will be designated as (+) and (-) respectively in contradistinction to centers of **positive or negative charge**, which will be designated as ⊕ and ⊖.



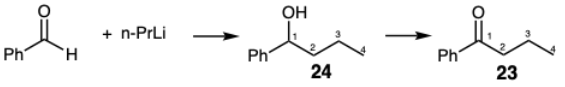
23

Let us consider all possible synthetic strategies for *direct* synthesis of the butyryl moiety of butyrophenone (**23**) from two fragments by a polar reaction exploiting the polar activation afforded by the carbonyl group or any functional group precursor which confers electrophilicity to the same carbon atom. There are three possible C-C disconnections of the target **23**. The three possible C-C connective strategies are summarized in equations 9-11. The strategies can be considered first in general terms by representing the required reactive polar precursors as synthons. The carbonyl group in **23** provides electrophilic reactivity at carbon 1 allowing a synthesis by polar creation of the 1- 2 bond by reaction with a three carbon nucleophile. The carbonyl group in **23** also *potentially* provides nucleophilic reactivity at carbon 2 allowing a synthesis by polar creation of the 2-3 bond by reaction with a two carbon electrophile. The carbonyl group in **23** also *potentially* provides electrophilic reactivity at carbon 3 allowing synthesis by polar creation of the 3-4 bond by reaction with a one carbon nucleophile. Usually the requisite synthons are recognized but only appropriate synthetic equivalents of these synthons are considered explicitly. For each of the above syntheses a large variety of alternative synthetic equivalents are possible. It is only necessary that the electrophilic precursor chosen has a functionality level one unit higher than the corresponding carbon in the target (or has a C=C bond conjugated with an electrophilically activating functional group) and that the nucleophilic precursor has a functionality level one unit lower than the corresponding carbon in the target in order to achieve a direct synthesis of the target.



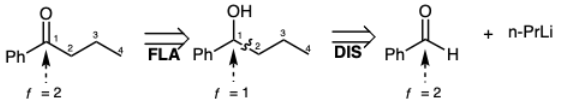
An indirect synthesis of the target may also be reasonable. For example, **23** could be prepared by addition of n-PrLi to benzaldehyde producing an intermediate **24** with the carbon skeleton of the target **23**. Subsequent adjustment of functionality level by oxidation then delivers the ketone **23** (equation 12). Retrosynthetically such a strategy requires recognition of the possibility that benzaldehyde is a readily available electrophilic precursor of the benzoyl portion of **23**. However, since the functionality level of this electrophile is the same at the incipient carbon 1 as in the target, the latter cannot be produced directly from benzaldehyde in a polar C-C bond forming process. Rather, the first dislocation of the target must be adjustment of its functionality level (FLA) prior to polar disconnection in the second dislocation (equation 13).

Indirect Polar Synthesis



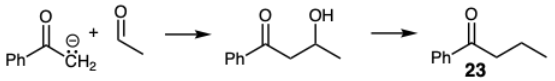
(12)

Retrosynthetic Analysis for Indirect Polar Synthesis

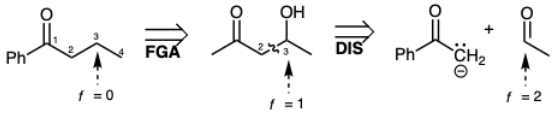


(13)

Topologically, the strategy of equation 13 is related to that of equation 9. An indirect synthesis of **23** by a strategy related topologically to that of equation 10 is outlined in equation 14. Retrosynthetically such a strategy requires recognition of the possibility that acetaldehyde is a readily available two carbon electrophile. However, since the functionality level of this electrophile is two units higher than the incipient carbon 3 in **23**, a polar bond-forming reaction with a carbon nucleophile leads to a product in which the functionality level at this carbon is one unit higher than required for **23**. Therefore, the first dislocation of the target must be adjustment of its functionality level (here functional group addition, FGA, a special case of FLA) prior to polar disconnection in the second dislocation (equation 15).



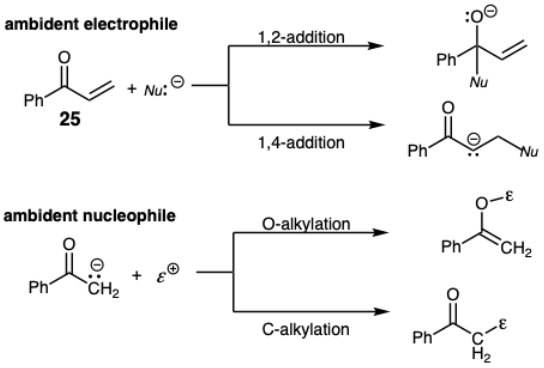
(14)



(15)

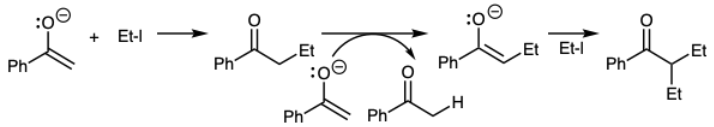
Regioselective Polar Reactions

It is important to recognize that all of the *strategies* considered above are hypothetical. The desired synthetic reaction between the chosen intermediates may not be the only reaction pathway available. For example, delocalized synthons are inherently ambident; they possess several centers of reactivity. Thus, the enolate in equation 14 is an **ambident nucleophile** that may react with an electrophile either at the carbonyl oxygen or α-carbon. Similarly, the conjugated electrophile **25** may react with a nucleophile either at the carbonyl carbon (1,2-addition) or the β-carbon (1,4- or Michael addition). Thus, **25** is an **ambident electrophile**. To be synthetically useful, bond formation must be accomplished at the desired position of an ambident nucleophile or electrophile, the reaction must be regioselective.

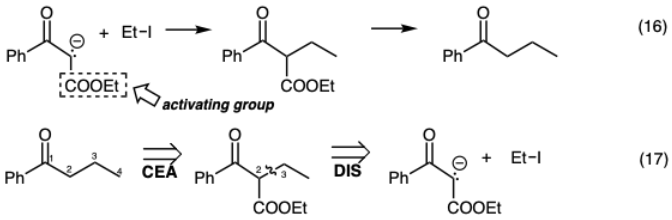


Reactivity Control Elements

We have now seen that indirect strategies, that involve dislocations of a target that do not directly reduce molecular complexity, may be desireable because: (1) they allow a subsequent dislocation of the target that efficiently simplifies molecular complexity, (2) they expliot readily available starting materials that have a high level of molecular complexity, or (3) they expliot certain readily available electrophiles or nucleophiles that have functionality levels that are inappropriate for direct C-C connective synthesis of a target. Indirect strategies may be desirable for other reasons. Thus, some atoms or groups of atoms may be exploited to control synthetic reactions by altering selectivity. We will refer to such molecular fragments as **control elements**.



For example, alkylation of ketones as in equation 10 often results in polyalkylation owing to rapid proton transfers from product ketone to starting enolate. The strong basicity of ketone enolates also can result in proton abstraction from alkyl halides (β-elimination) rather than nucleophilic substitution. The addition of a carboethoxy group provides a less reactive less basic nucleophile that can be alkylated in good yield (equation 16). Such a carboethoxyl group is often referred to as an **activating group** since it activates the molecule toward proton abstraction. It is perhaps more significant, however, that this group *deactivates* the resulting nucleophile making it a more selective reactant. After it has served its purpose, the control element must be removed. Retrosynthetically, the desirability of exploiting a **control element** requires **addition** of that element (**CEA**) in the first dislocation of the target prior to the reaction it is intended to control which then is the second dislocation of the target (equation 17).

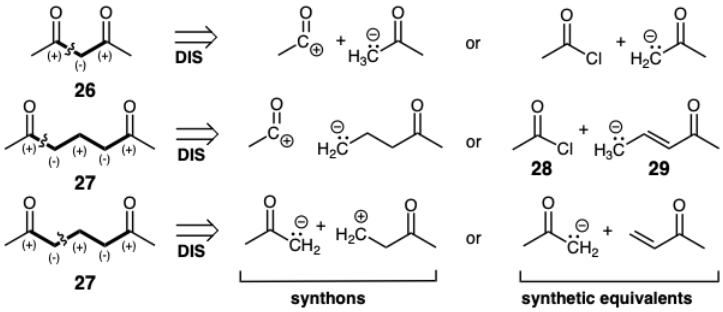


(16)

(17)

Difunctional Targets

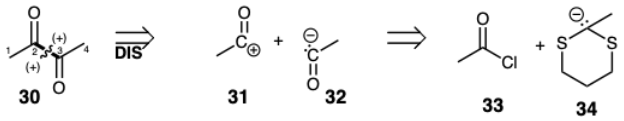
Polar syntheses of difunctional targets by strategies that exploit the polar activation provided by both functional groups to achieve C-C bond formation may be divided into two categories: those whose carbon skeleton can be assembled *directly* with the required functionality and those that cannot. C-C connective syntheses that directly generate difunctional targets with the required functionality are possible if both functional groups impart the same actual or potential polar reactivity to the atoms connecting the functional groups. We will refer to such functional groups and the atoms connecting them as **consonant circuits**. For example, **26** and **27** contain consonant circuits. Direct C-C connective synthesis of constant difunctional targets can be achieved by: (a) conjugate addition to an electrophile whose unsaturation level is one unit greater than that of the target, or (b) nucleophilic substitution or addition to an electrophile whose functionality level is one unit greater than that of the target. It should be noted that, while the carbon skeleton is assembled directly with the correct functionality level in the above strategies, it is not always possible to achieve a direct synthesis of consonant difunctional targets with the required unsaturation level. Thus, the reaction of **28** with **29** will generate a product with the carbon skeleton of **27** but with greater unsaturation. Thus, the **27** ⇒ **28** + **29** dislocation must be a two step process.



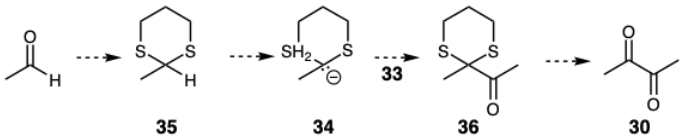
Indirect strategies are also possible for assembling consonant difunctional targets. Thus, during C-C bond formation, an intermediate may be generated that does not have the proper functionality level for the desired target. However, while the functionality levels of the precursors may be different than those of the target, the functionality in the synthetic equivalents of those precursors is electronically the same as the functionality of the consonant difunctional target. We shall refer to functionality in precursors whose nucleophilicity or electrophilicity is the same as that of the target -- but whose level may differ -- as **target-related functionality**.

Polar reactivity dissonance is present in difunctional targets if the polar reactivity imparted to the connecting atoms by one functional group is reversed by the other. We will refer to such functional groups and the atoms connecting them as **dissonant**

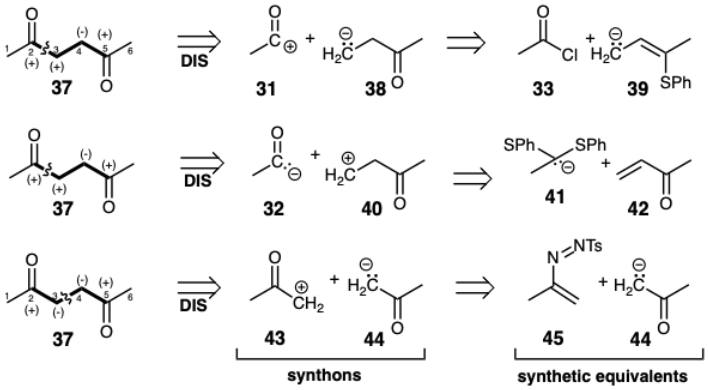
circuits. For example, **30** contains a dissonant circuit. Syntheses of dissonant difunctional targets can never be achieved by C- C connective routes that directly exploit the polar activation afforded by *both* functional groups. For example, polar disconnection of **30** at the 2,3-bond must generate an acyl nucleophile synthon **32**. But the carbonyl group usually provides electrophilic reactivity as in **31** and not nucleophilic reactivity at the carbonyl carbon. Synthetic equivalents such as **34** of such abnormal synthons, i.e. acyl carbanion equivalents, are known. They contain functionality that is related to that in the target but in which the usual polar reactivity of the target functionality is masked and the opposite polar reactivity is stabilized.



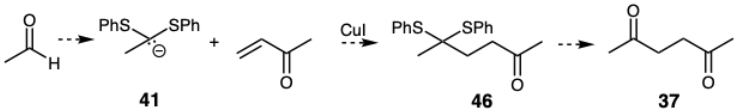
The normal polar reactivity of functional groups can be masked by conversion to unreactive derivatives.[11] The functional group is said to be **masked**, **blocked** or **protected** in such derivatives The unreactive functional groups thus created are called **masking** or **protecting groups**. Such groups are examples of **reactivity control elements**. There is a subclass of masking groups which not only block the normal polar reactivity of a functional group but also facilitate the opposite polar reactivity. Such **inversion** of the polar reactivity of a functional group has been called **umpölung**.[12] For example, the normal electrophilic reactivity of the carbonyl carbon in acetaldehyde can be transformed to nucleophilic reactivity by deprotonation of the derived thioacetal **35**. The dithioacetal group not only masks the electrophilicity of the carbonyl precursor but also facilitates deprotonation of the carbonyl carbon by stabilizing the derived carbanion. Thus, the anion **34** is a synthetic equivalent of the acyl carbanion synthon **32**. Acylation of **34** would deliver **36** from which the dissonant target **30** can be derived by hydrolysis. Note that the carbonyl group in the acetaldehyde starting material is exploited indirectly, i.e. after inversion of its usual polar reactivity, for the polar generation of a target C-C bond.



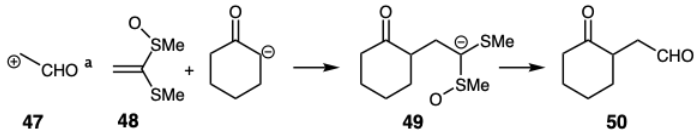
Polar disconnection of **37** at the 2,3-bond must generate a synthon **32** or **38** with inverted polar reactivity while disconnection at the 3-4 bond must generate a synthon **44** with inverted polar reactivity. It should be noted that synthetic equivalents of synthons with inverted polar reactivity, e.g. **34**, **39**, **41**, and **45,** by definition are dissonant molecules. Thus, for example, while the masked carbonyl carbon has nucleophilic reactivity in **41**, the nucleofugacity of thiophenyl groups also makes this carbon potentially electrophilic. In this case the opposing polar reactivities are conferred by a single functional group, the dithioacetal, a functional group that can provide both nucleophilic and electrophilic activation at the same carbon.



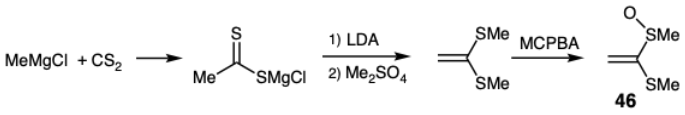
An acyl carbanion equivalent **41** is available by deprotonation of the di(phenylthio)acetal derivative of acetaldehyde. Conjugate addition of carbanion **41** to methyl vinyl ketone might produce the thioketal **46** from which the dissonant target **37** would be obtained by hydrolysis.



A large variety of synthetic equivalents of "umpoled synthons" are available.[13] Although they incorporate masked functionality with inverted reactivity, they are not necessarily prepared by umpolung of the target related functional group. For example, the synthetic equivalent **48** of the synthon **47** is an acetaldehyde enolonium ion equivalent. It reacts with cyclohexanone enolate to deliver **49** from which the dissonant target **50** is obtained upon hydrolysis.[14]

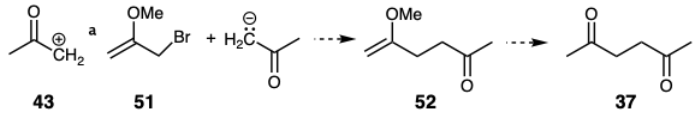


The acetaldehyde enolonium ion equivalent **48** can be obtained from methyl magnesium chloride and carbon disulfide by deprotonation of the intermediate dithioacetate followed by S-methylation and then by selective oxidation with m-chloroperbenzoic acid (MCPBA).[14]

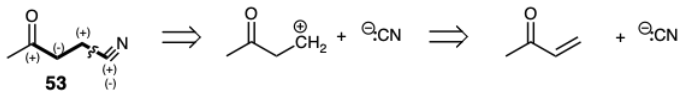


Dissonant Targets from Dissonant Precursors

C-C connective polar syntheses of dissonant difunctional targets may also be achieved by multistep sequences employing polar reactions that exploit the polar reactivity provided by only one of the two functional groups in a dissonant precursor. For example, allylation of acetone enolate with 2-methoxyallyl bromide (**51**), a synthetic equivalent of the acetone enolonium synthon (**43**), followed by hydrolysis of the enol ether intermediate **52** could afford the dissonant difunctional target **37**. Although **51** is prepared from acetone, the polar reactivity provided by the carbonyl group of the acetone precursor is not involved in the reaction of **51** with nucleophiles. Rather, the carbonyl group -- as an unreactive derivative -- is an innocent bystander. The polar reactivity required for C-C bond formation is provided by a *target non-related* second functional group, i.e. the bromo group. Also, it should be recognized that **51** is itself a dissonant difunctional molecule. The reaction of acetone enolate with **51** provides another example of a general principle: dissonant targets are available by polar C-C connective reactions of a dissonant precursor. Thus, **51** is a dissonant difunctional molecule.



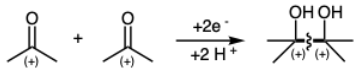
As noted above for dithioacetals, some functional groups not only provide electrophilic reactivity at the carbon to which they are appended but also facilitate carbanion generation (i.e. reduction) at that carbon. Since this allows both electrophilic and nucleophilic reactivity at the functional carbon or any carbon conjugated with it, we shall refer to it as a **biphilic functional group**. For example, ≡N confers electrophilicity to carbon in a nitrile and also facilitates deprotonation of HC≡N to confer nucleophilicity to the same carbon. Thus, although the nitrile carbon in **53** is electrophilic and **53** is therefore a dissonant difunctional target, the cyanide ion is a stable nucleophilic equivalent of the nitrile carbanion synthon. The dissonant target **53** is available directly by the polar conjugate addition of cyanide to methyl vinyl ketone.



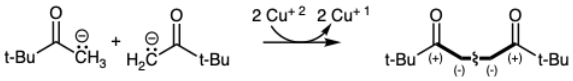
In summary, dissonant targets may be constructed by *multistep sequences employing polar reactions* that exploit: (a) inversion of the polar reactivity of one functional group in the target; (b) only one of the two functional groups in a dissonant precursor to provide polar reactivity; (c) a biphilic functional group.

Nonpolar Syntheses of Dissonant Targets

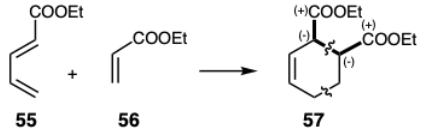
Dissonant difunctional targets are often prepared by direct C-C connective **nonpolar reactions**, such as oxidations, reductions, pericyclic bond-shift processes, or free radical additions. Thus, **reductive coupling** involves the union of two electrophilic centers accompanied by addition of an electron pair as in the pinacol reaction of acetone to produce the dissonant difunctional product pinacol.



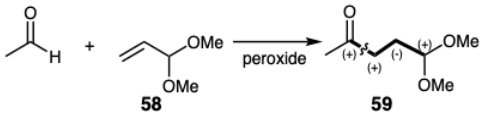
Oxidative coupling involves the union of two nucleophilic centers accompanied by removal of one electron pair. The dissonant diketone **54** is obtained upon oxidative coupling of pinacolone enolate.



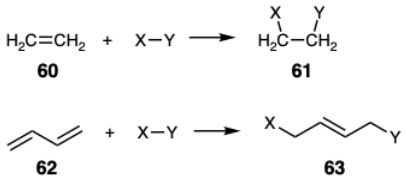
Generation of dissonant targets by ***pericyclic bond-shift processes*** is possible since the orientation of such reactions is controlled by p-orbital overlap which does not necessarily correspond with polar reactivity. For example, dissonant diester **57** is the major product from the cycloaddition of **55** with **56**.



The ***free radical*** chain ***reaction*** between acetaldehyde and acetal **58** to generate **59** exemplifies another nonpolar C-C connective route to dissonant difunctional products.

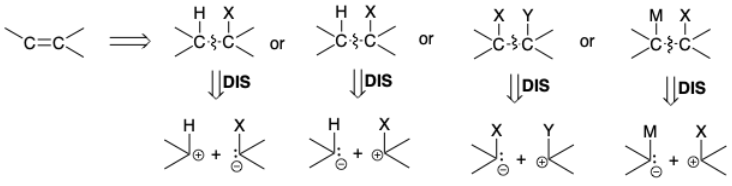


Dissonant difunctional targets are also available by ***non-C-C connective processes*** such as addition of electronegative atoms X and Y to both carbons of a C=C bond. We shall refer to such reactions as **dioxidative additions** since both carbons are oxidized. Dioxidative additions can also occur with polyenes. Such reactions, which we shall call 1,n-dioxidative additions, always generate dissonant difunctionality. Thus, the conversion of **60** into **61** involves 1,2-dioxidative addition while the **62** to **63** conversion is a 1,4-dioxidative addition.



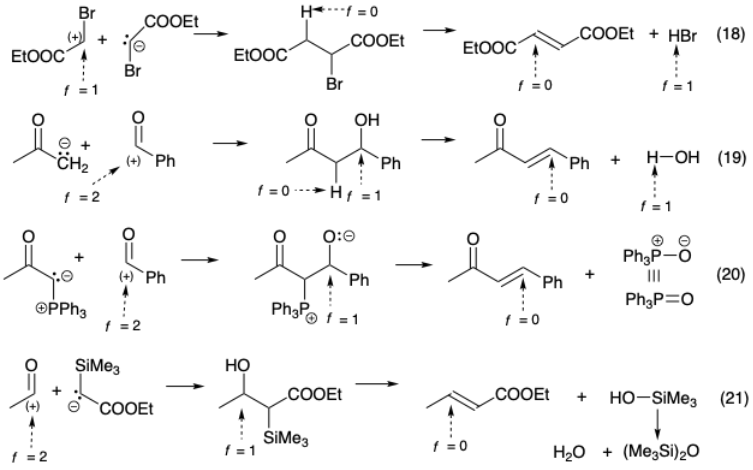
Disconnection of C=C Bonds

Retrosynthetic dislocations of a synthetic target involving disconnection of a carbon-carbon double bond, i.e. double disconnections, usually correspond to multistep synthetic sequences. *There are no polar reactions that generate two bonds between two carbon atoms in a single step*. (Note that dimerizations of carbenes are cycloadditions, that by definition, generate two bonds in a single step.) Therefore, if polar activation is to be exploited, a double connection during the synthesis must be made in two steps: the first, a polar union; the second, an elimination. The elimination step usually involves loss of HX, XY, or MX where X and Y are groups that are more electronegative than carbon while M is any group that is more electropositive than carbon. Thus retrosynthetically, disconnection across a C=C bond requires an addition as the first dislocation of the target.



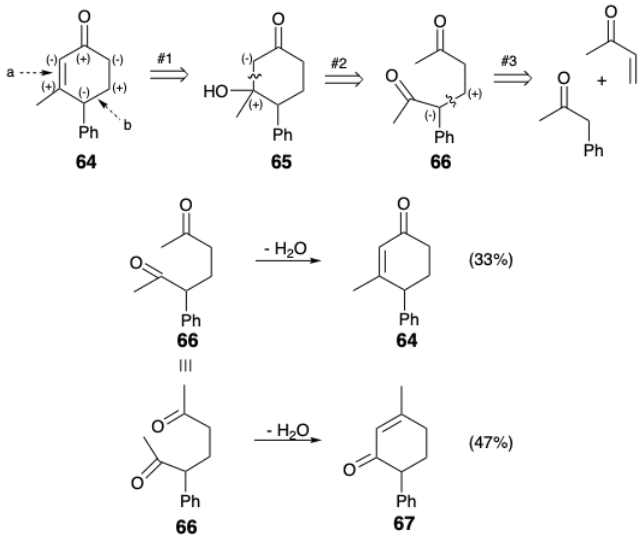
The synthesis outlined in equation 18 is a representative example of the first approach. Here an electrophilic activating group of functionality level = 1 resides on each carbon. The syntheses outlined in equations 19-21 are representative examples of each of the last three strategies. In each case, the functionality level of the electrophilic synthon decreases by two on going to the C=C target. The functionality level of the nucleophilic synthon goes from -1, -2, or 0 for equations 19, 20, and 21 respectively in the precursors

to 0 in the products. Also note that the second steps in equations 18 and 19 require oxidation of a hydrogen (deprotonation), and that the second step in equation 20 is a direductive elimination.



Strategic Flaws

The polar activation provided by a single functional group in a target can be exploited numerous times during a synthesis to facilitate several C-C connective steps. For example, the carbonyl group of the 2-cyclohexen-1-one **64** might be used to provide the requisite nucleophilic and electrophilic reactivity for generating two C-C connections in this target (bonds a and b) corresponding to dislocations #2 and #3 (synthetic steps 1 and 2) in a strategy for synthesis of **64** from methyl vinyl ketone and phenyl acetone. The first dislocation of the target, addition of water to the C=C bond shows the necessary intervention of an intermediate during the double connection (synthetic steps 2 and 3) corresponding to the **65** to **64** conversion. This synthetic plan also provides an example of a significantly flawed synthetic design since the intermediate δ-diketone **66** cyclizes in two different ways only one of which affords the desired product. The isomeric 2-cyclohexen-1-one **67** can even be the major product of this reaction.[15]



Theory and Practice

Besides failures to achieve the required regioselectivity during addition reactions of multidentate nucleophiles or electrophiles, or the reactions of molecules with several similar functional groups, the planned removal of activating functionality, or unsaturation, as well as the introduction, removal, or interconversion of functionality by oxidation, reduction, metathesis, etc., may not be feasible owing to limitations of known reactions and/or limitations imposed by the reactivity characteristic of a particular synthetic target. Polar reactivity analysis serves merely to systematically generate a set of synthetic strategies. These must be subsequently evaluated in terms of the availability of suitably selective reactions and appropriate starting materials.

1.5: A Protocol for Synthetic Design

In summary, some principles of synthetic planning that can provide a logical basis for designing a synthesis include the following (additional principles will be introduced on pages 83-84):

1. *Dislocate the target* to precursor synthons by connections (CON), by disconnections (DIS), adjustment of functionality level (FLA) – such as oxidations and reductions, polar reactivity inversion (PRI), or functional group addition (FGA) – by interconversion of functional groups (FGI) without a change of functionality level, or by addition of control elements (CEA).
2. *Devise synthetic equivalents* of precursor synthons by appropriate functional group addition (FGA, a subclass of FLA, i. e. from $f = 0$ to $f \neq 0$).
3. *Construct a synthetic tree* systematically generating sets of potential intermediates.
4. *Prune the tree* as it grows by eliminating schemes that do not follow logically imposed boundary conditions such as favoring dislocations that exploit target related functionality to facilitate the corresponding chemical reactions during synthesis.
5. *Rank alternative strategies* favoring efficient schemes that are most likely to deliver the desired target and synthetic intermediates by avoiding undesired side reactions. That is, disfavor schemes that probably incorporate flaws, especially ones that are fatal, i. e. will give 0% yield of the desired product.

1.6: Terminology

For definitions see the sections indicated.

(+), (-) (1.4)

⊕, ⊖ (1.4)

activating group (1.4)

ambident electrophile (1.4)

ambident nucleophile (1.4)

biphilic functional group (1.4)

boundary condition (1.2)

CEA (1.4)

CON, DIS (1.2)

consonant circuit (1.4)

difunctional target (1.4)

dioxidative addition (1.4)

direct associative strategy (1.2)

direct synthesis (1.4)

dislocation (1.1)

electrophilic center (1.4)

FGA (1.4)

FLA (1.4)

functionality level (1.3)

indirect synthesis (1.4)

key intermediate (1.2)

logic centered analysis (1.2)

masking group (1.4)

nonpolar reaction (1.4)

nucleophilic center (1.4)

oxidation state (1.4)

polar reaction (1.4)

polar reactivity analysis (1.4)

polar reactivity dissonance (1.4)

polar reactivity inversion (PRI) (1.4)

protecting group (1.4)

reactivity control element (1.4)

retrosynthetic analysis (1.1)

strategic flaw (1.4)

subtarget (1.2)

synthetic equivalent (1.2)

synthetic tree (1.2)

synthon (1.2)

target-related functionality (1.2)

transform (1.1)

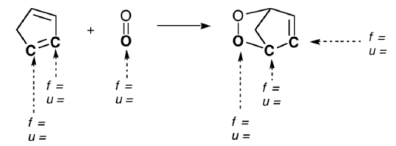
umpölung (1.4)

unsaturation level (1.3)

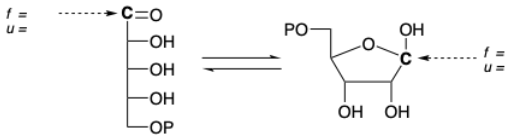
1.7: Study Questions

1. Indicate the functionality and unsaturation levels of the boldface atoms in the reactants and products of the following reactions.

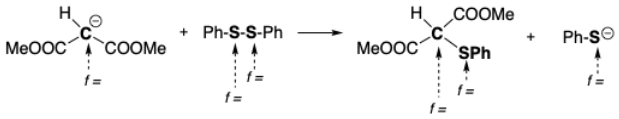
(a)



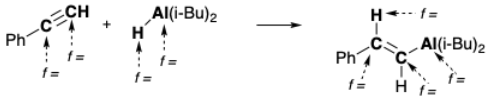
(b)



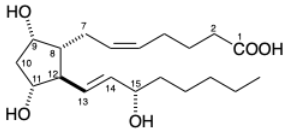
(c)



(d)



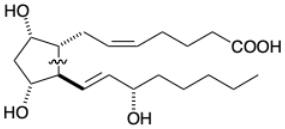
2. Consider possible strategies for construction of the $PGF_{2\alpha}$ carbon skeleton exploiting the functional groups at the 9, 11, and/or 15 positions to activate formation of various bonds in the cyclopentane ring by polar reactions.

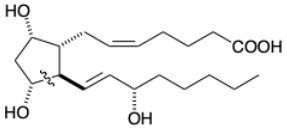


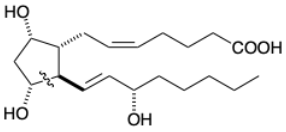
PGF_{2a}

(a) Categorize each of the following circuits as consonant or dissonant:

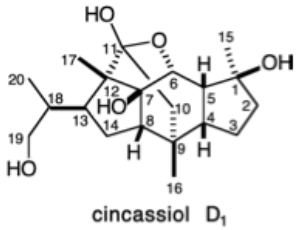
Circuit	Type
1-2-3-4-5-6-7-8-9	
9-10-11	
9-8-12-11	
9-8-12-13-14-15	
11-12-13-14-15	







3. Perform a thorough polar analysis of cincassiol D_1, a natural product of the "terpene" family.

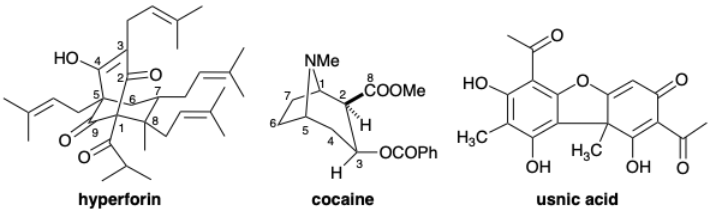


For all circuits consisting only of carbon chains of 14 carbons or less, list the polar relationships between functional groups with a table in the following format:

Positions	Circuit	Relationship
1 + 6	1-5-6	consonant
	1-2-3-4-5-6	dissonant
	1-2-3-4-9-8-7-6	dissonant

4.

(a) Find the dissonant polar reactivity circuits, if any, between functional groups in the natural products hyperforin and cocaine. List them in the table format described above for question 4.

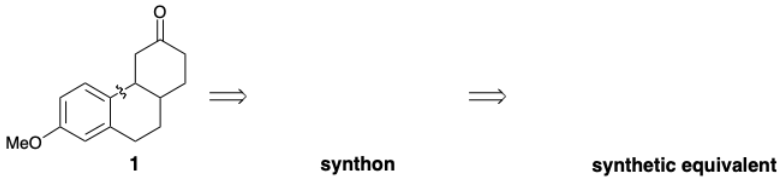


(b) Disconnection of one, and only one, C-C bond in usnic acid eliminates all dissonant circuits. Which is this unique bond in usnic acid that is incorporated in every dissonant circuit?

(d) What type of reaction could generate usnic acid directly from the subtarget identified in c?

5.

(a) With (+) and (-) next to appropriate atoms, indicate on structure **66** the polar activation provided to all atoms in a curcuit connecting the functional groups that could allow polar formation of the bond that is disected with a wavy line. Then draw structures for a synthon and a synthetic equivalent of the synthon for an immediate precursor of **66**.



(b) Draw structures of three alternative monomeric products that might be formed during an attempt at converting the above synthetic equivalent into the synthetic target **1**.

1.8: References

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11. For compilations see: (a) McOmie, J. F. W. (Ed.), "Protective Groups in Organic Chemistry", Plenum, New York (1973); (b) Greene, T. W., "Protective Groups in Organic Synthesis, John Wiley & Sons, New York (1981).
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CHAPTER OVERVIEW

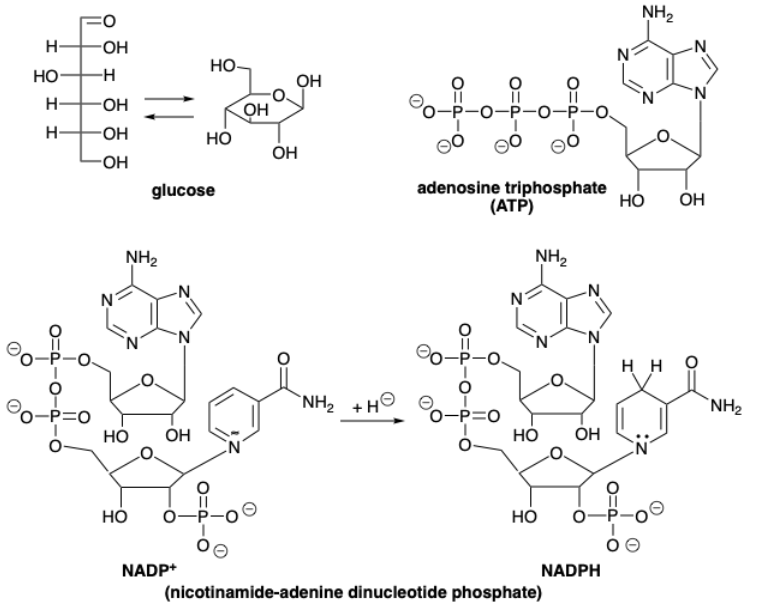
2: Sugars - Biosynthetic Starting Materials

2.1: Carbon Fixation - Biosynthesis of Sugars

Strategies for Glucose Biosynthesis

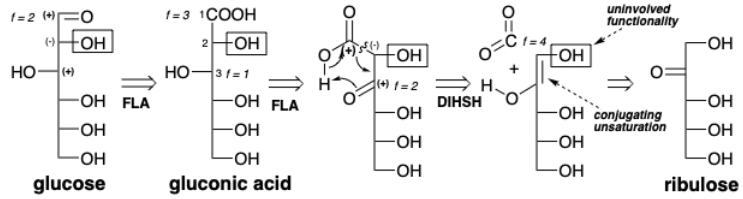
Glucose is the ultimate organic starting material from which all other organic carbon compounds can be synthesized in nature. The single carbons of six carbon dioxide molecules are stitched together to form glucose by photosynthetic organisms. The energy for this reaction is provided by hydrolysis of adenosine triphosphate (ATP) to produce adenosine diphosphate (ADP) and phosphate (P). Hydrogen atoms are provided by the 1,4-dihydro derivative (NADPH) of nicotinamide-adenine dinucleotide phosphate ($NADP^+$) and by protons. NADPH is a source of hydride, a "hydride transfer agent", that is stable in the aqueous environment of biosynthesis, i.e. at physiological pH it does not react with protons to generate molecular hydrogen. The high energy triphosphate ATP is produced by a photochemical phosphorylation of ADP to yield ATP. The reducing agent NADPH, a dihydropyridine, is produced in the same reaction by photochemical reduction of $NADP^+$. Another important product of this reaction is molecular oxygen that is needed for the oxidative catabolism of natural products to provide energy in the form of ATP, i.e. by oxidative phosphorylation of ADP.

$$6CO_2 + 18ATP + 12NADPH + 12H_2O + 12H^{\oplus} \longrightarrow \text{glucose} + 18P + 18ADP + 12\ NADP^{\oplus}$$



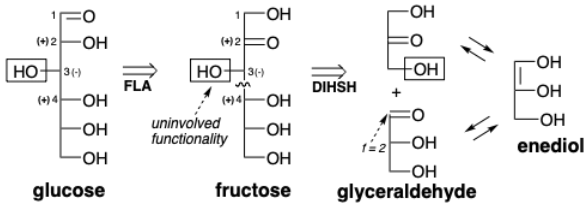
Elongation of a five carbon sugar chain to a six carbon chain by appending a molecule of the one carbon electrophile CO_2 is an especially obvious strategy for a synthesis of glucose from CO_2. Addition of a carbon nucleophile to CO_2 ($f = 4$) would produce a carboxyl group ($f = 3$). This suggests that the first dislocation of the target might be oxidation of the aldehyde group ($f = 2$) to a carboxyl. There is a consonant circuit between the carboxyl group and the oxygen functionality in position 3 of the resulting gluconic acid subtarget. However, expression of the requisite polar reactivity at the 2-position requires conjugation as in the enol of ribulose. Therefore, adjustment of the functionality level at position 3 is a second logical second dislocation. Disconnection of the terminal carboxyl (a retro Claisen condensation) as the third dislocation of the target then suggests ribulose as a starting material.

$$2\ NADP^{\oplus} + 4\ ADP + 4\ P + 2\ H_2O \xrightarrow{h\nu} O_2 + 2\ NADPH + 2H^{\oplus} + 4\ ATP$$

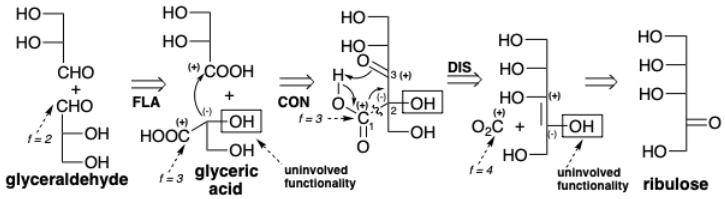


Interestingly, the above strategy is not operative in the *biosynthesis* of glucose although it is used, albeit in reverse, for the generation of ribulose from glucose by the **phosphogluconate pathway** (*vide infra*). Rather, the biosynthesis of glucose involves a

different strategy although the starting materials are indeed CO_2 and ribulose. Glucose has ample functionality to facilitate its construction by C-C connective strategies involving generation of any of its C-C bonds by polar reactions. For example, the 3,4-bond could be generated by reaction of a nucleophilic synthon corresponding to carbons 1-3 with an electrophilic fragment corresponding to carbons 4-6. This suggests a first dislocation of the target involving adjustment of functionality level to allow conjugation of the C-2 oxygen with position 3 to facilitate generation of nucleophilic reactivity at C-3. By coupling oxidation at the 2-position with reduction at the 1-position, the first dislocation is simply an isomerization of the target glucose, an aldose, to fructose, a ketose. Polar disconnection of the subtarget (a retro aldol condensation) in the second dislocation has the important consequence of dividing the target into two similarly functionalized fragments with identical carbon skeletons. Such dislocations potentially reveal **latent symmetry** which is defined as the possibility of deriving two halves of a target from a common starting material. The precursors generated in the second dislocation, dihydroxyacetone and glyceraldehyde are readily interconverted by isomerization through an enediol intermediate.



Once again, we note that incorporation of CO_2 into a precursor by a polar process will generate a carboxyl group. This suggests a carboxylic acid, glyceric acid, that can serve as a common precursor for both dihydroxyacetone and glyceraldehyde. Reterosynthetically this involves dislocation of dihydroxy acetone to glyceraldehyde (an isomerization) and dislocation of both molecules of glyceraldehyde to the same acid precursor (oxidation). Polar connection of two molecules of glyceric acid (a Claisen condensation) suggests a β-ketoacid subtarget from which a carboxyl group can be disconnected in the last dislocation of the target leading to the precursors CO_2 and ribulose.

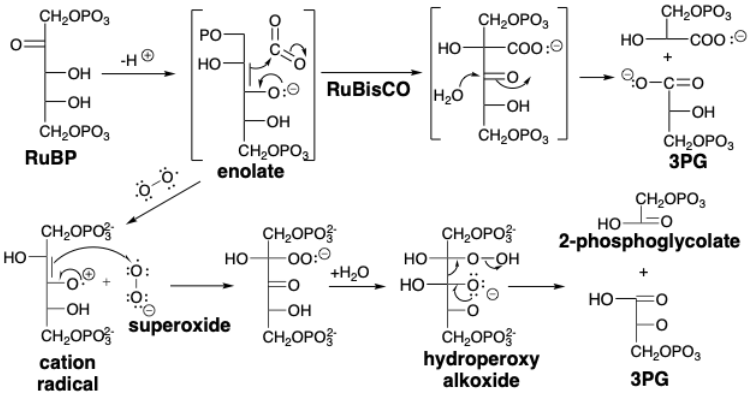


Biosynthesis of Glucose

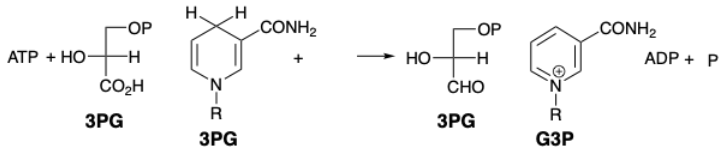
In fact, the actual biosynthesis involves carboxylation of this five carbon sugar, albeit in the form of a bisphosphate derivative, ribulose-1,5-bisphosphate (RuBP). A strategy for biosynthesis of the subtarget RuBP might proceed in a stepwise fashion adding one CO_2-derived carbon at a time to a growing carbon chain. Such a process might require a different enzyme to catalyze fixation of each molecule of CO_2 by addition to different subtargets. However, a much more ingenious strategy is adopted in nature. Carbon fixation occurs ***only*** by the reaction of CO_2 with RuBP. Therefore, only a single enzyme is required to catalyze the process. Six molecules of CO_2 are combined with six molecules of the five-carbon sugar derivative RuBP to produce twelve molecules of glyceric acid two of which are used to generate glucose by the above strategy. The thirty carbons of the remaining ten glyceric acid molecules are reshuffled to regenerate six five-carbon RuBPs. Thus, RuBP also functions as a catalyst for the bioconversion of CO_2 into glucose.

The photosynthetic formation of glucose (actually in "the dark reactions of photosynthesis") involves an intricate series of reactions known as the Calvin cycle. In the accompanying reaction schemes, P is used to represent a phosphate ester [P = $-PO_3^{2-}$]. The carbon fixation cycle begins with carboxylation of RuBP (see below), a reaction that is catalyzed by ribulose bisphosphate carboxylase oxidase (**RuBisCO**) that is probably the most abundant protein on Earth. Thus, carboxylation of the enol of RuBP leads to a presumed b-keto acid intermediate that is readily cleaved by water in a retro Claisen condensation to give two molecules of 3-phosphoglyceric acid (3PG). Given the importance of this chemistry for the biosynthesis of organic molecules and the success of carbon-based life forms, it is noteworthy that RuBisCo catalysis of this reaction is barely viable. At ambient levels of carbon dioxide and oxygen, the catalyst consumes only a few molecules of CO_2 per second in contrast with many enzymes that process thousands or tens of thousands of molecules of substrate per second. Furthermore, RuBisCO catalyzes another reaction that competes with carboxylation, the oxidative cleavage of RuBP to 3-PG plus 2-phosphoglycolate. This oxidative cleavage

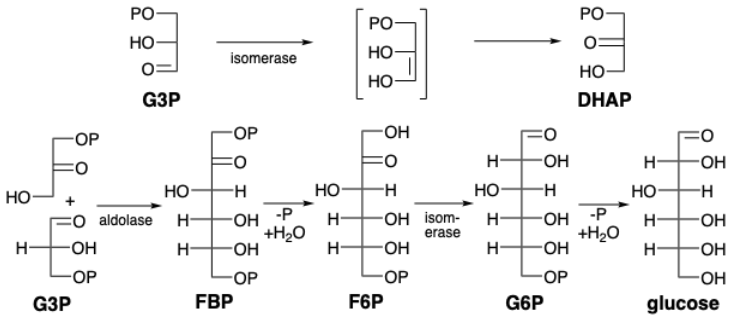
presumably involves electron transfer from than enolate intermediate to oxygen to produce superoxide and a cation radical. Bond formation between these two radicals then generates a hydroperoxy alkoxide. Fragmentation of this intermediate is driven by the exothermic generation of two carbonyl groups. The ratio of carboxylation versus oxidative cleavage is only about 4 to 1 and is even less favorable at higher temperatures. Thus, plants in high heat environments store carbon dioxide during the hot hours of intense sunshine, and generate glucose in the cooler hours in the absence of sunshine and its blistering heat.



The biosynthesis of all sugars, including glucose and the regeneration of RuBP, use 3PG as the common and only starting materisl. 3PG is first reduced to an aldehyde, glyceraldehyde-3-phosphate (G3P), by NADPH. ATP facilitates the reduction by converting the carboxyl into a more electrophilic derivative, a carboxylic-phosphoric anhydride. The remainder of the reactions of the Calvin cycle redistribute the thirty six carbon atoms of twelve G3Ps to yield one molecule of glucose (six carbon atoms) and regenerate six molecules of RuBP (thirty carbon atoms). The cycle will be summarized in Chart 1 below.

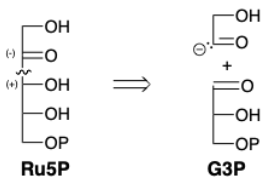


The aldose G3P is transformed to the ketose dihydroxyacetone phosphate (DHAP) under the influence of the enzyme isomerase. The six carbon atom skeleton of glucose is then assembled by an aldol condensation of G3P with DHAP. The initial product, fructose bisphosphate (FBP), is hydrolyzed (to F6P), isomerized (to G6P) which is hydrolyzed further to yield glucose.

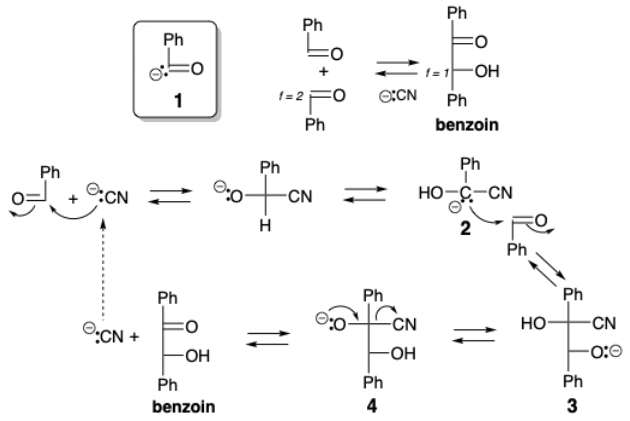


Regeneration of Ribulose Bisphosphate

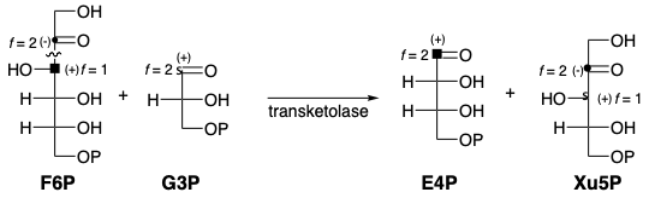
Retrosynthetic analysis reveals that a polar synthesis of Ru5P from G3P requires an umpoled synthon, the 2-hydroxyacetyl carbanion. A boundary condition, the aqueous reaction conditions of biosynthesis limit the choice of synthetic equivalents for this synthon. It is instructive to consider that a similar synthon **1** is required in the benzoin condensation, a cyanide ion- catalyzed polar coupling of two electrophilic benzaldehyde carbonyl groups that can be achieved in aqueous solution. Cyanide inverts the polar reactivity of a benzaldehyde carbonyl carbon by nucleophilic addition followed by a proton transfer that generates the carbanion **2**, a synthetic equivalent of synthon **1**. Anion generation at the former carbonyl carbon is favored by conjugation with the nitrile in **2**. It is the biphilicity of cyanide that is the basis of its ability to invert the polar reactivity of an aldehyde carbonyl carbon. Condensation of **2** with a second molecule of benzaldehyde delivers alkoxide **3** which affords



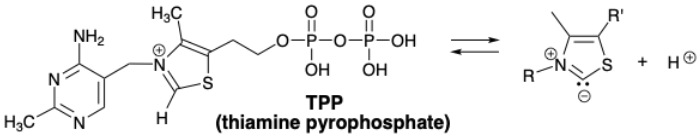
alkoxide **4** by proton transfer. Expulsion of cyanide from **4** then regenerates the catalyst and produces benzoin. Analogous cyanide-catalyzed reactions of other aldehydes are generically called benzoin condensations. All of the steps of the benzoin condensation are reversible. Therefore, the umpoled synthon **2** not only can be generated by reaction of cyanide with benzaldehyde, but also by retro benzoin condensation of benzoin.



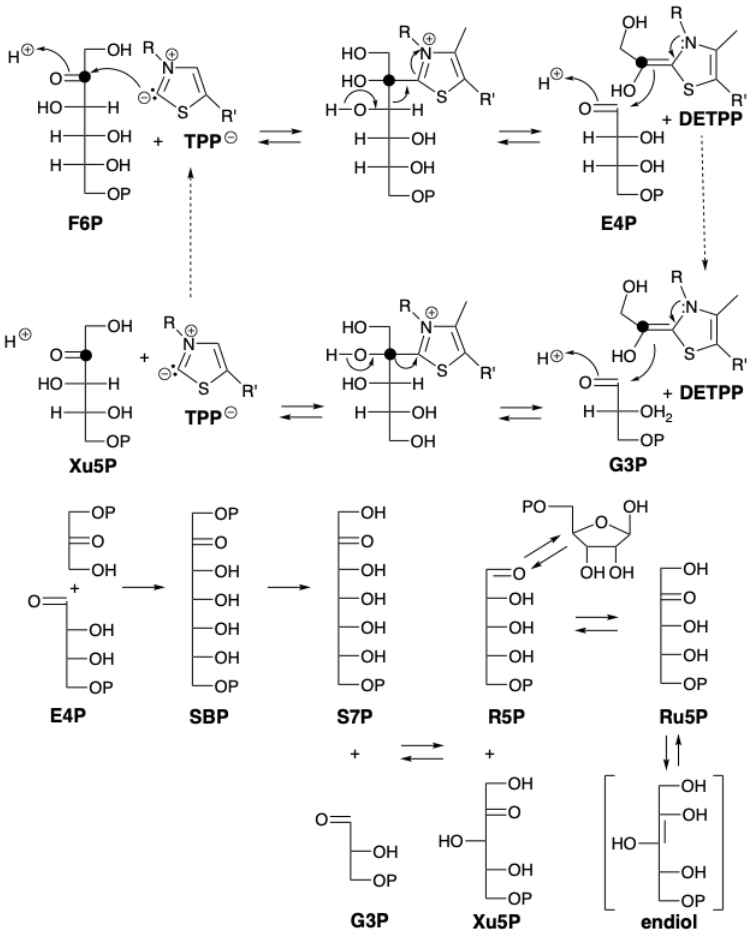
A similar retro benzoin condensation of fructose 6-phosphate (F6P), an intermediate generated in the biosynthesis of glucose from glyceraldehyde 3-phosphate (G3P), could provide a synthetic equivalent of the 2-hydroxyacetyl carbanion required for biosynthetic regeneration of RuBP from G3P. In fact, the biosynthesis of RuBP from G3P involves the transfer of a 2-hydroxyacetyl group from F6P to G3P that is promoted by the enzyme **transketolase**.



Needless to say, cyanide is not the cocatalyst which masks the usual electrophilic reactivity of a carbonyl group and imparts nucleophilic reactivity to it in nature. The biological equivalent of cyanide ion is a carbanion generated by deprotonation of the thiazole ring in **thiamine pyrophosphate (TPP)**.



The thiamine carbanion nucleophile condenses with the electrophilic carbonyl carbon of a ketose (e.g. F6P) to yield a 2-hydroxy iminium derivative. The latter readily undergoes a retro aldol-like reaction leading to an aldose, e.g. erythrose 4-phosphate (E4P), that has two carbons less than the original ketose. The resulting nucleophilic 2-hydroxyacetyl equivalent, 2-(1,2-dihydroxyethylidene)thiamine pyrophosphate (DETPP) can condense with a different aldose, e.g. G3P, to regenerate TPP and a ketose, e.g. xyulose 5- phopsphate (Xu5P) that has two carbons more than the aldose.



Further reactions in the Calvin cycle are aldolase promoted condensation of E4P with DHAP to yield sedoheptulose bisphosphate (SBP), hydrolysis of the latter to the monophosphate (S7P), transketolase promoted hydroxyacyl transfer from S7P to G3P to give Xu5P plus ribose 5-phosphate (R5P), isomerization of the latter to ribulose 5-phosphate (Ru5P), epimerization of Xu5P to give Ru5P, and phosphorylation of the latter to regenerate RuBP. The Calvin Cycle is summarized in chart 1.

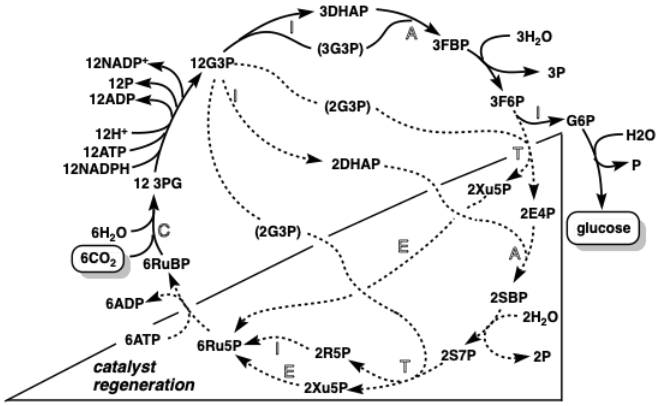


Chart 1. The Calvin Cycle Key: **ATP** = adenosine triphosphate, **DHAP** = dihydroxyacetone phosphate, **E4P** = erythrose 4-phosphate, **F6P** = fructose 6-phosphate, **FBP** = fructose 1,6-bisphosphate, **G3P** = glyceraldehyde 3- phosphate, **G6P** = glucose 6-phosphate, **P** = phosphate, **3PG** = 3-phosphoglyceric acid, **R5P** = ribose 5-phosphate, **Ru5P** = ribulose 5-phosphate, **RuBP** = ribulose 1,5-bisphosphate, **S7P** = sedoheptulose 7-phosphate, **SBP** = sedoheptulose 1,7-bisphosphate, **Xu5P** = xylulose 5-phosphate, A = aldolase, C = carboxylase, E = epimerase, I = isomerase, T = transketolase

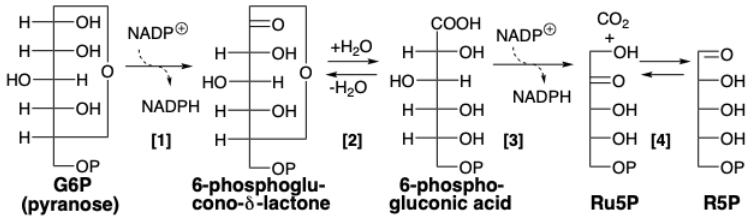
Summary of Biosynthetic Carbon Fixation

(1) There is only one reaction that converts carbon dioxide into organic starting materials: the generation of two 3PGs from RuBP and CO_2. This is step #1 in the biosynthesis of all natural products. (2) RuBP serves as a catalyst in a cycle that converts six CO_2

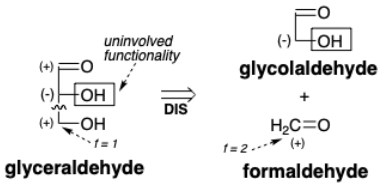
into one molecule of glucose. (3) The RuBP consumed in step #1 is regenerated by a series of reactions, that reshuffle the atoms of ten molecules of the three-carbon sugar G3P into six molecules of the five- carbon RuBP. (4) All C-C bond formation and cleavage involves condensations (aldol, Claisen, benzoin) that are readily reversible. Furthermore, aldolase, the enzyme that catalyzes the formation of glucose from three-carbon sugars, also catalyzes their regeneration. As we shall see, further biosynthetic transformations of glucose into fatty acids, terpenes, or polyketides begin with cleavage of glucose (**glycolysis**) by this retro aldol reaction.

Ribulose from Glucose

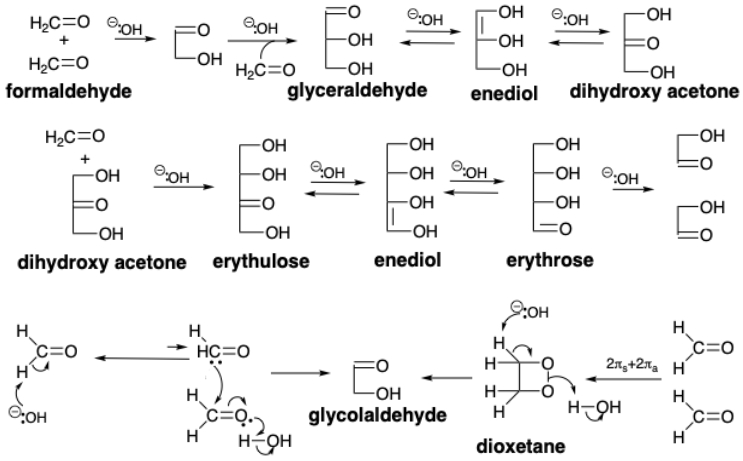
Before proceding with an examination of strategies for the synthesis of glucose starting materials, let us first return to the simple strategy outlined above that is not used for the biosynthesis of glucose. Thus, rather than serving as a synthetic route to glucose from RuBP, this strategy in reverse is used in nature to produce five-carbon sugars from glucose. This pathway for glucose degradation is important for biosynthesis because it generates pentoses for the synthesis of nucleic acids. The pathway begins with oxidation of glucose 6-phosphate to 6-phosphogluconate. It is known as the **phosphogluconate pathway**, the **hexose monophosphate shunt**, or the **pentose phosphate pathway**. Many of the enzymes and reactions of this pathway are also involved in the biosynthesis of glucose from CO_2 in the dark reactions of photosynthesis. The phosphogluconate pathway produces 2NADPH + CO_2 + R5P from glucose and 2NADP$^+$. Four enzymes are required: [1] 6-glucose phosphate dehydrogenase, [2] lactonase, [3] 6-phosphogluconate dehydrogenase, and [4] phosphopentose isomerase.



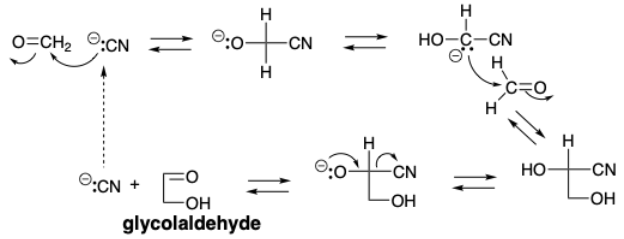
2.2: Synthesis of Sugars



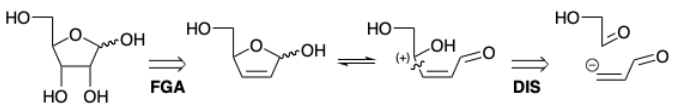
Retrosynthetic analysis reveals that a polar synthesis of glyceraldehyde can be achieved by condensation of a nucleophilic glycolaldehyde synthon with formaldehyde, a one-carbon electrophile of with f = 2. In fact, base-catalyzed aldol condensation of glycolaldehyde with formaldehyde not only generates glyceraldehyde but also dihydroxyacetone through tautomerization to an endiol and erythulose through aldol condensation with a second equivalent of formaldehyde.[1] These reactions are believed to be involved in the base-catalyzed oligomerization of formaldehyde that generates the same products. A tiny amount of glycolaldehyde is sufficient to accelerate the oligomerization that otherwise has a long induction period, but eventually proceeds with the same kinetics as the glycolaldehyde-promoted process. Under certain conditions, as much as 50% of the formaldehyde is converted to glycolaldehyde, apparently through tautomerization of erythrulose to erythrose that then undergoes retro aldol cleavage to two molecules of glycolaldehyde. Thus, the induction period in the ologomerization of formaldehyde presumably corresponds to a slow process that generates the first traces of glycolaldehyde that then catalyzes further ologomerization. One hypothesis is that the formation of glycolaldehyde from two molecules of formaldehyde involves proton abstraction to generate a tiny concentration of acylcarbanion that condenses with a second molecule of formaldehyde.[1] An alternative possibility is that a thermally allowed 2πs+2πa cycloaddition (see chapter 3, page 67) delivers a dioxetane intermediate that undergoes base catalyzed disproportionation to the hydroxyaldehyde.



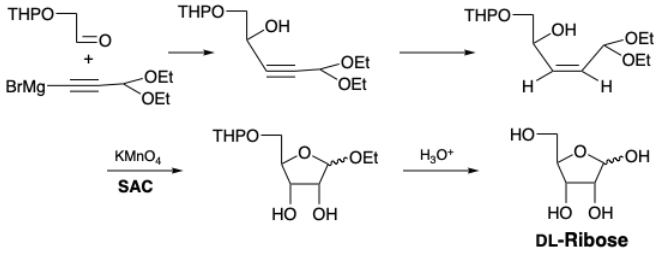
The oligomerization of formaldehyde to provide a variety of sugars is a likely (pre)biosynthetic route for the generation of these molecules in a prebiotic world. In the prebiotic world, it is likely that the formation of glycolaldehyde occurred mainly through a cyanide catalyzed condensation that involves a cyanohydrin carbanion intermediate.



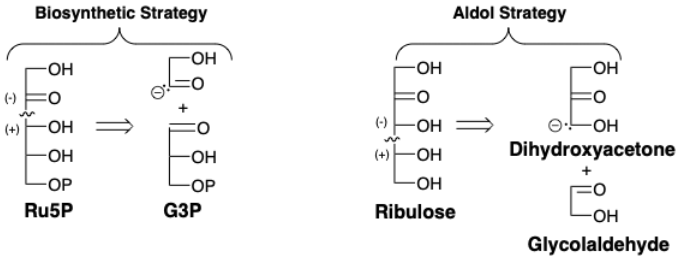
The major molecular complexity of sugars inheres in their abundance of functionality and stereochemistry. One strategy for the total synthesis of ribose exploits the prospect of stereospecific cis hydroxylation to introduce two hydroxyl groups with the requisite stereocontrol. Ribose exists predominantly in a cyclic hemiacetal form. The relatively rigid 5-membered ring can be expected to favor the appropriate stereocontrol. Disconnection of a cis alkene precursor at the carbinol carbon suggests the addition of a vinyl carbanion with glycolaldehyde.



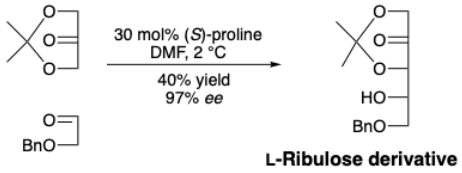
Two refinements are required to implement this strategy. The glycolaldehyde hydroxyl must be masked to prevent protonation of the carbanion and one aldehyde group must be masked as an acetal. Rather than a vinyl carbanion, an acetylide was chosen as the nucleophile with the prospect of stereospecific cis partial hydrogenation of a disubstituted alkyne as a route to the requisite cis alkene.[2]



In the biosynthetic route to ketoses such as Ru5P from G3P, thiamine pyrophosphate serves as catalyst to provide an equivalent of a glycolaldehyde with inverted polar reactivity of the carbonyl group. An aldol condensation strategy for the C-C connective synthesis of ribulose is suggested by the latent nucleophilicity of the α-carbon enabled by the carbonyl group of dihydroxyacetone to react with a glycolaldehyde electrophile.

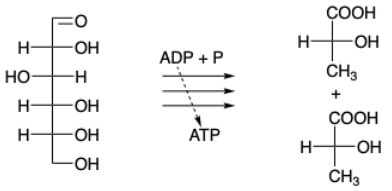


The biosyntesis of sugars generates single enantiomers owing to the asymmetry of the enzymes that catalyze their formation. The sugars generated by the hydroxide-catalyzed oligomerization of formaldehyde are a mixture of stereoisomers that are all racemic. However, asymmetric catalysis can be achieved in aldol C-C connective syntheses using chiral nonracemic (S)-proline as catalyst to promote the aldol condensation of dihydroxyacetone acetonide wih the benzyl ether of glyceraldehyde.[3]



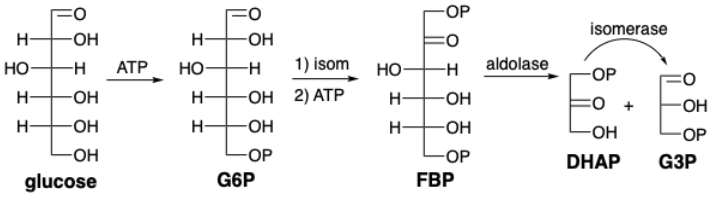
2.3: Acetyl CoA - a Sugar-Derived Starting Material

All of the carbon atoms of glucose are bound to oxygen. In contrast, many complex natural products are far less oxygenated. For example, fatty acids (Chapter 3) are long straight chains of often more than a dozen carbon atoms with no oxygen at all except for one terminal carbon that is fully oxidized to a carboxylic acid. Glucose **catabolism** (breakdown) can proceed **anaerobically** (doesn't require oxygen) producing biosynthetically useful small molecules in which some carbon atoms are less and some more highly oxidized. No net oxidation occurs. The oxygen atoms of glucose are merely reshuffled. The end product of the process is lactic acid, a molecule that is oxygen rich at one end and oxygen poor at the other. Perhaps most importantly for living organisms, anerobic catabolism of glucose also generates chemical energy in the form of ATP that can be used, *inter alia*, to power muscular contractions.

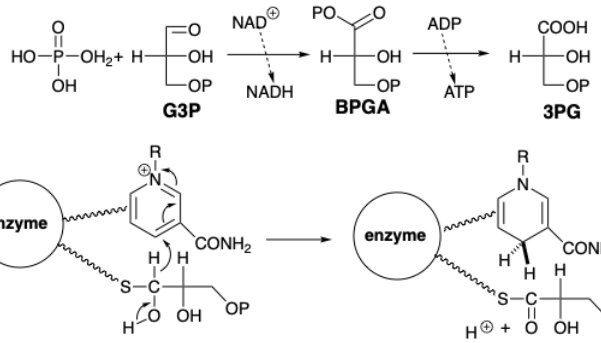


glucose $C_6H_{12}O_6 \Rightarrow 2 \times C_3H_6O_3$ **lactic acid**

Glycolysis begins with phosphorylation of glucose followed by isomerization to fructose 6- phosphate (F6P) that is then phosphorylated further. Fructose bisphosphate is then cleaved under the influence of aldolase in a retero-aldol reaction to yield DHAP and G3P. Isomerization of DHAP then produces a second molecule of G3P.

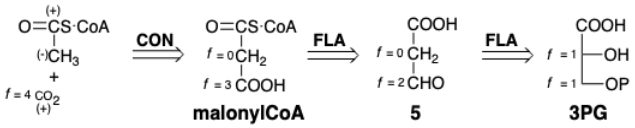


The final transformation of G3P into lactic acid begins with the removal of hydride from the aldehyde portion of the molecules (oxidation) by nicotinamide-adenine dinucleotide ($NAD^{\oplus}$). The reaction is catalyzed by the enzyme glyceraldehyde 3-phosphate dehydrogenase. The enzyme binds G3P as a hemithioacetal that readily transfers hydride to an enzyme-bound $NAD^{\oplus}$. The product, a reactive thioester of phosphoglyceric acid, readily acylates phosphate to yield bisphosphoglyceric acid (BPGA), a reactive mixed anhydride. BPGA then phosphorylates ADP. Hence, the chemical energy generated in this oxidation is stored in the phosphate bond energy of ATP.

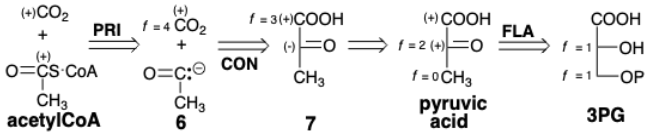


For the biosynthesis of fatty acids (Chapter 3), terpenes (Chapter 4), or polyketides (chapter 5), phosphoglyceric acid is dismantled further to form a molecule of CO_2 and a thioester of acetic acid with a structurally complex thiol, coenzyme A. This thioester, referred to as acetyl CoA, has one carbon that is completely reduced, a methyl group. Since the acetyl methyl is potentially nucleophilic and the carbon of CO_2 is electrophilic, an obvious strategy for the biosynthesis of acetyl CoA and CO_2 from 3PG uses malonyl CoA as the penultimate target and exploits polar cleavage of a C-C bond during decarboxylation. Adjustment of the functionality level of this subtarget suggests a precursor **5** which has the same overall functionality level as the desired starting material 3PG. Conversion of 3PG to **5** could be achieved by elimination of water followed by readdition and hydrolysis of the

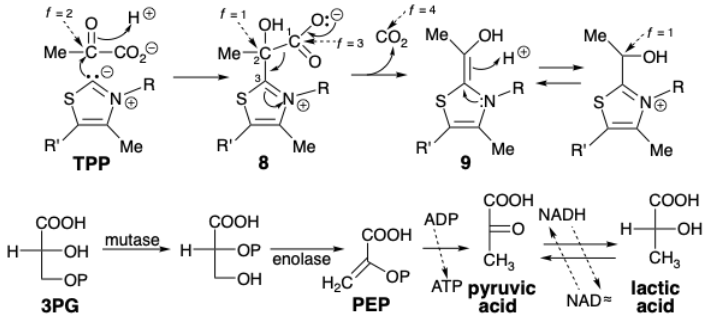
phosphate. Interestingly, this strategy is not used for the biosynthesis of acetyl CoA although the first dislocation is used, albeit in reverse, for generating malonyl CoA from acetyl CoA (*vide infra*).



An alternative strategy for biosynthesis of acetyl CoA from 3PG involves cleavage of CO_2 from the incipient acyl carbon. But this requires umpolung of the normal electrophilicity of the carbonyl carbon in acetyl CoA. That is, polar cleavage would have to generate an umpoled acyl nucleophile synthon **6** from an umpoled synthon **7** of pyruvic acid. Generation of pyruvic acid from 3PG only requires redistribution of functionality. This is the actual biosynthetic strategy for acetyl CoA.

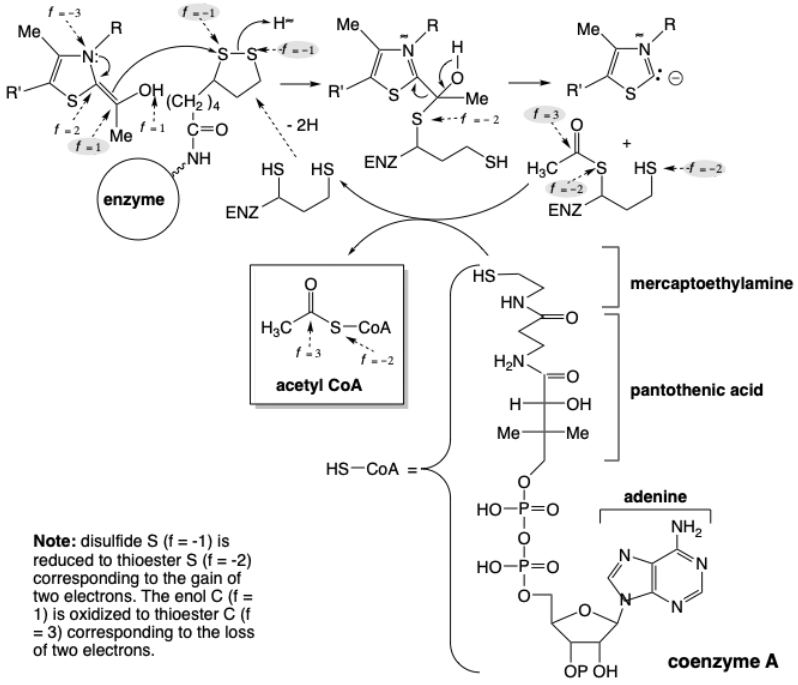


The biosynthesis of acetyl CoA uses many of the reactions involved in the anerobic catabolism of glucose. Therefore, let us resume our discussion of the biosynthesis of lactic acid from glucose (see above). The 3-phosphoglyceric acid (3PG) that results from oxidation of G3P (see above) undergoes a transfer of the phosphoryl group from the 3- to the 2-hydroxyl and subsequent dehydration to phosphoenolpyruvate (PEP). This enol ester is energy rich since its hydrolysis generates a relatively strong C=O bond at the expense of a relatively weak C=C bond. PEP readily phosphorylates ADP releasing pyruvic acid. The carbon atom of the ketone carbonyl group of this α-ketoacid is very electrophilic and readily accepts hydride from NADH under catalysis of the enzyme lactate dehydrogenase.



The biosynthesis of acetyl CoA from glucose involves decarboxylation of pyruvic acid that is regenerated by dehydrogenation of lactic acid. To allow a polar decarboxylation reaction, pyruvic acid mustistransformedbyumpolungoftheketonecarbonylintoamorereadilydecarboxylatedderivative. As in the transketolase reaction, the polar reactivity of this carbonyl group is temporarily inverted by the biphilic thiazole carbanion moiety of thiamine pyrophosphate (TPP). Thus, the nucleophilic thiazole ring carbon of TPP condenses with the highly electrophilic carbonyl carbon of pyruvic acid to give an adduct **8** that resembles a β-ketoacid. This undergoes decarboxylation by retro Claisen cleavage to deliver hydroxyethylidene TPP (**9**). The functionality level of the incipient carboxyl carbon is only $f = 1$ in **9**. Therefore, oxidation of **9** is required to produce an acetyl functionality level (i. e. $f = 3$).

This oxidation is achieved by a polar process that concomitantly reduces a disulfide to a dithiol. Thus, **9** transfers an acetyl group to the disulfide of a lipoic acid residue bound to the enzyme dihydrolipoyl transacylase. The acetyl group is then transferred from the enzyme bound thiol to the thiol group of a coenzyme (CoA) to give acetyl CoA.



2.4: Terminology

For definitions see sections listed.

adenosine triphosphate (ATP) (2.1)

anerobic (2.3)

Calvin cycle (2.1)

catabolism (2.3)

coenzyme A (CoA) (2.3)

glycolysis (2.1)

latent symmetry (2.1)

NADP (2.1)

phosphogluconate pathway (2.1)

RuBisCo (2.1)

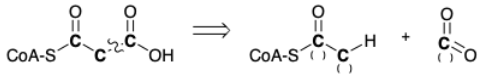
thiamine pyrophosphate (TPP) (2.1)

transketolase (2.1)

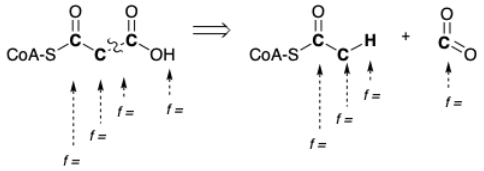
2.5: Study Questions

1. Different strategies are adopted in Nature for the disconnection of CO_2 from acetylCoA during the biosynthesis of acetylCoA and for the connection of CO_2 to acetylCoA during the biosynthesis of malonylCoA from acetylCoA.

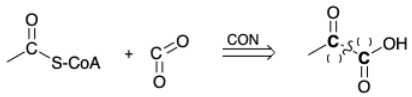
(a) Indicate with (+) or (-) next to each **C** in the following retrosynthetic analysis to show the polar activation provided by the carboxyl functionality for the carboxylation of acetylCoA.



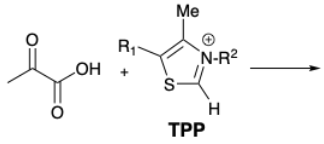
(b) Indicate the functionality levels of each atom in boldface type in the following strategy for the direct synthesis of malonylCoA from acetylCoA.



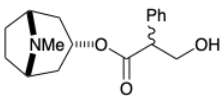
(c) Indicate with (+) or (-) next to each **C** in the synthon to the left the appropriate polar reactivity required for a strategy which generates acetylCoA by direct cleavage of CO_2 (decarboxylation) of a precursor.

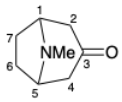


(d) Draw an intermediate, derived from pyruvic acid and thiamine pyrophosphate (TPP), that is a synthetic equivalent of the above synthon. With (+) and (-) next to the appropriate atoms, indicate the polar activation provided by functionality in the intermediate that allows the polar decarboxylation. Show the bond that cleaves in the biosynthesis with a wiggly line.



2. Tropinone is a key degradation product obtained during determination of the structure of atropine, a natural product of the "alkaloid" family.



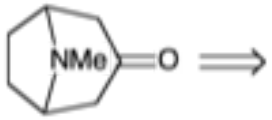


(a) Perform a thorough polar analysis of tropinone. List the polar relationships between functional groups by completing the following table:

Positions	Circuit	Relationship
N + 3	N-1-2-3	

(b) Write a retrosynthetic analysis that provides a synthetic strategy for tropinone *from acyclic symmetrical starting materials* each containing no more than five *contiguous* carbons and using *only polar* bond-forming reactions. In your analysis show pertinent polar reactivity patterns with (+) and (-) and indicate disconnections with wavey lines through the bond to be

severed in the dislocation of the target to its precursor. If you draw a synthon, label it as a "synthon" and also draw an appropriate synthetic equivalent and label it as a "synthetic equivalent". *All* of the starting materials must be symmetrical!



2.6: References

1. Breslow, R. *Tetrahedron Lett.* **1959**, 22-26.
2. Iwai, I.; Iwashige, T.; Asai, M.; Tomita, K.; Hiraoka, T.; Ide, J. *Chem Pharm Bull (Tokyo)* **1963**, *11*, 188-
3. Enders, D.; Grondal, C. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 1210-1212.

CHAPTER OVERVIEW

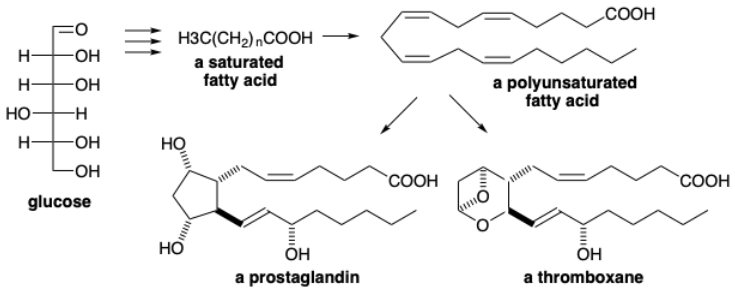
3: Fatty Acids and Prostaglandins

In the previous chapter, two hypothetical biosynthetic strategies were presented that are not used biosynthetically. That the individual steps in each of these hypothetical strategies are reasonable, is indicated by the interesting fact that both strategies are exploited in reverse in Nature; one for the conversion of glucose into ribulose and the other for the conversion of acetyl CoA into malonyl CoA. The actual biosynthetic strategies for acetyl CoA and malonyl CoA were then presented. This format is intended not only to exemplify the numerous potential strategic options available, but also to provide foils that highlight the unique features of the actual biosynthetic strategies. These contrasting strategies encourage the reader to go beyond understanding the logic that governs the success of the biosynthetic sequence of reactions, and to ask: why does Nature choose this particular strategy?

In the ensuing chapters, a variety of strategies will be presented, compared, and contrasted for each natural product. Besides unimplemented hypothetical biosynthetic strategies, fatally flawed strategies, and often several topologically unique successful strategies will be considered with the goal of familiarizing the student with the options and pitfalls presented by the challenge of designing and executing the total synthesis of structurally and functionally complex organic molecules.

3.1: Biosynthesis of Fatty Acids

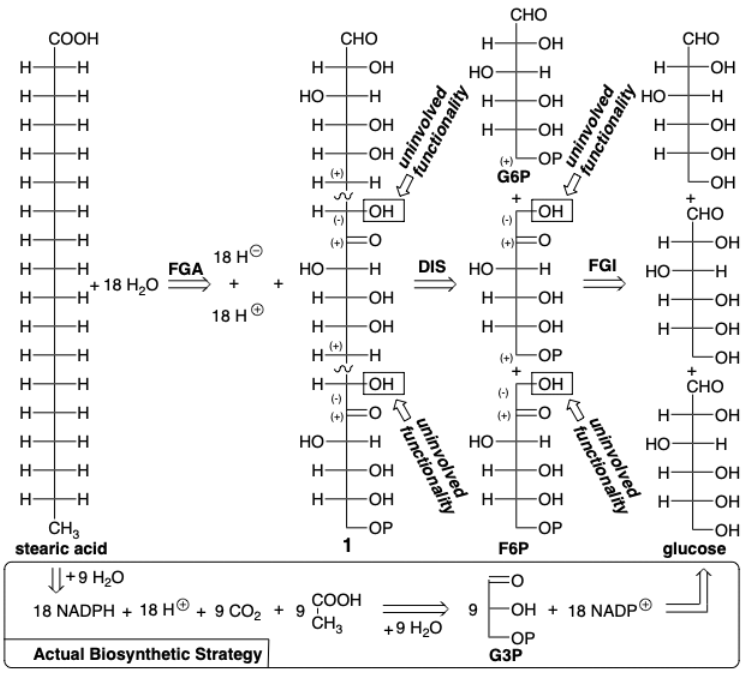
Fatty acids have larger carbon skeletons than sugars, but they are structurally simple. They have long unbranched chains of carbon atoms with much less functionality than sugars and no centers of asymmetry. Thus, they are more reduced (less oxygenated) than sugars. Higher animals have only limited capacity for storage of sugars as polysaccharides. Therefore, sugars are converted into fatty acids that may be stored as triesters of glycerol and used in the biosynthesis of the complex polar lipids of membranes and in the biosynthesis of prostaglandins and thromboxanes, two large groups of physiologically active substances.

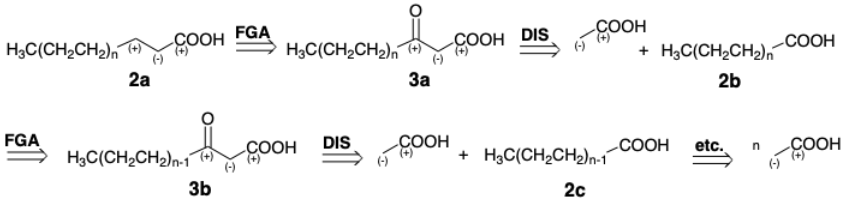


A plausible strategy for the biosynthesis of stearic acid, which consists of an eighteen-carbon chain, involves reductive deoxygenation of a highly oxygenated precursor **1** that could be assembled by polar union of three six-carbon sugar molecules (see below). Such a strategy would economically utilize all of the carbon atoms in glucose to build the skeleton of the target. The carbonyl group in fructose 6-phosphate (F6P) activates position 1 toward alkylation by carbon 6 in F6P or glucose 6-phosphate (G6P). The nucleophilic substitution at position 6 would displace the activating oxygen from two precursor sugars delivering the precursor **1** that lacks oxygen at positions 6 and 12. Removal of twelve remaining hydroxyl and two carbonyl groups and oxidation of the terminal aldehyde in the precursor **1** to provide the carboxyl of stearic acid would require eighteen equivalents of hydride from e.g. NADPH. The only byproduct from such a synthesis would be eighteen molecules of water. But *Nature not only uses glucose as the source of carbon but, except for the photosynthetic generation of NADPH, also uses glucose as the ultimate source of hydride for all organic biosynthesis*.

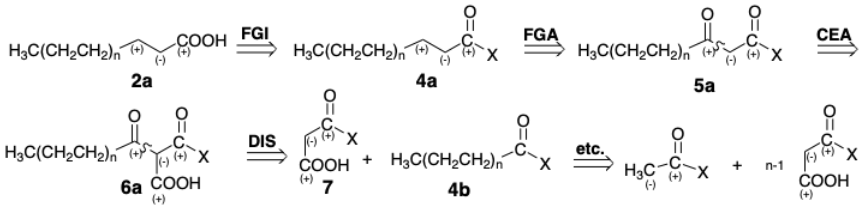
The actual biosynthetic strategy is an ingenious process that co generates all the reducing agent, NADPH, required for deoxygenation, by oxidation (hydride abstraction) from an aldehyde intermediate derived from glucose. The byproducts from the biosynthesis are eighteen equivalents of water as well as nine equivalents of a byproduct CO_2. Instead of three molecules of glucose, which would be required for the first strategy, the actual biosynthesis consumes four and a half molecules of glucose for every molecule of stearic acid produced. The carbons that are incorporated into the fatty acid product are almost all reduced while those in the CO_2 byproduct have been oxidized.

A boundary condition governing the biosynthetic strategy for fatty acids is that the reagents and reactions should be readily adapted to the biosynthesis of a large selection of fatty acids with *differing chain lengths*. This suggests a repeatable chain-growing strategy: addition of a two-carbon carboxylic (acetic) acid to the growing fatty acid chain by a Claisen condensation. Thus, if the strategy is to be repeatable, a shorter chain carboxyl will serve as electrophile and become a keto group after C-C connection by polar bond formation with a two-carbon carboxyl-stabilized nucleophile on the α-carbon, then the functionality level of the electrophile (*f = 3* for a carboxyl) will become (*f = 2* for a ketone) in the resulting β-keto group derived from the carboxyl group in a precursor **2b** that incorporates two less carbons.

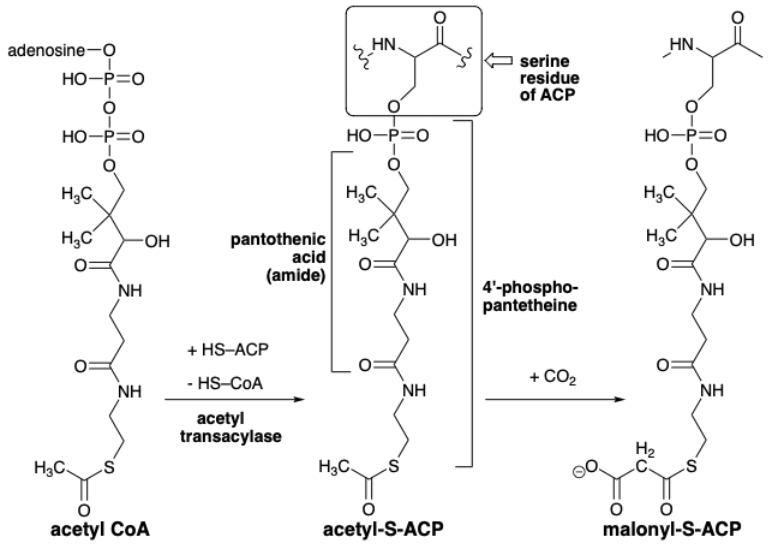




Further refinement of this strategy recognizes the need for a better leaving group than hydroxyl, especially considering that most of the carboxyl group will be in the form of carboxylate at physiological pH. This suggests replacement of the hydroxyl, functional group interconversion (FGI), in **2a** and **3a** with a better leaving group indicated by X in **4a** and **5a**.



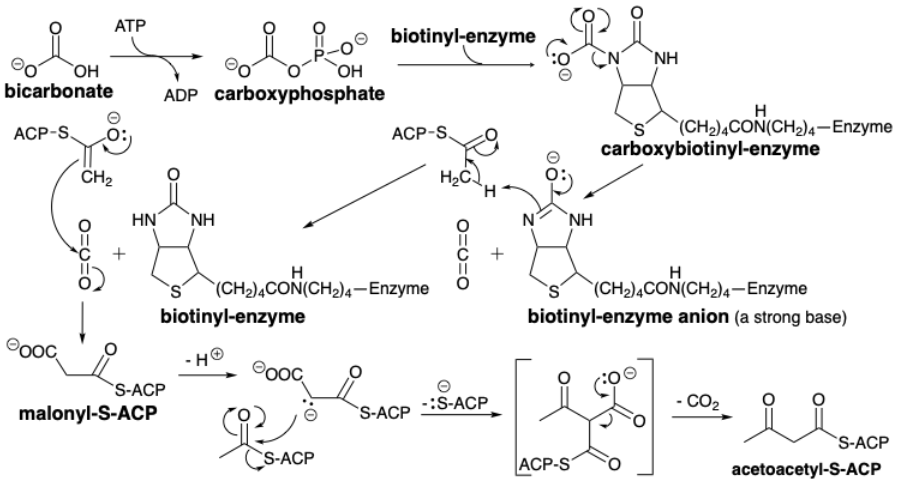
In the biosynthesis, all of the carbon atoms of a fatty acid are derived from acetyl CoA, that transfers its acetyl group to the thiol group of an a protein-bound acyl carrier protein (ACP). Both acetyl-S-ACP and acetyl-S-CoA are thioesters, acylating agents corresponding to H_3C-COX that are more electrophilic than their oxygen analogues because back donation of electron density of the nonbonding electrons from the large sulfur orbitals is far less important than back donation of nonbonding electrons from ester oxygen whose orbitals overlapp more effectively with those of the carbonyl π-bond.



A key feature in the biosynthesis of fatty acids is a *requirement for carbon dioxide* as bicarbonate ion, although the CO_2 or HCO_3^- is not incorporated into the fatty acids. This suggests a strategy in which CO_2 is temporarily added to a precursor and then eventually removed after it has served its purpose. In fact, except for two carbon atoms at the alkyl terminus, acetyl-CoA is not the immediate precursor of the fatty acid carbon chain. Rather, an activated form of acetyl CoA, malonyl CoA, is generated by carboxylation of acetyl CoA. The electron deficiency of CO_2 suggests that its function might be to remove electron density from an anionic intermediate, e.g., its function might be to stabilize a carbanion intermediate such as a carbanion on the α-carbon of an acetyl group. Thus, the nucleophile that reacts with acetyl-S-ACP might be a carbanion derived from malonate **7**. Carboxylation of acetyl-S-ACP delivers malonyl-S-ACP.

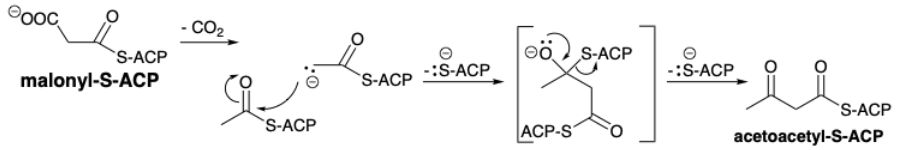
For this refinement of the retrosynthetic analysis of the β-keto fatty acyl **5a** would involve addition of an activating carboxyl group, reactivity control element addition (CEA), to a precursor **6a** to facilitate carbanion formation (see page 44). Thus, the last carbon-carbon bond forming synthetic step is suggested by a dislocation of the precursor **6a** involving carbon-carbon bond disconnection (DIS) suggesting a precursor **4b** with two less carbons than **5a** (three less than **6a**). The synthetic strategy suggested by the above retrosynthetic analysis involves Claisen condensation of a malonate carbanion derived from **7** with a precursor **4b** with two less carbons than the desired fatty acid **2a** followed by decarboxylation of **6a** to deliver **5a** and accomplish net chain elongation by two carbons.

The carboxylation of acetyl-S-CoA is promoted by acetyl CoA carboxylase and involves transfer of a carboxyl group from an enzyme bound CO_2 carrier, biotin. The role of carboxybiotin in thie biosynthesis deserves further consideration. It delivers anhydrous CO_2 to an active site that, presumably encapsulates the reactants in a water-free environment. In a aqueous environment, CO_2 is present as bicarbonate that is much less electrophilic than anhydrous CO_2. Thus, the energy expended, in the form of ATP hydrolysis to ADP, results in the conversion of a weak electrophile into a stronger electrophile. Simultaneously, a base, the biotinyl anion, is produced that is strong enough to abstract a proton from acetyl-S-ACP. This proton abstraction also must occur in an aprotic environment because otherwise water would protonate both the biotinyl anion and the acetyl-S-ACP carbanion.

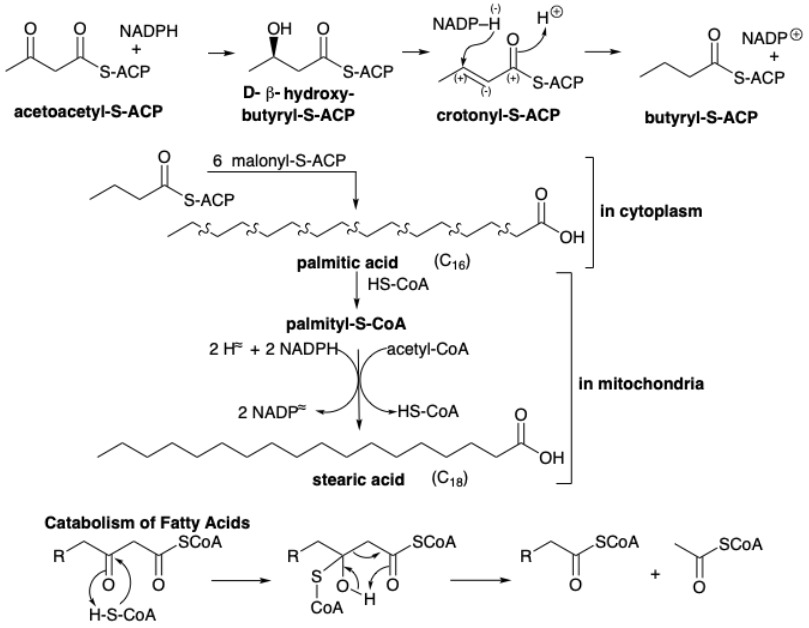


The fatty acid carbon chain is then assembled by a series of Claisen condensations starting with malonyl plus acetyl. In fact, the CoA derivatives of both synthons are first transformed into enzyme bound thioesters of the acyl carrier protein (ACP). The acyl groups are bound to the protein, located in the cytoplasm, by a 4'-phosphopantetheine ester of a serine residue. The acetyl group is then transferred to a specific cysteine residue of another enzyme of the fatty acid synthetase complex, β-ketoacyl-ACP synthetase (HS-synthetase). The activating carboxyl group in malonyl-S-ACP assures that the methylene of this acetyl synthon acts as the nucleophile. After condensation, the activating group is lost to give acetoacetyl-S-ACP.

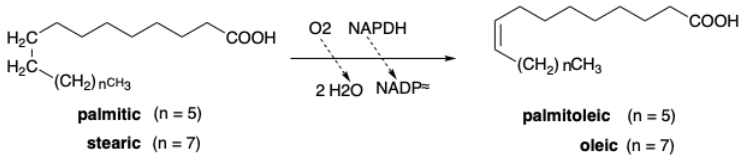
There is another reasonable hypothesis for the role of the carboxyl group in malonyl-S-ACP in the condensation with acetyl-S-ACP. Rather than serving as an **activating group** to facilitate generation of a malonyl carbanion, it may serve as a **latent carbanion**. Driven by the energy released upon formation of a C=O bond, decarboxylation may generate an acetyl-S-ACP carbanion in an anhydrous environment in an active site of the fatty acid synthetase complex. This strong nucleophile would be acylated by acetyl-S- ACP to form acetoacetyl-S-ACP directly. Thus, the role of the carboxylate group is to allow the generation of a strongly basic carbanion without the requirement for a strong base, and in the absence of water that would protonate the carbanion or a strong base. This putative role of the carboxyl group is related to its role in the carboxylation of acetyl-S-ACP, except that instead of the decarboxylation generating a strong base that abstracts a proton from acetyl-S-ACP to produce the acetyl-S-ACP carbanion, the decarboxylation of malonyl-S-ACP generates the acetyl-S-ACP carbanion directly. In both scenarios, the generation of a strongly basic intermediate is driven by the energy released by the formation of a C=O bond in a water-free environment required to preclude destruction of the strongly basic intermediate.



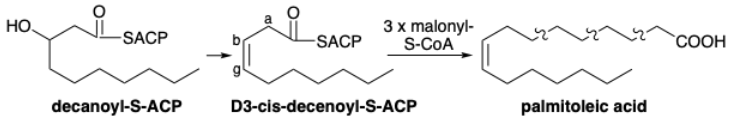
The β-keto group is then reduced to a methylene group in a series of hydride reductions involving NADPH. The first reduction enantiospecifically gives D-β-hydroxy-butyryl-S-ACP under catalysis by β-ketoacyl-ACP-reductase. The β-hydroxy ketone is readily dehydrated under the influence of enoyl-ACP dehydratase to give the α,β-unsaturated thioester, crotonyl-S-ACP. Reduction of the latter occurs via 1,4-addition of hydride from NADPH to the electrophilic β-carbon of this D-2,3-unsaturated ester catalyzed by crotonyl-ACP reductase. The resulting butyryl-S-ACP then condenses with a second malonyl-S-ACP leading ultimately to hexanoyl-S-ACP and so on until seven molecules of malonyl-S-ACP have been combined with one acetyl-S-ACP. The process stops at palmityl-S-ACP from which palmitic acid is released by the action of a hydrolytic deacylase. Further elongation of the carbon chain occurs in the mitochondria by addition of acetyl-S-CoA rather than malonyl-S-CoA. The same enzymes in the mitochondria catalyze the reverse reaction, the catabolism (oxidative degradation) of fatty acids except that hydride reduction of the α,β-unsaturated ester involves NADPH; whereas, the corresponding dehydrogenation steps in the breakdown of fatty acids to acetyl CoA involve a flavoprotein as hydrogen acceptor. Catabolism of fatty acids also differs mechanistically from their anabolism in that acetyl CoA is produced directly in the thiolytic cleavage of a 3-keto fatty acyl-CoA by CoASH. That is, malonyl CoA is not involved in fatty acid catabolism.



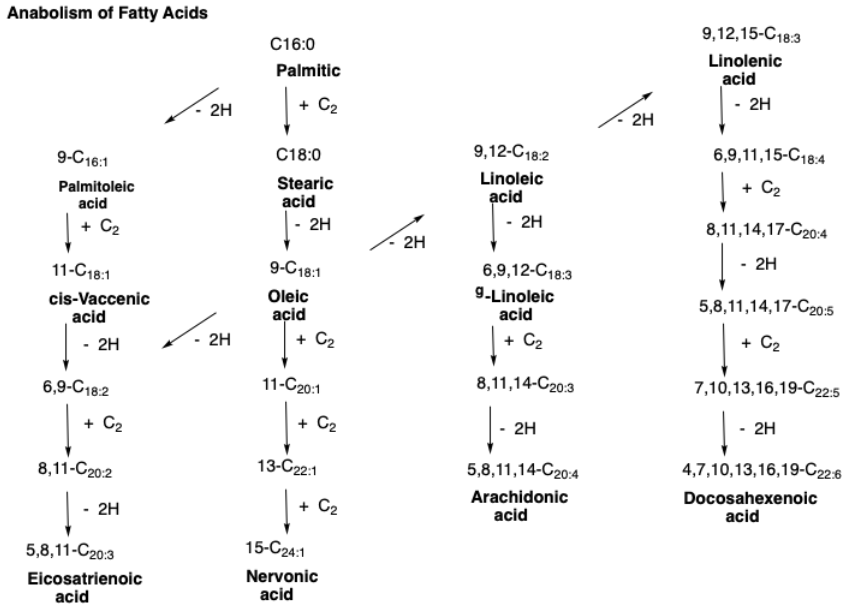
Two different pathways exist for the biosynthesis of unsaturated fatty acids. One of these involves **aerobic dehydrogenation** of palmitic or stearic acid to give palmitoleic or oleic acids respectively. This reaction is remarkable because of its regiospecificity, its stereospecificity, and because the hydrogen atoms removed are remote from any functional group and, therefore, are not activated toward chemical reactions. An interesting feature of the dehydrogenation reaction is the concomitant oxidation of NADPH. The enzyme system is an example of a class of oxygenases which require a coreductant, such as NADPH, known as a **mixed function of oxygenases**.

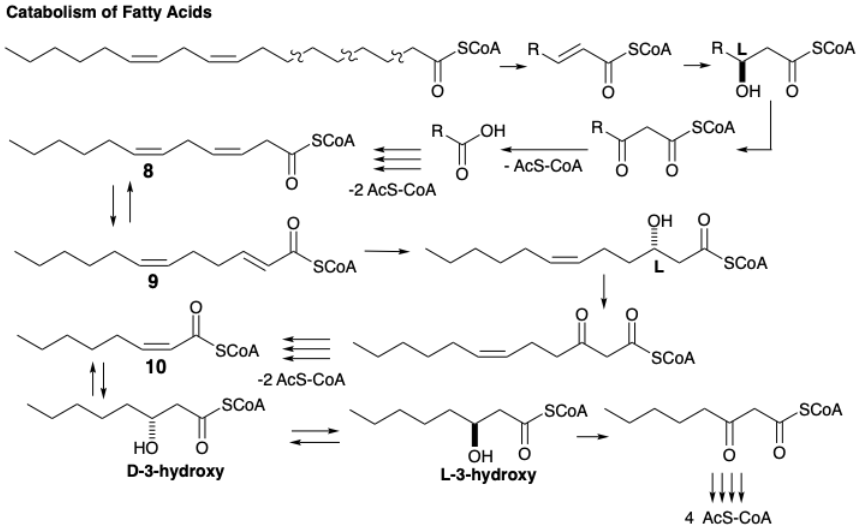


A different pathway is operative in **anaerobic** bacteria. Thus, β-hydroxy-decanoyl- ACP is dehydrated by a specific enzyme, β-**hydroxydecanoyl-ACP dehydratase** that yields the*cis*-β,γ(or Δ^3)-decanoyl ACP rather than the *trans*−α,β(or Δ^2)-isomer formed in saturated fatty acid biosynthesis. Further elongation by malonyl-ACP then leads to palmitoleic acid. All polyunsaturated fatty acids biosynthesized in animals arise from palmitoleic or oleic acid by further chain elongations or dehydrogenations similar to those described above. Two of these precursor fatty acids, linoleic and linolenic acids, cannot be synthesized in mammals and must be obtained from plant sources; they are therefore called **essential fatty acids**.



Oxidative degradation (catabolism) of unsaturated fatty acids to acetyl-CoA follows much the same pathway as the corresponding saturated acids. Thus, successive C2 units are removed by thiolytic cleavage of β-ketothioesters.

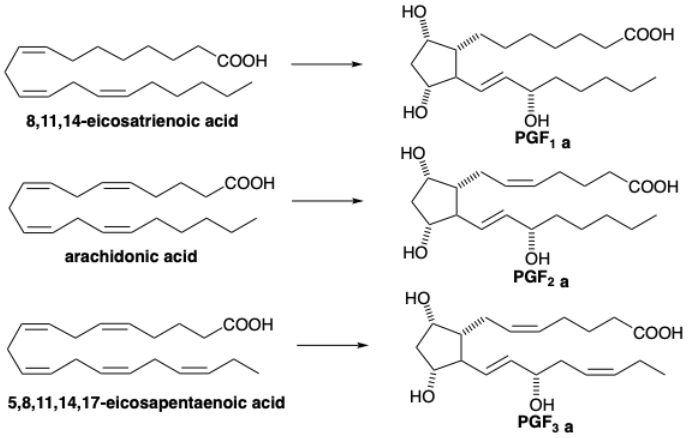




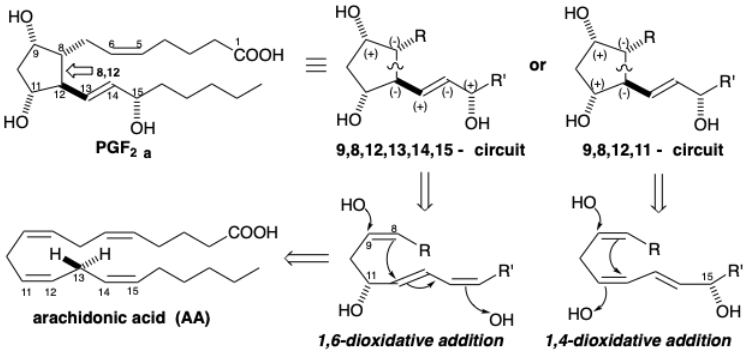
When a cis-β,γ-unsaturated thioester results (e.g. **8**), it is isomerized under catalysis by the enzyme enoyl-CoA isomerase to the *trans*-α,β-unsaturated isomer (e.g. **9**) that is an intermediate in the biosynthesis. Further degradation then proceeds as usual. Since hydration of a *cis*-α,β-unsaturated thioester (e.g. **10**), promoted by enoyl hydratase, gives a D-3-hydroxyacyl-CoA, epimerization, promoted by 3-hydroxyacyl CoA-epimerase, must occur before further degradation may occur. It is noteworthy that only the L-enantiomer is dehydrogenated to β-ketoacyl-S-CoA in oxidative degradation, while only the D-enantiomer is produced in the reduction of a β-ketoacyl-S-ACP during the biosynthesis of fatty acids.

3.2: Biosynthesis of Prostaglandins

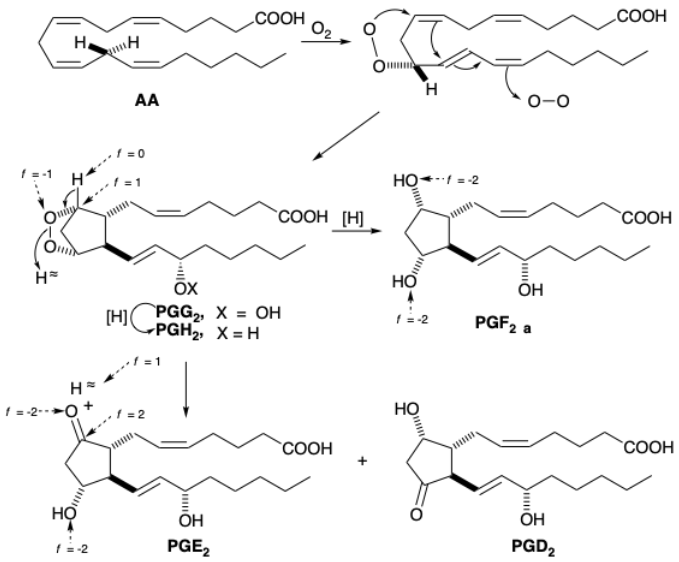
Prostaglandins are the skeletally most complex molecules we have yet considered. All prostaglandins are 1,3-dioxygenated cyclopentane derivatives with a 7-carbon carboxylic acid side chain and a vicinal 8-carbon γ-hydroxy- vinyl side chain. Three series of prostaglandins are known which are exemplified by prostaglandins $F_{1\alpha}$, $F_{2\alpha}$, and $F_{3\alpha}$. These are designated $PGF_{1\alpha}$, $PGF_{2\alpha}$, and $PGF_{3\alpha}$ and respectively have one,two, or three C=C bonds in the side chains. The prostaglandins are appropriately considered at this point since their biosynthesis from tri-, tetra-, or pentaenoic fatty acids is very simple, involving the formation of only one new C-C bond. Moreover, the plethora of strategically different syntheses of prostaglandins which have been achieved in the laboratory offer a unique opportunity to gain an appreciation for the myriad solutions to the problem of planning a complex molecular synthesis.



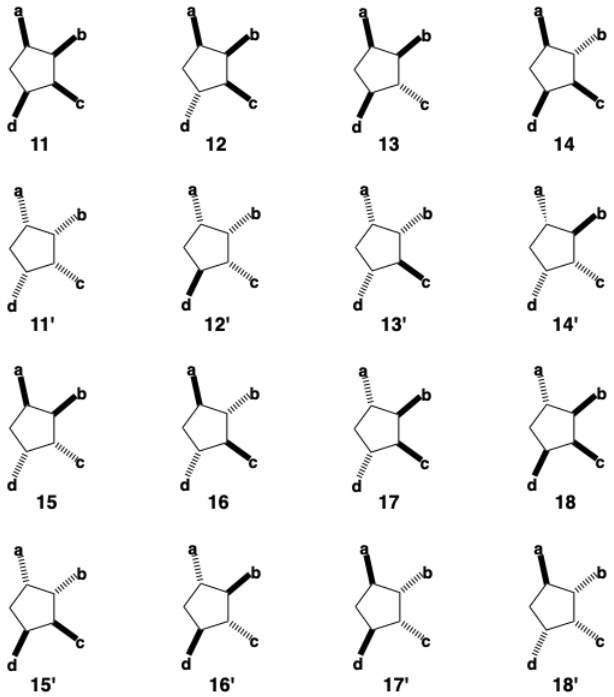
With the exception of a bridge between carbons 8 and 12, the topology -- an unbranched chain of twenty carbons -- as well as the terminal carboxyl functionality of prostaglandins suggests fatty acids as biosynthetic precursors. Polar reactivity analysis of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) reveals that the 8,12-bond lies on a dissonant circuit between the hydroxyl groups on carbons 9 and 11 (the 9,8,12,11-circuit) and a dissonant circuit between the hydroxyl groups on carbons 9 and 15 (the 9,8,12,13,14,15-circuit). The 8,12-bond cannot be formed in a polar reaction involving polar activation by any two target related functional groups. The observed dissonant functionality pattern could be generated by 1,4-dioxidative addition of two hydroxyls to a 15-hydroxy fatty acid precursor or by 1,6-dioxidative addition of two hydroxyls to an 11-hydroxy fatty acid precursor. The requisite hydroxy fatty acid precursors might reasonably be produced by allylic oxidation, e.g. of arachiconic acid (AA), involving hydrogen removal from position 13 and hydroxyl addition at position 11 or 15.



In nature, prostaglandins arise by an oxidative cyclization of poly-unsaturated twenty-carbon fatty acids, which begins with enantiospecific removal of the L-hydrogen atom of the prochiral methylene group at C-13 coupled with enantiospecific introduction of oxygen at the allylic C-15 position. Subsequent cyclization and termination by addition of a second molecule of oxygen leads to a 15-hydroperoxy bicyclic peroxide (PGG), that is reduced to a 15-hydroxy bicyclic peroxide (PGH). These intermediates, known as prostaglandin endoperoxides, have been isolated and shown to yield prostaglandins. Reduction of the peroxy bridge gives PGF, while disproportionation gives β-hydroxy ketones PGE and PGD. The carbons in prostaglandins are numbered one to twenty starting at the carboxyl carbon and following the numbering system of the biosynthetic precursor fatty acids.



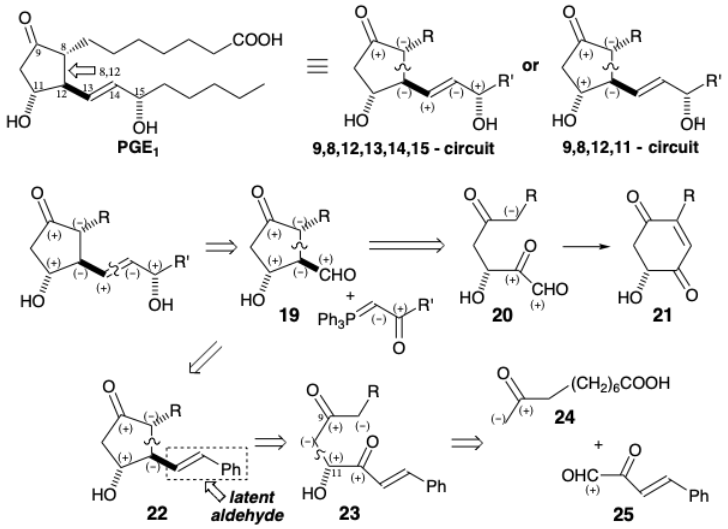
Important features of the biosynthesis of prostaglandins are its *dia-stereo-* and *enantioselectivity*. Consider the possible stereochemical relationships between the four substituents on the cyclopentane ring of $PGF_{2\alpha}$. There are 2^n different possible arrangements for n stereocenters each having two possible configurations. Of the sixteen possible stereoisomeric arrangements, only **13'** is found in the natural product. The isomers **11-18** are **diastereomers**. They possess unique stereochemical interrelationships of their four substituents. Thus, they are stereoisomers that have different configurations at one or more (but not all) of their stereocenters and, therefore, are not mirror images of each other. The remaining isomers **11'-18'** are mirror images or **enantiomers** of the other isomers. Taking into account a fifth stereocenter at position 15 in the sidechain, there are 32 possible stereoisomers of $PGF_{2\alpha}$, two enantiomeric sets of 16 diastereomers. The biosynthesis is completely stereoselective. For any synthesis of a complex molecule, this is important because the less stereoselective a synthesis, the lower the yield of the desired product. Also, purification of the product is usually difficult if it is contaminated by stereoisomers since these often possess chemical and physical properties that are very similar to those of the desired isomer. In the biosynthesis of PGF2α, the first stereocenter, that at position 11, is introduced enantioselectively by the action of an asymmetric reagent (enzyme) on a prochiral precursor generating only one enantiomeric intermediate. Such a process, known as **asymmetric induction**, is inherently more efficient than a synthesis involving separation of a racemic mixture of enantiomeric products (**resolution**) since no starting materials are wasted in the generation of wrong isomers. The biosynthetic strategy for $PGF_{2\alpha}$ involves a connection that ties the two ring hydroxyl groups together in a ***temporary bridge***. The latter serves as a **stereocontrol element** assuring a *cis* relationship between the hydroxyls at positions 9 and 11, and allows the introduction of both cyclopentane oxygens atoms as a single molecule of oxygen.



There are three topologically unique strategic categories for the synthesis of prostaglandins: (a) syntheses from acyclic precursors, (b) syntheses from multicyclic precursors by cleavage of temporary bridges, and (c) syntheses from precursors containing an isolated cyclpentane ring. Examples of each strategic type will be considered in the following three sections.

3.3: Syntheses of Prostaglandins from Acyclic Precursors

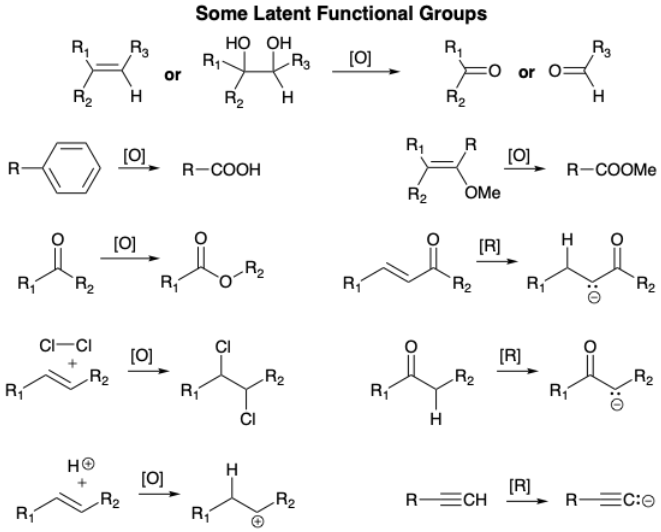
As in the biosynthesis of prostaglandins, several total syntheses feature generation of the cyclopentane ring by cyclization of acyclic precursors. We will first compare the biosynthesis with three total syntheses involving cyclopentane ring formation by generation of the prostaglandin 8,12-bond. Since the 8,12-bond lies on dissonant circuits between the functionality at positions 9 and 11 or at positions 9 and 15, a polar connection cannot be achieved which depends on polar activation by either pair of functional groups. Therefore, each of these syntheses exploits the polar activation provided by only one target-related functional group to promote polar creation of the 8,12 bond. In Miyano's strategy[1] (see below), polar disconnection of the lower side chain of PGE_1 at the C=C bond suggests subtarget **19**. Neither the aldehyde group nor functionality at C-11 in **19** can provide the requisite electrophilicity at C-12 for polar bond formation exploiting nucleophilicity at C-8 activated by the C-9 carbonyl. Therefore, a precursor of **19** must incorporate additional functionality to provide electrophilicity at the incipient C-12. This might be provided by a carbonyl group as in **20**. However this strategy is flawed since the electrophilic aldehyde in **20** will compete with the carbonyl at the incipient C-12 in **20** for reaction with a C-8 nucleophile. This will produce an undesired benzoquinone byproduct derived from the intermediate **21** by dehydration.



To prevent undesired competition by an electrophilic aldehyde, this group is not introduced until it is needed. Instead, it is *concealed* in a pre-cursor **22** of **19** as a C=C bond from which it can be generated by oxidative cleavage. The C=C bond does not possess the high electrophilicity of an aldehyde. Yet an aldehyde group can be readily generated from the C=C bond. Polar disconnection of **22** suggests electrophilic functionality at the incipient prostaglandin C-12 in a precursor **23**. Further disconnection of **23** to **24** and **25** exploits the polar activation provided by consonant functionality at the incipient C-9 and C-11 ignoring the carbonyl at C-12 in **23**.

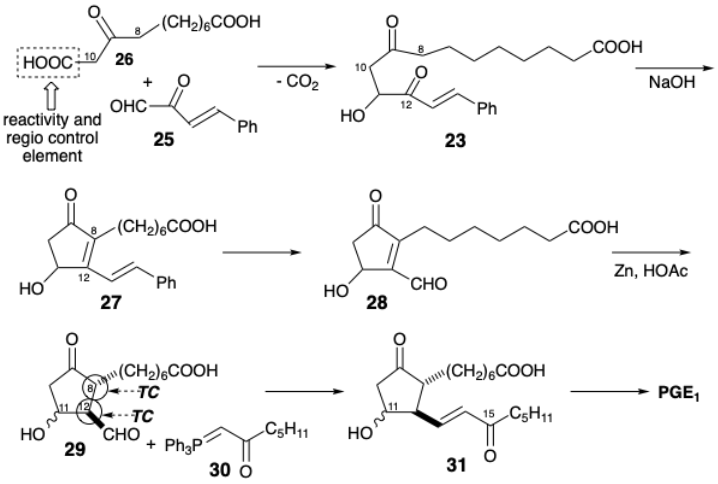
We shall refer to an *unreactive direct precursor group with a different functionality level than the target* as a **latent functional group** (see below for some examples).[2] Thus, (1) an alkene (f = 0), as in **22** above, or a vicinal diol (f = 1) can serve as a latent equivalent of an aldehyde or ketone (f = 2). Although the alcohol is electrophilic at the incipient carbonyl carbon, its electrophilicity is considerably less than that of an aldehyde or ketone. (2) An arene (f = 0) is a latent carboxyl group (f = 3). (3) An enol ether (f = 1) provides a latent ester (f = 3) since oxidative cleavage of the latent precursor can be achieved to provide the desired functional group. (4) A ketone (f = 2) is a latent ester (f = 3) since Baeyer-Villiger oxidation of the former will deliver the latter; and (5) a terminal alkyne (f = 0) is a latent acetylide anion (f = -1) or terminal vinyl carbanion (f = -1) equivalent since alkynyl hydrogen is readily abstracted by strong bases and the alkyne products from coupling of acetylides with electrophiles can be selectively reduced to the corresponding alkene. Note that generation of a functional group from its latent equivalent, by definition, involves oxidation [O] or reduction [R], i.e., increase or decrease of functionality level. Also note that generation of a carbanion by proton abstraction from carbon or hydride addition to an α,β- unsaturated carbonyl compound corresponds to a reduction. In other words, proton abstraction from a “carbon acid”, i.e., an acidic C-H bond, corresponds to reduction in functionality level of the carbon from which a proton is abstracted and oxidation of the hydrogen that is abstracted as a proton. Also note that addition of a proton to a C=C bond results in reduction of the proton and and oxidation of the carbon that becomes a

carbocation, and addition of Cl_2 to a C=C bond corresponds to oxidation of both carbons with concomitant oxidation of both chlorines, a process that is called “dioxidative addition”.

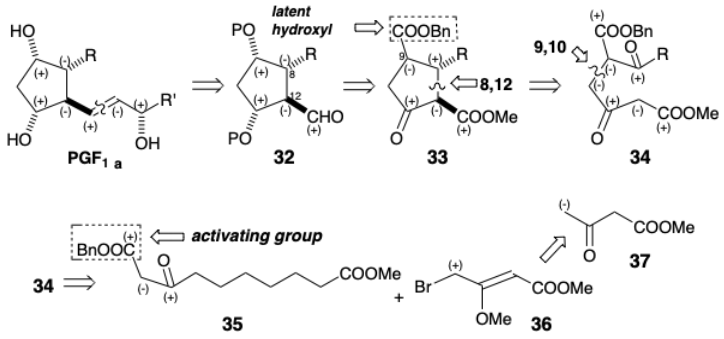


A closely related concept is the **masked functional group**, which is *an unreactive precursor group with the same functionality level as the target*. For example, a ketal is a masked ketone (f = 2). Another example is provided by esters (f = 3) that serve as masked carboxyl groups (f = 3). Esterification blocks the proclivity of the acid toward decarboxylation when β to a carbonyl or toward deprotonation by bases. As we shall see in the Kojima-Saki synthesis of prostaglandins (see below), different **masking groups** for the same functional group, such as a benzyl and a methyl ester for two carboxylic acid groups in a molecule, may allow selective removal (**unmasking**) to convert one ester to an acid while the other remains masked.

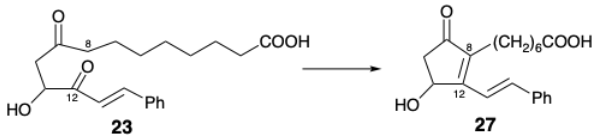
In Miyano's synthesis of PGE_1, β-ketoacid **26** rather than methyl ketone **24** (see above) is condensed with ketoaldehyde **25**. This decarboxylative condensation regioselectively achieves nucleophilic activation at the incipient 10-position without competition from condensation at the incipient 8-position that also can be activated by the C-9 carbonyl. Thus, the carboxyl group appended to position 10 in **26** serves as an activating group. It is a **reactivity control element** and, consequently, a **regiocontrol element**. Intramolecular aldol condensation then generates the 8,12-bond delivering cyclopentenone **27**. Selective oxidative cleavage of the more electron rich styryl C=C bond in **27** delivers an unsaturated aldehyde **28.** Saturation of the remaining C=C bond affords **29** in which the aldehyde and carboxyheptyl groups adopt the required *trans* relative configurations owing to a thermodynamic preference and epimerizability at both positions 8 and 12. Condensation of **29** with ylide **30** then delivers PGE1 after selective reduction of the 15-carbonyl. Neither the stereocenter at position 15 nor that at position 11 is generated with high stereocontrol: thermodynamic control (TC). Furthermore, this synthesis produces a racemic mixture of PGE_1 and its unnatural enantiomer since *any synthesis which begins with nonasymmetric or racemic starting materials and employs racemic reagents will ultimately generate only racemic products.*



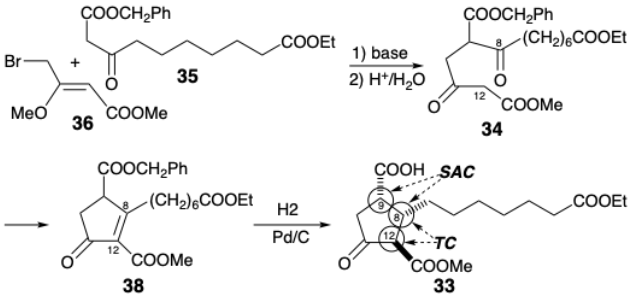
A second strategy[3] for prostaglandin synthesis involving cyclopentan-one annulationtion by formation of the 8,12-bond starts with polar disconnection of the lower side chain of PGF2α to suggest a subtarget **32**. However, instead of using a C-8 nucleophile and C-12 electrophile as in the Miyano synthesis, the Kojima-Saki synthesis achieves polar 8,12-bond formation by reaction of a C-8 electrophile with a C-12 nucleophile. The C-12 aldehyde in **32** or an ester in a precursor **33** can activate carbanion generation at C-12. To preclude β-elimination of the C-ll oxygen and provide additional stabilization of a C-12 carbanion, the C-11 oxygen is present as a carbonyl group in the precursor **33** of **32**. A possible β- elimination of the C-9 oxygen is precluded by concealing this functional group in a latent form as a benzyloxycarbonyl group in **33**. Polar disconnection of **33** requires electrophilic reactivity at C-8 which could be provided by conjugation with the benzyloxycarbonyl or an additional carbonyl group at C-8 as in **34**. This carbonyl group also can provide nucleophilic activation at C-9 for polar generation of the 9,10 bond. The benzyloxycarbonyl also can aid in formation of a carbanion at C-9 and prevent interference by carbanion generation at C-7. Thus, the benzyloxy-carbonyl also serves as an **activating group** and a **regiocontrol element**. The 9,10,11-circuit in **34** is dissonant. Therefore, polar disconnection at a nucleophilic C-9 requires electrophilic activation of the incipient C-10 in a precursor **36**. The carbonyl at C-11 in **34** is ignored in the polar disconnection to **36** which is an umpoled synthon from methyl acetoacetate (**37**).



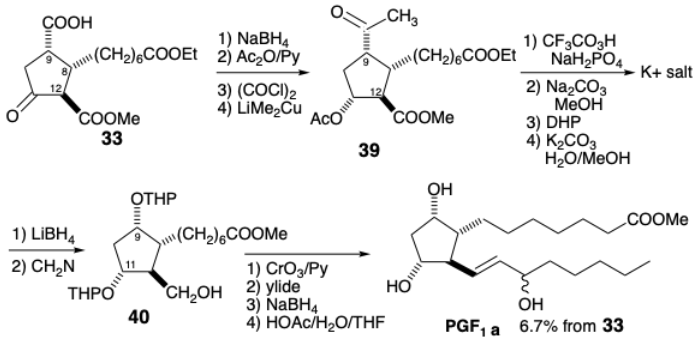
As in the **23** to **27** cyclization of the Miyano synthesis, cyclization of **34** produces a cyclopentanone **38**. But now the roles of nucleophile and electrophile are reversed. Thus, in the Miyano synthesis the nucleophilic center is at position 8 and the electrophilic center at position 12 in **23**.



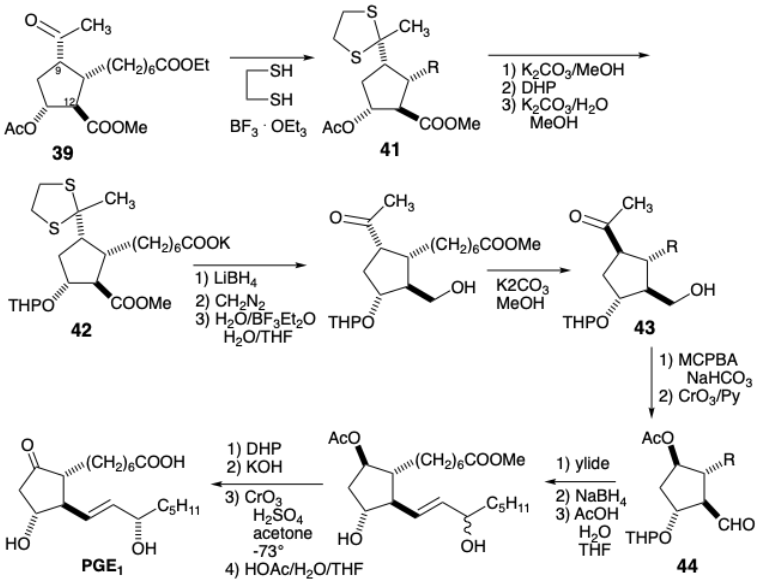
In the Kojima-Saki synthesis, the nucleophilic center is at position 12 and the electrophilic center at position 8 in **34**. This intermediate is stereoselectively converted to **33** by catalytic hydrogenation which saturates the C=C bond and also selectively converts the benzyl ester into a carboxylic acid without affecting the methyl or ethyl esters. Preferential generation of the α,α,β relative configurations at C-9, 8, and 12 respectively in **33** results from steric approach control followed by epimerization of the β-keto carbomethoxyl group. Conversion of **33** into $PGF_{1\alpha}$ is straightforward.



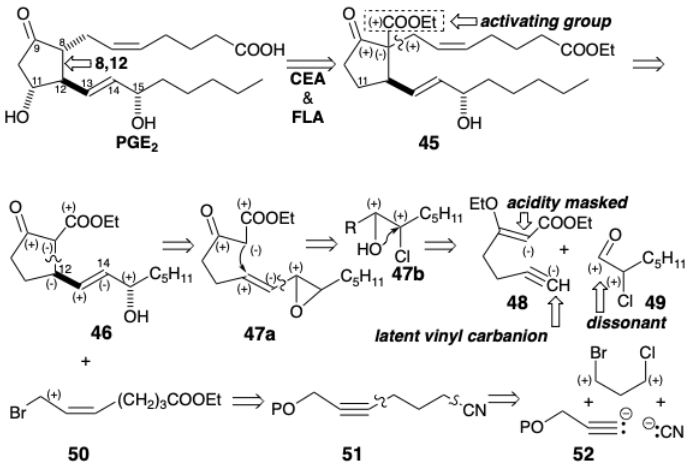
Generation of the C-10 hydroxyl from the latent precursor, a C-10 benzyloxycarbonyl, is achieved by Baeyer-Villiger oxidation of an intermediate methyl ketone **39**. Selective reduction of the carboxyl in **39** at C-12 is achieved by masking the electrophilic reactivity of the C-1 carboxyl as a potassium salt. To allow selective manipulation of the resulting alcohol, the hydroxyls at positions 9 and 11 in **40** are masked as tetrahydropyranyl (THP) ethers prior to reduction of the carbomethoxy group.



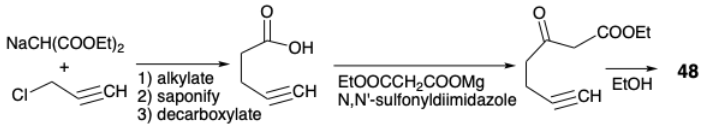
For a synthesis of PGE_1 from **39**, generation of the C-9 oxygen functionality from its latent precursor is delayed until after the C-11 acetoxy group in **39** is converted into a THP ether to allow differentiation from the C-9 acetoxy generated in a Baeyer-Villager oxidation of **43**. The dithioketal protecting group in **41** can be selectively removed from **42** after introduction of the THP ether. Addition of the lower sidechain to **43** after oxidation to aldehyde **44** parallels the sequence described for the Miyano synthesis.



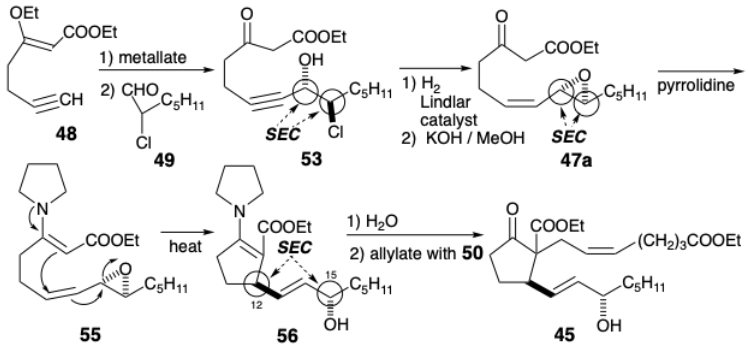
The β-hydroxycarbonyl array in PGE_2 is sensitive toward dehydration. If the C-9 carbonyl is to be exploited to activate nucleophilic reactivity at C-8 in a precursor, this sensitivity must be addressed. In the Miyano synthesis, dehydration of the cyclization product **27** is disfavored by the instability of the antiaromatic cyclopentadienone that would result. In a third strategy for prostaglandin synthesis4 that also mimics the biosynthetic cyclopentane annulation involving 8,12-bond creation, the problem is circumvented by introducing the C-11 hydroxyl at the end of the synthesis. This suggests a key intermediate **45** in which the C-11 functionality is removed and an activating group is added at C-8 to aid in carbanion generation at this position. Polar disconnection of the upper side chain from the subtarget **45** suggests electrophilic functionality at C-7 as in the precursor **50**. Polar disconnection of **46** at the 8,12- bond reveals the need for electrophilicity at C-12. However, rather than placing appropriate functionality at C-12 as in intermediate **23** of the Miyano synthesis (see above), a nucleofuge at C-14 in **47** provides the requisite activation by conjugation with C-12. An epoxide **47a** provides the appropriate electrophilicity at C-12 and oxygen functionality at C-15. A chlorohydrin **47b** is an alternative synthetic equivalent that is interconvertible with **47a**. Polar analysis of **47b** suggests disconnection to the electrophilic precursor **49** and **48** whose terminal acetylene serves as a latent vinyl nucleophile. The utility of terminal acetylenes as latent terminal vinyl nucleophiles also suggests a strategy for a C-C connective route to **50** via **51** from **52**, cyanide, and a 1,3-propane dielectrophile. Although **47a** and **47b** are alternative synthetic equivalents, conversion of **47b** to **47a** during the synthesis would provide a more reactive electrophile.



A synthesis of **48** might have been achieved by propargylation of ethylacetoacetate dianion. However, the potential for abstraction of the acetylenic hydrogen, by the strongly basic dianion, recommended an alternative approach.

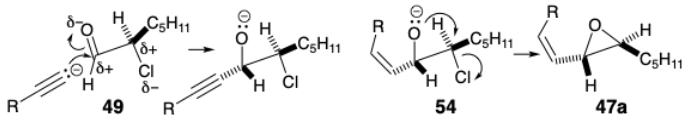


Thus, a malonic ester synthesis provided 4-pentynoic acid that was further elaborated to a β-ketoester by Claisen condensation.[4] Enoletherification then masks the ketone in **48** and allows selective deprotonation at the terminal acetylene. Condensation of the resulting acetylide nucleophile with α-chloroheptanal (**49**) produces **53** stereoselectively and then cis vinyl trans epoxide **47a** after partial hydrogenation and base promoted heterocyclization.



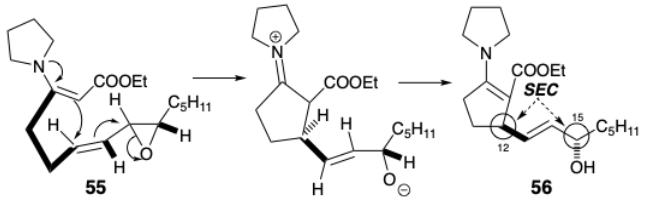
Cyclization of β-keto ester **47**, generating the prostaglandin 8,12-bond, might have been accomplished by intramolecular alkylation of an intermediate enolate. However, an alternative nucleophile, enamine **55** was employed. Hydrolysis of an intermediate enamine derivative **56** followed by allylation of the resulting β-ketoester delivered **45**. Especially noteworthy is the stereoselectivity of this synthesis of **45** with the correct relative stereochemistry at C-12 and C-15. This is the consequence of three consecutive stereoelectronically controlled (SEC) reactions.

First, addition of an acetylide nucleophile derived from **48** to the α-chloroaldehyde **49** occurs stereoselectively at the least hindered face of the carbonyl group in a conformation of **49** that achieves maximum separation of the C=O and C-Cl dipoles by an anti periplanar arrangement. Subsequent cyclization of the β-chloroalkoxide **54** with Walden inversion produces a trans disubstituted epoxide stereospecifically.

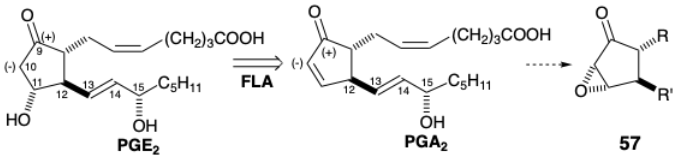


A stereoelectronically preferred mode of cyclization was expected to translate the stereochemical relationship between the chiral centers in the cis vinyl trans epoxide **55** into the requisite stereochemical relationship between the chiral centers at positions 12 and

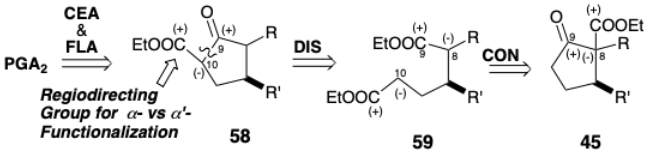
15 in **56**.[4] Thus, anti S_N2' displacement of alkoxide by the enamine nucleophile in **55** was expected to generate **56** after proton transfer in a presumed iminium alkoxide intermediate.



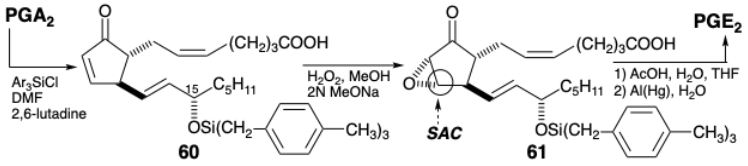
Introduction of a hydroxyl substituent at the 11-position in **45** is complicated by an absence of activating functionality adjacent to C-11. Reactivity can be provided by introducing unsaturation between carbons 10 and 11 taking advantage of the C-9 carbonyl to activate C-10 for introducing a leaving group. PGE_2 could then be obtained by epoxidation of the α,β-unsaturated ketone PGA_2 followed by reductive cleavage of the C-O bond adjacent to the carbonyl in **57**. This suggests PGA_2 as a synthetic precursor of PGE_2.



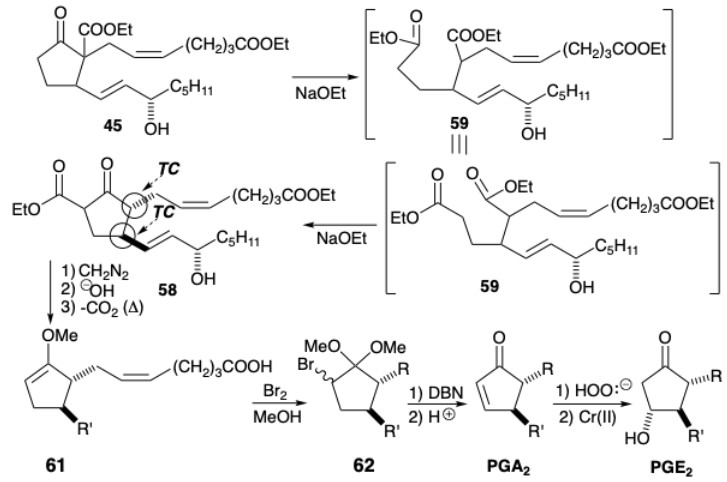
While **45** (see above) might be converted to PGA_2 by decarbethoxylation of the β-ketoester array and subsequent oxidative introduction of a leaving group at C-10, a more elaborate strategy was adopted. The process provides an example of a construction of the prostaglandin skeleton by generating the 9,10-bond of the cyclopentane ring as the last skeletal connection. Thus, a 10-carboethoxy precursor **58** would be well suited for the regioselective (α vs α') nucleophilic activation (proton abstraction) of the 10-position required for the conversion of a 10,11-dihydro-PGA_2 derivative into PGA_2. Also, **58** is suitably functionalized for polar generation by reaction of a C-10 nucleophile with a C-9 electrophilic center in a precursor **59**. Polar reconnection of **59** suggests the key intermediate **45** as a precursor of **58** via **59**.



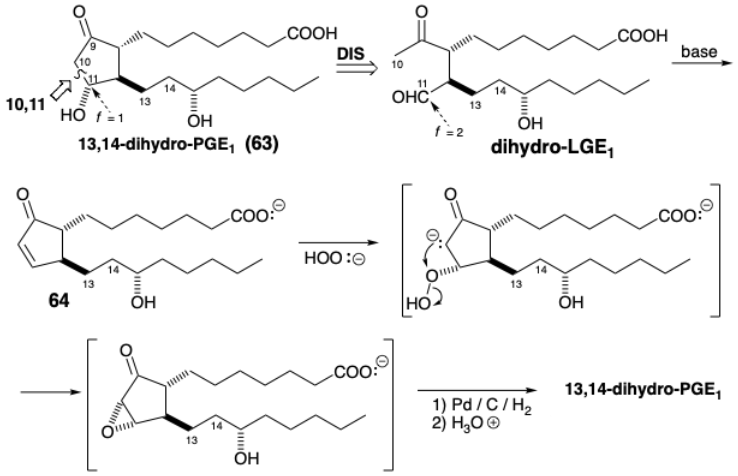
PGA_2 is a naturally occuring dehydration product from PGE_2, and the former has been prepared from the latter by an oxidation reduction sequence. Stereoselectivity during the epoxidation was achieved by employing a sterically demanding blocking group appended to the 15-hydroxyl in **60** to direct epoxidation to the α face of the cyclopentenone ring.[5]



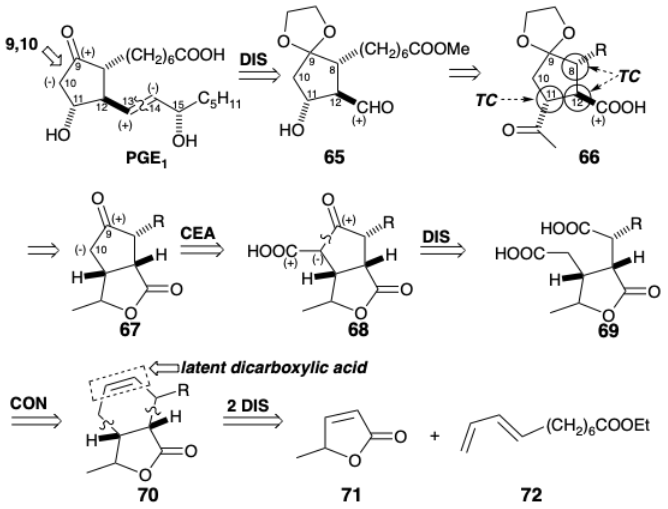
The conversion of **45** into **58** was achieved by an ethoxide-catalyzed rearrangement presumably involving retro Dieckmann cleavage to **59** followed by Dieckman cyclization to **58**. The carboethoxy transfer might also occur by decarboethoxylation and recarboethoxylation. In any event, the rearrangement is driven to **58** by formation of the corresponding enolate. The rearrangement allows regiocontrol in the formation of an enol ether **61,** the subsequent introduction of bromine by 1,2-dioxidative addition to give **62,** and ultimately in the introduction of unsaturation between carbons 10 and 11.



The previous three examples of prostaglandin synthesis illustrated polar synthesis of the 2,3-bond of a cyclopentanone ring corresponding to the 8,12-bond of the prostaglandin skeleton. In each case, this requried additional functionalization of a precursor because the 9,8,12,13,14,15 or 9,8,12,11-circuits are dissonant. Since the 9,10,11 circuit is consonant, either the 9,10 or 10,11- bond can be formed by a polar reaction that depends only on target-related functionality. As we shall see in section 3.7, seco prostaglandins (molecules lacking one C-C bond of the prostaglandin skeleton) are natural products for which the name levuglandin (LG) was coined to signify that they are derivatives levulinaldehyde with prostaglandin side chains. *In theory*, 13,14-dihydro-PGE_1 **(63)** could be generated directly from dihydro-LGE_1 by polar reaction of a C-10 nucleophilic enolate with the electrophilic carbonyl carbon of the aldehyde group at C-11, i.e an aldol condensation. However, although 11,13-dihydro-PGE_1 is undoubtedly an intermediate in this cyclization, it is not stable and dehydrates under the basic aldol condensation reaction conditions to afford olefin **64**, that must then be refunctionalized to deliver the target β-hydroxyketone **63**.[6]

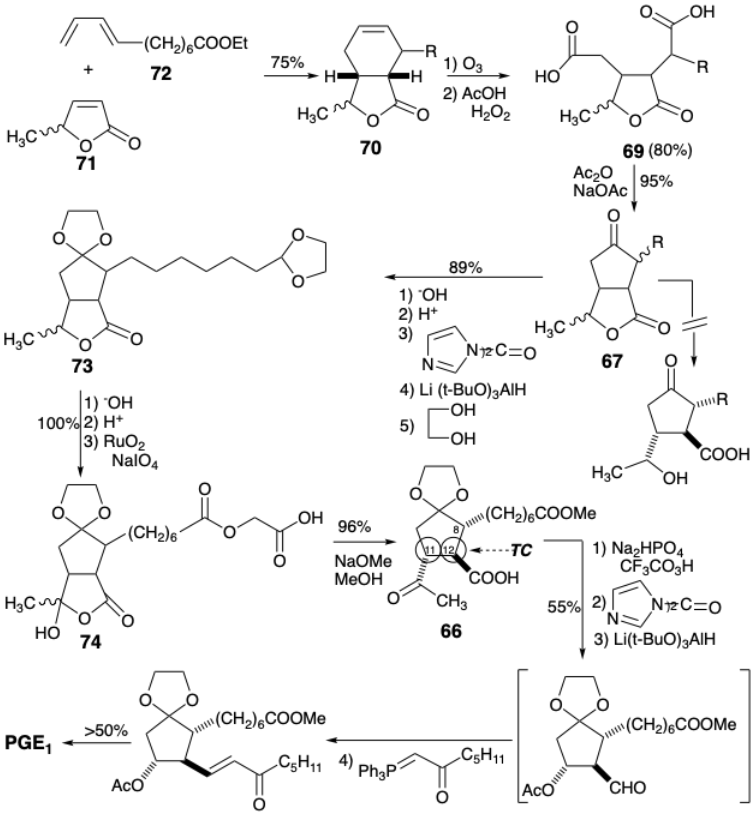


A Merck synthesis[7] of PGE1 achieves cyclopentanone annulation by creating the 9,10-bond in a polar process. However, to avoid generation of a sensitive β-hydroxy ketone intermediate, only one target related functional group is exploited. Polar disconnection of the lower side chain suggests a precursor **65** (see below). The C-11 hydroxyl is concealed in latent form until the end of the synthesis to avoid β-elimination. Thus, subtarget **65** is dislocated to a penultimate precursor **66** in which the C-11 hydroxyl is replaced by a methyl ketone and the C-9 carbonyl is masked to allow selective Baeyer-Villiger oxidation of the methyl ketone to deliver **65**. The reactive methyl ketone and carboxylic acid functionality in **66** can be internally masked as a lactone in a precursor **67**. Although the ring juncture in **67** is necessarily *cis*, the substituents at both positions 11 and 12 in **66** and its stereoisomers are epimerizable allowing generation of the required all-*trans* relative configuration of the substituents in **66** that is favored thermodynamically.

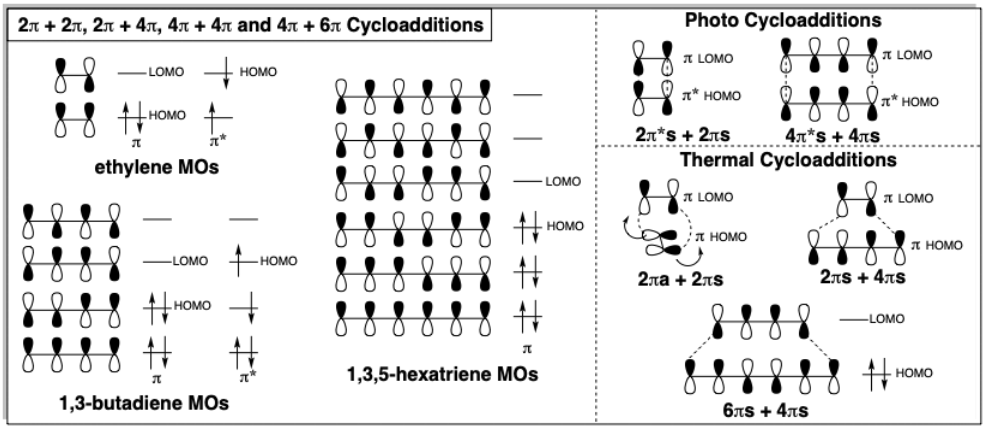


To facilitate polar synthesis of the cyclopentanone ring in **67**, a carboxyl group can be appended to the incipient C-10 in a precursor **69** to provide nucleophilic activation (CEA). This activating carboxyl will be removed readily from the cyclization product **68** by a polar cleavage. The two reactive carboxylic acid groups in **69** can be derived from a latent precursor **70** by oxidative cleavage. Finally, the cyclohexene moiety in **70** suggests a double disconnection to **71** and **72** that would provide the cyclohexene ring by a Diels-Alder cycloaddition. A preference for the required orientation of the cycloaddition is predicted owing to orbital overlap effects which favor an ortho relationship between the substituent on the diene and the electron withdrawing substituent on the dieneophile.

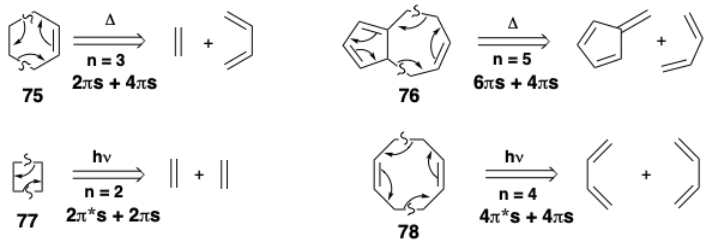
During the synthesis, it was discovered that opening of the lactone in **67**, to allow oxidation of the secondary hydroxyl and deliver ketone **66**, could not be achieved. To circumvent this flaw in the original plan, **67** was converted to an acetal **73** that could then be converted into a hemiacylal **74** by RuO_4 oxidation. Transesterification replaced the carboxymethyl ester in **74** with a methyl ester in **66** that could then be converted to PGE_1 as planned.



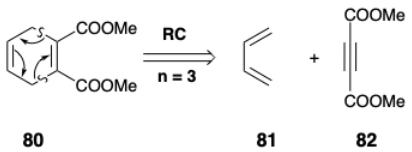
In the above synthesis, a cycloaddition was applied to generate a cyclohexene by a C-C double connective process. Cycloadditions generally provide a valuable nonpolar route to various cyclic products. Functionality is unnecessary for cycloadditions. Usually the targets contain unsaturation, but cyclobutanes, that can be generated by cycloaddition, do not even have unsaturation. A **retro cycloaddition** (**RC**) dislocation is feasible if a cyclic shift of two σ-bonds and n-2 π-bonds cleaves the ring into two poly and/or monoene precursors. Targets that are candidates for synthesis by cycloaddition of two poly and/or monoenes can be recognized by the presence of at least n-2 π-bonds in a 2n-atom closed circuit. If the precursors are bridged, the cycloaddition will be intramolecular. Cycloadditions may occur readily with thermal activation if n is an odd number but may require photochemical activation or transition metal catalysis if n is an even number. These rules are a consequence of the requirement for positive overlap between the lowest unoccupied molecular orbital (MO) of one reactant with the highest occupied molecular orbital (HOMO) of the other reactant. Sometimes this is only possible for the HOMO of the photoexcited π* state of one reactant and usually the interaction is suprafacial (on the same face of the π molecular orbitals. However, note that for 2π + 2π cycloadditions, a thermal reaction is favorable if one of the π-MOs interacts antarafacially (on opposite faces) and undergoes twisting of the two ends of the MO in opposite directions during the cycloaddition. For steric reasons, this is usually not feasible. However, it occurs readily for ketenes (see section 3.4).



Some examples of retro cycloaddition dislocations are presented below. The precursors of **75** and **76** may cycloadd with thermal activation while the precursors of **77** and **78** may require photoactivation, transition metal catalysis or involve antarafacial reaction of one π-bond, e.g., of a ketene.

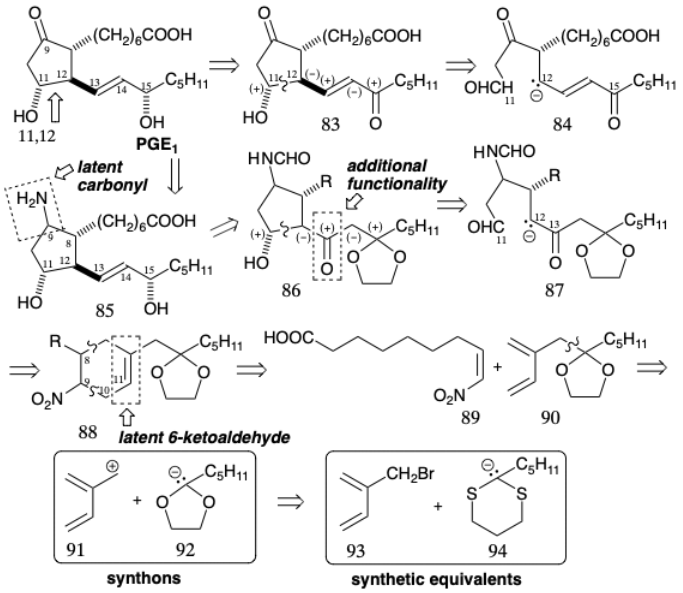


The 2n atom circuit may contain more than n-2 π-bonds. For example, dislocation of **80** to **81** and **82** corresponds to a cycloaddition that will readily occur thermally. Shift of two σ-bonds and n-2 = 1 π-bond cleaves the ring into two polyenes and n = 3 is an odd number.

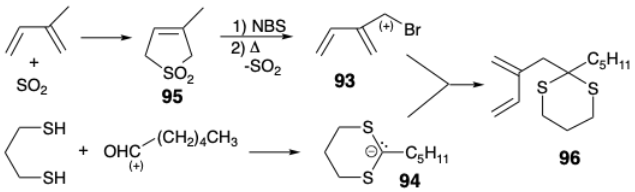


Since the 11,12,13,14,15-circuit in PGE_1 is consonant, *in theory* annulation of the cyclopentanone ring by forming the 11,12-bond can be achieved by exploiting the polar activation provided by the functional groups at positions 11 and 15. For example, conjugation with the C-15 carbonyl in **84** should facilitate generation of a carbanion at C-12 that could couple with the aldehyde carbonyl in **84** to generate **83** directly. However, PGE_1 contains a sensitive β-hydroxycyclopentanone array that readily dehydrates

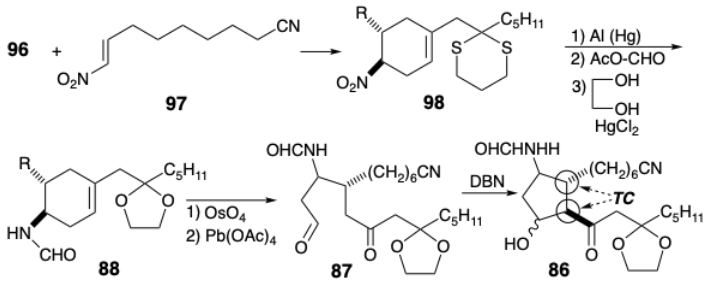
to give PGA_1. Therefore, early strategies for the synthesis of PGE_1 were dominated by efforts to mask the reactive β-hydroxy ketone array.



In the first total synthesis of PGE_1, achieved by E. J. Corey[8], the C-9 ketone carbonyl was carried along in latent form as a relatively unreactive formamide grouping which was transformed into a carbonyl group only at the end of the synthesis, *vide infra*. For the ultimate skeletal connection between carbons 11 and 12 in a precursor **87** of **85** in Corey's strategy for PGE_1, nucleophilic reactivity at C-12 is provided by a carbonyl group added to C-13. This carbonyl would be removed after polar cyclization to **86.** Furthermore, reduction followed by β-elimination fostered by a carbonyl group at C-15 would generate the required unsaturation between carbons 13 and 14. The two reactive carbonyl groups in **87** could be derived from a latent precursor, the C=C bond in a cyclohexene **88**. A double disconnection of the latter intermediate suggests diene **90** and dienophile **89** as precursors that would provide **88** by a Diels-Alder cycloaddition. The use of a nitro group in **88** and **89** as precursor for the formamido group in **87** is dictated by the favorable reactivity of electron deficient dienophiles toward electron rich dienes such as **90**. For the synthesis of diene **90**, the polar union of an electrophilic isoprenoid synthon **91** with an acetal carbanion synthon **92** was chosen since isoprenyl bromide **93** is readily available. A dithiane-derived carbanion **94** would serve as the synthetic equivalent of the umpoled ketal carbanion synthon **92**. The allylic bromide **93** was prepared by free radical allylic bromination of **95**, a cycloadduct obtained from isoprene and sulfur dioxide. Free radical abstraction of allylic hydrogen is favored by delocalization of the resulting allylic radical. Benzylic hydrogen abstraction and bromination with N- bromosuccinimide (NBS) is simillarly favored. Both **95** and the derived allylic bromide are crystalline solids from which the correspond-ing dienes can be generated by cycloelimination of SO_2. Allylation of **94** with **93** delivered a diene **96** that is a synthetic equivalent of **90** (see above).

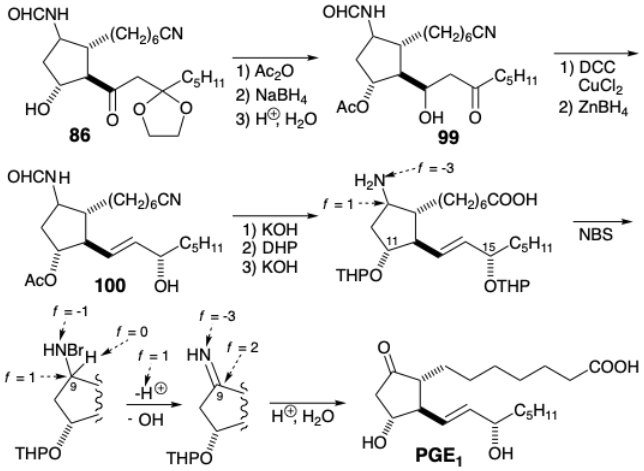


Rather than first convert thioketal **96** into ketal **90**, the former was reacted with dienophile **97** to produce cyclohexene **98**. Then the dithioketal was replaced with an ethylene ketal protecting group. Revelation of the latent carbonyl groups by oxidative cleavage of the alkene **88** provided the ε-keto aldehyde **87**. Base catalyzed aldol cyclization of **87** then delivered **86** stereoselectively. Thus, because the C-12 substituent is epimerizable in **86**, the required thermodynamically favored *trans* relationship between the two bulky side chains was produced. Because no control was exerted during generation of the C-11 stereocenter, some of the wrong epimer was also formed.



Although the prostanoid carbon skeleton was generated in the aldol cyclization of **87** to give **86**, completion of the synthesis required extensive adjustment of functionality and unsaturation level. The sensitive β-hydroxy ketone array was immediately acetylated and then the carbonyl group was reduced to avoid dehydration. After deprotection of the ketone and dehydration of the intermediate **99**, the allylic carbonyl in an intermediate enone was reduced with $Zn(BH_4)_2$, a mild hydride reducing agent, to produce an allylic alcohol **100**. Hydrolysis of the nitrile and acetate was followed by protection of the hydroxyl groups at positions 11 and 15 as tetrahydropyranyl ethers. Subsequent hydrolysis of the formamide required more vigorous conditions to deliver a THP protected derivative of **85**.

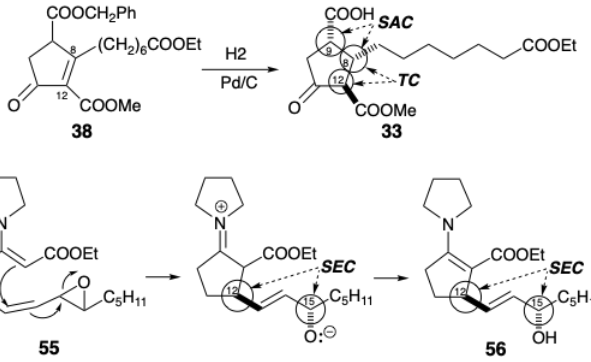
Production of PGE_1 by generation of the sensitive β-hydroxy ketone array under mild conditions was then accomplished in the key step of the synthetic plan. The strategy to use an amino group as a latent carbonyl in the immediate precursor **85** of PGE_1 depended upon a precedented sequence of reactions. Thus, selective oxidation to an imine was accomplished by N-bromination with NBS followed by base promoted elimination. Finally, hydrolysis of both the imine and the tetrahydropyranyl (THP) ether protecting groups under mildly acidic conditions delivered PGE_1.



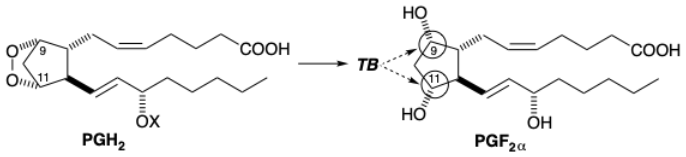
The key oxidation process is based entirely on polar reactions. Thus, N-bromination oxidizes the amino nitrogen from f = -3 to f = -1. Elimination of HBr then reduces the nitrogen to f = -3 while it oxidizes carbon and hydrogen.

3.4: Syntheses of Prostaglandins from Polycyclic Precursors

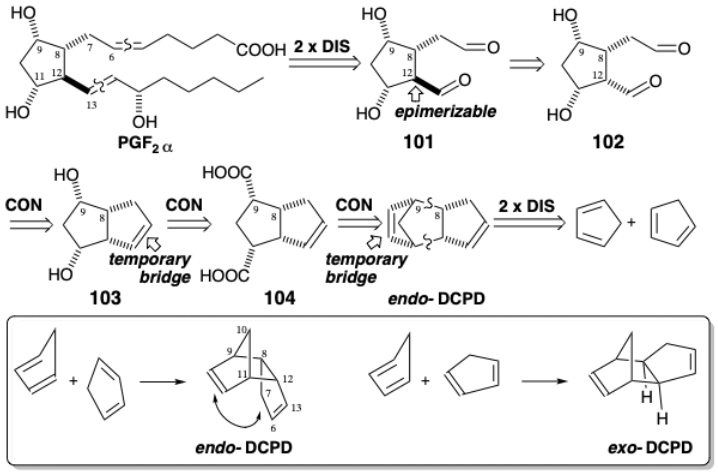
In the preceding syntheses of prostaglandins stereocontrol was achieved in several ways. For example, stereoselective generation of **33** from **38** depended on **steric approach control** (*SAC*) during catalytic hydrogenation to favor a *cis* relationship between substituents at positions 9 and 8. Subsequent **thermodynamic control** (*TC*) favored a *trans* relationship between the substituents at positions 9 and 12 by epimerization of a thermodynamically less stable *cis* intermediate to the more stable *trans* isomer. **Stereoelectronic control** (*SEC*) was adduced to account for the stereoselective generation of the correct relationship between the stereocenters at positions 12 and 15 in **56** during the cyclization of **55**.



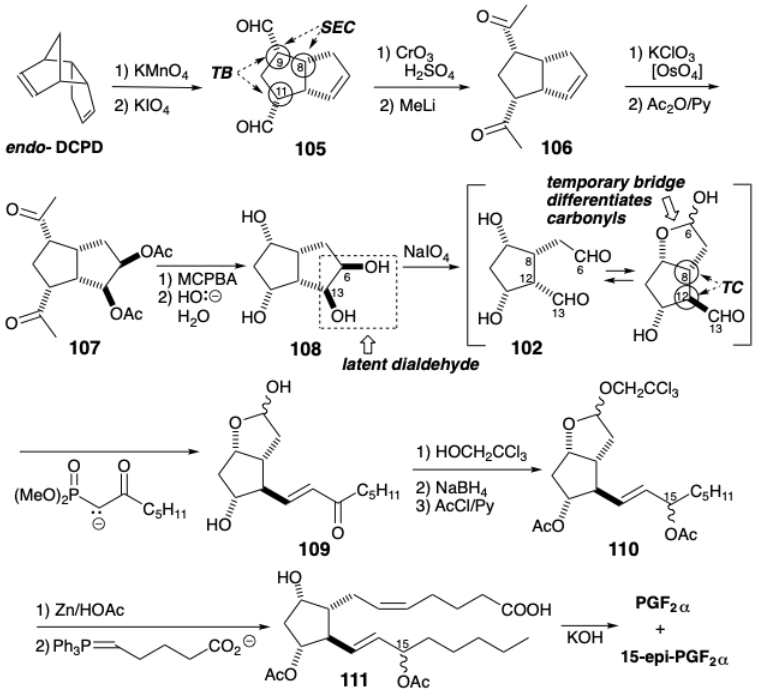
In this section, another technique for achieving stereocontrol will be considered. Thus, proximity of functional groups may be assured by the tactic of tying them together in a temporary ring which is ultimately cleaved. The biosynthesis of $PGF_{2\alpha}$ involves such a **temporary bridge** (*TB*) that enforces a *cis* relationship between the oxygen atoms at the 9 and 11 positions. These oxygens are tied together with an O-O bond in the intermediate prostaglandin endoperoxide PGH_2.



Often, temporary bridges contain functional groups in a latent form. We previously saw that cycloolefins may be oxidatively cleaved to yield dicarbonyl compounds. Creation of the $PGF_{2\alpha}$ skeleton by generation of both C=C bonds from carbonyl precursors suggests a 1,5-dialdehyde subtarget **101**. Since the aldehyde substituent at the C-12 stereocenter should be epimerizable, the less thermodynamically favored all *cis* aldehyde **102** can also serve as subtarget. The carbonyl groups in **102** can be concealed in latent form in the temporary unsaturated bridge of **103**. By employing a second temporary unsaturated bridge, a highly stereocontrolled synthesis of $PGF_{2\alpha}$ can be achieved. Thus, the cis-1,3-diol array found in $PGF_{2\alpha}$ and in the proposed intermediate **103** can be obtained -- by Baeyer-Villiger oxidation of the derived methyl ketone - from the cis-diacid **104** that can be produced by oxidative cleavage of *endo*-dicyclopentadiene (DCPD). In this strategy for prostaglandin synthesis[9], generation of the required *cis* relationship between the stereocenters at positions 8 and 9 ultimately depends upon a stereoelectronic preference for generation of the *endo* rather than *exo* isomer of DCPD during $2\pi + 4\pi$ cycloadditive dimerization of 1,3-cyclopentadiene. This is favored by secondary orbital overlap between the "nonparticipating" C=C bond and the cycloadding diene.

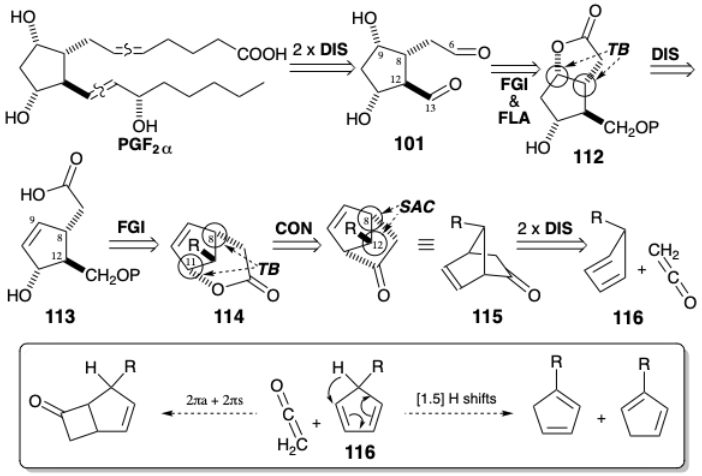


This synthesis exploits selective cleavage of one temporary bridge, the more strained C=C bond, to produce a dialdehyde **105**. After conversion to diketone **106**, the remaining C=C bond is partially oxidized to deliver **107** after acetylation. Baeyer-Villiger oxidation then produces a tetraacetate. Saponification followed by oxidative cleavage provides dialdehyde **102** from its latent precursor, the vicinal diol array in **108**. Epimerization of **102** at position 12 generates **101** that forms a hemiacetal in which one aldehyde carbonyl is adequately masked to allow chemoselective olefination of the remaining carbonyl to provide **109**. To prevent reduction of the aldehyde carbonyl, **109** is converted to a mixed acetal before a nonstereoselective reduction of the ketone carbonyl. Reductive cleavage of the β-trichloroethyl acetal in **110** then allows olefination of the remaining aldehyde group to provide **111** and ultimately racemic $PGF_{2\alpha}$ together with the racemic 15-epimer.

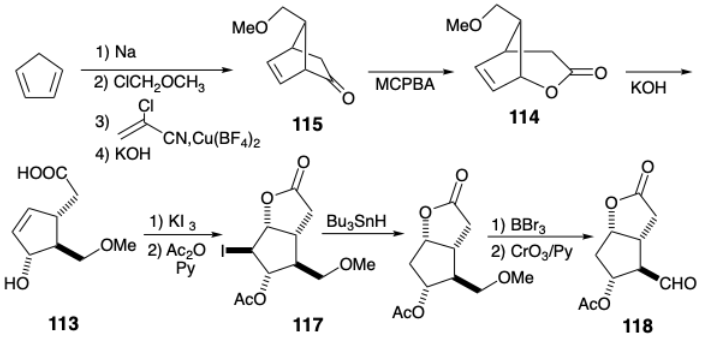


Corey's second strategy for total synthesis of prostaglandins[10] exploits two temporary bridges to assure the proper stereochemical relationships between the stereocenters at positions 9, 8, and 11. The *cis* relationship between the substituents at positions 8 and 9 in **101** is assured by a temporary ring in the lactone precursor **112** that is generated by stereoselective functionalization of an olefin **113**. Another temporary bridge, invloving the C-8 substituent, is used in the lactone **114** to assure a *cis* relationship with the hydroxyl at position 11. Since ketones are latent esters the cyclic ketone **115** can serve as a precursor of **114**. The required regiospecificity in the Bayer-Villiger oxidation of ketone **115** can be expected since this reaction involves 1,2-migration to an electron deficient terminus. The group that most readily supports a partial positive charge migrates preferentially. Thus, in **115** the secondary alkyl group that is also allylic migrates in preference to the primary alkyl group. A *trans* relationship between the

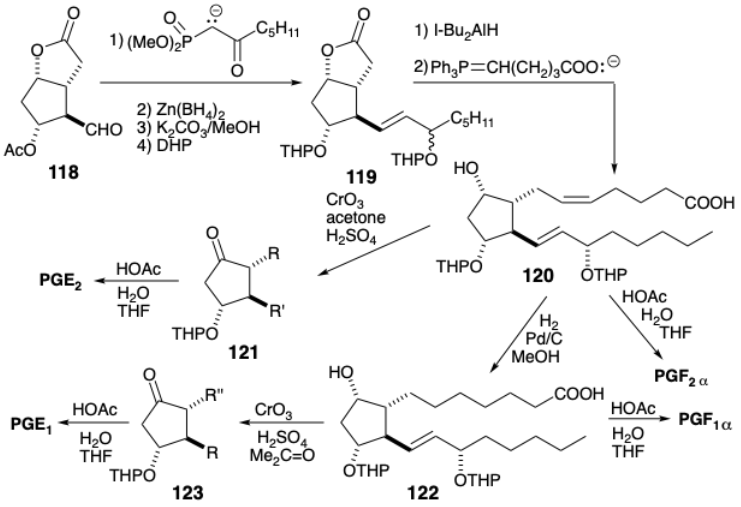
substituent at position 12 and the remaining stereocenters in the cyclopentane ring is ultimately the consequence of steric approach control during the cycloaddition of a 5-substituted 1,3-cyclopentadiene precursor **116** with ketene.



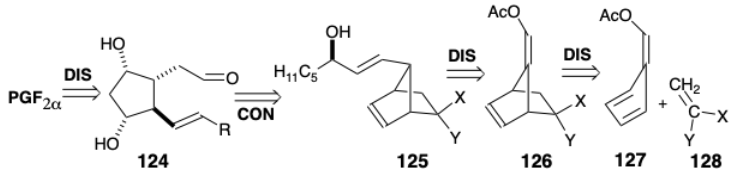
A potential flaw in this strategy arises from the instability of 5-substituted 1,3-cyclopentadienes that readily rearrange at room temperature, by [1.5]sigmatropic hydrogen migrations (see section 4.7), to generate mixtures of 1 and 2-substituted isomers. This isomerization was circumvented by using $Cu(BF_4)_2$ to catalyze the Diels-Alder reaction of 5-methoxymethyl-1,3-cyclopentadiene with α-chloroacrylonitrile at low temperature (to avoid rearrangement of the 5-substituted 1,3-cyclopentadiene). This chloronitrile -- a latent ketene -- undergoes 2π +4π cycloaddition with cyclopentadiene whereas ketene prefers to undergo 2πa + 2πs cycloaddition (see section 3.3). Another potential flaw, epoxidation of the C=C bond in **115** during Baeyer-Villiger oxidation, is apparently prevented by steric shielding of the C=C bond. **Stereoselective** (one configuration is generated preferentially at a new stereocenter) introduction of the C-9 hydroxyl results from the stereocontrolling influence of a **temporary bridge**. Thus, a nucleophile that is appended to C-8 in **113** is introduced intramolecularly (**internal nucleophile**) to an electrophilic center created at C-9 by the addition of $I^{\oplus}$ to the C-C π-bond to give **117**. Deprotection and oxidation generate the aldehyde **118**.



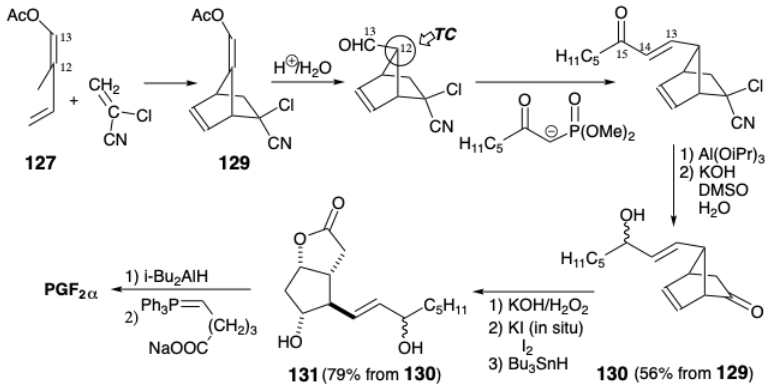
Appendage of the lower side chain to aldehyde **118** is achieved by olefination with a β-keto phosphonate. Reduction of an intermediate ketone followed by transesterification gives a lactone diol in which the hydroxyl at position 9 is differentiated from the remaining hydroxyls. The latter are then masked as tetrahydropyranyl (THP) ethers in **119.** Partial reduction of the lactone and Wittig olefination of an intermediate aldehyde delivers a key intermediate **120** that can be converted into E or F prostaglandins of the "1" or "2" series by appropriate manipulation of protecting groups to allow selective adjustments of functionality and unsaturation levels. Thus, the hydroxyl at position 9 in **120** or the derived **122** can be selectively oxidized to afford PGE_2 or PGE_1 respectively while deprotection of **120** or **122** delivers $PGF_{2\alpha}$ or $PGF_{1\alpha}$ respectively.



A closely related strategy for synthesis of prostaglandins[11] exploits exactly the same temporary bridges to enforce a *cis* relationship between the substituents at positions 9, 8, and 11 on the cyclopentane nucleus. However, a different order for generating the same skeletal connections obviates the necessity of using protecting groups. Thus, the upper side chain is added to a precursor **124**. However the lower side chain is already present in a bicyclo[2.2.1]heptene intermediate **125** prior to Baeyer-Villiger cleavage of the temporary bridge. Also the necessity for a difficult low-temperature Diels-Alder cycloaddition is avoided by using a fulvene **127** instead of a 5-substituted cyclopentadiene to react with a ketene equivalent **128**. The presence of an aldehyde enol acetate in **126** and **127** also avoids the requirement for a subsequent adjustment of functionality level after hydrolytic removal of the masking group.



The enol acetate in **129** is readily hydrolyzed selectively in the presence of the α-chloronitrile. The stereoselective generation of the requisite configuration at the incipient 12 position is undoubtedly the consequence of thermodynamic control. Thus, the aldehyde adopts the least sterically congested configuration. After olefination of this aldehyde with a β-ketophosphonate carbanion, the ketone carbonyl is reduced by a Meerwein-Pondorf-Verly reaction followed by hydrolysis of the α-chloronitrile delivering **130** in good overall yield. Since this ketone incorporates appreciable ring strain, an unusual Bayer- Villiger-like cleavage with hydroperoxide anion is possible. Peracids react with **130** to give epoxides, but the hydroperoxy anion reacts exclusively with the carbonyl group. The diol **131** can be masked to eventually allow selective oxidation of the 9-hydroxyl delivering PGE's while further elaboration to $PGF_{2\alpha}$ closely follows the synthesis from **120** except that THP protecting groups are unnecessary. Because no steps involving introduction or removal of protecting groups are required, this synthetic strategy is remarkably efficient.

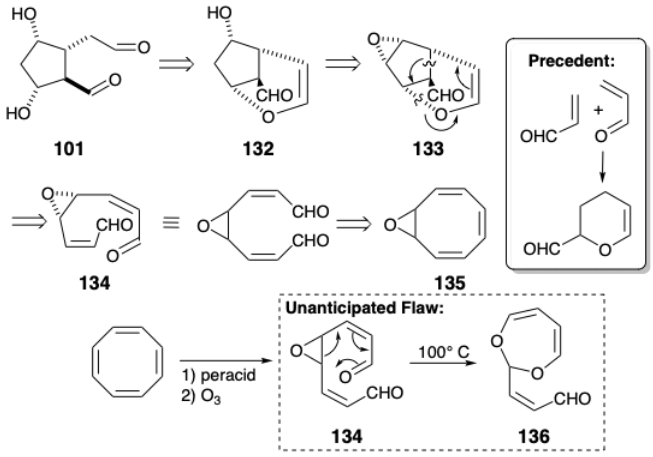


The strategies presented thus far all succeeded. Unfortunately, failed attempts are often not published. Sometimes they are described in doctoral theses. It would be a mistake to assume that synthetic planning for the total synthesis of complex molecules is

so dependable, even by the undisputed superstars of organic synthesis. Therefore, to maintain a realistic perspective, we will consider some flawed strategies from time to time.

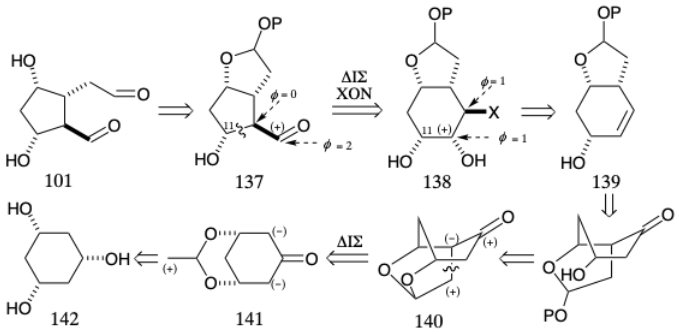
R. B. Woodward's Flawed Strategy

The dialdehyde **101**, that incorporates all the stereochemical information required for the cyclopentane ring of prostaglandins, might be derived from an enol ether **132** in which two functional groups are internally masked in a temporary bridge. The use of an epoxide **133** as a precursor of the alcohol **132** is recommended by the consequent possibility that **133** can be generated from a symmetrical precursor **134**. This strategy requires the discovery of a method to achieve regioselective reductive cleavage of epoxide **133** to generate **132**. The presence in **133** of a six-membered ring containing one C=C bond suggests the possibility of a 2π + 4π cycloaddition that would generate **133** from **134**. The intramolecular hetero Diels Alder cycloaddition of an aldehyde dieneophile to an α,β-unsaturated aldehyde diene to generate the dihydropyran ring in **133** is precedented by the corresponding intermolecular dimerization of acrolein which, however, favors the wrong orientation. Generation of **134** might be feasible by selective oxidative cleavage of the most electron rich C=C bond in cyclooctatetraene monoxide **135**. This strategy, devised by Woodward, is fatally flawed because the intermediate **134** undergoes a novel homo retro Claisen rearrangement producing **136** instead of the desired Diels-Alder cycloaddition.[1]



Ring Contraction Strategies

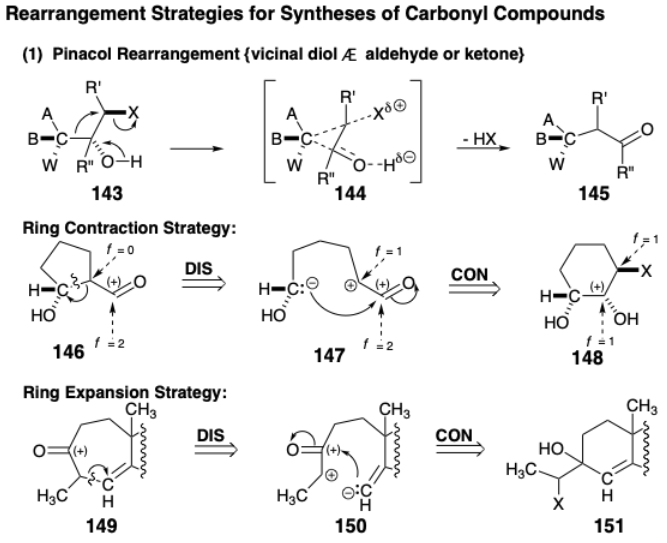
The mixed acetal **137** is another temporarily bridged precursor similar to Corey's aldehyde **118** (see above) except that the functionality level in **137** is identical with that in **101**. Therefore, the temporary bridge in 137, like that in 132, is an internally masked derivative of two functional groups as opposed to a latent precursor. Woodward[12,13] recognized that a potential precursor of **137** is **138** in which C-11 and the aldehyde carbonyl carbon are temporarily bridged by a C-C bond. The intermediates **137** and **138** are isomers with different connectivities and a different distribution of functionality but identical overall functionality level. The rearrangement of **138** to **137** involves oxidation to an aldehyde of a carbon bearing a hydroxyl and concomitant reduction of a carbon bearing an electronegative leaving group. Such a process, a pinacol rearrangement, is driven to completion by the energetically favorable generation of a C=O double bond at the expense of two C-O single bonds. The subtarget **138** can be simplified by dislocation to a less functionally substituted precursor **139** that might provide **138** by 1,2-dioxidative addition. Generation of the C=C bond in **139** from a ketone in **140** is suggested by the goal of disconnecting and functionally reorganizing this subtarget to a symmetrical precursor **141** by polar dislocation involving disconnection of an **internal electrophile**. The ketone carbonyl in 140 can provide nucleophilic reactivity to facilitate this C—C bond formation. A temporary bridge in **141** between the electrophile and nucleophile assure the necessary *cis* relationship between the masked hydroxyls in **141** and the newly created C-C bond in **140.** Ultimately, **141** might reasonably be available by selective protection of two of the three identical hydroxyl groups in all *cis* 1,3,5- cyclohexanetriol and oxidation of the remaining hydroxyl.

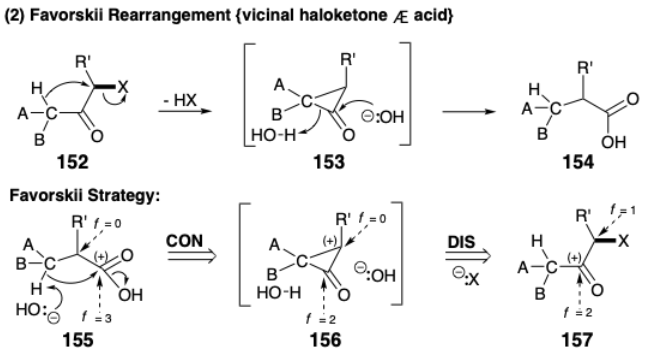


Stereospecific (the stereochemical configuration of the product isomer is determined by that of the reactant isomer) generation of the stereochemical relationships required in **137** is expected during the pinacol rearrangement of **138**. Thus, such rearrangements, i.e. **143** to **145**, generally proceed with retention of configuration at the migrating carbon owing to a temporarily-bridged transition state **144**.

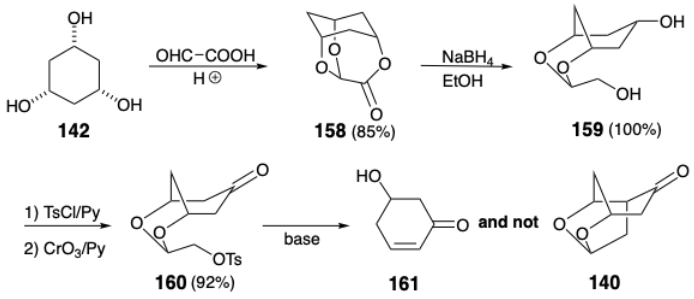
Two Step Reterosynthetic Analysis of Polar Rearrangements

Dislocation of a pinacol rearrangement product **146** to a precursor **148** may be viewed as polar disconnection of the migrating carbon as nucleophile resulting in oxidation of the migration terminus. Subsequent connection of the nucleophilic migrating carbon results in reduction of the migration origin (note that this is an **internal nucleophile**). In fact, the disconnection and connection steps occur simultaneously in pinacol rearrangements. Synthetically the **148** to **146** rearrangement results in ring contraction. Pinacol rearrangements can also result in ring expansion. This is exemplified retrosynthetically by generation of a precursor **151** with a six-membered ring for a target **149** with a seven-membered ring by disconnection to **150** and subsequent connection to **151**. This example, which also suggests that a vinyl carbon may serve as the migrating group, is a step in a strategy for total synthesis of the terpene longifolene that will be considered in chapter 4. Of course, pinacol rearrangements may also occur in acyclic systems. The Favorskii rearrangement of α-haloketones to generate ring-contracted or acyclic carboxylic acids is structrually and functionally related to the pinacol rearrangement. However, the Favorskii rearrangement involves a temporarily-bridged *intermediate* rather than *transition state*. Thus, 1,3-elimination from **152** generates a cyclopropanone intermediate **153** from which a ring-contracted product **154** is formed by nucleophile-induced cleavage. Retrosynthetically, Favorskii rearrangements generate a more connected precursor **156** from a carboxylic acid target **155**. Disconnection of the precursor **156** then suggests the skeletally and functionally reorganized precursor **157** in which the functionality level of the carboxyl group (f = 3) equals the sum of the functionality levels of a ketone carbonyl (f = 2) and a carbon bearing an electronegative leaving group (f = 1). Thus, as in the pinacol rearrangement, the Favorski rearrangement results in no net change in molecular functionality level, i. e. no net oxidation or reduction. Rather, these processes involve redistribution of functionality by an intramolecular redox process. Thus, rearrangement dislocations are complex because they involve coupled connection and disconnection steps as well as an associated redistribution of functionality.

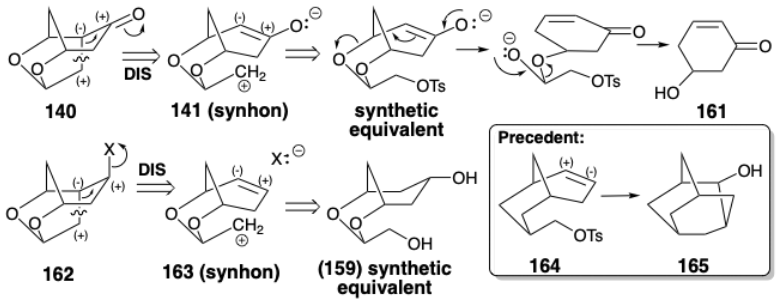




Although differentiation of the three hydroxyls in **142** was achieved by reaction with glyoxalic acid, the second Woodward strategy was also fatally flawed (see section 3.5). Reductive cleavage of **158** afforded diol **159** quantitatively, and the primary hydroxyl in **159** was readily activated selectively by tosylation. However, the ketone **160**, obtained by oxidation of the monotosylate, failed to produce **140** upon treatment with a variety of bases. Instead, elimination of a β-alkoxy group to produce **161** occurred to the complete exclusion of intramolecular alkylation.



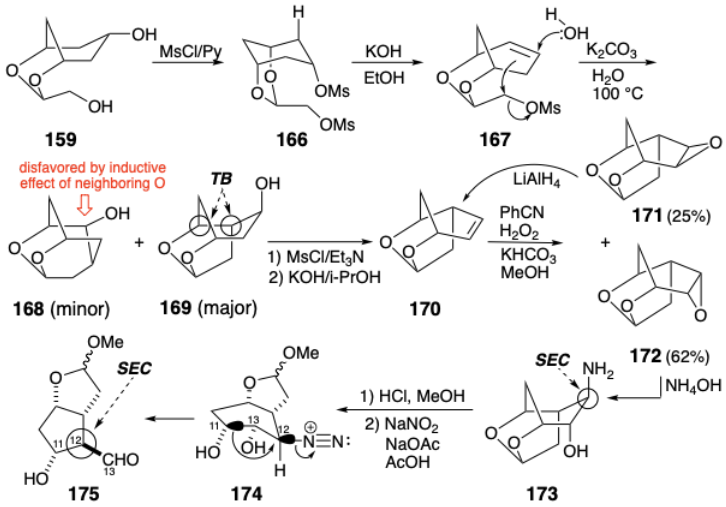
To obviate the necessity for enolate generation β to the alkoxy groups as in **141**, **162** was recognized as a direct precursor to olefin **139**. Polar disconnection of **162** suggests addition of a carbon electrophile to a C=C double bond as in **163**. The two dislocations, **140** to **141** and **162** to **163** are **isoelectronic** (mechanisms with identical electron movement patterns). That is, they both involve the movement of two pairs of electrons and the cleavage of a C-C σ-bond. However, whereas cleavage of a C- O bond in a synthetic equivalent of **141** to give **161** is driven by the production of a C=O bond, the similar cleavage of a C-O bond in a synthetic equivalent of **163** would generate a relatively unstable intermediate, an allylic carbocation.



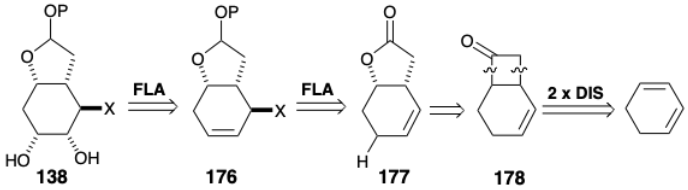
Synthetic equivalents of the unsymmetrical synthon **163** might be obtained from the available symmetrical diol **159** by β-elimination. Unfortunately, a precedent suggested that cyclization of **163** might not occur in the desired fashion. Thus, the carbocyclic analogue **164** produces the isomeric ring system **165** upon solvolysis. However, it could be argued that the allylic oxygen substituents in **163** might disfavor such a mode of cyclization that must generate an electron deficiency β to the alkoxy substituents.

This time the gamble payed off.[13] The bismesylate **166** from **159** afforded olefin **167** upon selective elimination of the secondary mesyloxy group. Solvolysis of **167** produced a mixture that contained only 5-8% of the undesired product **168**. Of course, the desired cyclization product **169** is racemic. It can be resolved. However, only one enantiomer leads to prostaglandins of natural configuration. Thus, while this synthesis (*vide infra*) solves "the main sterochemical problem inherent in prostaglandin $F_{2\alpha}$ synthesis -- the alignment of the four contiguous chiral atoms in the cyclopentane moiety", the process is not enantioselective. Half of the intermediate **169** is the wrong enantiomer, that is not readily recyclable. Dehydration of the appropriate cyclization product

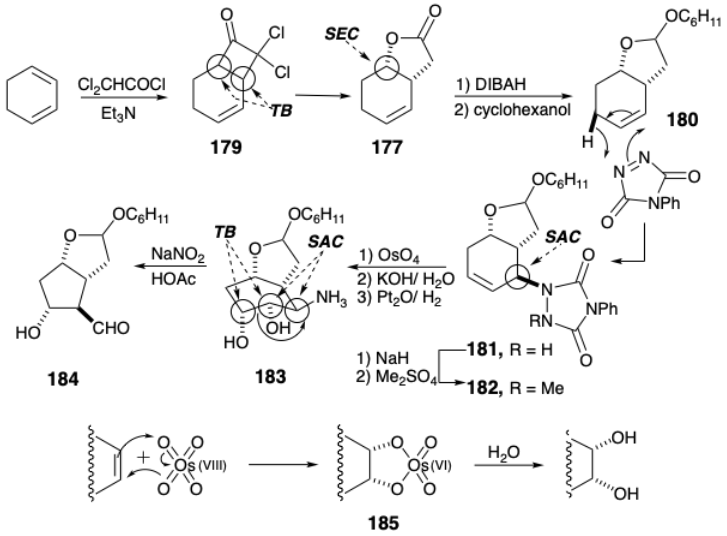
169 then provided **170**. The requisite stereochemical preference during 1,2-dioxidative addition to **170** was best achieved with the perimidic acid generated *in situ* from benzonitrile and hydrogen peroxide. This reaction delivered a mixture of the *exo* epoxide **171** and the *endo* epoxide **172**. The former epoxide could be recycled to **170**. Stereoelectronically controlled nucleophilic opening of the epoxy ring in **172** delivered **173** stereospecifically. This isomer is mandatory for the subsequent pinacol-like ring-contracting rearrangement that ensues upon deamination of the bicyclic mixed acetal **174**. Thus, migration of the incipient C-11 carbon is favored in **174** by an **anti periplanar** relationship (two bonds or groups lying in the same plane with a dihedral angle of 180°) with the leaving group. Rearrangement of **174** occurs not only with retention of configuration at the migrating carbon, but also stereospecifically generates the requisite configuration at C-12 in the product **175** owing to Walden inversion during the intramolecular S_N2 reaction. Further elaboration of the key intermediate **175** into prostaglandins followed well-precedented reactions.



Corey devised an alternative route[14] to key intermediates of the type **138**. Thus, **138** might be available by *cis*-1,2-dioxidative addition to alkene precursor **176**. Furthermore, a *trans* relationship between the incipient leaving group X and the newly introduced oxygen atoms might be anticipated on the basis of steric approach control. Steric approach control might also favor the required *trans* relationship between X and the lactone ring. This would be especially true if allylic oxidation were achieved by an ene mechanism which would involve a sterically demanding cyclic transition state. Furthermore, such a mechanism would assure the requisite regiocontrol, i.e., substitution with allylic rearrangement, during introduction of X. The lactone in **177** could be obtained from a latent precursor, the ketone in **178**, available in turn by a 2π + 2π cycloaddition of ketene to a symmetrical precursor, 1,3-cyclohexadiene.

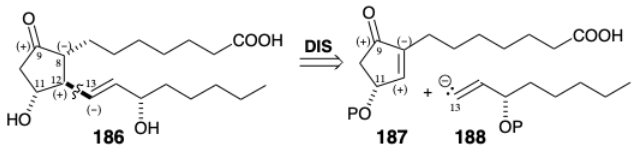


Structurally selective cycloaddition (see section 3.3) of dichloroketone to 1,3-cyclohexadiene delivered **179** from which the unsaturated lactone **177** was obtained by reductive dechlorination followed by Baeyer-Villiger oxidation (see section 3.5). Partial reduction followed by ketalization delivered **180** that stereoselectively afforded **181** upon ene reaction with N-phenyltriazolinedione. Hydroxylation of the derived **182** also proceeded stereoselectively. The latter reaction also involves a temporary ring, an osmate ester **185**, that enforces a *cis* relationship between the newly introduced oxygen atoms.

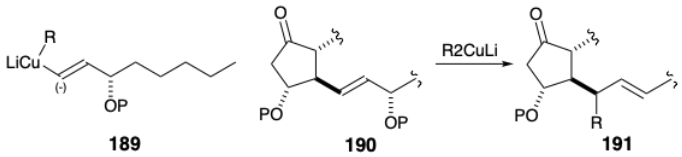


3.5: Syntheses of Prostaglandins from Cyclopentanes

Since the all *trans* stereochemistry of ring substituents should be thermodynamically preferred for cyclopentane derivatives such as PGE_1, a method of stereocontrol less powerful than the use of temporary bridges would seem adequate for prostaglandin synthesis. Furthermore, the availability of simple cyclopentanoid precursors including cyclopentadiene, that was used in many of the syntheses described above, led to the formulation of a simple strategy for stereocontrolled total synthesis of prostaglandins. Furthermore, such strategies are well-suited to enantioselective total synthesis (see section 3.6). Polar reactivity analysis of PGE_1 as in **186** suggests dislocation of this stereochemically complex target into two fragments **187** and **188** containing only one stereocenter each.[15] Thus, steric approach control might favor ddition of the vinyl nucleophile **188** from the less congested face of the cyclopentanone ring, the face opposite a substituent at position 11.



Furthermore, 1,4-additions of lithium diorganocuprates such as **189** with α,β-unsaturated ketones are especially susceptible to such SAC. However, lithium diorganocuprates were also known to displace allylic oxygen such as that at the 11-position in the cyclopentenone **187** or at the 15-position in the lower prostaglandin side chain as in the hypothetical reaction of **190** to generate **191**, a useless byproduct. Should such a potentially fatal flaw preclude further consideration of a synthetic strategy? The answer depends on the value of the possible discovery that the flaw is not fatal. This leads to another rule of thumb to be added to the list began in section 1.5:

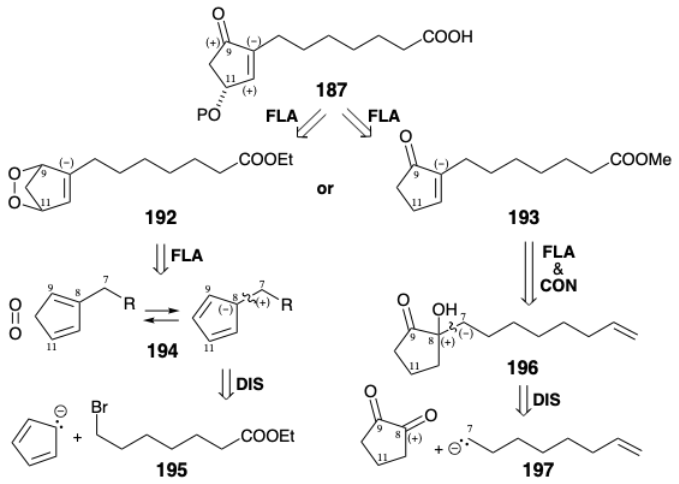


(6) *Favor potentially flawed strategies* only if the effort involved in further examination of the possible flaw is offset by the potentially great reward of an especially elegant and efficient synthesis.

Woodward's strategy involving intramolecular cycloaddition of **134** to generate **133** is an example of this principle not paying off. Woodward's strategy involving intramolecular alkylation of ketone **160** and his ultimate success in achieving the required skeletal connection by a modification of the strategy is an example of yet another principle of synthetic planning:

(7) *Devise backup strategies*, especially for ***risky steps***.

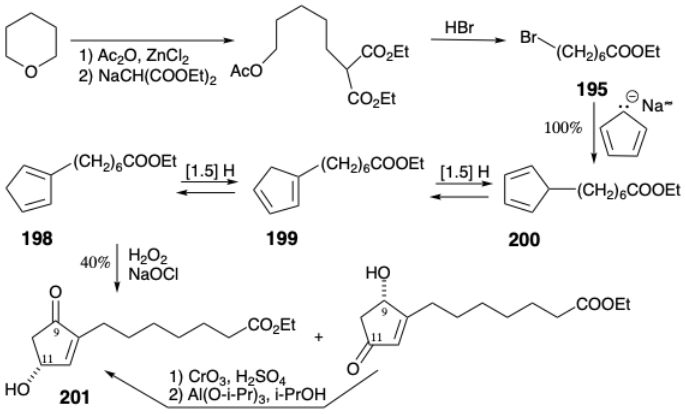
The 9,8,12,11-circuit in **187** is dissonant. One strategy for generation of this dissonant functional array (see page 88) involves 1,4-dioxidative addition (4πs + 2πs cycloaddition) of singlet oxygen to a monosubstituted 1,3-cyclopentadiene precursor **194** to generate an endoperoxide **192** that could undergo disproportionation to the required hydroxycyclopentenone in analogy with the disproportionation of PGH to PGE.[15] Alkylation of cyclopentadienide anion with bromoester **195** would produce a 5-substituted 1,3-cyclopentadiene. However, the requisite 2-substituted isomer is readily available because monoalkyl 1,3-cyclopentadienes exist at room temperature as an equilibrium mixture of mainly 1 and 2-substituted isomers that are formed from the 5-substituted isomer by [1.5] sigmatropic hydrogen migrations.



Alternatively, a simple monosubstituted cyclopentenone **193** might be converted to **187** by allylic oxidation. A route to **193** is suggested by the possibility that the C=C bond in this enone can be produced from a cyclopentanone **196** by elimination of water. If the leaving group is a hydroxyl, the presence of such functionality at the 8-position in a precursor **196** invites further dislocation to a nucleophilic upper side chain synthon **197** and a carbonyl electrophile, 1,2-cyclopentanedione. The electrophilic carboxyl functionality in **193** is latent in **197** to avoid undesired intramolecular reaction with the nucleophilic center at position 7.

It is interesting to note that the two routes to **187** outlined above involve electronically complimentary polar strategies for generating the 7-8 bond. One route exploits an upper sidechain electrophile and a cyclopentyl nucleophile (i.e. **195** and cyclopentadienide anion) while the other route exploits an upper sidechain nucleophile and a cyclopentyl electrophile (i.e. **197** and 1,2-cyclopentanedione).

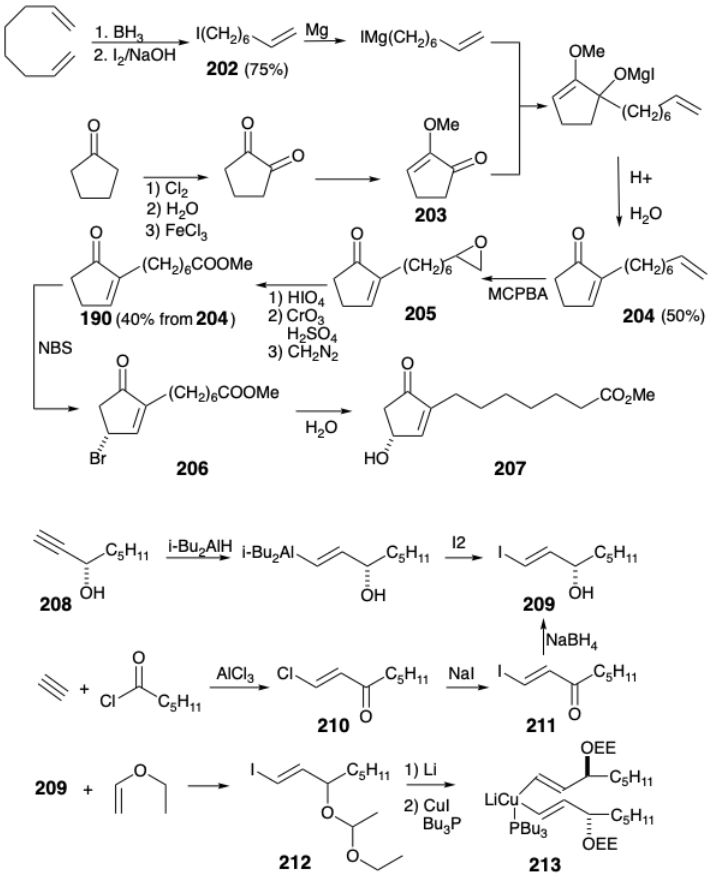
Bromoester **195** was prepared from tetrahydropyran and diethyl malonate. Singlet oxygen, generated chemically, reacts with the monosubstituted cyclopentadienes **198**-**200** under basic conditions to deliver hydroxycyclopentenone **201** and its isomer having a hydroxyl at the 9-position and a carbonyl at the 11-position. The latter isomer was readily converted to **201** by an oxidation and reduction sequence.



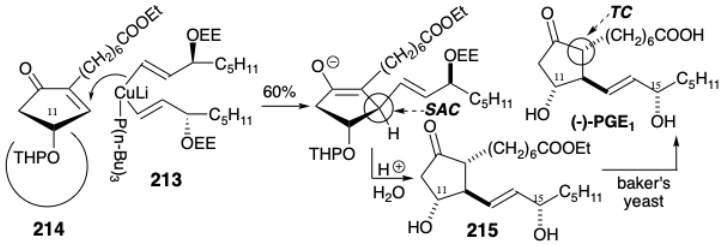
A Grignard reagent synthetic equivalent of nucleophilic synthon **197** was prepared by monohydroboration of 1,7-octadiene followed by iodo-deborination and reaction of the resulting iodide **202** with magnesium. Oxidation of cyclopentanone provides 1,2-cyclopentanedione whose methyl enol ether **203** delivered cyclopentenone **204** upon reaction with 7-octenyl-magnesium iodide followed by hydrolysis of the enol ether and dehydration. Generation of an ester from the latent precursor required selective oxidative cleavage of one C=C double bond in **204**. This was readily achieved by epoxidation of the more electron-rich C=C bond with peracid followed by oxidative cleavage of **205** with periodate. Methylation delivered ester **190** that was allylically brominated to provide **207** after hydrolysis of an intermediate bromide **206**.

A lower side chain vinyl nucleophile is prepared by hydroalumination of (S)-1-octyne-3-ol (**208**) followed by iododealumination of an intermediate vinyl alane to deliver optically pure vinyl iodide **209** of correct absolute configuration. This iodide is also available by chloroacylation of acetylene with valeryl chloride followed by iododechlorination of an intermediate vinyl chloride to deliver iodoketone **211** that affords racemic **209** upon borohydride reduction. Resolution of racemic **209** can be achieved with the

phenethylamine salt of the hemiphthalate derivative. The hydroxyl group in **209** must be masked prior to lithium-iodine exchange. Reaction of **209** with ethyl vinyl ether affords an α-ethoxyethyl (EE) derivative **212** that provides a divinyl cuprate **213** by metal-halogen exchange with t-butyllithium followed by addition of CuI and Bu_3P.

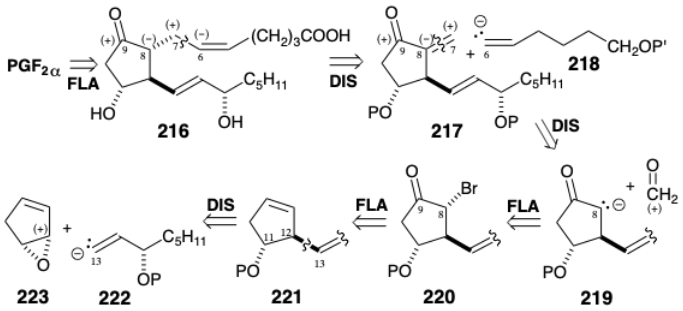


The key 1,4-addition of optically pure divinylcuprate **213** to the THP derivative **214** of racemic hydroxycyclopentenone **201**, followed by removal of THP and EE protecting groups, delivers an almost 1:1 mixture of (-)-PGE_1 ethyl ester **215** with the absolute stereochemistry of the natural product and its diastereomer that is epimeric at positions 8, 12, and 11. Hydrolysis of the ester to produce PGE_1 could be achieved under especially mild conditions by incubation with baker's yeast. Reaction of optically pure divinyl cuprate **214** with optically pure **214** (see section 3.6) delivers (-)-PGE_1 exclusively.[16]

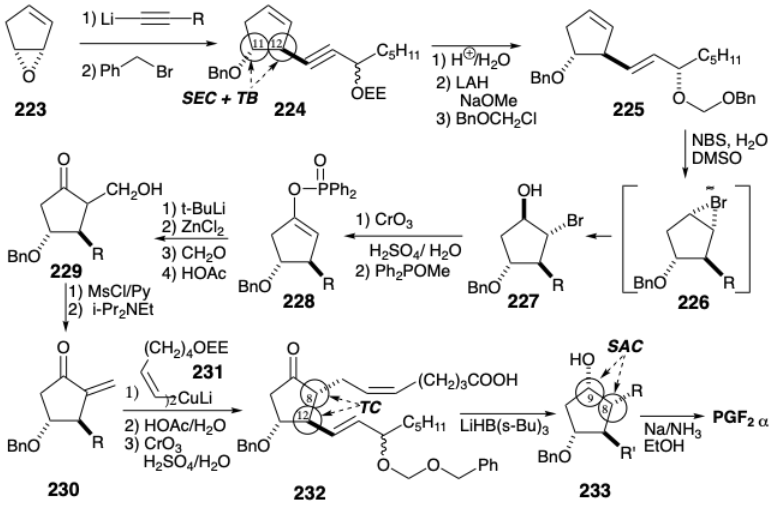


Another strategy for synthesis of prostaglandins from cyclopentane precursors[17] exploits steric approach control during hydride reduction of a PGE_2 derivative **216** to provide the correct configuration at the 9-position in $PGF_{2\alpha}$. Polar analysis of **216** suggests that the upper side chain can be appended by reaction of a *cis* vinyl nucleophile **218** with an α,β-unsaturated ketone **217**. Polar analysis of **217** suggests a further dislocation to ketone enolate **219** and formaldehyde. A regioselective synthesis of the requisite enolate could be accomplished by reductive cleavage of α-bromo ketone **220**. Appropriate functionalization of olefin **221** might be feasible through 1,2-dioxidative addition. That **221** might be obtained stereoselectively through regioselective nucleophilic opening of cyclopentadiene monoxide (**223**) by a vinyl nucleophile **222** is the reasonable consequence of an S_N2 mechanism with attack at the weaker allylic C-O bond. Thus, cleavage of a temporary bridge, the epoxide, will proceed with inversion of configuration at one

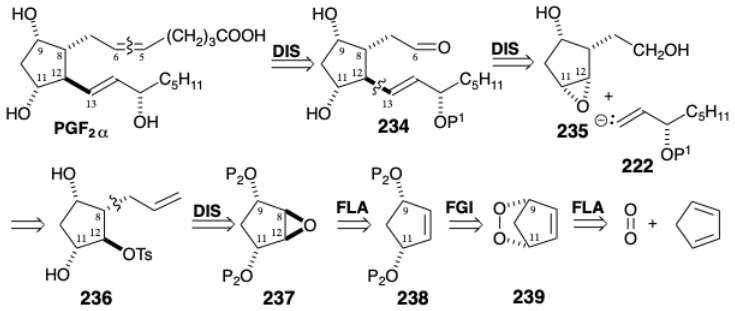
terminus leading to a *trans* relationship between the nucleophile and nucleofuge groups which become the substituents at positions 12 and 11 respectively.



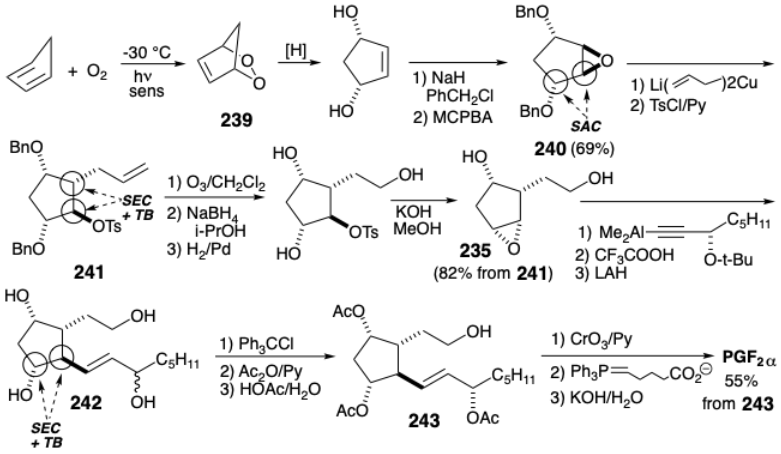
The lithium acetylide from 3-(α-ethoxyethoxy)-1-octyne can serve as a terminal vinyl carbanion equivalent. Thus, reacts with epoxide **223** to afford **224** after benzylation of an intermediate alkoxide. Hydrolysis of the EE protecting group followed by *trans* stereoselective hydride reduction of an intermediate propargyl alcohol in the presence of methoxide followed by masking of the resulting allylic alcohol affords **225**. That hydroxy bromination of **225** occurs stereo and regioselectively apparently results from a steric preference for the α-bromonium ion **226** that is attacked by water at the least sterically congested position, i. e. remote from the bulky substituent at position 12, delivering **227**. That the cyclopentene C=C bond reacts in preference to the side chain C=C bond is a consequence of the electron withdrawing deactivating effect of the allylic oxygen substituent. Oxidation of **227** to the corresponding ketone followed by a Perkow reaction delivers the enol derivative **228** regiospecifically. Generation of an enolate from **228** by reaction with t-butyllithium regiospecifically activates the 8-position for nucleophilic reaction with formaldehyde delivering **229.** This aldol condensation is promoted by a temporary bridge that is provided by a chelating zinc cation. Dehydration of **229** then affords enone **230** that adds a cis vinyl cuprate **231** to produce the upper side chain in **232** after selective hydrolysis of the EE protecting group and oxidation of the primary alcohol. Stereoselective, i.e. SAC, hydride reduction of **232** affords PGF2α after reductive removal of the benzyl and benzyloxymethyl ether protecting groups in **233**.



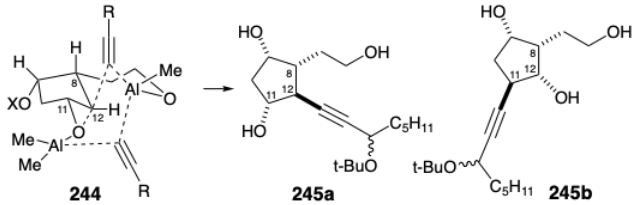
Stereospecific opening of epoxides by carbon nucleophiles can be exploited to introduce both prostanoid side chains onto a cyclopentane nucleus. A remarkable strategy for the total synthesis of $PGF_{2\alpha}$ from cyclopentadiene[18] first simplifies the target by disconnection of the upper side chain in the usual manner at the C=C bond. The key step in the strategy involves the regioselective S_N2 displacement of an electrophile at position 12 by a nucleophilic lower side chain *trans* vinyl carbanion synthon **222**. The requisite *trans* relationship between the substituents at positions 11 and 12 is assured by a temporary epoxide bridge in **235** between the stereocenters at positions 11 and 12. This epoxide might be generated from the corresponding *trans* diol monotosylate **236**. Introduction of a nucleophilic fragment of the upper side chain might also be achieved stereospecifically by an S_N2 attack on an epoxide **237**, a symmetrical electrophile containing a temporary bridge between the incipient 8 and 12-positions. Stereoselective generation of **237** might be achieved by steric approach control during epoxidation of a precursor cyclopentene **238**. Finally, the cis relationship between the oxygen substituents in **238** can be assured by a third temporary bridge, this time between two oxygen atoms in an endoperoxide precursor **239** that is available from 1,3-cyclopentadiene by 2π + 4π cycloaddition of singlet oxygen.



Reductive cleavage of the temporary peroxide bridge in **239** delivers a *cis* diol**.** The regiocontrol during cleavage of the epoxide intermediate **242,** that could be achieved with an aluminum acetylide, apparently results from a temporary bridge between nucleophile and electrophile. Thus, the hydroxy-ethyl substituent in **242** reacts with the organoalane nucleophile. The alkoxy alane then delivers the alkynyl nucleophile intramolecularly as in **243** to the desired position 12 and not position 11. The primary hydroxyl in the tetraol **238**. Finally, the cis relationship between the oxygen substituents in **238** can be assured by a third temporary bridge, this time between two oxygen atoms in an endoperoxide precursor **239** that is available from 1,3-cyclopentadiene by 2π + 4π cycloaddition of singlet oxygen.



It was postulated that regiocontrol during nucleophilic attack on the epoxide intermediate **235** might be provided by a temporary bridge between the nucleophile and electrophile. Thus, the hydroxyethyl substituent in **235** would react with an organoalane nucleophile. The resulting alkoxy alane can deliver the alkynyl nucleophile intramolecularly as in **244** to the desired position 12 and not position 11. Indeed, this reaction gave the desired regioisomeric adduct **245a** in 60% yield and no trace of the undesired regioisomer **245b**. Further support for this mechanistic explanation is provided by the observation that silylation of **235** prior to reaction with the alane produced a regioisomeric mixture of adducts and even favored nucleophilic attack at the 11 position by 2.6:1. Also noteworthy is the fact that the bridge involving the hydroxyethyl group and the acetylide nucleophile in **244** is fused in a *trans* fashion with the cyclopentane ring, whereas the epoxide bridge is *cis* fused. Thus, while small rings prefer *cis* fusions, *trans* fusions may be unstrained and even favored thermodynamically for larger rings.



To complete the prostaglandin skeleton, the primary hydroxyl in the tetraol intermediate **242** was differentiated by tritylation. After acetylation of the remaining hydroxyls and detritylation, the resulting primary alcohol **243** was oxidized to an aldehyde before final addition of the remaining portion of the upper side chain in the usual manner.

In the foregoing strategy for synthesis of prostaglandins, polar activation that is potentially afforded by target-related functionality is not exploited for skeletal construction. Rather, electrophilicity at the 8 and 12-positions is provided by added functionality, the

epoxides in **235** and **240**. Economy of functionality is sacrificed in favor of incorporating temporarily bridged leaving groups that assure stereocontrol.

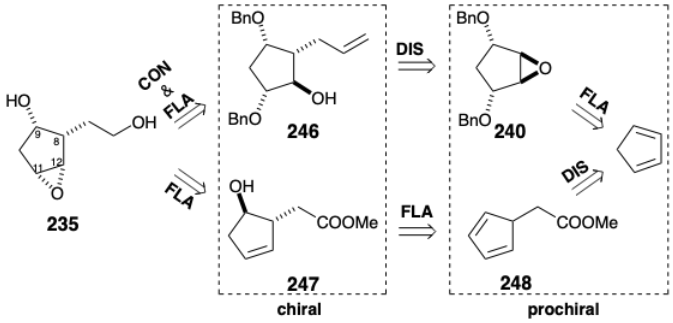
3.6: Enantioselective Syntheses of Prostaglandins

All of the foregoing total syntheses of prostaglandins produced these natural products together with their unnatural enantiomeric isomers because each synthesis began with nonasymmetric or racemic starting materials and employed racemic or nonasymmetric reagents. In some instances racemic mixtures of enantiomeric precursors were separated by resolution and then converted to the enantiomerically pure natural product. But this approach to the total synthesis of chiral nonracemic natural products is usually inherently wasteful since half of the racemic precursor, the wrong enantiomer, must be discarded. Very rarely, the wrong enantiomer can be converted to the correct enantiomer or converted into the natural product in an **enantio-convergent synthesis** by a unique reaction sequence.

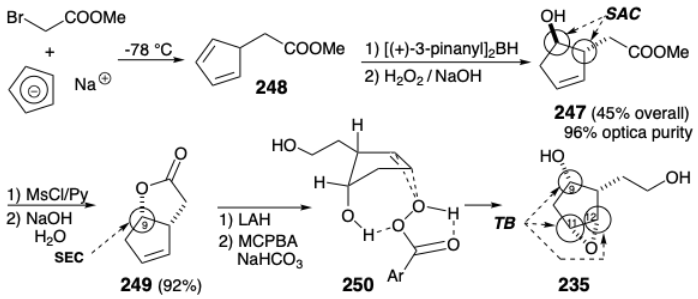
There are three tactics that allow enantioselective synthesis of natural products. They all depend on the chirality of natural products to provide asymmetric starting materials or to induce asymmetry during the generation of chiral intermediates from prochiral precursors. Presented in the ensuing discussion will be examples of syntheses that are enantiocontrolled by the use of: (1) chiral nonracemic reagents; (2) microbial metabolism -- a special case of category 1; or (3) chiral nonracemic starting materials.

Enantiocontrol by a Chiral Nonracemic Reagent

In the synthesis discussed above, the chirality of **235** is determined by an intermediate **246** that was generated by reaction of an allyl nucleophile with the prochiral epoxide **240**. Since the allylating reagent employed was nonasymmetric, the chiral product was racemic. The intermediate **235** has also been prepared in another manner, one that generates only the correct enantiomer required for the total synthesis of natural optically pure prostaglandins.[19] In this asymmetric synthesis, the chirality of **235** is determined by an intermediate **247** produced by hydroboration of the prochiral diene **248** with a chiral nonracemic dialkyl borane.

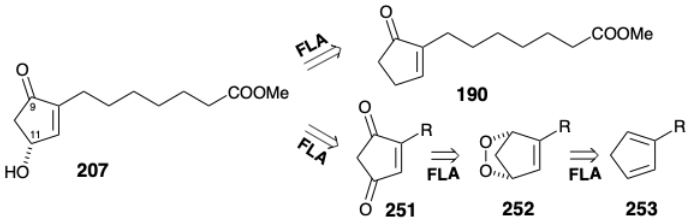


The 5-substituted 1,3-cyclopentadiene **248** was generated at -78° C by alkylation of sodium cyclopentadienide and treated *in situ* with (+)-di-3-pinanylborane, followed by alkaline hydrogen peroxide to yield hydroxy ester **247**, that was at least 96% optically pure. Owing to steric approach control during the syn addition of boron hydride to **248** and subsequent stereospecific retention of configuration during oxidative replacement of boron with oxygen, the new stereocenter at position 9 (PG numbering) in **247** is generated stereoselectively with the unnatural configuration, opposite to that required for prostaglandins. However, the required *cis* configuration is readily generated by S_N2 inversion of the hydroxyl, and lactonization delivers **249**. The stereoselective generation of the *cis* epoxide in **235** depends upon the influence of a temporary bridge. Thus, the hydroxyl at C-9 directs the delivery of oxygen by hydrogen bonding with MCPBA as shown in **250**. This temporary bridging in the transition state of a reaction is an example of a **neighboring group effect**.

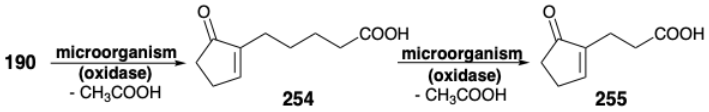


Enantiocontrol by Microbial Metabolism

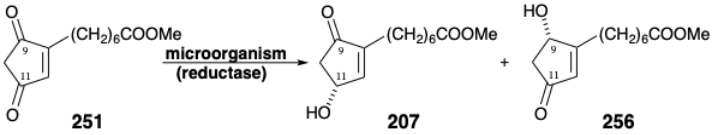
The enzymes which catalyze microbial oxidations and reductions are chiral nonracemic molecules that often promote highly enantioselective transformations of synthetic prochiral substrates.[20] Several strategies have been explored for enantioselective microbial generation of hydroxycyclopentenone intermediates for syntheses of prostaglandins. For example, the chiral intermediate **207** might be available by microbial allylic oxidation of the prochiral precursor **190** or by microbial reduction of the prochiral precursor **251**. The dione **251** should be readily available by oxidation of the hydroxycyclopentenone mixture obtained by base catalyzed disproportionation of a singlet oxygen 2π + 4π cycloadduct **252** with cyclopentadiene **253**.



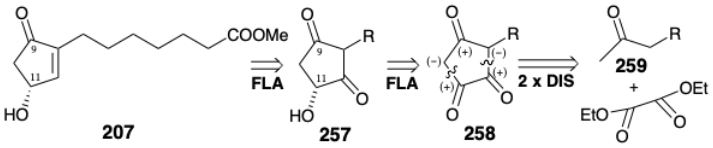
A flaw in the allylic oxidation strategy resulted from a general proclivity of fungi containing hydroxylases to degrade the carboxylic side chain of **190** by the β-oxidation-retro Claisen cleavage mechanism discussed in section 3.1. Thus, cleavage of one acetate unit produced **254** while **255** was generated upon loss of a second acetate.



A proclivity of dione **251** toward monoreduction is expected owing to the activating effect of opposed electron withdrawal by two conjugated carbonyl groups. Therefore enzyme-catalyzed monoreduction of **251** is anticipated to be readily achieved by microorganisms. However, two problems interfered with attempts to obtain a practical asymmetric bioorganic synthesis of enantiomerically pure **207** from the vinylogous α-diketone **251**. First, reduction of the C=C bond often accompanied C=O reduction. Saturation of α,β-unsaturated ketones is a common microbiological transformation. This undesired side reaction was prevented by microbiological reduction of **251** in the presence of excess 2-cyclohexenone or methyl vinyl ketone as **competitive substrates** for the C=C bond reductases but not for the C=O reductases.[16] Furthermore, with a wide variety of microorganisms, reduction of the incipient 9-keto group generating **256** competed with the desired reduction to generate **207** with a hydroxyl at the incipient 11-position.

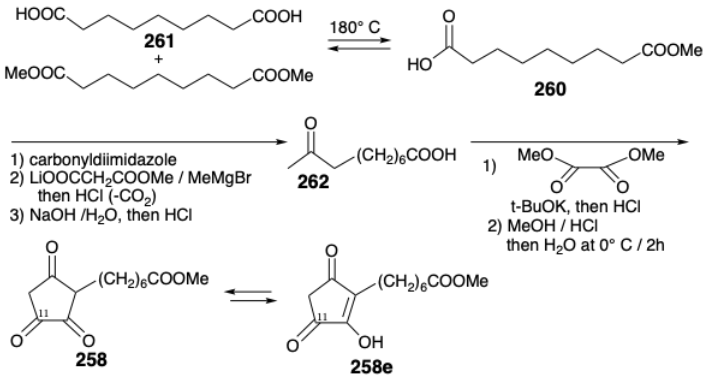


A less direct alternative strategy for enantioselective synthesis of **207** by asymmetric carbonyl reduction exploits functionality and unsaturation level adjustment of a hydroxydione precursor **257** that might be available by **enantioselective** (generating a pure enantiomeric product from an achiral precursor) reduction of a trione **258**. Polar analysis of **258** suggests a synthesis of this dissonant functional array by the condensation of a methyl ketone **259** with the dissonant diester, diethyl oxalate.

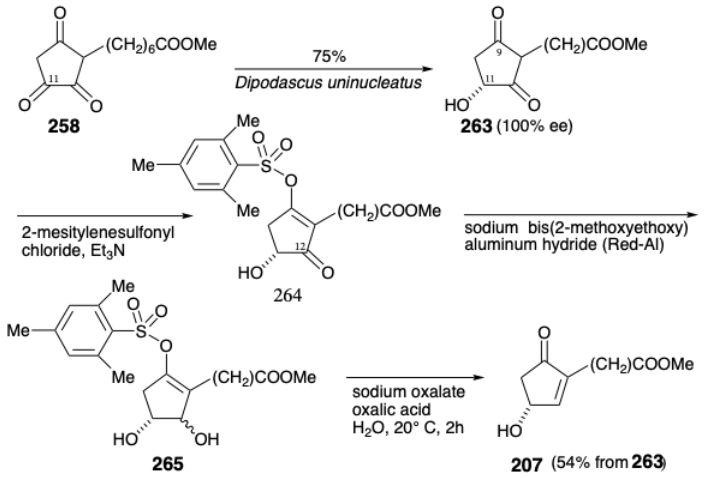


The trione **258** actually exists as an enol **258e** that is a hydroxy derivative of **251**. But this enol can be expected to have less proclivity than **251** toward saturation because the hydroxyl substituent will reduce the electrophilicity of the C=C bond by donation of a nonbonding electron pair. Furthermore, the carbonyl group at the incipient 11-position in **258e** should be especially susceptible to nucleophilic attack by hydride owing to the dipole effect of a vicinal hydroxyl group. A synthesis of trione **258** began with azelaic acid (**260**) and its dimethyl ester to afford monomethyl azelate (**261**) by thermal equilibration. Condensation of the derived imidazolide with the magnesium enolate of lithium monomethyl malonate followed by decarboxylation, hydrolysis, and a second

decarboxylation delivered methyl ketone **262**. Claisen condensation with dimethyl oxalate and subsequent Dieckmann cyclization and methylation of the carboxyl group produced the key intermediate **258**.

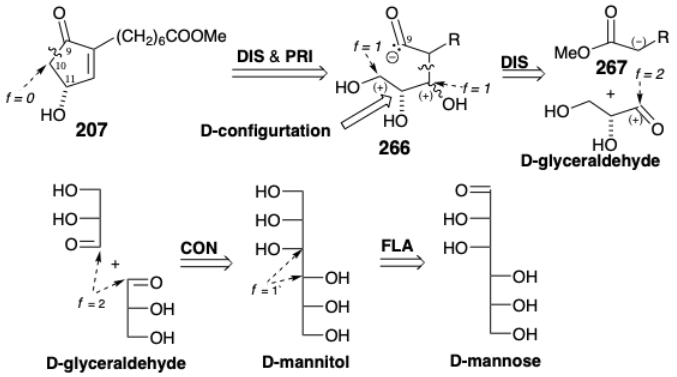


Trione **258** was cleanly and regioselectively reduced to hydroxydione **263** by a variety of microorganisms. *Dipodascus uninucleatus* catlayzed the completely asymmetric reduction of **258** to the 11(R) alcohol that is required for the total synthesis of prostaglandins. In contrast, *Mucor rammanianus* reduced **258** to the 11(S) alcohol. Conversion of optically pure hydroxydione **263** into the optically pure hydroxycyclopentenone **207** required selective reduction of the carbonyl at position 12. This was achieved by selectively masking the carbonyl at position 9 as an enol mesitylenesulfonate **264** followed by hydride reduction (see section 3.7). Subsequent hydrolytic allylic rearrangement of the intermediate allylic alcohol **265** delivered **207**.[16]

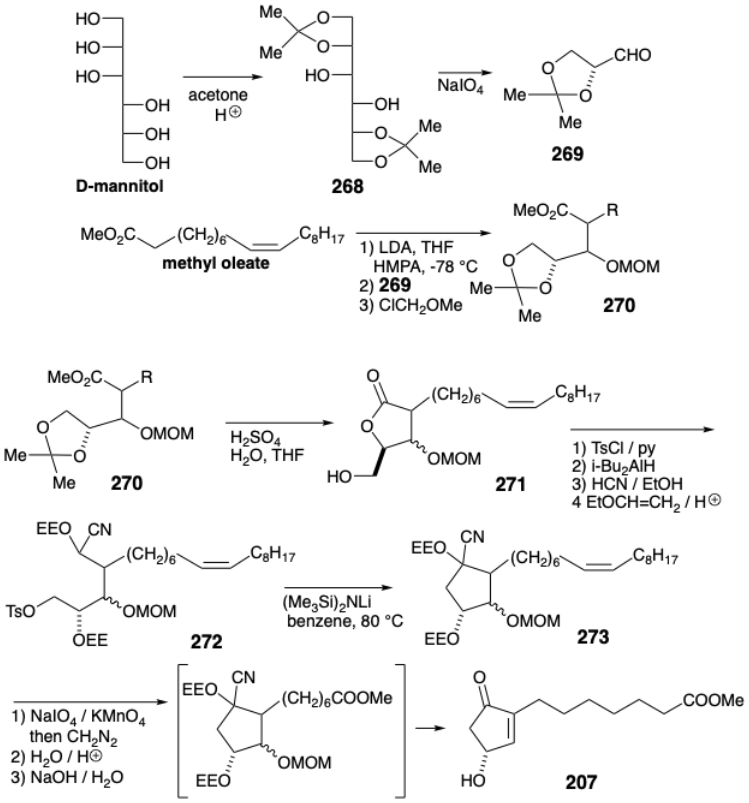


Enantiocontrol by Exploiting Chiral Nonracemic Starting Materials

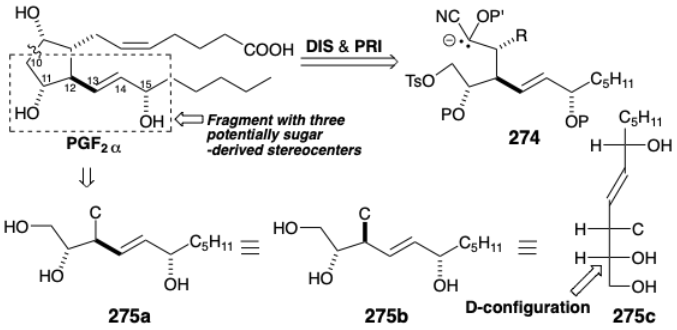
Instead of using the asymmetry of natural products, e.g. enzymes, to induce asymmetry during conversion of prochiral precursors into chiral synthetic intermediates, the asymmetry of readily available natural products, e.g. sugars, can be incorporated into synthetic targets by conversion into chiral nonracemic intermediates for total syntheses. For **207**, the chiral center at position 11 might be derived from a chiral center in a sugar. Since every carbon in a sugar is oxygenated, polar disconnection of chiral nonracemic **207** with the boundary condition of uncovering a sugar-derived chiral segment suggests a trihydroxy precursor **266** (see section 3.7). Note that **266** is a nucleophilic umpoled synthon generated by **polar reactivity inversion** (PRI) at the incipient 9-position carbonyl. Further polar disconnection suggests an α-carbomethoxy- stabilized nucleophile **267** and D-glyceraldehyde as electrophile. D-Glyceraldehyde should be available by oxidative cleavage of any D-sugar. An especially efficient synthesis is suggested by a dislocation involving reductive coupling to connect two molecules of glyceraldehyde. The axially symmetrical precursor D-mannitol is available by reduction of D-mannose.



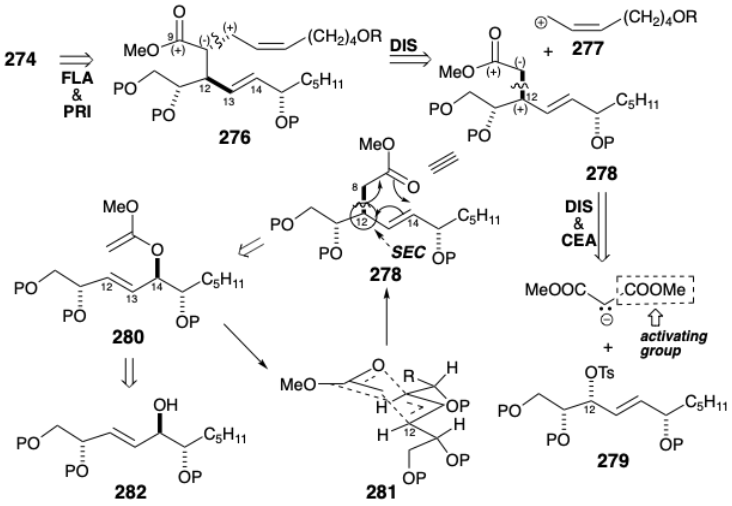
In an enantiospecific synthesis of optically pure **207** from D-mannitol, methyl oleate provided the nucleophile corresponding to **267**.[21] The C=C bond in methyl oleate comprises a latent carboxyl that is not unmasked until the end of the synthesis. Aldol condensation of methyl oleate with acetonide **269** of D-glyceraldehyde delivers **270**. Deketalization unmasks a vicinal dihydroxyl array (see section 3.7) and subsequent lactonization differentiates the primary and secondary hydroxyls exploiting an internal masking group and the favorable stability of a temporarily bridged butyrolactone. The free primary hydroxyl in **271** is then activated by tosylation, and the α-ethoxyethyl (EE) ether of a cyanohydrin is generated from the lactone carbonyl by reduction, cyanohydrin formation, and O-alkylation with ethyl vinyl ether. Cyclization of **272** then completes the carbon skeleton. Removal of protecting groups, oxidative cleavage of the side chain C=C bond and methylation of the resulting carboxylic acid, hydrolysis of the cyanohydrin, and dehydration then delivers the optically pure hydroxy-cyclopentenone **207** from **273**.



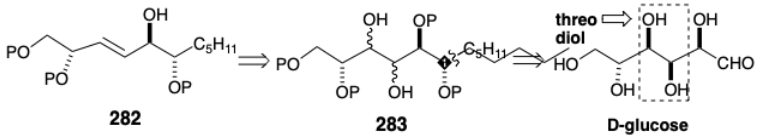
The abundant functional (oxygen on every carbon) and stereochemical information present in sugars suggests an even more ambitious synthesis of prostaglandins: incorporation of several sugar-related centers of chirality from a sugar starting material with a sugar-related hydroxyl at the incipient 10 position of $PGF_{2\alpha}$. Thus, polar disconnection of $PGF_{2\alpha}$ with the boundary condition of uncovering a sugar-derived homochiral segment suggests a precursor **274** in which the target related polar reactivity implied by the hydroxyl at the 9-position in $PGF_{2\alpha}$ must be inverted (PRI), e.g., as a nitrile-stabilized carbanion derived from an aldehyde cyanohydrin. Generalized representations **275** of **274**, especially the Fischer projection **275c** emphasize structural similarities with D-sugar precursors.



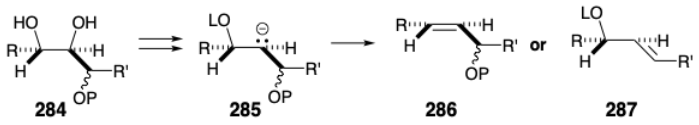
The necessity of deprotonating a cyanohydrin ether to generate **274** suggests replacement of the terminal carboxyl with a less reactive latent equivalent functional group such as an ether in **276** that also incorporates an ester as precursor for the cyanohydrin at the incipient 9-position with a view toward further polar disconnection of **276** to **278** is suggested by polar analysis which also reveals the possibility of disconnecting **278** to a methyl acetate nucleophile, or a malonic ester carbanion in which the added ester group serves as a reactivity control element (CEA), and a sugar derived electrophile **279**. The required stereochemistry at the incipient 12-position in **278** would be generated by stereospecific inversion during the nucleophilic substitution of an oxygen electrofuge by a carbanion. This strategy may be derailed by an alternative possible S_N2' nucleophilic substitution of the allylic nucleofuge in **2 7 9** . An alternative dislocation of subtarget **278** avoids this ambiguity. The sigma bond between incipient carbons 8 and 12 in **278** might replace a sigma bond between the incipient ester carbonyl oxygen and carbon 14 by a process involving allylic rearrangement of two π-bonds and a σ-bond in a precursor **280** by a cyclic three electron pair-shift. Such bond reorganizations, known generally as a **[3.3] sigmatropic rearrangements**, involve a temporary bridge in the transition state that, for the **280** to **278**, conversion might be expected to adopt a chair-like conformation (SEC) as in **281**. The rearrangement consequently involves predictable *transfer of chirality* from the migration origin at position 14 in **280** to the migration terminus at position 12 in **278**. The driving force for sigmatropic rearrangements is a net increase in thermodynamic stability.



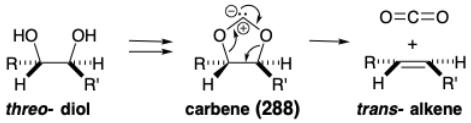
For the **280** to **278** conversion, an enol ester-Claisen rearrangement, this energetic advantage accrues from the generation of a C=O bond at the expense of a C=C bond. The ketene acetal **280** is a derivative of the allylic alcohol **282**. A sugar-like progenitor **283** for **282** is suggested by **1,2-dioxidative addition**. Such an intermediate might, for example, be produced by nucleophilic addition of an n-pentyl nucleophile to D-glucose.



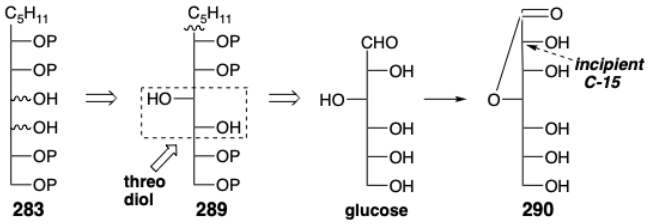
The conversion of diol **283** into *trans* alkene **282** must surmount several hurdles. Since the vicinal diol is surrounded by hydroxyl groups or derivatives of hydroxyl groups as in **284**, reductive cleavage generating an intermediate or transition state resembling carbanion **285** might lead to β-elimination of the wrong vicinal oxyanion producing **287** rather than **286**.



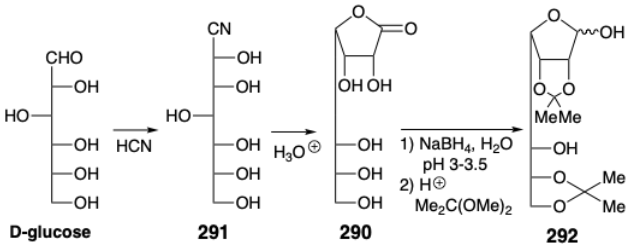
A more certain outcome can be assured by employing an alternative reaction, a concerted cycloelimination of carbon dioxide from a carbene-bridged derivative **288**, to generate the requisite *trans* alkene from a vicinal diol. Such a process involves the cyclic shift of three electron pairs -- two σ-bonds and a nonbonding electron pair on the carbene carbon -- and is driven by the creation of two C=O bonds. Since the cycloelimination is concerted, the carbene derivative generated from a *threo* diol necessarily fragments to a *trans* alkene while that derived from an *erythro* diol would fragment to give a *cis* alkene. Therefore, to be a precursor of a *trans* alkene, the intermediate **283** must incorporate a threo diol as in **289** and glucose.

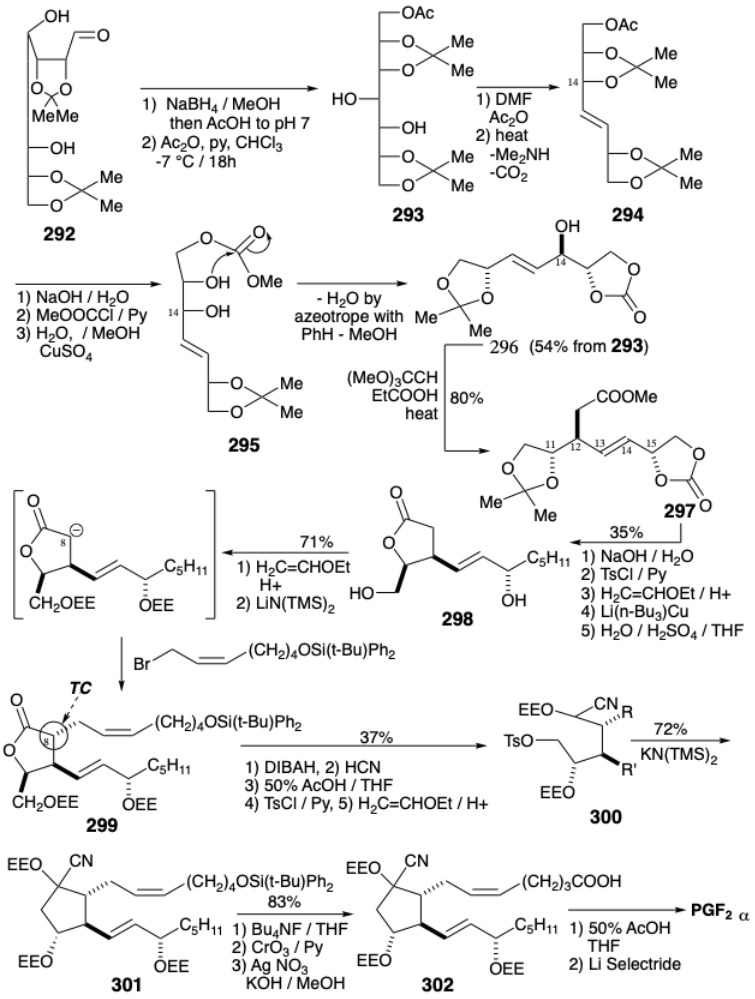


However, generation of **289** need not necessarily proceed directly from glucose by addition of an n-pentyl anion. In fact D-glycero-D-guloheptose (**290**), that can be prepared from glucose and incorporates the requisite configuration at the incipient position 15, is commercially available.



An enantiospecific synthesis of chiral nonracemic $PGF_{2\alpha}$ was executed that derives three centers of chirality from glucose.[22] Thus, glucose is chain extended by one carbon by addition of HCN. Acid-catalyzed hydrolysis and lactonization of the intermediate cyanohydrin **291** produces D-glycero-D-guloheptono-1,4-lactone (**290**). The hydroxyl groups in this intermediate must be differentiated to allow selective manipulation. Four hydroxyl groups can be masked by ketalization with acetone. Subsequent partial reduction of the lactone group delivers a lactol **292** that affords **293** upon further reduction and selective acetylation of a primary hydroxyl in the presence of two secondary hydroxyls. The *threo* diol array which remains unmasked in **293** may now be stereospecifically eliminated to generate a *trans* alkene.

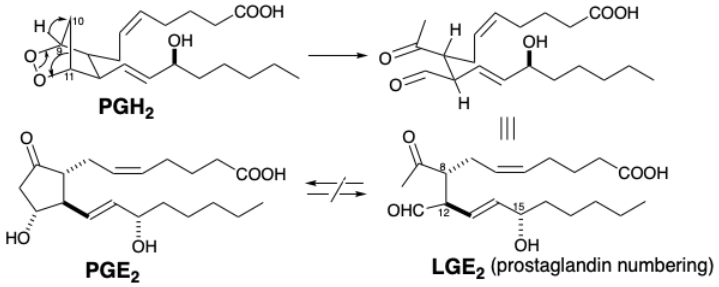




The requisite bridged carbene intermediate is generated by thermolysis of a dimethylformamide cyclic acetal derived from **293** in the presence of acetic anhydride. A concerted **cycloelimination** of this carbene then stereospecifically delivers the requisite *trans* alkene **294** in about 40% yield overall from **290**. The masked allylic hydroxyl at the incipient 14-position must now be selectively unmasked to set the stage for an ortho ester-Claisen rearrangement. But both this hydroxyl and its vicinal neighbor are masked in **294** by the same acetonide. To selectively capture its neighbor after removal of the acetonide, the acetate in **294** was initially converted into a methyl carbonate that then intramolecularly acylates the neighboring hydroxyl in **295**. One of two hydroxyls is thus protected by the temporary bridge of a carbonate. The remaining hydroxyl in **296** is then displaced with allylic rearrangement by a carbomethoxymethyl group. Thus, an orthoester Claisen reaction of **296** stereospecifically transfers the chirality of the hydroxyl substituted position 14 in **296** to a carbon substituted position 12 in **297**. This intermediate incorporates three of the five chiral centers as well as the 13,14-*trans* C=C bond of the target $PGF_{2\alpha}$. Appendage of the carboxylic side chain, after masking the hydroxyls as α-ethoxyethyl (EE) ethers, was achieved by allylation of an ester enolate delivering **299**. The stereochemistry at the incipient 8-position in **299** is a consequence thermodynamic control (TC) that favors a *trans* relationship between vicinal substituents on the five-membered lactone ring. Annulation of the cyclopentane ring required partial reduction of the lactone carbonyl, cyanohydrin formation, removal of the EE protecting groups, selective monotosylation of the primary hydroxyl and protection of the resulting triol as EE ethers. Finally treatment of **300** with base generated the corresponding nitrile stabilized carbanion which underwent intramolecular alkylation affording **301**. A carboxyl was then generated after removal of the silyl protecting group. Removal of the EE protecting groups from the carboxylic acid **302** delivered a cyanohydrin that was cleaved to the corresponding ketone and reduced stereoselectively *in situ* to produce $PGF_{2\alpha}$. This efficient interception of the ketone carbonyl is a noteworthy tactic. The carbonyl was reduced in order to avoid loss of the hydroxyl at position 11 by dehydration of the base sensitive PGE_2 intermediate.

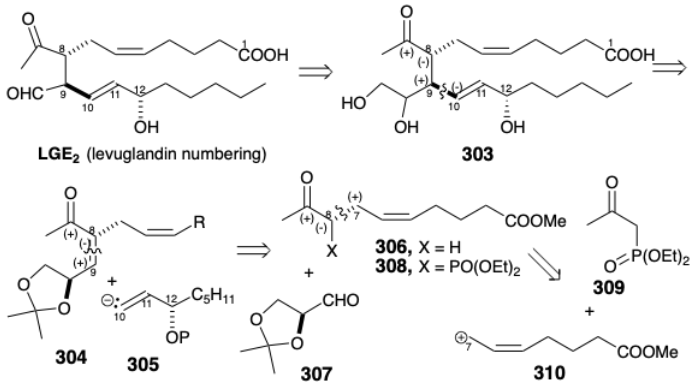
3.7: Levuglandins

Water-induced rearrangement of PGH_2 occurs rapidly under the conditions of its biosynthesis to generate PGE_2, PGD_2, and two seco-prosta-glandin levulinaldehyde derivatives known as levuglandins (see section 4.1). Thus, for example, intramolecular hydride migration from the 9 to the 10-position in PGH_2 accompanied by cleavage of the 10,11-C-C bond and the peroxide O-O bond generates levuglandin (LG) E_2. This levuglandin is formally related to PGE_2 by aldol condensation, although interconversion of PGE_2 with LGE_2 has never been observed.



Enantiocontrol with a Chiral Auxiliary

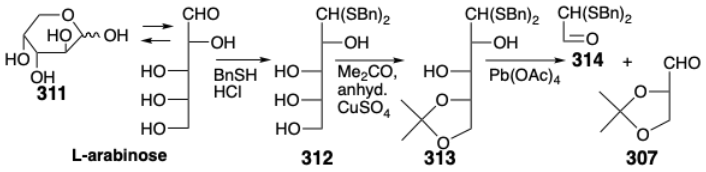
The availability of abundant supplies for biological testing and confirmation of the structure of LGE_2 depended on the development of an efficient asymmetric total synthesis. Another strategy for deriving asymmetry from chiral nonracemic natural starting materials is to use it as a chiral auxilliary (*vide infra*), as illustrated by a synthesis of LGE_2 from L-arabinose.[23] A dominant consideration in planning a total synthesis of LGE_2 is its proclivity toward dehydration, epimerization at positions 8 and 12 (prostaglandin numbering) and allylic rearrangement of the 14-15 (prostaglandin numbering) C=C bond into conjugation with the aldehyde carbonyl. Many of these difficulties are circumvented by replacing the aldehyde carbonyl with a latent equivalent, a vicinal diol as in **303**. Conversion of **303** into LGE_2 should be achievable under exceptionally mild conditions by oxidative cleavage with periodate. Stereocontrol is a more difficult challenge in the total synthesis of LGE_2 than it was for the total synthesis of PGE_2 since LGE_2 is acyclic and, therefore, more conformationally mobile than PGE_2 that has three of its four stereocenters arranged in the thermodynamically preferred all-*trans* configuration around a relatively rigid cyclopentanone ring.



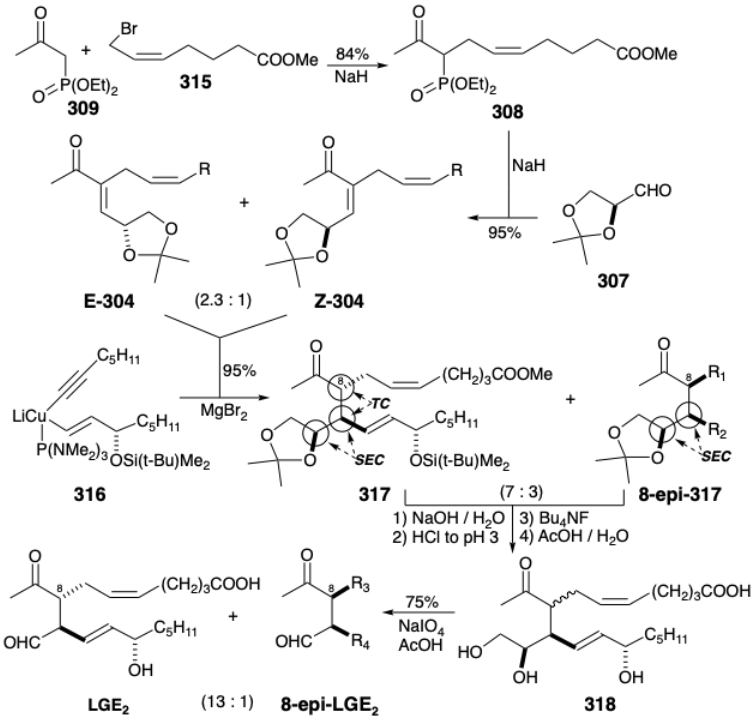
The tactic of using a vicinal diol as a latent aldehyde group apparently complicates rather than simplifies the synthetic target by adding a fourth stereocenter. On the contrary this additional center of chirality, that will not be incorporated in the final product, is the key to enantioselective generation of the correct absolute configuration at position 9 (levuglandin numbering). Furthermore, the correct configuration at position 8 should be available by epimerization of any 8-epi **303** that might be generated. Polar analysis of **303** suggests the possibility of exploiting electrophilicity at position 9 provided by the acetyl carbonyl as in **304** to allow polar bond formation with a chiral nonracemic nucleophilic vinyl synthon **305**. Most importantly, such conjugate additions are highly diastereoselective. The neighboring alkoxy substituent is expected to foster generation of only the requisite absolute confuguration at position 9 during 1,4-addition of a vinyl cuprate nucleophile to **304**. Further polar analysis of **304** suggests generation of this enone by aldol condensation of an enolate nucleophile with the aldehyde **307**, L-glyceraldehyde acetonide. This chiral nonracemic starting material is readily available from L-arabinose (*vide infra*). Because its chiral center provides enantiocontrol but is not incorporated into the final product, **307** said to serve as a **chiral auxiliary** (a chiral unit that is incorporated into an intermediate to bias the stereoselectivity of one or more subsequent reactions after which it is cleaved from the substrate or its chiral center is

removed). To activate enolate generation and control the regiochemistry of the aldol condensation, a diethylphosphono group is added to **306** as in **308.** Further exploitation of the polar activation afforded by the acetyl carbonyl and phosphono groups should allow construction of **308** by allylation of **309** with the upper sidechain electrophile **310**.

A synthesis of the chiral auxillary **307** from L-arabinose starts with interception of the acyclic aldose from its equilibrium with a pyranose form **311** by thioacetalization with benzylmercaptan. Selective ketalization of the resulting tetraol **312** delivers monoacetonide **313**. Oxidative cleavage of the latter then produces **307** in admixture with **314** from which it is readily separated by distillation.[24]



A short, highly stereocontrolled, asymmetric total synthesis of LGE2 was executed[23] from the commercially available 1-(diethylphosphono)-2-propan-one (**309**) that was allylated in good yield with bromoester **315**. The main side reaction was diallylation. Horner-Emmons olefination of L-glyceraldehyde acetonide (**307**) with the carbanion derived from **308** delivers in excellent yield a mixture of geometric isomers **E**-**304** and **Z**-**304** in a 2.3:1 ratio. It is unnecessary to separate this mixture because either isomer reacts stereoselectively (i. e. SEC) with cuprate **316** to deliver an identical 7:3 mixture of **317** and its 8-epi diastereomer in excellent yield. This key reaction proved refractory. Little or no 1,4-addition could be achieved until it was discovered that anhydrous $MgBr_2$ catalyzes the required reaction presumably by serving as a Lewis acid that enhances the electrophilicity of enone **304**. Again separation of isomeric products is unnecessary because saponification of either diastereomeric ester **317** or **8-epi**-**317** generates an identical 7:3 mixture of the corresponding carboxylic acids. This is apparently the equilibrium ratio.



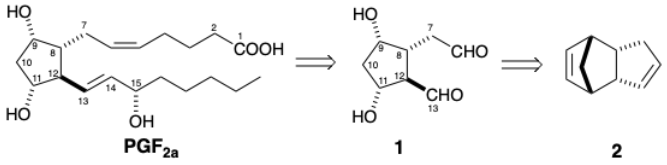
Most fortunately, separation of the diastereomeric acids was also unnecessary because either isomerically pure acid gave the same 13:1 mixture of LGE_2 and its 8-epi diastereomer upon desilylation followed by acid-catalyzed hydrolysis of the acetonide and finally periodate cleavage of the resulting vicinal diol. The favorable diastereoselectivity of the acid-catalyzed epimerization that accompanied the deketalization of the vicinal diol was entirely unexpected. The vicinal diol also plays an important role in this serendipitous process. Thus, epimerization occurs in **318** but not in LGE_2 or 8-epi-LGE_2 under these conditions for hydrolysis and oxidative cleavage.

3.8: Terminology

[3.3]sigmatropic rearrangement (3.6)
aerobic dehydrogenation (3.1)
anti-periplanar (3.4)
asymmetric induction (3.2)
β-hydroxy decanoyl-ACP dehydratase (3.1)
chiral auxiliary (3.7)
competitive substrate (3.6)
diastereomer (3.2)
enantioconvergent (3.6)
enantiomer (3.2)
enantioselective (3.6)
enoyl-CoA isomerase (3.1)
essential fatty acid (3.1)
Favorskii rearrangement (3.4)
internal electrophile (3.4)
internal nucleophile (electrophile) (3.4)
isoelectronic (3.4)
latent carbanion (3.1)
latent functional group (3.3)
masked functional group (3.3)
masking group (3.3)
mixed function oxygenase (3.1)
neighboring group effect (3.6)
pinacol rearrangement (3.4)
regiocontrol element (3.3)
resolution (3.2)
retro cycloaddition (RC) (3.3)
ring contraction strategy (3.4)
ring expansion strategy (3.4)
stereocontrol element (3.2)
stereoelectronic control (SEC) (3.3)
stereoselective (3.4)
stereospecific (3.4)
steric approach control (SAC) (3.4)
temporary bridge (3.4)
thermodynamic control (TC) (3.4)
unmasking (3.4)

3.9: Study Questions

1. Turner's synthesis of $PGF_{2\alpha}$ uses endo dicyclopentadiene (**2**) as starting material and generates an intermediate **1**.



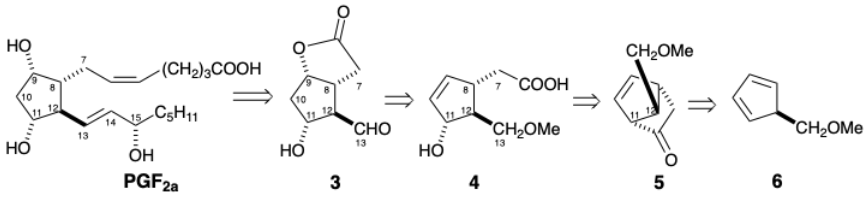
Use one or more of the following terms to answer each of the following questions: thermodynamic control, stereoelectronic control, steric approach control, or temporary bridge. How is stereocontrol achieved:

(a) at the 11 position relative to the 9 position in **1**?

(b) at the 8-position relative to the 9-position in **1**?

(c) at the 12-position relative to the 8-position in **1**?

2. Corey's second synthesis of $PGF_{2\alpha}$ exploited a lactone intermediate **3** that contains all of the cyclopentane ring stereochemical information present in $PGF_{2\alpha}$.



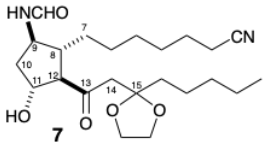
Use one or more of the following terms to answer each of the following questions: thermodynamic control, stereoelectronic control, steric approach control, or temporary bridge.

(a) Two factors favor the correct relative stereochemistry for the aldehyde substituent in **3** during its synthesis from **6** by way of **5** and **4**. What are these two stereocontrolling factors?

(b) How is stereocontrol achieved at the 9-position relative to the 8-position in **3**?

(c) How is stereocontrol achieved at the 11-position relative to the 8-position in **3**?

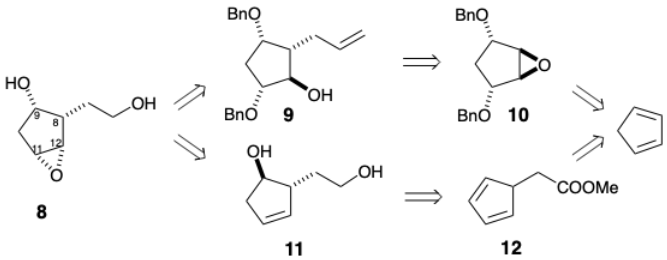
3. In Corey's first synthesis of PGE_1, he uses a substituted cyclohexene precursor that is suggested by a polar disconnection of the subtarget **7** and by his intention to use target-related functionality at the 15-position to stabilize a carbanion at that carbon during assembly of the lower side chain.



(a) What is the structure of Corey's cyclohexene intermediate in his synthesis of **7**?

(b) Why does Corey choose an *[Math Processing Error]* group in his cyclohexene intermediate to serve as a precursor of the *[Math Processing Error]* group in **7**?

4. Two syntheses of the $PGF_{2\alpha}$ precursor **8** were described as outlined in the following retrosynthetic analysis:

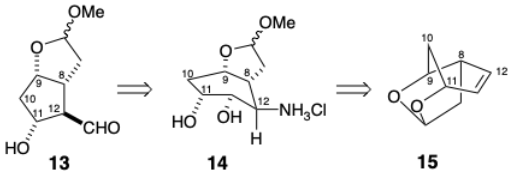


(a) Why was the **10** to **9** conversion **not** achieved enantioselectively?

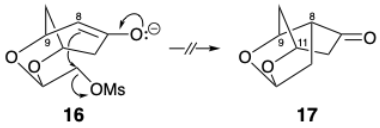
(b) How was the **12** to **11** conversion accomplished enantioselectively?

(c) What stereocontrolling factor is responsible for the configuration of the epoxy group relative to the other stereocenters in **8** when this epoxide is prepared from the alkene **11**?

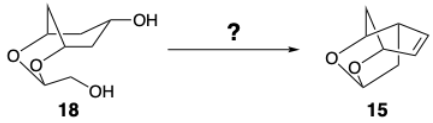
5. Woodward's $PGF_{2\alpha}$ synthesis generates the key intermediate **13**, that is similar to Corey's lactone **3**, by a ring contraction of **14**.



(a) In an attempt at preparing the precursor **15** of **14** by intramolecular alkylation of enolate **16**, the desired ketone **17** was not obtained. Why?



(b) Woodward achieved the synthesis of **15** from **18** by a multistep sequence that began with a polar process closely related to the **16** to **17** reaction. How did he accomplish the **18** to **15** conversion?



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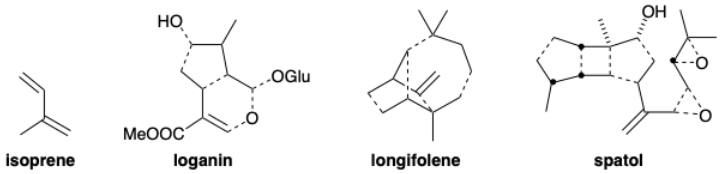
CHAPTER OVERVIEW

4: Terpenes

A trivial pattern characterizes the structures of fatty acids: their carbon skeletons generally have even numbers of carbons. This is a consequence of their biosynthetic origins. They are oligomers of the two-carbon building block, acetyl CoA. Terpenes are a structurally and functionally diverse family of natural products. Nevertheless, a pattern that characterizes their structures is often discernible. They appear to be oligomers of isoprene. In the ensuing discussion, for clarity, we occasionally will represent bonds that that are not in these isoprene units with dashed lines as in the following examples.

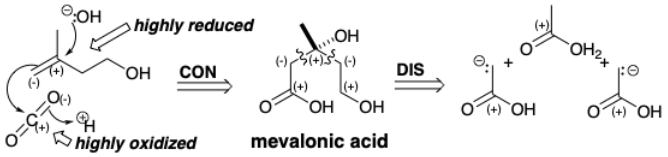


isoprene **loganin** **longifolene** **spatol**

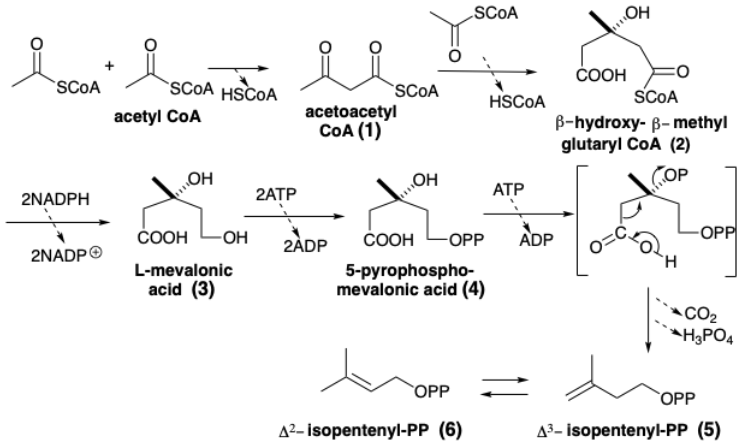
The biosynthesis of some terpenes involves such intricate carbon skeletal transmogrifications that the terpenoid biosynthetic origin is not at all obvious. Moreover, the intricate multicyclic skeletons of some terpenes are devoid of functionality. For such molecules, polar reactivity analysis is of little value. Instead, it is the topology of these molecules that must be analyzed in order to perceive potentially effective dislocations to generate precursors, and ultimately, to identify starting materials.

4.1: Biosynthesis of Monoterpenes - Loganin

Terpenes have a large variety of carbon skeletons characterized by branched chains, and often complex multicyclic ring systems. They are oligomers of the biological **isoprene unit**, Δ^3-isopentenol, which is a relatively reduced hydrocarbon comprised of five carbons. It is produced in nature from three molecules of a relatively oxidized two carbon starting material, acetic acid in the form of acetyl CoA. A likely candidate for the byproduct containing the carbon atom lost from three molecules of acetic acid during the biosynthesis of Δ^3-isopentenol is carbon dioxide. Polar analysis suggests a more highly oxidized precursor, mevalonic acid, that could be decarboxylated by polar fragmentation of a CO_2 electrofuge and a hydroxide nucleofuge. Such a fragmentation can benefit from the thermodynamic advantage of generating a C=O bond and produces easily disposable highly oxidized byproducts, CO_2 and water. Further retrosynthetic analysis of **mevalonic acid** suggests polar disconnection to two acetic acid carbanion synthons which would condense with an acetyl electrophile.

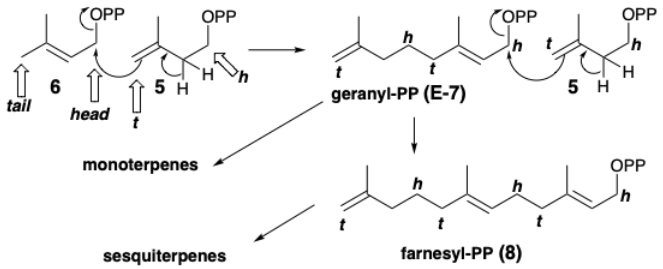


A very large variety of lipids are derived in nature from the oligomerization of Δ^3-isopentenyl pyrophosphate (**5**). This five carbon biosynthetic building block is produced by condensation of three molecules of acetyl CoA. Acetoacetyl CoA (**1**), produced by Claisen condensation of two molecules of acetyl CoA, reacts at the ketone carbonyl with a second equivalent of acetyl CoA as nucleophile. This condensation is enantioselective. The asymmetry of the enzyme, **hydroxymethylglutaryl CoA** synthetase, directs the attack of the acetyl CoA nucleophile to one side of the prochiral acetoacetyl CoA electrophile. The product is symmetrical. Nevertheless, the condensation is accompanied by the enantioselective hydrolysis of the CoA-SH ester derived from the acetyl group. The monothioester **2** is then reduced by hydride attack at the more electrophilic thioester carbonyl to give L-mevalonic acid (**3**). Phosphorylation of **3** leads, via a 5-monophosphate and 5-pyrophosphate, to an unstable intermediate phosphorylated at the C- 3 hydroxyl. This tertiary phosphate readily undergoes **decarboxylative elimination** to give Δ^3-isopentenyl pyrophosphate that readily isomerizes to Δ^2-isopentylpyrophosphate.

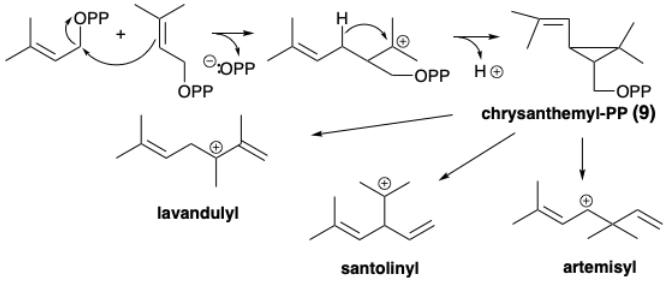


A **head to tail dimer**, geranyl pyrophosphate (**E-7**), is formed by addition of the allylic electrophile **6** to the terminal olefin **5** accompanied by proton loss. The resulting ten carbon allylic pyrophosphate **E-7** readily alkylates a second molecule of **5** to give a trimer, the fifteen carbon allylic pyrophosphate farnesyl pyrophosphate (**E-8**). The **monoterpenes** are C10 compounds biogenetically derived from geranyl pyrophosphate (**E-7**), its Z-isomer neryl pyrophosphate (**Z-7**), or from a cyclopropyl dimer, chrysanthemyl pyrophosphate (**9**), that is formed directly from two molecules of Δ^2-isopentenyl pyrophosphate. Isoprene units are often discernable embeded in the skeletons of terpenes. However, some terpenes, e.g. derivatives of the santolinyl cation, are not composed entirely of intact isoprene units owing to rearrangements during their biosynthesis (*vide infra*). These are called **irregular terpenes**.

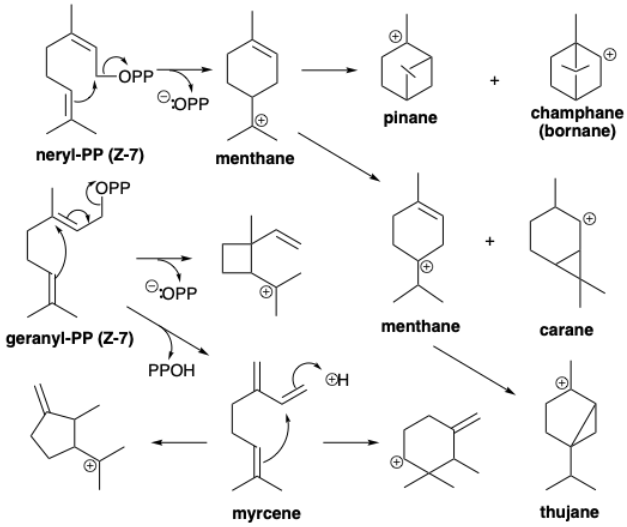
Head to Tail Oligomerization of Isopentenyl Pyrophosphates



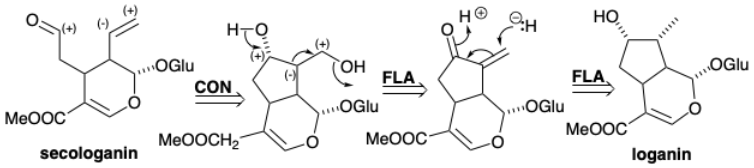
Non Head to Tail Dimerizations of Isopentenyl Pyrophosphates



Intramolecular nucleophilic attack by a C=C π-bond on the electrophilic pyrophosphate generates various isomeric carbocationic intermediates such as menthane, pinane, carane, camphane, or thujane carbenium ions.

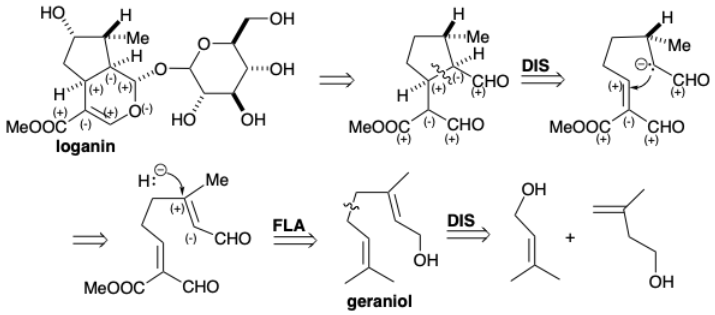


The monoterpene loganin is the biosynthetic precursor of secologanin, a natural product whose terpenoid origin is unobvious. Secologanin, whose isoprene units are not intact, is derived biosynthetically by a polar cleavage of the cyclopentane ring of loganin exploiting the polar activation afforded by the cyclo pentane hydroxyl substituent.

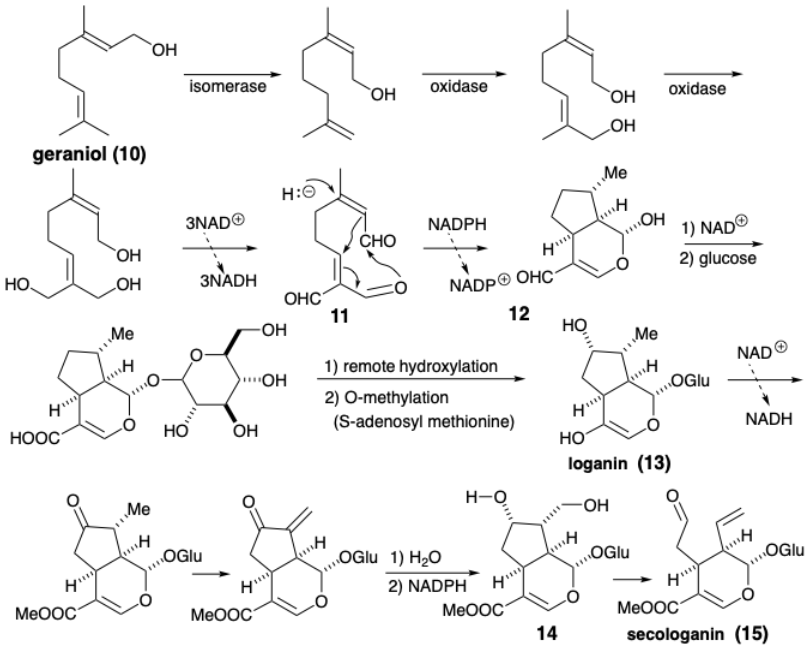


Polar analysis of loganin shows that the hydroxyl substituent is not essential for facilitating generation of the cyclopentane ring by a polar C-C bond formation since adequate functionality is located in the proximity of the key bond. In the biosynthesis of loganin, this hydroxyl group is introduced at the end of the synthesis by a remote oxidation. The dihydropyran is simply a derivative of a 1,5-dialdehyde whose structure is simplified by polar disconnection of a ring C-C bond located between two consonant functional groups. This dislocation represents a retro Michael addition. The requisite nucleophile could be generated by deprotonation of a

saturated precursor. An alternative precursor for this nucleophile, the one involved in the biosynthesis, is an unsaturated aldehyde. Thus, conjugate addition of hydride to an a,b-unsaturated aldehyde provides the nucleophile which will be Michael alkylated. The highly oxidized cyclization substrate is derived from geraniol by multiple allylic oxidations, and geraniol is a dimer of two isopentenol precursors, Δ^2 and Δ^3-isopentenol.

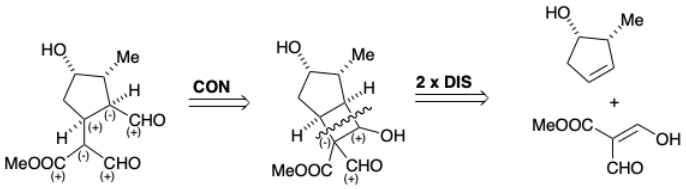


Loganin (**13**), the **glucoside** (a mixed acetal of glucose and an alcohol) of a monoterpene, is a key intermediate, which affords secologanin (**14**), the immediate precursor of the non-tryptamine portion of the corynanthe, aspidosperma, iboga, ipecacuanha and cinchona groups of indole alkoloids (see chapter 7). Loganin is produced from geraniol (**10**), which is first oxidized to a trialdehyde (**11**). Reductive cyclization of **11** to **12** is followed by further oxidations. Hydroxy loganin (**14**) gives secologanin (**15**) by a retro-Prins cleavage. The origin of secologanin from isoprenoid precursors is not immediately obvious from a cursory examination of its structure.

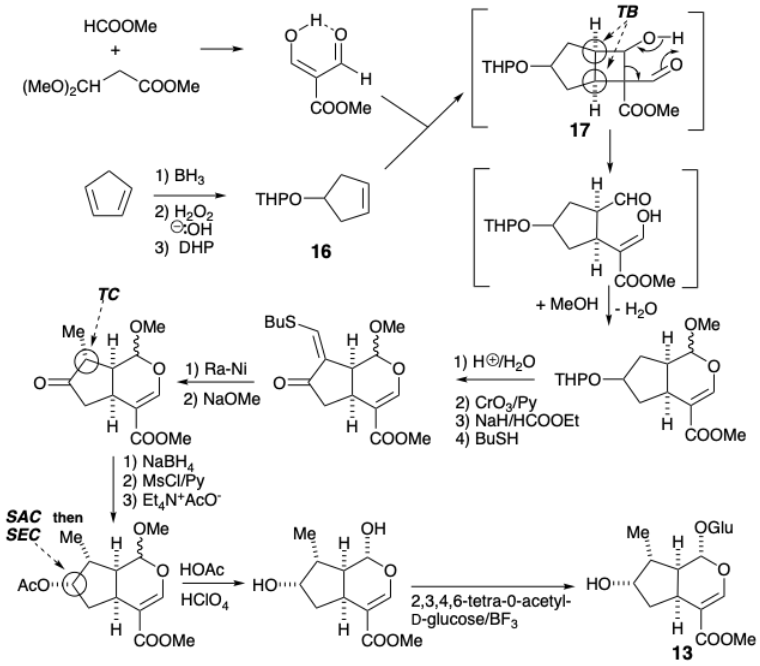


4.2: Syntheses of Loganin

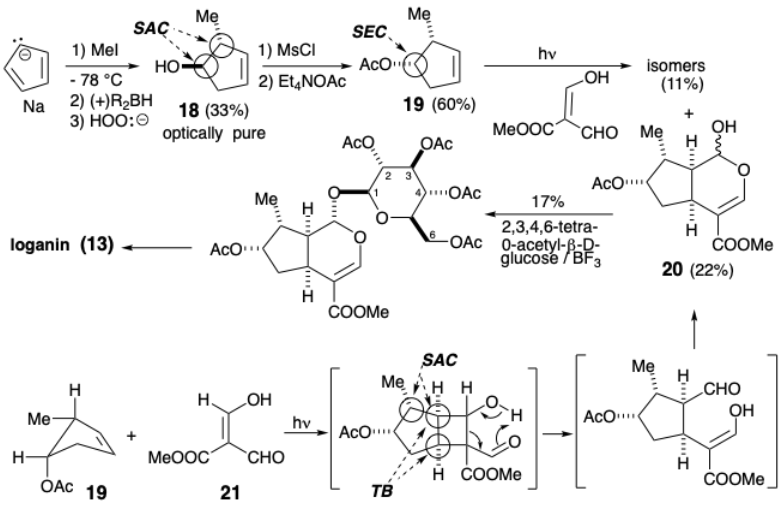
Total syntheses of loganin, that invole polar connection as the first step in the retrosynthetic analysis, have been described. Thus, dislocation of the monocyclic target to a bicyclic target recognizes the potential of retroaldol cleavage of a cyclobutane ring for generation of the required vicinal cis relationship of the malonyl and carboxaldehyde substituents of the target. The cyclobutane can be generated in a two bond-forming cycloaddition process, which, owing to the strain expected for the alternative trans-fused bicyclic product, can be expected to favor the required cis-fused bicyclic intermediate.



Loganin was synthesized in the laboratory by an ingenious scheme involving photochemical cycloaddition to a preformed symmetrical cyclopentene synthon **16**.[1] The desired cis ring fusion is assured by a temporary bridge in the intermediate **17**.



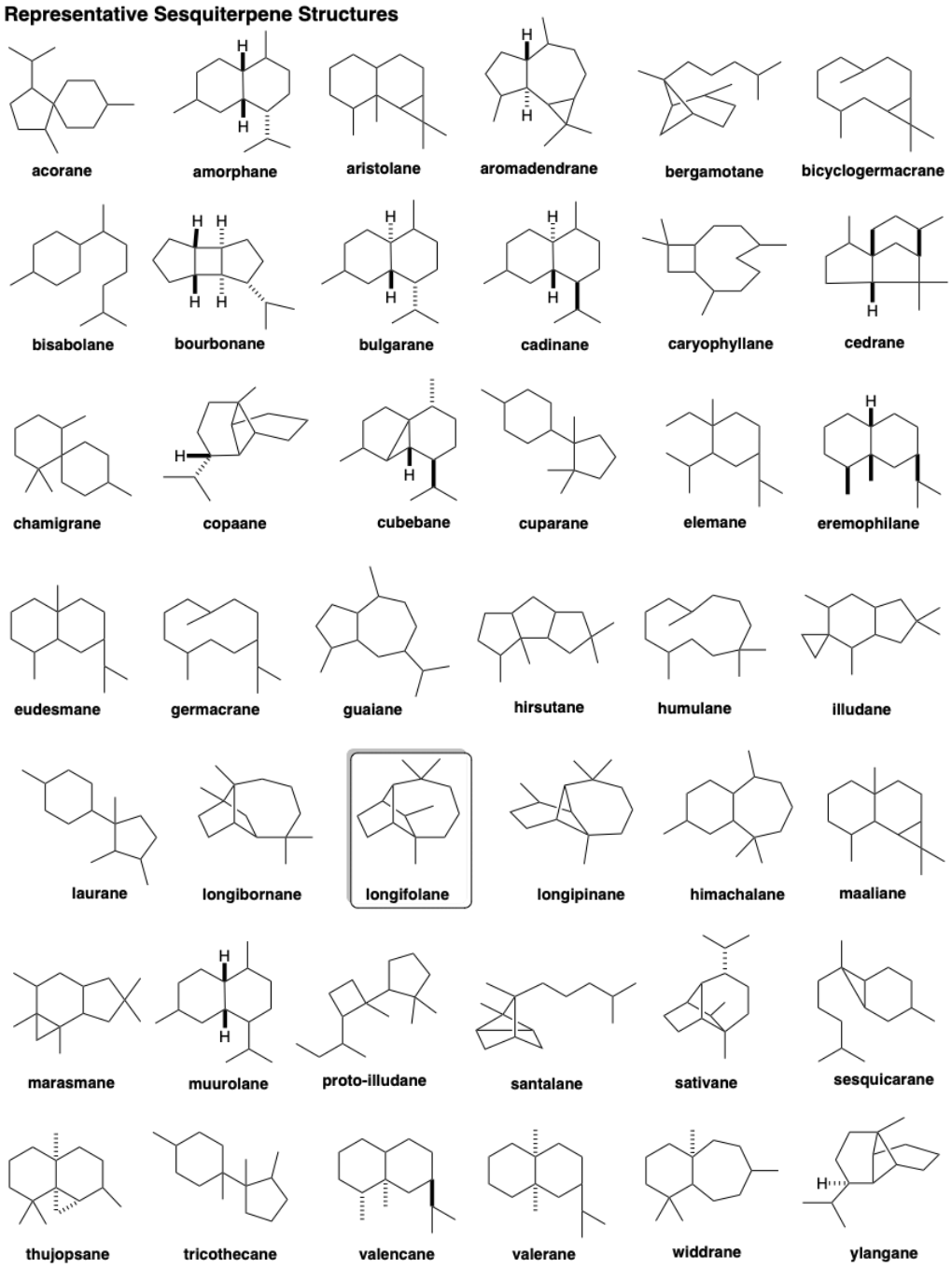
An asymmetric total synthesis of loganin was achieved[2] by an overall strategy for skeletal construction which is similar to, although shorter than, the previous approach. The asymmetric intermediate **18** was produced in high optical purity (at least 98%) by hydroboration of the prochiral symmetrical substrate, 5-methyl-cyclopentadiene, with (+)- or (-)-di-e-pinanylborane.



Since this involves stereospecific addition of the borane to the least hindered face of **18**, the configuration at the carbinol carbon had to be inverted during the preparation of the acetate **19**. The regioselective formation of the isomer **20** results from the steric approach control during the photoannealation. The enol (**21**) attacks the less hindered face of **19**.

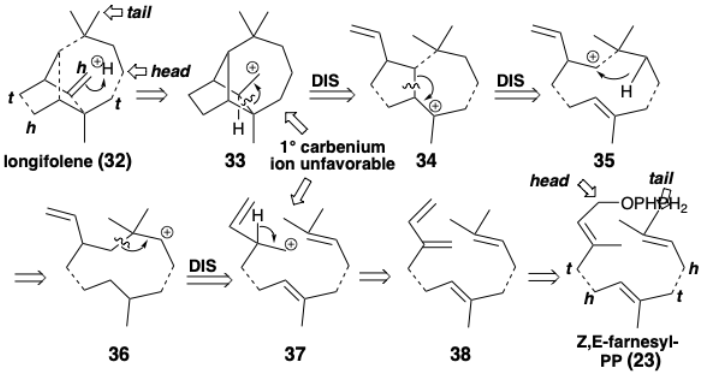
4.3: Biosynthesis of Sesquiterpenes - Longifolene

The sesquiterpenes are C15 compounds derived biogenetically from E,E-farnesyl-PP (**8**), the allylic isomer nerolidyl-PP (**22**), or the geometric isomer Z,E-farnesyl-PP (**23**). Nucleophilic attack by a C=C π-bond on the electrophilic pyrophosphate generates various isomeric cationic intermediates such as **24**-**31** which undergo proton loss, nucleophilic capture by external nucleophiles (especially water) or by another C=C π-bond to generate a wide variety of carbon networks.

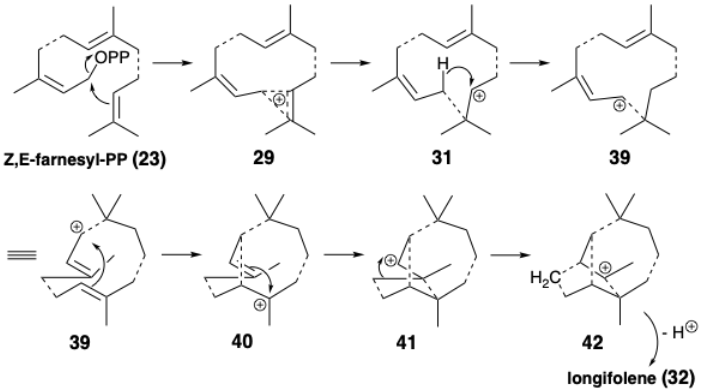


Retrosynthetic analysis of the biosynthesis of the sesquiterpene longifolene (**32**) is channeled by the boundary condition that the starting material most probably is a head-to-tail-head-to-tail trimer of isopentenyl pyrophosphates. The longifolene skeleton is an intricate network of carbon. The analysis must simplify the tricyclic topology by disconnections which generate or lead to an acyclic precursor such as Z,E-farnesyl-PP (**23**). Three isoprene units are clearly discernable embeded in the skeleton of longifolene. Unmasking of the acyclic trimeric starting material requires disconnection of some bonds between these isoprene units. A series of

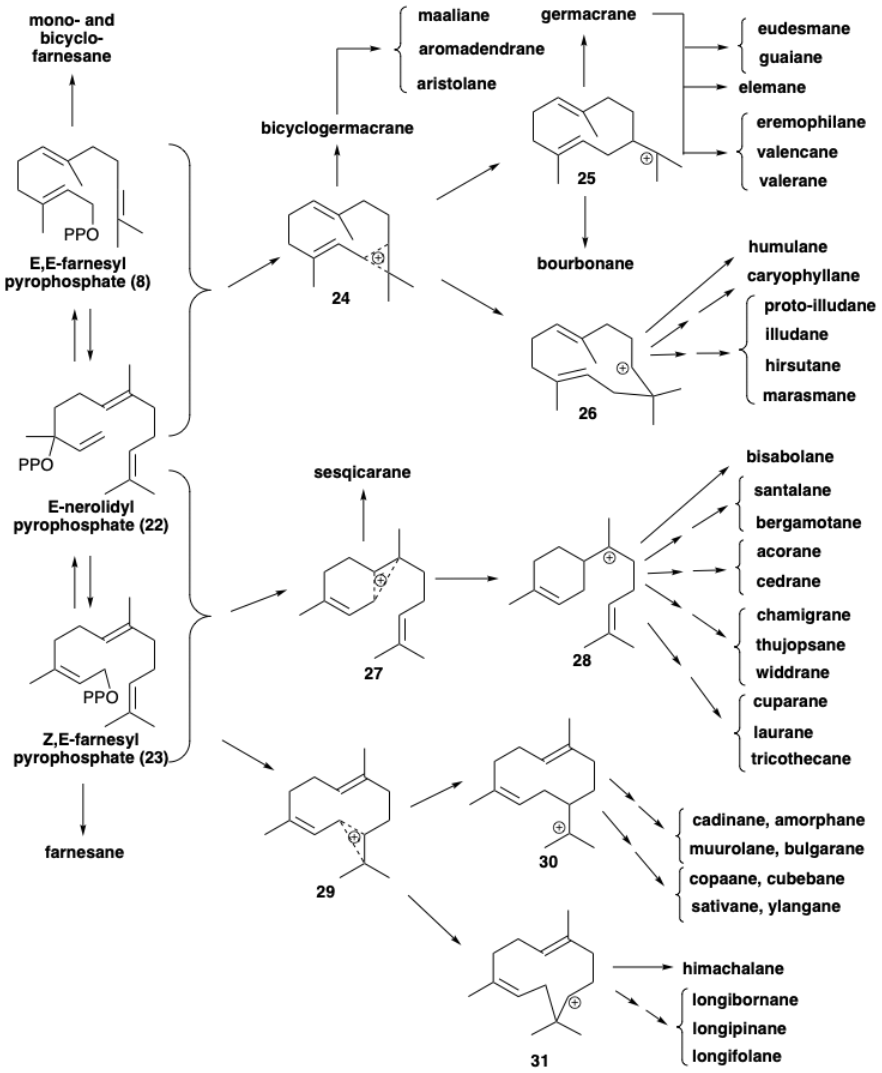
disconnections of C=C π-bond nucleophiles from carbocationic electrophiles can be achieved by proton addition to **32** to give **33**. Retropolyene cyclization of **33** disconnecting a nonisoprenoid bond suggests the precursor **34**. Similar disconnection of this carbocationic intermediate suggests a precursor **35**, but further disconnection of nonisoprenoid bonds cannot proceed from this carbocationic precursor. Therefore, hydride migration producing an isomeric carbocation must follow the cyclization that generates the carbon skeleton of **35**. The isomeric carbocation **36**, on the other hand, can be generated by addition of a carbon electrophile to a C=C bond in **37** which has the carbon skeleton of a head-to-tail-head-to-tail isoprenoid trimer. Intermediate **37** could be generated from Z,E- farnesyl-PP (**23**) by elimination of pyrophosphoric acid and subsequent addition of a proton to an intermediate tetraene **38**.



The actual biosynthetic strategy for longifolene (**1**) is similar to that inferred above but avoids generating relatively unstable 1° carbenium ions such as **33** or **37** by exploiting a skeletal rearrangement step. Such carbenium ion rearrangements are a common occurrence during the biological construction of carbon networks, particularly those of many terpenes. Addition of the allylic electrophile to a nucleophilic trisubstituted C=C π-bond in **23** generates **29** or **31** that can rearrange to a more stable 2° allylic carbenium ion **39** by 1,3-hydride shift. Cationic polyene cyclization then delivers a bicyclic 3° carbocation **40** and then tricyclic 2° carbocation **41** that undergoes [1.2] sigmatropic rearrangement of carbon, a Wagner-Meerwein rearrangement, to produce a more stable 3° carbocation **43** with the longifolane skeleton. The **41** to **42** rearrangement is readily reversible (*vide infra*). Deprotonation of **42** delivers longifolene.



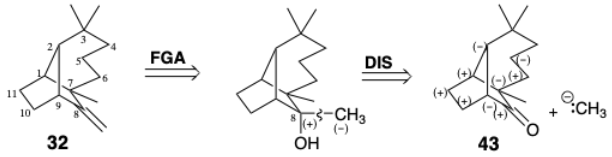
The biosyntheses of all the multicyclic sesquiterpenes involve similar carbocationic polyene cyclizations. Channeling the cyclization to specific structures is undoubtedly influenced by the folding of the acyclic pyrophosphate substrate by various protein catalysts (enzymes) promote the reactions and also limit the access of water to the carbocationic intermediates. Otherwise, the carbocationic intermediates would be captured by water to produce various alcohols resulting from interception of the numerous intermediates. It is also possible that folding causes juxtapositions of p-bonds that favor a concerted formation of several sigma bonds without the generation of numerous discrete carbocationic intermediates such as those shown in the above scheme for the biosynthesis of longifolene.



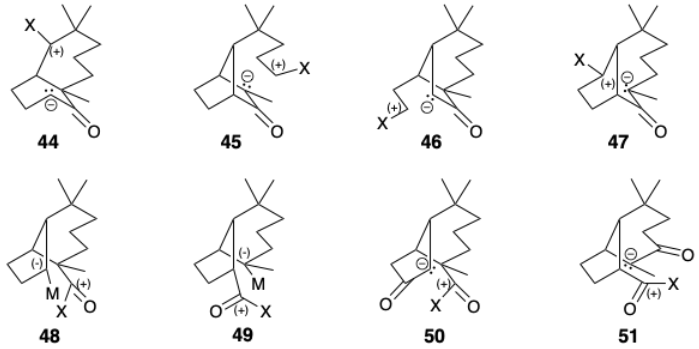
4.4: Syntheses of Longifolene

Polar Analysis of Functionalized Precursors

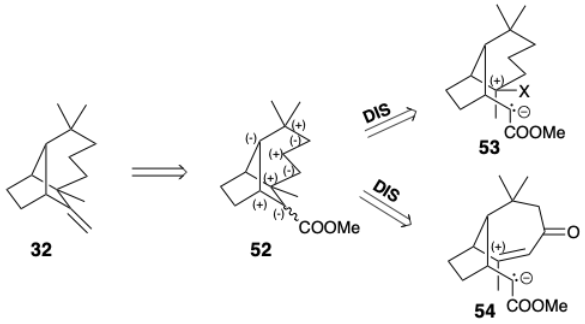
Polar reactivity analysis is not very helpful for dislocaton of longifolene because it has no polar functionality. However, functionalized precursors are suggested by considering possible syntheses of the exocyclic methylene. Thus, an alcohol could produce **32** by dehydration, and the alcohol could arise by addition of a methyl nucleophile to ketone **43**.



For a *direct* polar C-C connective synthesis of **43**, any additional polar activating functionality in a precursor must be lost during C-C bond formation. Thus, **44**-**47**, precursors for a direct synthesis of **43**, result from the four possible disconnections that exploit the potential nucleophilicity of carbon a to a carbonyl, whereas **48** and **49** result from the two possible disconnections that exploit the electrophilicity of a carbonyl carbon. However, it may be advantageous to use an indirect strategy, one that incorporate additional functionality in the penultimate intermediates of skeletal construction (eq. **50** or **51**).



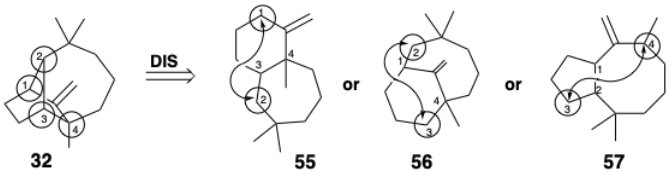
That functionality must then be removed after the completion of the carbon network. For example, because the exocyclic methylene of **32** might reasonably be derived from an ester **52**, another set of intermediates that has a different reactivity pattern than the first set may be generated by polar reactivity analysis (e.g. **53** and **54**). A great many additional precursors may be generated by considering dislocations involving additional activating groups or unsaturation.



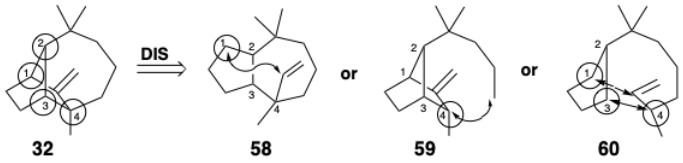
Topological Analysis

For molecules like **32**, that have minimal functionality and complex skeletons, another approach has been suggested for identifying useful dislocations. Thus, attention is first directed to "an exhaustive analysis of the *topological properties of the carbon network* to define the range of possible precursors...from which the desired skeleton can be produced by the establishment of one or two connecting bonds."[3] Possible reactions, appropriate activating functionality, etc., are only considered after the topological analysis**.**

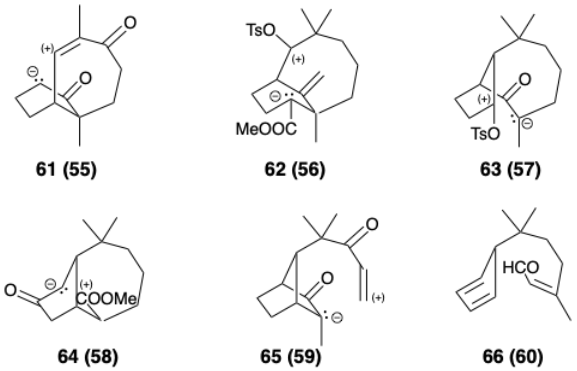
In many cases, the most synthetically useful dislocations result from removing one bond between ring-member atoms, called **common atoms**, that are bonded to three or four other ring members (but not two). For longifolene (**32**), in which the common atoms are numbered 1-4, this generates three topologically simplified structures **55**-**57**.



Another useful series is generated by removing one bond between a common atom and a noncommon atom. Two members of this series are **58** and **59**. Since some reactions generate two new bonds, e.g. Diels-Alder cycloaddition, structures generated by removing two bonds of the original network **32**, especially which join two adjacent atoms to one or more common atoms as in **60**, should be considered. However, intermediates suggested by dislocations involving removal of a bond between noncommon atoms cannot be disregarded *a priori*.



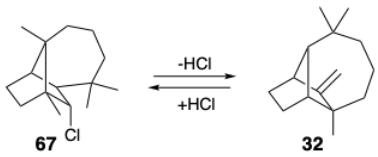
After the topological analysis, specific reactions and appropriate functionality to permit bond formation are considered. The process is repeated until a series of potential precursors is generated for each penultimate intermediate and so on until the synthetic tree is complete. ***As functionality is added to intermediates, topological analysis becomes less relevant. "Maximum utilization of (sub)target-related functionality"*** (see section 1.2)***, and hence polar reactivity analysis*** (see section 1.4)***, becomes a major factor in synthetic planning.*** Compounds **61-66** are possible functionalized derivatives corresponding to structures **55-60**, respectively.



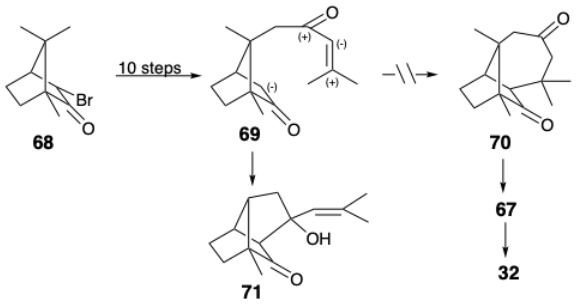
At some point, a choice between a broad range of possibilities is made. It must necessarily be "very much a function of the methodology of synthetic chemistry available at the time, of certain practical considerations such as the availability of the necessary materials and reagents, and of certain subjective judgments relating to the feasibility of key reactions or the existence of alternatives."[3]

Fatally Flawed Strategies

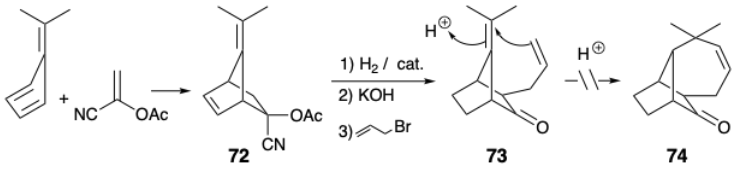
To illustrate the pitfalls of designing a complex molecular synthesis, we will first consider some unsuccessful strategies for the synthesis of longifolene. One strategy[4] was based on the interconvertibility by rearrangement of longifolene (**32**) and its hydrochloride **67**.



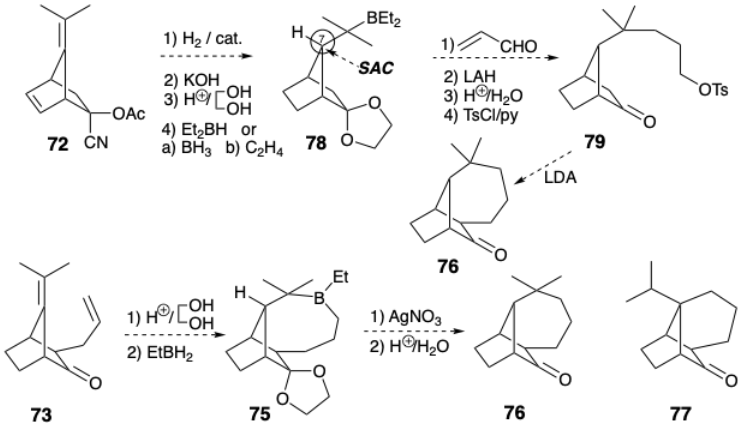
An intermediate **69**, related to **65**, was prepared in ten steps from D-α-bromocamphor (**68**), that is readily available from a natural product. However, **69** gave aldol product **71** rather than the desired product **70** under Michael reaction conditions. Thus, the ready availability of the starting material notwithstanding, the ambident electrophilicity of the enone moiety in **69** derailed the synthetic plan.



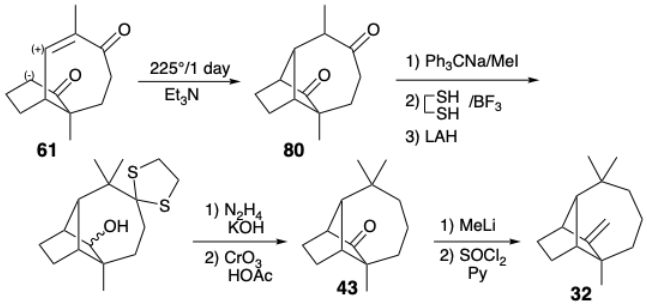
Removal of a bond between two noncommon atoms in the first dislocation from **32** led to consideration of the potential intermediate **73** for the synthesis of longifolene.[5] This route is especially attractive since **73** is easily prepared in a few steps from readily available starting materials. The key cyclization of **73** to **74** failed upon treatment of **73** with acids.



Other modes of cyclization should be examined, such as **73** → **75** → **76**. But preferential initial hydroboration of the monosubstituted C=C bond will preclude the required orientation for the addition to the tetrasubstituted C=C bond and lead to **77**. Alternatively, an intermediate **79**, related to **65**, may be available from the Diels-Alder adduct **72** and may undergo intramolecular alkylation delivering **76**. Steric approach control should favor the requisite stereochemistry at position 7 in **78**.

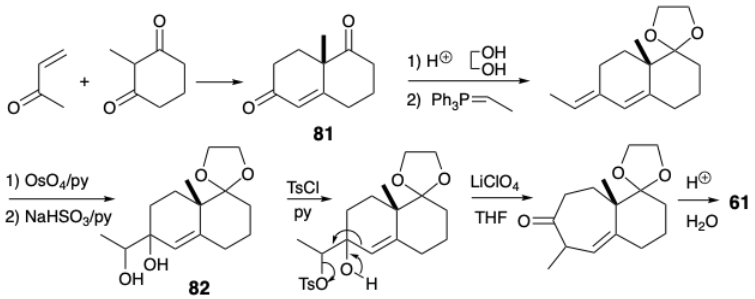


The first successful synthesis of longifolene (**32**) involves the key cyclization **61** → **80** as the last step of skeletal construction.[3] Incidentally, **61** is suggested not only by topological considerations (i.e. structure **55**), but also by polar reactivity analysis (i.e. structure **44**). After much experimentation, only a 10-20% yield could be achieved in this crucial step. Conversion of **80** to **32** then involved final addition of a methyl and methylene group and removal of the carbonyl groups.



The synthesis of the key intermediate **61** illustrates a strategy that is useful for carbon skeletal construction, namely **ring size modification** (**RSM).** Thus, **61** was prepared from the readily available Wieland-Miescher ketone (**81**) by expansion of a six to a

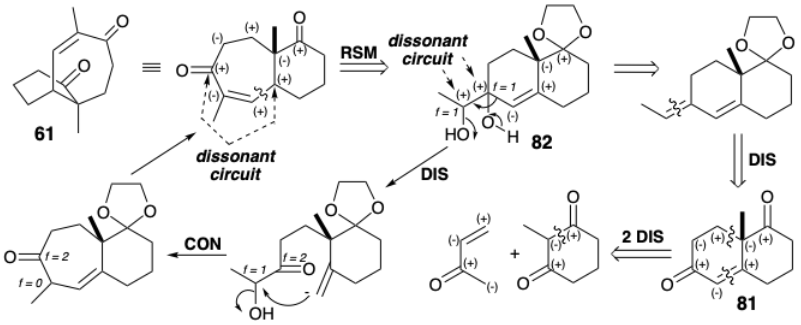
seven membered ring. The selective ketalization of the saturated carbonyl group in **81** is possible owing to deactivation of the unsaturated carbonyl by the adjacent π-electron system.



Exposure of diol **82** to the usual acidic conditions for pinacol-pinacolone rearrangement would result in ionization of the tertiary allylic alcohol and produce an acetyldecalin derivative. It was, therefore, necessary to devise a modified procedure to direct the rearrangement of the diol **82** along the desired pathway by facilitating ionization of the secondary hydroxyl. Therefore, the secondary hydroxyl was selectively tosylated. Ionization of the labile tosylate leaving group was accompanied by migration of the vinyl group. The saturated carbon chain is less prone to migrate than the unsaturated one because p- electron participation is possible in the latter but not the former rearrangement.

The Ring Size Modification Tactic

The logic of a synthetic route can be used as *a tool* for devising a strategy or, *ex post facto*, as *a framework* to achieve a fundamental understanding of a known synthesis. The decision to employ ring size modification in the above synthesis of **61** is a *logical consequence* of topolgical and polar analysis of this target. *Topological analysis* suggests disconnection of the bicyclic ring system at bonds to the bridgehead carbons which are *common atoms*. Double disconnection of the seven-membered ring suggests a symmetrical precursor, a 2-substituted 2-methylcyclohexan-1,3-dione. *Polar analysis* reveals the possibility of a polar annealation for construction of the cyclohexandione that exploits the activation provided by two consonant carbonyl groups. However, one of the desired disconnections of **61** lies on a dissonant circuit. Removal of one atom of this dissonant circuit (ring contraction) produces a consonant circuit in **82** and the possibility of skeletal construction by polar annelation; i.e the Robinson annelation producing **81**.

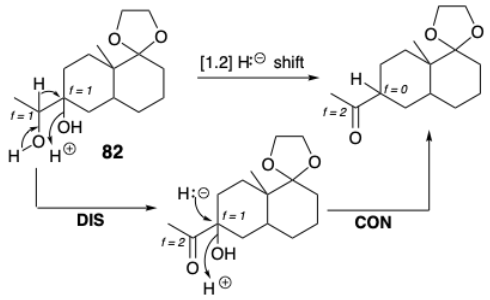


It is important to note that a dissonant circuit in **61** is produced from a dissonant precursor **82.** Also, as noted in the previous chapter (see section 3.4), the ring expanding rearrangement of **82** is equivalent to a *hypothetical* two stage dislocation of the target, disconnection followed by connection. It is also instructive to note the changes in *f*s that accompany the **82** → **61** rearrangement. Polar disconnection raises *f* (from +1 to +2) for the electrophilic center undergoing polar disconnection from **82** and lowers *f* (from +1 to 0) for the electrophilic center undergoing polar connection. The requisite polar reactivity dissonance is created by a *nonpolar* reaction, oxidative vicinal hydroxylation of an alkene (dioxidative addition). This alkene is obviously derivable from dione **81** by selective Wittig olefination. **81** is entirely consonant. It can be constructed by polar reactions from 2-methylcyclohexan-1,3-dione and methyl vinyl ketone. Had the Robinson annelation process and Wieland-Miescher ketone (**81**) not been known, the above retrosynthetic analysis would have led to their invention.

Check for Flaws

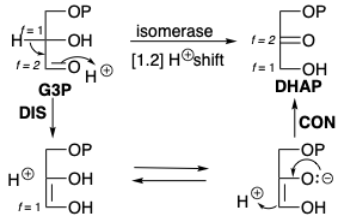
Having devised the above strategy, it is mandatory to apply step 4 of the "Protocol for Synthetic Design" outlined on page 23. We must *examine the strategy for possible flaws*. In fact, polar rearrangment of **82** under acid catalysis is expected to follow an

alternative pathway involving hydride migration to a tertiary carbenium ion that would be formed more readily than the requisite secondary carbenium ion. Therefore, the strategy was modified to provide selective activation of the secondary hydroxyl. Thus, tosylation enhanced its nucleofugacity.

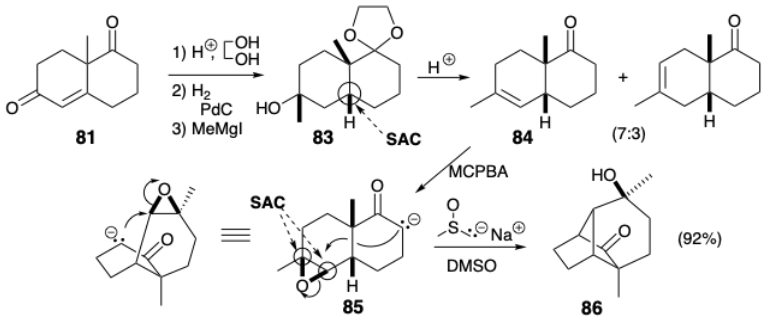


Also note that the concerted hydride migrating rearrangement is equivalent to a two stage dislocation of the target, disconnection followed by connection of $H^{\ominus}$. Furthermore, polar disconnection of hydride raises *f* (from +1 to +2) for the *electrophilic* carbon center undergoing polar disconnection (the migration origin) in **82** and lowers *f* (from +1 to 0) for the *electrophilic* carbon center undergoing polar connection (migration terminus).

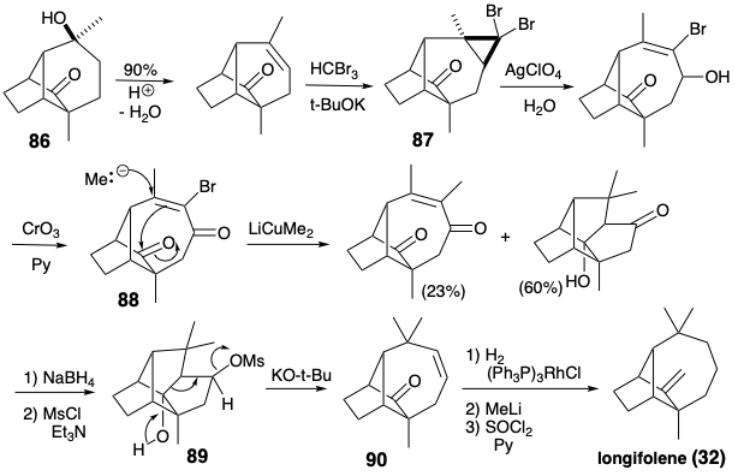
Similar changes in *f*s accompany polar rearrangements involving *nucleophilic* carbon at the migration origin and terminus as, for example, in the rearrangement of G3P to DHAP (see section 2.1). This process is actually a two-stage dislocation of the target DHAP: disconnection of $H^{\oplus}$ from C-1 followed by connection of $H^{\oplus}$ at C-2.



Ring size modification can be applied at any stage of skeletal construction. In the following synthesis, ring expansion is applied after completion of a skeletal network that is **topologically equivalent** to that in longifolene (**32**).[6] Although the skeletal network in **86** has bridges of different lengths than those in **32**, it has the *same connectivity* as **32**. Expansion of one of the bridges in **86** leads to the longifolene ring system (see below). The synthesis of **86** has several important features. As in the previous synthesis of **32**, the present appraoch begins with the Wieland-Miescher ketone (**81**). Catalytic hydrogenation proceeds with stereoselective formation of the *cis*-decalone **83** owing to steric approach controlled addition of hydrogen to the *convex* side of the folded ring system of **81**. Similarly, epoxidation of **84** occurs with stereoselective delivery of oxygen from the *convex* side. The stereochemistry of epoxide **85** is ideally suited for nucleophilic attack during intramolecular S_N2 alkylation of the corresponding enolate anion. This key cyclization in Mc Murray's longifolene synthesis proceeds in excellent yield (92%).

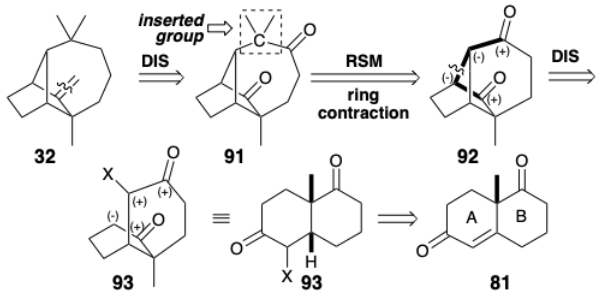


The longifolene ring system was then generated from **86** by a ring expansion involving pericyclic opening of a cyclopropyl carbenium ion that is generated during solvolysis of **87**. The required nucleophilic 1,4-addition of a methyl nucleophile to an enone **88** was accompanied by two undesired reactions. One, the replacement of a vinyl bromo substituent with methyl, generated a useless byproduct. However, the other, an intramolecular aldol condensation, was not a fatal flaw because the extra ring thus formed could be cleaved by a *fragmentation* reaction (**89** → **90**).

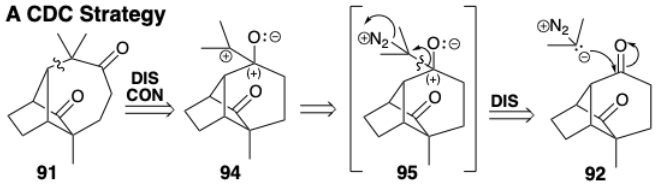


Ring Expansion as a Three Step Process

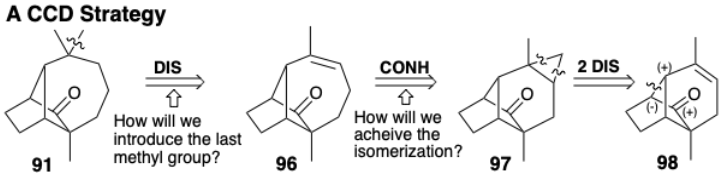
Again, let us perform a retrosynthetic analysis *ex post facto* to achieve a more fundamental understanding of the longifolene synthesis via key intermediates **81**-**90**. We will consider some alternatives that were not adopted, and examine strategic considerations that underlie the pathway that was chosen. In this analysis, we will presume the *boundary conditions* of using **81** as *starting material* and generating a tricyclic carbon network by formation of a bond between the incipient common atoms 1 and 2 (numbered as in **55** on page 116) in a bicyclic precursor. Also, functionality will be introduced by presuming a ketone as the progenitor of the exocyclic methylene group. However, instead of forming the tricyclic skeleton at the end of the synthesis after expansion of a 6 to a 7-membered ring, we will first form the tricyclic skeleton and then perform a ring expansion. We could presume that the quaternary carbon bearing the gem dimethyls is inserted into the six-membered ring of a precursor **92** to generate **91**. That **91** might contain a second carbonyl adjacent to the bridgehead is the suggested by the fact that this carbon in **92** corresponds to a carbonyl carbon in the starting material **81** (*vide infra*). The bond to be disconnected between two common atoms in **92** lies on a dissonant circuit between the carbonyls. Therefore, additional functionality, i.e., a nucleofuge, is required in a precursor, X in **93**, to allow polar bond formation.



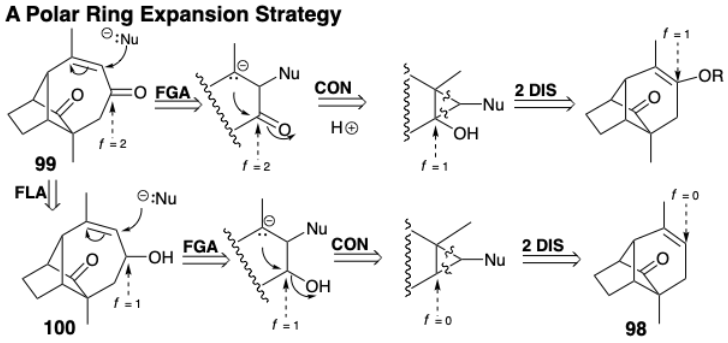
Ring expansion involves insertion of a carbon atom between two ring members. One bond must be formed between the new carbon and each ring member while the bond between ring members must be severed. There are two topologically different ways to accomplish a ring expansion. One possibility for generating **91** from **92** is analogous to the ring expansion of **81** via **82** (see above). Thus, a retro pinacol dislocation of **91** is achieved by disconnecting the bridgehead carbon (as nucleofuge) in **91** from the quaternary carbon and reconnecting it (as nucleophile) to the neighboring carbonyl carbon. This suggests a synthon **94** and synthetic equivalent **95** as precursors of **91**. In this strategy, ring expansion is achieved by a connection-disconnecion-connection (**CDC**) sequence that starts with connection of the nucleophilic carbon of 2-diazopropane to an electrophilic carbonyl carbon of **92**.



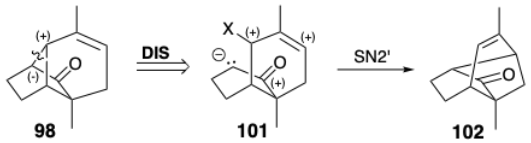
A topologically different strategy, connection-connection-disconnection (**CCD**), necessarily involves a cyclopropane intermediate that might be formed by cycloaddition to an alkene **98**. Thus, **91** could be derived from a cyclopropane **97** that could isomerize to a cycloheptene precursor **96**. Necessarily, only one of the gem methyl groups of **91** can be present in **96** because the carbon bearing this methyl is quaternary in the cyclopropyl precursor **97**. Thus, provision must be made for introducing the last methyl group. This might be done by adding functionality to **96**, as in **99** that has a carbonyl group conjugated with the carbon center to which a methyl must be added. If the ring expansion that will produce **99** is to involve a polar fragmentation of the ring fusion bond in a cyclopropane intermediate, then retrosynthetic polar analysis suggests two routes to **99**. In both routes, the ring fusion bond is provided by retrosynthetic connection to a carbon bearing electropohilic subtarget-related functionality, a carbonyl in **99** or a hydroxyl in **100**. The electrons for this connection are provided by an incipient nucleofuge (Nu) through addition to the C=C bond.



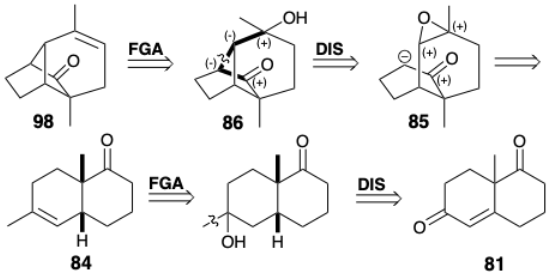
The less direct route via **100** is compatible with an alkene precursor **98**. Both routes revealed by this analysis involve the cycloadditon of a carbene to which is appended a nucleofuge (Nu). Although departure of the nucleofuge could occur after fragmentation of the ring-fusion bond, alternative timing is possible. The solvolysis of the dibromocyclopropane derived from **98** probably would be a concerted process.



Polar dislocation of **98** to an allylic electrophile and enolate may provide a flawed strategy because the C=C bond in **99** introduces ambident electrophilicity. Thus, cyclization might generate **102** by an S_N2' reaction.

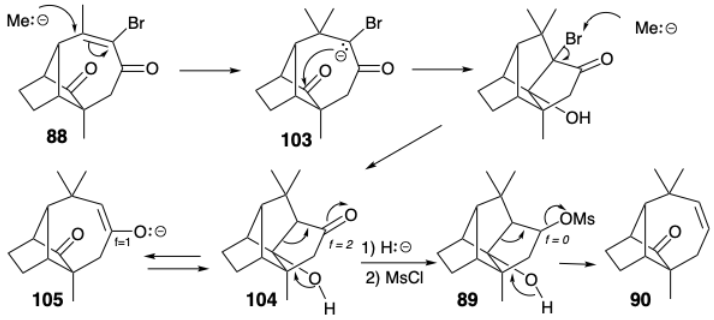


Therefore, the C=C bond in **98** is best introduced after cyclization, e.g. by dehydration of alcohol **86**. The bond to be disconnected between two common atoms in **86** lies on a dissonant circuit between the carbonyl and hydroxyl groups. Therefore, additional functionality is required in a precursor, e.g. **85**, to allow polar bond formation. This epoxide would be obtainable by dioxidative addition to an alkene **84**. Generation of **84** from starting ketone **81** is trivial.

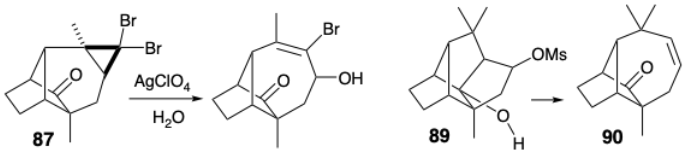


Fragmentation of Fused Bicyclics: A Tactic for Generating Larger Rings

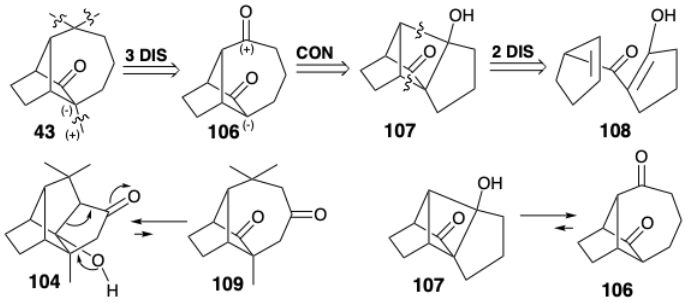
During the Mc Murray synthesis of longifolene, an undesired connection formed by intramolecular aldol condensation of enolate **103** generated in the conjugate addition of a methyl nucleophile to intermediate **88**. Owing to a proclivity of enolate **105** toward aldol condensation, retro aldol fragmentation of the pentacyclic product **104** could not provide the requisite ring system. This problem was circumvented by an isoelectronic (see page 80) fragmentation after lowering the functionality level of the ketone in **104** to an alcohol. Thus, retro Prins fragmentation of mesylate **89** generated **90** in which the weakly nucleophilic alkene, in contrast with the more strongly nucleophilic enolate in **105**, showed no proclivity toward condensation with a carbonyl group.



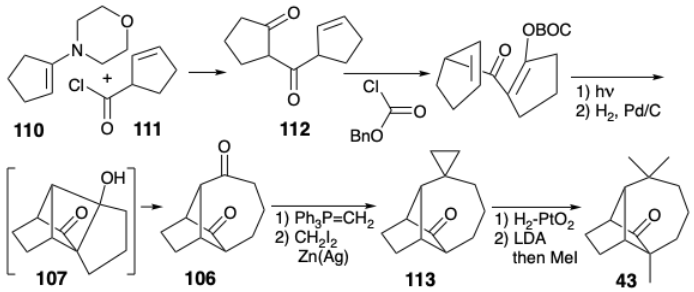
The Mc Murray synthesis of longifolene provides two examples of fragmentation of a bond shared by two fused rings to generate a single larger ring. The first example exploited fragmentation of the cyclopropane **87** as part of a ring expansion tactic, while the second, an unplanned step in the synthesis, involved fragmentation of **89**.



Another synthesis of longifolene was designed to exploit the fragmentation of a fused cyclobutane. This strategy recognizes the possibility of using carbonyl functionality in **43** to provide polar reactivity for introducing the methylene and a-methyl groups, and another carbonyl group to allow introduction of the gem dimethyl array into a precursor **106**. Dislocation of this subtarget by a polar connection suggests that dione **106** might be generated by the retroaldol fragmentation of a β-hydroxyketone **107**. In contrast with the equilibrium between aldol **104** and dione **109** that favors the former, the equilibrium between aldol **107** and dione **106** is expected to favor the latter owing to relief of ring strain associated with cleavage of a cyclobutane.

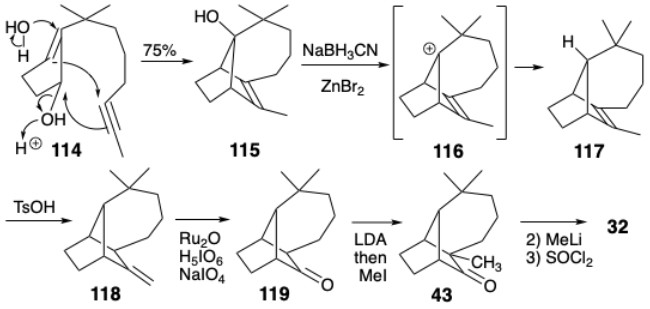


An exceptionally efficient synthesis of longifolene resulted from the application of this strategy.[7a] Only 10 steps are used to convert enamine **110** and acyl halide **111** into longifolene in 26% overall yield. Phototolysis of an enol ester derivative of dione **112** folowed by hydrogenolytic removal of the benzyloxycarbonyl (BOC) group generated dione **106** via **107**. Selective methylenation of the less sterically congested carbonyl in **106** followed by cyclopropanation, hydrogenolysis of **1 1 3** , and methylation delivered ketone **43**, an intermediate in both the Corey and McMurray longifolene syntheses.

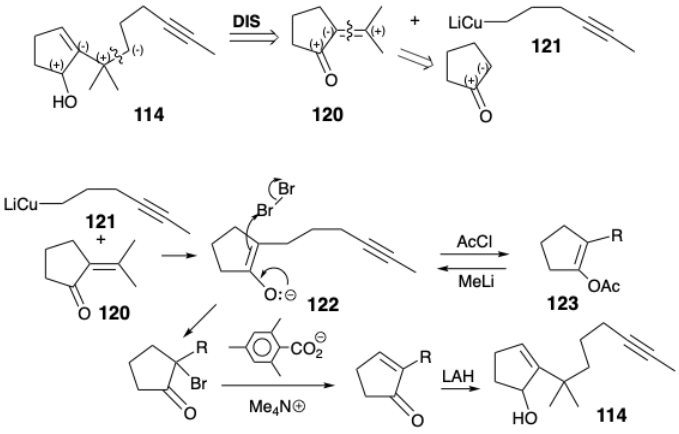


A Polyene Cyclization Route

Another efficient synthesis of longifolene (**32**) is based on a structural simplification suggested by topological analysis. Thus, dislocation to a subtarget **60** (see page 116) by removal of two bonds involving common atoms suggests a precursor containing only one ring. In the synthesis, these two bonds were generated in a key acid-catalyzed polyene cyclization (**114** → **115**).[7b] The conversion of **115** to **32** requires reductive removal of the hydroxyl. This was accomplished by an S_N1 replacement of hydroxyl by hydride through an intermediate carbenium ion **116**. To provide polar activation that could be exploited for introducing the angular methyl group, the C=C bond in **117** was isomerized to an exocyclic methylene in **118**. Oxidative cleavage then delivered ketone **119**.

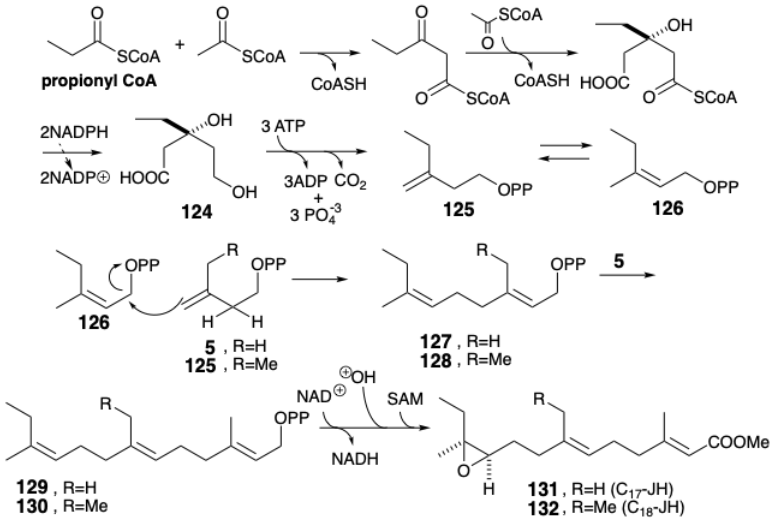


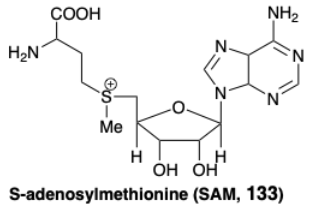
A synthesis of **114** from a methylenecyclopentanone electrophile **120** and nucleophilic side chain synthon **121** is suggested by polar analysis. Two extra steps were added to the synthesis to allow purification of the enolate **122** produced by the 1,4-addition of **120** to **121**. Thus, **122** was trapped by O-acylation. After purification of the enol acetate **123**, the enolate **122** was regenerated and then brominated. Dehydrobromination and reduction completed the synthesis of **114**.



4.5: Homo and Bishomo Sesquiterpenes ii Cecropia Juvenile Hormones

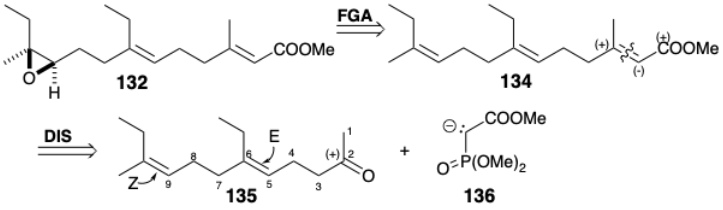
The Cecropia juvenile hormones are biogenetic close relatives of farnesol that contain one or two extra carbon atoms in their sesquiterpenoid carbon skeletons. These terpenoid homologues are referred to as homo and bishomo sesquiterpenes respectively. The extra carbon atoms arise through the incorporation of one or two molecules of propionate in place of acetate during a biosynthetic skeletal construction that is otherwise identical to that of farnesol. Thus, propionyl CoA condenses with two molecules of acetyl CoA to give homomevalonic acid (**124**) after reduction with NADPH. Conversion of **124** to **125** via decarboxylative elimination and isomerization to **126** is followed by addition of the allylic electrophile **126** to the terminal C=C bond in Δ^3-isopentenyl-PP (**5**) or to its six carbon homologue (**125**). The allylic electrophiles **127** or **128** then alkylate Δ^3-isopentenyl-pyrophosphate to deliver homo and bishomo farnesylpyrophosphates **129** or **130**, respectively. These are oxidized to the corresponding acids by hydride donation to NAD+. Enantio-selective epoxidation, and O-methylation of the carboxyl by methyl transfer from S-adenosyl-methionine (**SAM, 133**) gives optically active epoxyesters **131** and **132** which are known as C_{17} and C_{18} juvenile hormones respectively.

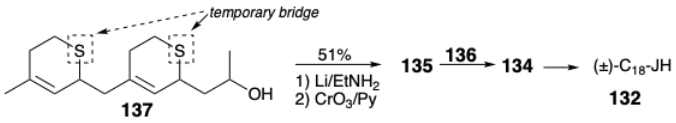




Stereocontrolled Generation of Trisubstituted Alkenes

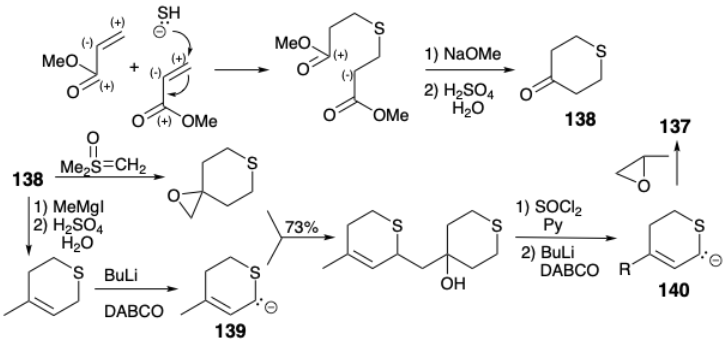
The primary synthetic challenge presented by the Cecropia juvenile hormones is stereocontrol during the construction of trisubstituted C=C double bonds. Temporary rings may be effectively utilized to control alkene geometry. A variety of different applications of this tactic have been employed to achieve stereocontrolled syntheses of juvenile hormones. These syntheses generally involve stereocontrolled construction of methyl bishomo farnesoate (**134**), that is converted into C_{18}-JH (**132**) by regioselective epoxidation as in the biosynthesis of **132**. Polar analysis of **134** suggests a synthesis from the phosphono ester-stabilized carbanion **136** and dienone **135**.



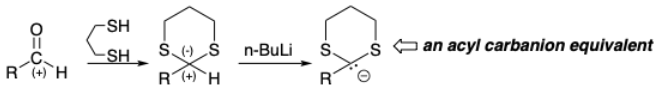


A Temporary Bridge Strategy

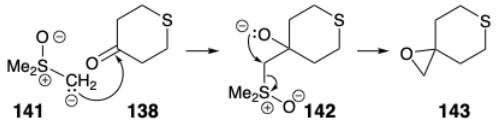
One tactic for stereocontrolled synthesis of **135** employs temporary thioether bridges in **137** to enforce the 5-E and 9-Z configurations.8 The sulfur bridges are reductively cleaved after the carbon skeleton of **135** is complete. Both of dihydrothiapyran fragments in **137** were derived from a common intermediate, tetrahydro-1,4-thiapyrone (**138**). Sulfur serves a dual strategic role in this scheme. Besides enforcing the required configuration at the carbon-carbon p-bonds (stereocontrol), sulfur stabilizes a neighboring nucleophilic center (reactivity control) in the carbanions **139** and **140**. The mercapto and sulfide functional groups readily provide activation for either nucleophilic or electrophilic reactivity. They are *biphilic* functional groups, and, as previously encountered for the biphilic nitrile functional group (see pages 19 and 31), they can be used to produce polar reactivity inversion. We encountered this phenomenon previously in the conversion of an electrophilic carbonyl into a nucleophilic dithiane carbanion, an acyl carbanion equivalent.



In the present synthesis of JH, the electrophilic β-carbon of methyl acrylate is transformed by the thioether functional group into a nucleophilic center in **139** and **140**.

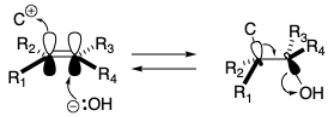


Another instance of biphilic activation by sulfur is found in the reaction of the electrophilic carbonyl carbon of **138** with dimethyloxosulfonium methylide (**141**), a *sulfur stabilized nucleophile*, to produce epoxide **143**. Sulfur then provides *electrophilic* activation at the same carbon by serving as a nucleofuge in the intermediate betaine **142**.



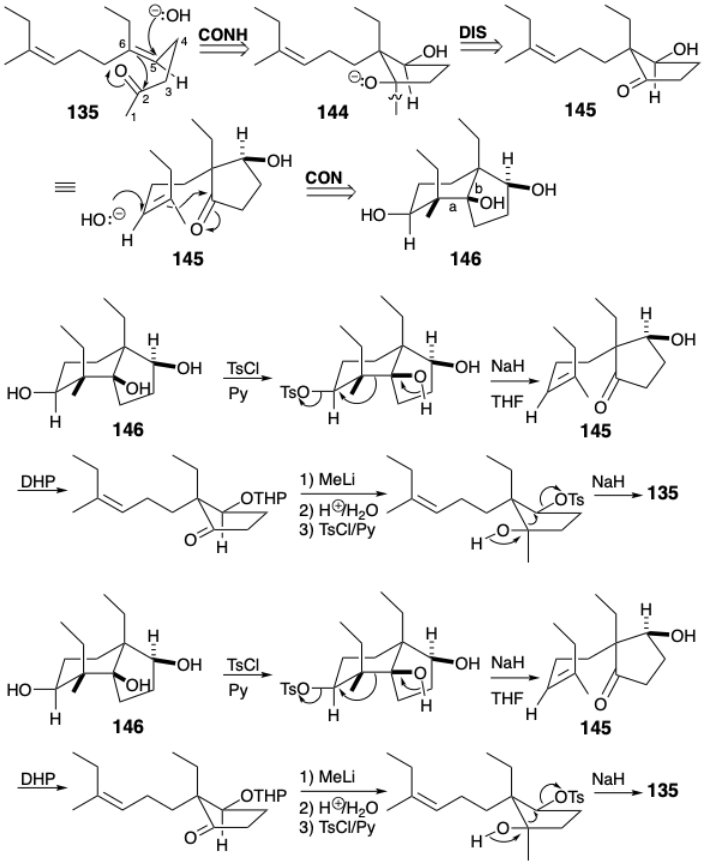
SEC in Fragmentations

Another stereocontrolled synthesis of **135** exploits reversible stereospecific, anti-periplanar addition to a carbon-carbon π-bond to transpose the stereochemical relationships in monocyclic and bicyclic intermediates into those of acyclic products.[9] The anti-periplanar arrangement allows continuous overlap during a concerted fragmentation. Thus, the E configuration of the 5,6-π-bond in **135** is preserved in latent form in the cyclic intermediate **144** by a dislocation involving anti-periplanar addition of a carbon electrophile and hydroxyl nucleophile to **1 3 5** . A new electrophilic carbonyl carbon is generated by the dislocation **144** fi

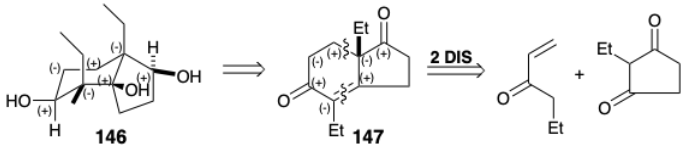


145. The Z configuration of the C=C bond in **145** is preserved in latent form by a dislocation involving antiperiplanar addition of a carbon electrophile and hydroxyl nucleophile to the C=C bond in **145**. Thus, all of the stereochemical information in the acyclic intermediate **135** is contained in latent form in the bicyclic precursor **146**. Control of alkene geometry in an acyclic carbon skeleton is thereby transposed to control of relative stereochemistry in a multicyclic carbon network. Since the conformations of multicyclic carbon networks are more rigid than acyclic ones, the influences of steric and neighboring group effects are more easily predicted and usually more pronounced.

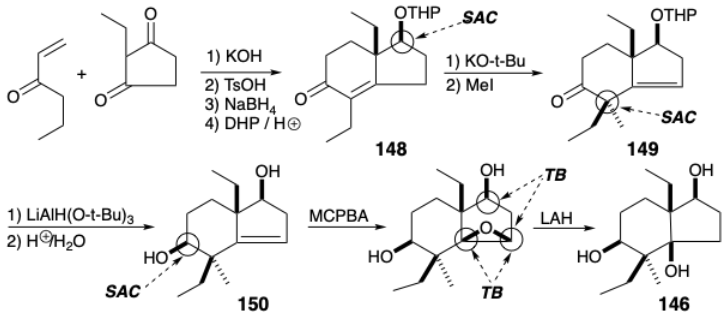
Fragmentation of bonds a and b in **146** was promoted by converting hydroxyl into toluenesulfonate leaving groups. The triol **146** was readily selectively monotosylated at the least sterically congested secondary hydroxyl. Fragmentation of the resulting b-tosyloxy 3° alcohol delivering the Z-alkene **145** proceeded stereospecifically upon treatment with NaH. Addition of MeLi to the tetrahydropyranyl derivative of **145** occurred stereoselectively (57%). After deprotection and selective tosylation of the secondary hydroxyl in the resulting diol, fragmentation of an intermediate β-tosyloxy 3° alcohol occurred smoothly to afford **135** stereospecifically (80%).



Since the functionality in **146** was introduced by polar reactions, it is a foregone conclusion that the functional groups are connected by consonant circuits. Polar analysis of **146** shows that all circuits in the cyclohexane ring are consonant. This allows disconnection of bonds to the ring fusion *common atoms*. However, activation of nucleophilic reactivity vicinal to the secondary hydroxyls requires conjugation that is only afforded by carbonyl groups as in **147**. Polar disconnection of **147** then suggests propyl vinyl ketone and 2-ethylcyclopentan-1,3-dione as starting materials.

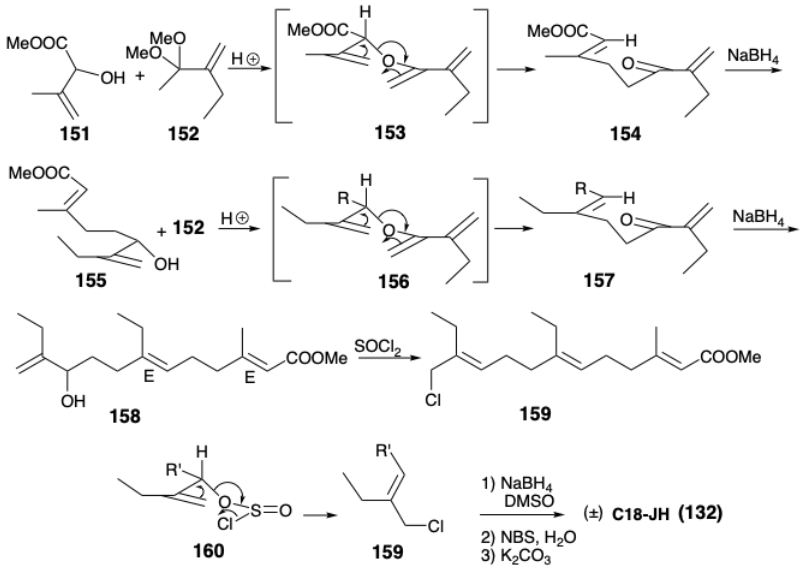


A synthesis of **146** based on the strategy outlined above began with Robinson annelation of 2-ethylcyclopentane-1,3-dione with propyl vinyl ketone. Steric approach controlled hydride delivery to the resulting dione provided **148** after protection of the hydroxyl. Steric approach control also resulted in stereoselective methylation from the less sterically congested α-face of the enolate from **148**. Similarly, hydride delivery to the less sterically congested face of **1 4 9** gave **1 5 0** stereoselectively. The stereochemistry of the final hydroxyl group required for the triol **146** was dictated by the effect of the neighboring hydroxyl in **150** on the epoxidation of this alkene. The hydroxyl group hydrogen bonds with MCPBA thereby enforcing oxygen delivery *cis* to the neighboring hydroxyl as for **250** in section 3.6.

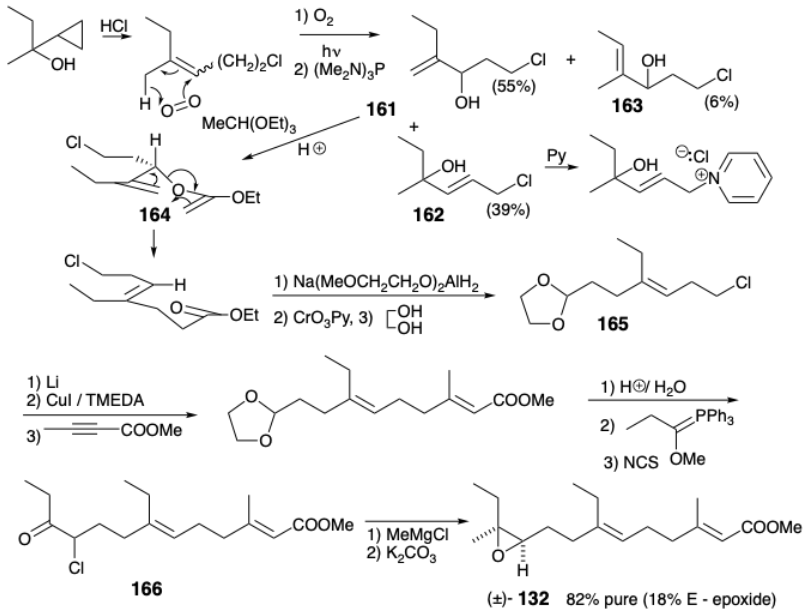


SEC Through Preferred Conformations

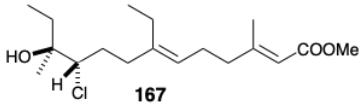
Conformational effects in cyclic *transition states* can also result in substantial, as well as predictable, stereoselectivity in the generation of acyclic alkenes. In another stereocontrolled synthesis of C_{18}-JH (**132**), Claisen rearrangement of the allyl vinyl ether **153** from transketalization of **152** with **151**, followed by elimination, generates the γ,δ-unsaturated ketone **154** stereoselectively.10 A chair transition state with an equatorial carbomethoxyl substituent is preferred for this [3.3] sigmatropic rearrangement. Borohydride reduction of **154** gives an allylic alcohol **155**, which was again homologated stereoselectively with **152** to give allylic alcohol **158** via **156** and **157**. A cyclic transition state is also the key to a stereocontrolled conversion of **158** to the allylically transposed chloride **159**. Thus, the chlorosulfite ester **160** of **158** gives **159** via S_Ni' rearrangement involving a chair conformation with the bulky substituent in an equatorial position.



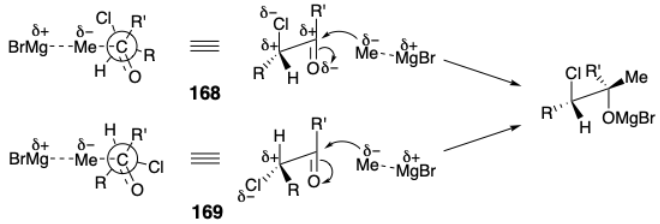
Another synthesis of C_{18}-JH (**132**) that exploits a Claisen rearrangement to generate the 6,7-trisubstituted double bond stereoselectively is outlined below.[11] An interesting step in this synthesis is the selective destruction of an undesired byproduct **162**. This allylic chloride is more reactive than the isomers **161** and **163** and, therefore, selectively forms a water soluble pyridinium salt. Claisen rearrangement occurs via a transition state conformation **164** with an equatorial chloroethyl group. The 2,3-double bond is generated stereoselectively by *cis*-1,4-addition of an organocuprate derived from **165** to methyl 2-butynoate.



In this synthesis, the epoxide is produced by base-induced cyclization of a chlorohydrin rather than epoxidation of an olefin. Stereoselective HO generation of the Z-epoxide is possible because the reaction of chloroketone **166** with methyl magnesium chloride leads predominately to one diastereomer, the *threo* chlorohydrin **167**.

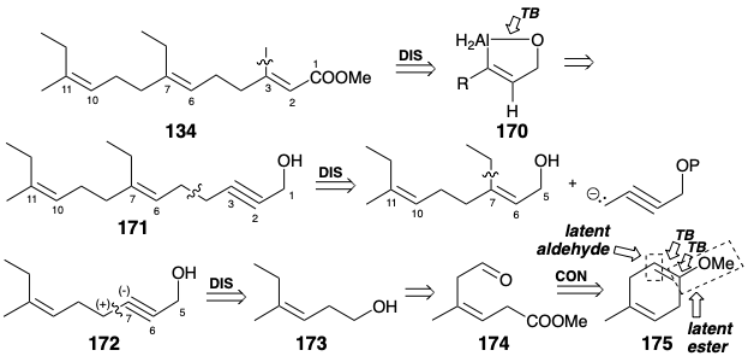


This stereoselectivity is not the consequence of a cyclic transition state. Rather, for acyclic ketones which contain polar α-substituents (e.g. halogens) that are unlikely to coordinate with metal atoms, a combination of torsional strain, steric interactions, and electrostatic interactions must be considered. Two models have been formulated to explain such stereoselectivity. One model presumes that the reactive conformation of such ketones is a structure (e.g., **168**) in which the carbonyl group and the polar α substituent are anti-periplanar to minimize dipole-dipole repulsion. Alternatively, the transition state may resemble **169** that allows maximum separation of the electronegative a substituent and the negatively charged nucleophilic reagent. Another example of such stereoelectronically controlled stereoselection is provided by the **48** + **49** → **53** conversion presented in Chapter 3 (section 3.3).

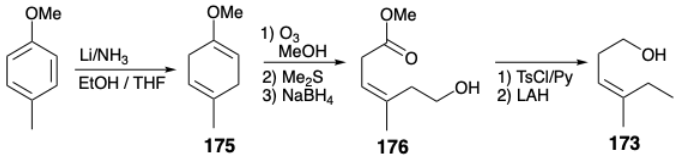


Other TB Strategies

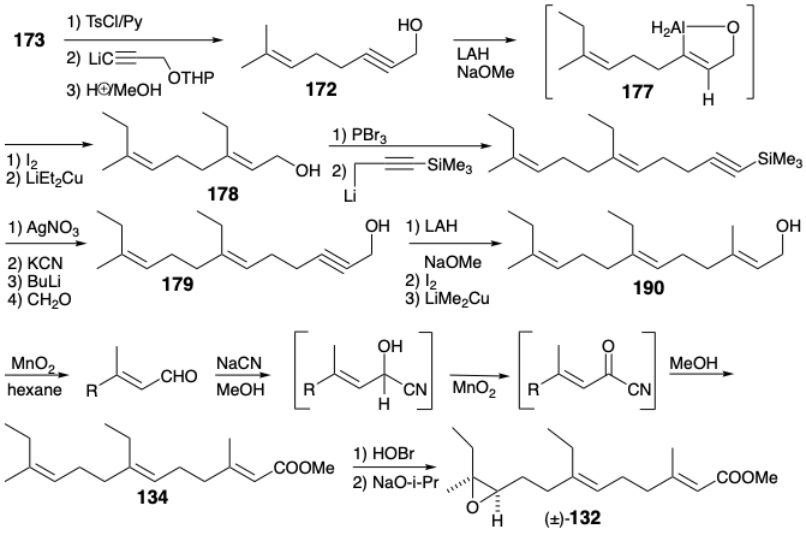
Two tactics for stereoselective construction of trisubstituted C=C bonds not encountered in the previous examples are exploited in a strategy for synthesis of C_{18}-JH that was devised by Corey.[12] The 2,3-E configuration in **134** can be assured by a temporary ring during pseudo-intramolecular hydroalumination of a propargyl alcohol **171** that produces an intermediate vinyl alane **170** which is subsequently alkylated. This tactic can also produce the 6,7-E configuration by a similar hydroalumination-alkylation sequence applied to **172**. The fact that a terminal alkyne is a latent carbanion suggests a polar dislocation of **172** to a propargyl alcohol-derived acetylide nucleophile and an electrophilic precursor **173**. The E configuration of **173** can be assured by a temporary bridge that is suggested by dislocation to a more highly functionalized precursor **174** with differentiated carbonyl groups. Thus, reductive coupling of these two carbonyl groups provides a bridged latent dicarbonyl precursor **175**.



Especially noteworthy is the synthetic role of the aldehyde carbonyl group in **174**. This functional group is exploited solely to facilitate stereocontrol.

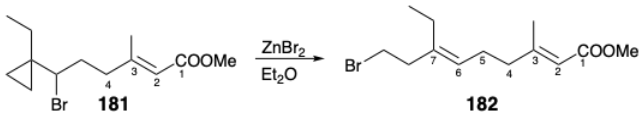


The substituents in the acyclic product **176**, from selective oxidative cleavage of **175**, are necessarily *cis* since only a *cis* double bond can be accommodated in a six membered ring. The *cis* relationship between the aluminum and hydroxymethyl substituent enforced in the intermediate **177** by a temporary bridge is preserved in the subsequent halogenolysis of the C-Al bond and alkylation of the resulting vinyl iodide delivering **178**. Both transformations occur with retention of configuration. A similar sequence delivers **180** stereoselectively from **179**. Conversion of the allylic alcohol **180** into key intermediate **134** requires oxidation followed by O-methylation.

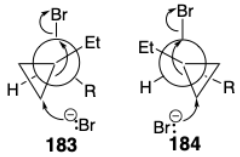


SEC Through Preferred Conformations

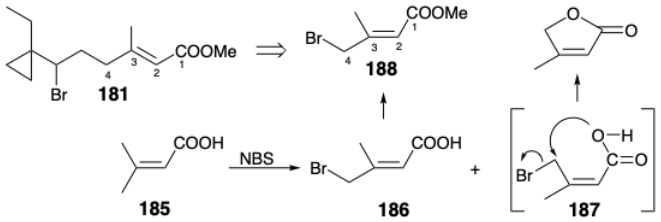
Highly stereoselective formation of trisubstituted alkenes can sometimes be achieved by processes not involving intermediates with temporary bridges or cyclic transition states. Thus, occasionally, a combination of conformational and stereoelectronic effects may produce high stereoselectivity in reactions of acyclic molecules. For example, the 6,7-C=C bond of JH can be generated stereoselectively during transformation of the cyclopropyl carbinyl bromide **181** into the homoallylic bromide **182**.[13]



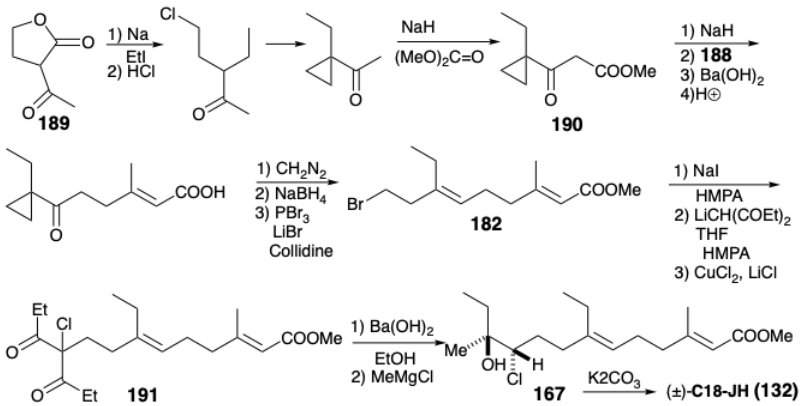
Stereoselectivity arises from a stereoelectronic preference for an anti-periplanar arrangement of cleaving bonds that leads to generation of the new carbon-carbon double bond in a concerted stereocontrolled fashion. That is, a coplanar arrangement of the breaking C-C and C-Br bonds allows coupling of these bond cleavages with carbon-carbon double bond formation. Either transition state conformation **183** or **184** satisfies this requirement, but **183** is clearly preferred because the cyclopropyl group eclipses only hydrogen. Thus, a conformational bias, coupled with a stereoelectronic preference, favors a transition state **183**, that leads to E-olefin **182**.



The preparation of an early intermediate, **188**, for the C1 to C4 segment of **181** illustrates a useful tactic for the synthesis of pure stereoisomers: selective destruction of one of two isomeric products from a nonstereoselective reaction. Thus, N-bromosuccinimide brominates dimethyl acrylic acid (**185**) nonselectively to give a mixture of bromoacids **186** and **187**.



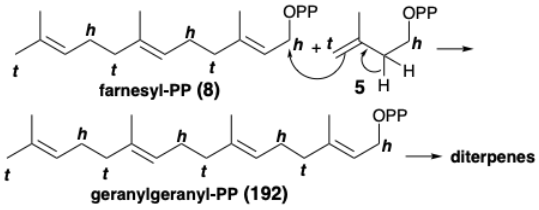
The undesired Z-isomer **187** undergoes spontaneous lactonization, leaving the desired E-isomer **186** as the only acidic organic product, that can be extracted into mild base and subsequently methylated to provide the intermediate **188** for the synthesis of JH. This is combined with a nucleophile derived from ketoester **190** that is available, in turn, from 1-acetyl-γ-buryrolactone **189**. Symmetry was exploited during completion of the JH carbon skeleton by alkylation of the enolate of 3,5-heptanedione with **182**. Chlorination of the product gave **191**. The extra propionyl group was cleaved in a retro Claisen reaction by $Ba(OH)_2$. The resulting chloroketone **166** reacted stereoselectively with MeMgCl to give **167** with less than 8% of the unwanted diastereomer (see section 4.6). Base-induced heterocyclization of the *threo* chlorohydrin **167** delivered racemic C_{18}-JH.[13]



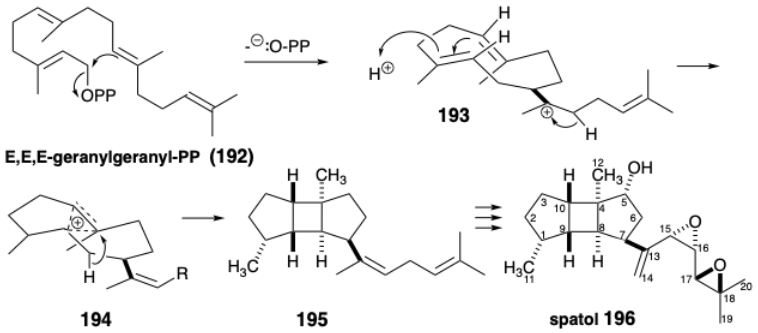
4.6: Biosynthesis and Total Syntheses of Diterpenes - Spatol

Biosynthesis

As for all natural products, a successful synthetic strategy for spatol existed before any human endeavor. It is always interesting to examine Nature's strategy because an analogous approach, a **biomimetic strategy** (mimicing Nature), may be effective in the laboratory. Thus, the diterpenes are C_{20} compounds derived biogenetically from E,E,E-geranylgeranyl-PP (**192**) or its geometrical isomers.

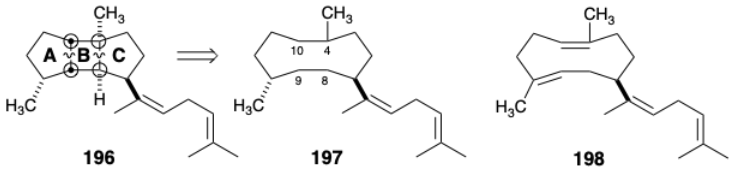


These acyclic tetramers of Δ^3-isopentenyl-PP (**5**) arise from reaction of **5** with a trimer such as E,E-farnesyl-PP (**8**). Subsequent intramolecular electrophilic addition of the allylic pyrophosphate to the trisubstituted C=C bonds can lead to various mono and multicyclic carbocations such as **193**. Another general route to carbocationic electrophiles involves protonation of C=C bonds. A hypothetical pathway for the biosynthe- sis of spatol (**196**) involves protonation of a C=C bond and intramolecualr electrophilic addition of the resulting carbocation to produce a cyclobutane (**195**) by proton loss from **194**. This hypothesis derives support from the natural occurrence of **195**.[14] The oxygen functionality in **196** is presumed to arise from oxidative metabolism of **195** by the marine organisms that produce this tricyclic diene and a wide variety of oxygenated metabolites with the spatane carbon skeleton.



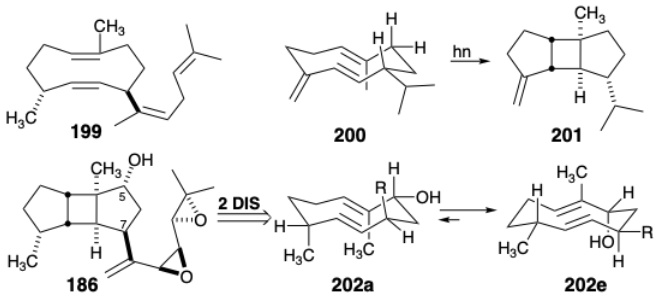
Topological Analysis of Spatol

Ex post facto topological retrosynthetic analysis of the biosynthetic strategy reveals an important feature. The tricyclo[5.3.0.$0^{2,6}$]decane nucleus of the spatane diterpenes incorporates 4 common atoms (circled in **196**), the four atoms of the B-ring. The biosynthetic strategy benefits from the powerful topological simplification that accrues from removing bonds between two sets of common atoms, 4-8 and 9-10. This suggests a monocyclic topological synthon **197**. For this synthon, one synthetic equivalent, **198**, is suggested by our biogenetic hypothesis.



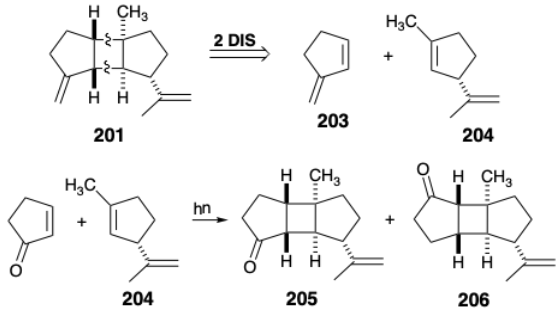
Another synthetic equivalent, **199**, is suggested by the possibility of an intramolecular 2π + 2π cycloaddition. An expeditious synthesis[15a] of the sesquiterpene b-bourbonene (**2 0 1**) exploits intramolecular photocycloaddition of germacrene D (**200**) an intermediate analogous to **199**. UV evidence (λ_{max} = 259 mm, ε = 4500 in n-hexane) indicates a significant transannular interaction between the two endocyclic C=C bonds in the sesquiterpene **200**. Thus, **200** probably prefers a conformation in which the two endocyclic C=C bonds are situated parallel and face to face with each other, and the isopropyl substituent occupies the less sterically hindered equatorial configuration. Thermodynamic control of the conformation of **200** assures the proper configuration at the isopropyl bearing carbon while stereoelectronic control (syn periplanar = suprafacial addition) assures the correct *cis,anti,cis*

configurations at the cyclobutane stereocenters. An analogous photocyclization to generate a precursor **202** for spatol is not favorable since a substituent R which is to become the side chain must occupy a more sterically encumbered axial position as in **202a** rather than the more thermodynamicaly favorable conformation **202e**.

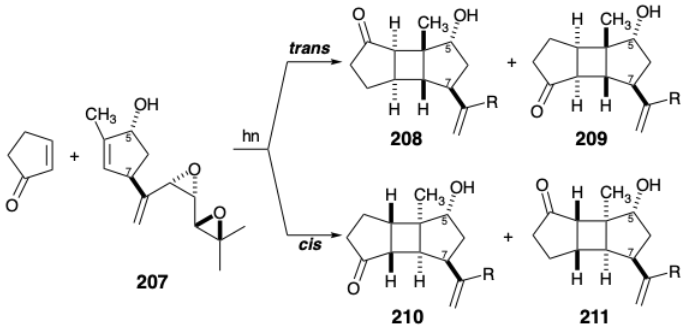


A Topological and Stereochemical Strategy

A different topological disection of the *cis-anti-cis*-tricyclo[5.3.0.0^{2,6}]decane nucleus of β-bourbonene (**201**) has also been exploited for its synthesis. Thus, removing two bonds between pairs of common atoms can generate two cyclopentene precursors, **203** and **204**, that could be united by a 2πs + 2πs photocycloaddition (see section 3.3). In fact, UV irradiation of 2-cyclopenten-1-one with **204** results in a photocycloaddition that is orientationally nonselective, producing a 1:1 mixture of structural isomers **205** and **206**.[15b] However, the cycloaddition is favorably stereoselective owing to a steric approach controlled preference for cycloadddition to the face of the cyclopentene ring opposite the isopropyl substituent. This stereoselectivity detracts from the utility of a similar synthesis for spatol because the allylic diepoxide side chain in spatol (**196**) is *cis* to the cyclobutane rather than *trans* as is the isopropyl group in **201** or **205**.

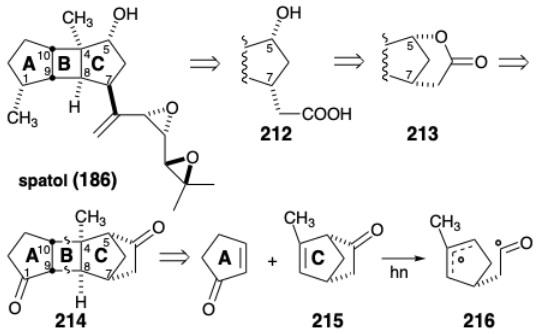


Thus, the allylic diepoxide side chain or its precursor in a cyclopentene intermediate **207** can be expected to favor the wrong stereoselectivity in a photocycloaddition with 2-cyclopenten-1-one, i.e., favoring **208** or **209** rather than the desired adduct **210** or its structural isomer **211**.

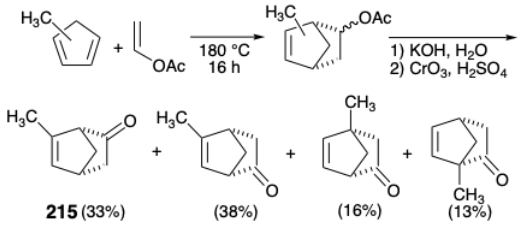


One strategy to surmount this shortcoming of cyclopentene photocycloadditions for the total synthesis of spatol uses a temporary bridge to shield one face of a cyclopentene ring to preclude addition to that face.[16] Thus, such a bridge can be provided by linking the hydroxyl group at the 5-position with a carboxymethyl group that also serves as a progenitor of the sidechain at position 7 as in lactone **213**. Furthermore, the lactone can be derived from a latent precursor, ketone **214**, by a Baeyer-Villiger oxidation. Double disconnection of **214** by a cycloelimination suggests photocycloaddition of a norbornenone **215** with cyclopent-2-en-1-one. Thus,

in **214** a temporary oxoethano bridge shields the α-face of the incipient C-ring enforcing stereoselective cycloaddition of the A-ring precursor cyclopent-2-en-1-one *trans* to the incipient 5-hydroxyl group.

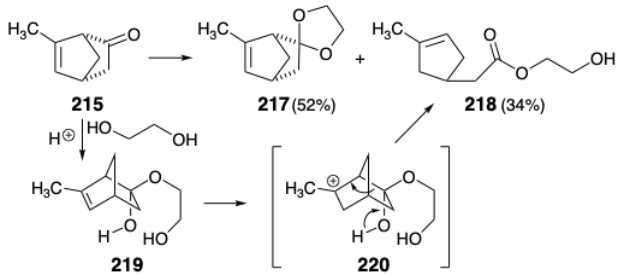


This strategy has one obvious flaw. The strained bicyclic homoallylic ketone **215** was expected to readily undergo photoinduced cleavage to diradical **216**. However, masking of the carbonyl in **215** would circumvent this problem and facilitate differentiation between the two carbonyl groups in the photocycloadduct **214**. Also, the configuration at the 7-position in **212** would have to be inverted to provide the requisite configuration at this stereocenter in spatol. A synthesis of 6-methylbicyclo[2.2.1]hept-5-ene-2-one (**215**) from vinyl acetate and methyl-1,5-cyclopentadiene is possible through a Diels-Alder reaction of these starting materials. Although the reaction produces a mixture of structural isomers, saponification followed by oxidation gives a mixture of isomeric ketones from which **215** can be isolated by distillation.



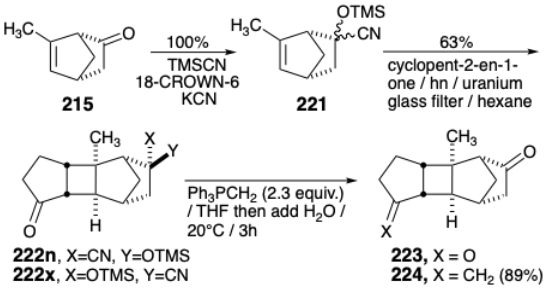
Masking a Sensitive Ketone

Masking of the carbonyl group in **215** proved unexpectedly difficult. Only a moderate yield of the ethylene ketal **217** was available by acid-catalyzed ketalization of **215** under conditions which give an excellent yield of ketal from the 6-unsubstituted analogue, bicyclo-[2.2.1]hept-5-en-2-one, owing to a competing fragmentation to **218**. The proclivity of **215** toward this fragmentation undoubtedly arises from the relative stability of the tertiary carbocation **220** and the relief of ring strain attending conversion of **219** to **220**.



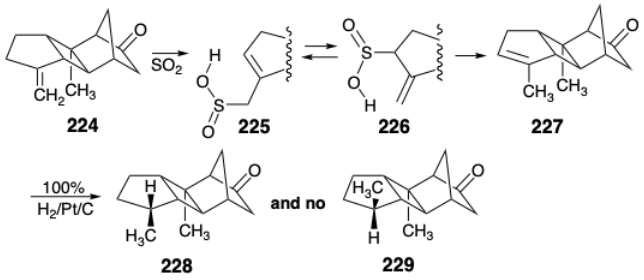
An unusual choice for the masking group was developed during a search for a group that could be introduced under nonacidic conditions. Thus, ketone **215** is converted quantitatively into an epimeric mixture of cyanohydrin silyl ethers **221** by reaction with trimethylsilyl cyanide. While the use of an unsymmetrical masking group might seem unwise since this leads to epimeric mixtures of several intermediates, this is a small price to pay for the otherwise ideal characteristics of the cyanohydrin silyl ether masking group. Thus, photocycloaddition with cyclopent-2-en-1-one delivered two epimeric adducts **222x** and **222n** with high stereo (cis,anti,cis ring fusions and exo addition to the bicyclohept[2.1.1]ene) and orientational (cyclopentane carbonyl remote from the bridgehead methyl group) selectivity. Serendipitously, the major adduct **222x** crystallized from the photoreaction mixture together with the dimer of cyclopentenone from which it was readily separated by trituration with hot hexane leaving behind pure dimer. Pure **222x** was then obtained in 51% yield, based on **2 2 1** , by elution of the partially purified product through a column of silica

gel with ethyl acetate- hexane. Column chromatography of the hexane soluble photoproduct afforded a fraction from which nearly pure minor cycloadduct **222n** crystallized together with a little **222x**. This mixture is suitable for Wittig olefination to produce methylidene ketone **224**, *vide infra*. The combined isolated yield of **222x** plus **222n** exceeds 60%. A sample of pure **222n** was obtained by HPLC. The epimeric relationship between **222x** and **222n** was demonstrated by production of the same diketone **223** upon hydrolysis of the cyanohydrin silyl ether masking group and also by production of the same methylidene ketone **224** upon reaction with methylenetriphenylphosphorane followed by hydrolysis of the cyanohydrin silyl ether. The conversion of **222** into **224** was performed as a one-pot procedure affording pure **224** in 89% overall yield. The utility of the cyanohydrin silyl ether masking group in the above transformations is noteworthy. It is introduced under mild neutral reaction conditions. It is sufficiently robust to survive UV irradiation, chromatography on silica gel, and Wittig olefination; but it is readily converted to a carbonyl group by the aqueous base generated upon addition of water to the Wittig reaction mixture.



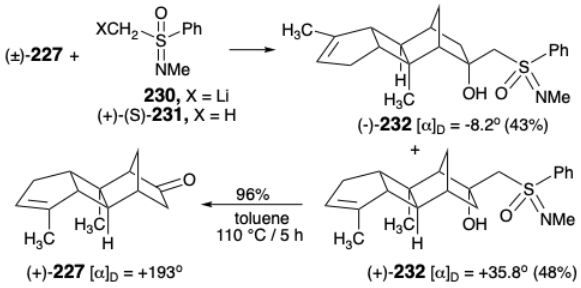
Amplifying SAC

Catalytic hydrogenation of **224** favored the required epimer **228** over the useless byproduct **229** by 10:1 owing to steric approach control by the methyl group in **224** that shields the α-face of the A-ring. However, separation of **228** from the mixture could not be achieved by any method except fractional crystallization, and this only allowed isolation of the desired epimer in only fair yield. To circumvent this separation problem, **224** was isomerized to the endocyclic alkene **227** by SO_2. This clean, quantitative isomerization presumably involves ene addition of SO_2 to **224** producing **225**. Subsequent [1.3] sigmatropic rearrangement of sulfur affords **226** that undergoes retro ene fragmentation delivering **227**. Catalytic hydrogenation of **227** delivers **228** cleanly and quantitatively. Apparently the closer proximity of the endocyclic C=C bond to the methyl group in **227** than the exocyclic C=C to the methyl group in **224** results in greater steric hindrance to α hydrogen delivery in **227** than in **224**.



Resolution

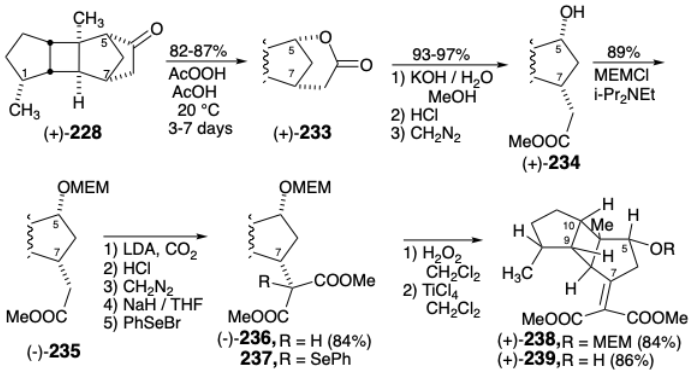
Efficient, virtually quantitative resolution of ketone **227** was readily achieved by flash chromatography and crystallization of the 1,2-adduct with chiral lithiosulfoximine **230**. Retro ene elimination of the less soluble dextrorotatory diastereomer (+)-**232** delivered ketone (+)-**227** that was correlated with (+)-spatol by conversion to a degradation product from natural spatol (*vide infra*). The sulfoximine (+)-(S)-**231** was recovered in 96% yield.



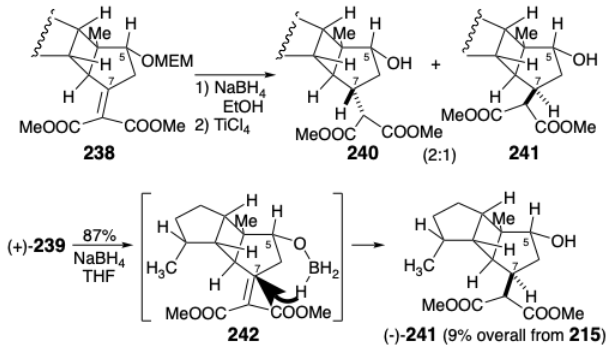
A Temporary Bridge During Hydride Delivery

Catalytic hydrogenation of (+)-**227** provided ketone (+)-**228**. Introduction of oxygen at position 5, cleavage of the temporary bridge, and inversion of configuration at the 7-position were then addressed. Thus, Baeyer-Villiger oxidation to give lactone

(+)-**233**, saponification, and methylation of the resulting acid provided alcohol (+)-**234**. Masking of the 5-hydroxyl provided (-)-**235** that was carboxylated to give malonic ester (-)-**236**. Epimerization at the 7-position was initiated by selenenylation followed by oxidative deselenenylation of the resulting **237** to deliver alkylidene malonic ester **238**. Reduction of **238** with $NaBH_4$ followed by removal of the MEM protecting group with $TiCl_4$ afforded a 2:1 mixture respectively of the *cis* hydroxy malonic ester **240** and its C-7 epimer, the desired *trans* hydroxy malonic ester **241**. This disappointing result suggested that the 2-methoxyethoxymethoxy (OMEM) substituent at the 5-position sterically hinders hydride delivery to the α- face of the C=C bond in **238**.

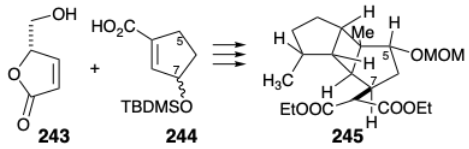


A remote hydroxyl group was found to foster pseudointramolecular *syn* hydride delivery via an alkoxyborohydride intermediate **242**. Thus, treatment of the derived hydroxy alkylidene malonate (+)-**239** with $NaBH_4$ delivered the desired *trans* hydroxy malonic ester (-)-**241** completely stereoselectively. The overall yield was 9% from C-ring precursor **215** in 21 steps including the resolution.

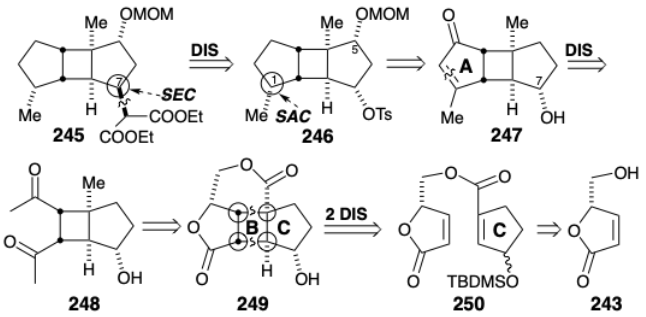


Enantiospecific Synthesis with a Chiral Auxillary

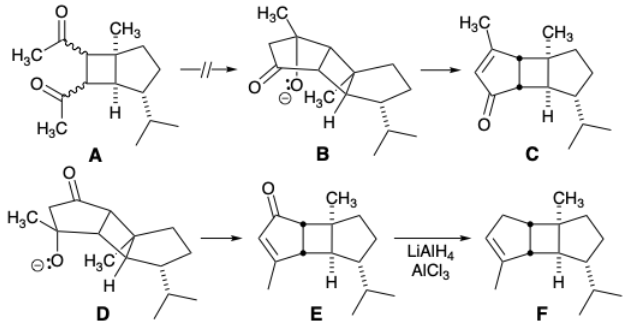
A different synthesis[18] of a homochiral tricyclodecylmalonic ester intermediate **245** (an analogue of **241**) was designed with a focus on exploiting butenolide **243** as a chiral auxiliary to establish the correct absolute configuration during generation of the B-ring by a 2π + 2π photocycloaddition with A-ring precursor **244**. Homochiral butenolide **243** is readily available from L-glutamic acid. An allylic oxygen substituent in **244** provides a point of attachment for the malonic ester side chain and activation for the introducing oxygen at the 5-position.



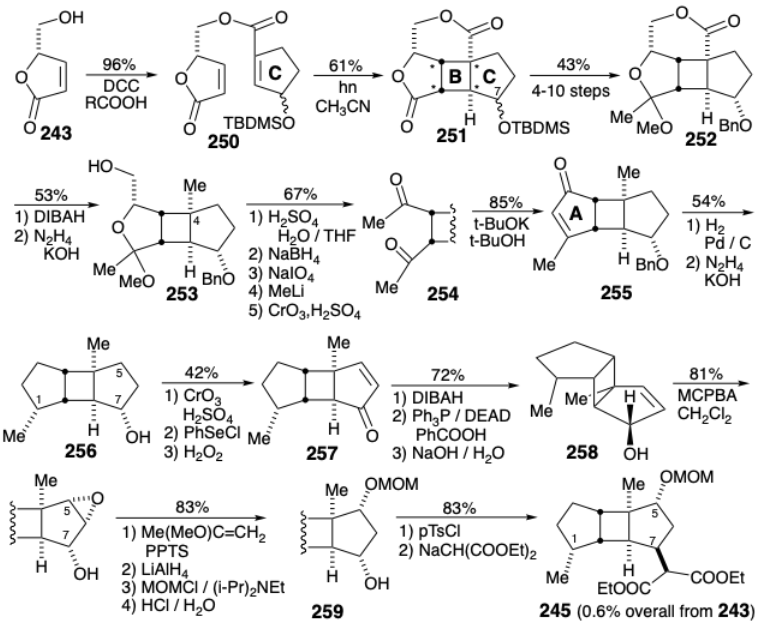
In a retrosynthetic format, the strategy envisions attachment of the malonic ester last by a stereospecific S_N2 alkylation with **246**. Since the chiral auxiliary **243** does not provide the cyclopentane ring required for the A-ring of **245**, this ring will have to be generated after the photocycloaddition of **250**.



The A-ring might be created by an intramolecular aldol condensation of a bis methylketone precursor **248**. This step is potentially flawed because an undesireable alternative aldol condensation is possible. However, an excellent precedent is provided by a similar step in a total synthesis of the sesquiterpene α- bourbonene (**F**). Thus, intramolecular aldol condensation of **A** delivers cyclopentenone **E** and none of the isomeric cyclopentenone **C**. Apparently, cyclization to the aldol condensation product **B** is disfavored by steric hinderance by the angular methyl substituent in the alternative aldol condensation product **D**. Steric approach control (*SAC*) should favor β-delivery of hydrogen during reduction of **247** to give the requisite configuration at position 1 in **246**. The proper orientation during generation of the B-ring can be assured by a temporary bridge, an ester, between **243** and the C-ring precursor **244**.



Intramolecular photocycloaddition of the ester **250** from the chiral auxiliary **243** delivered cyclobutane **251**. Addition of a methyl group, the one carbon needed to complete the A-ring required 4-10 steps depending on the configuration of the C-7 substituent in **251**. Reduction of the remaining ester in **252** then provided the methyl group at position 4 in **253** which had been functionalized solely to allow construction of the temporary bridge in **250**. Functional group manipulation then provided dione **254** which underwent completely selective aldol condensation affording **255**. Stereoselective hydrogenation of **255** created the stereocenter at position 1 and removed the benzyl protecting group. Wolff-Kishner reduction of the resulting saturated ketone delivered **256**. Introduction of the 5-hydroxyl and 7-malonic ester substituents then required oxidation to **257**, reduction and Mitsunobu inversion to give **258**, stereoselective epoxidation followed by hydride reduction, protection, and deprotection to deliver **259** and nucleophilic substitution which provided malonic ester **245** in *0.6% yield overall from **243** in 29-35 steps*.

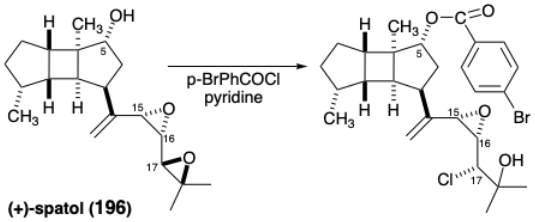


Convergent and Linear Strategies

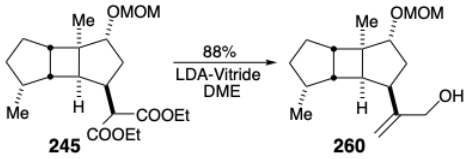
The overall yield of homochiral malonic ester (-)-**241** from racemic (±)-**215** in the first synthesis was 9%, more than an order of magnitude higher than the 0.6% overall yield of homochiral malonic ester **245** from homochiral **243** in the second synthesis. The success of the first synthesis, that relies upon resolution to introduce asymmetry, is especially noteworthy because resolution is inherently inefficient -- it provides at best as 50% yield of the correct enantiomer. Two factors diminish the penalty for using resolution. First, the resolution is performed very early in the first synthesis and, therefore, the effort wasted by discarding half of the racemic product is minimized. Second, Johnson's sulfoximine method is spectacularly effective. Furthermore, the advantages of the clever plan to exploit the readily available chiral auxiliary **243** to introduce asymmetry into the second synthesis cannot overcome the penalty arising from the absence of a methyl group at position 4 or a hydroxyl group at position 5, and the lack of an A-ring in the photocycloadduct **251** from **243**. The first synthesis is more **convergent** than the second. Thus, two large fragments are constructed that contain most or all of the skeletal atoms and functionality of the target and these fragments are then united. Such an approach has several advantages over a **linear** synthesis, that is one in which the molecule is constructed by sequentially uniting many small fragments or introducing functionality after skeletal construction is complete. A convergent synthesis is more efficient as measured by overall yield. If the average yield of an n-step synthesis is Ψ%, then the overall yield will be $100(\Psi/100)^n$%. A 21-step ***linear synthesis*** with an average 95% yield will have an overall 34% yield, or an overall 11% with an average 90% yield, or *an overall 0.9% with an average 80% yield*. In contrast for a ***convergent synthesis*** that combines two intermediates each prepared by 10-step syntheses (i.e. a total of 21 steps), the overall yield will be 56% with an average 95% yield, or an overall 31% with an average 90% yield, or *an overall 9% with an average 80% yield*. In effect the convergent synthesis is only 11 steps. The two abovementioned syntheses are a case in point. The average yield per step, 84-87%, in the second synthesis was almost as high as the 89% average per step yield in the first synthesis. The 15 fold lower overall yield for the second synthesis is almost entirely the consequence of its greater length, 29-35 steps versus 21 steps.

Stereocontrolled Sidechain Construction

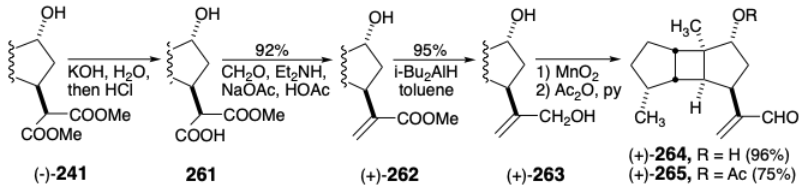
Two strategic challenges must be met for completion of a total synthesis of spatol (**196**). First, the unique allylic vicinal diepoxide in **196** was presumed to be highly electrophilic because epoxide ring opening by chloride, a weak nucleophile, accompanies esterification upon treatment of **196** with p-bromobenzoyl chloride and pyridine. Second, the three stereocenters of the flexible sidechain must be assembled with the correct configurations relative to those in the rigid tricyclic nucleus.



The malonic ester group in the intermediates (-)-**241** and **245** could provide a three-carbon allylic precursor of the spatol side chain. Koga converted **245** into allylic alcohol **260** by a modified Marshall reduction.

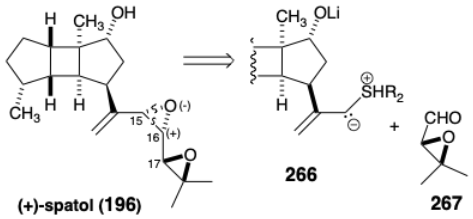


However, attempted one-step conversion of (-)-**241** into the allylic alcohol **263** by the Marshall reduction, i.e. LAH reduction of the sodium enolate, failed completely. Therefore, this transformation was accomplished by monosaponification to **261** and decarboxylative aldol condensation with formaldehyde to provide acrylic ester (+)-**262**. Hydride reduction then delivered allylic alcohol (+)-**263** that was selectively oxidized with MnO_2 to the aldehyde (+)-**264**. To correlate this synthetic intermediate with the natural product, (+)-**264** was acetylated. The totally synthetic acetate showed $[\alpha]_D^{22}$ +25.1° that compares well with the naturally derived acetate which showed $[\alpha]_D^{22}$ +26.5°.[1]

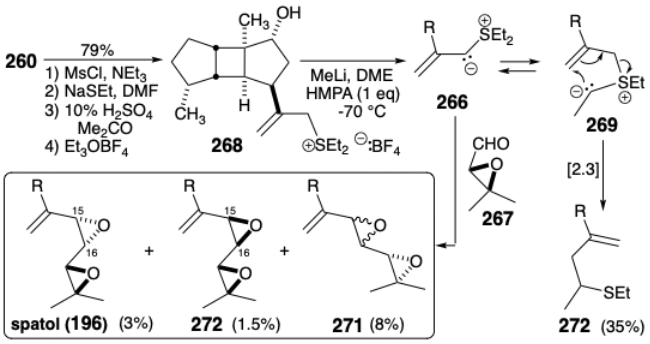


An Absolute Asymmetric Strategy

Disconnection of both a nucleophilic oxygen and an electrophilic carbon from carbon 15 of spatol suggests a precursor **266** in which the sulfonium functional group provides the requisite biphilic reactivity at carbon 15.[19] The correct relative configurations for the stereocenters in the tricyclic nucleus and at position 17 are assured in an **absolute asymmetric synthesis** by using building blocks **266** and **267** with the correct absolute configurations. Although very short, this convergent strategy provides no control over the configurations at positions 15 and 16.

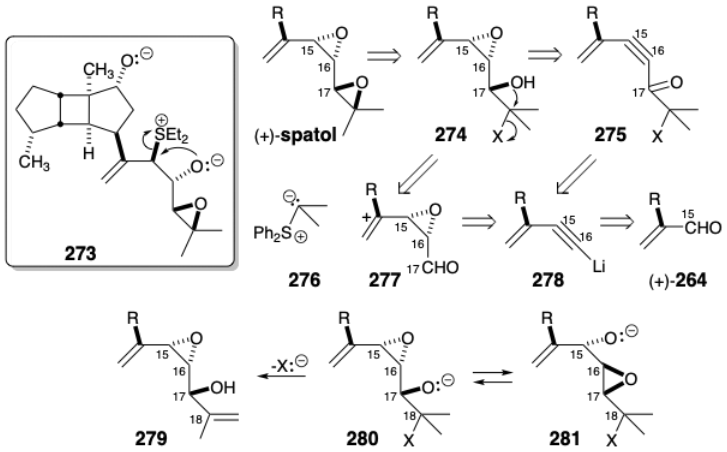


Ylide **266** was prepared from allyic alcohol **260** through sulfonium salt **268**. Reaction of ylide **266** with aldehyde **267** produced spatol in only 3% yield together with the isomeric allylic *cis* diepoxide **270** (1.5%) and a mixture of *trans* diepoxides **271** (8%). Moreover, **266** exists in equilibrium with an alternative ylide **269** that underwent [2.3] sigmatropic rearrangement producing the homoallylic sulfide **272** (35%) as the major product of the reaction.

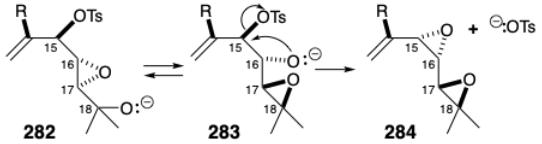


A Stereospecific Epoxydiol Rearrangement Strategy

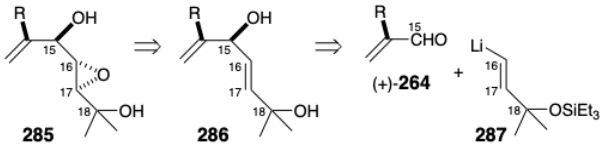
The last step in the reaction of ylide **266** with aldehyde **264** involves vicinal alkylation of an alkoxide during cyclization of **273**. The reaction of aldehyde **277** with ylide **276** is a related strategy. The epoxy aldehyde **277** might be available from aldehyde (+)-**264** by Corey-Fuchs alkynylation to give **278**, homologation with formaldehyde, Lindlar reduction of the resulting propargyl alcohol, asymmetric epoxidation of the derived allylic alcohol, and Swern oxidation of the resulting epoxy alcohol. Alternatively, **278** might be homologated to **275**. Then, after assymmetric reduction of this propargyl ketone, Lindlar reduction, and $VO(acac)_2$-catalyzed epoxidation, heterocyclization of the resulting **274** might deliver (+)-spatol. However, these strategies are too long, and ring closures of intermediates such as **274** may be derailed considering the potential, *inter alia*, for E-1 elimination and transepoxidation. Thus, intramolecular attack of the alkoxide in **280** at the 2° 16-position to give **281** rather that at the 3° 18-position to give spatol might even be favored. Such transepoxidation reactions (Payne rearrangements) are well known. However, the rearrangement to **281** is reversible while heterocyclization of **280** would be irreversible. Nevertheless, E1 elimination to give **279** seemed a reasonable concern.



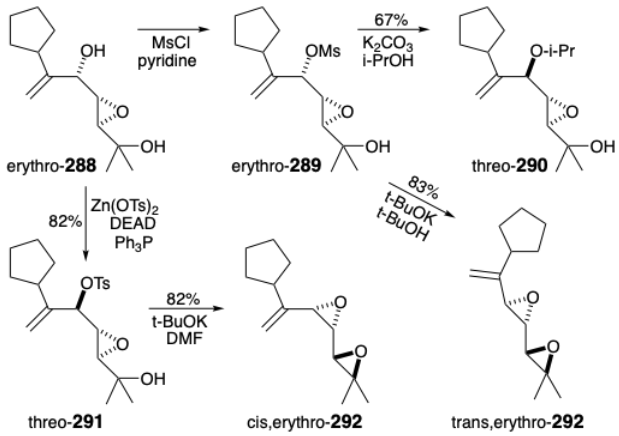
An alternative strategy is possible involving an epoxy alkoxide similar to **281** but with the positions of the nucleofuge and alkoxide exchanged. Thus, Payne rearrangement should produce **283** but the *trans* stereochemistry of the epoxide in **282** should virtually preclude direct attack of the alkoxide at the 15-position to produce a tetrahydrofuran. The allylic electrophile at position 15 in **283** should be particularly effective in alkylating the neighboring alkoxide producing an allylic diepoxide **284**.



Furthermore, an efficient strategy for assembling an epoxydiol precursor **285** for **282** seemed feasible. Thus, **285** should be available by regioselective epoxidation of **286** which should, in turn, could be prepared by the union of a C_{15} electrophile (+)-**264** with a C_5 nucleophile **287**.

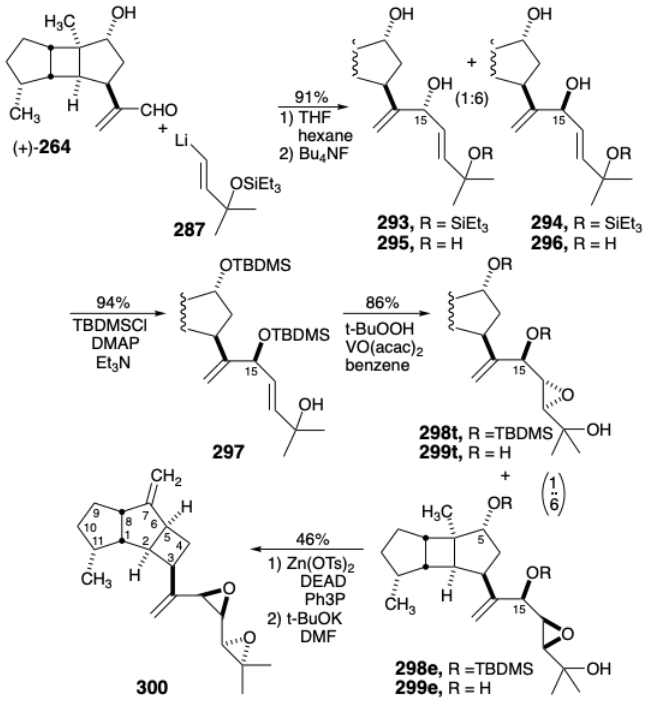


In model studies, a method was sought to produce the allylic diepoxide array of the spatol side chain from appropriately activated derivatives of epoxydiol **285**. Initial results were disappointing. Thus, activation of erythro-**288** as a mesylate, erythro-**289**, followed by treatment with solid K_2CO_3 in boiling isopropanol delivered threo-**290** by intermolecular S_N2 displacement rather than the desired vicinal diepoxide by Payne rearrangement followed by heterocyclization. Since the tertiary hydroxyl group in erythro-**289** appeared not to be sufficiently nucleophilic to displace the epoxy leaving group, conditions were sought that would generate an alkoxide from the tertiary hydroxyl. Treatment with t-BuOK in t-BuOH promoted a clean, stereospecific rearrangement and heterocyclization to deliver the diepoxide trans,erythro-**292**. A route from the erythro-**288** to an activated derivative of the *threo* epoxy alcohol requires activation with concomitant inversion of configuration. This was accomplished by the Still modification of the Mitsunobu reaction. Thus, reatment of erythro-**288** with $Zn(OTs)_2$, diethyl azodicarboxylate, and triphenylphosphine, gave tosylate threo-**291** that, upon treatment with t-BuOK in DMF, afforded the allylic diepoxide cis,erythro-**292** in 82% yield.

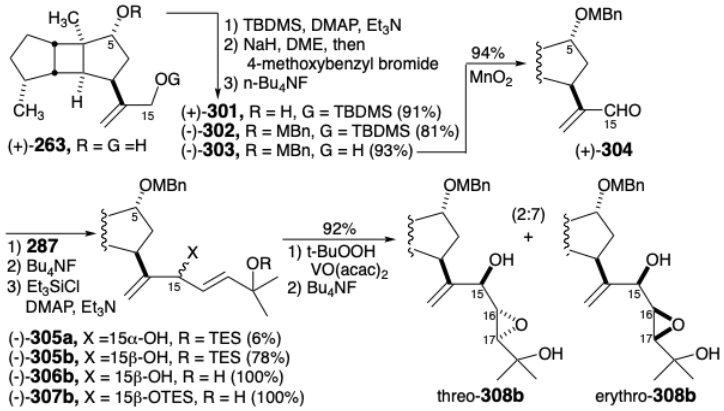


The substitution reaction of mesylate erythro-**289** with isopropanol to give threo-**290** suggested that a similar substitution with tetrabutylammonium hydroxide might provide a route to the inverted alcohol. Instead, however, a high yield of diepoxide trans,erythro-**292** was obtained. The unexpected stability of this allylic diepoxide toward hydroxide is especially interesting in view of the epoxide-cleaving substitution reaction of spatol with the less nucleophilic chloride anion that gives a chlorohydrin (*vide supra*). Apparently, the latter reaction is an *acid-catalyzed epoxide opening induced by pyridinium hydrochloride*, a byproduct of the acylation with p-bromobenzoyl chloride in the presence of pyridine.

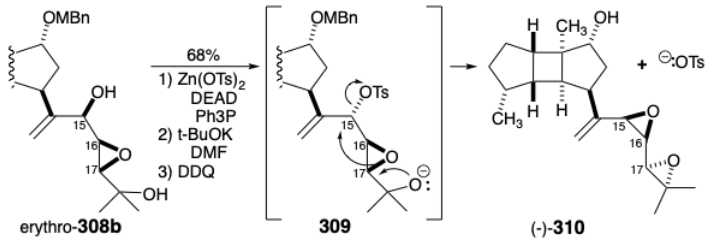
In a first attempt to implement the plan, addition of vinyllithium **287** to aldehyde (+)-**264** provided a 1:6 mixture of triols **295** and **296** respectively after desilylation of the intermediate monosilyl ethers **293** and **294**. To control the regioselectivity of epoxidation, the triol **296** was selectively disilylated. Vanadium-catalyzed epoxidation of **297** was then directed to the 15,16-C=C bond by the remaining allylic hydroxyl. Since the major epoxide product was the erythro derivative **298e**, selective activation of the less hindered 15-hydroxyl in the corresponding triol **298e** was performed with inversion of configuration. However, treatment with base produced an allylic diepoxide **300** with a *cis,anti,cis*- tricyclo[5.3,0,$0^{2,5}$]decane nucleus. Thus, Wagner-Meerwein rearrangement of the *cis,anti,cis*-tricyclo[5,3,0,$0^{2,6}$]decane nucleus of **298e** to give **300**, apparently owing to an unintended activation of the 5-hydroxyl that accompanied the desired activation of the hydroxyl at the 15-position.



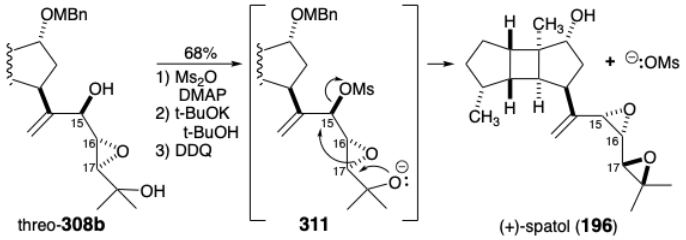
These results suggested that derivatives of epoxy triols **299e** and **299t** in which the hydroxyl at position 5 is masked were needed for generation of the spatol side chain without accompanying rearrangement of the tricyclic nucleus. The lability of the allylic diepoxide array in spatol (**196**) under acidic conditions limited the choice of derivatives to those with masking groups that would be removable under neutral or basic reaction conditions. The further requirement for stability towards a vinyllithium reactant and the presence of unsaturation in the synthetic target recommended p-methoxybenzyl (MBn) ether derivatives. The MBn masking group is removable under mild conditions by oxidative cleavage with DDQ. Therefore, the MBn derivatives *erythro*-**308b** and *threo*-**308b** of **298e** and **298t** were prepared from diol (+)-**263**.



The assignment of an S absolute configuration at the 15-position to the major epimer (-)-**305b** was based on correlation with natural (+)-spatol (*vide infra*). Epoxidation of the derived silyl ether (-)-**307** provided a 2:7 mixture of threo and erythro epoxides **308b**. The major isomer, erythro-**308b**, was converted into a cis, erythro diepoxide (-)-**310** by conversion to a threo tosylate with inverted configuration at the 15-position followed by base-induced Payne rearrangement, heterocyclization, and finally by deprotection of the 5-hydroxyl. That (-)-**310** was not spatol (**196**) was evident from its optical activity, $[\alpha]_D$ = -10.0° in contrast with $[\alpha]_D$ = +45.6° reported for the natural product. Small chemical shift differences, e.g. vinyl ^{1}H NMR resonances at δ5.14 and 5.09, confirmed that (-)-**310** is epimeric at positions 15, 16, and 17 with (+)-spatol which exhibits vinyl resonances at δ5.13 and 5.02.

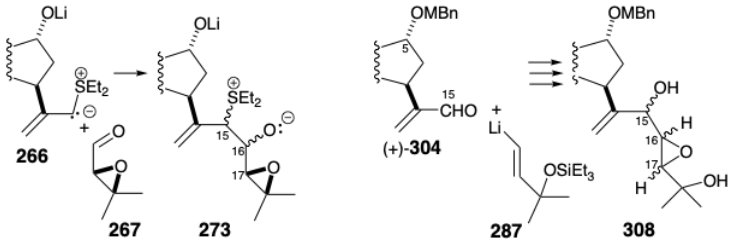


The minor isomer, threo-**308b**, was converted into (+)-spatol (**196**) by monomesylation followed by base-induced Payne rearrangement, heterocyclization, and deprotection of the 5-hydroxyl. Each resonance in the ^{1}H NMR spectrum of synthetic (+)-spatol coincided within 0.01 ppm with a spectrum of an authentic sample of natural spatol.

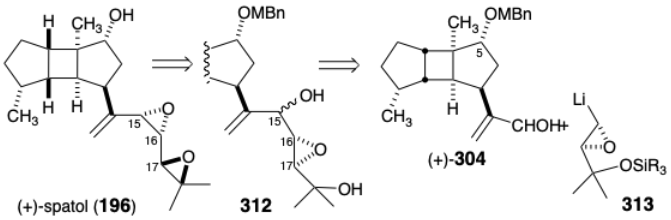


An Absolute Asymmetric Stereoconvergent Strategy

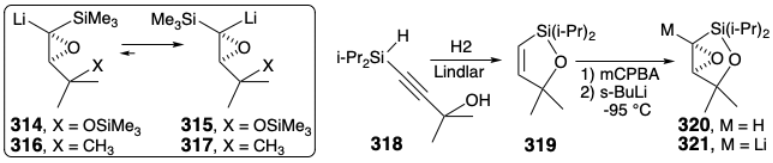
Both of the aforementioned strategies for the spatol allylic diepoxide suffer from inadequate stereocontrol. Thus, while the correct absolute configuration at position 17 in **273** is assured by using the correct enantiomer of **267**, generation of the stereocenters at positions 15 and 16 in **273** is not selective. Similarly, although either epimer at position 15 in **308** can provide an activated derivative with the correct configuration, i. e. by activation with retention or inversion of configuration, generation of the stereocenters at positions 16 and 17 in **308** is not favorably selective.



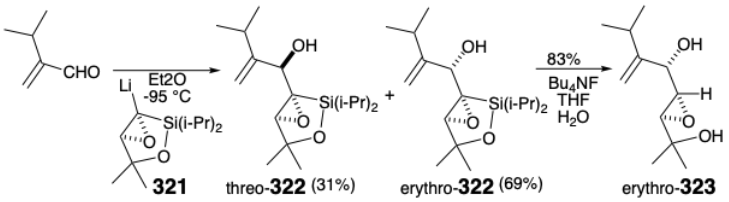
Since *either* epimer of epoxydiol **312** can be converted stereospecifically into spatol, the synthesis is **stereoconvergent**, and stereocontrol at the 15-position is unnecessary for an efficient total synthesis.. The correct stereochemistry at positions 16 and 17 could be assured by an **absolute asymmetric strategy** that combines the homochiral C_{15} aldehyde (+)-**304** and a homochiral C_5 α-epoxy nucleophile **313**.



Because α-silyl epoxides are readily hydrodesilylated by moist fluoride with complete retention of configuration, a possible synthetic equivalent of synthon **313** is the silyl-stabilized α-lithioepoxide **314**. However, a serious flaw could sabotage this strategy. Thus, although α-lithioepoxides are generally configurationally stable, the α-lithioepoxide **316**, a close analogue of **314**, exhibits an unusual configurational instability rearranging completely to **317** owing, no doubt to steric strain that is relieved upon trans-cis isomerization. A similar isomerization of **314** to **315** would derail the synthesis. This pitfall was circumvented by a temporary bridge between the C-silyl substituent and neighboring oxygen in **321**. Thus, intramolecular O-silylation precludes isomerization of the carbanion **321** obtained by metallation of **320**. Racemic **321** was prepared through epoxidation of a vinylsilane **319** that was generated by a novel hydrogenation-dehydrogenative-heterocyclization of **318**.



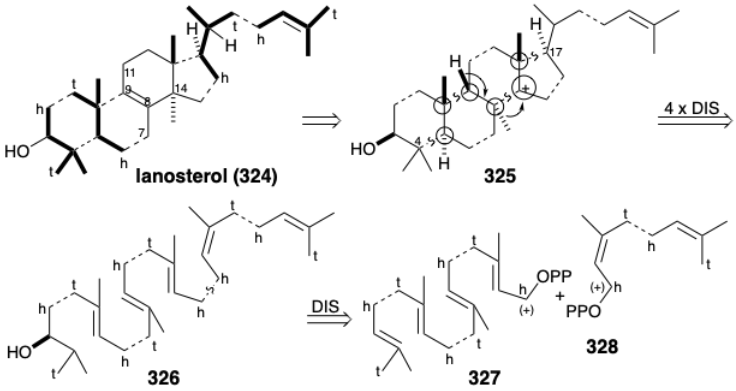
In a model study, reaction of α-lithioepoxide **321** with 2-(i-propyl)acrolein delivered an epimeric mixture of adducts **322** favoring the erythro diastereomer by 7:3. Desilylation of erythro-**322** gave epoxydiol erythro-**323**. Thus, the racemic intermediate **321** provides a two-step synthesis of epoxydiol precursors of the spatol allylic diepoxide. However, only conjunction of aldehyde (+)-**304** with the correct enantiomer of **321** will provide the correct absolute configurations at positions 16 and 17 in **312** that are required to accomplish an efficient construction of natural spatol (**196**). A route to optically pure epoxide **321** must yet be found.



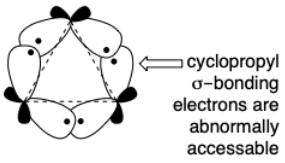
4.7: Biosynthesis and Total Synthesis of Steroids

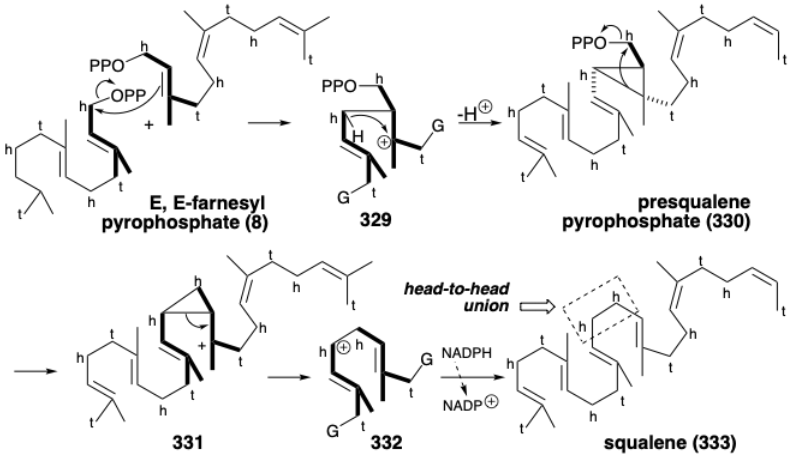
Biosynthesis of Lanosterol

Lanosterol (**324**) is a member of steroid family of natural products. The isoprenoid origin of this triterpene, biogenetically a C_{30} hexamer of isopentenyl pyrophosphate, is not entirely evident from its structure. Thus, while two isoprene units are discernable in the right hand portion of **324** and two in the leftand portion, the ten carbon atoms in the central region of the molecule do not show isoprenoid connectivity. If, however, a methyl group were appended at position 8 or 9 of the four carbon 7,8,9,11-chain an isoprene unit would be formed. Since generation of the multicyclic carbon networks of terpenes occurs by electrophile-induced polyene cyclizations, the 8,9-C=C bond in **324** might arise by elimination of a proton from a carbocation precursor. A carbocation at the 8 position could have been generated by 1,2-migration of a methyl group from position 8 to a carbocation at position 14. Two more isoprene units are discernable in the central portion of the putative precursor **325**. Topological analysis of **325** reveals six common atoms. Two disconnections between common atoms and two between a common and a noncommon atom greatly simplifies the structure suggesting an acyclic triterpene precursor **326** that might arrise by the head to head union of a diterpene pyrophosphate **327** with a monoterpene pyrophosphate **328**. The strategy inferred above is close to that involved in the biosynthesis of lanosterol.

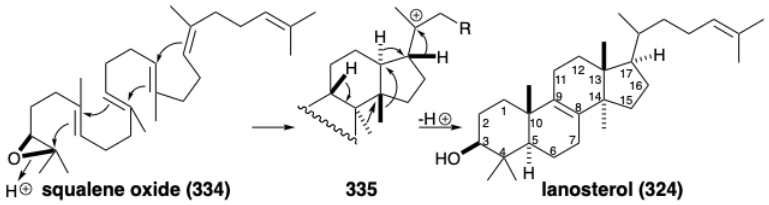


The actual biosynthetic strategy does indeed involve a head to head union of terpenoid pyrophosphates. However, a more efficient construction is achieved through a symmetrical acyclic triterpene intermediate, squalene (**333**), formed by the union of two molecules of a sesquiterpene precursor, E,E-farnesyl pyrophosphate (**8**). Since both carbons to be joined are electrophilic, polar formation of the central C-C bond of squalene cannot be direct. Rather, only the electrophilic activation provided by the functional group of one molecule of farnesyl-OPP is utilized to form a C-C bond with the nucleophilic C=C bond of a second molecule of farnesyl-OPP. Proton loss from the putative intermediate 3° carbocation **329** (or, possibly, the corresponding adduct with a nucleophilic moiety of the enzyme that catalyzes the process) produces a cyclopropylcarbinyl intermediate, presqualene pyrophosphate (**330**), that can be isolated from biosyntheses conducted in vitro in the absence of NADPH. In the presence of NADPH, **330** undergoes a reductive rearrangement formally involving a rearranged cyclopropyl 3° carbinyl cationic intermediate **331** and an allylic cation **332** that is captured by hydride to deliver squalene (**333**). The σ-bond in the cyclopropyl-carbinyl pyrophosphate **330** serves as nucleophile that displaces a pyrophosphate nucleofuge. The σ-bond electrons in cyclopropanes are especially accessible.

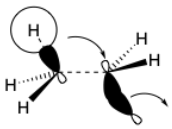


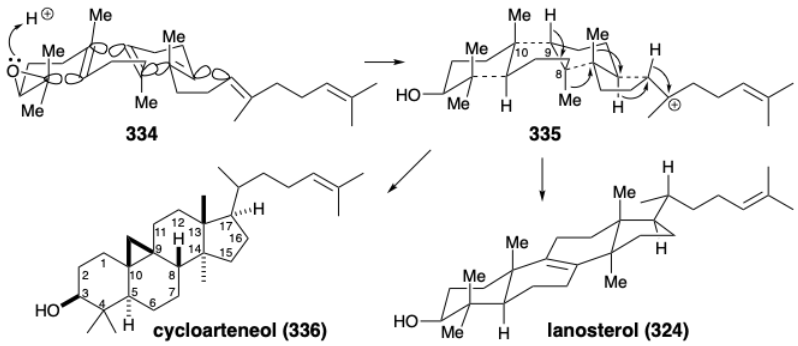


Asymmetric epoxidation converts the prochiral acyclic triterpene precursor **333** into a homochiral epoxide, squalene oxide (**334**). Generation of the four fused rings of lanosterol is then initiated by intramolecular alkylation of a C=C bond by a tertiary electrophile provided by protonation of the epoxide. A total of four consecutive alkylations, known as a polyene cyclization, deliver the putative intermediate **335** that rearranges by a series of two 1,2-hydride and two 1,2-methyl shifts to give lanosterol (**324**) after proton loss from the 9 position.



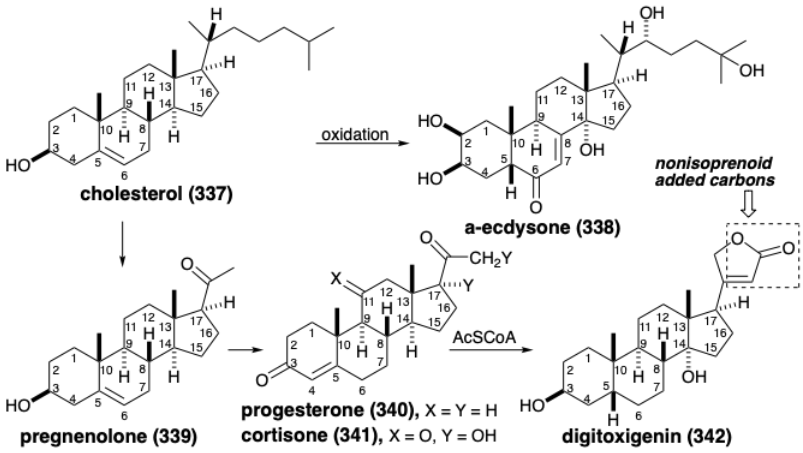
Especially interesting are the stereochemical details of the polyene cyclization and subsequent rearrangement of **335** to deliver **324**. The polyene cyclization involves stereospecific **anti-periplanar** addition across three C=C bonds in **334** (see below). The folded conformation of **334**, required for cyclization to **335**, is probably imposed by the enzyme involved since appreciable steric congestion is present in both **334** and the intermediate **335**. Relief of steric strain provides a large driving force for the rearrangement of **335** to **324** that involves stereospecific inversion of configuration at each stereocenter during 1,2-hydrogen or methyl shifts. Thus, each 1,2-hydride or 1,2-methyl shift occurs to the backside of the orbital connected to the departing nucleofuge in what can be viewed as a series of nucleophilic substitution reactions – where σ-bonding electron pairs serve as the nucleophiles. Instead of proton loss to give **324**, the rearrangement of **334** in some higher plants and algae ends with proton migration from the 9 to the 8 position and proton loss from the methyl group at position 10 forming a cyclopropane ring in cycloarteneol (**336**). This mechanism for the generation of a cyclopropane is analogous to that for the production of presqualene pyrophosphate (**330**) from **329**.



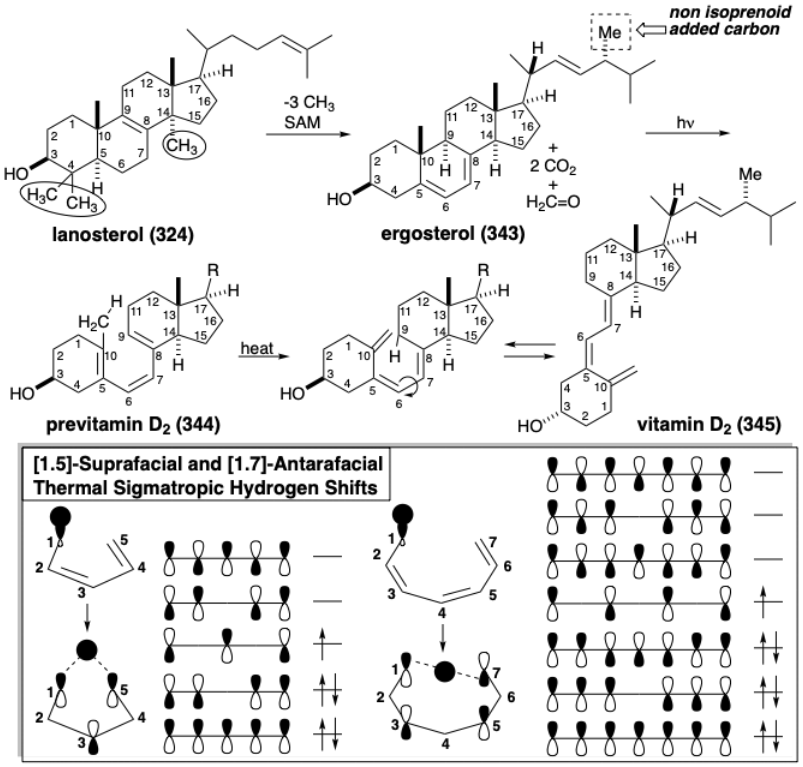


Nor and Seco Steroids. Although lanosterol (**324**) and cycloarteneol (**336**) are **irregular triterpenes**, i.e. their carbon skeletons are not composed of intact isoprene units, these triterpenes possesses the expected thirty carbons. Many steroids, that are derived biologically from lanosterol, contain fewer than thirty carbons and are referred to as **nor triterpenes**. Thus, for example, formation of cholesterol (**337**) from lanosterol (**324**) occurs by oxidative conversion of three methyl groups into formyl or carboxyl

substituents that are lost as formate or cabon dioxide to give a tris nor triterpene after saturation of the side-chain C=C bond and migration of the $\Delta^{8,9}$ C=C bond to the $\Delta^{5,6}$ position. The biosynthesis of some steroids from cholesterol, such as the insect molting hormone α-ecdysone (**338**), simply involves oxidative introduction of functionality and C=C bond migrations. The loss of six carbons from the sidechain of cholesterol (**337**) leads to pregnenolone (**339**) the biosynthetic precursor of the female reproductive hormone progesterone (**340**) and the adrenocortical hormones such as cortisone (**341**) that is generated by oxidative functionalization of **340**. The biosynthesis of the cardiac steroids such as digitoxigenin (**342**), that occurs in plants, creates the butenolide moiety by addition of a two carbon nucleophile from acetylCoA to the electrophilic side-chain carbonyl of **340**.

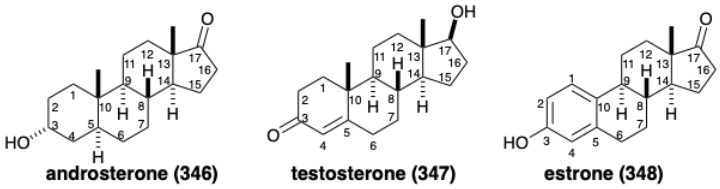


Addition of a carbon atom as an electrophilic methyl group from S-adenosylmethionine (SAM) occurs during the biosynthesis of ergosterol (**343**). A pericyclic rearrangement of **343** to **344** followed by a thermally allowed antarafacial [1.7]-sigmatropic rearrangement of hydrogen from the methyl at position 10 to the 9 position leads to the generation of vitamin D_2 (**345**). Sigmatropic shifts of hydrogen necessarily involve positive overlap, i.e., with the same phase, of the hydrogen half-occupied σ-orbital with the ends of the highest occupied pentadienyl π-orbital Both **344** and **345** are **seco steroids**, i.e. their carbon skeletons lack one of the ring C-C bonds of the tetracyclic steroid skeleton.

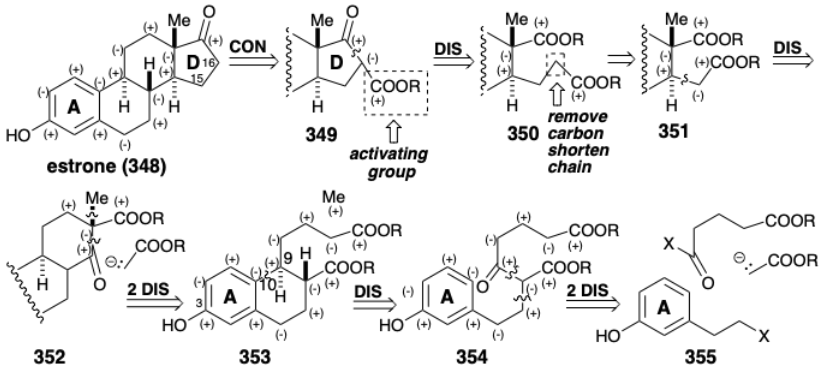


The entire cholesterol sidechain is removed during biosynthesis of the male sex hormones androsterone (**346**) and testosterone (**347**) and biosynthesis of the female reproductive hormone estrone (**348**) even requires loss of the angular methyl substituent from

position 10. Noteworthy is the fact that the biosynthetic strategy for **348** is exceptionally circuitous and lengthy considering the structural simplicity (only four centers of chirality) of this target. The justification, of course, is the availability of the starting material, the ubiquitous biological steroid precursor, cholesterol. Furthermore, Nature has at its disposal a vast armementarium of selective reagents (enzymes) to achieve surgically clean removal of unwanted carbon atoms or groups by activation of C-H bonds, even those that are remote from functionality.

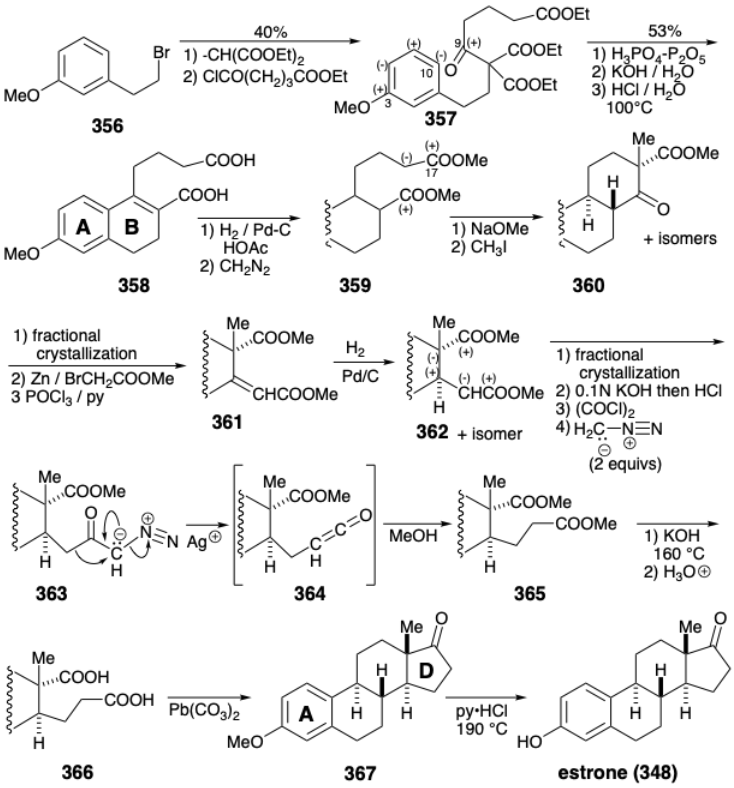

androsterone (346) testosterone (347) estrone (348)

Total Syntheses of Estrone. All circuits between the oxygen functionality in the A and D rings of estrone are consonant except those involving carbons 15 and 16. Therefore, activating functionality is essential to allow polar C-C bond formation between the D ring carbonyl carbon and carbon 16. Disconnection of this bond in **349** suggests a diester **350** which still has functional dissonance, e.g. between the two carboxyl groups. All dissonance is removed by shortening the propionic to an acetic sidechain as in **351**. Polar disconnection of an ester stabilized nucleophile sugggests a β-keto ester **352** and further polar disconnections then suggest **353** and a methyl electrophile, as precursors. Finally, polar disconnection of **353** suggests a monocyclic aromatic precursor **354** with an entirely consonant side chain in which the added carbonyl at the incipient 9 position can facilitate further polar disconnections to **355**, an ester stabilized nucleophile, and a glutaryl electrophile. The foregoing retrosynthetic analysis provides a **linear strategy** for the synthesis of estrone that starts with an intact A ring and then builds the B, C, and D-rings in succession by polar reactions.



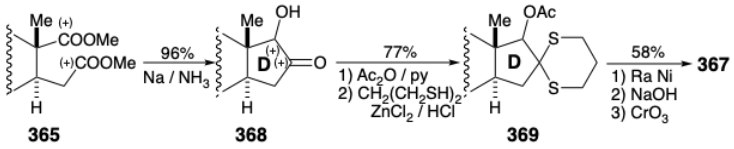
estrone (348) 349 350 351 352 353 354 355

The first total synthesis of estrone, was completed[21] in 1948. It assembled a methyl ether **357**, related to **354**, from the bromoethylanisole (**356**) by alkylation and then acylation of diethyl malonate. Cyclialkylation of the resulting ketotriester **357** makes use of the polar activation provided by target related functionality at position 3 that is conjugated through the aromatic ring with position 10. Hydrolysis and decarboxylative elimination then delivered alkene **358**[22] that upon hydrogenation, O-methylation, Dieckman cyclization, and C-methylation delivered an epimeric mixture from which the required ketoester **360** was isolated by fractional crystallization. Once again target related functionality, here the incipient carbonyl at position 17, facilitates polar bond formation. It is also noteworthy that target unrelated functionality, a carbonyl group on the carbon that will become position 9, serves as a lynchpin for connecting major segments in the **356** to **357** conversion and for generating the last connection for the B-ring in the **357** to **358** conversion. Reformatsky condensation followed by dehydration and hydrogenation provided diester **362** and an epimer from which it was separated by fractional crystallization. The lack of stereocontrol in this synthesis of **362** necessitated tedious isolations from isomer mixtures and resulted in a low overall yield.

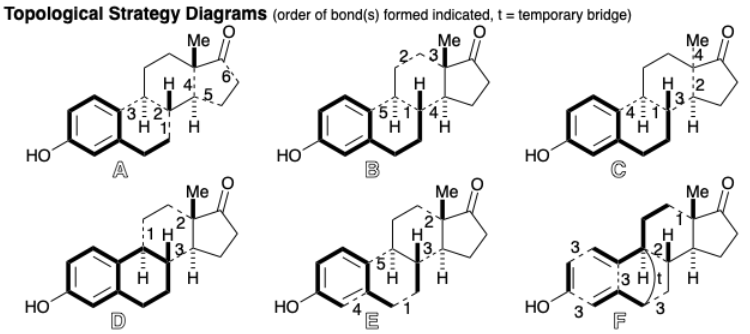


Chain elongation of the consonant 1,5-diester **362** generated a dissonant 1,6-diester precursor **365** of the dissonant D-ring cyclopentanone in **367**. *The creation of a dissonant product by polar reactions requires a dissonant reactant.* In the present case this role is played by diazomethane that is dissonant by virtue of the presence of a biphilic activating group. Thus, the diazonium group stabilizes an α carbanion providing nucleophilicity for C-C bond formation with an acyl chloride and subsequently serves as a nucleofuge promoting migration of a nucleophilic alkyl group from the carbonyl carbon in **363** to the neighboring carbon in **364**.

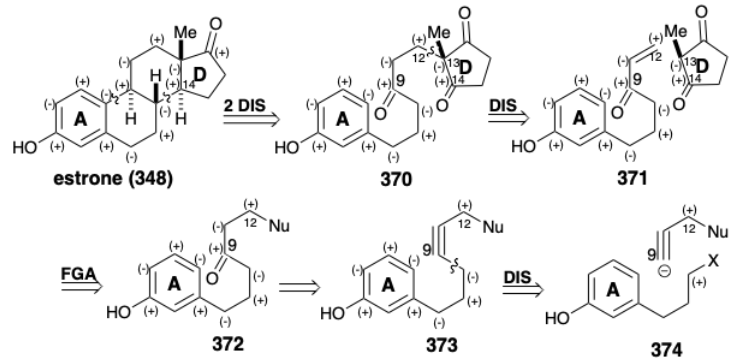
An alternative construction of the dissonant D-ring cyclopentanone in **367** from the consonant 1,5-diester **365** generates a C-C bond between the two electrophilic ester carbons by a nonpolar process, reductive coupling.[23] Thus, an acyloin condensation provides **368** from which the unneeded carbonyl is removed by reductive desulfurization of the derived thioacetal **369**.



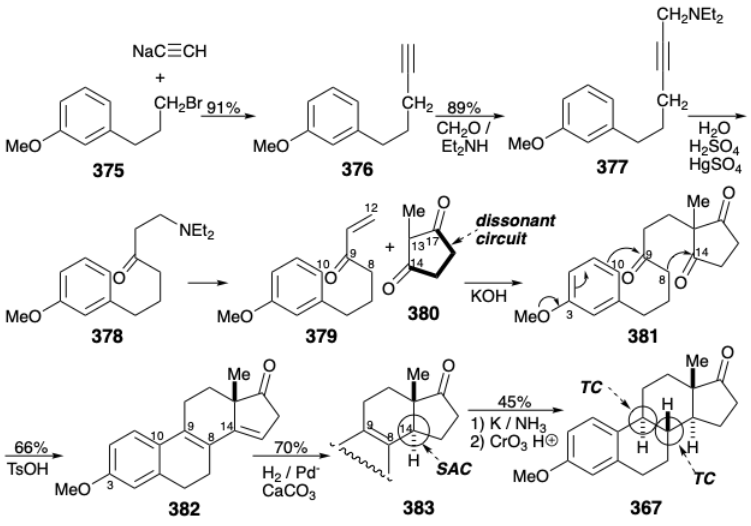
Topological Analysis of Estrone. The topological strategy for a synthesis can be summarized in a diagram that shows the starting material with bold outline and bonds formed in completing the skeleton with dashed lines. The two previous estrone syntheses illustrate strategies featuring late construction of the dissonant D-ring as in diagram **A** which allows the sequence of C-C connections employed. Greater efficiency can be accomplished by incorporation of the dissonant D-ring as a preformed unit as in **B**. Almost as efficient is the use of a dissonant precursor from which the D-ring is readily generated immediately after assembling an intermediate containing all the carbon atoms required for the skeleton as in **C**. A highly convergent and, therefore, exceptionally short synthesis is achievable by joining a preformed AB-ring unit with a D-ring unit as in **D**. The strategies summarized by **A**-**D** use aromatic starting materials for the aromatic moiety in the synthetic target. This tactic benefits from the relative stability of aromatic systems by avoiding potential yield-decreasing side reactions that might occur during manipulation of nonaromatic intermediates containing more reactive functionality. Interestingly, some efficient modern syntheses, summarized by **E** and **F**, generate the A-ring after assembly of a nonaromatic precursor containing all the skeletal carbons of the final target. Further discussion of the strategies **B**-**F** is deferred to a full consideration of each synthesis.



A strategy summarized topologically by **B** introduces nontarget related functionality, carbonyl groups in **370** on the carbons that will become positions 9 and 14, to activate the polar union of two pairs of common atoms and polar union of a symmetrical D-ring nucleophile with **371**. Dislocation of this enone to a saturated ketone **372** with a nucleofuge (Nu) β to the carbonyl and the latter to an alkyne **373**, reveals the possibility of exploiting a terminal alkyne nucleophile to assemble **373** from an arylpropyl electrophile **374**.

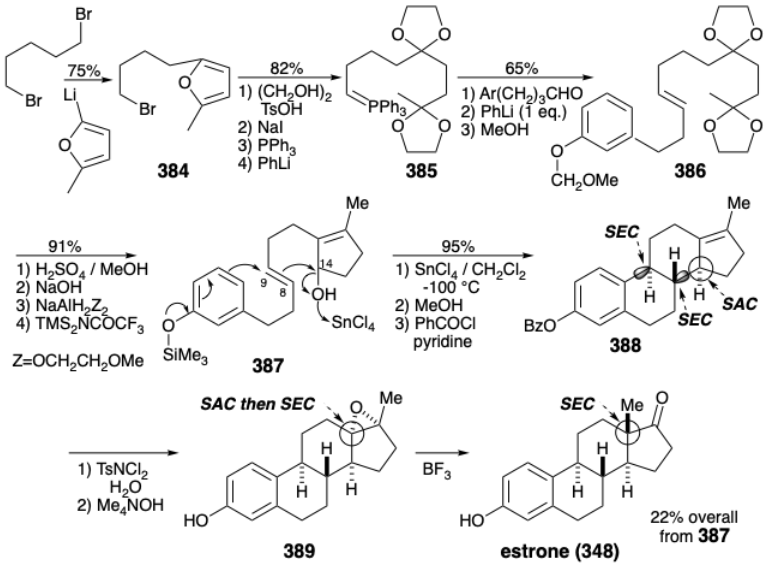


The use of a preformed D-ring in the dissonant building block **380** makes the synthesis[24] more convergent. Greater efficiency is also provided by the consecutive formation of two connections, between the 8 and 14 and then between the 9 and 10 positions, in a single reaction that produces **382** from **381**. Noteworthy is the regioselectivity of the **377** to **378** conversion. Clearly the diethylamino group provides a regiocontrolling influence, perhaps owing to a coordinative interaction with the Hg^{2+} catalyst or to inductive destabilization of the development of a vinyl cation β to the electronegative nitrogen. Generation of the requisite stereochemical relationships is achieved by SAC during the delivery of hydrogen to **382** and TC during protonation of the preferred conformations of anionic intermediates in the reduction of **383**.

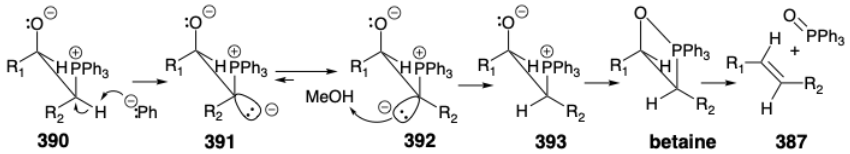


Another more recent synthesis,[25] summarized topologically by **C** , is closely related to the B topological approach discussed above. Thus, the topology and polar reactivity involved in the **381** to **382** conversion is the same as that in the **387** to **388** conversion.

However, a preformed D-ring is not exploited. Rather, this moiety is present in latent form in **386** that contains a dissonant circuit between masked 1,4-dicarbonyl groups. The dissonance derives from a latent 1,4-dicarbonyl array that protected by the aegis of aromaticity in the furan ring of **384** that is readily prepared by lithiation and then alkylation of α-methylfuran.

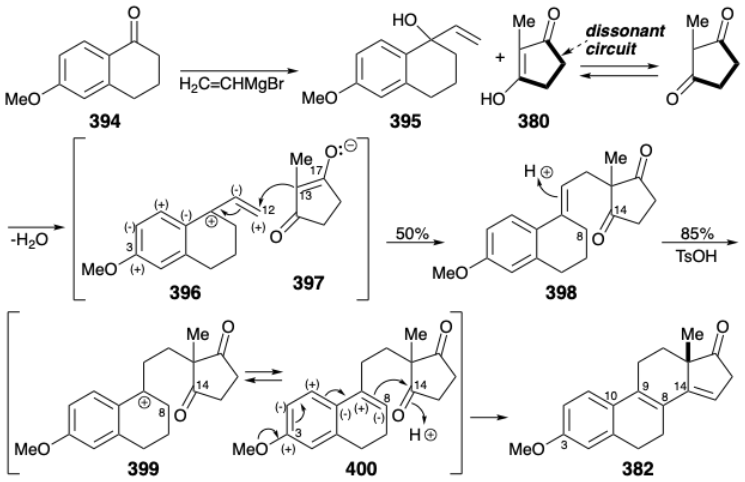


Stereoselective generation of the trans disubstituted C=C bond in **387** is accomplished by the Schlosser modification of the Wittig olefination. Thus, the β-oxidophosphonium intermediate **390**, that is the major product from the addition of ylide **385** to an aldehyde, is converted to an epimeric β-oxidophosphonium intermediate **393** by protonation of a β-oxido ylide **392**. This carbanion is thermodynamically favored over the epimeric carbanion **391**. Subsequent syn elimination (perhaps through 2πs + 2πa cyclo-elimination of $Ph_3P{=}O$ from a betaine intermediate) delivers the trans alkene stereospecifically.

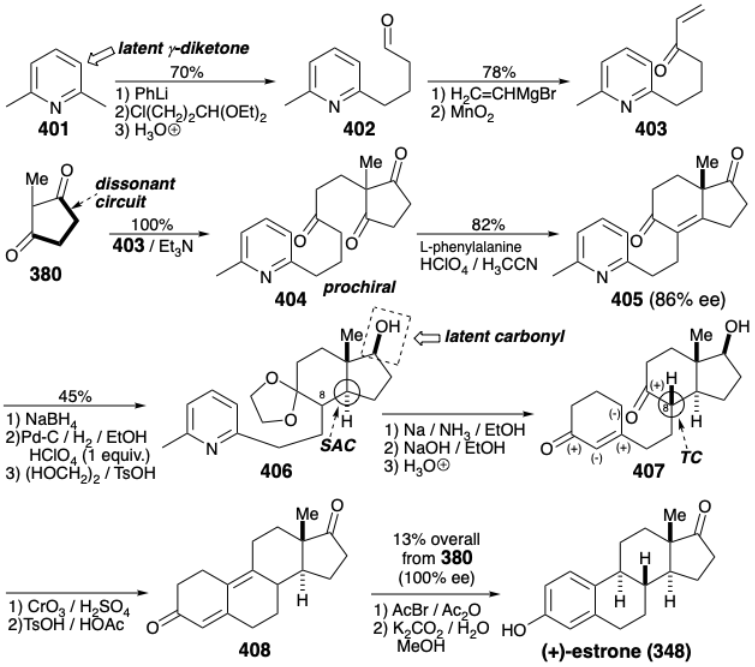


Although **387** has no polar functionality at position 9, the 9-position participates as electrophile and the 8 position as nucleophile during polar cyclization to **388** in analogy with the **381** to **382** bis annelation. The stereoselectivity of this cyclization derives from a stereoelectronic preference for anti periplanar addition to the C=C bond in **387** and steric approach control during bond formation between positions 8 and 14. Stereoselective introduction of the angular methyl is accomplished by generation of the α-epoxide **389**. Here SAC favors β attack by Cl^+ on the C=C bond. This is followed by stereospecific configurational inversion during intramolecular S_N2 displacement. Finally, 1,2-migration of methyl during a pinacol rearrangement generates the required β-methyl configuration and a trans CD ring junction.

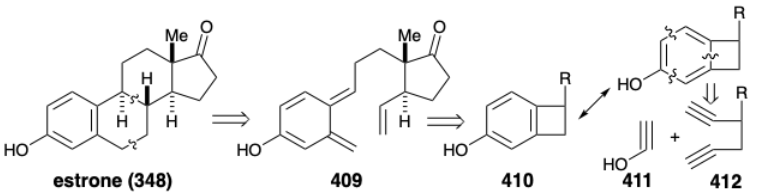
The most efficient strategy for total synthesis of estrone is also the most convergent, joining a preformed AB-ring unit **394** with a D-ring unit **380** as in **D**. This, the Velluz synthesis[26], provides an industrial source of estrone that is more economical than biosynthesis. The polar union of **395** with **380** epitomizes the efficient use of functionality to facilitate skeletal construction. Interestingly, **380** is a vinylogous carboxylic acid sufficiently acidic to protonate **395**. The resulting carbocation **396** is stabilized by target related functionality at position 3 while nucleophilicity at position 13 is stabilized by the target related oxygen functionality at position 17 in the enolate **397**. Target related functionality at position 3 also facilitates generation of the 8-14 C-C bond during acid catalyzed cyclization of **400** to **382**. A stereoselective route from **382** to estrone methyl ether (**367**) was described above.



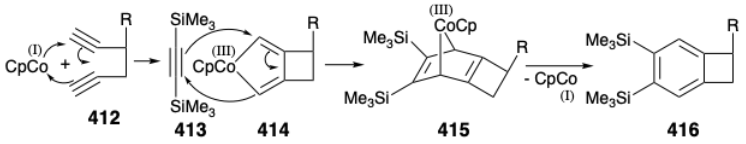
An Enantioselective Synthesis. The foregoing strategies all produce racemic estrone that must be resolved to provide the natural enantiomer. An enantioselective synthesis of natural (+)-estrone was reported in 1975.[27] The key step converts prochiral trione **404** into enantiomerically enriched dione **405** by an enantioselective aldol condensation. Except for the use of a pyridine ring as a nonnucleophilic latent 1,5-dicarbonyl precursor of the estrone A ring, the topological and polar strategy is identical with that described above involving Michael condensation of **379** with **380**. In the present synthesis, all the carbons required for the final target are united in a Michael condensation of **403** with **380**. After the crucial enantioselective generation of ring C, the required trans CD ring junction is established by steric approach control during catalytic hydrogenation of an unsaturated alcohol derived from **405** by selective hydride reduction of the more electrophilic unconjugated carbonyl. Completion of the last two skeletal connections required unmasking of a latent 1,5-dicarbonyl array by Birch reduction of **406** followed by base catalysed hydrolysis of the resulting 1,4-dihydropyridine intermediate and aldol condensation. Hydrolysis of the ketal at position 9 then allows equilibration of the C8 stereocenter, and generation of the final skeletal connection by another aldol condensation. Aromatization of **408** delivers crude estrone. A single recrystallization gave optically pure (+)-estrone (13% from **380**) as well as racemic estrone (3% from **380**) from the mother liquor.



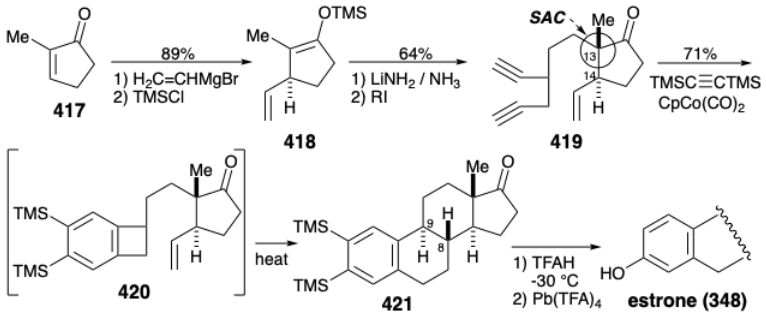
Estrone Synthesis by Cycloadditions. Since the B ring of estrone (**348**) contains one C=C bond in a six-membered ring, a thermal cycloaddition synthesis is possible. An intramolecuar Diels-Alder reaction could provide estrone from **409**. Furthermore, another pericyclic rearrangemant can be employed for the synthesis of **409**. Thus, the 1,3-diene array in **409** can be generated by electrocyclic rearrangement of a cyclobutene **410**.



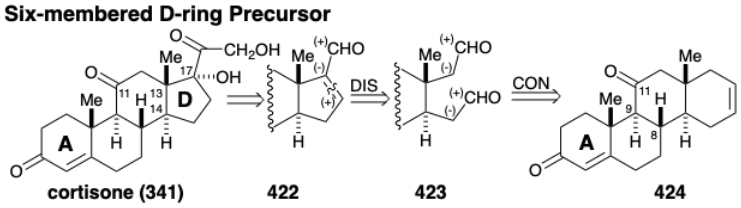
One particularly striking application[28] of this strategy[29] generates a benzocyclobutene intermediate **416** in an intramolecular cobalt(I)-catalyzed alkyne cyclotrimerization involving 1,5-diyne **412** with a synthetic equivalent **413** of the ketene enol **411**. The trimerization is actually a stepwise process involving **oxidative addition** to cobalt(I) to generate a cobalt(III) cyclopentadiene **414**. Diels Alder cycloaddition of **413** with **414** then produces **415** from which the cobalt(I) catalyst is regenerated by a **reductive elimination** that delivers **416**.



The correct relative configurations at positions 13 and 14 were established by steric approach control during alkylation of an enolate that was produced regiospecifically by 1,4-addition to **417** and regenerated from **418**. Cycloaddition of **419** with bis(trimethylsilyl)acetylene in the presence of cyclopentadienylcobalt dicarbonyl generated an intermediate benzocyclobutene **420**. Heat promoted generation of the derived ortho xylelene followed by intramolecular cycloaddition afforded **421** in 71% yield overall from **419**. The stereoselective generation of the correct configurations at positions 8 and 9 arises from a preference for an exo transition state in the Diels-Alder cycloaddition. Steric congestion destabilizes the alternative endo transition state that would otherwise be favored by secondary orbital overlap. Mono protodesilylation of **421** removed the 2-silyl group with a 9:1 preference over the 3-silyl group. Oxidative desilylation generated the 3-hydroxyl and delivered estrone in 24% overall yield from 2-methyl-2-cyclopenten-1-one (**417**) in seven steps.

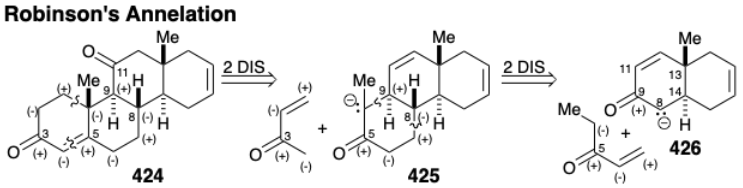


Total Synthesis of Cortisone. The strategy for the first total synthesis[30] of cortisone (**341**) focused on the problem of assembling a trans fusion between the C and D rings. The challenge was to overcome the thermodynamic preference for a cis fusion between a five and a six-membered ring. Since a trans fusion is favored thermodynamically between two six-membered rings, an attractive solution seemed to be to create an intermediate with a six-membered D ring and to contract the six to a five-membered ring. With this goal in mind, an aldehyde group at position 17 in a cyclopentene precursor **422** ought to provide a starting point for building the sidechain found at this position in cortsone. Polar disconnection between carbons 16 and 17 of the D ring suggests a dialdehyde precursor **423** that would provide **422** by intramolecular aldol condensation. Connection of the two reactive aldehyde groups in **423** suggests a latent dialdehyde precursor **424** containing a six-membered trans-fused D ring.

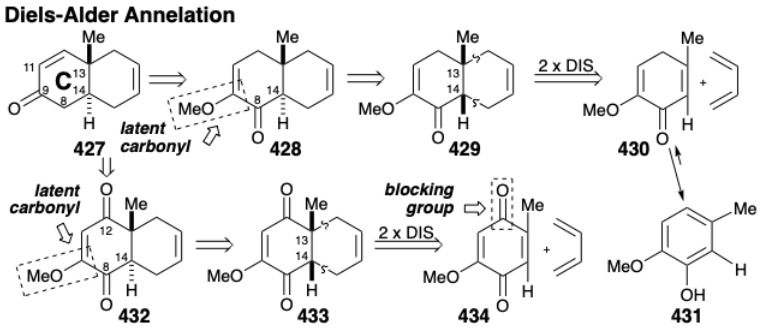


Disconnection of two bonds in the A ring at the ring fusion results in a major topological simplification. The ring fusion carbons in the A ring of **424** are common atoms, and disconnection of these two bonds, each between a common and a noncommon atom,

completely removes the A ring. All circuits between the two carbonyl groups in **424** are dissonant. Therefore, both carbonyls cannot be used simultaneously to provide polar activation for generating C-C bonds. Rather, additional functionality, e.g. a carbonyl group at position 5, must be added to a precursor **425** to provide electrophilic activation at position 5 and nucleophilic activation at position 10 that can be exploited in conjunction with target related functionality at position 3 to assemble the A-ring. Such a polar cyclohexenone annelation process, the "Robinson annelation", had recently been devised in which an alkyl vinyl ketone serves first as an electrophile at the β-position of the vinyl group and then as a nucleophile at the α' position. Thus, two- step polar condensation of **425** with methyl vinyl ketone could be expected to provide the A ring in **424**. A similar process could also be used to add the B ring to a bicyclic precursor **426**. Because the carbonyl group at the 11 position in cortisone cannot provide the polar reactivity required for the annelation described above, its introduction can be delayed until the latter stages of the synthesis.

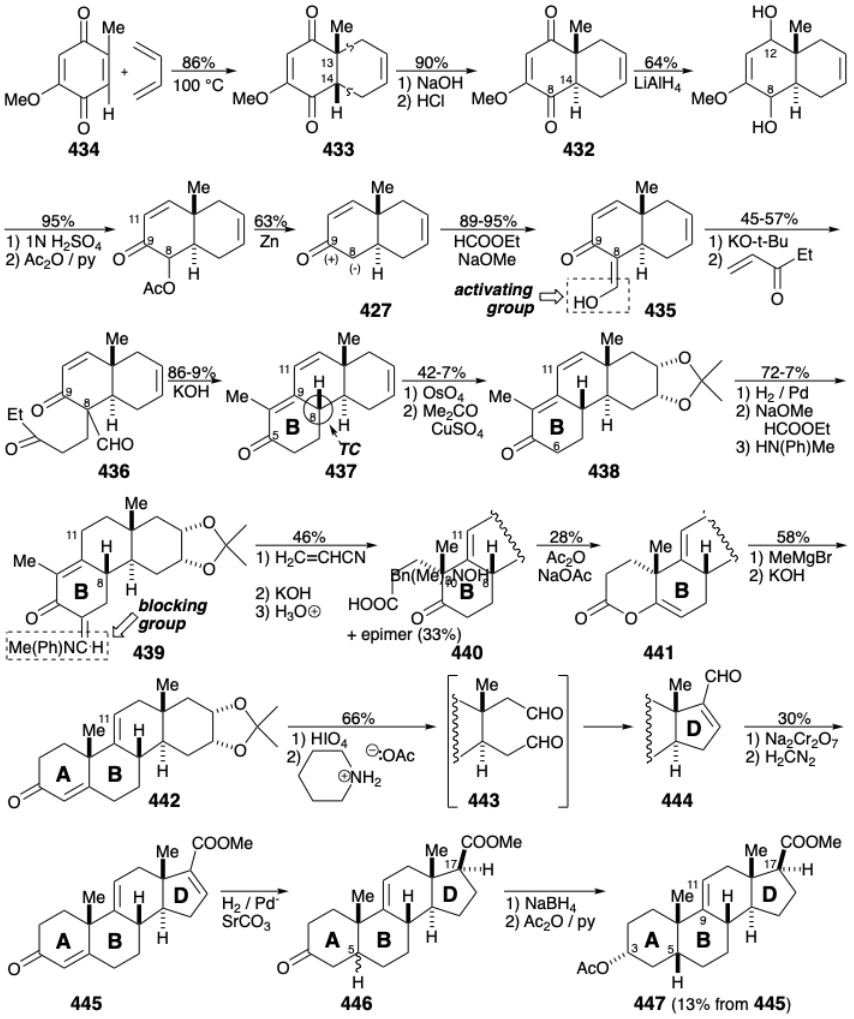


The cyclohexene unit in **427** suggests a cycloaddition synthesis involving a Diels-Alder reaction between a C ring precursor dienophile and 1,3-butadiene. However, generation of a trans ring fusion would require a C ring precursor containing a severely strained trans C=C bond in a six-membered ring. A more reasonable strategy would be to generate the thermodynamically favored trans ring fusion by epimerization of a cis fused precursor that would be produced, in turn, by a Diels-Alder reaction of a cis C=C bond in a dienophile. The carbonyl at the 9-position in **427** could be present in latent form in a precursor **428**. A carbonyl group at position 8 in **428** could provide the polar activation required for epimerization of a cis ring fusion in **429** into a trans ring fusion. This carbonyl would also activate the conjugated C=C bond in **430** toward Diels-Alder reaction with a relatively electron rich diene. However, *this strategy is fatally flawed* because **430** can be expected to aromatize by enolization to afford **431**. To block aromatization and provide additional activation of the dienophile, a second carbonyl can be added at position 12. This suggests a p-quinone dienophile **434** that would deliver a cis fused adduct **433** by Diels Alder reaction with 1,3-butadiene, and a trans fused intermediate **432** by epimerization.

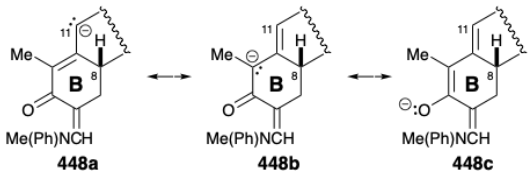


The more electron deficient methyl-substituted C=C bond in **434** is expected to be a more reactive dienophile towards 1,3-butadiene than the more electron rich methoxy-substituted C=C bond.

After having provided activation for epimerization at position 14 in **433**, the carbonyl substituent at position 8 in **432** is removed by reduction to a hydroxyl, acetylation, and reductive cleavage. Simultaneously, the blocking carbonyl group at position 12 is removed by reduction and dehydration affording **427**. Nucleophilic activation at position 8 is then enhanced by adding a formyl group that exists in the enol form in **435**. Robinson annelation with ethyl vinyl ketone (EVK) then creates the B ring in **437**. Thus, after facilitating the Michael alkylation, the activating formyl group is removed by a retro Claisen condensation upon treatment with KOH. Simultaneously, KOH catalyzes an intramolecular aldol condensation in **436** generating the B ring in **437**.



The stereoselectivity of this annelation can be ascribed to a thermodynamic preference for the requisite configuration at position 8 that is epimerizable owing to conjugation with the carbonyl group at position 5. Selective dioxidative addition to the unconjugated C=C bond in triene **437** is feasible because the electrophilic OsO_4 is less reactive toward the electron deficient conjugated C=C bonds. Selective saturation of the sterically less encumbered, less substituted C=C bond in **438** is followed by installation of an enamine derivative of a formyl substituent as a blocking group at position 6 in **439**. The contrasting applications of formyl substituents in **436** and **439** is noteworthy. Of the three remaining acidic hydrogens in **439**, proton abstraction from position 11 is least sterically encumbered. The resulting ambident dienolate nucleophile, as expected, is selectively Michael alkylated α to the carbonyl group owing to greater electron density at the central compared with the terminal carbon atom of the 1-oxa-pentadienyl array in the intermediate carbanion. In other words, the resonance form **448b** is more important than **448a** of **448c**.

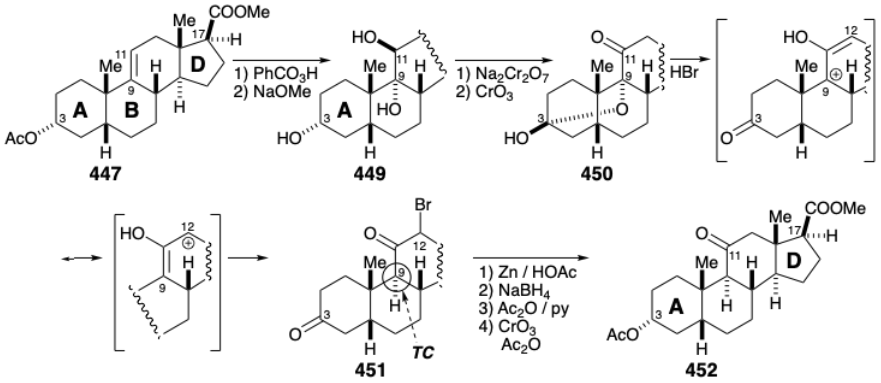


Unfortunately, alkylation of **448** is nonstereoselective producing carboxylic acid **440** and an epimer after hydrolysis of an intermediate nitrile. The final carbon required for the A ring of cortisone was to be provided by MeMgBr. However, to prevent addition to the ketone carbonyl in **440**, the latter group was masked as an enol lactone in **441**. The methyl ketone produced by addition of MeMgBr to **441** delivered **442** by intramolecular aldol condensation. The poor yield for the **440** to **442** conversion would be improved, no doubt, by modern methods. Thus, a chemoselective reaction of the acid chloride from **440** with $LiMe_2Cu$ would provide a high yield of the corresponding methyl ketone.

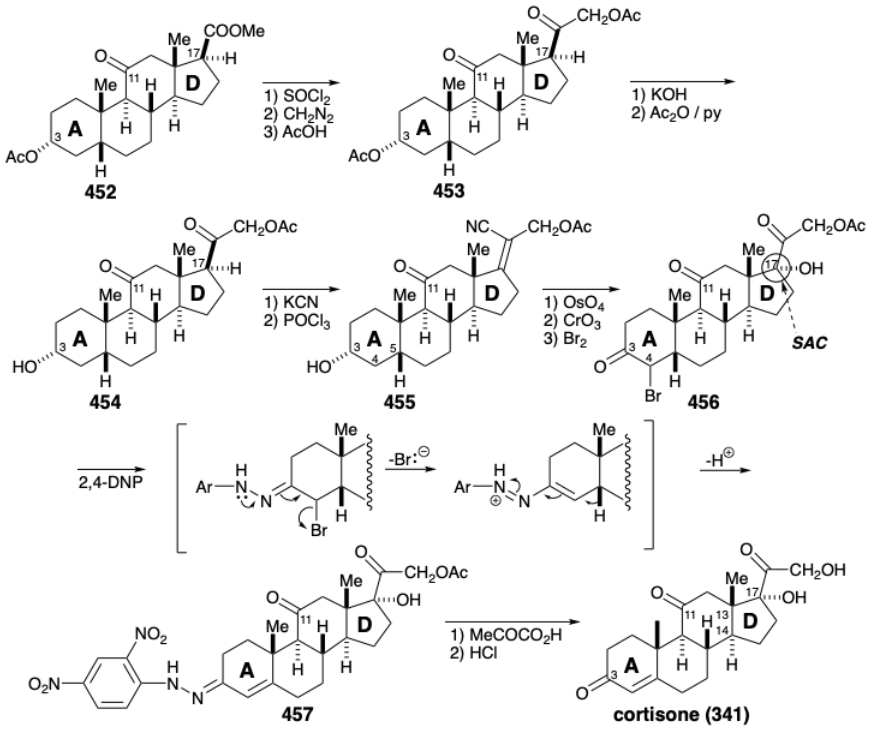
Contraction of the D-ring was accomplished by oxidative cleavage to dialdehyde **443** that gave **444** by a remarkably regioselective aldol condensation. Saturation of the two least sterically encumbered C=C bonds in the derived ester **445** gave a mixture of epimers

446 (at the 5 position) separation of which was best achieved after conversion to the 3-hydroxy derivative that then provided **447** by acetylation.

At this point the total synthesis intersected with "extensive prior investigations by many groups on the partial synthesis, from natural sources, of cortisone." Thus, introduction of the 11 carbonyl group was accomplished by epoxidation of alkene **447**, hydrolysis of the epoxide to triol **449**, and oxidation to dione hemiketal **450**. Nucleophilic replacement of the oxygen at position 9 by Br proceeded with allylic rearrangement upon treatment of **450** with HBr. Selective generation of a trans A-B ring fusion and the required configuration at position 9 in **451** is a consequence of thermodynamic control. Reductive debromination of bromoketone **451** followed by reduction to a diol, selective acetylation of the less sterically encumbered hydroxyl at position 3, and oxidation delivered the 11-keto steroid **452**.

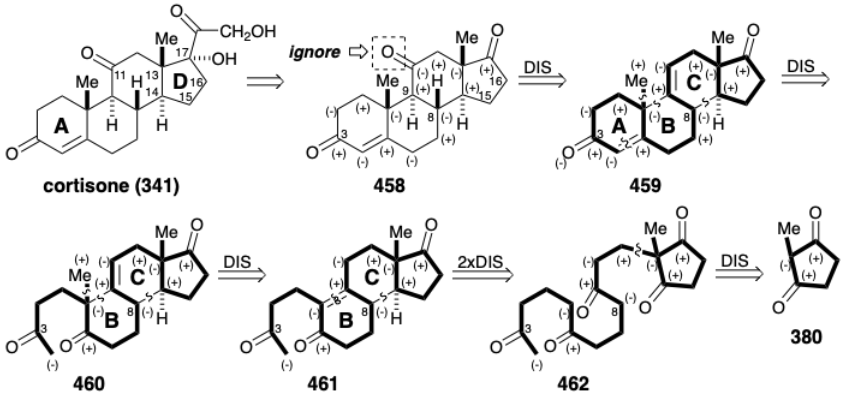


Assembly of the dissonant cortisone side chain was accomplished by polar condensation of the acid chloride from **452** with a dissonant building block, diazomethane, and reaction of an intermediate diazoketone with acetic acid. Saponification of the resulting diacetate **453** and selective reacetylation of the primary hydroxyl delivered **454**. Introduction of a hydroxyl group at position 17 was then accomplished by 1,2-dioxidative addition to **455**. Steric approach control favored the requisite configuration at the 17 position. Finally, introduction of unsaturation between carbons 4 and 5 was accomplished by bromination followed by dehydrobromination of **456**. Dehydrobromination of α-bromoketones can be complicated by α' proton abstratction that leads to a Favorskii reaction through the formation of a cyclopropanone. The mild Mattox-Kendall method avoids this pitfall because α-bromo hydrazones readily eliminate bromide to generate intermediate α,β-unsaturated hydrazones, e.g. **457**. Pyruvic acid effects removal of the hydrazine while hydrolysis of the side chain acetate occurred upon treatment with HCl completing the first total synthesis of cortisone (**341**) by R. B. Woodward in 1952.

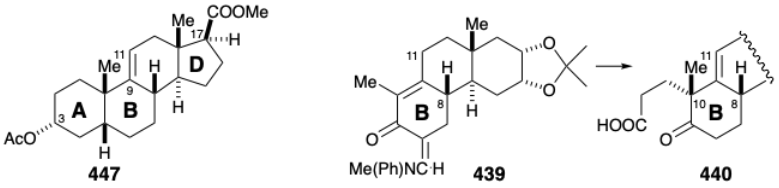


As a practical source of supply for medicinal applications, Woodward's synthesis could not compete with partial syntheses from other natural steroids that are readily available from plants. A major shortcomming of the total synthesis is the generation of a racemic product. The natural enantiomer was available by resolution of the intermediate **445**, but at least half of this precious advanced intermediate was discarded, i.e. the wrong enantiomer. Although the biosynthesis of cortisone is circuitous, it produces only one enantiomer owing to an entirely enantioselective epoxidation of squalene.

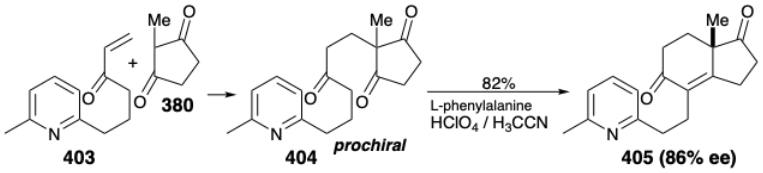
An Enantioselective Strategy for Cortisone. The achievement of an industrially viable total synthesis of cortisone depended on the development, in 1966, of an enantioselective strategy.[31] Interestingly, the strategy evolved from methods and intermediates developed during a synthesis of cortisone that employs methoxytetralone (**394**) as a BC ring precursor[32] in contrast to the Velluz estrone synthesis mentioned earlier (see section 5.3) that used this starting material for the AB ring moiety. But the key development in the evolution of an enantioselective strategy was the conception of a prochiral starting material and a route for its elaboration into a steroid.[33] Thus, extensive research on the partial synthesis of cortisone from naturally derived 17-ketosteroids had established methods that allow the elaboration of the cortisone sidechain from precursors like **458**.



Polar analysis of this subtarget, ignoring the 11-keto group, reveals that all circuits between the oxygen functionality in the A and D rings are consonant except those involving carbons 15 and 16. Introduction of the 11-keto group by addition to a C ring C=C bond in a precursor **459** is precedented by the similar functionalization of **447** (see section 5.4) in the Woodward synthesis.

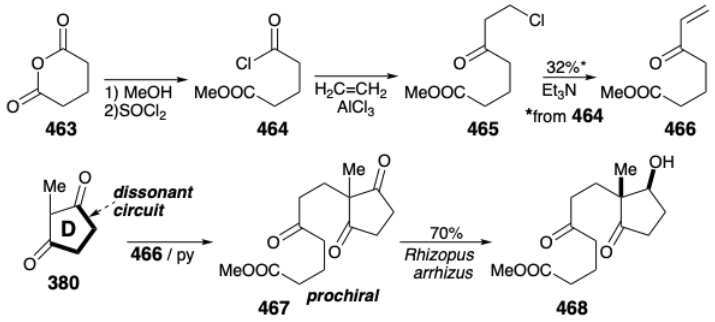


Polar disconnection of the 4,5-C=C bond in **459** suggests intramolecular aldol condensation of **460** for generating the A ring. In the Woodward synthesis, a similar intermediate, i.e., **440**, was generated by alkylation of **439**. Methylation of the analogue **461** of **439** might similarly provide **460**. Further polar disconnections of the B and C rings suggests a monocyclic precursor **462** that is achiral. We saw a similar intermediate in Danishefsky's enantioselective synthesis of estrone. Thus, **404** (see above) contains two of the carbonyl groups of **462** in latent form. In the estrone synthesis, asymmetry was introduced by an *enantioselective aldol condensation* of **404** to give **405**. Also, in that synthesis, **404** was prepared from an intact D-ring precursor **380** by Michael addition to enone **403**.

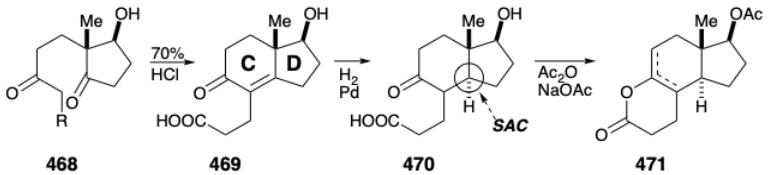


A similar strategy was employed a decade earlier to prepare an analogous prochiral precursor for cortisone. However, as we shall see, a different enantioselective transformation of the prochiral precursor **467** (see below) was used to introduce asymmetry into this synthesis of cortisone by Velluz.

A symmetrical starting material **463** is converted to the Michael acceptor **466** through Friedel-Crafts acylation of ethylene with the acid chloride **464** and dehydrochlorination of the intermediate β-chloro ketone **465**. Although the yield of **466** is poor, it is readily available in kilogram quantities from inexpensive starting materials. Condensation of **466** with the intact D ring precursor **380** delivers **467**. Enantioselective microbiological reduction provides the optically pure mono reduction product **468** in good yield as a single diastereomer.

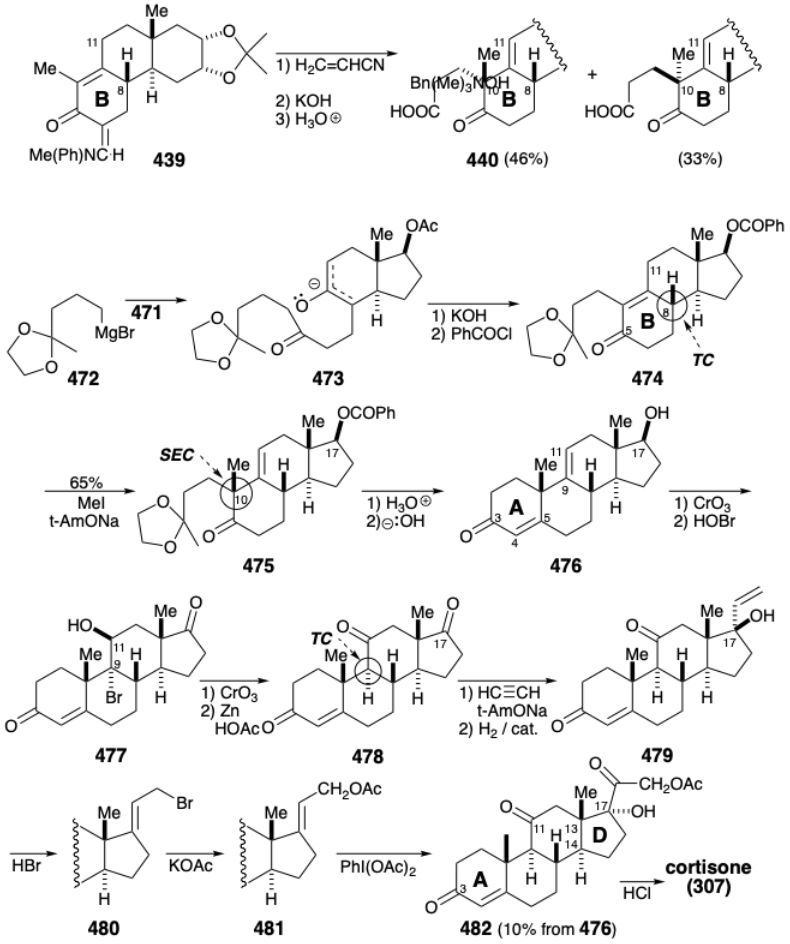


Acid-catalyzed intramolecular aldol condensation then creates the C ring in **469**. Stereoselective saturation of the C=C bond in **470** creates the requisite trans CD ring fusion, without a need for the lengthy ring contraction process of the Woodward construction of the trans CD ring fusion. To achieve selective polar connection at the carboxyl carbon in **470** of a nucleophilic fragment containing the remaining carbons required for the A and B rings, the ketone carbonyl must be masked. This is accomplished intramolecularly by enol esterification to give **471**.



Grignard reagent **472** reacts with **471** to deliver **473** that is cyclized by intramolecular aldol condensation to provide the B ring in **474**. The correct configuration at position 8 is assured by thermodynamic control because this center is conjugated with the carbonyl at position 5. Nevertheless, proton abstraction from **474** occurs primarily at the 11 position leading upon angular methylation to **475** *completely stereoselectively with the requisite configuration for cortisone*. The stereoselectivity of this

alkylation contrasts sharply with the lack of stereoselectivity observed in the corresponding **384** to **385** conversion in the Woodward synthesis. The contrasting stereochemical behavior of these two alkylations are a consequence of mechanistic differences. Thus, the alkylation of **439** is a reversible, *thermodynamically* controlled, Michael reaction whereas the methylation of **474** is a *kinetically* controlled process. Axial methylation from the β face of the enolate is stereoelectronically preferred because it leads directly to the chair conformer of **475**.



Generation of the A ring is then accomplished with a third intramolecular aldol condensation providing **476** after hydrolysis of the 17 benzoate. Oxidation of the 17 hydroxyl, and introduction of oxygen at the 11 position by addition of HOBr provides **477** that, upon oxidation and reductive debromination, delivers **478** stereoselectively with the thermodynamically preferred configuration at position 9 which is α to the carbontyl at position 11. Finally, elaboration of the cortisone side chain was accomplished by ethynylation of the more electrophilic unconjugated 17 carbonyl. Catalytic hydrogenation then provided the tertiary allylic alcohol **4 7 9** . Bromodehydroxylation of **4 7 9** occurred with allylic rearrangement, presumably through an allylic cation intermediate, while replacement of Br in **480** with OAc proceded by a direct S_N2 substitution. The unusual oxidizing agent, phenyliodosodiacetate and a catalytic quantity of OsO_4, converted the more nucleophilic C=C bond in **481** directly into the α hydroxy ketone **482**.

4.8: Terminology

absolute asymmetric synthesis (4.6)

bishomo terpene (4.5)

CCD (4.4)

CDC (4.4)

convergent synthesis (4.6)

decarboxylative elimination (4.1)

glucoside (4.1)

head-to-tail dimer (4.1)

homo terpene (4.5)

irregular terpene (4.1)

isoprene unit (4.1)

linear synthesis (4.6)

mevalonic acid (4.1)

monoterpene (4.1)

nor terpene (4.7)

oxidative addition (4.7)

RSM (4.4)

reductive elimination (4.7)

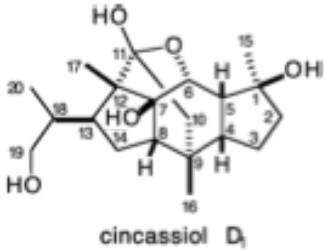
seco steroid (4.6)

stereoconvergent (4.6)

topological analysis (4.4)

4.9: Study Questions

1. Circle the "common atoms" in cincassiol D_1, a diterpene, and then draw wavy lines through each C-C bond that involves at least one common atom and that lies on a consonant circuit (refer to your answer to question 4 in chapter 1 for a polar reactivity analysis of cincassiol D_1). You may wish to use the structures below as templates for some of your drawings. Simply "white out" unwanted bonds.

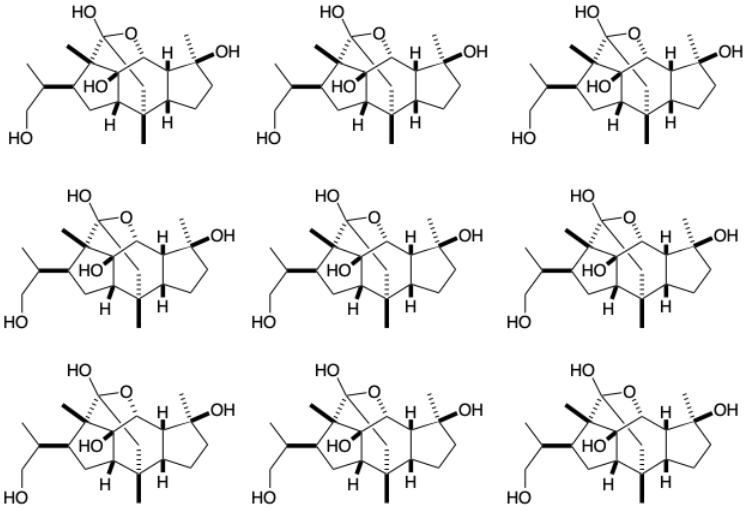


cincassiol D_1

(a) For each of the dislocations suggested by your topological analysis and refering to your previous polar analysis, draw a synthon that could theoretically provide the target skeleton by polar C-C bond-forming reactions.

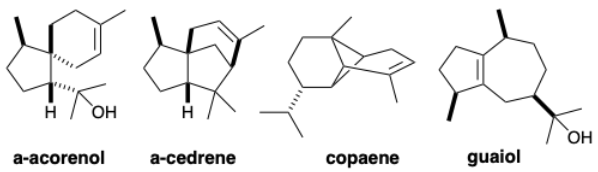
(b) For some of these synthons draw a functionalized precursor (synthetic equivalent) that could be used in a *direct polar syntheses* of the target or that could be used in a polar synthesis requiring addition of a methyl group and/or formation of a a heterocyclic C-O bond after completion of the multicyclic *carbon* skeleton by polar C-C bond formation.

(c) For the remaining synthons which contain consonant circuits that are blocked by quaternary centers, synthetic equivalents exploiting the polar activation afforded by target-related functional groups are not available since conjugation of these functional groups with one or both of the reacting carbon centers is not readily achieved without prior cleavage of additional carbon-carbon bonds. Label these synthons as "BLOCKED".



2. The deduction of likely biosyntheses of terpenes provides an excellent opportunity to practice retrosynthetic analysis with a set of boundary conditions: (a) isopentenyl pyrophosphate as starting material, (b) head to tail acyclic oligomer as an intermediate, (c) carbocationic electrophile and C=C π-bond nucleophile for C-C bond formation, (d) all of the reactions of carbocation intermediates as potential steps, e. g. β-proton loss, and rearrangements by 1,2-C shifts or hydride shifts.

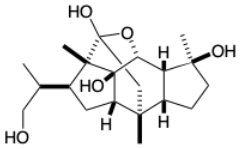
(a) Deduce likely biosyntheses for the following regular sesquiterpenes:



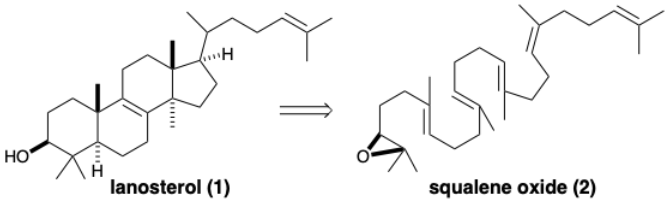
a-acorenol a-cedrene copaene guaiol

Hint: notice and think about any similarities in the structures of α-acorenol and α-cedrene.

(b) Cincassiol D_1 is a regular diterpene. In the following structure: (a) circle the isoprene units, (b) draw wavey lines through all C-C bonds that are not bonds within the isoprene units, (c) for those nonisoprene bonds that would be present in the acyclic geranylgeranyl pyrophosphate precursor of cincassiol D_1, label the ends with h or t to indicate a head or tail atom of an isoprene unit.



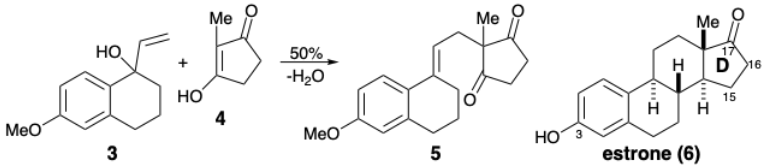
(c) Draw a circle around each of the "common atoms" (as defined by Corey) in the following structure of lanosterol (**1**).



(d) Describe the *topological* strategy of the biosynthesis of lanosterol (**1**) from squalene oxide (**2**).

(e) Write a mechanism for the polyene cyclization and rearrangement involved in the biosynthesis of lanosterol (**1**) from squalene oxide (**2**). Show the flow of electrons with arrows pointing from electron pairs in the reactants to their impending location in the incipient products. Show the polyene cyclization as a single concerted process involving several electron pairs and leading to an intermediate cation. Then show the rearrangement of that intermediate to lanosterol as another concerted process involving the movement of several electron pairs.

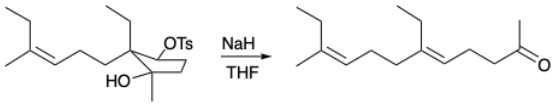
3. By drawing the appropriate resonance forms of a key cationic and a key anionic intermediate, write a mechanism that shows how the C-C bond forming reaction between **3** and **4** generates **5** by a process that relies upon the stabilizing influence of functionality in **3** and **4** that is related to the 3-hydroxyl and 17-keto groups in the final synthetic target, estrone (**6**).



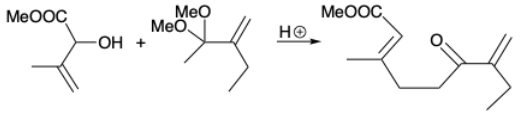
Hint: 4 is a vinylogous carboxylic acid.

4. For each of the following reactions that generate a trisubstituted alkene stereoselectively, what is the driving force and why is it stereospecific?

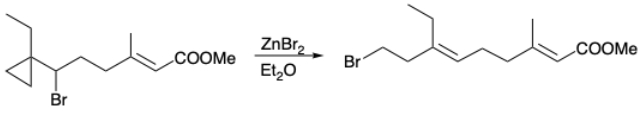
(a)



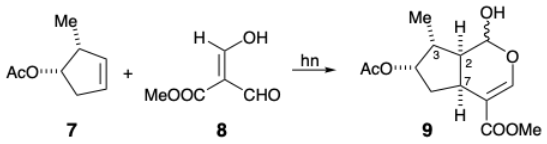
(b)



(c)



5. A remarkable reaction occurs upon UV irradiation of **7** and **8**. A product **9**, that contains the loganin skeleton is generated stereoselectively.

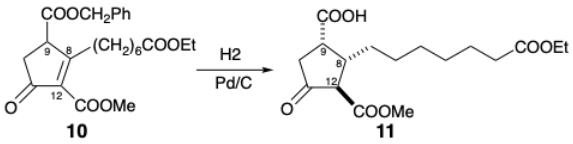


7 8 9

(a) Write a mechanism for this reaction. Show the flow of electrons with arrows pointing from electron pairs in the reactants to their impending location in the incipient products.

(b) Use one or more of the following terms to answer each of the following questions: thermodynamic control, stereoelectronic control, steric approach control, or temporary bridge. How is stereocontrol achieved: (i) at the 3 position relative to the 2 position in **9**? (ii) at the 7-position relative to the 2-position in **9**?

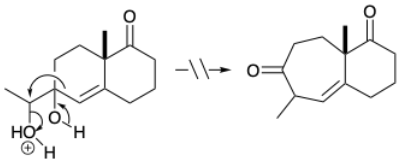
6. In the Kojima-Saki synthesis of $PGF_{1\alpha}$, the relative stereochemistry at positions 8, 9, and 12 is set in the conversion of **10** into **11**.

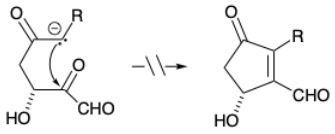


10 **11**

How is stereocontrol achieved: (i) at the 12 position relative to the 9 position in **11**? (b) at the 8- position relative to the 9-position in **11**?

7. Each of the following reactions fails because of a fatal flaw. For each reaction draw the structure of the actual product.

(a)


(b)


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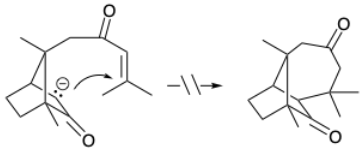

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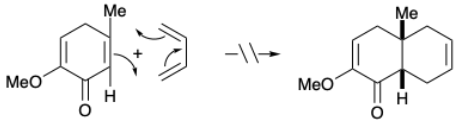

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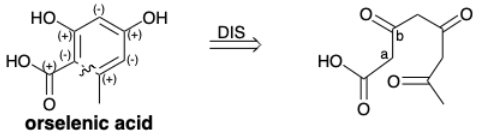
CHAPTER OVERVIEW

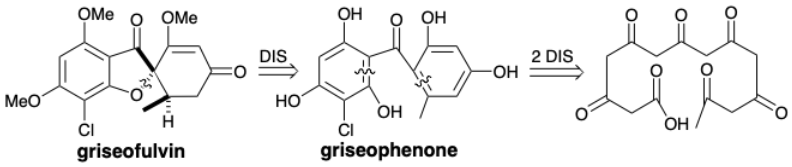
5: Polyketides

The polyketides, a diverse family of highly oxygenated natural products, are characterized by the presence of many β-dihydroxy or β-hydroxycarbonyl consonant polar functional relationships. Some polyketides have carbon skeletons comprized of a long straight chain of carbon atoms that is often crosslinked into one or more six-membered rings. Thus, a variety of aromatic compounds is produced in nature from acetate-derived (poly-β-keto)carboxylic acids through **dehydrocyclization**, i.e. intramolecular aldol condensation. For example, orselenic acid is topologically and functionally related to a mono crosslinked 3,5,7-triketo octanoic acid.

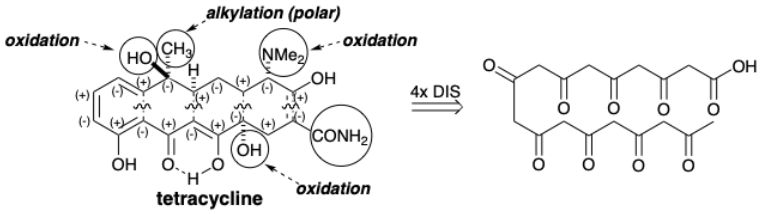


orselenic acid

Some polyketides are further modified by oxidative coupling, as in the conversion of griseophenone into griseofulvin. Other modifications include alkylations at the nucleophilic carbon atoms, reduction of carbonyl groups, and electrophilic aromatic substitutions. For example, tetracycline is topologically related to a tetra crosslinked 3,5,7,9,11,13,15,17-octaketo octadecanoic acid. However a dimethylamino and two hydroxyl groups are present that do not fit the otherwise entirely consonant polar reactivity pattern of the remaining functionality. Also a methyl and carboxamido group are also present that are not deriveded from a (poly-β-keto)carboxylic acid precursor.

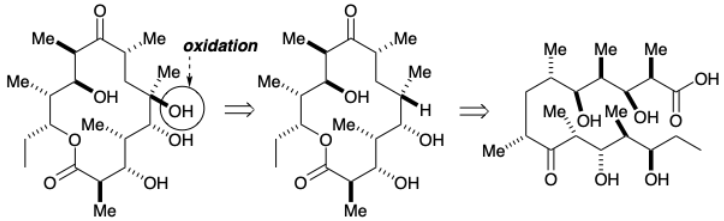


griseofulvin griseophenone



tetracycline

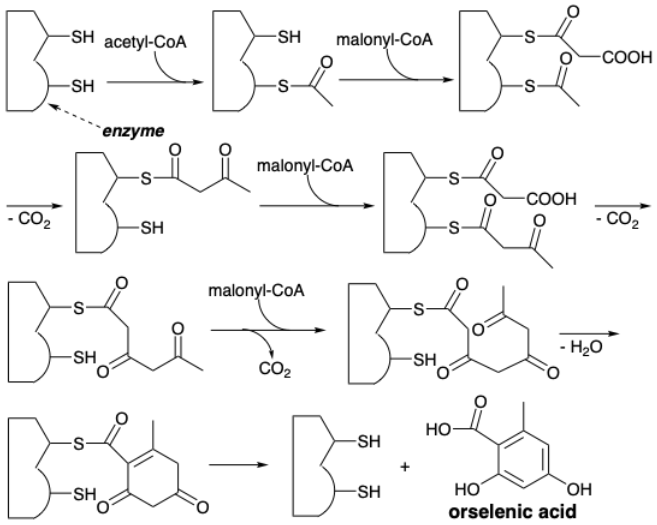
A large family of polyoxygenated macrolide antibiotics, that contain 12-, 14-, or 16-membered lactone rings, share a polyketide biogenesis. For example, erythromycin B is a diglycoside of erythronolide B, a propionate-derived aglycone.



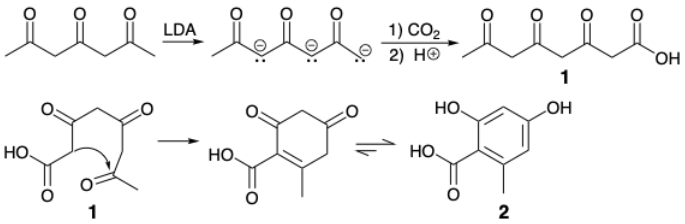
erythronolide B 6-deoxyerythronolide B

5.1: Orselenic Acid

Formation of the intermediate polyacetyl or propionyl chains in the biosynthesis of polyketides is closely related to fatty acid biosynthesis. Thus, for example, acetyl CoA acylates an enzyme-bound malonylthioester to yield an enzyme bound acetoacetylthioester. In fatty acid biosynthesis, this would then be reductively deoxygenated prior to undergoing Claisen condensation with a second molecule of malonyl-S-ACP (see section 3.1). In polyketide biosynthesis, repeated aldol condensations yield an enzyme bound polyacetyl chain in which many acetyl carbonyls are retained or only partially reduced to hydroxyls. The name **acetogenin**, a synonym for polyketides, arises from their poly- acetyl biogenesis. Cyclization of the polyacetyl chain occurs completely, or at least partially, prior to its release from the polyacetyl synthetase enzyme surface. For example, orselenic acid is constructed biosynthetically from acetyl CoA and three molecules of enzyme-bound malonyl-thioester.

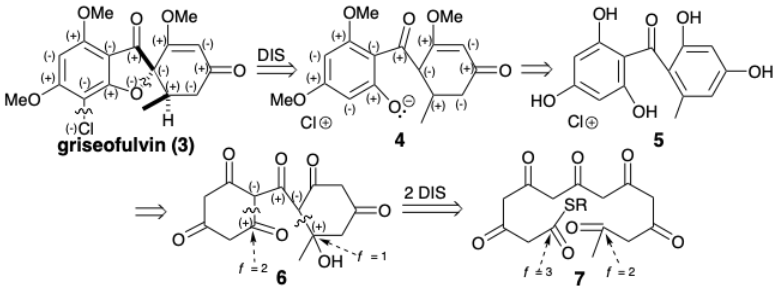


A total synthesis of orselenic acid was achieved by a **biomimetic strategy**, that is, by a strategy that mimics the biosynthesis of this acetogenin.[1] Thus, the trianion of 2,4,6-heptanetrione was carboxylated to yield 3,5,7-triketo octanoic acid (**1**) that readily underwent intramolecular aldol condensation and dehydration to give orselenic acid (**2**).

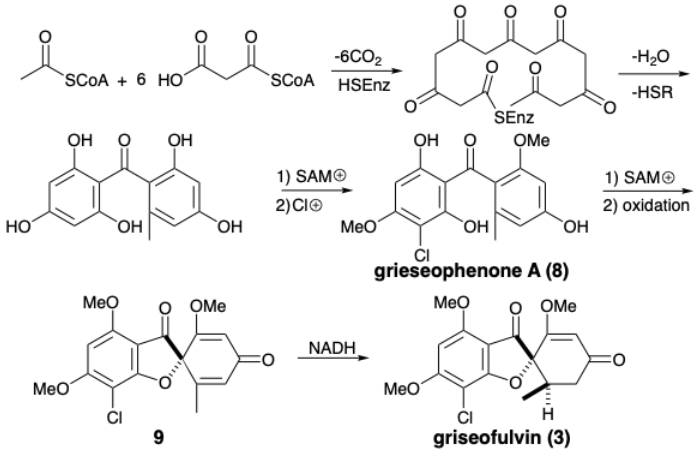


5.2: Griseofulvin

Polar reactivity analysis of griseofulvin (**3**) reveals dissonant circuits involving the chloro substituent and furan oxygen. A dislocation cleaving these dissonant circuits suggests an entirely consonant precursor **4** or the aromatic close relative **5**. This disconnection -- between a common atom, the spiro carbon, and a non common atom, the furan oxygen -- also leads to major topological simplification. Disconnection of the rings ring in **5** to generate an acyclic precursor must be preceded by conversion of ring C=C bonds into C-C bonds. Thus, addition of water or tautomerization gives a precursor **6** in which polar disconnection of C-C single bonds is feasible. The functionality level at the electrophilic centers in the acyclic precursor **7** suggested by this polar disconnection must be one unit higher than in the intermediate **6** if the cyclization of **6** is to yield **7** *directly*.

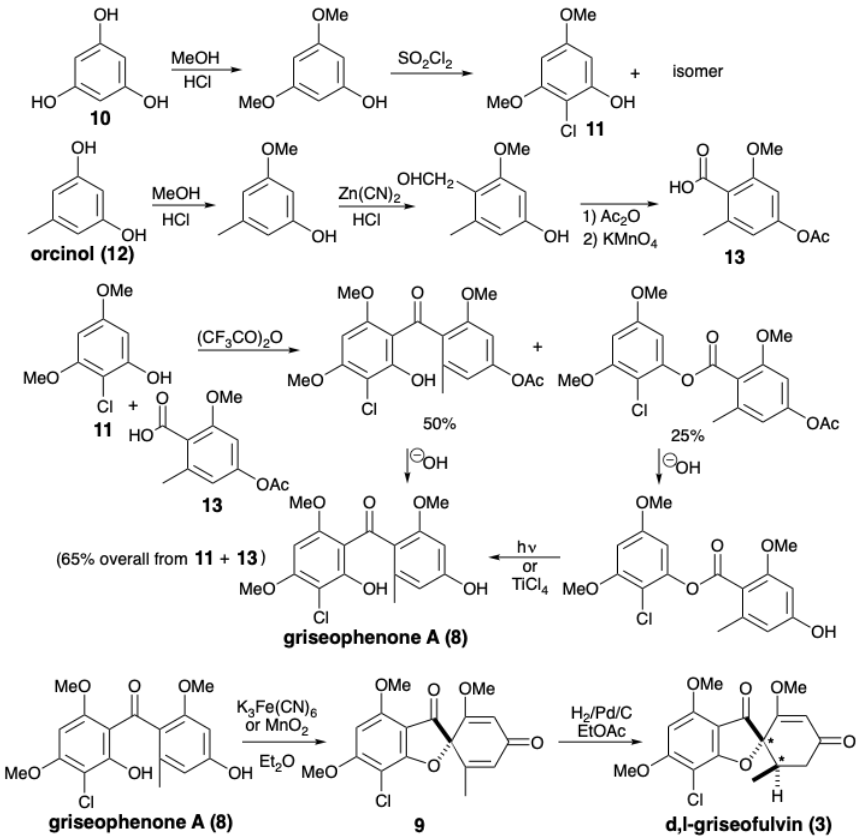


The biosynthesis of griseofulvin (**3**) illustrates the involvement of electrophilic aromatic substitution and oxidative coupling in the transformation of a poly-β-ketomethylene chain into a functionally and skeletally complex acetogenin. Thus, intramolecular aldol condensations of an enzyme- bound 3,5,7,9,11,13-hexaketohexadecanoic acid thioester followed by hydrolysis, O-methylation with S-adenosylmethionine (SAM) and electrophilic aromatic chlorination generates an intermediate, griseophenone A (**8**). A dissonant connection in the furan ring of griseofulvin is created by an oxidative coupling that generates dehydrogriseofulvin (**9**) from **8**. Stereo-selective reduction of **9** with NADH then delivers griseofulvin (**3**).



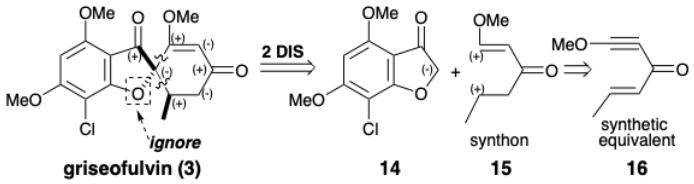
A Biomimetic Synthesis of Griseofulvin

A ferricyanide-induced oxidative coupling of griseophenone A (**8**) to dehydrogriseofulvin (**9**) with was exploited in a biomimetic total synthesis of racemic griseofulvin.[2] The symmetrical starting materials, phloroglucinol (**10**) and orcinol (**12**) were elaborated into the intermediates **11** and **13** by well precedented electrophilic aromatic substitutions. Acylation of **11** with **13** occurred mainly at carbon. The O-acylation product was readily rearranged to the C-acylation product, thus affording griseophenone A (**8**) in good overall yield. Conversion of **8** to d,l-griseofulvin (**3**) closely paralleled the biosyn-thetic pathway.

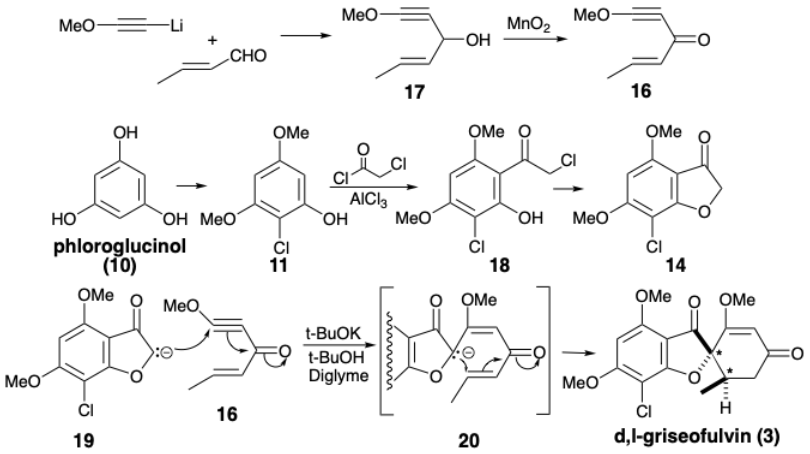


Polar Cyclohexenone Annelation Strategies for Griseofulvin

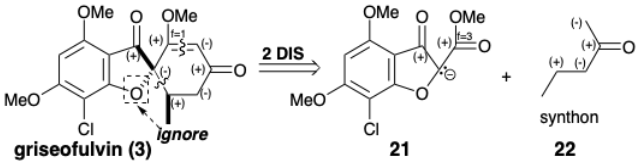
A strategy for the total synthesis of griseofulvin is suggested by a polar analysis that ignores the polar activation afforded by the furan oxygen. Disconnection of two bonds to a common atom, the spiro carbon, in **3** leads to major topological simplification, and suggests a nucleophilic precursor synthon **14** and a biselectrophilic precursor synthon **15**. The eneyne **16** is a synthetic equivalent of **15** that should provide **3** directly because 1,4-addition of a nucleophile will decrease the unsaturation level of each electrophilic center by one unit.



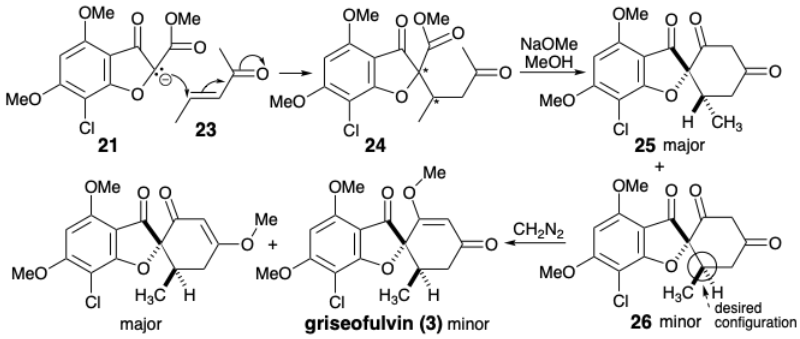
The biselectrophile **16** was prepared from methoxyacetylene and crotonaldehyde, and the precursor **14** of the requisite dissonant nucleophile was obtained from phloroglucinol (**10**) via **18** produced by acylation of **11** with chloroacetyl chloride. It should be noted that the dissonance in the furan ring of **14** is derived from the dissonant precursor chloroacetyl chloride. Treatment of a mixture of **14** and **16** with base delivered **3** via anions **19** and **20**.[3]



A different strategy is also suggested by a polar analysis that ignores the polar activation afforded by the furan oxygen. Disconnection of two bonds of the cyclohexenone ring as in **3** suggests a well precedented annelation of cyclohexanediones that is similar to a Robinson annelation (see section 4.7). In contrast to the previous strategy, a methyl enol ether is not produced directly. The enone **23** serves as synthetic equivalent for the synthon **22**.

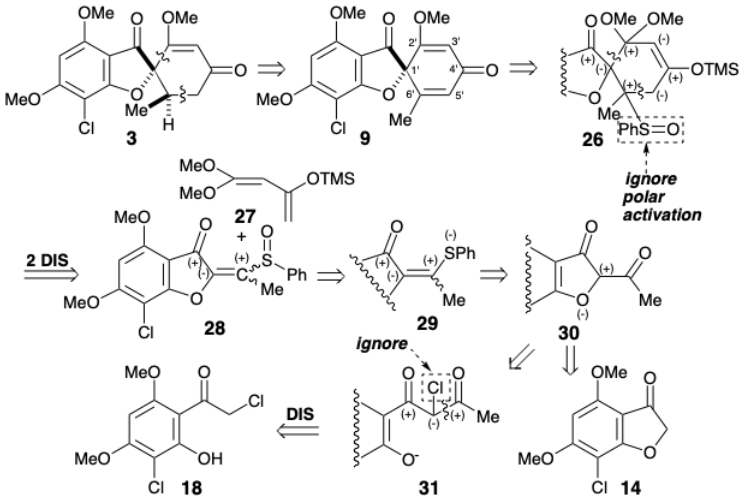


Condensation of **21** with **23** gives two diastereomeric cyclohexanediones **25** and **26**. This synthesis is less efficient than the previous one because the major diastereomer **25** is epimeric with the natural product **3** and methyletherification of the minor diastereomer **26** occurs with unfavorable regioselectivity.[4]

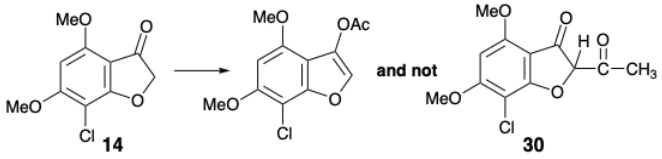


A Cycloaddition Strategy for Griseofulvin

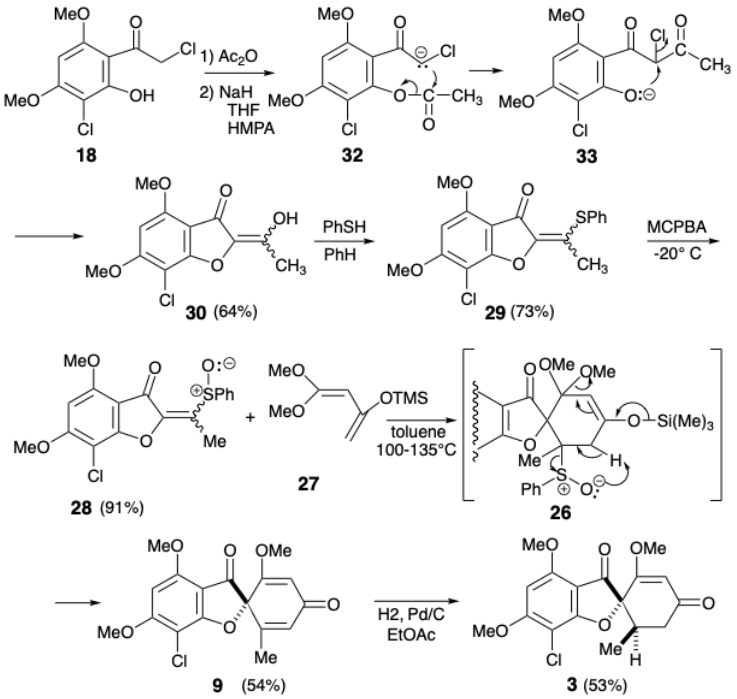
Danishefsky's strategy for a total synthesis of griseofulvin[5] was designed around his method for cyclohexenone annelation through Diels-Alder reaction of highly oxygenated dienes, e.g., **27**.



This *boundary condition* guides and channels the retrosynthetic analysis to seek a two-bond disconnection of the cyclohexenone ring to a butadiene and dienophile precursor. Furthermore, the stereoselective conversion of **9** to give **3** established previously[2] was adopted to simplify the stereochemistry of the target. The dislocation to **9** removes one asymmetric center, that can be introduced at the end of the synthesis by stereoselective hydrogenation. For the desired Diels-Alder *reaction*, a C=C bond between carbons 3' and 4' is required. Therefore, the 2',3' and 5',6' C=C bonds in **9** must be generated after the key Diels-Alder step. The requisite 3',4' C=C bond is provided by dislocation of **9** to the enol-keta1 derivative **26**. The 5',6' C=C bond could be introduced in **26** by a variety of elimination processes. The choice of a sulfoxide as leaving group is dictated by the additional utility of the sulfoxide group for activating the dienophile **28** toward Diels-Alder reaction with the diene **27** which is necessarily electron-rich. The sulfoxide can also be expected not to control the structural selectivity of the Diels-Alder reaction, that will be controlled instead by the carbonyl group of the furanone ring in **28**. The electron withdrawing sulfoxide group is dissonant with respect to the furanone carbonyl in **28**, but it can be obtained by oxidation of the corresponding electron donating sulfide group in **29.** This consonant vinyl sulfide is simply an enol sulfide derivative of the dione precursor **30**. This dione might be available by acylation of the furanone **14** that was used in a previous synthesis of griseofulvin. Alternatively, construction of the dissonant C-O bond in **30** could be achieved after completion of the carbon skeleton but a nucleofuge would be required in **31** because the carbonyl groups can not provide the requisite electrophilicty. Ignoring the chloro group in **31**, the 1,3-dicarbonyl array is consonant and can be constructed by Claisen acylation of the ketone **18** that was also used in the previous stereoselective synthesis discussed above.

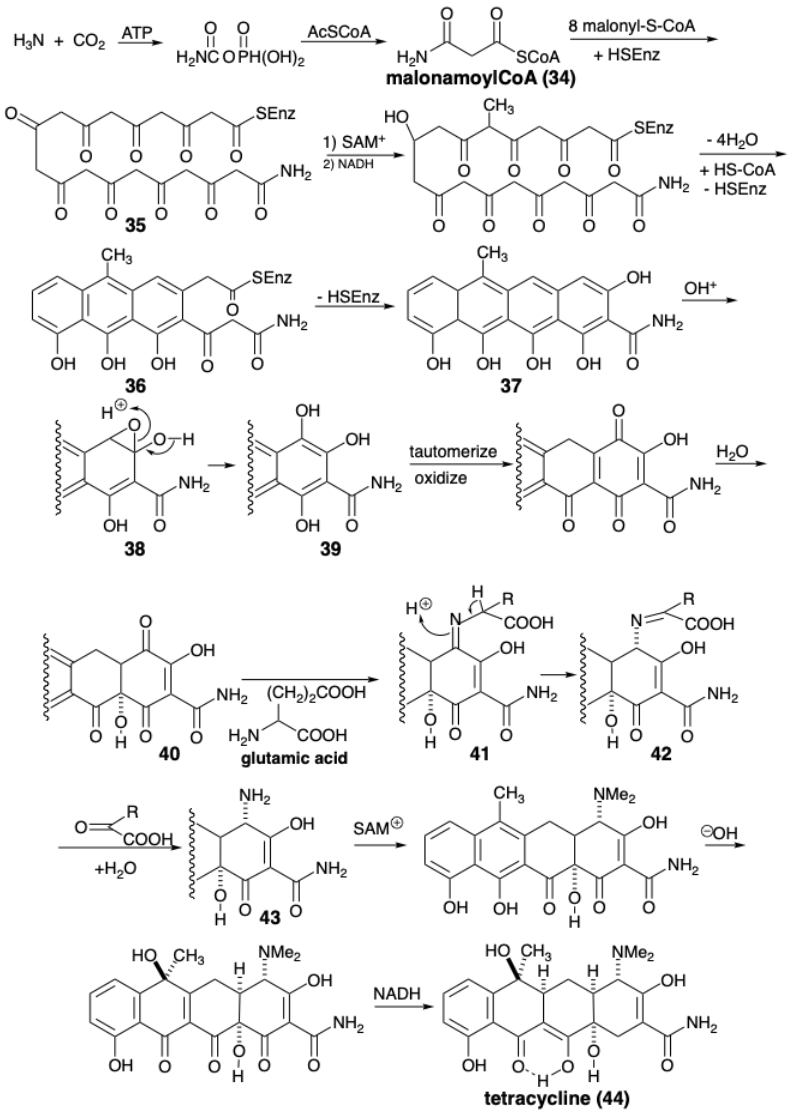


In fact, O-acylation of the enolate anion from **14** occurs to the complete exclusion of carbon acylation required to produce **30**. On the other hand, an intramolecular delivery of the acetyl electrophile in **32** served to unmask Intramolecular O-alkylation of the intermediate phenolate **33** delivered the desired dione **30** that exists as an enol tautomer. Conversion of the enol sulfide **29** from **30** into the corresponding sulfoxide was accomploshed by selective oxidation of the sulfide in the presence of a C=C bond with MCPBA at low temperature. Diels-Alder addition of the resulting vinyl sulfoxide **28** to the 1,3-diene **27** was followed, in situ, by thermal elimination of phenylsulfenic acid and methoxytrimethylsilane from an intermediate cyclohexene **26** to deliver cyclohexadienone **9**.



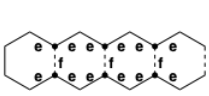
5.3: Tetracyclines

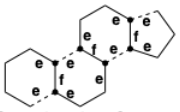
Acetyl CoA is not the only thioester that may initiate the enzyme matrix oligomerization of malonyl CoA. Thus, for example, a biosynthesis has been postulated for tetracycline (**44**) involving condensation of malonamoyl CoA (**34**) with eight molecules of malonyl CoA to produce an enzyme bound polyketoamide thioester **35**, that is partially dehydrocyclized after methylation of one methylene and reduction of one carbonyl.[6] The final ring of the tetracycline ring system is formed by Dieckmann cyclization of **36** to **37** after release of the partially cyclized polyketide from the polyketide synthetase. Two aromatic hydroxylations increase the functionality after completion of the carbon skeleton. These hydroxylations may involve intermediate arene oxides, e.g. **37** → **38** → **39**. The reductive amination of **40** via **41** and **42** to yield **43** is accompanied by oxidative deamination of glutamic acid.



Topological Analysis of Fused-Ring Systems.[7]

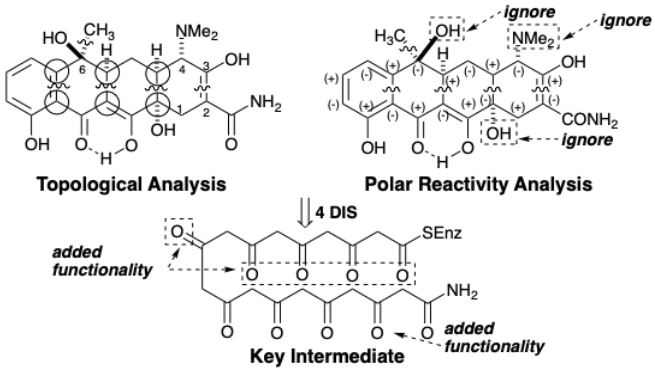
A ring pair is a **fused-ring** system if two rings share one and only one common bond, the **fusion bond**. The steroid and tetracycline ring systems are examples of multicyclic structures containing only fused-ring pairs, as opposed to spirocyclic or bridged-ring pairs. Besides fusion bonds (marked **f**), the diagrams below indicate common atoms (shown as •), and **exendo bonds** (marked **e**) which are exo to one ring and endo to another, and bonds (indicated as dashed lines) that are formed during the biosyntheses of these ring systems from acyclic precursors.


Tetracycline Ring System


Steroid Ring System

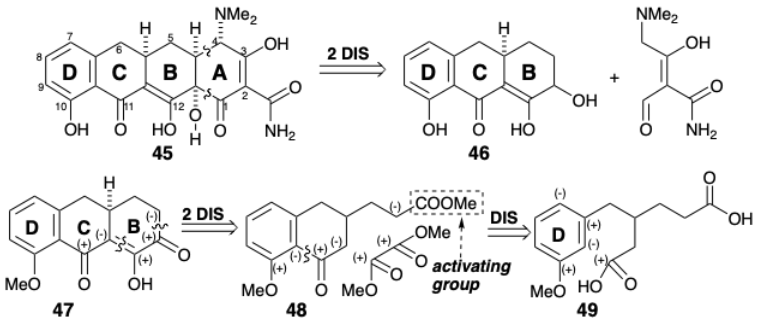
There is an interesting contrast between the topological strategies of tetracycline and steroid biosyntheses. Both strategies involve key acyclic intermediates that incorporate all of the skeletal carbon atoms. However, the biosynthesis of the tetracycline skeleton involves formation of all of the ring fusion bonds, whereas only exendo bonds are formed during the biosynthesis of the steroid skeleton. Another contrast is found in the biosynthetic generation of the **peripheral ring**, i. e. the ring that remains after cleavage of all fusion bonds. Thus, only one peripheral bond is generated during the biosynthesis of the tetracycline skeleton, whereas four bonds of the peripheral ring are generated during steroid biosynthesis.

Also noteworthy is the fact that, in both biosyntheses, bonds between pairs of common atoms are **strategic bond**, i.e., strategically important in achieving rapid reduction of molecular complexity by disconnection during dislocation of the synthetic target. The dislocations of the tetracycline biosynthetic strategy are recommended both by topological and polar reactivity analysis. Topologically, the strategy disconnects all bonds between pairs of common atoms. Polar reactivity analysis reveals ample functionality. If the activation provided by several functional groups is ignored, numerous functional groups remain with solely consonant connecting circuits that can be generated by exploiting target related functionality in precursors in conjunction with several added consonant functional (carbonyl) groups.

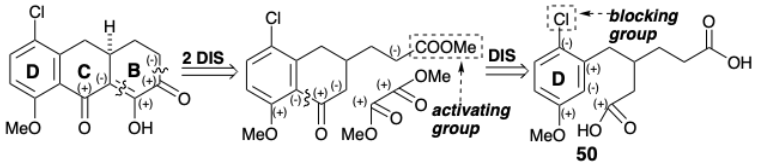


A Linear Strategy for Tetracyclines

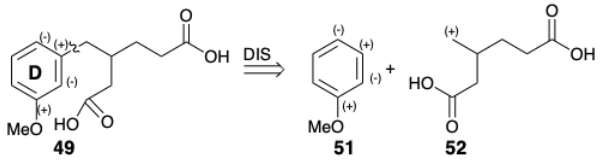
The first synthesis of a biologically active (though unnatural) tetracycline derivative was achieved by Woodward and collaborators.8 These workers simplified the synthetic goal by not including the labile tertiary 6-hydroxyl as well as the 6-methyl of tetracycline (**44**). Ring A of **45** is functionally and stereochemically the most complex portion of this simplified target. This ring is so highly functionalized that polar analysis is ambiguous. It contains a plethora of polar reactivity dissonances. If this ring is severed from **45**, a tremendous simplification of the synthetic target results. Not only is an abundance of reactive functionality removed, but a topological simplification is also realized. Thus, by cleaving a pair of exendo bonds that are vicinal and **cocyclic** (in the same **primary ring**, i. e. one that is not disected into a pair of smaller rings by a transanular bridge), all vestiges of the A-ring are removed. The remaining BCD synthon is a relatively chemically stable, structurally simple fragment **46**. A possible synthetic intermediate, i. e. appropriately functionalized molecular fragment, that corresponds to **46** is **47**. The carbonyl group in ring B in **47** provides activation for elaboration of ring A. The methyl ether in ring D blocks deprotonation of the phenol. Polar analysis of the nonaromatic portion of **47** suggests a dislocation to **48** and dimethyloxalate, a symmetrical dissonant biselectrophile. Annelation of **48** by Friedel-Crafts acylation of **49** would exploit the nucleophilic reactivity of the aromatic D-ring in **49**, that is activated by a target-related methoxy group, and the electrophilic reactivity of a carbonyl.



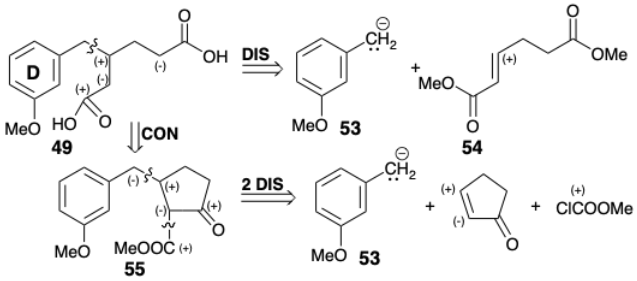
However, this strategy is potentially flawed because electrophilic substitution that must occur ortho to the methoxy substituent in the D ring of **49** during conversion to **48**, could also occur at the nucleophilic position para to the activating methoxy group. To preclude para acylation, a chloro substituent in the precursor **50** could be used as a **blocking group** (a substituent introduced to control reactivity and subsequently removed).



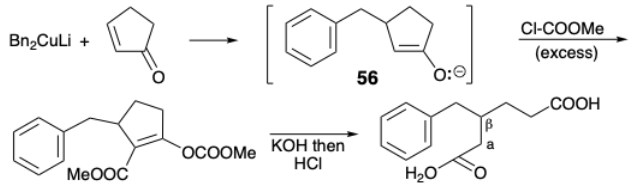
Topologically, a dislocation of **49** to **51** + **52** is desireable because all vestiges of the sidechain are removed from the aromatic ring. However, polar analysis of **49** shows that electrophilic alkylation or acylation of an anisole precursor would favor ortho or para substitution rather than the meta substitution required to generate **49**.



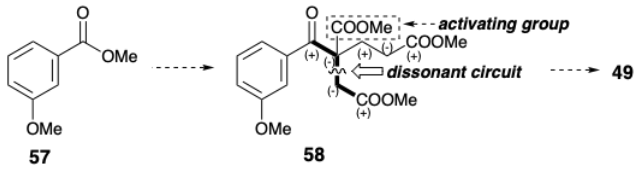
The dislocation **49** ⇒ **53** + **54** is recommended by the ready availability of benzylic organometallics corresponding to **53**. A nucleophilic synthon such as **53** might afford a diester of **49** by 1,4-addition to **54**. In fact, a general synthesis of β-substituted alkanedioic acids such as **49** is known that is related to this approach.[9] Dislocation to more connected, cyclic β-ketoester intermediates **55** reveals the possible utility of readily available cycloalkenone precursors for the synthesis of β-substituted alkanedioic acids by retro Dieckman cleavage.



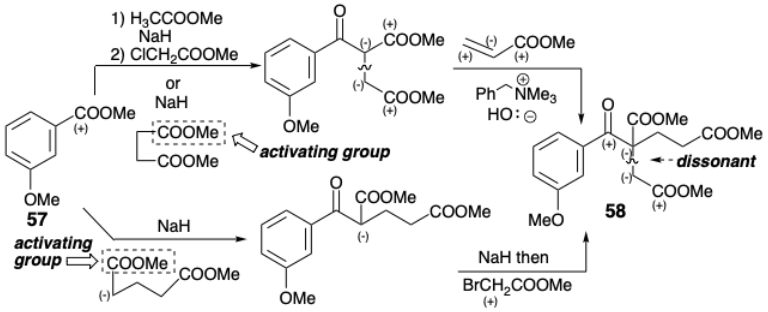
In practice, C-acylation of enolate intermediates such as **56** is accompanied by O-acylation of the resulting β-keto esters. However, no additional steps are required because the resulting enol esters are hydrolyzed to β-keto esters under the reaction conditions required for retro Dieckman cleavage of the latter to generate the target β-substituted alkane dioic acids.



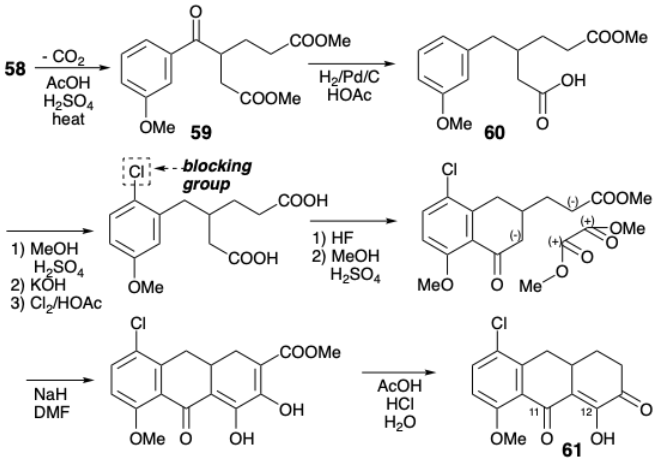
Instead of a benzylic nucleophile as starting material, Woodward's strategy was based on the choice of a readily available benzylic electrophile, methyl m-anisate (**57**), as starting material. This choice channels retrosynthetic analysis to a precursor **58** with an activating functional group, the benzylic carbonyl, that must be removed subsequently to provide **49**. Although conjugation with the remote carbomethoxyl in **58** could provide the nucleophilic activation required to unite a hexanedioic ester starting material with **57**, Woodward chose to exploit a classical synthetic method for ketones, alkylation of a β-keto ester followed by hydrolysis and decarboxylation (an acetoacetic ester synthesis), to assemble the carbon skeleton of **49**. This choice mandates the inclusion of a carboxylic ester activating group in **58**.



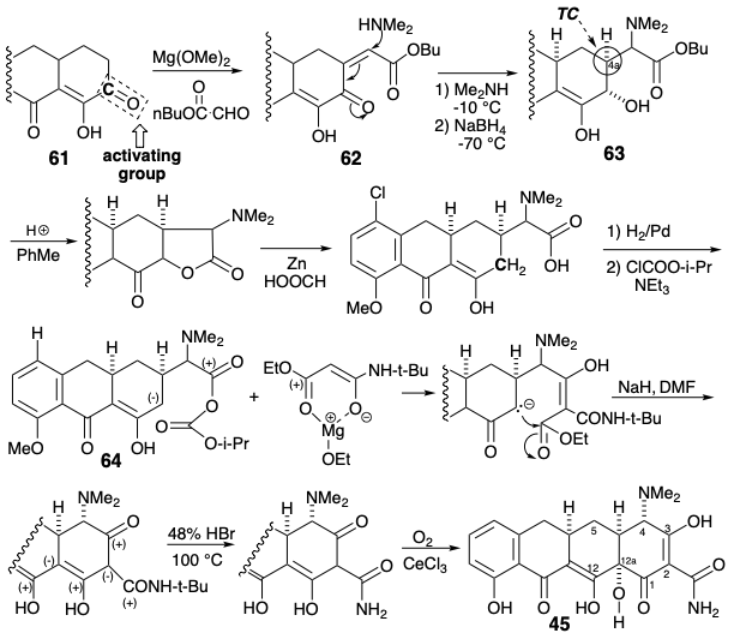
Woodward examined three different strategies to discover which route actually provides the best overall yields of **58** from **57**. Each pathway exploits readily available starting materials. Interestingly, the longer (less convergent) route, using methyl acetate and methyl chloroacetate as building blocks, gave better overall yields than the other two routes that exploit symmetrical diester precursors. It is also significant that, in each route, a dissonant starting material is used to provide the dissonant circuit in **58**.



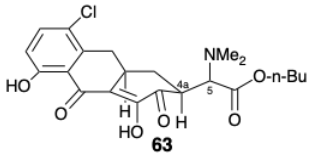
Conversion of **58** to the key tricyclic intermediate **61** was then achieved by hydrolysis, decarboxylation, hydrogenolysis, chlorination, Friedel-Crafts acylation, Claisen condensation-Dieckmann cyclization, and then another hydrolysis and decarboxylation. The interesting selective demethylation that produced **60** results from intramolecular transesterification of an intermediate benzyl alcohol followed by hydrogenolysis of the resulting benzylic ester. Methylation of **60** was performed solely to facilitate purification.



Woodward anticipated different properties for the three carbonyl groups in **61**. Thus, the β-dicarbonyl array (C-11 and 12) is "a stabilized vinylogous carboxylic acid system, while the third, like that in simple α-keto acids, should be both highly susceptible to addition reactions and readily enolizable. The latter property should confer high nucleophilic reactivity upon the adjacent methylene." This reactivity was exploited to append to **61** a precursor fragment for ring A, and then the dimethylamino group by polar reactions. The third carbonyl, having served its purpose, was then removed by reduction to α-hydroxy-ketone **63**, activation by intramolecular transesterification, and reductive cleavage of the resulting lactone.

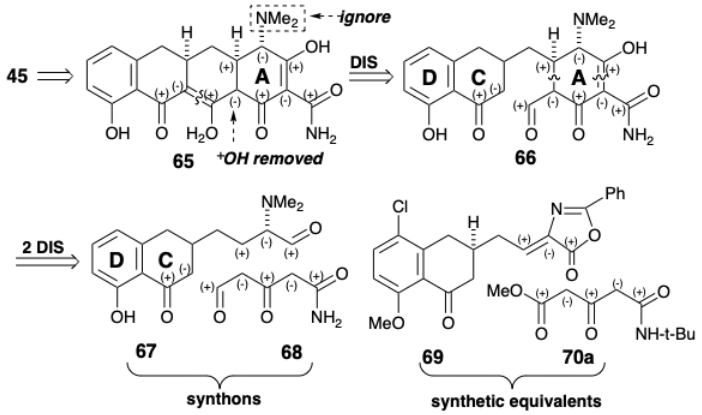


A fully functionalized acyclic precursor was then elaborated for ring A by acylation of a methyl malonamate carbanion with the mixed anyhdride **64**. Dieckman cyclization, exploiting the nucleophilic reactivity conferred to the adjacent methylene by the carbonyl at position 12, produced ring A. The required stereochemistry at position 4a in **64** is produced during addition of dimethylamine to **62**, which favors the more stable equatorial epimer of **63**. Installation of the last functional group, the hydroxyl at position 12a was then accomplished oxidatively to deliver **45**.



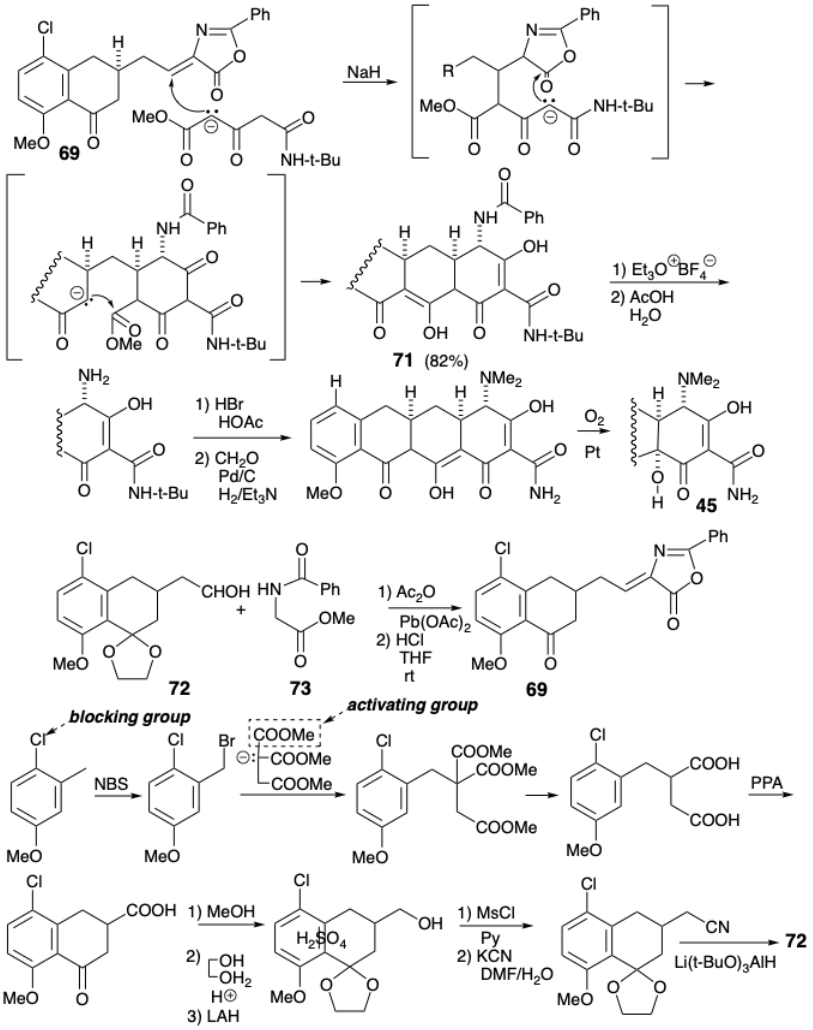
A More Convergent Strategy for Tetracyclines.

In another strategy for the total synthesis of 6-desmethyl-6-desoxytetracycline (**45**), as in the previous synthesis by Woodward, the target is simplified by removing the C-12a hydroxyl. Then, except for the polar activation afforded by the C-4 dimethylamino substituent, the polar reactivity provided by the remaining functional groups is entirely consonant along any circuit as shown in **65**. The polar disconnection **65** ⇒ **66** separates the molecule into two large fragments united by a simple methylene bridge. Further bond disconnections disect the A ring into two straight chain precursors **67** and **68**, that can be reunited by polar reactions. The synthetic equivalents that Muxfeldt utilized for the synthons **67** and **68** were **69** and **70a**, respectively.[9]

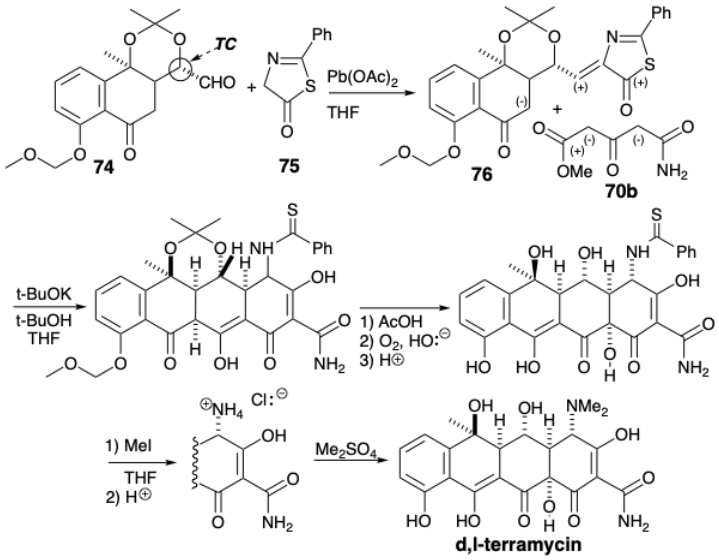


The highlight of the Muxfeldt synthesis is the ingenious reaction that produces the tetracyclic intermediate **71** in one step from the bicyclic precursor **69** in 82% yield! Final adjustment of functionality readily affords **45** from **71**. The strategy benefits from a high

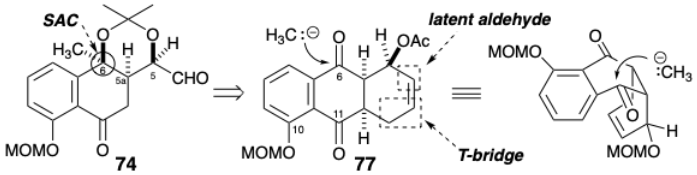
degree of convergence. Moreover, **69** is readily available by an azalactone synthesis from **72** and **73**. Finally, the intermediate CD-ring aldehyde **72** was prepared in good overall yield from 4-chloro-3-methylanisole.



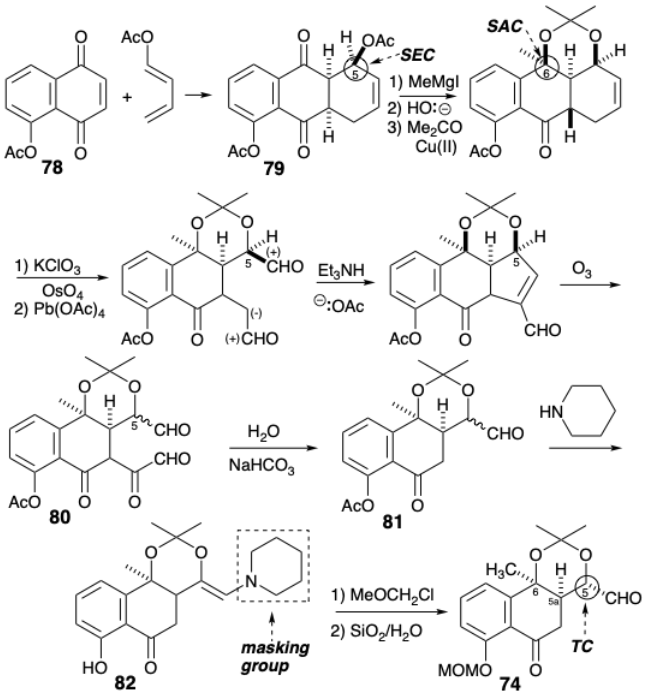
The first total synthesis of a natural tetracycline, the 5-hydroxy derivative terramycin, was achieved by Muxfeldt.[10] The A and B rings were assembled by the same strategy used above to generate **45**. Thus, a CD-ring aldehyde **74**, analogous to **72**, was condensed with a preformed azathio lactone **75** analogous to an azalactone intermediate involved in the reaction of **73** with **72**. The resulting Michael acceptor **76**, analogous to **69** was then condensed with the unprotected amide **70b** corresponding to **70a** to generate the tetracycline ring system in one synthetic step. Subsequent deprotection of the masked hydroxyls and oxidative introduction of the last hydroxyl at position 12a was followed by removal of the thiobenzoyl masking group under exceptionally mild conditions upon treatment with methyl iodide. This reaction involves the generation and subsequent hydrolysis of a methyl thioimidic ester intermediate. Finally, controlled dimethylation of the primary amine gave terramycin.



The strategy employed for generating the key intermediate **74** exploits a temporary bridge in **78** to mask the aldehyde in latent form as an alkene and to create a folded tricyclic precursor that is expected to add a methyl nucleophile to the carbonyl at position 6 from the least sterically congested convex face. This assures a *cis* relationship between the methyl group and the neighboring bridgehead proton. The vinylogous α-diketone array in **77** is expected to be especially electrophilic, sufficiently activated that competition from addition to the acetate carbonyl can be avoided. Selectivity favoring addition to the carbonyl at position 6 rather than 11 may result from decreased electrophilicity owing to conjugation of the 11- but not the 6-carbonyl with the oxygen at postion 10. The presence of a cyclohexene in 77 recommends a cycloaddition synthesis involving a doubly activated electron-deficient quinone dienophile and relatively electron rich 1-acetoxy-1,3-butadiene.



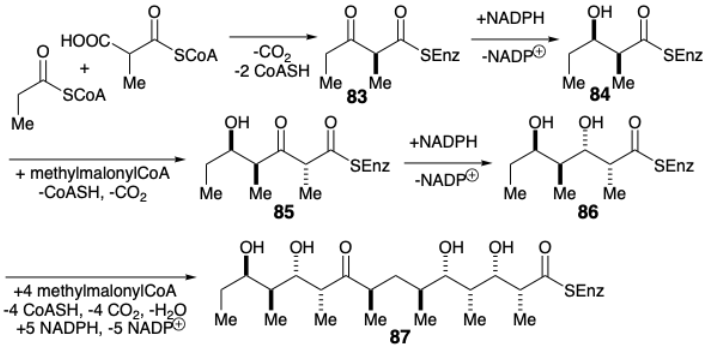
In fact, the Diels-Alder reaction of acetoxybutadiene with juglone acetate (**78**) gave the diacetate **79** regioselectively, and addition of a methyl Grignard reagent to **79** is regio- and stereoselective. The cyclohexene ring, having served its purpose, was then oxidatively cleaved to generate an aldehyde from its latent equivalent, the carbon-carbon double bond. An unneeded two-carbon fragment was then removed by a sequence involving aldol condensation, oxidative cleavage, and finally retro Claisen cleavage of an intermediate β-diketone array in **80**.



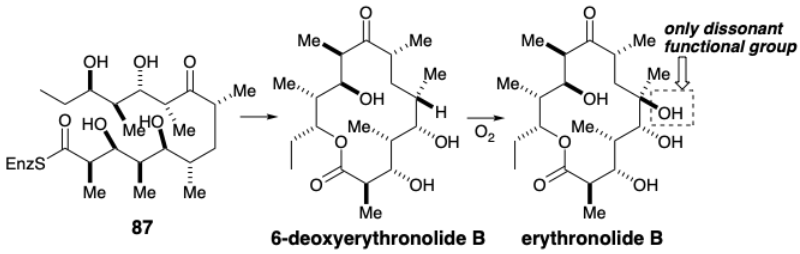
Because of a stereoelectronic preference for an endo transition state in the Diels-Alder reaction of **78**, **79** is generated with the correct configuration at position 5. However, the oxidative cleavage that generates **80** produces a mixture of epimers at position 5. During replacement of the acetyl protecting group with a methoxymethyl, piperidine is used as a nucleophile to cleave the acetate and as a masking group to hide the sensitive aldehyde during alkylation of the phenol. Fortunately, hydrolysis of the enamine **82**, by treatment with moist silica gel, generated epimerically pure **74** with the requisite configuration at position 5.

5.4: Erythronolide B

An enzyme promoted reaction of propionylCoA with methylmalonylCoA generates **83** enantioselectively. Diastereoselective reduction then delivers the b-hydroxy thioester **84**. In contrast with fatty acid biosynthesis, dehydration and conjugate reduction of the resulting α,β-unsaturated thioester does not preceed Claisen condensation with a second equivalent of methylmalonylCoA during the biosynthesis of the seco acid precursor **87** of the macrolide 6-deoxyerythronolide B.

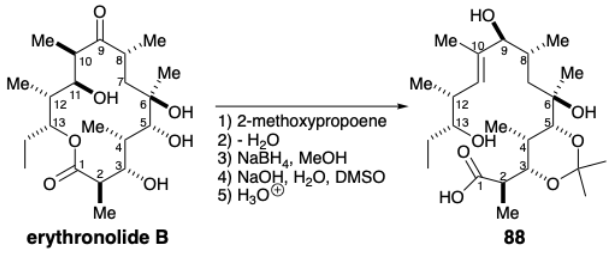


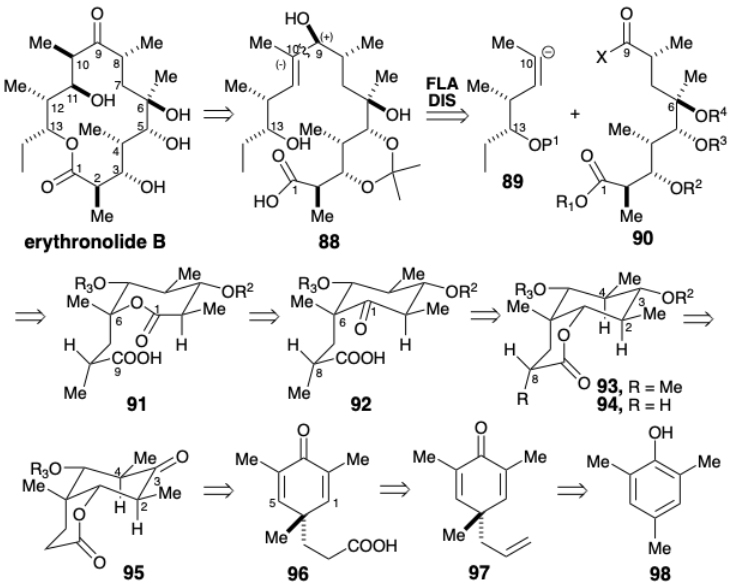
The resulting β-ketothioester **85** is reduced to a β-hydroxyester **86** that reacts with additional methylmalonylCoA and NADPH to generate **87**. Lactonization then provides 6-deoxyerythronolide B from which erythronolide is formed by oxidation. Generation of only 1 of the 2048 possible diastereomers of the acyclic intermediate **87** is the remarkable consequence of the asymmetry of the homochiral catalysts (enzymes) that promote the condensations and reductions responsible for producing ten asymmetric centers.



A Relay-directed Strategy for Total Synthesis of Erythronolide B.

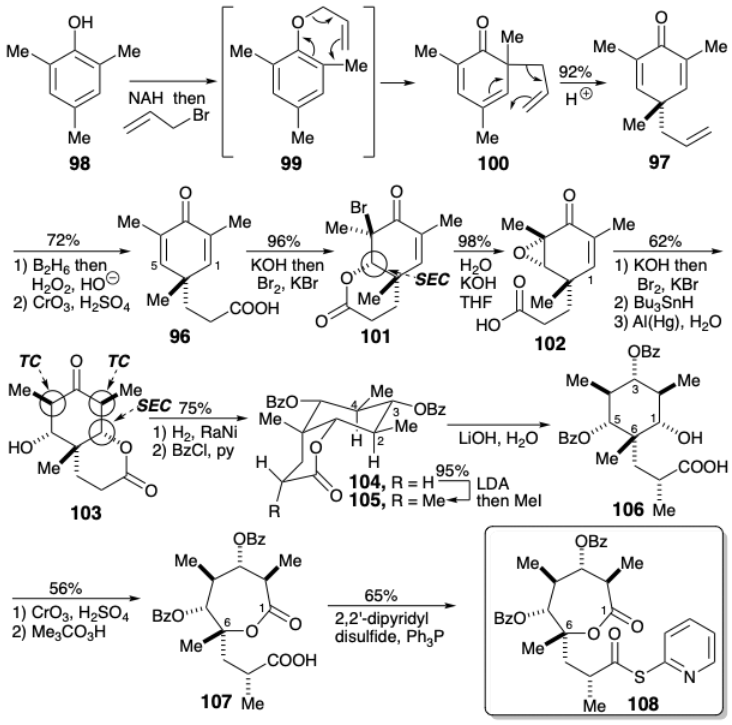
In a feasibility study, naturally derived erythronolide B was converted into an acyclic hydroxy acid **88** that was used to work out the final steps for a total synthesis.[12] The synthetic design process was then channeled by the choice of this naturally derived precursor, a **relay compound**. The two stereocenters at positions 12 and 13 in **88** are remote from those at positions 2-6 and 8. Therefore, it would be difficult to generate one set of stereocenters under the stereo-controlling influence of the other. Rather, building blocks containing these stereocenters with the correct absolute configurations can be assembled and then united to provide the relay compound **88**. The first total synthesis of Erythronolide B1 3 adopted a convergent **absolute asymmetric** (see section 4.6) strategy designed to provide **88** by the union of two homochiral segments, a nucleophile **89** and an electrophile **90**.





To provide a more conformationaly rigid platform for generating and confirming the relative configurations of stereocenters, a cyclic temporarily-bridged precursor **91** was envisioned for the acyclic subtarget **90**. Even greater rigidity is provided by the smaller ring of a six-membered ketone **92** that incorporates the lactone functionality in latent form. Stereoelectronically favored axial delivery of hydrogen to the isomeric cyclohexanone **94** can be expected to generate an equatorial hydroxyl at position 3. Furthermore, dislocation of **93** to **94** allows a carbonyl at position 3 to promote a thermodynamically favored equatorial disposition for the methyls at positions 2 and 4, and sets the stage for uncovering a symmetrical precursor, *vide infra*. Another temporary bridge, a six-membered lactone can be exploited to favor generation of the required configuration at the relatively remote stereocenter at position 8 in **92** during a methylation of **95** that can be expected to favor an equatorial methyl in **94**. Lactone bridges can also be exploited to assure the proper stereo and regiochemical orientation during introduction of oxygen substituents at positions 1 and 6 by polar additions to the C=C bonds in a symmetrical dienone precursor **96**. A search of the literature for available starting materials with the carbon skeleton of **96** can be used to identify the allyl cyclohexadienone **97** that is readily prepared from the trimethylphenol **98**.

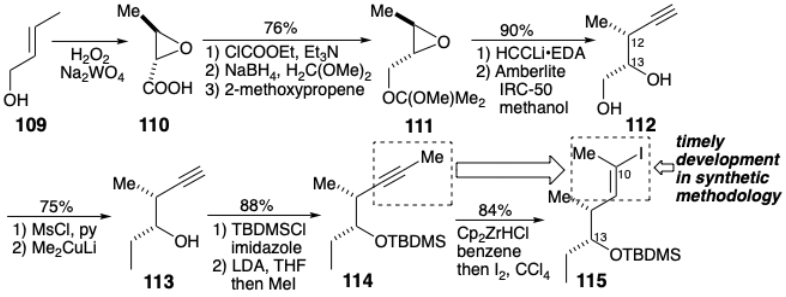
Reaction with allyl bromide of a phenolate from **98** provides **100** by Claisen rearrangement of the initial O-allylation product **99**. An acid-catalyzed Cope rearrangement of **100** delivers the symmetrical dienone **97** that is selectively hydroborated at the terminal vinyl group and then oxidized to produce the carboxylic acid **96**. Stereo and regioselective delivery of oxygen to position 5 is accomplished by intramolecular addition of a carboxylate to a C=C bond in **96**. Capture of the reversibly formed enolate carbanion intermediate with electrophilic bromine produces **101**. To repeat this process on the remaining C=C bond, the lactone is saponified to regenerate a carboxylic acid. This also generates an epoxide by intramolecular displacement of the bromo substituent by alkoxide. A second stereo and regioselective delivery of oxygen, this time to position 1, is again accomplished by intramolecular addition of a carboxylate to a C=C bond. Subsequent reductive removal of unneeded heteroatom functionality at positions 1 and 4 provides **103**.



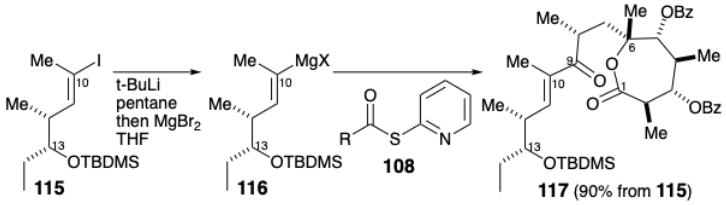
The nucleophilic activation afforded by the lactone carbonyl in **103** could now be exploited to introduce a methyl group at position 8. However, prior adjustment of functionality level at position 3 avoids nucleophilic activation adjacent to the ketone carbonyl. Methylation of **104** then afforded **105** stereoselectively. The lactone in **103** differentiates the hydroxyl substituents at positions 1 and 5. To maintain this diferentiation after saponification of the lactone, the other hydroxyls in **105** had to be suitably masked. The choice of benzoate ester masking group is particularly subtle. The feasibility of selective saponification of the lactone in the presence of benzoate esters relies upon the diminished electrophilicity of the benzoate carbonyl group owing to conjugation. Oxidation of the alcohol **106** to a ketone and then a lactone **107** followed by activation of the carboxylic acid as a thioester provided an electrophilic C1-9 segment equivalent to **90** where the masking groups R^1 and R^4 are replaced by a lactone bridge.

The synthesis outlined above provides racemic compounds. Resolution of an early intermediate, the carboxylic acid **102**, by fractional crystallization of diastereomeric 1-α-naphthylethylamine salts, was employed to generate intermediates with the absolute configurations shown above that are required for natural erythronolide B.

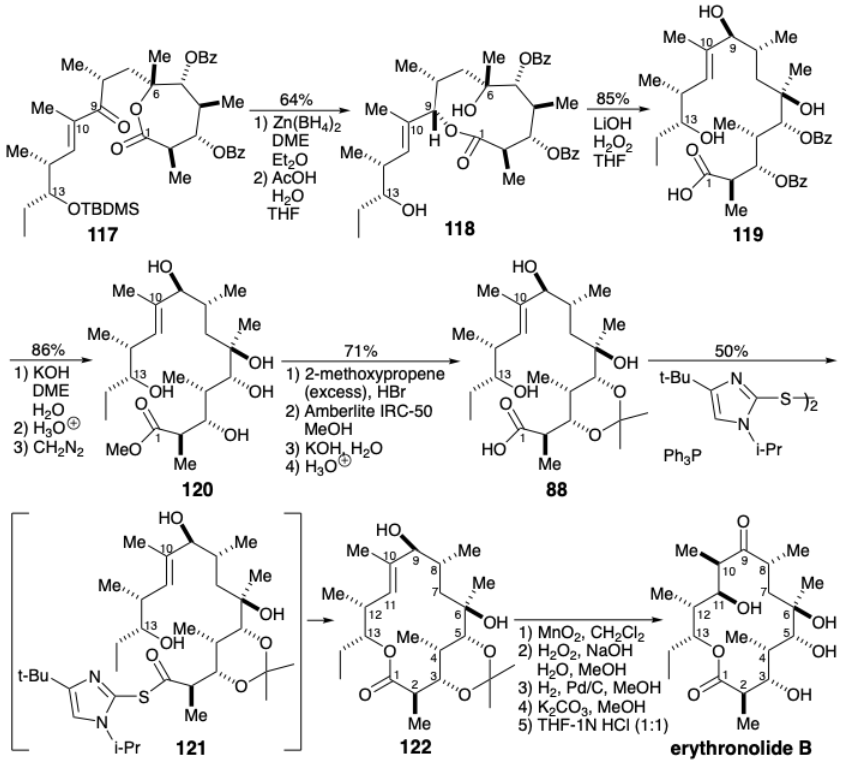
Resolution of an early intermediate was also employed to prepare the requisite enantiomer of a precursor **115** (see section 6.3) for the nucleophile **89**. Thus, the epoxy carboxylic acid **110**, that is readily available by a one-step oxidation of *trans*-crotyl alcohol (**109**), was resolved by fractional crystallization of diastereomeric 1-α-naphthylethylamine salts. Stereospecific nucleophilic substitution on **110** generated the absolute configuration required at position 12. The regioselectivity of this epoxide opening is controlled by the bulky ether substituent in **111**. Use of the corresponding epoxy alcohol in the displacement showed much inferior regioselectivity. Replacement of the terminal hydroxyl in **112** by a methyl group to give **113** could be accomplished without masking of the secondary hydroxyl by using an excess of Me_2CuLi. The completely regioselective conversion of acetylene **114** into vinyl iodide **115** depended upon the outstandingly high regioselectivity that had recently been reported for hydrozirconation of unsymmetrically disubstituted acetylenes. This step in the Corey erythronolide B synthesis is a poignent example of the impact of developments in synthetic methodology on our ability to achieve efficient syntheses of complex organic molecules.



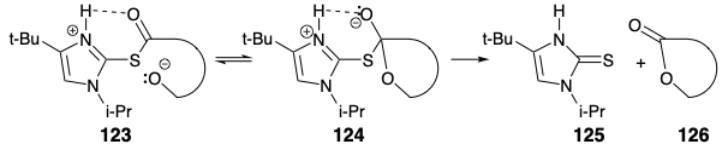
Although both building blocks **108** and **115** were available in homochiral form with the correct absolute configurations for erythronolide B, the synthesis was actually carried out by coupling the correct enantiomer of **115** with racemic **108**. Thus, a Grignard reagent **116** derived from **115** was acylated with thioester **108** to produce ketone **117** and a diastereomer in 90% total yield. The mixture was caried through several additional steps before separation by preparative thin layer chromatography.



Thus, reduction of the ketone carbonyl in **117** proved unexpectedly difficult owing to suprisingly similar reactivity of the keto and lactone carbonyls toward most reducing agents and also because of a proclivity toward conjugate reduction of the enone. Reduction with zinc borohydride was accompanied by two unexpected phenomena, a very welcomed complete stereoselectivity and an essentially irrelevant translactonization that generated a 10-membered lactone **118** after removal of the silyl protecting group at position 13. Saponification of this lactone was most effectively accomplished with LiOH and aqueous H_2O_2 which presumably benefits from the supernucleophilicity of the hydroperoxide anion. Hydrolysis of the less reactive benzoate esters in **119** was then accomplished with aqueous KOH. Subsequent methyl- ation delivered **120** together with a diastereomer from which it was sepatated by TLC on silica gel.

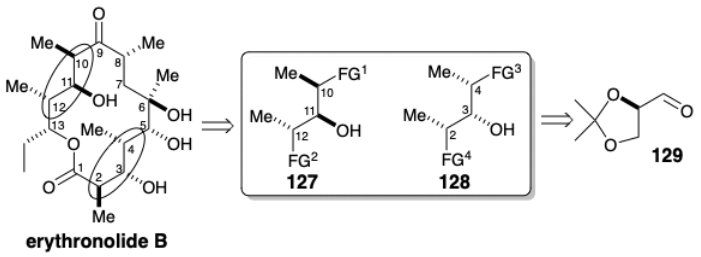


The relay compound **88** was obtained from **120** by ketalization with 2-methoxypropene, selective hydrolysis of 2-methoxy-2-propyl ethers that were also formed, and saponification of the methyl ester. Macrolactonization was accomplished by the "double activation method" that involves simultaneous activation of the hydroxyl and carboxyl functions. Presumably, a doubly activated intermediate **123** collapses to a tetrahedral carbonyl adduct **124** from which the lactone **126** is formed by elimination of **125**. Thus, heating the thioester **122** at reflux in dry toluene provided erythrololide B in 50% yield.

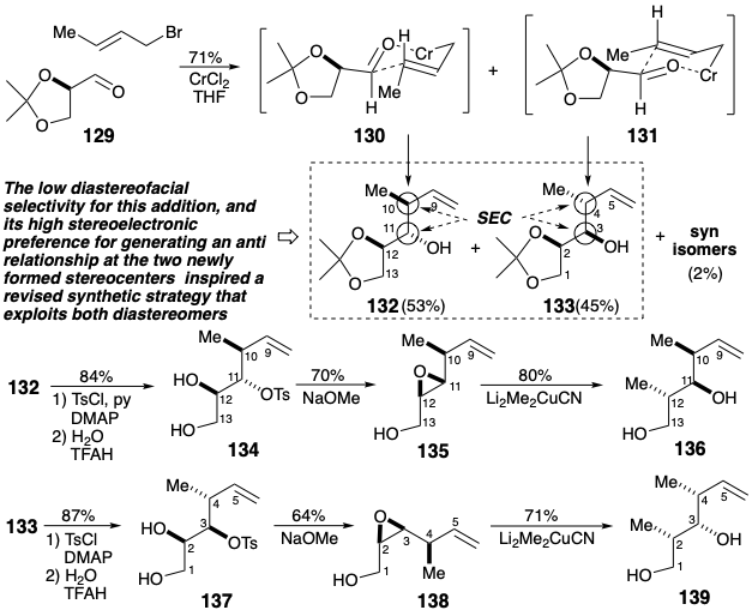


Erythronolide B from Sugar-derived Homochiral Building Blocks.

A strategy for an enantiospecific total synthesis of erythronolide B evolved from the recognition that the C2-4 and C10-12 segments are identically substituted but have different absolute stereochemistries. Such segments, differentially substituted at each end, i.e. **127** and **128**, might be elaborated and joined to generate the natural product. Therefore, studies were launched to define synthetic routes to such intermediates. Since (R)-2,3-O-isopropylideneglyceraldehyde (**129**) is a readily available homochiral building block (see section 3.7), it's possible utility as a starting material for the enantiospecific synthesis of such segments was explored.[14]



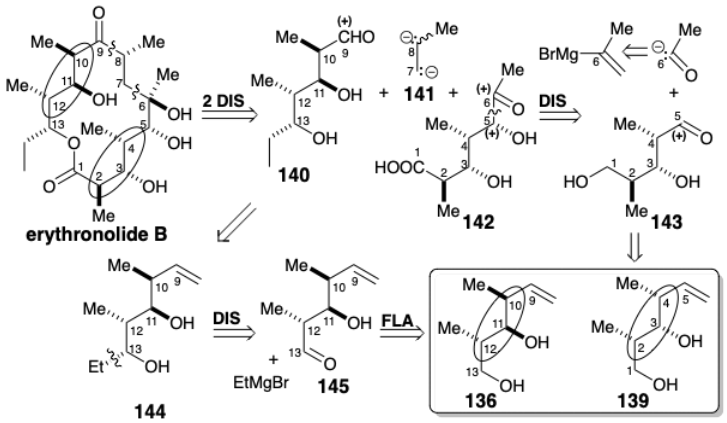
The addition of a crotylchromium reagent to aldehyde **129** showed virtually no diastereofacial selectivity for addition to the aldehyde but a high preference for generating an anti relationship at the two newly formed stereocenters owing to a stereoelectronic preference for chair-like transition state structures **130** and **131** that lead to **132** and **133**. These diastereomers were readily separable by preparative column chromatography on a large scale. Conversion of **132** to an intermediate of type **127** and of **133** to an inter- mediate of type **128** requires inversion of the free secondary hydroxyl and substitution of the other secondary oxygen substituent by methyl with inversion of configuration. Inversion of the free hydroxyl was accomplished by activation as a tosylate followed by intramolecular S_N2 displacement by a vicinal hydroxyl. This stereospecifically produced **135** from **134** and **138** from **137**. Reaction of these epoxides with Li_2Me_2CuCN accomplished the second configurational inversion during replacement of an oxygen substituent with methyl. The diols **136** and **139** correspond to the fragments **127** and **128** respectively, where FG^1 and FG^3 are both latent aldehydes while FG^2 and FG^4 are both hydroxymethyl groups.



The availability of the homochiral building blocks **136** and **139** channeled a second phase of strategic planning.[15] Polar disconnection of erythronolide B at the C6-C7 and C8-C9 generates two precursors, **140** and **142**, both with terminal carbonyl functions. Polar union of these fragments would require a "vicinally dianionic two-carbon (C6/C7) synthon" **141** with a pendant methyl group. Although the identification of a synthetic equivalent for **141** was postponed, it was recognized that "the methyl branching excluded the straightforward application of some acetylenic derivative."

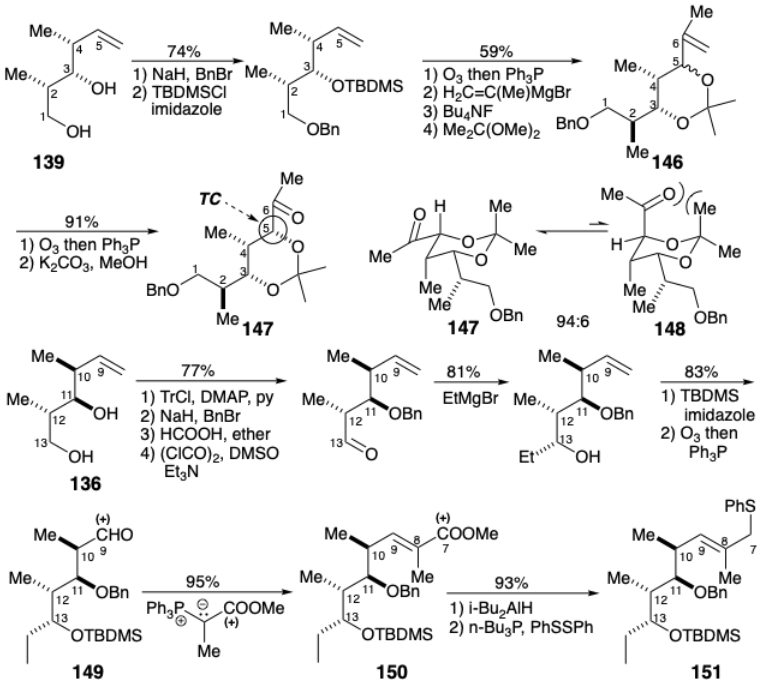
Further polar disconnection of **142** to generate an aldehyde **143**, that should be available from the building block **139**, requires an acetyl carbanion synthon for which isopropenylmagnesium bromide is a latent synthetic equivalent. The alkene **144** is a latent

equivalent of aldehyde **140**. Further polar dislocation of **144** suggests an ethyl nucleophile and aldehyde electrophile **145** that should be available by oxidation of **136**.

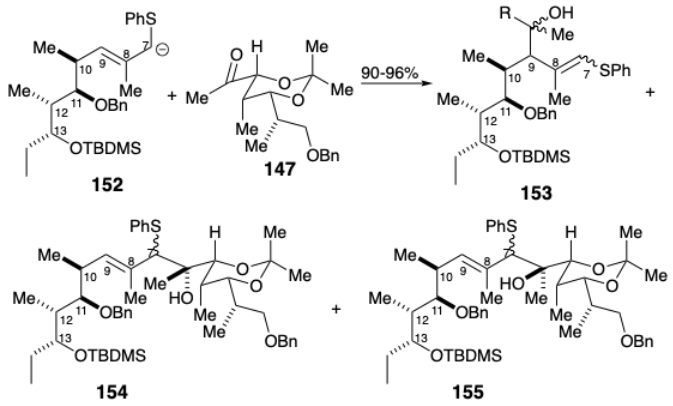


A masked derivative **147** of **142**, containing the carboxylic acid functionality in latent form as a benzyloxy ether, was prepared from the homochiral building block **139** (see below). The addition of a Grignard reagent to an aldehyde intermediate generated the stereocenter at position 5 nonstereoselectively, leading to **146** as a 2:1 mixture of diastereomers. However, the requisite configuration at this carbon could be established by equilibration of the epimeric ketones **147** and **148**. The equatorial ketone was favored over the axial epimer **148** by 94:6 at equilibrium.

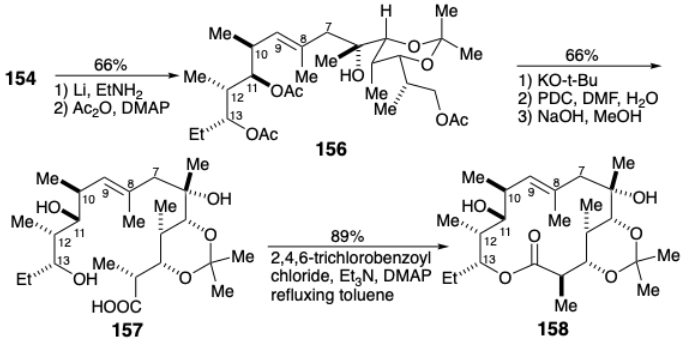
A masked derivative **149** of aldehyde **140** was prepared from the homochiral building block **136.** Although a polar union of the two carbonyl containing fragments **147** and **149** might exploit a dissonant dianionic fragment corresponding to **141**, a synthetic equivalent of **141** was not devised. Rather, a nucleophilic reagent that was nucleophilic at C6 and contained an electrophilic carbon at position 7 was joined with aldehyde **151**, and then the polar reactivity of C7 was inverted by conversion to an allylic thioether that could be deprotonated to provide nucleophilic reactivity at C7.



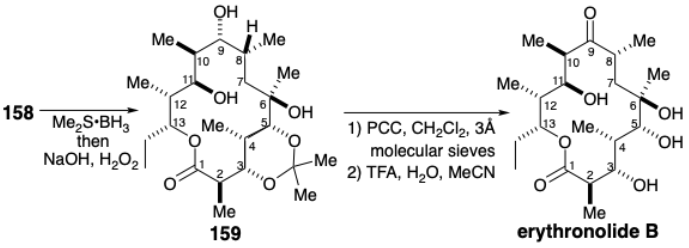
The carbon skeleton of erythronolide B was completed by joining ketone **147** with the allylic carbanion **152** produced by deprotonation of sulfide **151** with n-BuLi in the presence of TMEDA. Initial results were disapointing because the major product was the γ-adduct **153** rather than the desired α-adduct **154**. By addition of HMPA, the formation of **153** could be suppressed almost completely. However, under these conditions, the main product was an epimeric α-adduct **155**. Finally, it was discovered that precomplexation of the ketone **147** with BF_3 strongly favored the required regio and stereoselecivity.



Having served its purpose as a polar reactivity inversion operator, the allylic phenylthio substituent was removed reductively. Differentiation of the hydroxyl groups was then accomplished by acetylation followed by selective deacetylation of **156** to unmask the primary hydroxyl. Oxidation followed by exhaustive deacetylation delivered the trihydroxy acid **157**. Macrolactonization was accomp- lished in very good yield by conversion to a mixed anhydride that was cyclized in dilute toluene solution. Apparently a strain-free conformation that is ideally suited for cyclization is available to **157**, whereas serious congestion is present in conformations suitable for forming a 12-membered lactone by acylation of the 11-OH.



Completion of the synthesis required introduction of oxygen at position 9. Anti Markovnikov hydration of the 8,9-C=C bond in **158** by hydroboration-oxidation accomplished this functionalization, and apparently owing to macrocyclic conformational effects, generation of the correct configuration at position 8 was favored by 9:1. Conformational effects also fostered selective oxidation of the secondary hydroxyl at position 9 in the presence of another secondary hydroxyl at position 11. Thus, the accumulation of many favorably selective steps owing to subtle, unanticipated consequences of molecular shape -- i. e. the remarkably effective macrolactonization, and favorably stereo and regioselective processes - - resulted in a total synthesis that rivals the Corey strategy that was more meticulously planned by thorough reterosynthetic analysis.



5.5: Terminology

acetogenin (section 5.2)

biomimetic strategy (section 5.2)

cocyclic bond (section 5.3)

dehydrocyclization (section 5.1)

exendo bond (section 5.3)

fused-ring (section 5.3)

fusion-bond (section 5.3)

peripheral ring (section 5.3)

primary ring (section 5.3)

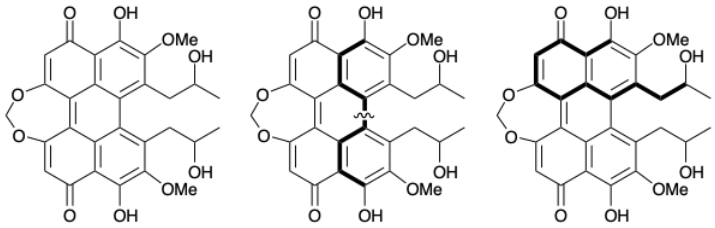
relay compound (section 5.4)

strategic bond (section 5.3)

5.6: Study Questions

1. **Biosynthetic Strategies**

(a) Draw a circle around each of the "common atoms" (as defined by Corey) in the carbon skeleton in the following structure of cercosporin (**160**).



cercosporin (160) **161** **162**

(b) What is the polar reactivity relationship between the two functional groups at the ends of the circuits that are highlighted in **161** with respect to the bond indicated with a wavy line?

(c) What are the polar reactivity relationships between all of the functional groups with respect to all bonds along the circuit that is highlighted in **162**?

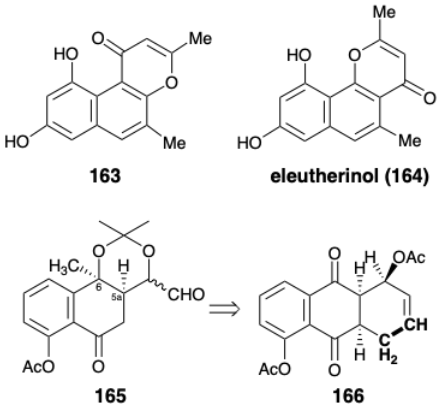
(d) Presuming that this symmetrical molecule is generated in Nature by dimerization of a precursor, write a structure for that precursor of cercosporin (**160**).

(e) Name one type of reaction that could generate the bonds which unite two molecules of the biosynthetic precursor of cercosporin (**160**) that you proposed in d above.

(f) On the basis of a biogenetic hypothesis, the correct structure of eleutherinol was postulated to be **164** and not **163**. In the space provided, write the structure of an acyclic precursor of **164** that is suggested by the biogenetic hypothesis.

2. **Tactics in Polyketide Synthesis**

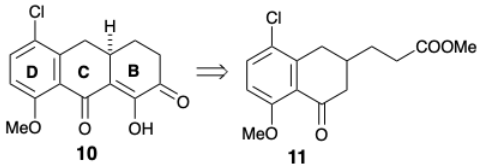
(a) In his total synthesis of terramycin, Muxfeldt utilized **166** as a precursor for **165**. Two of the carbons in **166**, the ones that are highlighted, are not needed in the skeleton of **166**. Explain **all** of the benefits of incorporating these two carbons in **166**.



163 **eleutherinol (164)**

165 **166**

(b) In his total synthesis of 6-desmethyl-6-desoxytetracycline, Woodward exploits chloroester **168** as a precursor for **167**. Neither the cholro nor the carbomethoxyl groups in **168** are incorporated into the final product, 6-desmethyl-6-desoxytetracycline. Explain the strategic roles of these two groups in the synthesis.



10 **11**

5.7: References

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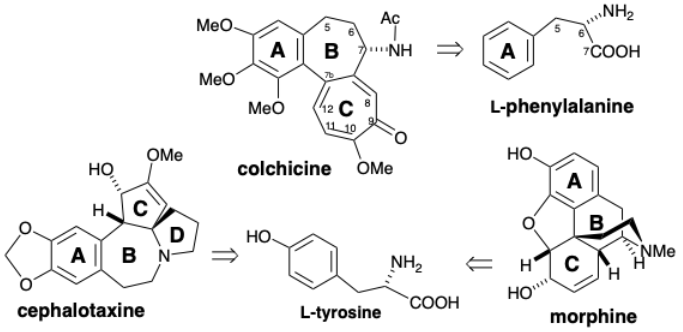
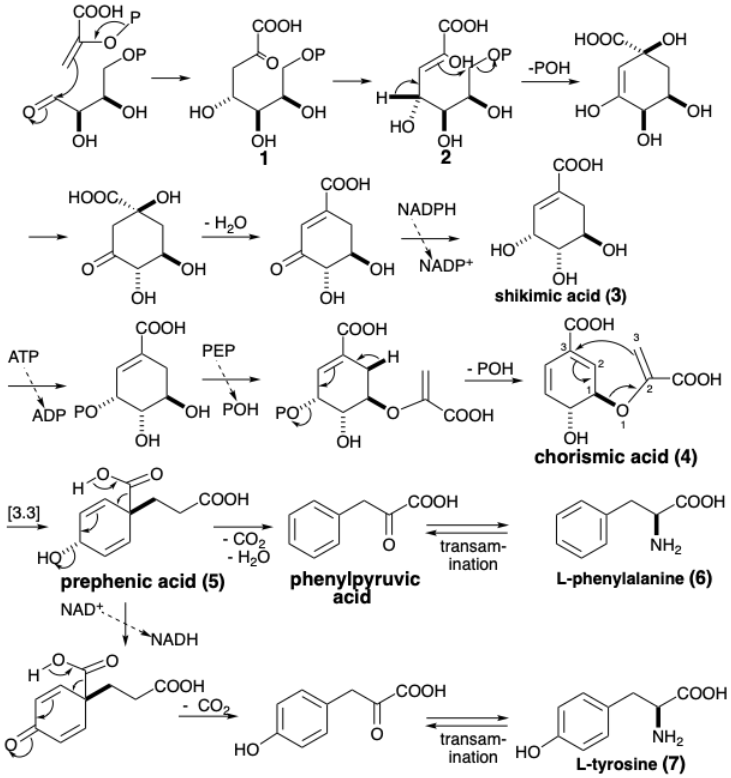
CHAPTER OVERVIEW

6: Amino Acids and Alkaloids

The alkaloids are a diverse family of nitrogen-containing natural products that generally are produced from amino acids in plants. Phenyl rings derived from aromatic amino acids may often be discerned embedded in the skeletons of some alkaloids. For example, the A ring of colchicine is derived from L-phenylalanine and the A rings of cephalotaxine and morphine are derived from L-tyrosine. Interestingly, the remaining carbons of the above mentioned alkaloids are also derived exclusively from L- phenylalanine or L-tyrosine. The loss of aromaticity that is common during such biosyntheses is an example of the unusual synthetic strategies that must be adopted in Nature owing to a limited selection of available starting materials.



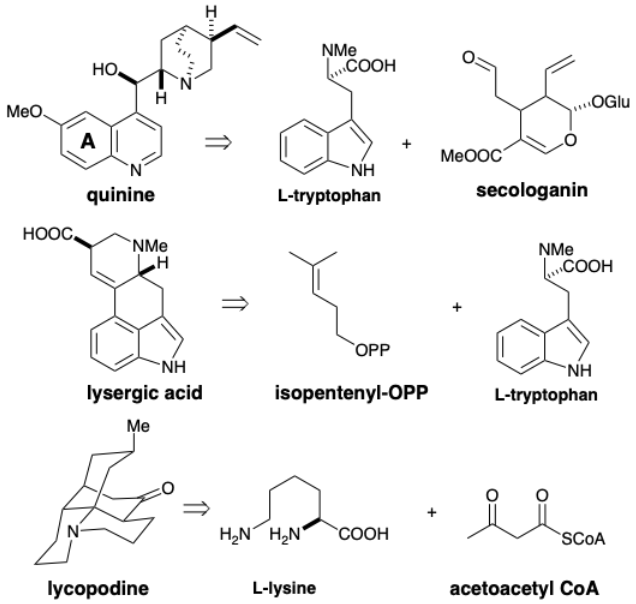
The aromatic rings of polyketides (see chapter 5) arise from acetyl-CoA by a *linear route* culminating in dehydrocyclization of intermediate poly-β-ketoalkanoic acids. In the biosynthetsis of the aromatic amino acids L-phenyl-alanine, L-tyrosine, and L-tryptophan, the aromatic rings are assembled by a more *convergent route* starting with an aldol condensation of phosphoenol pyruvate (PEP) and erythrose 4-phosphate (E4P). These starting materials are available from glucose metabolism (see chapter 2).



Cyclization of the enol tautomer **2** of the resulting 3-deoxy-D-arabinoheptulosonic acid 7-phosphate (**1**) is reminiscent of the polyene cyclizations that are initiated by allylic pyrophosphates which are encountered in the biosynthesis of terpenes (see chapter 4). Dehydration and reduction then provide shikimic acid (**3**), the intermediate for which this biosynthetyic pathway is named.

Phosphorylation of **3** and transetherification with a second molecule of PEP leads to a pivotal intermediate, chorismic acid (**4**). Appendage of the final three carbons of tyrosine and phenylalanine is achieved by a Claisen, i.e. [3.3] sigmatropic, rearrangement of **4** that produces prephenic acid (**5**). Decarboxylative elimination generates phenylpyruvic acid from **5** while oxidation and decarboxylation of the resulting vinylogous b-keto acid affords p- hydroxyphenylpyruvic acid. Transamination of the arylpyruvic acids (see **40** → **43** on section 5.3) delivers the corresponding α-amino acids L-phenylalanine (**6**) and L-tyrosine (**7**).

Amino acids are not the only building blocks incorporated into alkaloids. Thus, for example, some alkaloids incorporate starting materials of terpenoid origin. Quinine is assembled in Nature by the union of L-tryptophan with secologanin, a monoterpene. Interestingly, neither the tryptophane origin of the aromatic portion of quinine nor the terpenoid biogenisis of secologanin are at all obvious.

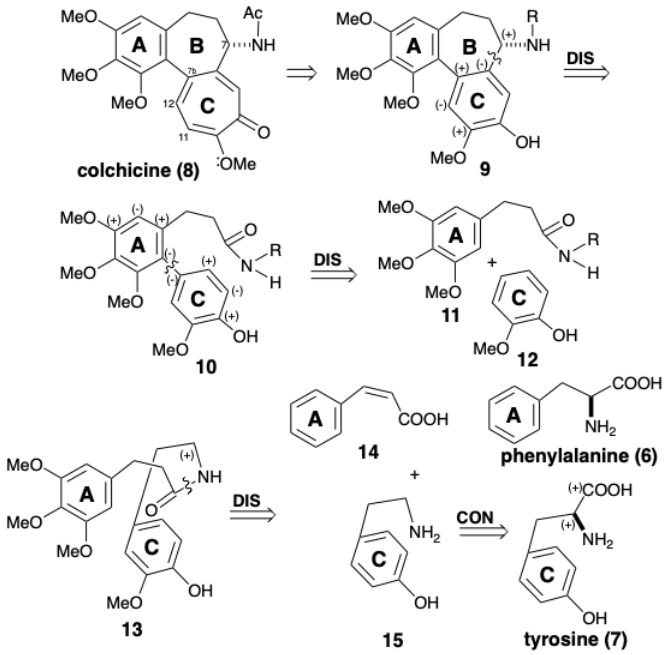


Much more obvious is the presence of L-tryptophan and an isopentenyl group embedded in the skeleton of lysergic acid. Polyketide fragments and nonaromatic amino acids may also serve as building blocks for alkaloids. For example, lycopodine is derived in nature from two molecules of L-lysine and one of acetoacetyl CoA.

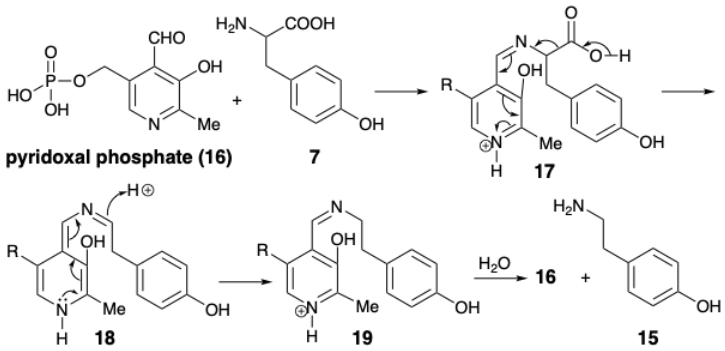
6.1: Colchicine

Biosynthetic Strategy

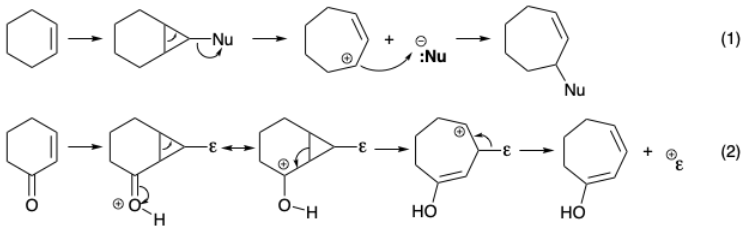
The use of aromatic amino acids, i.e. phenylalanine or tyrosine, as the sole starting materials for colchicine (**8**) requires preparing the seven-membered C-ring by expansion of an aromatic six-membered ring in a precursor such as **9**. How the ring expansion is accomplished will considered later. Since the starting amino acids do not have benzylic amino groups, it is likely that the bond between the C ring and the benzylic carbon is formed by electrophilic aromatic substitution. Since the starting amino acids are aryl propionic acid derivatives, the electrophile could be derived from an aryl propionic amide such as **10**. Clearly the bond between the A and C rings in **10** would be formed by oxidative coupling of electron rich aryl precursors **11** and **12**. Since the nitrogen in **11** probably comes from an amino group in the C ring amino acid precursor, and since **12** should also be derived from an a-amino arylpropionic acid, it is likely that the structure **12** must be revised so that the R group in **11** incorporates **12** as in the amide **13** (see below). A cinnamic acid **14**, generated by elimination of ammonia from phenylalanine (**6**) could be the progenitor of the arylpropionic acid portion of the amide **13**.



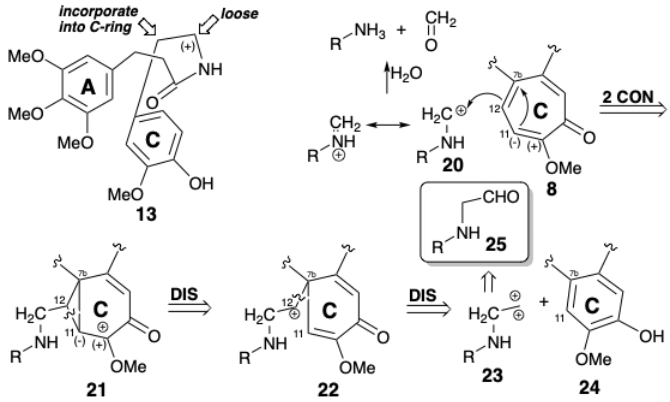
Generation of a phenylethyl amine **15** by decarboxylation of tyrosine (**7**) requires cleavage of a bond lying on a dissonant circuit. Such a cleavage is achieved biosynthetically by a polar process which converts the amino group temporarily into a derivative that can stabilize electronic excess on the amino carbon. The decarboxylation of tyrosine (**7**) to give p-hydroxy-b-phenthyl amine (**15**) is an example of a general reaction of amino acids that is promoted by the coenzyme pyridoxal phosphate (**16**). The process is initiated by the formation of a Schiff base **17**. The pyridine nitrogen is conjugated with the carbon a to the carboxyl and can stabilize electronic excess at that carbon. The imine nitrogen does not provide polar activation; it serves merely as a linking atom. Schiff base **17** readily undergoes acid catalyzed decarboxylation to form **18**. Protonation of **181** leads to rearomatization delivering the Schiff base **19.** Hydrolysis delivers the phenylethyl amine **15** and regenerates **16**. Thus, *pyridoxal phosphate (16) acts as a polar reactivity-inverting catalyst.*



We encountered polar ring expansion strategies in the total synthesis of longifolene (see section 4.4). There, a fused bicyclic intermediate, generated by cyclopropanation of a cyclohexene, underwent cleavage of the fusion bond in conjunction with departure of a nucleofuge to deliver a cycloheptenyl array (eq 1). An analogous process, involving departure of an electrofuge in conjunction with cleavage of the fusion bond in a similar intermediate, depends on a cyclopropyl carbinyl to homoallyl carbocation rearrangement (eq 2). The presence of oxygen substituents in the colchicine C ring suggests the possibility that such a ring expansion mechanism may transpire during the biosynthetic conversion of a six-membered C ring precursor into the seven-membered C ring.



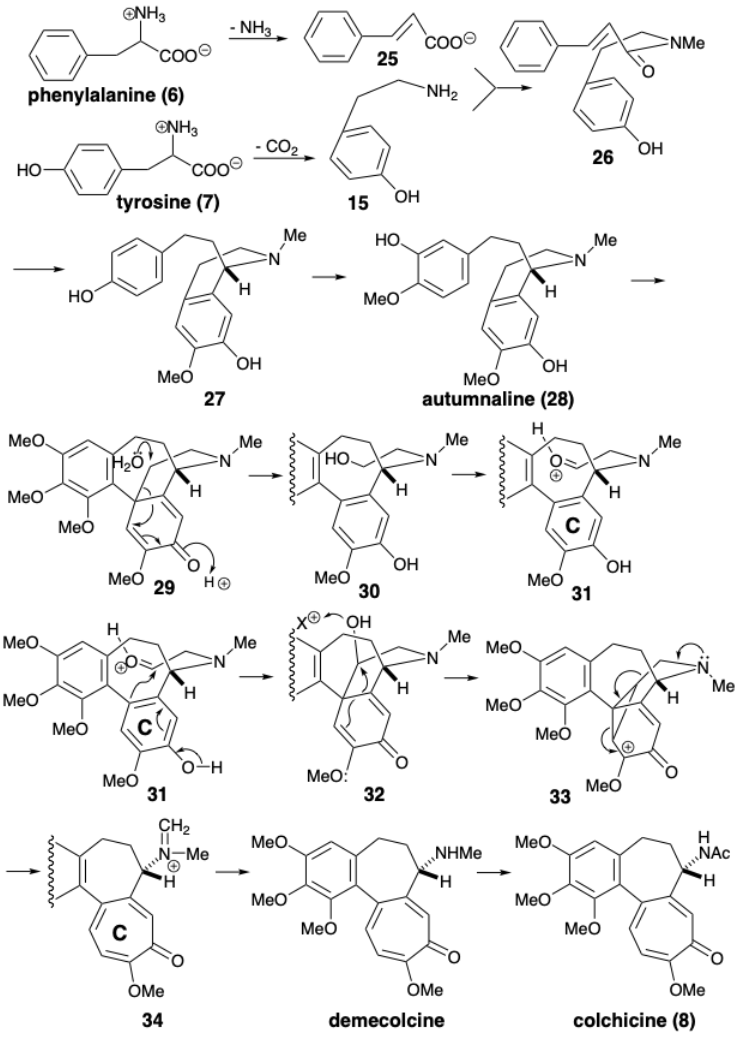
One carbon of the phenethyl sidechain in **13**, the benzylic carbon, could be incorporated in an aromatic precursor to generate the seven-membered C ring. The remaining carbon of the sidechain must be disconnected. Disconnection of this carbon as a carbocation can be stabilized by the amino group as in **20**. Retrosynthetic analysis of the colchicine biosynthetic ring expansion, presuming **20** as electrofuge, suggests cyclopropyl carbinyl and homoallyl carbocation intermediates **21** and **22**. The carbon that is inserted into the aromatic ring of the starting material **24** corresponds to the dication synthon **23** for which an aldehyde might serve as a synthetic equivalent.



Biosynthesis

In the biosynthesis of colchicine (**8**), NH_3 is eliminated from phenylalanine (**6**), and tyrosine (**7**) is decarboxylated, before an amide **26** is formed by joining the resulting intermediates **25** and **15**. The seven-membered B ring is created by an enantioselective intramolecular electrophilic aromatic substitution that gives **27** and an oxidative coupling of **28** that delivers **29**. Functionalization of an apparently unactivated methylene in **29** is accomplished by a sequence involving polar hydrolytic fragmentation to **30** followed by oxidation to an aldehyde suitable for insertion into the six-membered C ring progenitor in **31**. Expansion of the aryl ring to generate a seven-membered tropolone is initiated by intramolecular electrophilic aromatic substitution. Intramolecular

alkylation of **32** followed by a fragmentation of an intermediate cyclopropane **33** produces the ring expanded skeleton in **34** of the biosynthetic target. Final hydrolysis of the imminium group, N-demethylation and N-acetylation delivers colchicine (**8**).



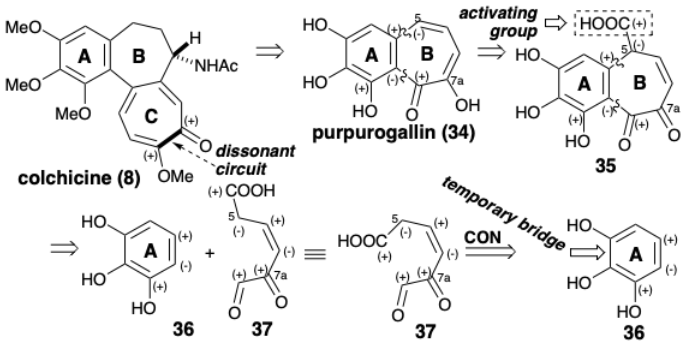
Molecular Characteristics

The stability of aromatic derivatives is often exploited in synthesis by strategies that incorporate preformed aromatic moieties. Thus, in the biosynthesis of colchicine (**8**), the aromatic A-ring is derived from the preformed aromatic ring of phenylalanine (**6**). The four different total syntheses of colchicine to be considered in this section all adopt this same strategy. In contrast with the biosynthesis, however, the total syntheses all employ fully functionalized aromatic starting materials. This is because the *regioselective* hydroxylations, that are acheived enzymatically in the biosynthesis, are not so readily achieved in the laboratory.

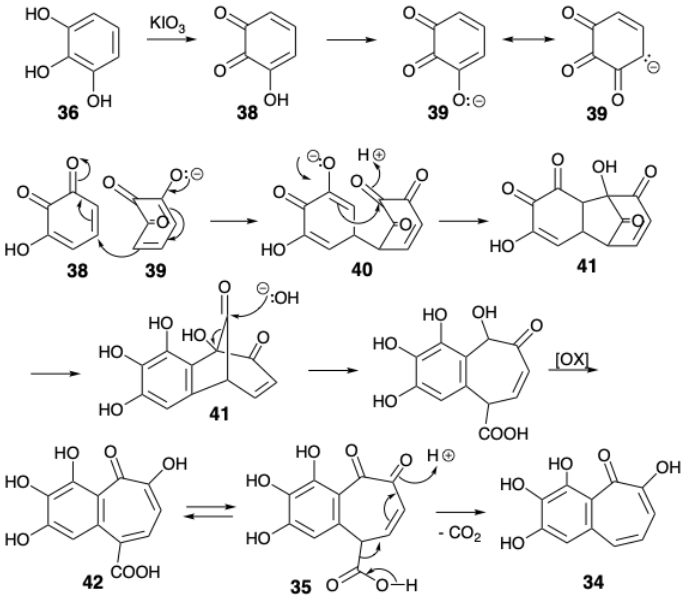
It should also be noted that the C ring of colchicine (**8**) contains two functional groups that provide electrophilic activation on adjacent carbon atoms, a polar reactivity dissonance. Thus, these functional groups cannot be exploited directly in a polar reaction (i.e. without umpölung) to create the C-C bond of the dissonant circuit between these carbon atoms. In each of the following syntheses, the seven- membered C ring is added to an AB-ring precursor. In each case, a different strategy is exploited for annelation of the C ring.

Key Intermediate-Directed Strategies for Conchicine

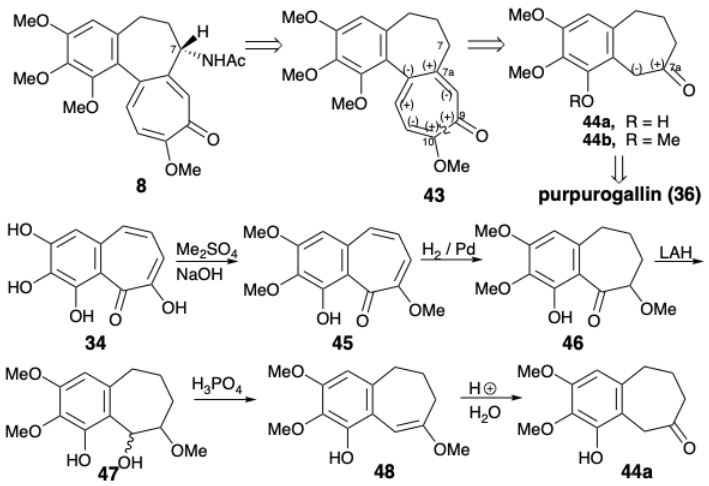
Two syntheses of colchicine exploited a readily available key intermediate, purpurogallin (**34**), for the AB ring moiety of **8** and formed the seven-membered C-ring by *nonpolar* reactions. Polar reactivity analysis of **34** suggests a synthesis from an aromatic precursor **36**. Thus, appendage to **36** of the B-ring in **34** can be facilitated by addition of an activating carboxyl as in **35** that could be generated from **36** and **37** by two polar bond-forming reactions. In fact, the aromatic starting material **36** can also be the precursor of a temporarily-bridged synthetic equivalent **39** (*vide infra*) of the synthon **37**.



Purpurogallin (**34**) was a well-known product from the oxidation of pyrogallol (**36**). It is probably formed by dimerization of 3-hydroxy-o-quinone (**38**). An initial Michael addition of the enolate **39** to **38** to give **40** followed by an intramolecular aldol condensation leads to a tricyclic intermediate **41** (see below). This is cleaved in a retro Dieckman reaction, typical for β-diketones, to produce a bicyclic carboxylic acid **37**, which can be isolated. This vinylogous β-keto acid readily undergoes decarboxylation to deliver **28**.

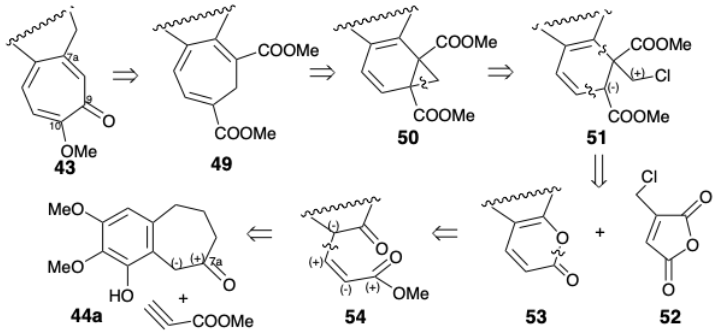


Both syntheses employing **34** for the A and B rings simplified the target by neglecting the acetamido group. This could be introduced by benzylic oxidation after completion of the carbon skeleton of the target **8**. Both syntheses construct the simplified target **43** from benzosuberone derivative **44**, in which the carbonyl functional group provides activation for annelation of the C ring. Eschenmosher[1] prepared **39a** by reducing the trimethyl ether **45** of purpurogallin (**34**) via **46**, **47**, and **48**.

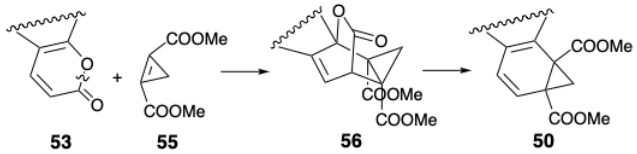


A Cycloaddition-Pericyclic Rearrangement Strategy for the C Ring

Eschenmosher's strategy[1] for annelation of the seven membered ring C was to build a diene onto **44a**, then construct a six membered carbocycle by a Diels-Alder reaction of the diene and finally expand the six to a seven membered ring by pericyclic rearrangement of a norcaradiene. Facile interconversion of cycloheptatrienes such as **49** with norcaradienes such as **50** is a well-known [3.3] sigmatropic (Cope) rearrangement that is driven to favor cycloheptatrienes by the relief of ring strain associated with cleavage of the cyclopropane. It is *doubtful that the strategy was concieved by rigorous retrosynthetic analysis* since conversion of **49** to **43** would certainly require extensive functional group manipulations. The decision to employ **49** as a precursor for **43** almost certainly evolved as a consequence of the decisions to employ: (1) a Cope rearrangement of a norcaradiene.

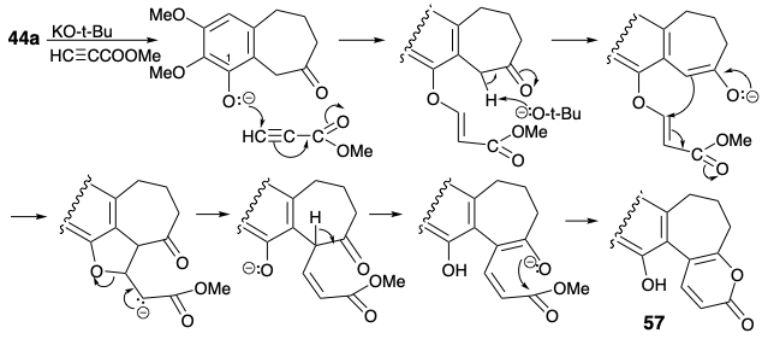


Therefore, chloromethylmaleic anhydride (**52**) is ideally suited to cycloadd to the reletively electron rich diene **53**. Perhaps a more obvious dislocation of **50** would be to **53** and the cyclopropene **55**. This branch of the retrosynthetic tree would, most probably, be considered first because it would provide a more convergent synthesis. Thus, reaction of **55** with α-pyrone **53** would deliver **50** directly by a Diels alder cycloaddition, followed *in situ* by a retro Diels Alder cycloelimination of carbon dioxide from an intermediate **56**.

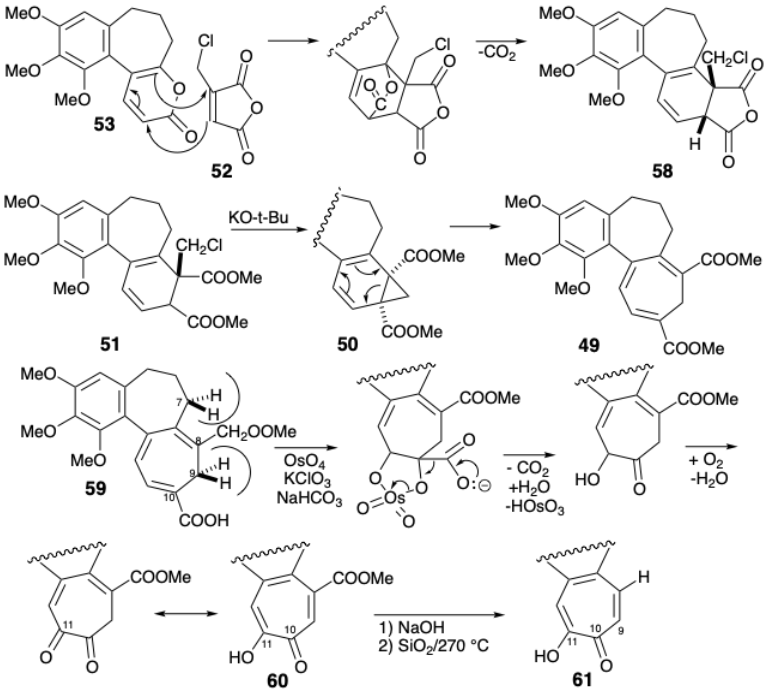


The alternative precursor, dienophile **52** with a chloromethyl substituent, is suggested by polar disconnection of **50** to **51** that can be derived from **53** by a Diels-Alder-retro Diels-Alder sequence. Dienophile **52** rather than **55** was chosen because it is more readily available than **55**. A Diels-Alder addition of **52** to **53** followed by a retro Diels-Alder elimination of CO_2 from an intermediate adduct, a carbonyl-alkene exchange process, will provide the cyclohexadiene **51**. The driving force for the process is the generation of a relatively stable C=O bond in exchange for the C=C bond of the dienophile **52**. The diene **53** is an enol lactone derivable from the acid **54**. Polar analysis of **54** suggests construction from **44a** and methyl propiolate by a polar 1,4-addition. Apparent Michael alkylation of **44a** with methyl propiolate provided pyrone **57**. Though **44a** could give **57** via direct Michael

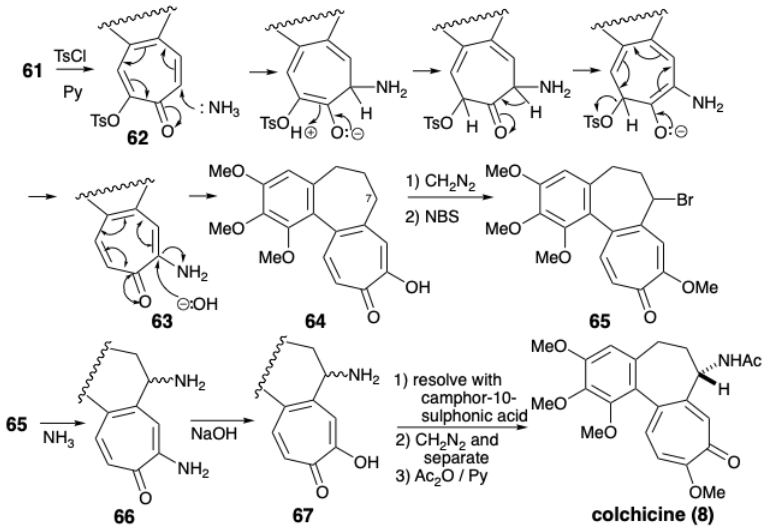
addition to the yneone, in fact the reaction was more complex. It involved participation by the phenolate anion. Thus, the electrophile was delivered intramolecularly to the rather hindered benzylic carbon of **44a**.



After methylation of phenol **57**, the annelation of a cyclohexadiene **58** was achieved by the well- known cycloaddition-cycloelimination reaction of α-pyrones. Base-catalyzed intramolecular alkylation of the diester **51** from **58** led, via the norcaradiene **50**, to the cycloheptatriene **49**. The least hindered ester in **49** was readily hydrolyzed selectively, and the resulting acid afforded a tropolone **61** via osmium catalyzed vicinal hydroxylation-decarboxylation, saponification of the remaining ester in **60** and a second decarboxylation.

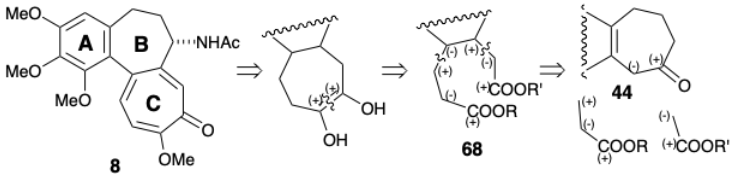


Unfortunately, the sequence leads to an oxygen function on C-11 rather than C-9 as required for colchicine. Transposition of the functional group was achieved by a well-precedented sequence of nucleophilic displacements on the tosylate derivative **62** of **61** first with NH_3 to give **63** then with -OH to deliver **64**. The tropolone **64** was then methylated and functionalized at C-7 by allylic bromination with N-bromosuccinimide to provide **65**. Nucleophilic displace-ment of bromide by ammonia gave the required C-7 amine accompanied by ammonolysis of the tropolone, a vinylogous ester. Saponification of the resulting vinylogous amide **66** gave **67**, that afforded colchicine upon methylation and acetylation.

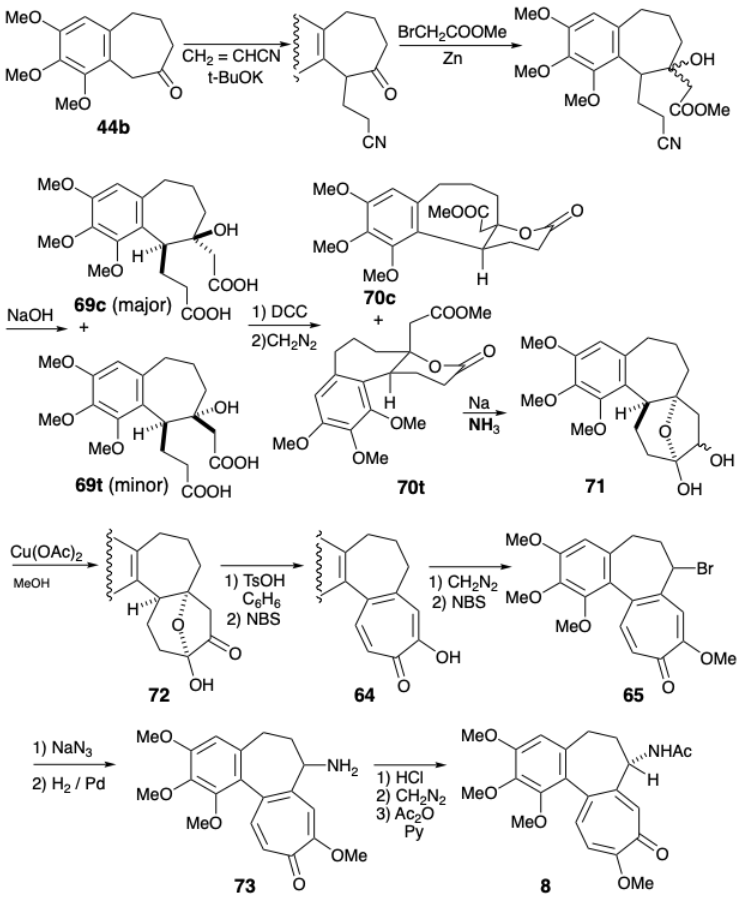


An Acyloin Strategy for the C Ring

Van Tamelen's strategy for annelation of the C-ring with vicinal oxygen functionality recognizes the applicability of an intramolecular acyloin reaction for creation of the dissonant circuit between vicinal electrophilic activating groups.[2] Further polar analysis suggests a synthesis of the requisite diester intermediate **68** by exploiting the polar activation provided by a carbonyl group in an AB-ring precursor **44**. Thus, appendage of acetic and a propionic acid side chains should be feasible respectively by a Reformatsky reaction and Michael alkylation.



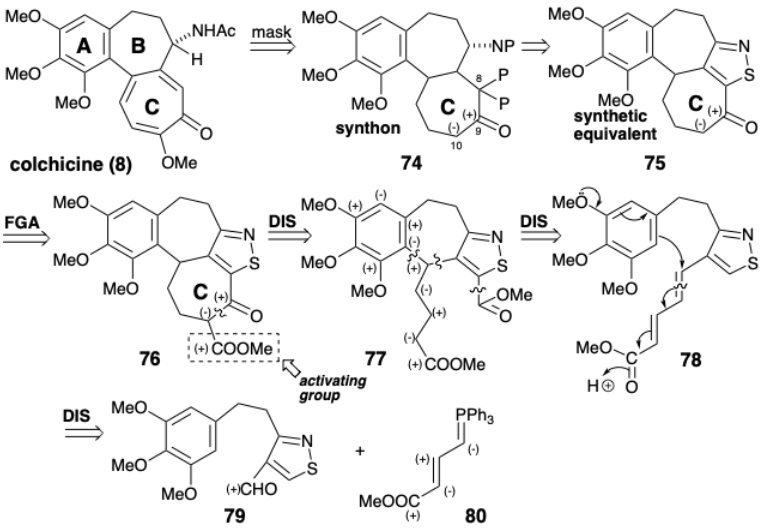
A pair of isomeric hydroxy diacids **69c** and **69t** was obtained by Michael alkylation of **44b** with acrylonitrile, Reformatsky reaction of the intermediate ketonitrile and hydrolysis. The hydroxyl group was masked intramolecularly as a lactone, and the remaining carboxyl group was methylated. Only one of the isomeric lactone esters **70** underwent an acyloin reaction which provided **71**. Unfortunately, this was the minor isomer **70t**, with an axial carbometh-oxymethyl substituent. The ester groups in the major isomer **70c** could not readily attain juxtaposition suitable for intramolecular acyloin reaction. The acyloin product **71** was oxidized to **72** with Cu(II) and further oxidized with NBS to provide tropolone **64.** Methylation and bromination delivered the bromide **65,** an intermediate also prepared by Eschenmosher. Substitution of an amino group for the bromo substituent in **65** followed by hydrolysis, remethylation of the vinylogous carboxylic acid, and N-acetylation produced colchicine **8**.



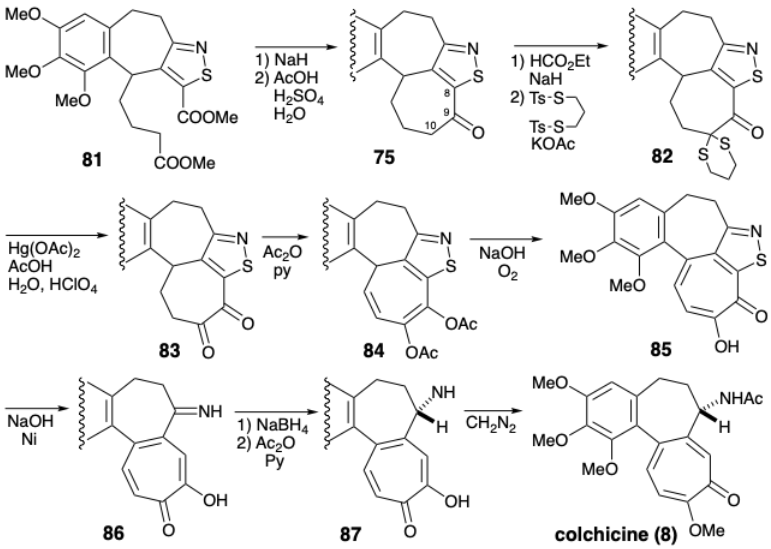
Extensive functional group manipulations after completion of the carbon skeleton were required in the Eschenmosher synthesis because an annelation strategy for the C ring was adopted that ignored target related functionality. Van Tamelen could complete his synthesis with less functional group manipulations because more target related functionality, that had been exploited to facilitate skeletal construction, was present after completion of the C ring.

A Target-related Functionality-promoted Polar Bond Formation Strategy

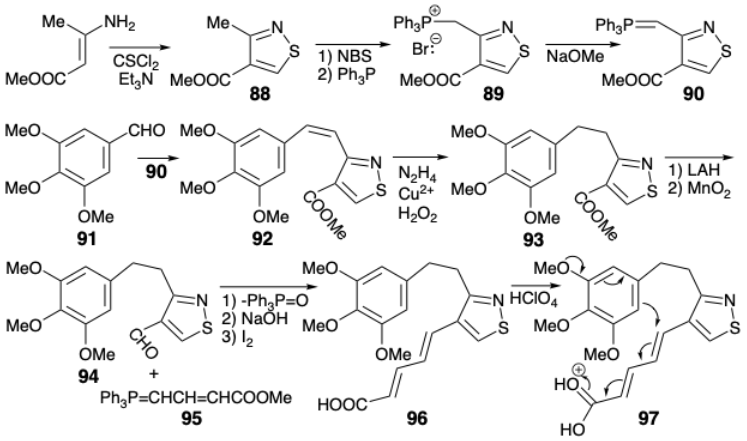
Another synthesis of colchicine (**8**), also involving annelation of ring C on a preformed AB-ring intermediate, was devised by R. B. Woodward.[3] The strategy is unique in incorporating the 7-amino substituent early and in its extensive use of target related functionality to facilitate carbon skeletal construction. Dislocation of the target **8** to derivative **74** in which the 8-position is also blocked allows selective introduction of oxygen at C-10. In the synthetic equivalent **75** of the synthon **74**, an *aromatic* isothiazole ring masks both the amino substituent and C-8. Annelation of the C-ring can be achieved by a Dieckman cyclization **77** → **76** exploiting the polar activation provided by the C-9 carbonyl and an activating carbomethoxyl group appended to C-10 in a precursor **77**. The polar activation provided by this carbomethyl group in **77** suggests an electrophilic aromatic substitution **78** → **77** for annelation of the B- ring. Of course, for the appropriate electrophilicity to be expressed, the carbomethoxyl group in **77** must be conjugated with the γ-position as in **78**. The isothiazole also serves as a temporary bridge in **78**, that assists entropically in the **78** → **77** cyclization. The carbomethoxyl in **78** also allows a polar elaboration of the dienoic ester array from an isothiazole aldehyde precursor **79** by stabilizing a carbanion in the ylide fragment **80**. The sulfur atom in the isothiazole ring even provides activation for carbanion generation a to sulfur in **78** allowing polar connection of the carbomethoxyl required in **77**. The extensive strategic utilization of the isothiazole unit in Woodward's strategy is a hallmark of this synthetic plan.



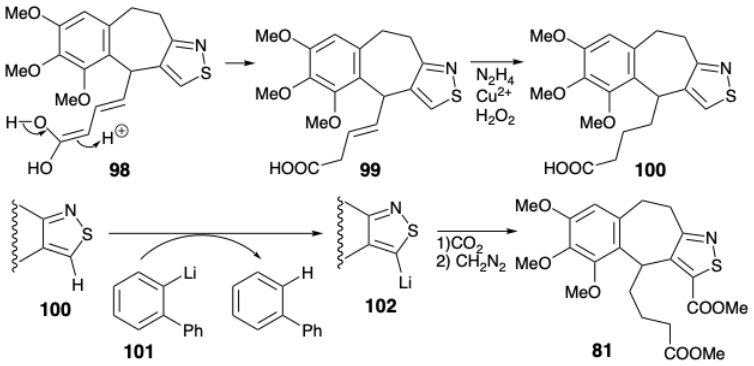
After Dieckman cyclization of **81**, the C-9 monoketone **75** is selectively oxidized at the C-10 by a polar reaction exploiting the nucleophilic activation at C-10 provided by the C-9 carbonyl group. Nucleophilic attack by the C-10 carbanion on a sulfur electrophile leads to oxidation of C-10 (and concomitant reduction of sulfur). The resulting thioketal **82** is hydrolyzed to **83**, that affords the enol acetylation product **84**. The enediolate obtained by saponification of the diacetate **84** is readily oxidized to deliver **85**. Desulfurization of **85** with Raney nickel removes the isothiazole masking group. Reduction of the resulting imine **86** followed by acetylation provides **87** that is N-methyl-ated to deliver colchicine (**8**).



Woodward's synthesis of the key intermediate **81** is centered around the novel aromatic isothiazole ring. The starting material, an isothiazole **88,** is readily available from methyl β-aminocrotonate, an enamine derived from methyl acetoacetate. The conjugated methyl group in **88** is readily brominated with NBS. Alkylation of Ph_3P affords a phosphonium bromide **89**, that gives ylide **90** upon deprotonation. Wittig olefination of 3,4,5-trimethoxybenzaldehyde (**91**) with ylide **90** produces alkene **92** that was selectively hydrogenated with diimide. Catalytic hydrogenation of **92** was precluded by the susceptibility of the isothiazole ring to hydrogenolysis. Hydride reduction of the ester **93** and partial oxidation of an intermediate conjugated carbinol gave the aldehyde **94**. Wittig olefination of **94** with ylide **95** followed by saponification and cis-trans isomerization provided **96**.

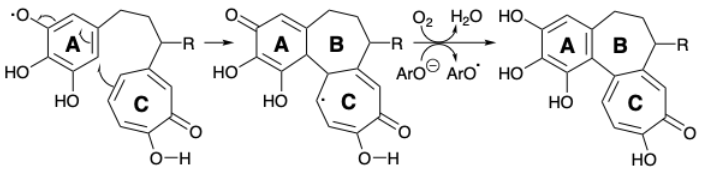


This diene underwent intramolecular electrophilic aromatic substitution upon treatment with perchloric acid. The temporary bridge provided by the isothiazole ring undoubtedly facilitates this cyclization by favorably juxtaposing the reacting carbon centers. Selective reduction of the cyclization product **99** with diimide gave **100**. The final carbon required for the C ring was introduced by carbonylation of an organolithium derivative **102** from the thiazole **100**. Thus, selective metallation in the presence of a carboxylate was achieved with the relatively non nucleophilic, sterically encumbered aryl lithium **101**. The lithiated thiazole **102** gave the key intermediate **81** upon carbonation followed by methylation.

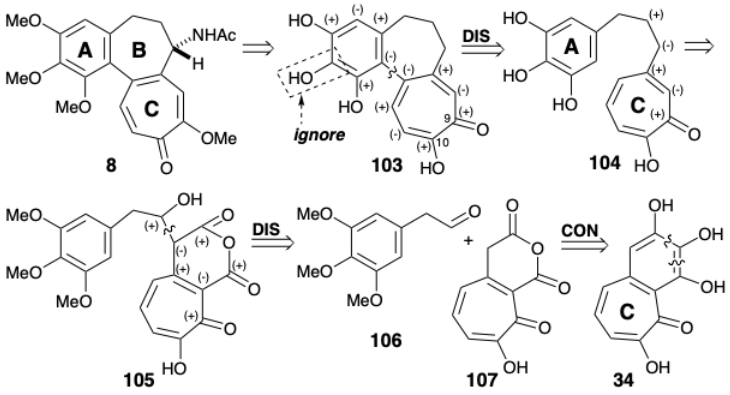


A Hypothetically Biomimetic Strategy

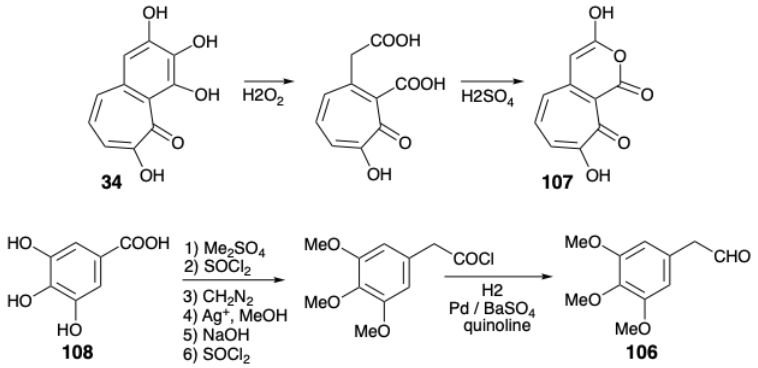
A fourth synthesis of colchicine, devised by Scott[4], differs from the previous three in its strategy for skeletal constuction. Scott assembled an intermediate containing the A and C rings and then created the B ring by an intramolecular oxidative coupling. This strategy was based on a hypothetical mechanism for colchicine biosynthesis, that is now know not to be operative. In this mechanism, in contrast with the actual biosynthetic mechanism (see above), generation of a tropolone C-ring by ring expansion of an aromatic precursor preceeds the oxidative coupling that creates the B-ring.



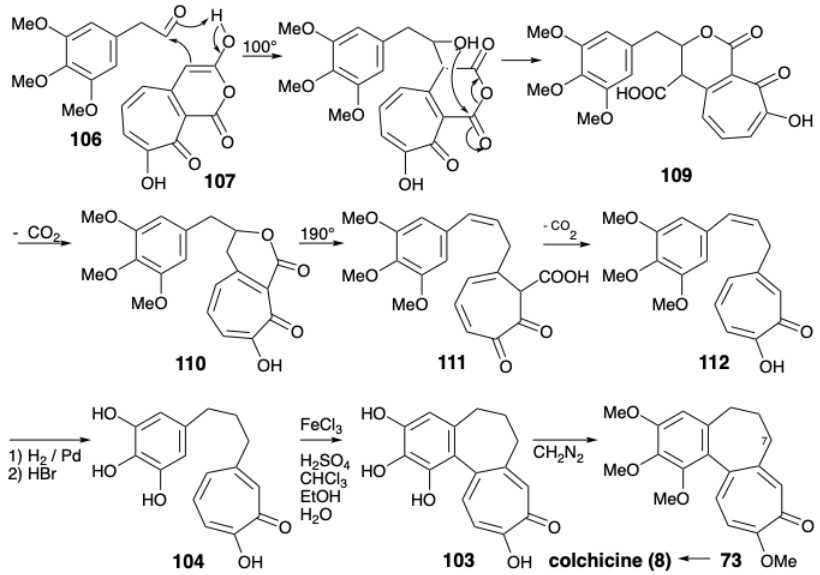
The tactic of introducing the colchicine amino group at the end of the synthesis was well-precedented. Thus, the Scott strategy begins with dislocation of the target **8** to a precursor **103**. The bond between aryl and tropolone rings lies along a dissonant circuit between the oxygen functionality at positions 1 + 9, 1 + 10, 3 + 9, or 3 + 10. Thus, polar analysis reveals that formation of this bond cannot be achieved by a polar process using these functional groups to provide activation since union of two nucleophilic centers would be required. Such a process can be achieved oxidatively, suggesting dislocation of **103** to a precursor **104** with two monocyclics joined by a simple trimethylene bridge. The polar reactivity afforded by the carbonyl group in **104** can be reinforced by activating carboxyl groups in a precursor **105** allowing polar bond formation between an electrophilic intermediate **106** and a nucleophile derived from **107** by deprotonation. The unobvious choice of **107** as a precursor for **104** was undoubtedly dictated by its ready availability from purpurogallin **34** by selective oxidative cleavage of the relatively electron rich aryl ring.



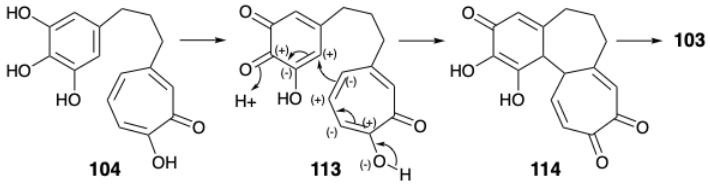
Thus, oxidation of **34** with hydrogen peroxide followed by dehydration gave the enol anhydride **107**. It is interesting that Scott utilized purpurogallin (**34**) as a precursor for the C ring of colchicine in contrast to Eschenmosher and Van Tamelen who built the A and B rings of colchicine from **34**.



An A-ring synthon, 3,4,5-trimethoxy acetaldehyde (**106**) was obtained by Arndt-Eistert homologation of 3,4,5-trihydroxybenzoic acid (**108**). Union of the electrophilic A ring synthon **106** with the nucleophilic C-ring synthon **107** was best achieved thermally without base catalysis by a process that starts with an aldol condensation. At 100°C, a lactone **110** was formed, presumably by decarboxylation of an intermediate vinylogous β-keto acid **109**. Further heating of **110** at 190°C gave **112**, presumably by decarboxylation of an intermediate β-keto acid **111**. Reduction and demethylation gave the A+C ring intermediate **104**. The electron rich product **103** from the desired oxidative coupling of **104** was highly susceptible to undesirable further oxidation. Nevertheless, the mild oxidant, $FeCl_3$, in a two phase system gave **103** after paper chromatography in an inert atmosphere albeit in low yield (5%).

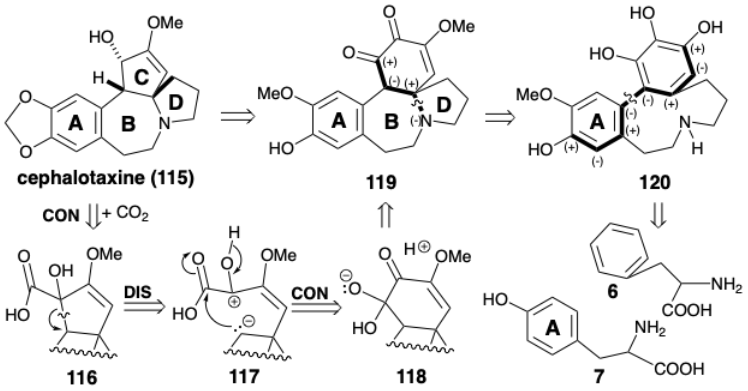


It has been suggested that the annelation may involve an ionic process rather than the radical coupling originally envisioned.[5] Thus, utilizing the aryl oxygen functionality at position 2, that was ignored in the polar analysis of **103** above, it can be seen that the bond between the aryl and tropolone rings lies on a consonant circuit between positions 2 and 10. This allows Michael addition of a tropolone nucleophile to an enone electrophile as shown in **113** to deliver **114**. Final adjustment of functionality gave **8** from **103** through **73** as discussed previously.



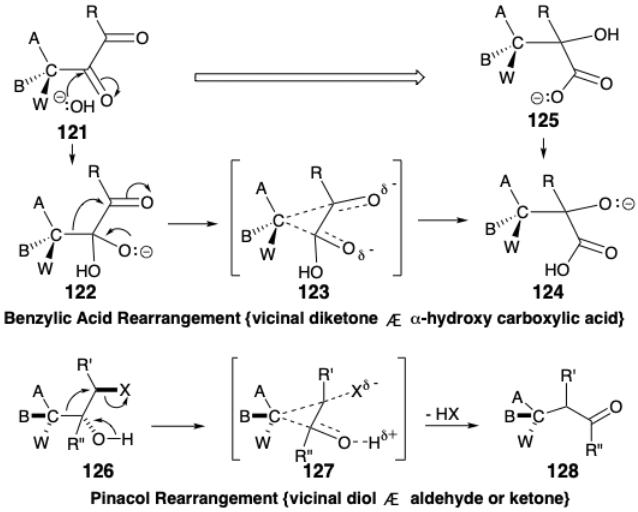
6.2: Cephalotaxine

The biosynthesis of cephalotaxine (**115**) involves a convergent strategy that assembles an intricate multicyclic skeleton from two aromatic amino acid precursors, phenylalanine (**6**) and tyrosine (**7**). As in the biosynthesis of colchicine (**8**), one aromatic ring is incorporated intact while the other is extensively modified. Thus in the biosynthesis of colchicine (**8**) the seven-membered C-ring is elaborated by a one- carbon expansion of a tyrosine-derived aromatic ring. In contrast, the biosynthetic strategy for cephalotaxine (**115**) exploits a one-carbon ring contraction to produce a five-membered C-ring from a phenylalanine-derived six-membered ring. The logic of the strategy is based on: (1) the ready availability of highly oxygenated cyclohexyl derivatives such as **119** by oxidative metabolism of aromatic precursors and (2) the possibility of extruding a carbon atom as carbon dioxide from an α-diketone by a benzylic acid rearrangement to an α-hydroxy acid. This suggests the α-hydroxy acid **116** as precursor to **115**.

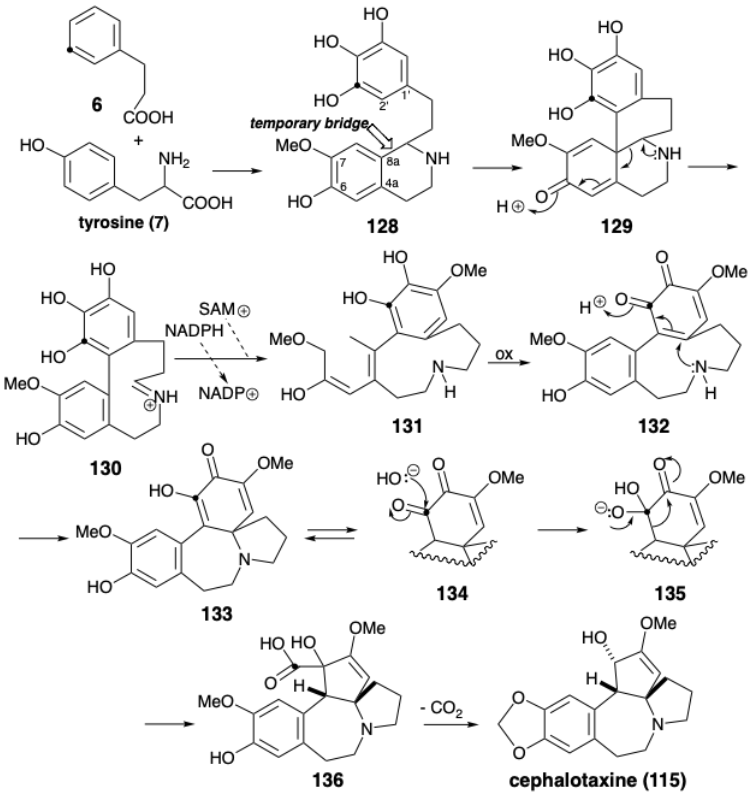


Retrosynthetically, dislocation of a benzylic acid rearrangement product **116** to a precursor **119** corresponds to polar disconnection of the migrating carbon as nucleophile resulting in oxidation of the migration terminus. Subsequent connection of the nucleophilic migrating carbon in **117** results in reduction of the migration origin in the precursor **118**. Polar analysis of **119** suggests polar disconnection of nitrogen as nucleophile from an electrophilic carbon β to a carbonyl group. Polar analysis of the precursor **120** suggests that the aromatic rings of two precursors **6** and **7** might be joined by an oxidative coupling.

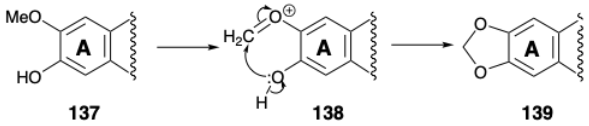
The connection-disconnection sequence of the benzylic acid rearrangement, generalized in the **121** to **125** conversion, is mechanistically analogous to the pinacol rearrangement discussed in chapter 4 (see section 3.4). The rearrangement of **122** into **124**, involved in the benzylic acid rearrangement, is **isoelectronic** with the **126** to **128** conversion of the pinacol rearrangement, i. e. the same electronic movements in identical arrays of atoms, bonds, and nonbonding electrons are involved. Nucleophilic addition of hydroxide to an α-diketone **121** initiates the benzylic acid rearrangement, that proceeds through a temporarily-bridged transition state **123**, and ultimately produces an α-hydroxy acid **125**. The pinacol rearrangement proceeds through a temporarily-bridged transition state **127**. In both the benzylic acid and pinacol rearrangements, the migrating group acts as an internal nucleofuge-nucleophile that adds to an electrophilic migration terminus. In both rearrangements the functionality level of the migration origin increases while the functionality level of the migration terminus decreases.



The biosynthesis of cephalotaxine (**115**) is believed to involve oxidative coupling of two electron rich aromatic rings in a phenethylisoquinoline[6] intermediate **128** delivering a tetracyclic δ-amino-α,β- unsaturated ketone **129**. The polar formation and subsequent polar cleavage of a temporary six-membered nitrogen heterocycle in **128**, facilitates the oxidative coupling by making it an entropically more favorable intramolecular cyclohexannelation rather than a cyclodecannelation that must generate **130** directly. It is reasonable to postulate the presence of a methoxyl group at position 7 in **128** since this could account for the regioselective oxidative coupling at position 8a which is *para* to the hydroxyl group presumed to be present at position 6. This regioselectivity contrasts with that observed in the oxidative coupling of autumnaline (**28**) at position 4a (see section 6.1). Thus, the O-methyl groups in **28** and **128** serve as regiocontrol elements in the oxidative couplings of these phenethylisoquino-lines. Reduction and regioselective methylation of **130** set the stage for regioselective electrophilic activation by oxidation of the *ortho* hydroquinone **131** to an *ortho* quinone **132**.

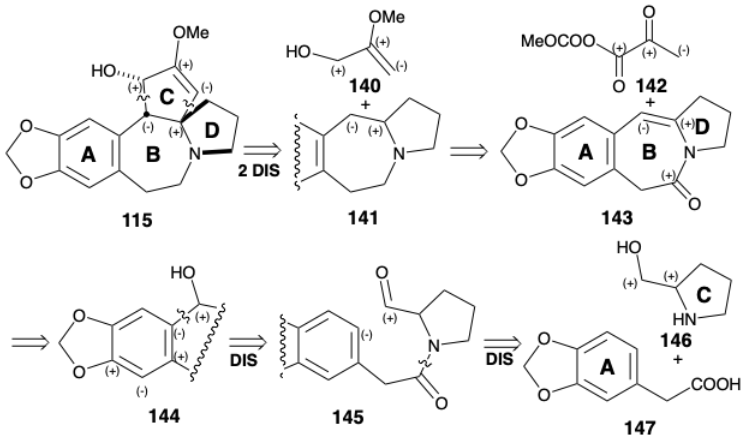


Nucleophilic Michael addition of the secondary amine then delivers **133** whose keto tautomer **134** is an α-diketone. Benzylic acid rearrangement initiated by conversion to **135** delivers α-hydroxy acid **136** in which the carboxyl carbon is derived from a *meta* carbon of the phenylalanine (**6**) starting material. Loss of this carbon as carbon dioxide then generates cephalotaxine (**115**) after conversion of the *ortho* methoxy-phenol array into a methylenedioxy group. This conversion, i.e. **137** to **139**, is common in Nature and presumably involves oxidative generation of an electrophile **138**.

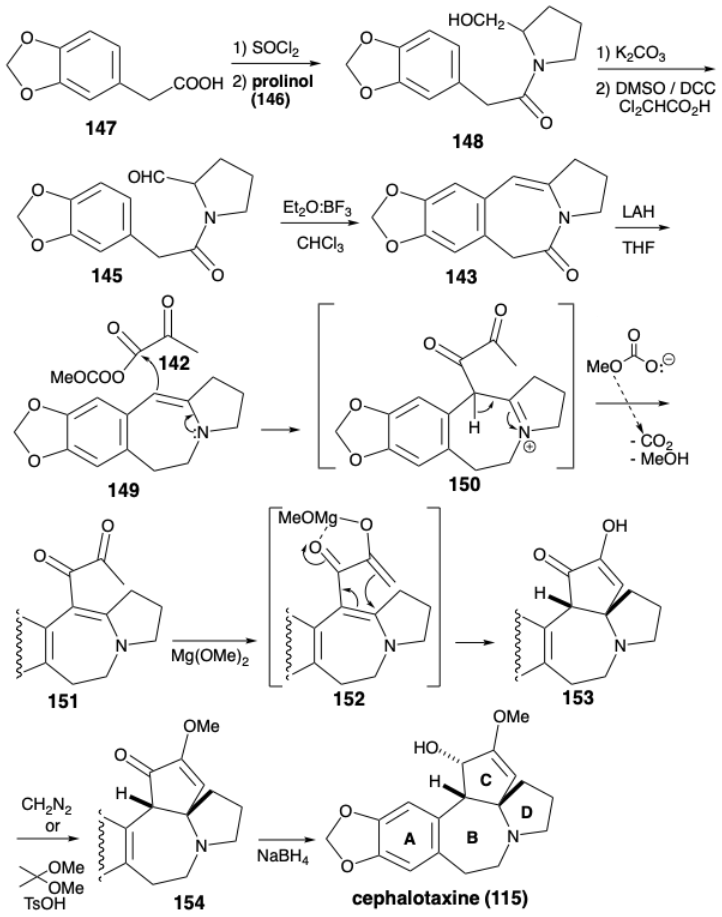


B Ring Annelation by Electrophilic Aromatic Substitution

As in the biosynthesis of cephalotaxine (**115**), the stability of aromatic derivatives recommends the utilization of an aromatic precursor for ring A. The Weinreb strategy for construction of the cephalotaxine skeleton7 recognizes the potential utility of the amino group and dissonant C-ring functionality for activating polar reactions that could append the C-ring onto an ABD-ring precursor. Synthetic equivalents **142** and **143** correspond to the polar synthons **140** and **141**. A carbonyl group in **143** is added to facilitate generation of a precursor **145**, the amide of prolinol (**146**) and the arylacetic acid **147**. The enamine in **143** could be produced by dehydration of a β-hydroxy amine precursor **144** that, in turn, should be available directly by polar union of an aromatic nucleophile and aldehyde electrophile in **145.**

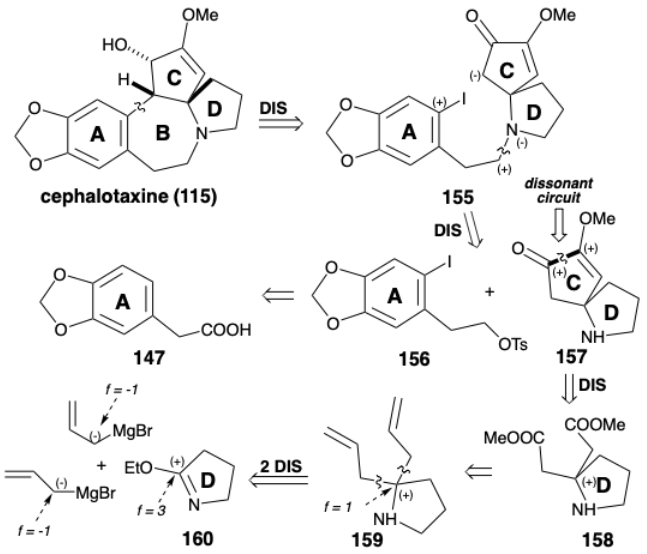


The enamine **143** was constructed by annelation of ring B between an aromatic ring A precursor **147** and a preformed ring D precursor **146**. Masking of the hydroxyl group in **146** is unnecessary since acylation occurs at the more nucleophilic nitrogen to give amide **148** rather than at the less nucleophilic oxygen to produce an ester. The final bond of ring B was formed by electrophilic aromatic substitution which occurred exclusively at the less congested aryl position in **145.** Having served its purpose, the amide carbonyl was reductively removed from **143** to deliver **149**. The polar activation afforded by the acyl group in **142** is first exploited to unite **142** and **149** to give **150**. Then the polar activation afforded by both carbonyl groups is exploited to complete the annelation of ring C. An intramolecular Michael addition of an enolate anion to the electrophilic β-carbon atom of an α,β-unsaturated carbonyl system leads to **153**. The required *cis*-ring fusion of ring C is undoubtedly the most stable. The methyl carbonate anion leaving group in **142** is especially noteworthy. Decarboxylation of this anion generates methoxide *in situ* that then deprotonates an intermediate iminium ion **150** to produce the Michael acceptor **151** under exceptionally mild conditions. Also noteworthy is the use of magnesium methoxide as base to generate the enolate **152** in the Weinreb synthesis of cephalotaxine. Magnesium can assist the cyclization by chelation that enforces a favorable cisoid conformation. Final adjustment of functionality involved enol etherification and hydride reduction. Delivery of hydride occurs from the less sterically congested convex face of **154** producing **115** with the correct relative configuration at the third asymmetric center in ring C. A regioisomeric enol ether was obtained together with **154**. This isomer could be recycled by acid catalyzed equilibration.

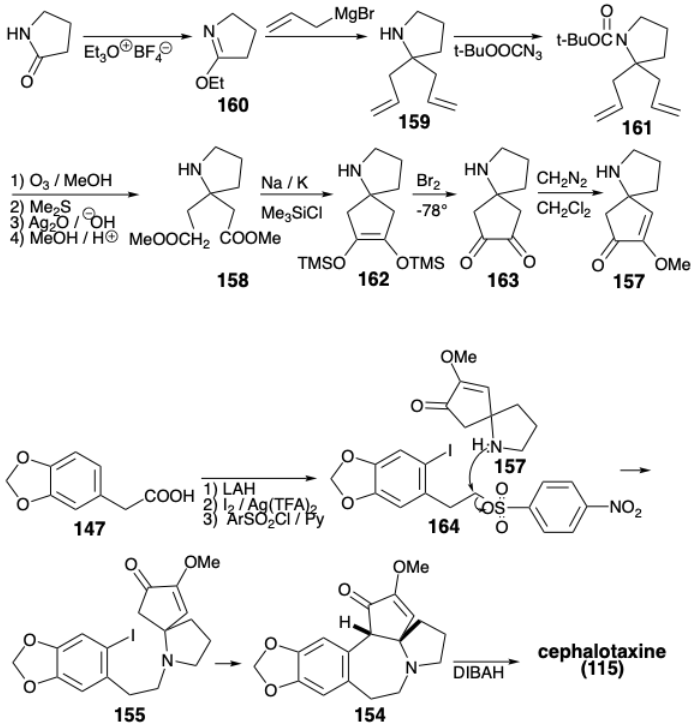


B Ring Annelation by Nucleophilic Aromatic Substitution

Whereas annelation of ring B in the Weinreb synthesis of cephalotaxine (**115**) was achieved by *electrophilic* aromatic alkylation, Semmelhack's synthesis creates the same connection by *nucleophilic* aromatic alkylation.[8] Semmelhack's strategy exploits a C-ring carbonyl to provide the requisite nucleophilicity in a final intermediate **155**. As in the biosynthesis and the Weinreb strategy, an aromatic precursor is exploited for ring A. N-alkylation of a CD-ring amine fragment **157** with the A-ring fragment **156** provides **155**. The same A-ring starting material **147** is used for both total syntheses. Ring C in **157** contains two oxygen functionalities that provide electrophilic activation at their respective carbon atoms. Thus, these functional groups cannot be exploited directly to create the bond between those carbon atoms by a polar reaction. In the Weinreb synthesis of cephalotaxine (**115**), ring C was constructed by polar reactions by using a starting material **142** that incorporates the dissonant circuit between the two oxygen functionalities in the C-ring. The Semmelhack strategy recognizes that this dissonant circuit in **157** can be formed by a nonpolar reaction, reductive coupling of the two electrophilic carbonyl carbons in a precursor **158**. Although **158** might be available directly by polar addition of two carbomethoxymethyl nucleophiles to an electrophilic D-ring precursor **160**, Semmelhack opted for the alternative strategy of adding two allyl nucleophiles to **160** followed by oxidative revelation of the latent carboxyl groups in an intermediate **159**.

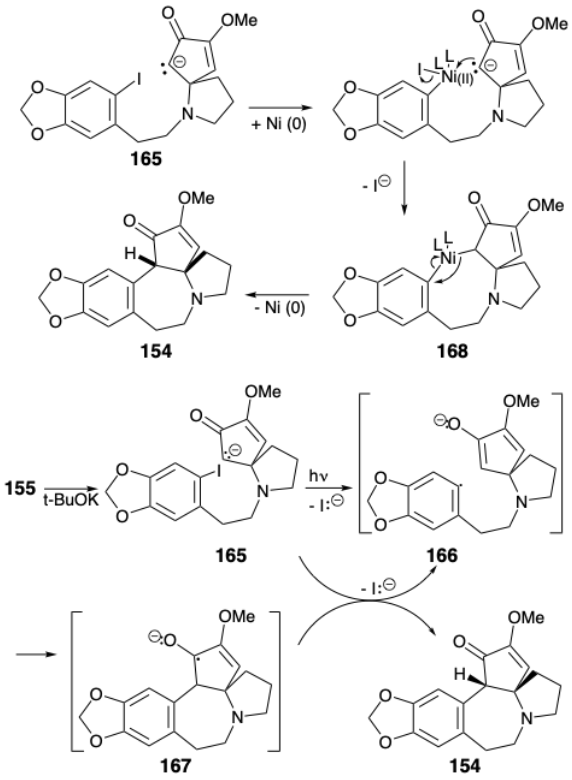


The CD-ring intermediate **157** was prepared from pyrrolidinone. The reaction of an imino ester **160** with an allyl nucleophile gave **159**. Masking of the amino group as an acid labile amide **161** was required prior to oxidative cleavage of the C-C π-bonds in **159** which ultimately provided the diester **158**. Intramolecular acyloin coupling of **158** in the presence of chlorotrimethyl silane (the Rühlmann modification) produced **162**, that was oxidized directly to **163** by a one-pot addition of bromine and elimination of TMSBr. Methylation of this symmetrical dione delivered **157**. Alkylation of this amine with the nitrosylate **164** provided **155**. Cyclization of **155**, *vide infra*, followed by reduction of the intermediate **154** delivered cephalotaxine (**115**). This synthetic strategy leads *directly to the correct enol ether* **154** *without formation of the regioisomeric enol ether that is a byproduct in the Weinreb synthesis.*



The key cyclization of **155** to **154** was achieved by a variety of reactions all involving nucleophilic aromatic substitution. Of course, direct nucleophilic attack on the electron rich A ring aryl iodide does not occur when an enolate nucleophile is generated from **155**. However, net nucleophilic substitution could be accomplished by photolysis of the enolate **165** or by treatment of **165** with Na/K or a nickel(0) catalyst. Best yields of the cyclization product **154** (94%) were obtained by a photostimulated $S_{RN}1$ reaction presumably involving the chain carrying anion radicals **166** and **167**. The $S_{RN}1$ reaction could also be achieved (45%) by

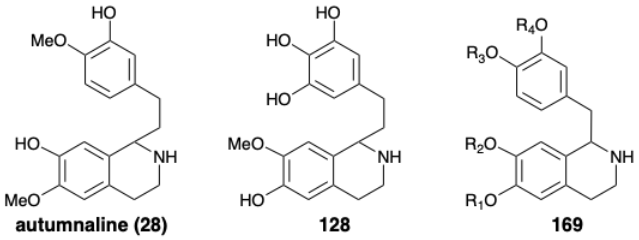
reaction of the enolate **165** with Na/K. A nickel(0)-catalyzed reaction of **165** provided **154** in 30% yield presumably by oxidative addition of the aryl halide to Ni(O) and nucleophilic substitution of iodide by a carbanion producing a σ-aryl-nickel(II) intermediate **168**, that undergoes reductive elimination of **154** to regenerate the Ni(0) catalyst.

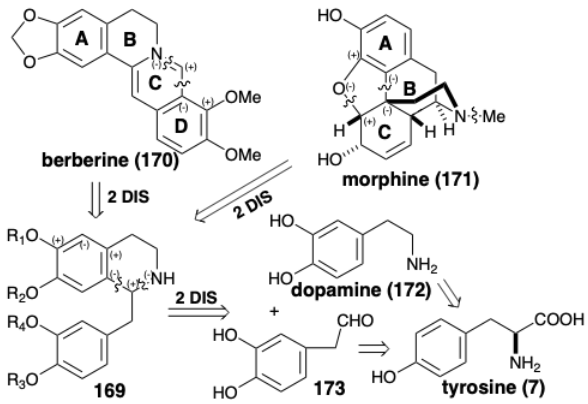


6.3: Morphine

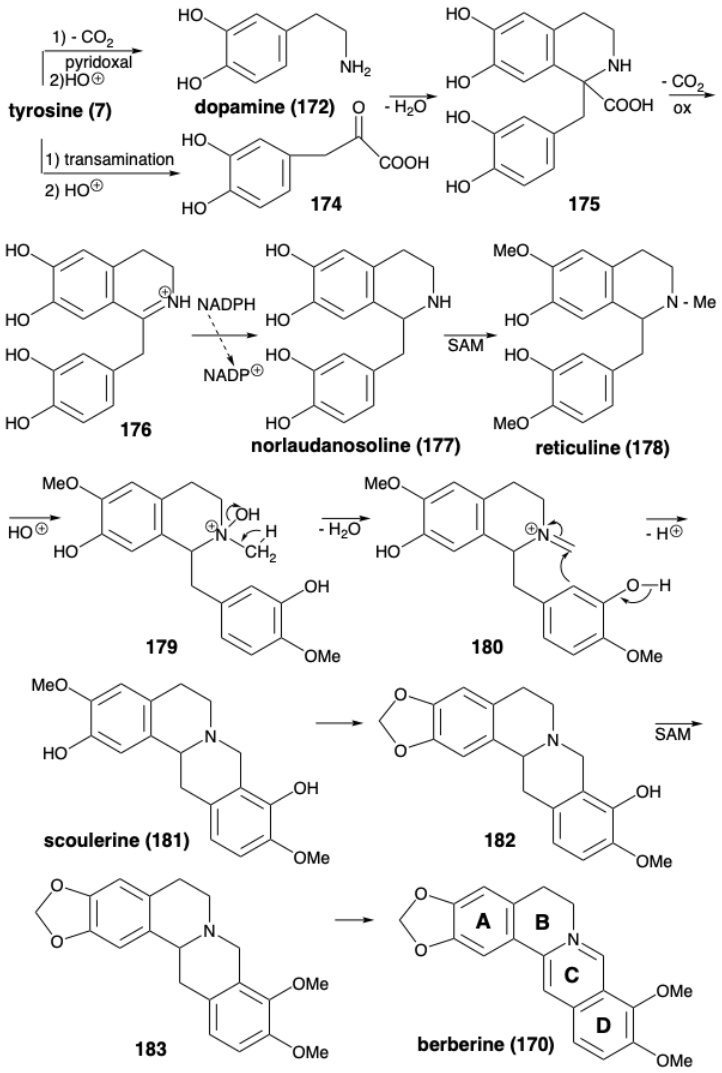
Biosynthesis of Benzylisoquinoline Derived Alkaloids

The biosyntheses of colchicine and cephalotaxine involve *phenylethyl*isoquinoline progenitors **28** and **128**. Many alkaloids, that are derived biologically from two molecules of tyrosine, share *benzyl*isoquinoline progenitors of general structure **169** (see below). In addition, both six membered rings derived from the aryl nuclei are often retained. Both may be aromatic as in berberine (**170**), or one may be nonaromatic as in morphine (**171**). The biogenetic strategy for berberine (**170**) involves a simple dislocation to a benzylisoquinoline precursor by disconnection of a one-carbon electrophile from the nucleophilic nitrogen and D-ring arene. An intact benzylisoquinoline structure is less evident in the convoluted multicyclic skeleton of morphine (**171**). If an electron rich aromatic precursor is presumed for the highly oxygenated C-ring, then polar disconection of a furan C-O bond suggests that oxidative coupling of aromatic A and C-rings of a benzylisoquinoline precursor can generate the B-ring of **171**. The key benzylisoquinoline intermediates **169** could be produced by Mannich reactions. These condensations might involve polar bond formation between a phenylacetaldehyde electrophile **173** and dopamine (**172**) as bisnucleophile.

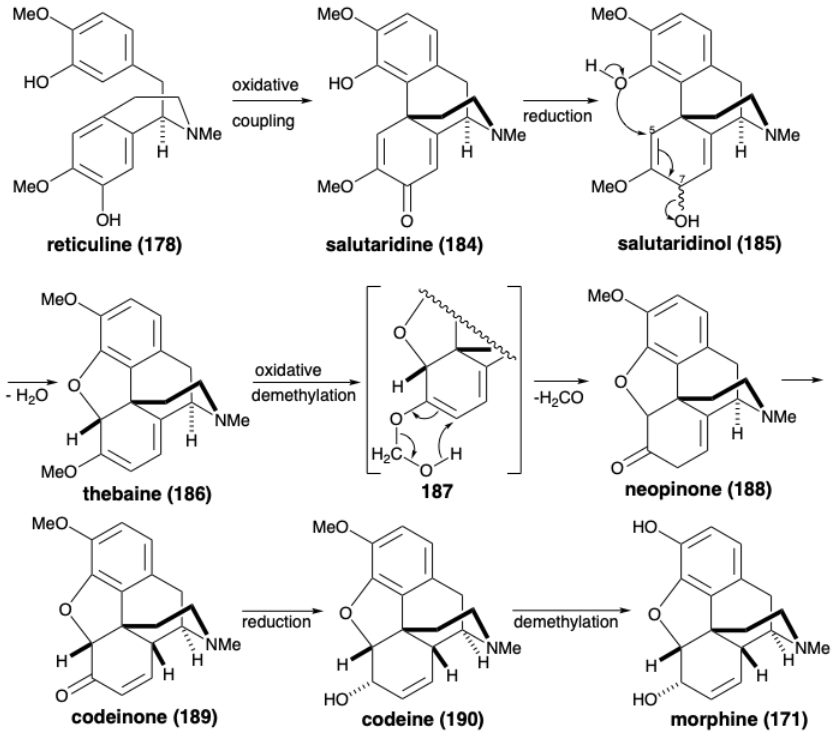




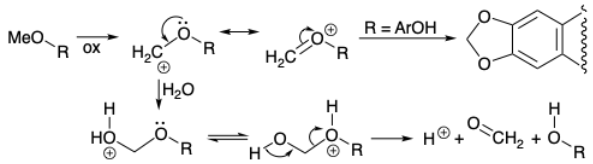
The biosynthesis of berberine (**170**) from two molecules of tyrosine (see below) commences with pyridoxal-catalyzed decarboxylation and electrophilic hydroxylation that produces dopamine (**172**). Replacement of the α-amino group of tyrosine with a carbonyl by transamination and electrophilic hydroxylation produces 3,4-dihydroxyphenylpyruvic acid (**174**). This highly reactive ketone, rather than a phenylacetaldehyde, serves as the electrophile in a Mannich reaction with dopamine (**172**). Polar condensation of the highly electrophilic carbonyl in **174** with **172** as bisnucleophile generates the benzylisoquinoline ring system in **175**. Oxidative decarboxylation of this α-amino acid followed by reduction of the intermediate **176** delivers norlaudanosoline (**177**) from which reticuline (**178**) is produced by O and N-methylation. The N-methyl group is incorporated into the berberine skeleton by a Mannich condensation of iminium derivative **180** produced by dehydration of an intermediate protonated N-oxide **179**. Conversion of an o-methoxyphenol array in the product **181** to a methylenedioxy group in **182**, methylation and aromatization of the product **183** delivers berberine (**170**).



The more topologically complex skeleton of the morphine alkaloids is also produced from reticuline (**178**). Thus, oxidative *ortho-para* coupling delivers salutaridine (**184**). Generation of the benzofuran ring of thebaine (**186**) occurs after adjustment of functionality level resulting in loss of functionality from position 7 of **185**. Interestingly, although simple hydroly-sis of enol ether **186** could produce ketone **188**, the oxygen of the methoxyl group is retained in **188**. Therefore, a different mechamism must be involved. Perhaps demethylation of **186** occurs through an oxidized intermediate **187** that undergoes retroene fragmentation. Allylic isomerization, reduction, and demethylation then deliver morphine (**171**).

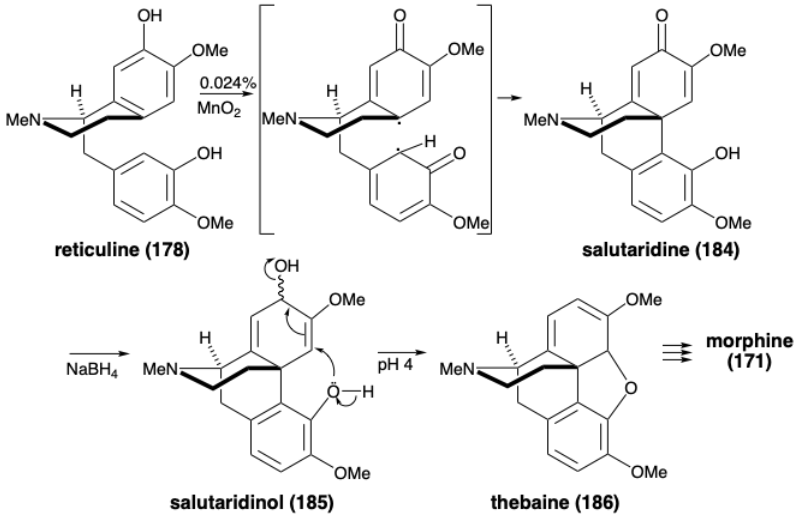


The demethylation of codeine (**190**) and of the enol ether **187**, as well as the conversion of ortho methoxy phenols **137** into methylenedioxy derivatives **139** (see section 6.2) may all be related mechanistically by the initial oxidative conversion of a methyl ether into an α-oxygen-stabilized carbocationic intermediate. Demethylation would occur upon nucleophilic capture by water and fragmentation of the resulting formaldehyde hemiacetal.

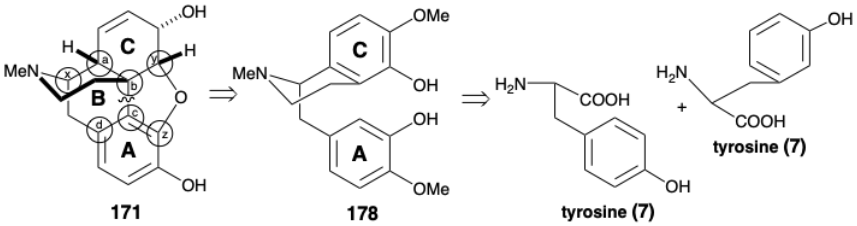


A Biomimetic Synthesis of Morphine

Morphine has been assembled in the laboratory by a biomimetic strategy involving oxidative coupling of reticuline (**178**).[9] Oxidative coupling of **178** was accomplished by treatment with manganese dioxide. Salutaridine (**184**) was obtained, albeit in miniscule yield. Hydride reduction provided the allylic alcohol **185**. With mild acid catalysis, **185** underwent intramolecular S_N2' displacement of the allylic hydroxyl by the phenolic hydroxyl to afford thebaine (**186**) from which morphine (**171**) can be produced (*vide infra*).

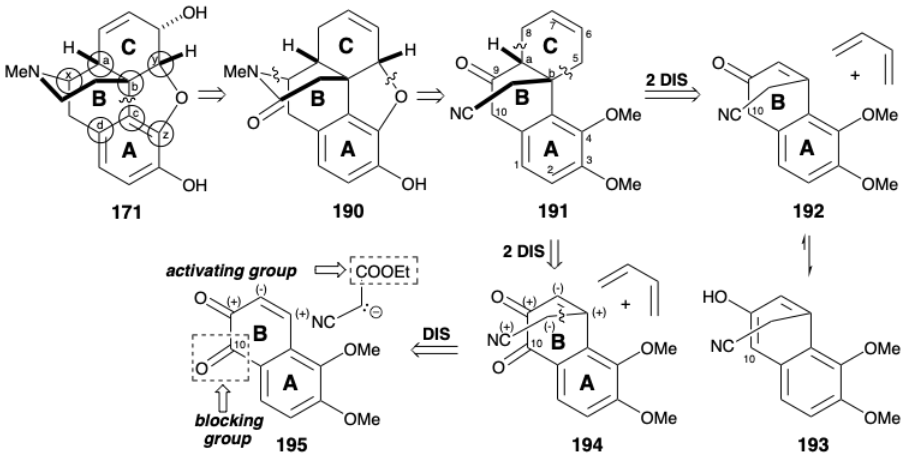


The bridged multicyclic skeleton of morphine has considerable topological complexity. A topological analysis (see section 4.4) may, therefore, be useful for synthetic planning. Considering only the *carbocyclic* skeleton of **171**, there are four common atoms, a-d, and three possible disconnections between them. Of these disconnections, only one, removal of the bond between common atoms b and c, leads to a structural simplification. If the *heterocyclic* skeleton is also considered, there are also three more common atoms, x, y, and z. Disconnection of bonds between these latter common atoms and a heteroatomic ring member are generally trivial because the heteroatoms are reactive functionality. Disconnection of the b-c bond (and the bond between common atom y and oxygen) suggests a precursor such as **178** (reticuline), the biosynthetic progenitor of morphine alkaloids. Interestingly, this is the only cleavage of a bond between a pair of common atoms that leads to simplification of the morphine carbon skeleton. Thus, cleavage of the bond between common atoms a and b leads to an intermediate with two fused ten membered rings, that would be a redoubtable synthetic challenge. Because it does not lead to reduction of molecular complexity, this dislocation is probably not useful. Cleavage of the π-bond between common atoms c and d disrupts an aromatic system and creates a ten membered ring. The stability of aromatic systems usually disfavors synthetic strategies involving annelation of aromatic rings in the final stages of a synthesis. Therefore, this dislocation is also probably not useful.

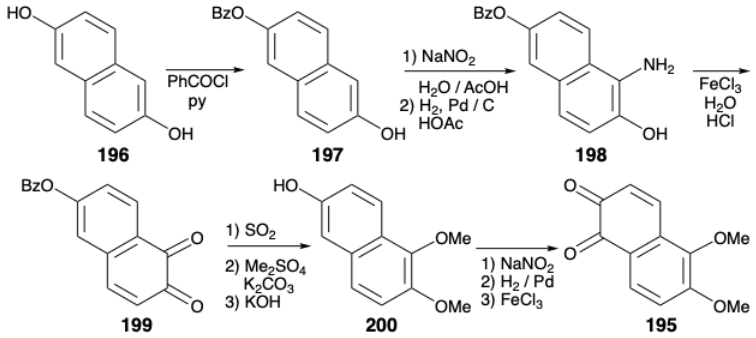


A Diels Alder Strategy for C Ring Annulation

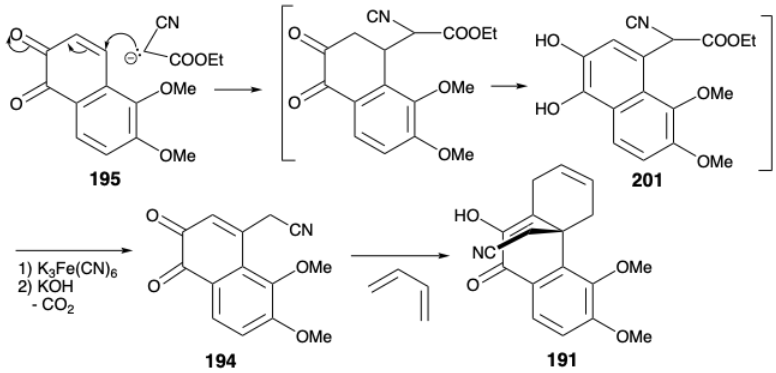
The presence of a cyclohexene array in the C ring of morphine (**171**) recommends consideration of a Diels-Alder reaction to generate two vicinal exendo bonds, each involving one common atom (i. e. a or b) and one noncommon atom. This topological simplification was exploited in the first total synthesis of morphine.[10] However, the C=C bond in the C ring of **171** is in the wrong location. Therefore, with the use of a Diels-Alder tactic as a boundary condition, dislocation of **171** to an amide **190** sets the stage for a retro Diels Alder dislocation. To allow the incorporation of a C=C bond for a dienophile, **190** is first dislocated to **191** by cleavage of carbon-heteroatom bonds to the common atoms x and y. The carbonyl at position 9 in **191** provides activation for a Diels-Alder construction of the C-ring from an AB-ring dienophile **192** and 1,3-butadiene, a relatively electron-rich diene. However, this strategy is fatally flawed because **192** is expected to exist almost exclusively in the aromatic enol form **193** that would not be a reactive dienophile. To block this undesirable enolization, a carbonyl group can be exploited at position 10 (morphine numbering) in a precursor **194.** The cyanomethyl sidechain can be appended by the polar union of a nitrile-stabilized nucleophile with the electrophilic β carbon of the α,β-unsaturated carbonyl array in **195**. The C-10 carbonyl in **195** also would facilitate this Michael addition of the sidechain nucleophile by preventing enolization of the enone in conjunction with aromatization.



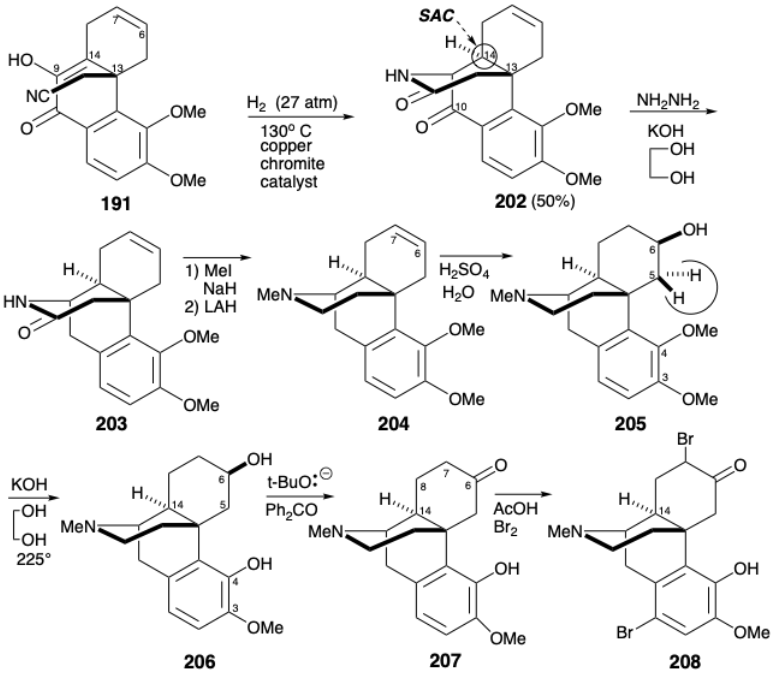
The scheme used for the synthesis of **195** exploits the symmetry of 2,6-dihydroxynaphthalene (**196**) that readily undergoes electrophilic substitution at the α-position. The electron withdrawing effect of the benzoyl group in the monobenzoate **197** diminishes the electron donating ability of the benzoylated hydroxyl. Therefore, nitrosation occurs regiospecifically at the α-position next to the free hydroxyl. Reduction of the nitroso group affords an amine **198**, that is oxidized to an ortho quinone **199.** Reduction, methylation, and saponification then delivers phenol **200** that affords **195** by regioselective nitrosation, reductive N-O cleavage and oxidation.



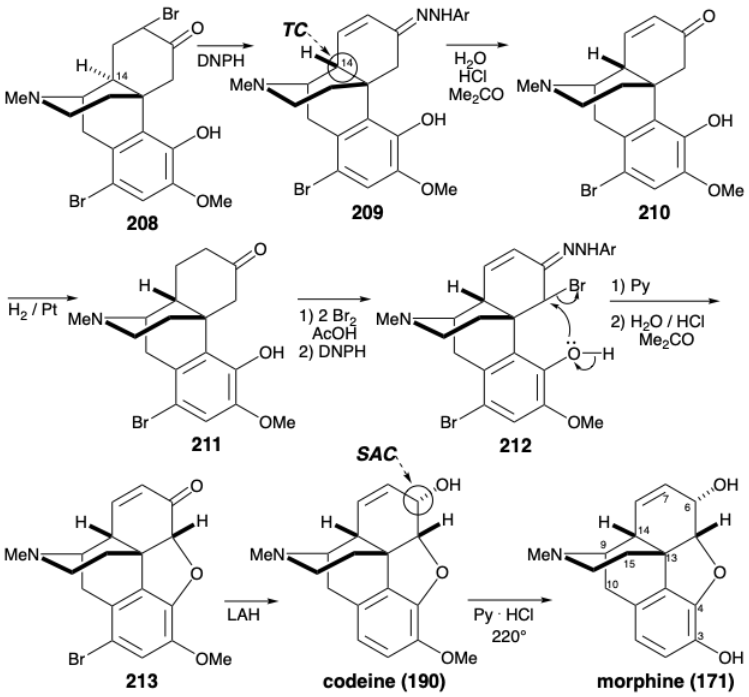
The carbon skeleton of the dienophile **194** is completed by Michael addition of ethyl cyanoacetate carbanion to **195**. After saponification, decarboxylation and aromatization, an intermediate hydroquinone **201** is oxidized to give the ortho quinone **194**. The carbocyclic skeleton of morphine is completed by a Diels-Alder cycloaddition that provided **191**. Elaboration of a piperidine ring began with a reduction that gave the lactam **202** directly. This lactam is epimeric with the morphine skeleton at position 14 presumably owing to steric approach control during delivery of hydrogen to the enolic 9-14 C=C bond in **191**.



The resulting alcohol presumably adds to the C≡N bond producing an iminoether intermediate that rearranges to the lactam **202**. Remarkably, the sterically far more congested 9-14-C=C bond is reduced while the 6,7-C=C bond remains unreduced under these conditions.



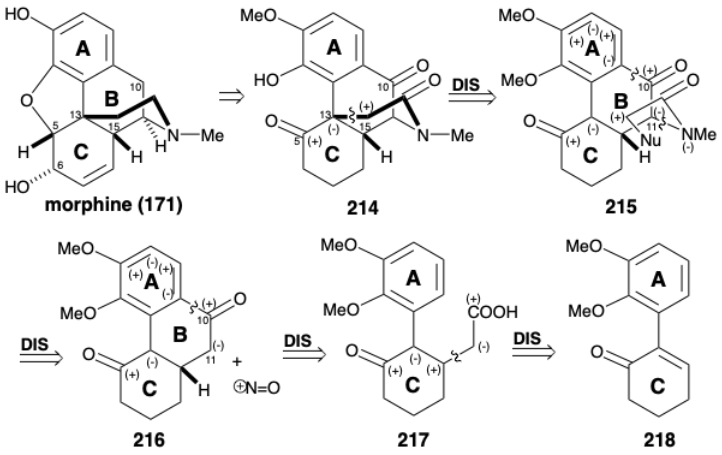
The C-10 carbonyl in **202**, having served its purpose was then removed by Wolff-Kishner reduction. After N-methylation of **203**, the amide carbonyl was removed by hydride reduction. Hydration of the isolated π-bond in **204** proceeded completely regio and stereoselectively to give **205** in "yields up to 28%". This fortunate selectivity is understandable in terms of a stereoelectronic preference for *anti* periplanar diaxial addition to the C=C bond with addition of the nucleophile preferentially *syn* to the protonated amino substituent. The original intention had been to demethylate both ether groups of **205** and to attempt a selective remethylation of the less sterically congested 3-hydroxyl. The action of pyridinium hydrochloride, however, not only cleaved both phenolic ether groups but also dehydrated the secondary alcohol. Fortunately some demethylation of the C-4 methyl ether had been observed during the **202** to **203** conversion. This discovery was exploited by developing conditions that afforded **206** in 54% yield upon heating with KOH in ethylene glycol. Presumably releif of steric congestion fosters demethylation of the 4-methoxy group by an S_N2 displacement of phenolate by hydroxide. Completion of the morphine skeleton by generating a furan ring required considerable adjustment of functionality and stereochemistry in **206**. A carbonyl at position 6 could be exploited both to allow activation of the 5-position toward intramolecular nucleophilic attack by the C-4 hydroxyl and to allow epimerization at the 14 position. Thus, oxidation of the C-6 hydroxyl in **206** by a variation of the Oppenauer reaction gave ketone **207**. To provide the conjugation with the C-6 carbonyl needed to allow epimerization at C-14, a C=C bond was introduced between carbons 7 and 8. Thus, bromination followed by Mattox-Kendall de-hydrobromination (see section 5.4) provided the epimerized tosylhydrazone **198**.



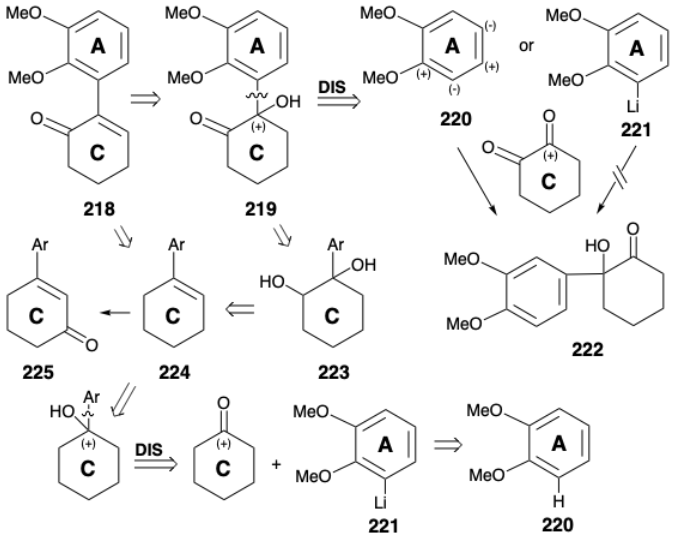
After hydrolysis to an enone **210** and reduction to a ketone **211**, activation at the 5-position was achieved by bromination with two equivalents of bromine. It is not clear why **207** could not be converted directly into **212** without the intermediacy of **210** and **211**. Subsequent monodehydrobromination of an intermediate α,α'-dibromo ketone with DNPH delivered **212**. This underwent cyclization in pyridine to yield benzofuran **213** after hydrolysis of the hydrazone. During the **207** to **208** conversion an adventitious bromo group was introduced into the A ring. This was conveniently removed during the reduction of the C-6 carbonyl with lithium aluminum hydride to give codeine (**190**), the monomethyl ether of morphine (**171**). Hydride delivery to **213** occurred stereoselectively from the more sterically accessible convex face. Demethylation of **190** was achieved by nucleophilic displacement by chloride of phenol from the protonated ether.

A Friedel-Crafts B Ring Annelation Strategy

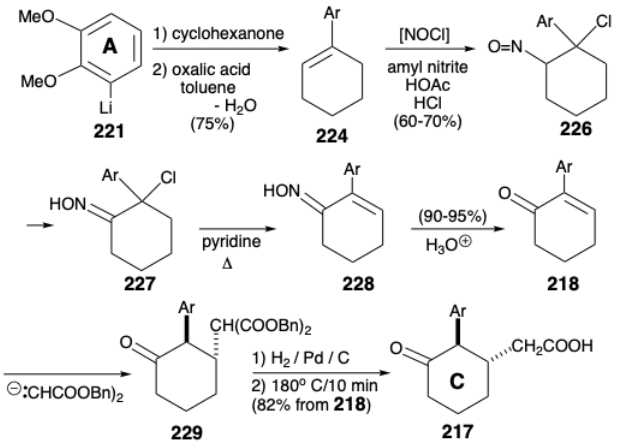
Another strategy for synthesis of morphine (**171**) is channeled by the decision to generate the B ring by electrophilic substitution of an electron-rich A ring nucleophile.[11] This tactic requires temporary carbonyl functionality at the incipient 10 position that would have to be removed in the final steps, e. g. by reduction of a precursor **214**. Target- related oxygen functionality at position 5 can be exploited to facilitate introduction of the remaining C-ring functionality and unsaturation and to facilitate generation of the nitrogen heterocycle by alkylation of a carbon nucleophile at position 13. This requires activation of the incipient carbon 15, i.e. α to the amide carbonyl in **214**, with a nucleofuge. Appendage of an amino *nucleophile* to position 11 in a precursor **216** for **215** cannot be achieved by a polar process since neither keto group in **216** can provide electrophilic activation at the 11 position. On the other hand, a nitrogen *electrophile* could be added to an intermediate that is nucleophilic at position 11 because of activation by the neighboring ketone carbonyl, e.g. by nitrosation of ketone **216**. The ABC-ring carbocyclic skeleton of morphine can be assembled by intramolecular Friedel-Crafts aromatic substitution of an electron rich AC-ring precursor **217**. Polar analysis of **217** recommends an a,b-unsaturated enone electrrophile **218** that would provide **217** by addition of a carboxy activated nucleophile.



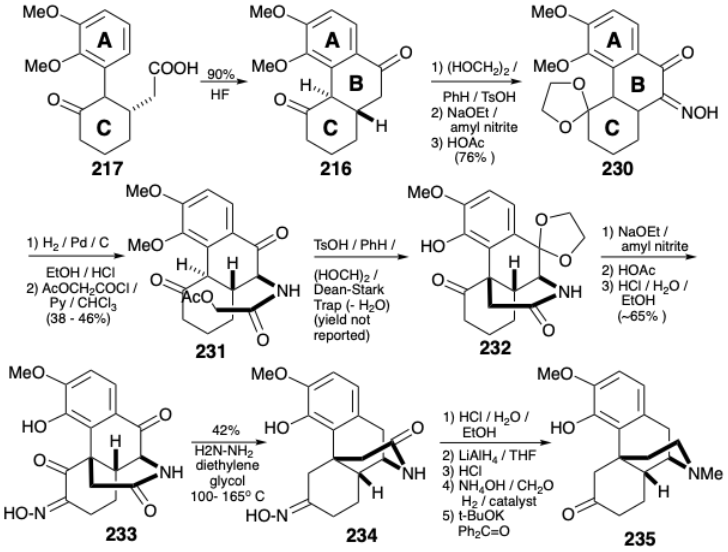
A precursor **219** of **218** might be generated by electrophilic aromatic substution of **220** by a carbonyl activated electrophile, 1,2-cyclohexanedione. However, steric congestion would favor the alternative regioisomeric product **222**. The use of an alternative nucleophile, the regioselectively ortho lithiated aromatic diether **221** as nucleophile, avoids this ambiguity. Alternative routes to **218** are recommended by the possibility of employing cyclohexanone as a more readily available C ring starting material. Thus, the arylcyclohexene **224** could be functionalized by a dihydroxylation-oxidation sequence to give **218** through **219** and **223**. The possibility of generating **218** directly from **224** by allylic oxidation suffers from the ambiguity of an alternative regiochemical course leading to **225**.



An arylcyclohexene **224** is readily available by ortho lithiation of veratrole (**220**) with butyllithium and reaction of the resulting aryllithium **221** with cyclohexanone followed by acid-catalyzed dehydration. Allylic bromination (with NBS) or chlorination (with t-butylhypochlorite) followed by hydrolysis and oxidation did deliver the requisite enone **218**. But this intermediate was more readily available (overall yields of 40 - 50%) by addition of nitrosyl chloride (from amyl nitrite, acetic acid, and 30% HCl), dehydrochlorination of the intermediate nitrosochloride **226** as the oxime tautomer **227** to the unsaturated oxime **228** and hydrolysis.



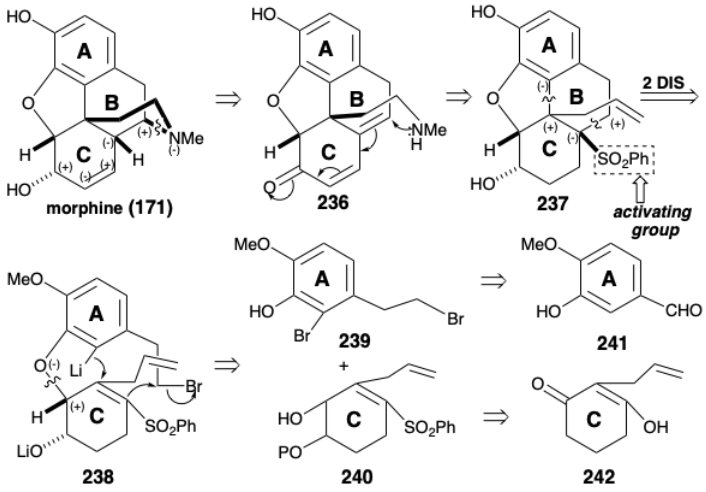
The two carbons required to complete the B-ring were appended by Michael addition of dibenzyl malonate carbanion to the enone **218**, hydrogenolysis of the resulting **229**, and decarboxylation. Friedel-Crafts cyclization of **217** provided the B-ring in **216**. Differentiation of the carbonyls in **216** could be accomplished by selective ketalization of the more electrophilic carbonyl. An amino substituent was introduced by nitrosation of an enolate. Reduction of the oxime **230** under acidic conditions was accompanied by deketalization. N-acylation delivered α-acetoxyacetamide **231**. Intramolecular alkylation and selective ketalization (now of the less sterically congested carbonyl) occurred upon treatment of **231** with acid. Transposition of the C-ring carbonyl was initiated by nitrosation of the enolate of **232**. Deketalization followed by Wolff-Kishner reduction of the intermediate diketo oxime **233** delivered oxime **234** removing two carbonyl groups but not the oxime-masked carbonyl. Hydrolysis of the oxime, reductive removal of the amide carbonyl, reductive methylation of the resulting amine, and oxidation of an intermediate secondary alcohol delivered the ketone **235**. Conversion of an analogous intermediate **208** to morphine (**171**) was described above.



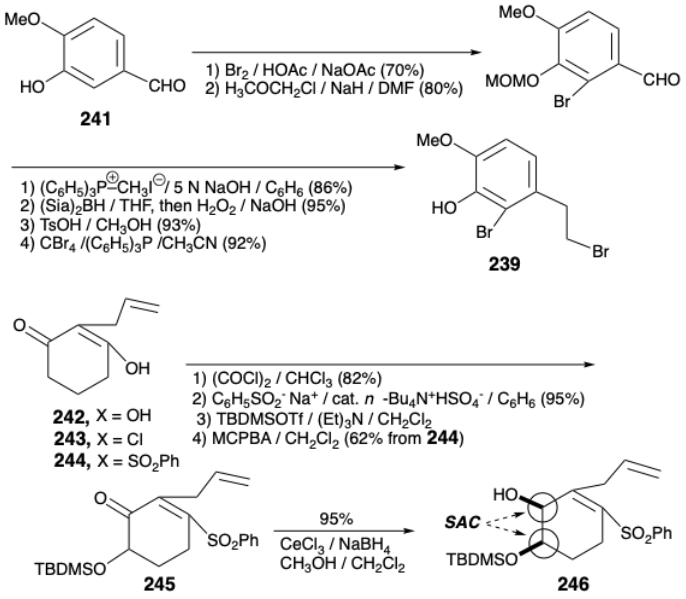
A Conjugate Addition-Alkylation Strategy for B Ring Annulation

Both of the foregoing syntheses of morphine involve: (1) extensive functional group manipulation after construction of the ABC and piperidine rings, (2) generation of the furan ring last, and (3) a dependence on carbonyl groups to activate or control reactivity. A completely different strategy was employed to achieve a more convergent synthesis of morphine.[12] This strategy involves: (1) generation of the piperidine ring last, (2) minimal functional group manipulation after completion of skeletal construction, and (3) exploitation of a sulfonyl group to provide polar activation. As for the biosynthesis and previous syntheses of morphine, the aromaticity of the A-ring recommends an aromatic starting material for this ring. A consonant circuit between C-ring oxygen and B-ring nitrogen substituents in morphine (**171**) suggests a construction of the piperidine ring, that exploits the polar reactivity provided by target-related functionality in an α,β,γ,δ-unsaturated ketone precursor **236**. A polar double disconnection of the B-ring, between a pair of common atoms and between a common and a noncommon atom, is made possible by a strategically placed phenylsulfonyl *activating group* in a precursor **238** of **237**. Polar disconnection of **238** suggests A and C-ring precursors **239** and

240 that should be available from isovanillin (**241**) and the symmetrical 2-allylcyclohexane-1,3-dione (**242**) by functional group additions and interconversions.

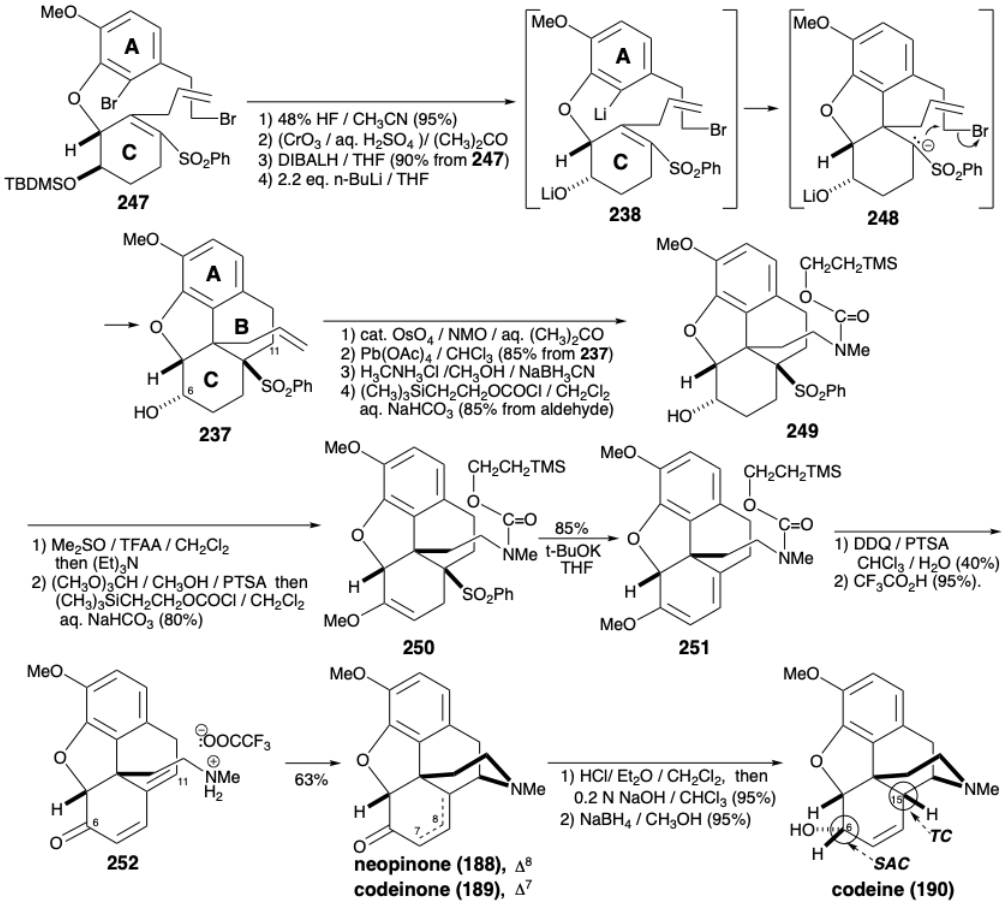


The key A-ring intermediate **239** is available on a large scale from isovanillin (**241**) in 40% overall yield as outlined below. Substitution of the enolic hydroxyl in 2-allylcyclohexane-1,3-dione (**242**) by a phenylsulfonyl group is accomplished through the vinylogous acyl chloride **243** to provide **244** by addition of phenylsulfinate and elimination chloride, respectively, in 74% yield overall. Oxidative functionalization of **244** was accomplished by a Rubottom reaction, i.e. treatment of the corresponding enol silyl ether with m-chloroperbenzoic acid. Neither the electron deficient α,β-unsaturated sulfone nor the terminal C=C bond are oxidized in competition with the more electron rich silyl enol ether. Steric approach control in a hydride reduction of **245** delivers the allylic alcohol **246** stereoselectively.



O-alkylation of **246** with **239** provides the key intermediate **247**, that undergoes a remarkable cyc- lization upon halogen-metal exchange. Intramolecular Michael addition of the intermediate aryllithium **238** leads *via* sulfone-stabilized carbanion **248** to **237**. Construction of the piperdine ring requires conversion of the allyl group in **237** into an ethylamino sidechain and conjugation of C-11 with the oxygen functionality at position 6 in **237**. Oxidation and enol etherification delivers **250** from **249**. Elimination of phenylsulfinate to give **251**, and hydrolysis to deliver **252** sets the stage for the completion of the morphine ring system by generation of the piperidine ring. Thus, neutralization of the ammonium salt **252** generates an amino group that undergoes spontaneous intramolecular 1,6-Michael addition to the dienone to deliver a mixture of neopinone (**188**) and codeinone (**189**) in 63% yield. Conversion of this mixture via codeine (**190**) to morphine (**171**) was accomplished as described previously by Rapoport. The required configuration of the hydroxyl at position 6 is established during a steric approach controlled delivery of

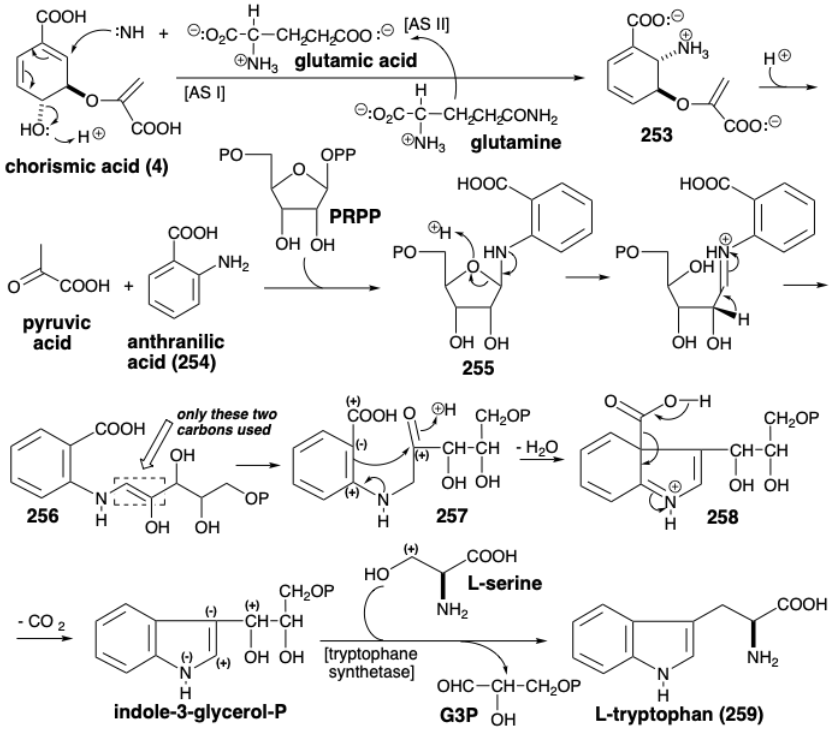
hydride to the carbonyl carbon in **189**. The correct configuration at the 15-position in **190** arises from equilibration through the common enol derivative of ketones **188** and **189**.



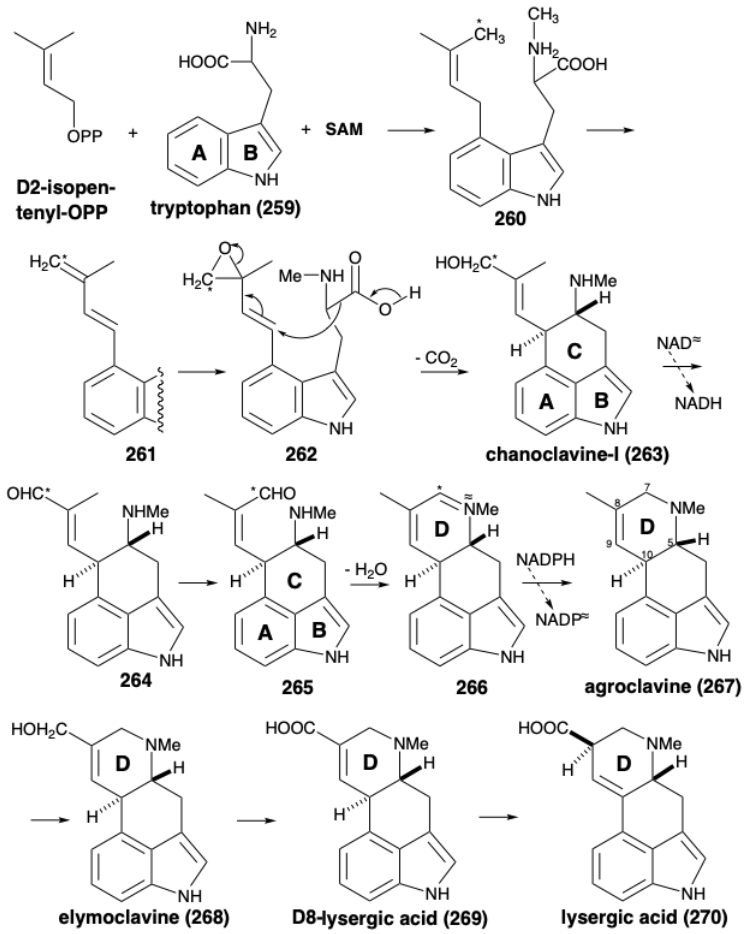
6.4: Lysergic Acid

Biosynthesis of Tryptophan and Lysergic Acid

The carbon skeleton of anthranilic acid (**254**) is constructed in nature from two molecules of phosphoenol pyruvate and one of erythrose 4-phosphate via chorismic acid (see section 5.1). The two-component enzyme complex of *anthranilate synthetase* (AS) then promotes the transfer of NH_3 from glutamine to chorismic acid (**4**) affording amino acid **253** by conjugate displacement of a hydroxyl group. During the strategically intricate biosynthesis of tryptophan (**259**), the carboxyl carbon of **254** is ultimately lost. A five-carbon unit from ribose is appended to the amino group of **254**, but suprisingly all five carbons of phosphoribosyl pyrophosphate (PRPP) are not retained to complete the tryptophan skeleton (*vide infra*). Deprotonation of the imine derived from **255** delivers an enamine **256** that is also the enol tautomer of ketone **257**. Intramolecular Friedel-Crafts cyclization of the latter delivers a β-iminocarboxylic acid **258** that, being the nitrogen analogue of a β-keto acid, readily decarboxylates producing indole-3-glycerol phosphate. While the biosynthesis of tryptophan might be completed by simple functionality adjustments, Nature adopts a different, more convoluted, strategy. Thus, *tryptophan synthetase* catalyzes a remarkable Friedel-Crafts alkylation with L-serine coupled with a dealkylation that cleaves glyceraldehyde-3-phosphate (G3P) and delivers L-tryptophan (**259**).

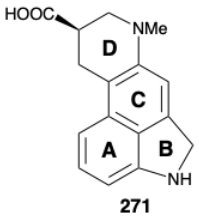


So far, we have seen that complex alkaloids may be assembled in Nature by a convergent strategy involving the union of two large fragments derived from aromatic amino acids. Alkaloids may also be constructed in Nature by the conjugation of amino acid-derived intermediates with terpenoid starting materials. Thus, as outlined below, lysergic acid (**270**) is forged from tryptophan (**259**) and Δ^2-isopentenyl pyrophosphate. Later, we shall see how indole **259** is united in a variety of ways with secologanin, a terpene, to generate a vast array of structurally complex tryptophan-derived alkaloids. The carbons of these starting materials remain connected in the product, although the carboxyl carbon is lost. Thus, the biosynthetic strategy is simple.

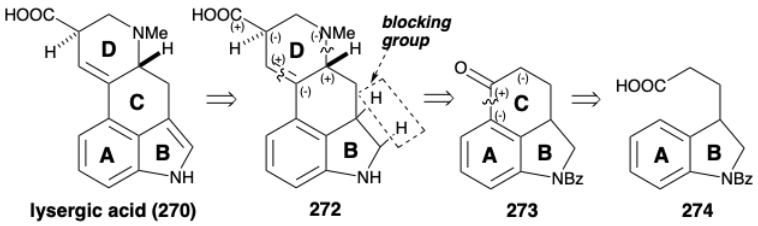


The biosynthesis of lysergic acid commences with the prenylation of tryptophan. Thus, Δ^2-isopentenyl pyrophosphate is a potent electrophile that readily alkylates the nucleophilic benzene ring of tryptophan **259** to afford 4-prenyltryptophan (**260**). The cyclization of **260** to lysergic acid requires addition of functionality to the Δ^2-isopentenyl (prenyl) group by oxidations. The process is accompanied by a remarkable odyssey of the allylic carbon marked with an asterisk in the intermediates **260** - **265**. Allylic hydroxylation and dehydration provide **261.** The diene **261** has free rotation, that allows interconversion of the E and Z-methyl carbons during the **260** to **263** conversion. Formation of the D-ring is believed to occur by a decarboxylative S_N2' alkylation in the allylic epoxide **262**. Oxidation of the cyclization product, chanoclavine-I (**263**), to an E allylic aldehyde **264** is followed by *cis-trans* isomerization to the Z-isomer **265**. Condensation to the Schiff base **266** completes the lysergic acid skeleton. Final adjustment of functionality by reduction to agroclavine (**267**), allylic oxidation to elymoclavine (**268**), further oxidation to Δ^8-lysergic acid (**269**), and isomerization gives lysergic acid (**270**).

Dihydrogen as a Masking Group for an Alkene

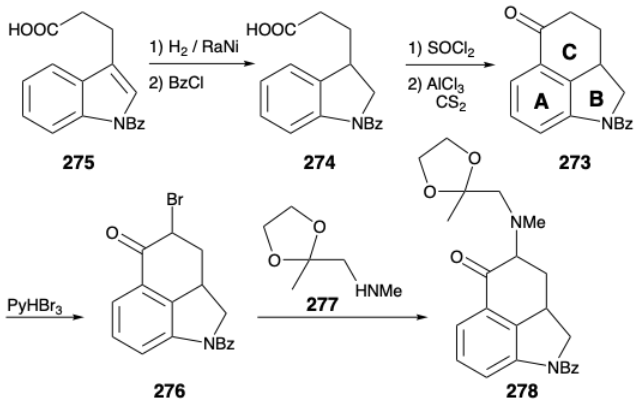


Lysergic acid is thermodynamically unstable. Acids, base, or noble metals readily catalyze the irreversible rearrangement of lysergic acid (**270**) into a naphthalene isomer **271** by migration of a D-ring and a B-ring C=C bond into the C ring. Therefore, the stability of aromatic derivatives, that may often be advantageously exploited in complex molecular synthesis, was seen by Woodward as a major obstacle for the synthesis of lysergic acid (**270**). A central tactic in the first successful synthetic strategy,[13] was the scrupulous avoidance of aromaticity in ring C. On the other hand, the crucial last step of the scheme, dehydrogenation of an indoline **272**, ingeniously exploits the aromaticity of the indole array in **270**. What is remarkable about this strategy is Woodward's recognition that, although it might seem unlikely that a way could be found to dehydrogenate **272** without also inducing isomerization of **270** to **271**, the search for a method to achieve such a selective reaction could provide an excellent solution to the central challenge of the synthesis, and, therefore, was well worth the effort.

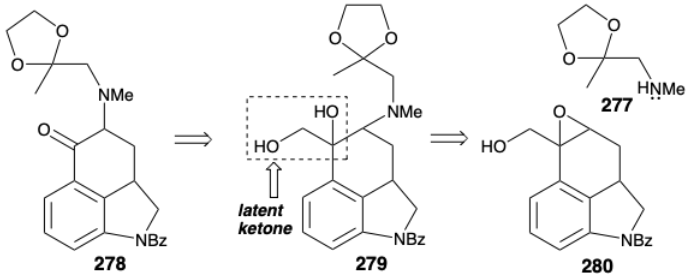


The Woodward strategy was channeled by the decision to use an intramolecular Friedel-Crafts acylation of the electron-rich A ring in **274** to generate the C ring in **273**. This approach is recommended by the ready availability of **274** as starting material, and by the potential utility of the carbonyl group in **273** to activate bond forming reactions required to add the D ring. However, construction of **272** from **273** can be achieved by polar reactions only if polar reactivity inversions are employed, because the polar reactivity patterns of **272** and **273** are opposed.

The ABC-ring intermediate **273** is readily available from **275** by selective catalytic hydrogenation followed by intramolecular Friedel-Crafts acylation of **274**. The carbonyl group in **273** provides activation at the adjacent methylene position that may be exploited for the attachment of the requisite nitrogen atom. However, an amino group is a nucleophile. To allow polar C-N bond formation, the potential nucleophilic reactivity of the methylene α to a ketone carbonyl must be inverted. This was achieved by bromination to afford **276** in excellent yield. An early attempt at alkylation of the amine **277** with **276** was unsuccessful. After exploring a very large number of alternative approaches for annelation of the D ring and developing an eleven stage sequence for preparing **278** from **273**, it was discovered that a nonpolar solvent was uniquely effective for the alkylation of **277** with **276**. Under these reaction conditions, the ketone ketal **278** was produced in excellent yield. This scenario is a poignant epitome of the vicissitudes of organic synthesis. It serves to underscore a caveat mentioned earlier (see section 1.2) that is worth repeating: *as the availability of starting materials or methods (new or more effective) for uniting and manipulating them vary, so will the relative merits of different pathways. A poor synthesis can become the method of choice if a way to improve a bad step can be discovered.*

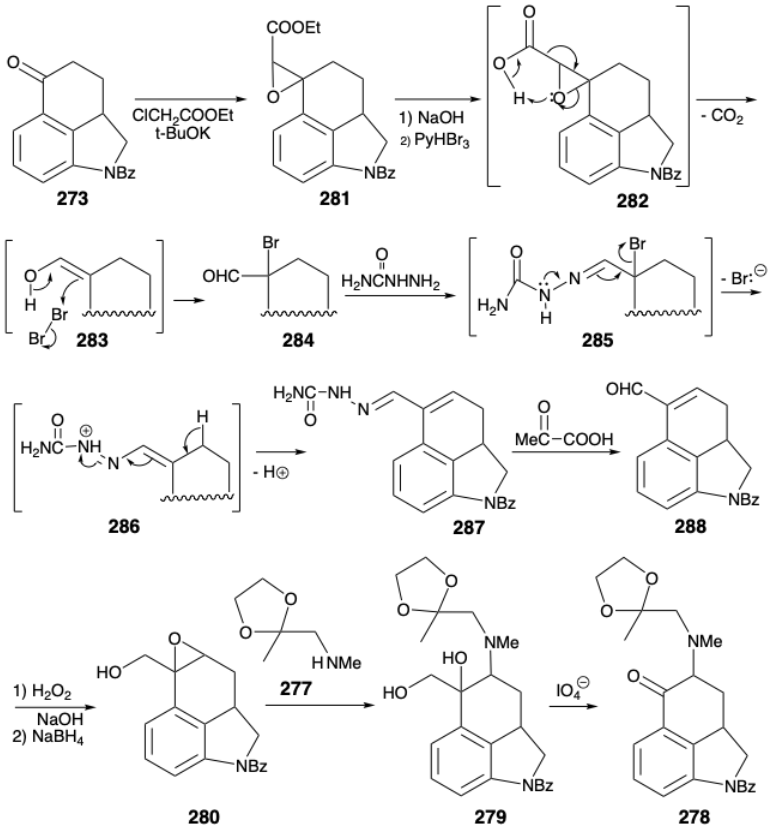


It is instructive to examine the alternative strategy for the synthesis of **278** from **273**, and to keep in mind that this alternative sequence was one of a great many that were painstakingly explored. The alternative route involves a strategy analogous to the **276** → **278** conversion, except that the carbonyl group of **276** and **278** is present in latent form as a vicinal diol in the corresponding key intermediates **280** and **279** respectively. Thus, the carbonyl is generated in the last step of the synthesis by oxidative cleavage.

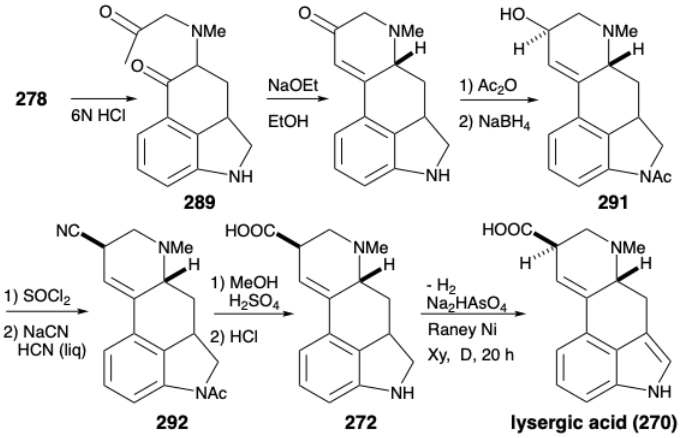


The synthesis of **279** involves a novel sequence in which the enol **283** from decarboxylation of the glycidic acid **282** is intercepted by bromine (Br_2 is in equilibrium with Br_3^-) delivering α-bromoaldehyde **284** from the Darzens condensation product **281**.

Dehydrohalogenation of the α-bromoaldehyde **284** was effected by the mild Mattox-Kendall procedure via semicarbazone **285** and unsaturated semicarbazone **287**, that afforded the unsaturated aldehyde **288** by transfer of the semicarbazide residue to pyruvic acid. Nucleophilic epoxidation delivered the key intermediate **280**. The latent carbonyl in **279** was deblocked by oxidative cleavage with periodate. This cumbersome route to **278** was abandoned when *conditions* for achieving the direct preparation of **278** from the bromoketone **276** were discovered.



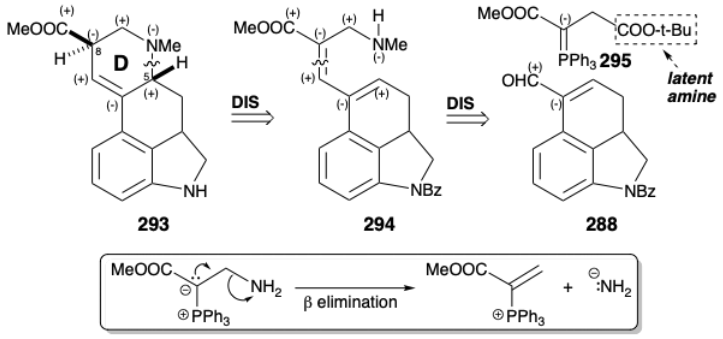
Completion of ring D was straightforward via intramolecular aldol condensation of the diketone **289**. The carbonyl group in the resulting enone **290** then provided reactive functionality in an alcohol **291** and the derived chloride for attachment of cyanide (a carboxy carbanion equivalent) as the final carbon atom of lysergic acid. After hydrolysis of **292** to **272**, the *two hydrogen atoms*, placed at the outset by design at C-5 and C-5a to *mask a rearrangement-prone C=C bond*, needed only to be removed to afford lysergic acid (**270**).



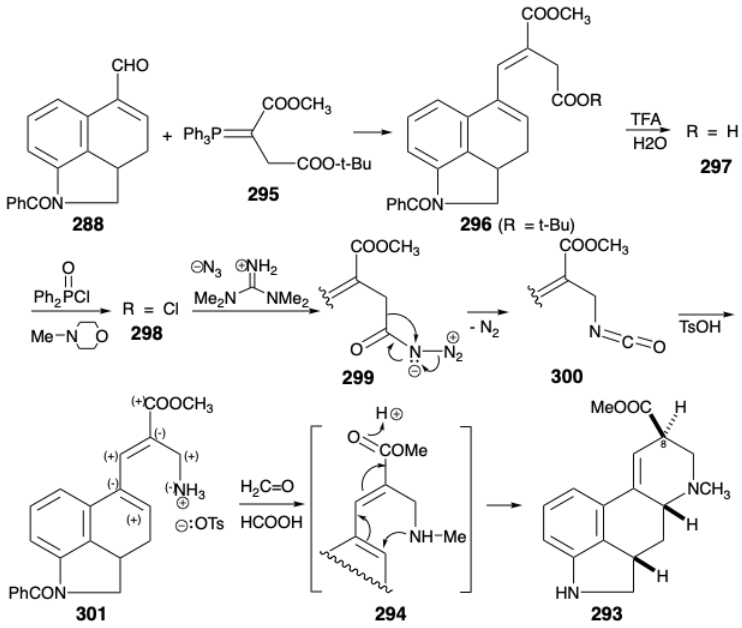
A Polar D Ring Annelation Exploiting Target-related Functionality

The D-ring ester and amino functionality provide entirely consonant polar reactivity patterns in the derivative **293** of Woodward's carboxylic acid intermediate **272**. An alternative strategy[14] for annelation of the D-ring of lysergic acid exploits the polar activation

provided by these functional groups that suggests a dislocation to **294**. Dislocation of **294** to the aldehyde **288**, prepared previously by Woodward, suggests an ylide precursor **295** in which a t-butyl ester serves as a latent amine. A more direct approach using an α-amino ylide seemed inadvisable in view of a possible β-elimination.

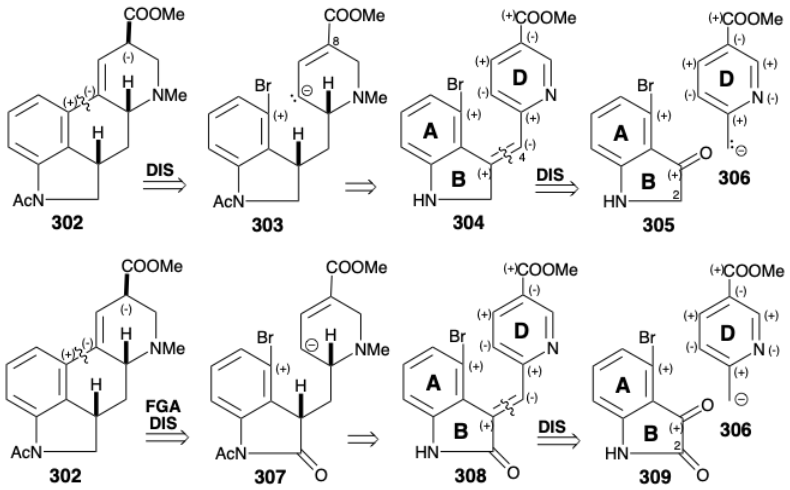


Introduction of the amino substituent was initiated by selective hydrolysis of the t-butyl ester in **296** under acidic conditions. The carboxylic acid **297** was then transformed into the corresponding chain shortened primary amine **301** in 80% yield by a Curtius degradation. Cyclization, i.e. of **294**, accompanied the reductive amination of formaldehyde with primary amine **301** to afford a 3:1 mixture of the desired ester **293** and its C-8 epimer.

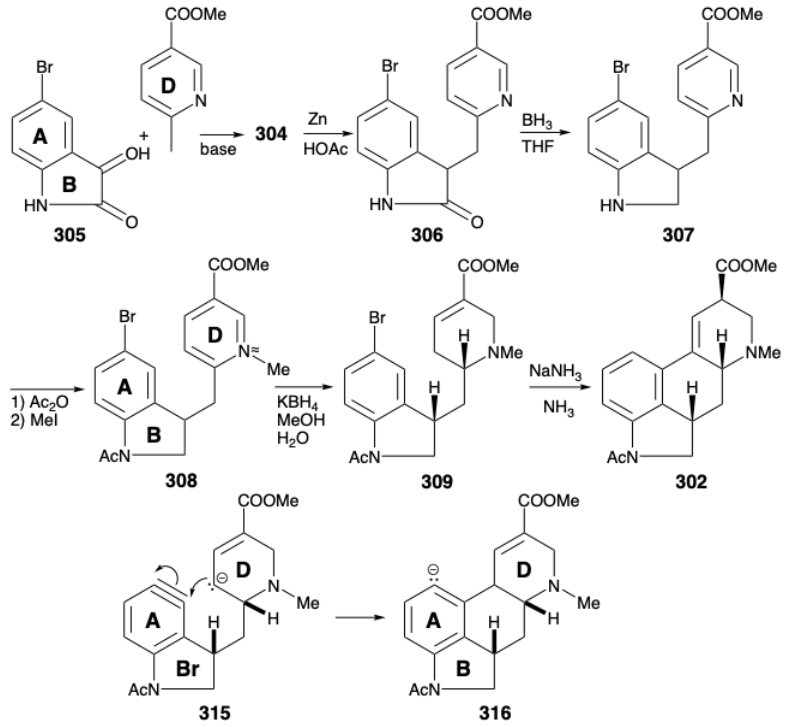


C-Ring Annulation by Nucleophilic Aromatic Substitution

Another synthesis of the key ester intermediate **302** involves annelation of ring C in a preformed ABD-ring precursor by intramolecular nucleophilic substitution with a carbanion **303** that is conjugated with the carboxyl functionality found at position 8 in the target.[15] The same carboxyl also provides nucleophilic activation at position 4. Thus, polar analysis of **304** suggests a polar dislocation to two aromatic starting materials that can be joined by an aldol condensation between ketone **305** and carbanion **306**. However, this strategy is fatally flawed owing to a preference for ketone **305** to exist as an enol. The addition of another carbonyl group at position 2, as in **309**, precludes enolization (blocking group), enhances the electrophilicity of the ketone carbonyl, in **309**, and activates the C=C bond in **308** toward dissolving metal reduction.



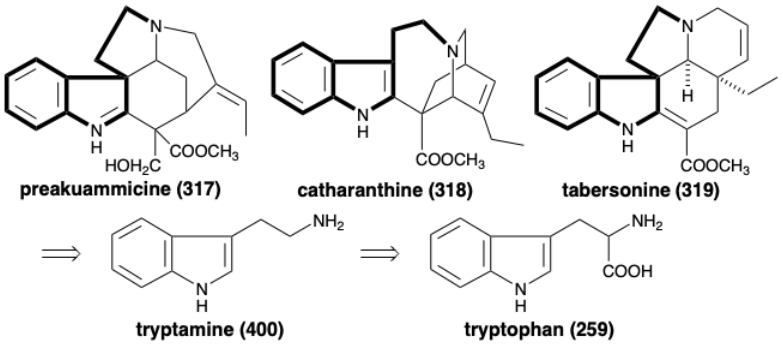
Actually, generation of an isomer of **309**, i.e. **310** with the bromo group para to nitrogen, is favored during a synthesis by electrophilic aromatic substitution owing to the powerful activating influence of the nitrogen substituent. However, this is not a flaw because a mecahanism exists for nucleophilic aromatic substitution with rearrangement. Thus, elimination of the nucleofuge leads to a benzyne intermediate **315** to which the nucleophile then adds regioselectively at the required position to give **316**. Having served its roles as a *reactivity* control element, the carbonyl group in **311** is then selectively removed by reduction with diborane. The pyridine ring of the product **312** is activated toward hydride reduction by N-methylation after acetylation of the indole nitrogen. Unfortunately, hydride reduction of the D-ring in **313** produces two epimers only one of which, i.e. **314**, cyclizes upon treatment with base delivering **302** in only 15% yield.



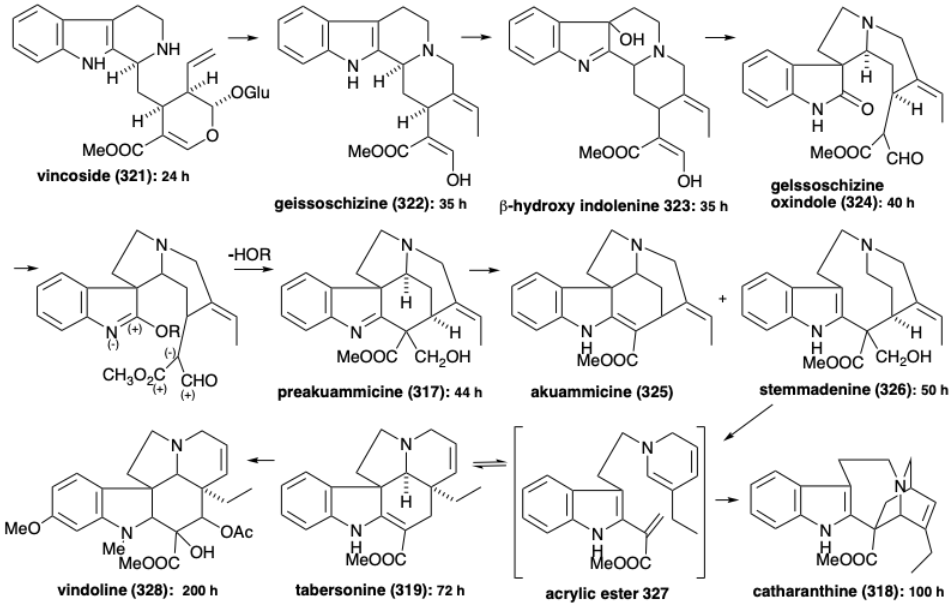
6.5: Quinine

Biosynthesis of Alkaloids from Secologanin

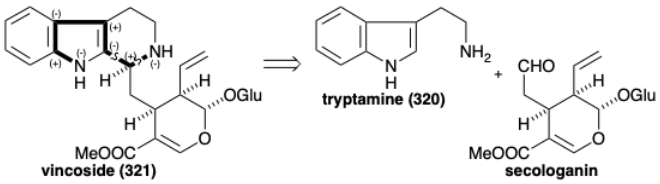
A comparison of the structures of polycyclic alkaloids with a variety of topologically different skeletons, such as preakuammicine (**317**), catharanthine (**318**), and tabersonine (**319**), suggests a biosynthetic strategy which assembles these heteromulticycles by the union of an aminoethyl indole starting material **400** with ten additional skeletal carbons. The aminoethyl indole, tryptamine (**400**), is reasonably derived from decarboxylation of the amino acid L-tryptophan (**259**) by a process analogous to the decarboxylation of tyrosine (**7**) discussed in section 6.4.



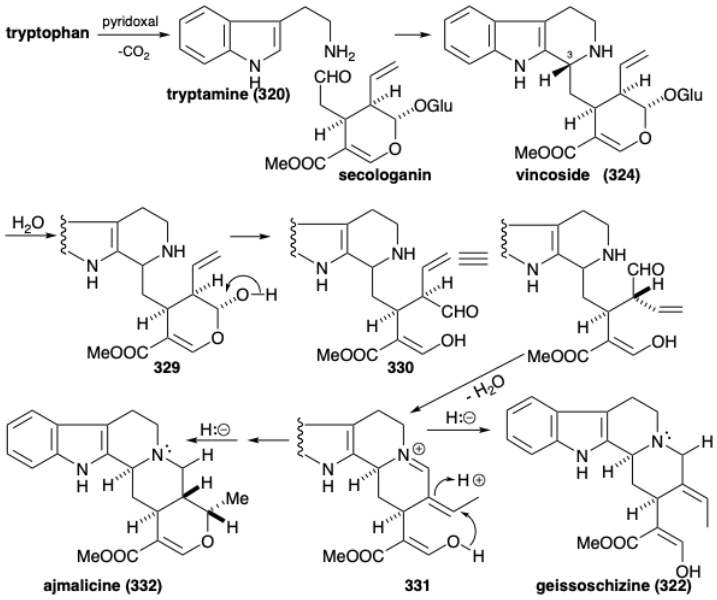
The origin of the remaining ten skeletal carbons is less obvious. The remarkable fact that these remaining carbons have a *common* origin is nicely illustrated by studies on the time evolution of alkaloid production in germinating seedlings of Vinca Rosea.[16] Thus, the alkaloids **317** - **326**, and **328** are all isolable from this plant while **327** is a putative common intermediate for the generation of **318** and **319** by two different $2\pi + 4\pi$ cycloadditions.



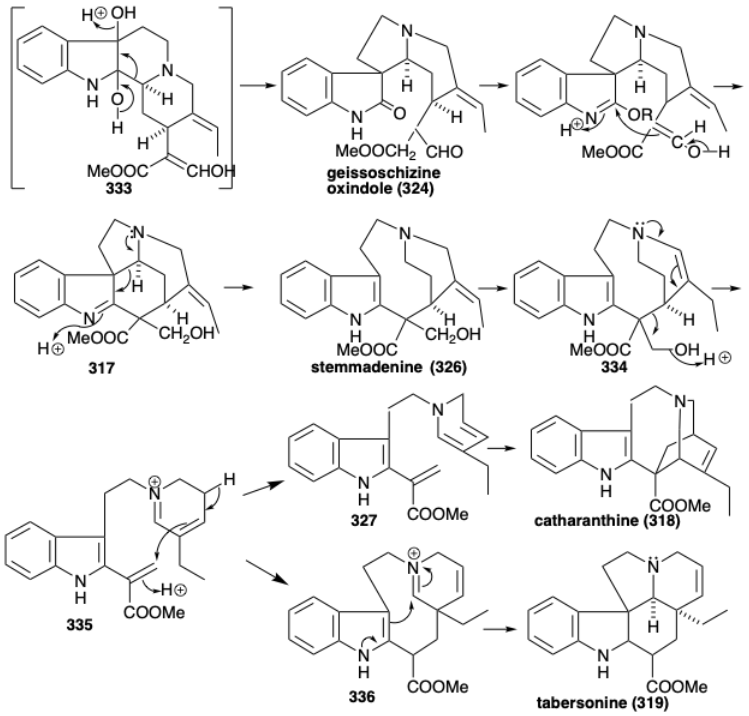
In the early intermediate vincoside (**321**), there is a consonant circuit that connects the two nitrogens. Two polar disconnections in this circuit reveal an aldehyde precursor that bears little resemblence to a monoterpene besides its ten skeletal carbon atoms. Nevertheless, this aldehyde is secologanin whose terpenoid origin was discussed in chapter 4 (see section 4.4).



The biosynthesis of over 1,000 **indole alkaloids** from tryptophan (**259**) begins with a Mannich reaction between tryptamine (**320**) and secologanin to produce vincoside (**321**). Hydrolysis of the glucoside **321** and deketalization of the resulting hemiketal **329** affords amino-aldehyde **330**. Cyclization of the latter gives an iminium derivative **331**. Intramolecular Michael addition of an oxygen nucleophile followed by reduction affords another isolable product, ajmalicine (**332**). Alternatively, reduction of **331** affords **322**.

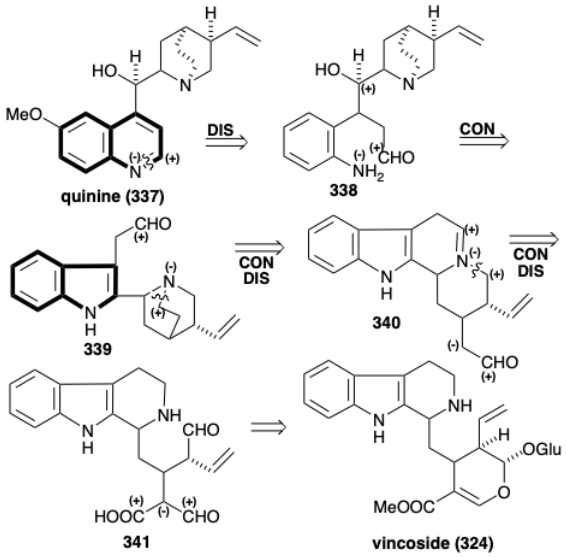


Generation of the other skeletal types from **322** involves rearrangements that are enabled by oxidative introduction of a vicinal diol array to produce **333**. This vicinal hydroxylation is accomplished by a stepwise process through the hydration of an isolable intermediate, the β-hydroxyindolenine **323**. A pinacol rearrangement of **333** produces **324**. Conversion to an imino ester would endow **324** with the reactivity required to form preakuammicine (**317**) by cyclization and reduction. Retero-aldol-like fragmentation of **317** followed by the reduction of the resulting immine affords stemmadenine (**326**). A second fragmentation of the enamine isomer **334** of **326** apparently produces an acrylic ester intermediate **335**. The dienamine tautomer **327** of **335** provides the iboga alkaloid skeleton of catharanthine (**318**) by an intramolecular Diels-Alder reaction (not necessarily concerted). Alternatively, the aspidosperma alkaloid skeleton of tabersonine (**319**) arises from the acrylic ester **335** via polyene cyclization to **336** and subsequent aldol-like cyclization of the latter followed by proton loss to afford tabersonine **(319)**.

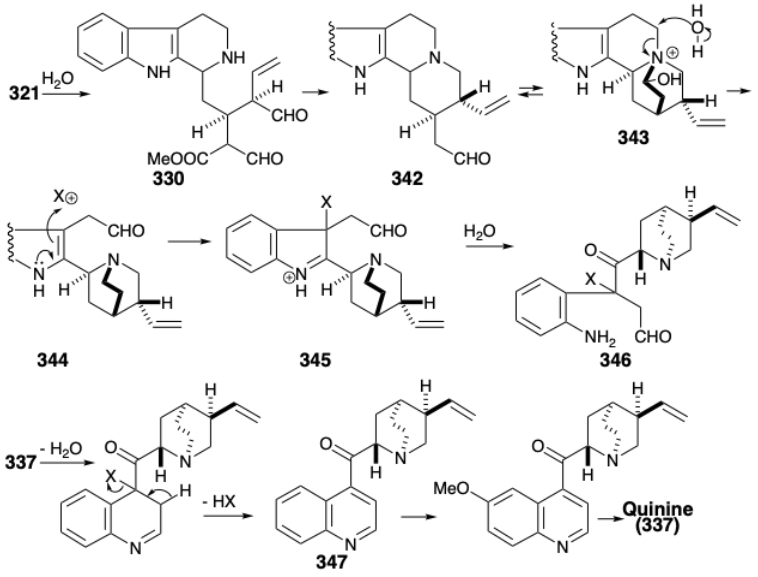


Biosynthesis of Quinine

Even more cryptic is the biosynthesis of several alkaloids containing the quinoline heterocyclic ring system such as quinine (**337**). The surprising fact that the carbon skeletons of these alkaloids are also derived from tryptophan and secologanin further illustrates the lengths to which Nature must go to achieve the biosynthesis of some natural products owing to a limited inventory of available starting materials. It is an instructive exercise to infer the biosynthetic pathway by retrosynthetic analysis. Given the boundary condition of an indole precursor, the pyridine ring of the quinoline ring system in **337** must be generated. This might be accomplished by dehydrogenation of the imine produced from an amino aldehyde precursor **338**. The alcohol functionality in **338** could be the residue of electrophilic activating functionality in a precursor that was involved in a connection with the nucleophilic amino group in a pyrrole ring, as in the tryptophan **339**. Referring to the boundary condition of tryptophan as the biosynthetic starting material, the aldehyde in the precursor **339** could be generated by hydrolytic cleavage of an imine derivative **340** of the ethylamine sidechain of tryptamine. A concomitant disconnection of one bond to the tertiary amino group in **339** is required to make room for the connection. Referring to the boundary condition of vincoside as starting material, **340** could arise from acarboxy dialdehyde **341** by polar decarboxylation and heterocyclization.

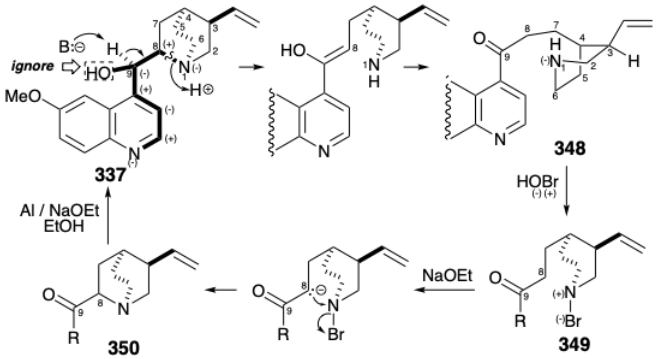


The biosynthesis of the quinuclidine portion of quinine (**337**) from the secologanin portion of vincoside (**321**) involves hydrolysis of the glucoside to give a dialdehyde **330**, followed by intramolecular reductive alkylation and decarbomethyoxylation to give **342**, that is in equilibirum with a hemiaminal **343**. Hydrolytic fragmentation of the latter accompanied by oxidation of a primary alcohol to an aldehyde and reduction of the hemiaminal to an amine affords **344**. The rearrangement of the indole portion of **344** to a quinoline skeleton is initiated by an oxidation to **345** followed by ring cleaving hydrolysis and recyclization of the resulting amino aldehyde **346**. Arene oxidation, methylation, and then reduction of the resulting quinoline derivative **347** delivers quinine (**337**).



A Relay Synthesis of Quinine

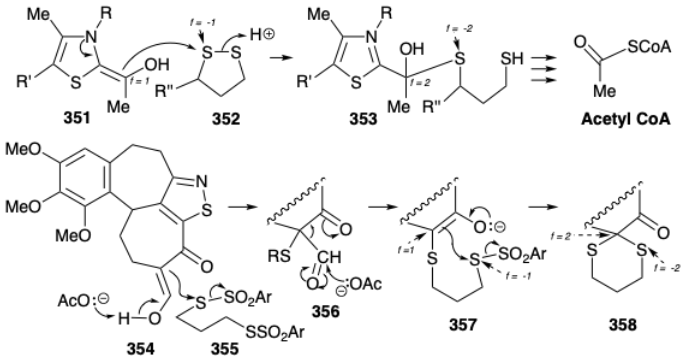
A major topological simplification of the quinine skeleton arises by disconnection of a bond between atoms 1 and 8. Atom 1 is a common atom of the multicyclic quinuclidine portion of **337**. Though atom 8 is a noncommon atom, its role as a link between the two major portions of **337** recommends removal of skeletal connections to this atom. This disconnection was actually achieved by Rabe during degradative studies on the structure of **337**.[17] The fragmentation of **337** to **348** depends upon the polar activation provided by the quinoline and quinuclidine amino groups (ignoring the activation provided by the C-8 hydroxyl).



Polar Redox Reactions

Rabe also demonstrated that the reverse process, a synthesis of **331** from **347**, can be achieved by exploiting the polar activation of C-8 in **347** (quinine numbering).[17] This approach requires a *nitrogen electrophile* and involves oxidation via polar intermediates. Thus, the nucleophilic secondary amino group in **348** is converted into an electrophile in **349** by appending a more electronegative atom, i.e. bromine. This constitutes oxidation of the amino group. Electrophilic attack on carbon in **349** to give **350** produces a bond between carbon and a more electronegative atom (i.e. nitrogen). This constitutes oxidation of carbon coupled with reduction of the amino group. We shall refer to such reactions as **polar redox reactions**. An example of this reaction type occurs in the biosynthesis of acetyl CoA (see section 2.3) during nucleophilic attack by hydroxyethylidene TPP (**351**) on the the disulfide **352**. Thus, the nucleophilic carbon is oxidized from *f* = 1 in **351** to *f* = 2 in **353** while a sulfur atom in **352** is reduced from *f* = -1 to f = -2

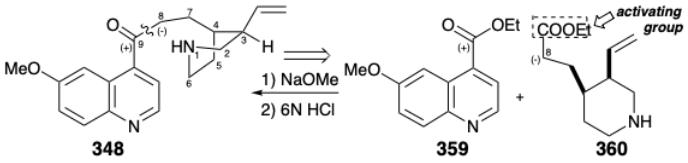
in **353**. This reaction is complex because another carbon in **351** is concurrently oxidized from *f* = 2 to *f* = 3 in **353** in conjunction with reduction of the second sulfur in **352** from *f* = -1 to *f* = -2 in **353**.



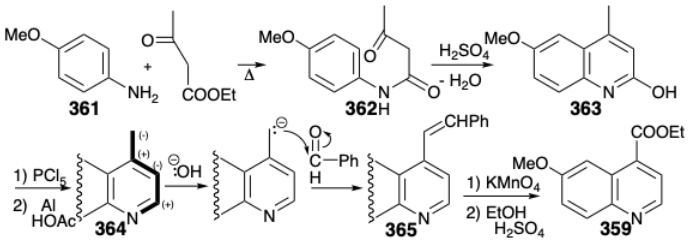
Another polar redox reaction, again with sulfur as electrophile, was encountered in the Woodward synthesis of colchicine (see section 6.1). In fact, the introduction of a dithioketal at the nucleophilic carbon α to a cabonyl group involves two successive oxidations of the α carbon, first of **354** to **356** then of the latter into **358**, coupled with two reductions of sulfur, first in the conversion of **355** to **356** then in the conversion of the latter, via **357**, into **358**. This reaction is also complex because another carbon in **354**, α to the enolic hydroxyl, is concurrently oxidized from *f* = 1 to *f* = 2 in **356** in conjunction with reduction of a second sulfur in **355**, and a second carbon is oxidized from *f* = -1 in **357** to *f* = -2 in **358** (the carbonyl carbon) in conjunction with reduction of a second sulfur.

A Convergent Strategy for Key Intermediate 348

It should be noted that **350** (see above) is a mixture of epimers at C-8, and the reduction that produces **337** introduces another asymmetric center (at C-9). Fortunately, **337** was a major component of the isomeric mixture produced by this nonstereocontrolled conversion of **348** to **337**. This conversion makes quinotoxine (**348**) an attractive subtarget for the total synthesis of quinine (**337**). The subtarget **348** is further simplified by a dislocation, that breaks the molecule into two large fragments by severing one of the four bonds connecting the quinoline and piperidine rings. The dislocation chosen by Woodward and Doering for the first *total* synthesis of quinine (**337**) was dictated by the fact that the reverse process, synthesis of **348** from **359** and **360**, had excellent precedent. A dihydro derivative of **348** (with an ethyl instead of a vinyl group) was prepared by Rabe from **359** and a dihydro derivative of **360** which had been obtained from degradation of natural quinine (**337**).

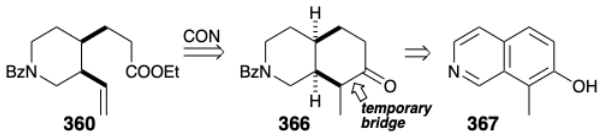


Total syntheses of the subtarget ethyl quininate (**359**) were also known when the total synthesis of **337** was undertaken. A particularly effective route introduces the carboxyl group in latent form as a benzylic methyl group, and constructs the nitrogen heterocycle on a preformed aromatic precursor **361** by polar reactions. Cyclodehydration of **362** affords **363**, that is reduced to **364**. Benzylic oxidation of **364** is achieved by oxidative cleavage of a latent carboxylic acid, a C=C bond in the precursor **365**, that is available by a polar condensation of **364** with benzaldehyde. The condensation exploits the nucleophilic activation of the benzylic methyl, that is provided by the nitrogen in **364**.

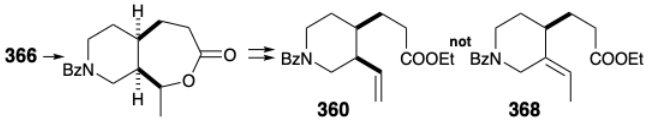


The only remaining synthetic objective was, thus, ethyl N-benzoylhomomeroquininate (**360**). The two side chains in **360** could be generated stereospecifically cis by oxidative cleavage of a temporary bridge in **366**. The cis ring fusion in **366** could be produced,

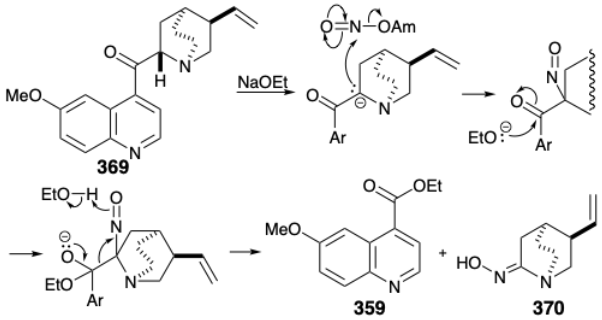
in turn, by catalytic hydrogenation of an aromatic isoquinoline precursor **367**.



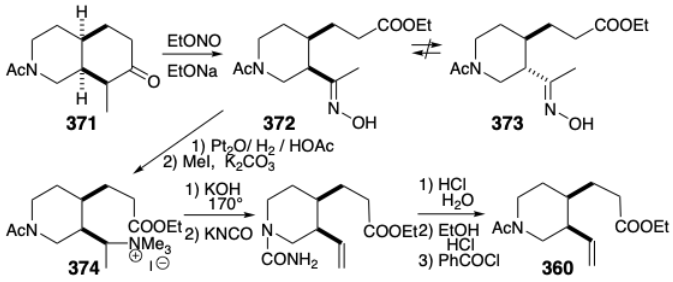
Several potential flaws must be avoided in designing a detailed scheme for the **366** to **360** conversion. For example, cleavage of the temporary bridge in **366** by a Baeyer-Villiger oxidation followed by an elimination to generate the vinyl group in **360** must avoid generating the alternative, thermodynamically favored, ethylidene derivative **368**.



Interestingly, the reaction chosen to achieve the ring cleavage was a reaction used earlier in degradation studies for determining the structure of quinine. Thus, Rabe effected cleavage of quininone (**369**) into ethylquininate (**359**) and an oximino compound **370** by treatment with amyl nitrate and sodium ethoxide. This cleavage is analogous to a retro-Claisen reaction, that occurs especially readily for nonenolizable β-keto esters.

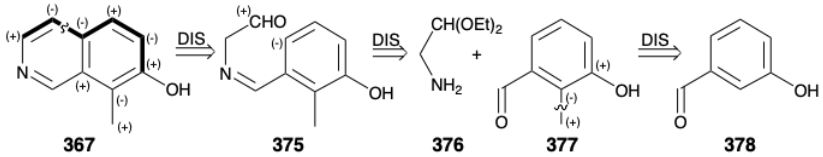


Application of this cleavage process to the N-acetyl analogue **371** of **366** generates oxime **372**. A potential flaw, epimerization of the cis-1,2-disubstituted product **372** into the thermodynamically more stable trans isomer **373**, was not a problem. In contrast to what would be expected for the corresponding acetyl derivative, the oxime **372** is not prone toward epimerization. Thus, the hydroxyl proton rather than an α-proton is preferentially abstracted upon treatment of oximes with base. Reduction and methylation of **372** readily affords a quaternary ammonium derivative **374**, that affords the requisite terminal vinyl group in **360** by base promoted Hofmann elimination involving regioselective abstraction of hydrogen from the less substituted β carbon.

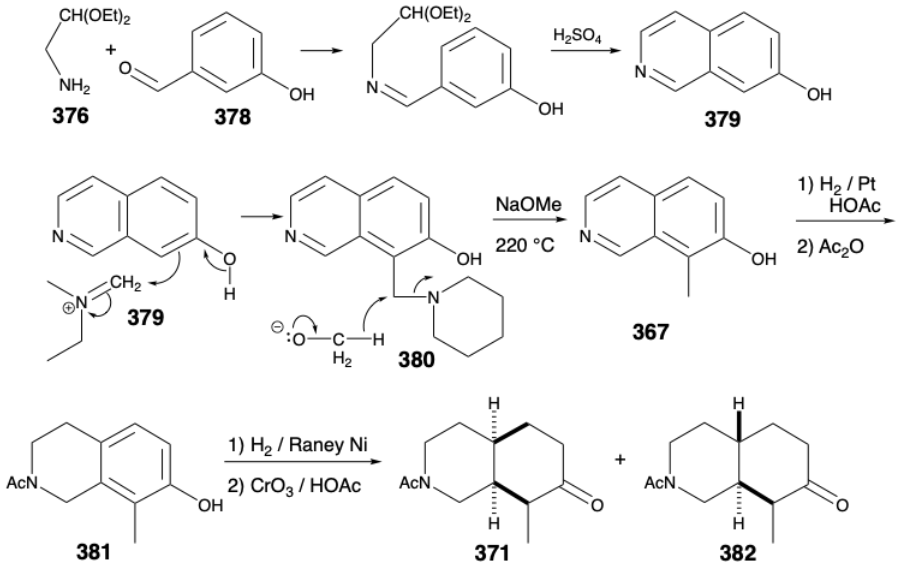


As noted above, an aromatic precursor **367** was chosen for the synthesis of ethyl N- benzoylhomomeroquininate (**360**). A monocyclic aromatic precursor for **367** could be either a pyridine derivative or a benzene derivative. Choosing the latter allows exploitation of electrophilic aromatic substitution on an electron-rich precursor to accomplish annelation of the pyridine ring. This annelation requires carbon-carbon bonds meta and para to the hydroxyl group. Formation of the para bond by electrophilic aromatic substitution is favored over meta by the strong electron donating activating effect of the hydroxyl group. Formation of this para carbon-carbon bond in the last step of annelation suggests a phenolic precursor **375** with the four atoms of the incipient pyridine ring appended to the meta position. The bond between this meta substituent and the phenol ring can not be generated by electrophilic aromatic subsitution because ortho and para rather than meta substitution is favored. However, disconnection of this substituent by removal of the bond between nitrogen and the benzylic carbon suggests a dissonant carbonyl-masked amino acetaldehyde **376** and a benzaldehyde derivative **377**. The methyl substituent in **377** might also be introduced by electrophilic

aromatic substitution on the readily available m-hydroxy-benzaldehyde (**378**). However, achieving the requisite regiocontrol in such an alkylation might be difficult.

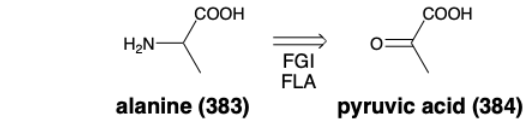


In fact, a different order of steps was adopted. Introduction of the ortho methyl substituent was postponed until after annelation of the pyridine ring was completed because introduction of a methyl group can be readily achieved regioselectively by electrophilic aromatic substitution on the β-hydroxy isoquinoline **379**. Thus, aminomethylation with piperidine and formaldehyde produced the benzylic amine **380** that was reduced to **367** upon heating in the presence of sodium methoxide. This unusual reduction involves hydride transfer from methoxide. Technical difficulties arose in the hydrogenation of **367** to **371**. Thus, because the amine poisoned the catalyst, the hydrogenation stopped after only the nitrogen containing ring had been reduced. The amine had to be blocked as an amide before reduction of the benzene ring could be achieved. The desired cis-stereospecificity in the reduction of **381** to **371** could not be achieved. Fortunately, however, this was not a fatal flaw because the required isomer could be isolated from the trans-fused hydrogenation reaction product **383**. Thus, catalytic hydrogenation is not entirely reliable for stereoselective delivery hydrogen to one face of an aromatic ring.

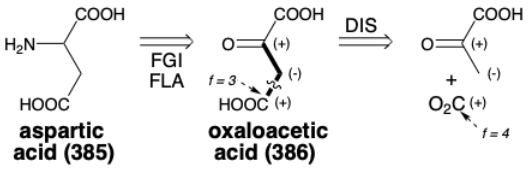


6.6: Biosynthesis of Nonaromatic Amino Acids

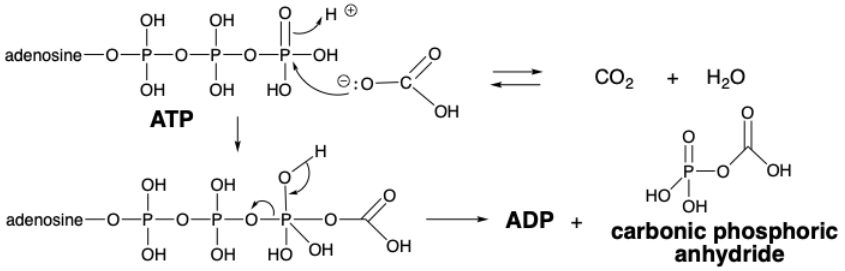
The availability of an appropriate starting material dictates a biosynthetic strategy for alanine (**383**). Pyruvic acid (**384**) is a key intermediate in the biosynthesis of acetyl CoA. A functional group interchange (FGI) coupled with functionality level adjustment (FLA), i. e. reductive amination, can provide the α amino substituent of **383** from the carbonyl group in pyruvic acid.

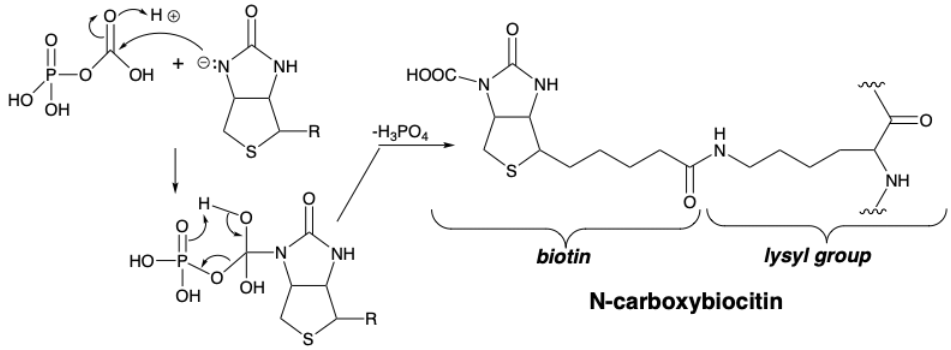


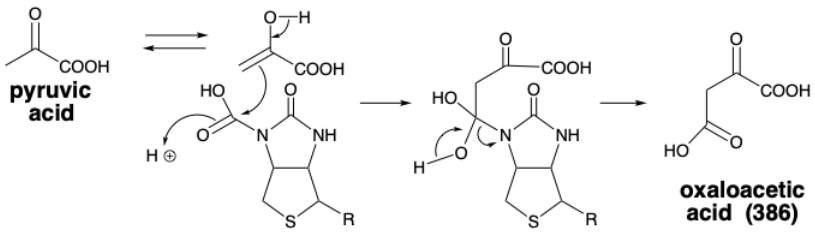
Adopting a similar strategy for the biosynthesis of aspartic acid (**385**) suggests oxaloacetic acid (**386**) as a precursor. The consonant circuit in the β-keto acid array of **386** suggests a polar synthesis from pyruvic acid and carbon dioxide.

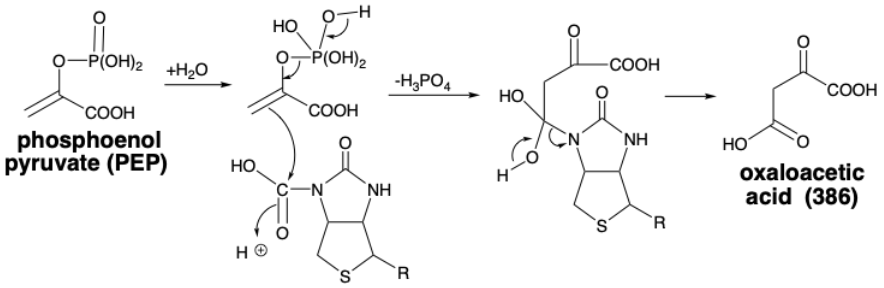


In the biosynthesis of **386**, carboxylation does not involve the direct reaction of pyruvic acid with CO_2. Rather, the carboxylating agent is an enzyme-bound N-carboxy biotin derivative that is generated by a series of reactions that begin with the activation of carbonate by phosphorylation with ATP. The resulting carbonic phosphoric anhydride acylates the biotinyl nitrogen of N-carboxybiotin which is bound to an enzyme, pyruvate carboxylase, as N-carboxybiocytin. Pyruvate carboxylase catalyzes the transfer of a carboxy group to pyruvate from N-carboxybiotin. Alternatively, in some plant cells phosphoenol pyruvate is carboxylated producing oxaloacetic acid directly.

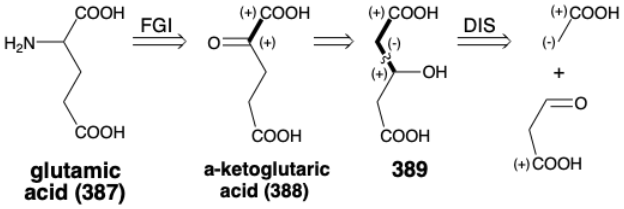




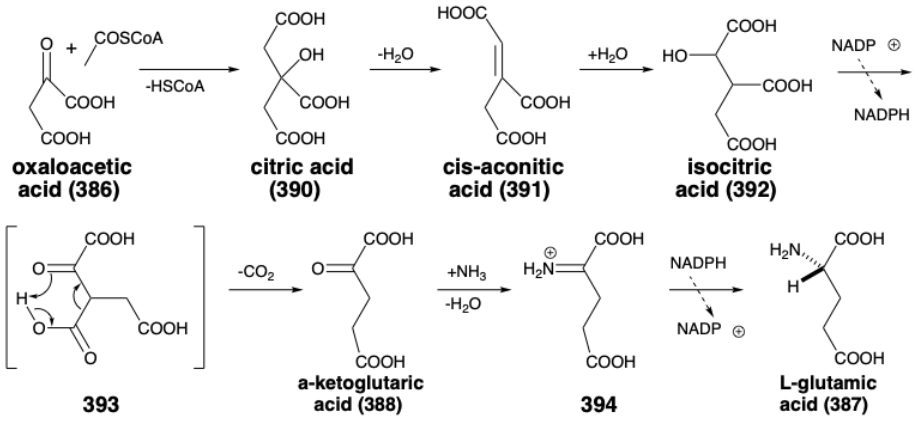




The biosynthetic strategy for glutamic acid (**387**) is more intricate. Thus, the potential precursor α-ketoglutaric acid (**388**) contains dissonant circuits in both the g and the α-keto acid arrays precluding a direct polar synthesis by a C-C connective route from smaller precursors. One way to invert the polar reactivity pattern generated by a functional group is 1,2-transposition of the functionality. Thus, the transposed precursor **389** has consonant β-hydroxy acid arrays that could be created by polar condensation of an acetate C-nucleophile with malonaldehydic acid as a carbonyl electrophile.

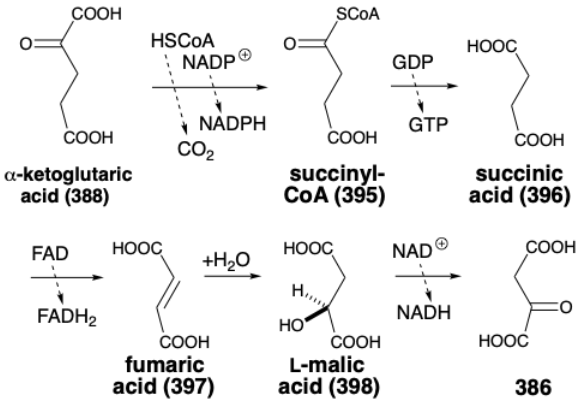


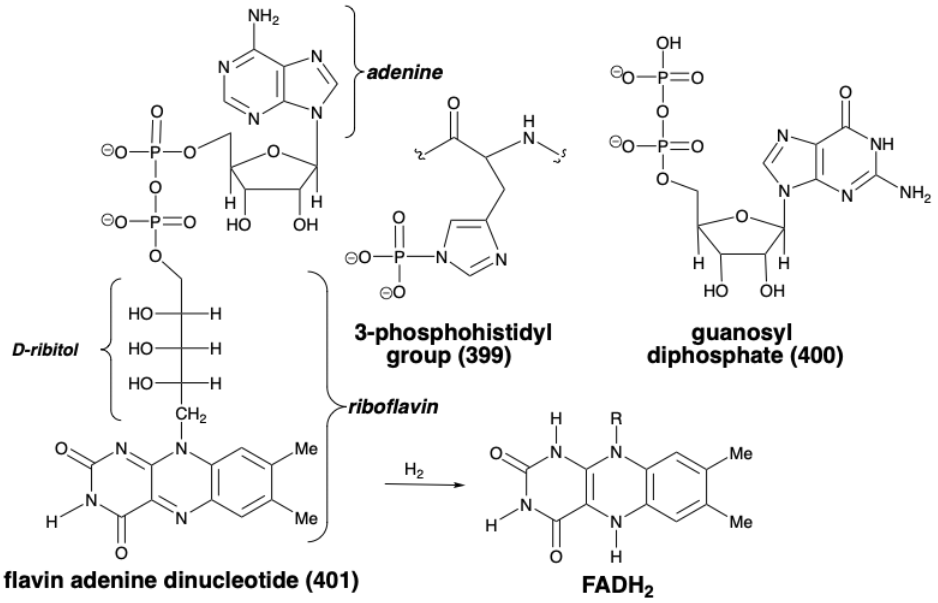
This polar strategy is adopted by Nature except that oxaloacetic acid (**386**) rather than malonaldehydic acid is used as the electrophile. This starting material has an extra carboxyl group that must be removed during the construction of **388**. The 1,2-oxygen transposition also creates a polar pathway for the requisite decarboxylation. The biosynthetic strategy also has other idiosyncrasies. Thus, besides a plan for assembling the carbon skeleton, the biosynthetic strategy for glutamic acid includes cogeneration of a reducing agent. We encountered a similar tactic in the biosynthesis of fatty acids from glucose (see section 3.1) where the conversion of glucose to the starting material, acetyl CoA, cogenerates all the reducing agent, NADPH, required for deoxygenation of β-ketoacyl intermediates. Nature's remarkable strategy for the biosynthesis of glutamic acid simultaneously generates a starting material, α-ketoglutaric acid **388**, and the requisite reducing agent, NADPH, for the subsequent reductive amination of **388** to produce **387**.



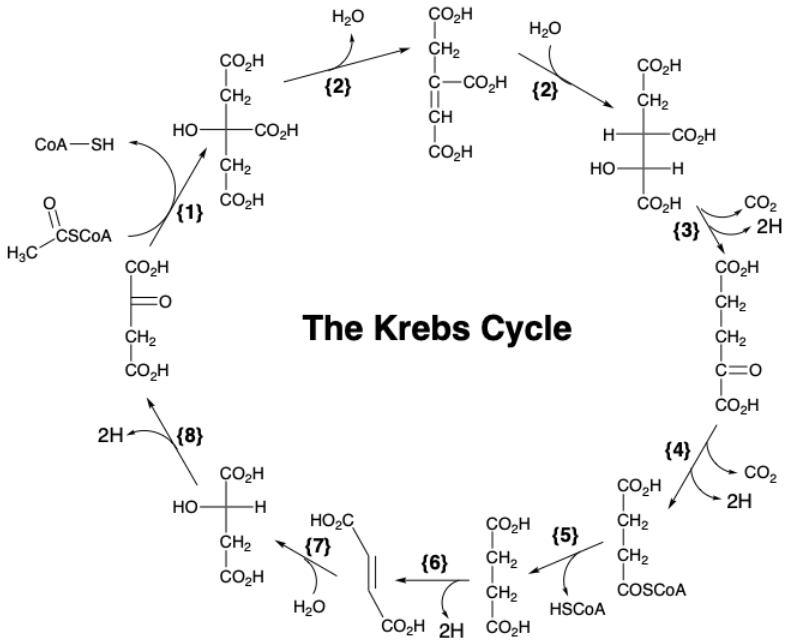
The biosynthesis begins with condensation of an acetyl CoA nucleophile with the highly electophilic carbonyl carbon of oxaloacetic acid to form citric acid (**390**). The reaction is catalyzed by the enzyme, citrate synthetase (or condensing enzyme). Dehydration of citric acid gives cis-aconitic acid (**391**) that is then hydrated to isocitric acid (**392**). Dehydrogenation of the latter is coupled with decarboxylation of a presumed β-ketoacid intermediate **393** to yield α-ketoglutaric acid (**388**). The hydrogen is transferred to NADP+ generating the NADPH needed for the nitrogen-fixing reductive amination of **388**. Thus, the protonated imine **394**, that is produced by reaction of the ketone carbonyl with NH_3, is reduced by hydride transfer from NADPH to deliver L-glutamic acid (**387**) with enzyme-induced enantioselectivity. This is an example of asymmetric induction by a homochiral reagent (the enzyme) during the reaction of a prochiral intermediate, the imine **394**.

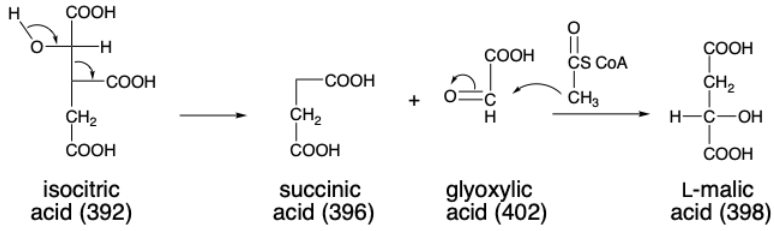
Interestingly, an oxidative pathway exists in Nature for conversion of α-ketoglutaric acid (**388**) back into oxaloacetic acid (**386**). Thus, oxidative decarboxylation of α-ketoglutaric acid occurs by the same thiamine pyrophosphate-catalyzed mechanism as for the pyruvate-acetate conversion (see section 2.3) that cogenerates NADH from NAD+. The initial product, succinyl CoA (**385**), is a high energy thioester. Its hydrolysis is coupled with phosphorylation of ADP, through an indirect process involving phosphorylation of a histidine residue of the hydrolyzing enzyme (see **399**), transfer of phosphate to guanosyl diphosphate (**390**, GDP), and finally, transfer of phosphate from the resulting GTP to ADP. Dehydrogenation of succinic acid (**396**) is then catalyzed by succinate dehydrogenase producing fumaric acid (**397**). The hydrogen is transferred to flavin adenine dinucleotide (**401**, FAD) producing $FADH_2$. The reversible hydration of fumaric acid to give L-malic acid (**398**) is catalyzed by fumarase, that promotes enantioselective stereospecifically trans addition of water to the symmetrical prochiral olefin. This is another example of asymmetric induction by a homochiral reagent, the enzyme fumarase. Finally, L-malate dehydrogenase catalyzes the oxidation of L-malic acid to oxaloacetic acid by transfer of hydride to NAD+.



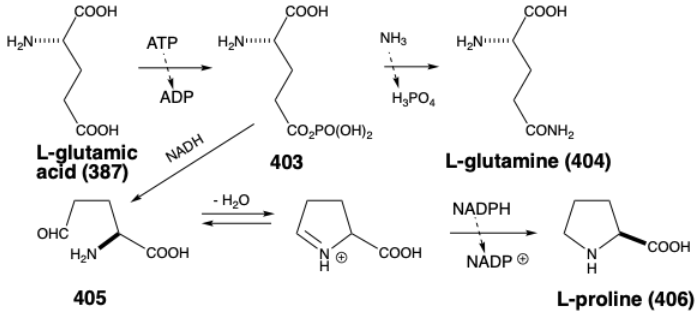


The overall process, generation of α-ketoglutaric acid from acetyl CoA plus oxaloacetic acid and regeneration of oxaloacetic acid from α-ketoglutaric acid also produces two molecules of CO_2, four molecules of reducing agent (2 x NADH, NADPH, and $FADH_2$), and one molecule of ATP. This cycle of reactions, known as the Krebs cycle or the tricarboxylic acid cycle (citric acid is a tricarboxylic acid) results in the aerobic oxidative catabolism of acetyl CoA. Besides providing a source of useful *reagents* for biosynthesis from fatty acids or sugars (via acetyl CoA), it also generates a variety of biosynthetically useful *intermediates*, e.g., α-keto glutaric acid) that can be diverted from the cycle. If Krebs cycle intermediates are to be removed from the cycle for biosynthesis, then other cycle intermediates must be generated somehow to replace them. The most important anaplerotic (filling up) reaction is the pyruvate carboxylase-catalyzed carboxylation of pyruvate to form oxaloacetate. Another modification of the Krebs cycle, known as the glyoxylate cycle, is important in plants and microorganisms for production of biosynthetic starting materials from acetyl CoA. Acetyl CoA condenses with oxaloacetic acid giving isocitric acid by way of citric and cis aconitic acids. But, rather than being oxidized to α-ketoglutaric acid, isocitric acid is cleaved to succinic and glyoxalic acids in a retro-aldol reaction that is catalyzed by isocitrase. Succinic acid may then be used for biosynthesis, while glyoxalic acid (**392**) reenters the Krebs cycle by malate synthetase-catalyzed condensation with aceyl CoA to form L-malic acid.

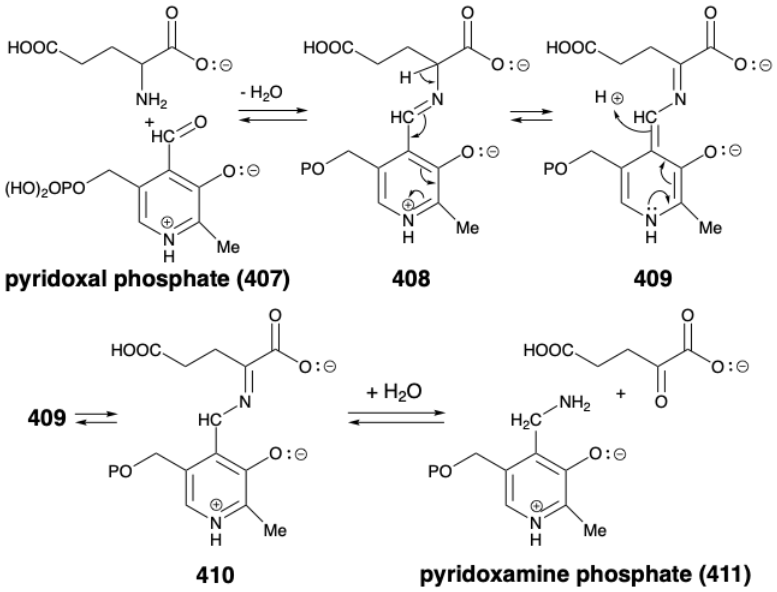




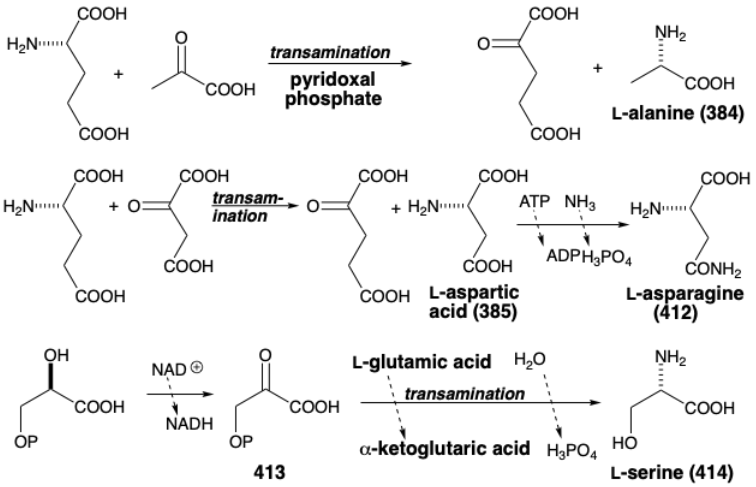
Glutamic acid is the direct biosynthetic precursor of glutamine (**404**) and proline (**406**). Activation of one carboxyl as a mixed phosphoric carboxylic anhydride (**403**) followed by acylation of NH_3 delivers **404**. Selective partial reduction of one carboxyl and intramolecular reductive amination of the resulting γ-amino aldehyde **405** delivers **406**.



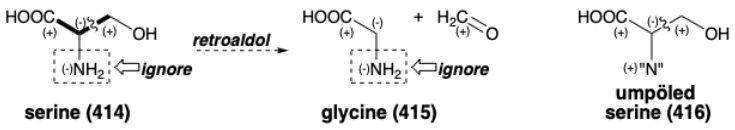
The biosynthesis of glutamic acid from α-ketoglutaric acid by reductive amination with ammonia is not typical. Generally, the conversion of α-keto acids into the corresponding amino acids involves transfer of an amino group from glutamic acid, a process called **transamination**. Pyridoxal phosphate (**407**) and divalent metal cations are cocatalysts for the transfer that occurs by a polar process. Thus, the imine from **4 0 7** and glutamic acid undergoes prototropic shift to generate the tautomer **4 0 9** . Rearomatization by another prototropic shift generates a new imine **410** that is hydrolyzed to pyridoxamine phosphate (**411**) and α-keto glutaric acid. Transamination is then completed by the reaction of an α-keto acid with **411** to produce the corresponding α-amino acid and regenerate pyridoxal by a process that is analogous to the reverse of the reaction that generates **411** plus α-keto glutarate from **407** plus glutamic acid.



Thus, transamination of pyruvic and oxaloacetic acids yields alanine (**384**) and aspartic acid (**385**), respectively. The biosynthesis of asparagine (**412**) from **385** parallels that of glutamine from glutamic acid (see above). Serine (**414**) is produced in Nature from 3-phosphoglyceric acid via oxidation to 3-phosphopyruvic acid (**413**), followed by transamination with glutamic acid.

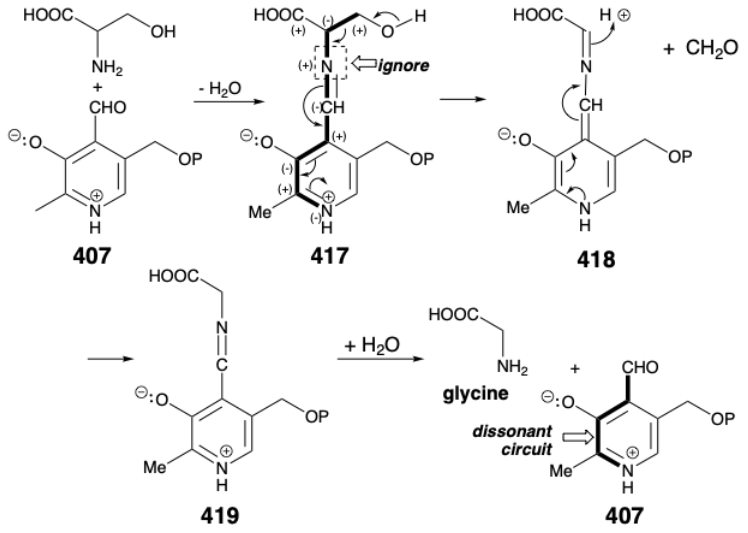


The consonant circuit between the carboxyl and hydroxyl groups of serine (**414**) suggests a polar strategy for the biosynthesis of glycine (**415**) involving retroaldol cleavage. The α-amino group is in a dissonant relationship with the other functional groups in **415** and, therefore, cannot assist in the polar cleavage. However, Nature adopts a strategy that allows the desired cleavage to occur under mild conditions by prior umpölung of the α-amino group as in **416** that has two functional groups stabilizing the buildup of electron density at the α-carbon.

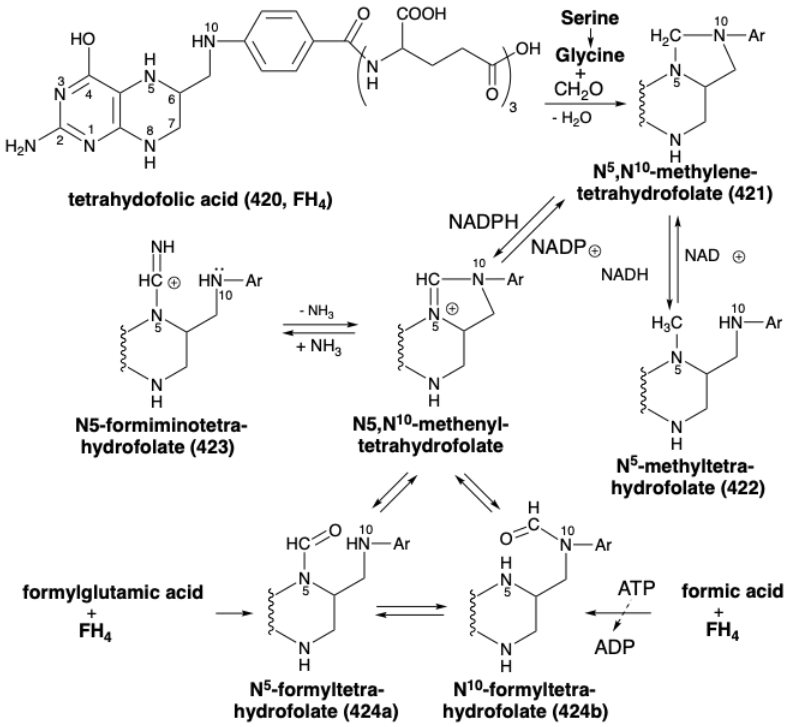


Pyridoxal phosphate (**407**) is the reagent, a **polar reactivity inversion operator**, that converts the amino group by a polar process into a derivative in **417** which stabilizes an anion at the α-carbon. It is instructive to consider how this process works. The key feature of the reagent **417** is a dissonant relationship between the aldehyde and pyridinium nitrogen. The electrophilic reactivity of the aldehyde carbon is used to form a C=N bond with the nucleophilic amino nitrogen in serine. The polar reactivity of this C=N bond is then ignored, and it is the dissonant pyridinium nitrogen in **417** that stabilizes the buildup of electron density on the serine α-carbon. The C=N bond derived from the serine amino group serves only to conjugate the pyridinium nitrogen with the serine α-carbon. Retroaldol fragmentation of **417** produces **418** and formaldehyde. The latter is captured by tetrahydrofolic acid (vide infra)

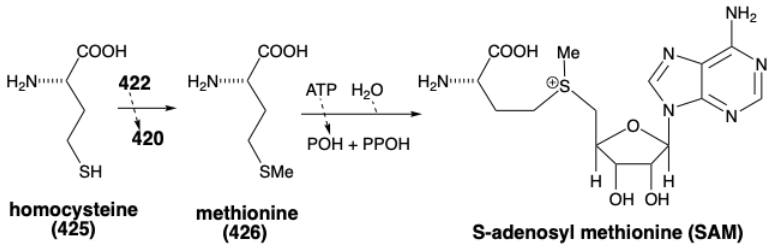
while **418** is rearomatized and protonated to produce an imine **419** of glycine. Hydrolysis produces glycine and regenerates pyridoxal phosphate that is, thus, a true catalyst for the retroaldol fragmentation.



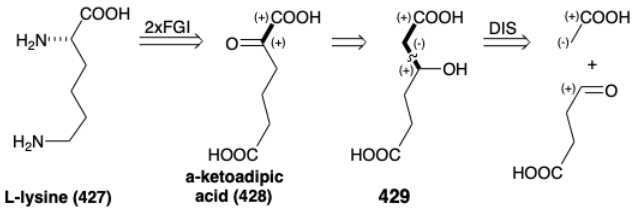
The formyl group lost in the conversion of **417** to **418** is transferred to tetrahydrofolic acid (**420**, **FH_4**). The product, N^5,N^{10}-methylene FH_4 (**421**), is one member of a family of folic acid coenzymes that *carry one-carbon groups*, such as methyl, formimino, and formyl in **422**, **423**, and **424**, respectively.



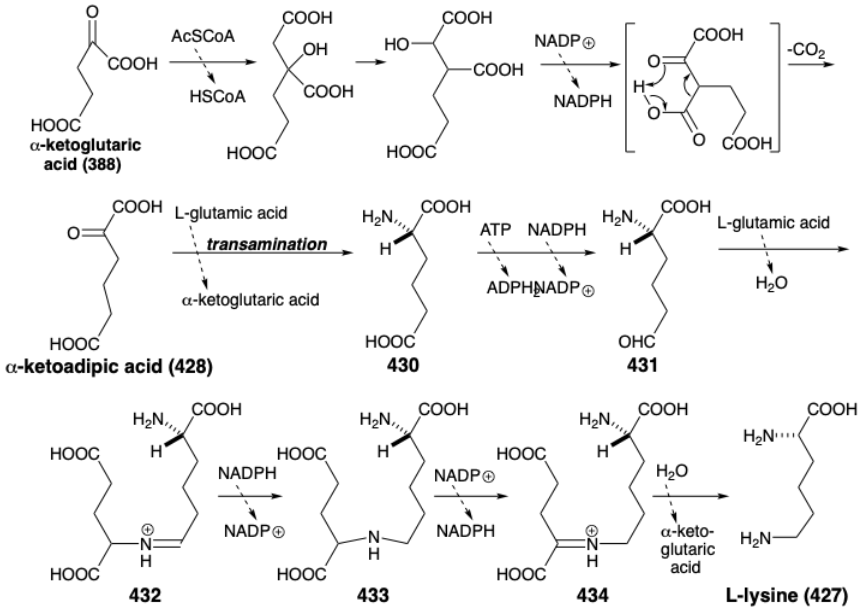
The major portion of these one-carbon transfers is achieved via methyl transfer to homocysteine (**425**) from N^5-methyltetrahydrofolate (**422**), which yields methionine (**426**) and, hence, S-adenosylmethionine (**SAM**+). Hence, serine and, ultimately, 3-phosphoglyceric acid is the source of the ubiquitous methyl groups donated by SAM+ to a wide variety of acceptors.



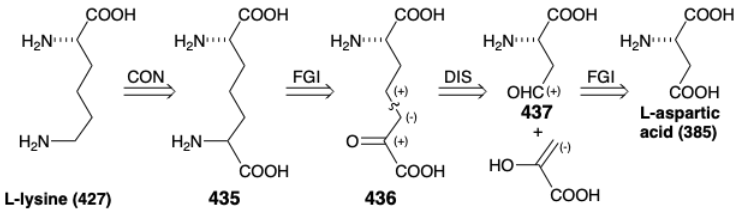
One biosynthetic strategy for L-lysine (**427**) is closely related to that involved in the biosynthesis of glutamic acid (see above). Thus, double reductive amination of a precursor α-keto diacid **428** could provide the two amino groups in **427**. A precursor **429** containing a consonant β-hydroxy acid array is suggested by 1,2-transposition of oxygen functionality in **428**. The precursor **429** could be created by polar condensation of an acetate C-nucleophile with succinaldehydic acid as a carbonyl electrophile.



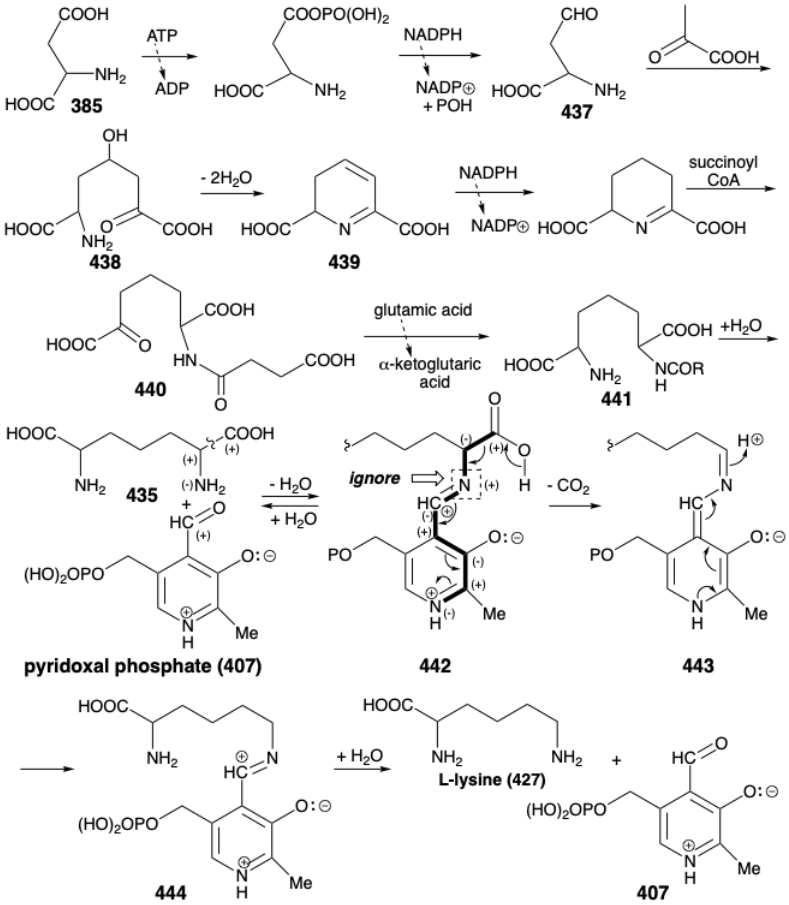
This is the biosynthetic strategy for lysine that is adopted by most fungi except that α- ketoglutaric acid (**388**) rather than succinaldehydic acid is used as the electrophile. The biosynthesis proceeds via α-aminoadipic acid (**430**) by a scheme commencing with a Claisen-Schmidt condensation between α-ketoglutaric acid (**388**) and acetyl CoA. Rearrangement, oxidation, and decarboxylation occur in reactions analogous to the conversion of oxaloacetic acid into α-ketoglutaric acid (see above). Transamination of the resulting a-ketoadipic acid (**428**) enantioselectively produces the L isomer of α-aminoadipic acid (**430**). Reduction of **430** to **431** followed by reductive alkylation of glutamic acid by **431** affords **433**. Oxidation followed by hydrolysis gives L-lysine (**427**). Note that the iminium group in **434** is stabilized relative to that in **432** owing to conjugation with the carboxyl in **434**.



An alternative strategy for the biosynthesis of L-lysine (**427**) generates the ε-amino array by decarboxylation of an α-amino acid group in a symmetrical precursor **435**, a process which can be catalyzed by pyridoxal phosphate (see below). As is common in α-amino acid biosynthesis, **435** could be derived from an α-keto acid precursor **436**. The carbon skeleton of this ketone can be assembled by an aldol condensation between a pyruvic acid enolate and an aldehyde electrophile **437** derived from L-aspartic acid (**385**).



The primary route for biosynthesis of L-lysine in bacteria and higher plants generates a seven carbon diacid intermediate **438** from the three carbons of pyruvic acid and four carbons of aspartic acid (**385**). Reduction of **385** to the aldehyde **437** with concomitant hydrolysis of ATP is analogous to the reduction of 3-phosphoglyceric acid (**3PG**) to glyceraldehyde-3-phosphate (**G3P**) (see section 2.1) and the production of **431** from **430**. Aldol condensation of **437** with pyruvic acid delivers **438**. Intramolecular imine formation and dehydration produces **439** that is reduced and then hydrolyzed and succinoylated to produce a masked (N-succinylated) derivative **440** of 2-amino-6-ketopimelic acid. Transamination and hydrolysis of the resulting amino amide **441** delivers diamine **435**. Monodecarboxylation of this α-amino acid, catalyzed by pyridoxal phosphate, then delivers L-lysine (**427**). As in the pyridoxal phosphate-catalyzed retro-aldol cleavage of serine to glycine (see above), pyridoxal serves as a ***polar reactivity inversion operator*** that temporarily converts the amino group by a polar process into a derivative in **442** which stabilizes electronic excess at the α-carbon. The consonant circuit between the pyridinium nitrogen and carboxyl carbon in **442** (ignoring the polar reactivity of the imine group) facilitates polar cleavage of a C-C bond generating the imine **443**. Aromatization by prototropic shift then produces **444**. Finally, the polar reactivity of the imine is utilized to achieve hydrolysis, releasing the amine **427** and regenerating the aldehyde catalyst **407**.



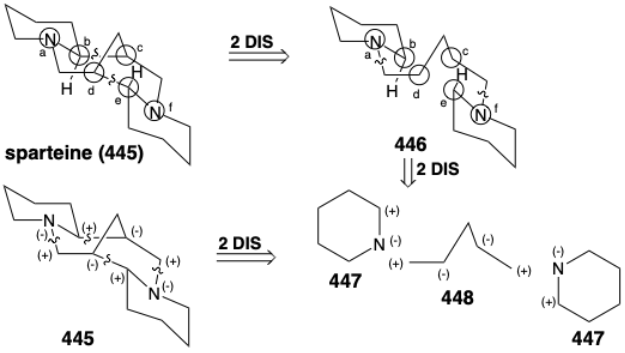
Note that both the α-amino acid array in **435** and the amino aldehyde array in **407** incorporate dissonant circuits. It is the polar union of one functional group in each dissonant reactant (**407** and **435**) that creates a consonant relationship between the remaining functional groups in these molecules. Thus, umpölung of the amino group in α-amino acids is accomplished by a dissonant difunctional reagent, pyridoxal pyrophosphate. Previously umpölung of the ketone carbonyl group in α-keto acids was encountered in the cyanide ion catalyzed benzoin condensation (section 2.1), in the thiamine pyrophosphate (**TPP**) catalyzed transketolase

reaction (section 2.1), and in the TPP catalyzed decarboxylation of pyruvic acid (section 2.2). It is now instructive to note that both HC≡N and TPP contain biphilic functionality. They are both readily metallated (i.e. deprotonated). This introduces a nucleophilic functional group (the carbanion) in a dissonant relationship with other functionality in these molecules, and allows them to serve as catalytic ***polar reactivity inversion operators***. One of the functional groups, the nucleophilic carbanion, is exploited to link the catalyst to the ketol or aldehyde carbonyl, in the transketolase or benzoin reactions respectively, or the α-keto acid carbonyl in the pyruvate decarboxylation reaction. The other functionality in the catalyst then stabilizes electronic excess at the formerly electrophilic ketone or aldehyde carbonyl carbon.

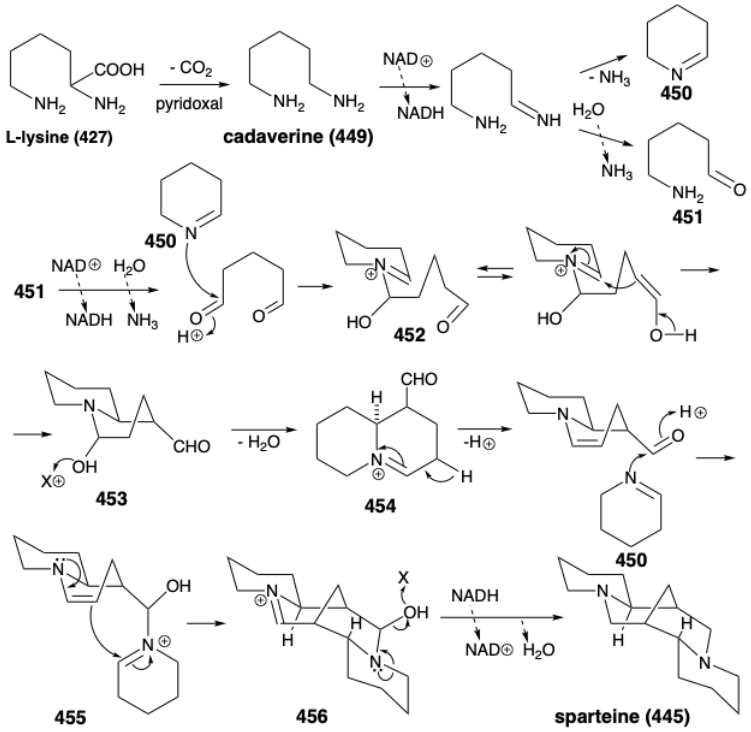
6.7: Lycopodine

Biosynthesis of Alkaloids from L-Lysine

A variety of topolgically complex saturated nitrogen heterocycles are constructed in nature from simple acyclic precursors. The incisive logic of these biosyntheses is especially striking when viewed either from a topological or a polar reactivity standpoint. For example, the *efficiency* with which the intricate multicyclic skeleton of sparteine (**445**) is assembled, exclusively from three molecules of a symmetrical synthon, is remarkable. Topological analysis of **445** reveals the presence of six common atoms a-f. Cleavage of two bonds between two pairs of common atoms, b-c and d-e, simplifies the topology to two piperidine rings joined by a straight chain in **446**. This intermediate is readily derived from two five carbon synthons **447** and **448**. Polar reactivity analysis of **445** reveals that polar reactions, activated by the amino groups in **445** should readily allow its construction from **447** and **448**.



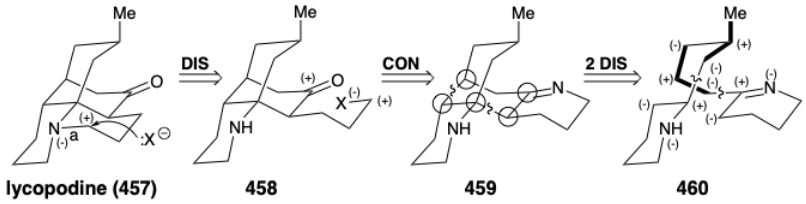
In fact, functionalized synthetic equivalents for both **447** and **448** are prepared in nature from L-lysine (**427**). Thus, pyridoxal catalyzed decarboxylation of **427** produces the symmetrical diamine **449**. Oxidation and hydrolysis of **449** via **451** afford pentanedial, which provides iminium derivative **452** by reaction with **450**. Intramolecular aldol condensation then affords **453**. The iminium derivative **454** from dehydration of **453** yields an iminium derivative **455** by reaction of the corresponding enamine with a second equivalent of the imine **450**. A second intramolecular aldol condensation affords **456**. Dehydration and reduction provides sparteine (**445**).



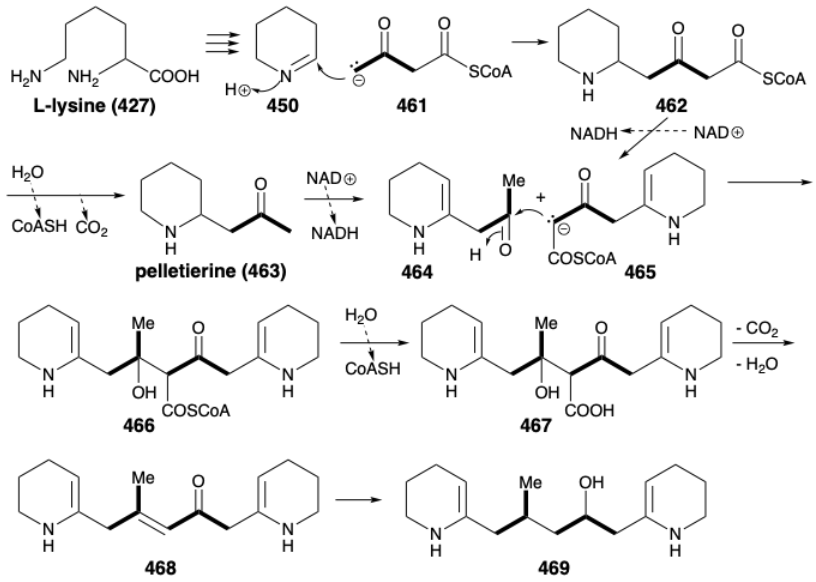
Biosynthesis of Lycopodine

We have seen that many natural products are formed from a single starting material, such as (a) many polyketides, fatty acids, or prostaglandins from acetyl CoA, (b) many alkaloids from shikimic acid, or (c) terpenes from mevalonic acid. However, some natural products are formed by ***mixed biosyntheses*** from combinations of these starting materials. Thus, lysergic acid (see section 6.4) arises from chorismic acid plus the mevalonic acid-derived isopentenyl pyrophosphate plus a sugar, D-ribose. Similarly, indole alkaloids (see section 6.5) arise from chorismic acid plus a mevalonic acid-derived terpene, secologanin, plus a sugar, D-ribose.

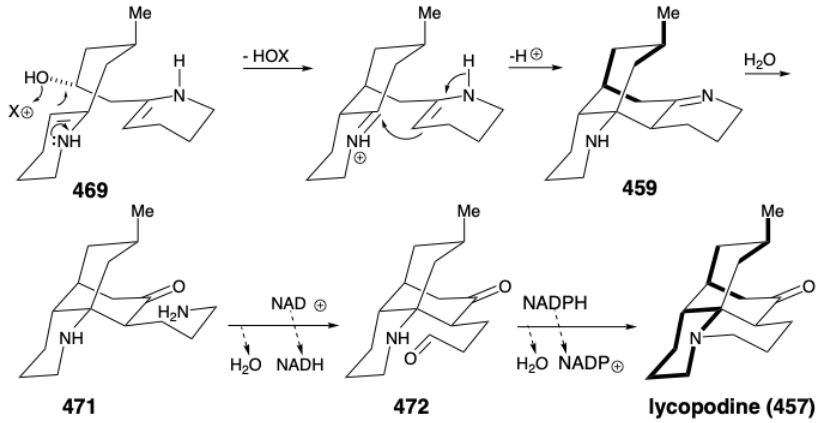
Now we shall see that the bridged multicyclic skeleton of the alkaloid lycopodine (**457**) arises from acetoacetyl CoA plus L-lysine (**427**). As for sparteine above, both topological and polar analysis of the biosynthetic strategy for **457** reveal its incisive logic. The carbonyl group in **457** is generated in nature by solvolytic cleavage of a temporary bridge. In the process, a propyl substituent with electrophilic activation at the end is generated, that is then used to construct the final ring of **457**. Retrosynthetically, this involves disconnection to **458**, followed by reconnection to **459**. A considerable simplification of this subtarget results from disconnection of two bonds between pairs of common atoms in **459** to afford **460**. Polar analysis of **460** reveals that reconnection of these bonds could be achieved by exploiting the polar activation provided by the nitrogen atoms in **460**. Furthermore, **460** could be assembled from two large fragments by a polar reaction forming any of the bonds in the carbon chain connecting the two nitrogen heterocycles.



In nature, the two piperidine rings in **460** are derived from L-lysine (**427**), and the connecting chain is assembled from two three carbon units derived from actetoacetyl CoA (**461**). Aldol condensation of **461** with **450** affords **462**. Note that alkylation of **461** occurs at the less acidic δ carbon. Perhaps this involves an enzyme-bound enamine derivative **470** (see below) of **461**. Oxidation and deprotonation of **462** provides **465**, while **462** also yields pelletierine (**463**) by hydrolysis and decarboxylation. Aldol condensation between **464** and **465** then provides **466**, that is hydrolyzed to **467**. Decarboxylative elimination gives **468**, that is reduced to provide **469**, a synthetic equivalent of the synthon **460** generated in the strategic analysis presented below.

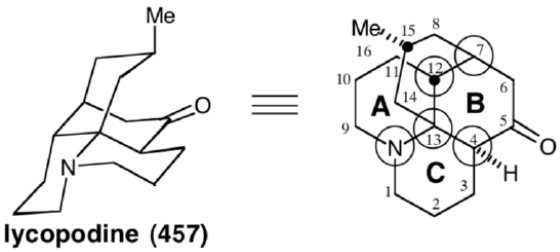


Cyclization of **469** by intramolecular enamine alkylation, followed by intramolecular aldol-like condensation, produces the intermediate **459** suggested in the strategic analysis. Hydrolysis of the imine in **459** generates the carbonyl group required for lycopodine. Oxidation of the resulting propyl amine **471** to an aldehyde **472** followed by intramolecular reductive alkylation then produces lycopodine (**457**) in which one lysine derived piperidine ring is clearly discernable while the two polyketide derived acetonyl units and a five carbon unit from a second molecule of lysine are intricately interwoven.

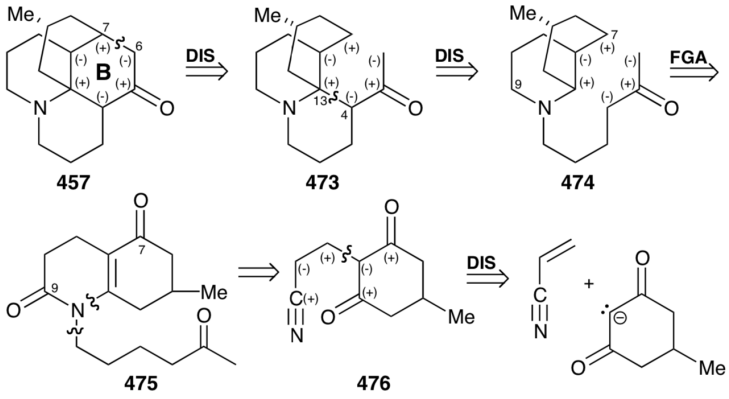


A Fatally Flawed Strategy for Lycopodine Synthesis

We have seen that both topological and polar analysis of the biosynthetic strategy for lycopodine (**457**) illuminate the logic of the process. The two functional groups in **457** can be exploited in a variety of strategies to facilitate construction of the skeletal network using polar reactions. There are five *common atoms* in **457**, four carbon atoms that are all in ring B, and the nitrogen. We will first consider a fatally flawed strategy that only generates an epimer rather than the natural product itself.

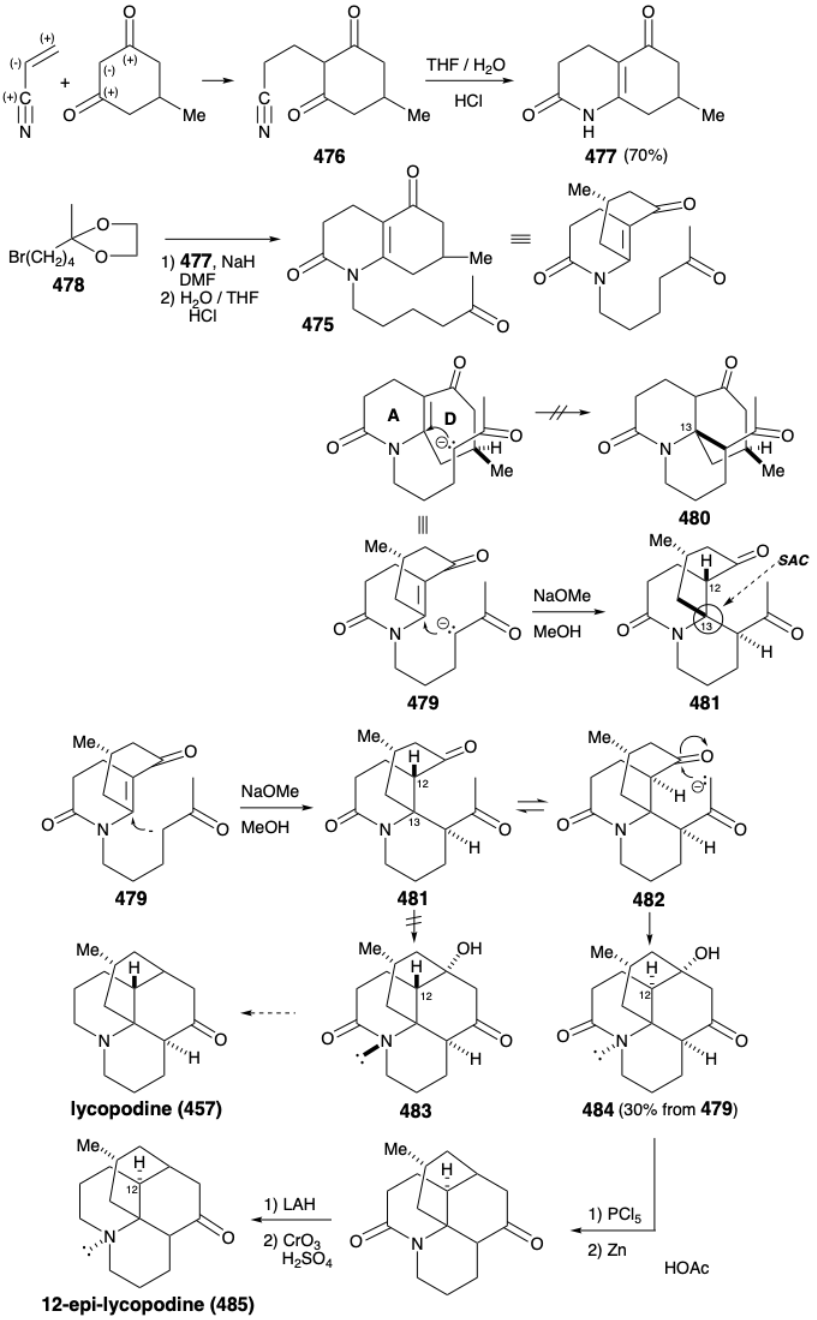


Polar analysis of ring B reveals that polar reactions, exploiting the polar activation afforded by the amino and carbonyl functionalities in **457**, could be used to construct any bond of this ring. In the Wiesner approach to lycopodine,19 the final skeletal bond formed is between common atom 7 and noncommon atom 6, corresponding to the dislocation of **457** to **473**. The penultimate bond formed is that between common atoms 4 and 13, corresponding to the dislocation of **473** to a bicyclic precursor **474**. The elegance of the strategy lies in the plan to accomplish cyclization of the bicyclic intermediate **474** to the tetracyclic skeleton of the target **457** in a single step. The synthetic equivalent **475** of **474** has additional carbonyl groups at the 7 and 9 positions. The former provides additional electrophilic activation at C-7, while the latter deactivates the nucleophilicity of the amino group. The bicyclic intermediate **475** might be available from a symmetrical monocyclic precursor **476**. The incipient amino group of **457**, the nitrile nitrogen in **476**, even provides polar activation for the construction of **476** from acrylonitrile and dihydroresocinal.



In fact, acid-catalyzed hydrolysis of **476** leads directly to the enamide **477** that afforded **475** by N- alkylation with the alkyl bromide **467** and subsequent hydrolytic removal of the masking ketal group. Base-catalyzed intramolecular Michael reaction of **475** could generate two stereoisomers at position 13 which result from addition of the carbanion to either face of the D-ring in **479**.

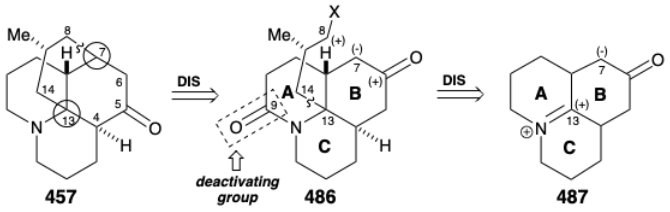
However, as expected, steric approach control fosters stereoselective addition on the side of the D-ring opposite the methyl substituent to afford an intermediate **481** rather than undesired stereoisomer **480**. Nevertheless, the synthesis is fatally flawed because the subsequent aldol reaction gave exclusively **484**, whose skeleton is epimeric with lycopodine at a C12. Thus, C-12 in the intermediate **481** is epimerizable, and the epimer **482** apparently cyclizes in complete preference to **481**. This produces **484** rather than **483**, that is required for the synthesis of lycopodine (**457**) . Reductive removal of the amide carbonyl and tertiary hydroxyl groups from **484** delivered 12-epi-lycopodine (**485**).



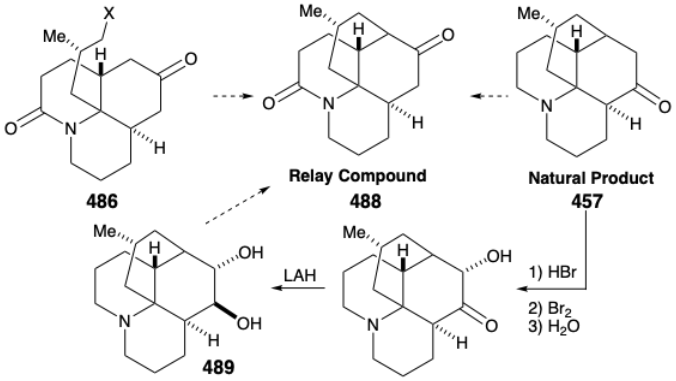
A Relay Strategy and a Symmetrical Precursor for Lycopodine

A second strategy for lycopodine synthesis generates ring D by cyclization of a tricyclic synthon **486** with preformed AB and C rings.[20] This strategy was channeled by the prospect of exploiting a symmetrical fused tricyclic ketone **487** as a starting material. Thus, topological analysis of **457** recommends disconnection of two bonds between a common (circled) and a noncommon atom, the 7-8 and 13-14 bonds, to entirely remove the D-ring. A concomitant transposition of the carbonyl group from C-5 in **457** to C-6 is required to generate a symmetrical precursor **487**. Furthermore, this transposition in **486** allows formation of the 7-8 C-C bond of

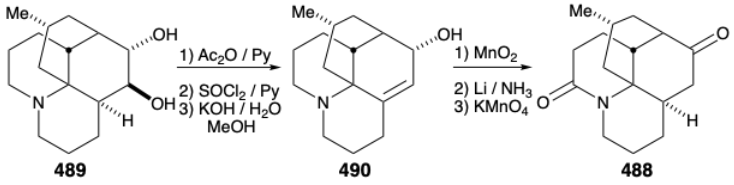
the lycopodine skeleton by an intramolecular alkylation that exploits the polar activation afforded by a carbonyl at position 6. Whereas, the nitrogen in **486** can provide electrophilic activation for C-C bond formation at position 13 in **487**. An amide carbonyl at C-9 in **486** is included as a **deactivating group** to decrease the nucleophilicity of the amino group disfavoring an undesired quaternization that might compete with alkylation of a carbanion nucleophile at C7.



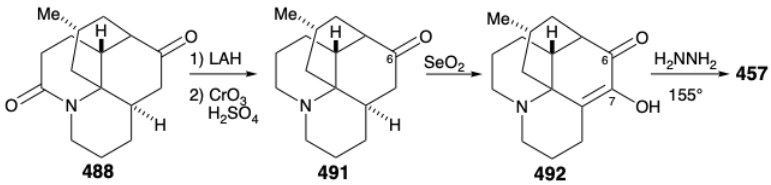
Intramolecular alkylation of the ketone 4**86** would yield **488**. It would be reassuring if the final steps in the synthesis could be worked out with a sample of **488** that might be readily prepared from the natural product **457**, perhaps via the diol **489**, that had already been prepared from **457** during structural studies on the lycopodium alkaloids. This sample of compound **488** could then be used, instead of the synthetic material, to work out the details of the conversion of **488** to **457**. This is another example of the strategem known as the *relay approach*, that we saw employed in syntheses of erythronolide B (see section 5.4) and quinine (see section 6.5). The advantage of this approach is that a valuable key intermediate can be obtained readily in quantity. The ***relay compound*** (e.g. **488**) becomes the target of the synthesis.



Let us first consider the *interconversion* of the relay compound **488** and **457** before examining the *total synthesis* of the relay compound. To differentiate the hydroxyls at positions 5 and 6, the diol **489** from natural lycopodine (**457**) was monoacetylated at the sterically most accessible C-6 hydroxyl. Dehydration followed by hydrolysis afforded **490**. Oxidation of the allylic hydroxyl followed by reduction of the resulting α,β-unsaturated ketone and permanganate oxidation α to the tertiary amine gave the proposed relay compound, amide **488**, in 13% overall yield from natural lycopodine (**457**).

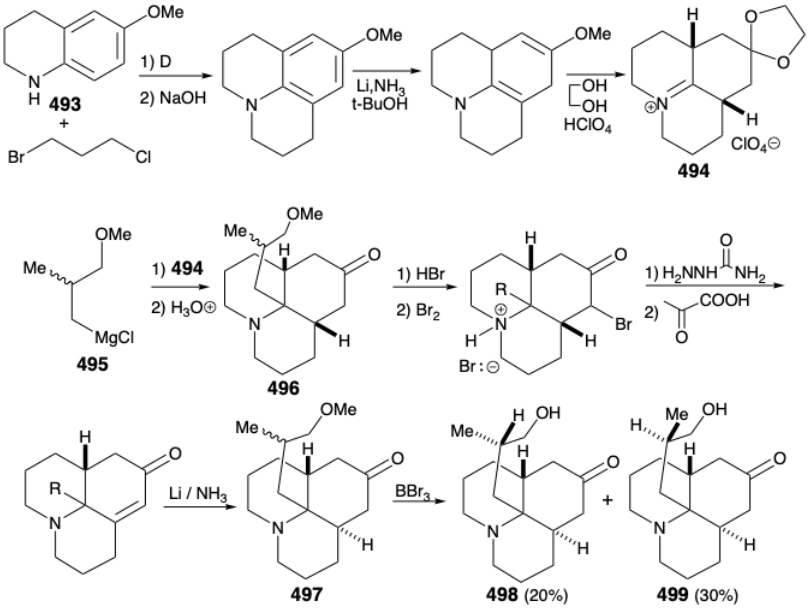


Reconversion of the relay compound **488** into lycopodine (**457**) was then achieved by removal of the amide carbonyl, by reduction with LAH, and oxidation of the resulting C-6 epimeric alcohols. The amino ketone **491** was then oxidized to the diosphenol **492**, that was reduced selectively by a Wolff-Kishner reaction with hydrazine hydrate to afford lycopodine (**457**).

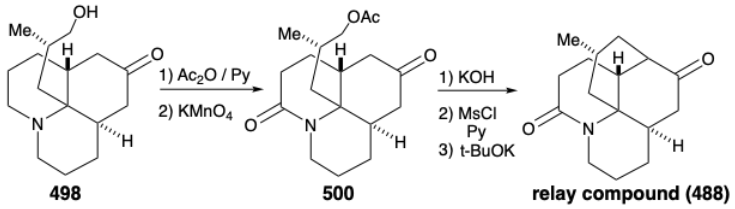


As noted above, a synthesis of **486**, and hence the relay compound **488**, *from a symmetrical starting material* was envisioned (see above). In particular, **486** might be prepared from **487** by reaction with a nucleophilic side chain synthon. With a provision for

masking the electrophilicity of the carbonyl group, this strategy proved viable. Thus, **494** was prepared from thalline (**493**) by alkylation with 1-bromo-3-chloropropane followed by dissolving metal reduction and ketalization. Reaction of **494** with the nucleophilic fragment **495** followed by hydrolysis gives the cis,cis-fused tricyclic amine **496**. Ring closure of this epimer is impossible. Epimerization to the trans,cis isomer **485** must precede ring closure. Therefore, epimerization was accomplished by exploiting the carbonyl functionality in **496** by bromination followed by Mattox-Kendall dehydrobromination and dissolving metal reduction. Demethylation of the product **497** then afforded a mixture of racemic diastereomeric ketones **498** and **499**. These were separated by chromatography on alumina. The *minor* isomer **498** possessed the natural relative configuration of the methyl substituent. Thus, the present synthesis is nonstereospecific, and a near fatal major loss of valuable material occurs owing to the formation of an unwanted stereoisomer **499**.

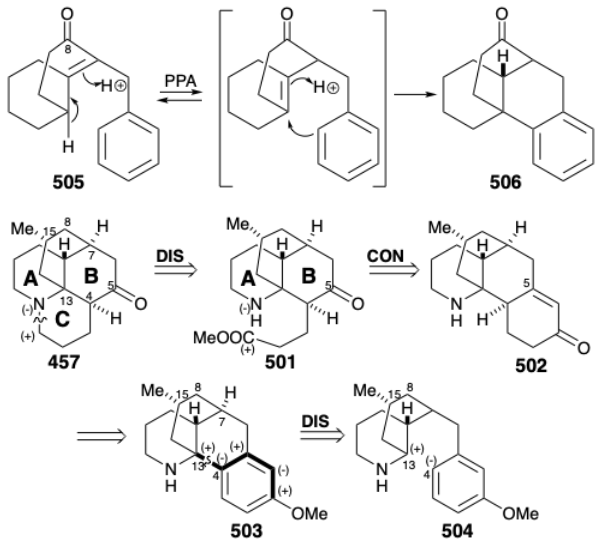


Before intramolecular alkylation of the tricyclic ketone could be accomplished, the nucleophilicity of the amino group had to be attenuated by conversion of the amino group in **498** into an amide **500** to avoid N-alkylation. Saponification, mesylation, and intramolecular alkylation then provided the relay compound **488** in racemic form. Since **476**, albeit homochiral, derived from natural lycopodine (**457**) had already been converted to **457** as discussed above, the total synthesis was complete.

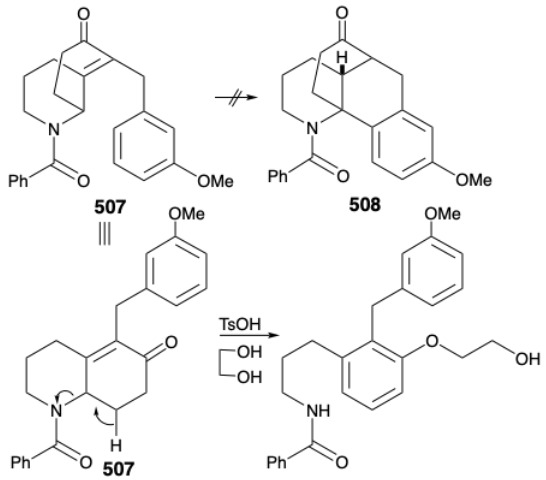


An Unintentionally Biomimetic Strategy

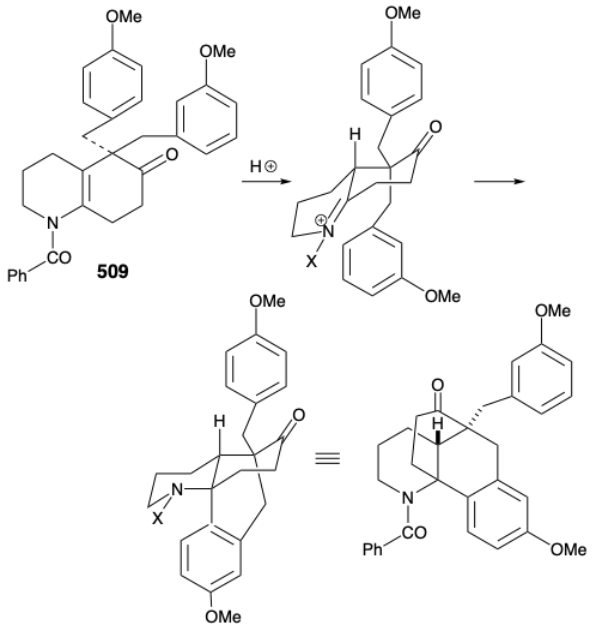
In the two strategies for lycopodine (**457**) discussed above, one generated ring B last and one generated ring D last. Now we shall consider a strategy that generates ring C last as found in the biosynthesis of **457**. Moreover, in further analogy with the biosynthetic strategy, the three carbon chain substituent on ring B of **501**, that is the used to complete ring C, is incorporated into a temporary ring in a precursor **502** by attachment at the (latent) carbonyl carbon at C-5. Finally, the consonant circuit between the amino and methoxy groups in the aromatic precursor **503** suggests a polar construction from **504** of the 4-13 C-C bond, again in analogy with the biosynthetic strategy, by attack of a C-13 electrophile on a nucleophilic center at the incipient C-4. However, this strategy was conceived before the biosynthesis of lycopodine had been elucidated. In the words of the author of the strategy, "although the particular synthetic plan followed for the construction of the tetracyclic system had no particular basis in biogenetic considerations, very recent work has suggested a biogenetic pathway in which the crucial cyclization step is strikingly similar to the one we devised."[21]



Before we consider the successful implementation of this plan, it is instructive to note that it was developed with the aid of lessons learned during attempts to achieve a synthesis using other, fatally flawed, strategies. One unsuccessful early plan for a transformation analogous to the generation of **503** from **504** was supported by successful model studies. Thus, a carbocyclic model **505** readily underwent an analogous cyclization to **506** on heating with polyphosphoric acid. It was anticipated that the methyl substituent at position 15 on the D-ring of **504** could be introduced subsequently by exploiting the nucleophilic activation afforded by a carbonyl group at position 8. Furthermore, the inclusion of this carbonyl group could enhance the general utility of the synthesis because oxygen substitution is found at position 8 in many lycopodium alkaloids. However, in contrast to the carbocyclic model **505**, cyclization of the heterocyclic analogue **507** to give **508** could not be achieved. Rather **507** was apparently prone toward elimination leading to aromatization.

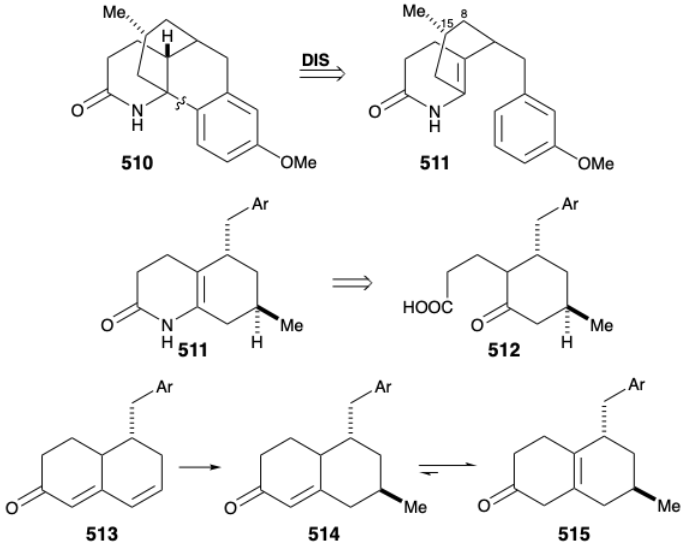


Nevertheless, an encouraging observation emerged from this model study. Thus, the dialkylated derivative **509**, a byproduct in the synthesis of **507**, underwent the desired type of cyclization. The success of this cyclization seemed attributable to two factors, an *axial orientation* of a benzyl substituent and *blocking of the elimination pathway*.

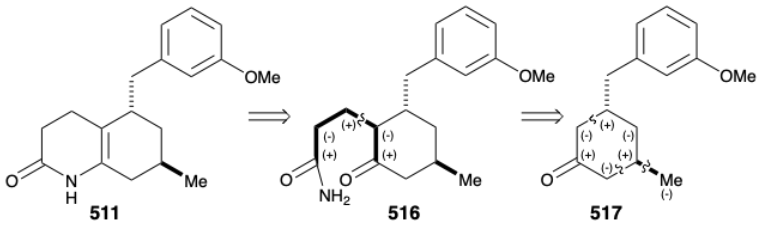


A modified strategy was then devised in which the methyl substituent required at position 15 was introduced prior to the annelation of ring B and the carbonyl group at position 8 was deleted. Moreover, the stereochemistry of this methyl substituent in lycopodine dictated a *trans* relationship of the methyl and m-methoxybenzyl groups in the new subtarget. The functionalized derivative chosen to embody these requirements was **511**. It was further recognized that the *trans* methyl subtituent in **511** should virtually eliminate the energy barrier to achieving the axial orientation of the benzyl substituent required for cyclization to **510**.

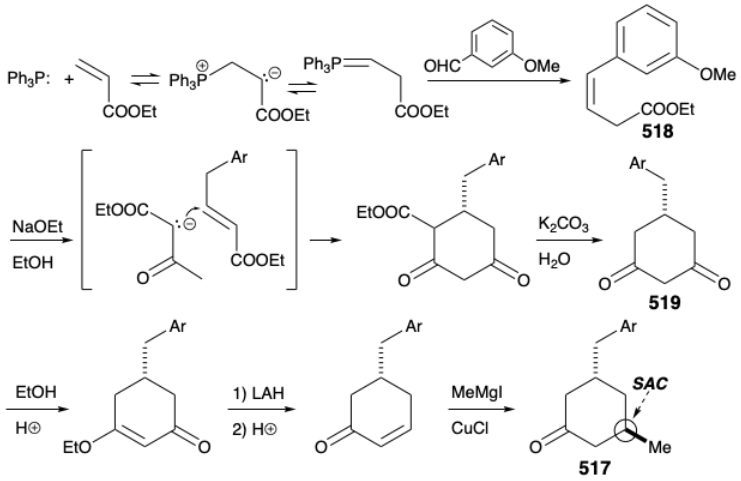
Several strategies were explored for synthesis of the subtarget **511**, that is obviously derivable from **512**. An approach to **512** via conjugate addition of a methyl nucleophile to **513** followed by oxidative cleavage of the cyclohexenone **514** was precluded by the proclivity of **514** to isomerize into the β,γ-unsaturated isomer **515**.



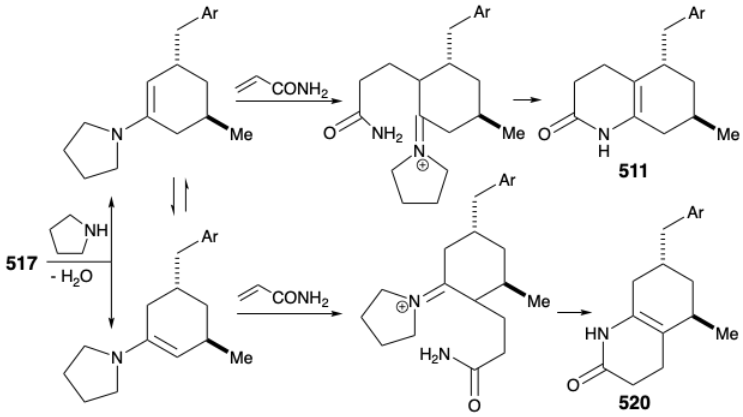
A second approach to **511** exploits the consonant circuit between the carbonyl carbon and enamide nitrogen in **511** or the related consonant circuit between the two carbonyl groups in keto amide **516**. Disconnection of the three carbon side chain suggests a cyclohexanone precursor **517** that can be generated by polar connections activated by the carbonyl group.



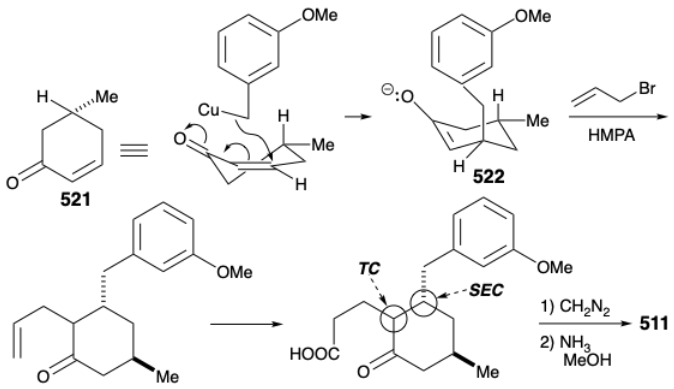
Cyclohexanone **517** was prepared by polar reactions between an acrylic ester and acetoacetic ester. Thus, a symmetrical dione **519** was generated from β,γ-unsaturated ester **518** by prototropic allylic rearrangement, followed by Michael addition of ethyl acetoacetate, Dieckmann cyclization, hydrolysis, and decarboxylation. Selective reduction of only one carbonyl group in **519** was facilitated by masking the second carbonyl of this dione as a vinylogous ester. Acid-catalyzed dehydration then provided a cyclohexenone that delivered **517** upon stereoselective 1,4-addition of a methyl nucleophile.



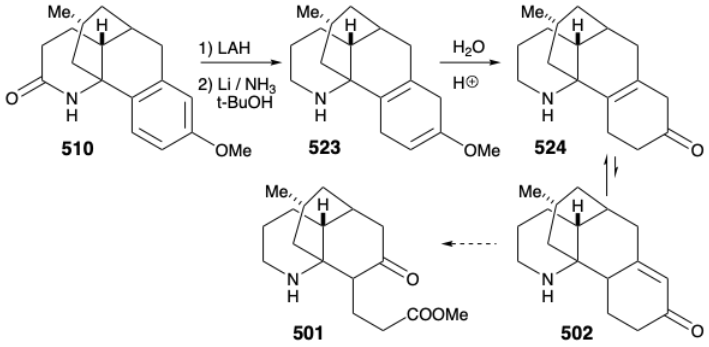
The original strategy for construction of key intermediate **511** from cyclohexanone **517** had one major shortcoming. Thus, conversion of **517** into **511** requires regioselective Michael alkylation. However, alkylation of **517** occurred nonregioselectively at both carbons α to the carbonyl producing a mixture of **511** and **520**.



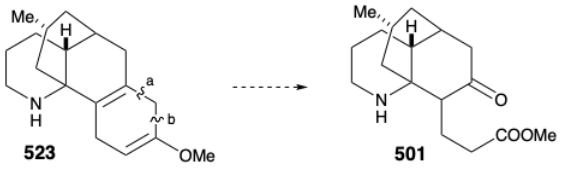
An improved, completely *structurally specific* synthesis of the subtarget **511** was finally devised that exploited regiospecific generation and electrophilic trapping of the enolate **522**. This was achieved by Michael addition of a benzyl nucleophile to the cyclohexenone **521**. The resulting regiospecific enolate was then alkylated with allyl bromide. The process is also highly stereoselective owing to a preference for axial attack in Michael additions of organocopper nucleophiles and a preference for an equatorial disposition of the methyl substituent in **521**. Furthermore, the required trans relationship between the allyl and benzyl substituents is assured by thermodynamic control owing to epimerizability α to the ketone carbonyl. Hydroboration and oxidation of the allyl side chain, esterification, and reaction of the resulting ketoester with ammonia afforded the key intermediate **511**.



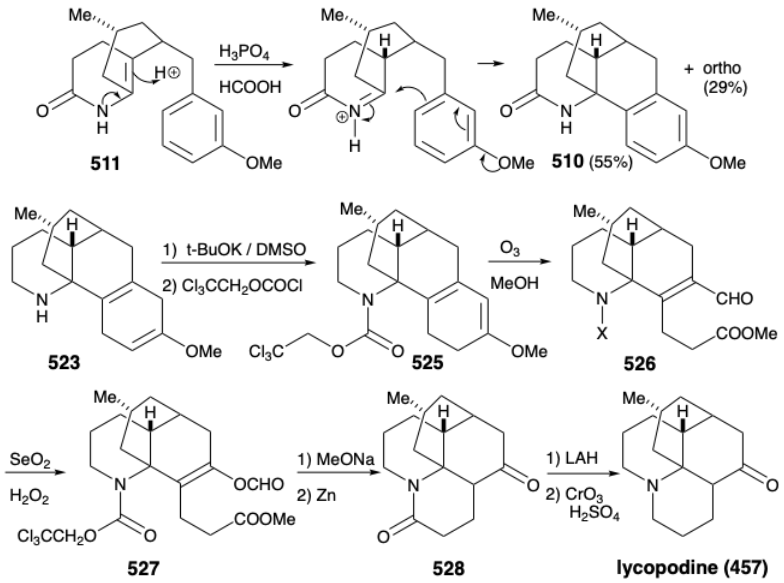
Intramolecular electrophilic aromatic substitution gave mainly the desired *para* substituted cyclization product **510** (55%) together with some *ortho* substitution product (29%). The amide carbonyl was then removed by reduction with LAH, and the protective aromaticity of the aryl ring was removed by Birch reduction. A plan to effect ring cleavage by oxidation of an α,β-unsaturated cyclohexenone failed owing to a thermodynamic preference for the required enone **502** to exist as the corresponding β,γ-unsaturated tautomer **524**.



Once again, therefore, an alternative strategy had to be formulated. The original plan for generating **489** from **497** was fatally flawed. Indeed, while the each step in the original plan was well precedented, so was the likelihood that **502** would be in equilibrium with a substantial amount of **524**. Indeed, this same problem derailed an attempted synthesis of **512** from **514** (see above). As is so often the case, a shortcoming of well-known methodology for achieving an important synthetic goal, especially if it impedes the conclusion of an ambitious total synthesis, inspires the application of novel chemistry to provide a solution to the dillema. Necessity is the mother of invention! Thus, generation of **501** from **523** required oxidative cleavage of two bonds, "a" and "b", in the cyclohexadiene ring. The original plan called for cleavage of bond "a" first after an isomerization that placed a readily cleavable C=C bond in this position. In the alternative strategy, bond "b" is cleaved first after an isomerization that placed a readily cleavable C=C bond in this position.



Thus, the 1,4-cyclohexadiene **523** was isomerized to a conjugated 1,3-diene, and the amino group was masked to protect it from oxidation. Selective ozonolysis of the more electron rich C=C bond in **525** then afforded the aldehydo methyl ester **526**. An unusual Baeyer-Villager oxidation of **526** gave the enol formate **527** that afforded keto amide **528** after methanolysis of the enol ether, removal of the carbamate protecting group from the amino nitrogen, and lactamization. The amide carbonyl was then removed to provide lycopodine (**457**) by reduction with LAH followed by reoxidation of the C-5 hydroxyl to the required C-5 carbonyl group.



6.8: Terminology

For definitions see the sections listed.

deactivating group (section 6.7)

polar reactivity inversion operator (section 6.6)

polar redox reaction (section 6.5)

pyridoxal phosphate (section 6.6)

transamination (section 6.6)

6.9: Study Questions

6.10: References

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Glossary

Sample Word 1 | Sample Definition 1

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