# LOGIC OF ORGANIC SYNTHESIS

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R. Balaji Rao



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# Licensing

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# 1: Synthesis of Organic Molecules

Wöhler synthesis of Urea in 1828 heralded the birth of modern chemistry. The Art of synthesis is as old as Organic chemistry itself. Natural product chemistry is firmly rooted in the science of degrading a molecule to known smaller molecules using known chemical reactions and conforming the assigned structure by chemical synthesis from small, well known molecules using well established synthetic chemistry techniques. Once this art of synthesizing a molecule was mastered, chemists attempted to modify bioactive molecules in an attempt to develop new drugs and also to unravel the mystery of biomolecular interactions. Until the middle of the 20th Century, organic chemists approached the task of synthesis of molecules as independent tailor made projects, guided mainly by chemical intuition and a sound knowledge of chemical reactions. During this period, a strong foundation was laid for the development of mechanistic principles of organic reactions, new reactions and reagents. More than a century of such intensive studies on the chemistry of carbohydrates, alkaloids, terpenes and steroids laid the foundation for the development of logical approaches for the synthesis of molecules.

The job of a synthetic chemist is akin to that of an architect (or civil engineer). While the architect could actually see the building he is constructing, a molecular architect called Chemist is handicapped by the fact that the molecule he is synthesizing is too small to be seen even through the most powerful microscope developed to date. With such a limitation, how does he 'see' the developing structure? For this purpose, a chemist makes use of spectroscopic tools. How does he cut, tailor and glue the components on a molecule that he cannot see? For this purpose chemists have developed molecular level tools called Reagents and Reactions. How does he clean the debris and produce pure molecules? This feat is achieved by crystallization, distillation and extensive use of Chromatography techniques. A mastery over several such techniques enables the molecular architect (popularly known as organic chemist) to achieve the challenging task of synthesizing the mirade molecular structures encountered in Natural Products Chemistry, Drug Chemistry and modern Molecular Materials. In this task, he is further guided by several 'thumb rules' that chemists have evolved over the past two centuries. The discussions on the topics **Name Reactions, Reagents** for synthesis, **Spectroscopy** and **Chromatography** are beyond the scope of this write-up. Let us begin with a brief look at some of the important ***'Rules'*** *in organic chemistry that guide us in planning organic synthesis.* We would then discuss Protection and Deprotection of some important functional groups. We could then move on to the Logic of planning Organic Synthesis.

# CHAPTER OVERVIEW

## 2: Rules and Guidelines Governing Organic Synthesis

There are a few rules that provide guidelines for planning strategies in organic synthesis. These rules and guidelines have come from the keen observations of chemists after looking into several examples from their own research and other published work in the literature. *These observations are to be treated as thumb-rules to be applied with caution. They may not be applicable for all situations.* Nonetheless, they serve as guidelines to avoid pit-falls in planning. Since all these rules are governed by the underlying principles of *mechanistic organic chemistry* and *stereochemistry*, these basic mechanistic principles are the touchstones against which the conclusions reached are to be tested. Most of the rules that are useful in planning synthesis are collected here for convenience.



### Contributors and Attributions

- Prof. R Balaji Rao (Department of Chemistry, Banaras Hindu University, Varanasi) as part of Information and Communication Technology

# 2.1: Baldwin's Rule for Ring Closure Reactions

J.E. Baldwin proposed a set of rules for ring closure reactions. He suggested that the rules are applicable to reactive intermediates as well and supported his views with several examples from literature and special experiment designed to test the validity of the rules.

The ring closure reaction of a reactive intermediate could be one of the three types. An attack could be on a triple bond center (called Digonal center, *Dig*-), a double bond center (called Trigonal center, *Trig*-) or at a single bond center (called Tetrahedral center, *Tet*-). The attacking species could be a carbanion, a carbonium ion or a free radical. The attack could be *endo*- or *exo*-. With respect to the newly developing ring in the transition state, when the pair of electrons in the displaced bond is exo- to the developing ring, the transition state is described as **exo- attack**. When they form part of the newly developing ring (or transition state) the system is described as **endo- attack (Fig 2.2.1).**

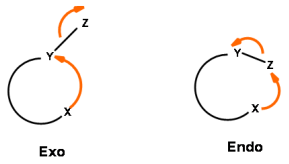



Fig 2.2.1

For each pair of reactive center, there could be two modes of attack – endo- or exo- as shown for the attack of an anion **(Fig 2.2.2).**

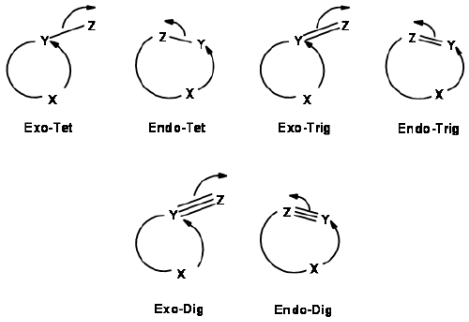



Figure 2.2.2

Reactions take place only when the orbitals concerned overlap efficiently. For this purpose, Baldwin suggested the following geometry **(Fig 2.2.3).** In a ring formation reaction, the optimal geometry could be achieved only when the length of the chain (a ***tether*** of atoms) connecting the reactive centers have a minimum optimal length.

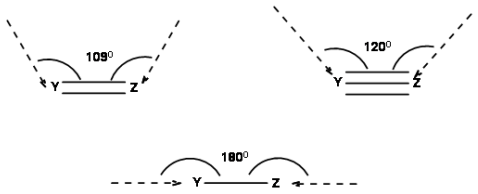
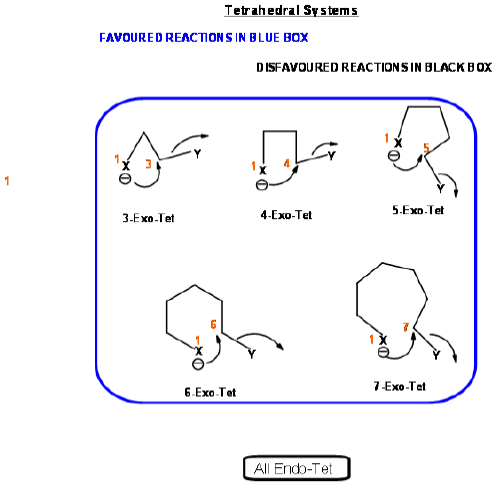


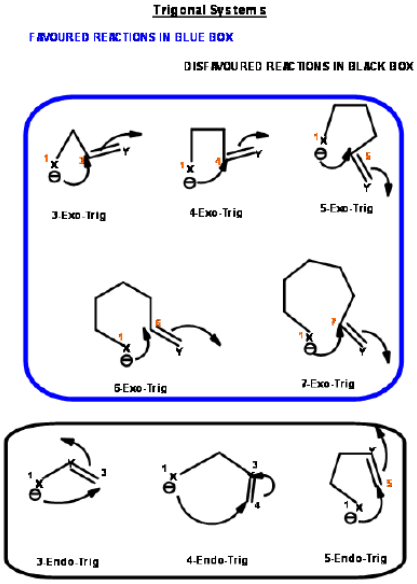

Figure 2.2.3

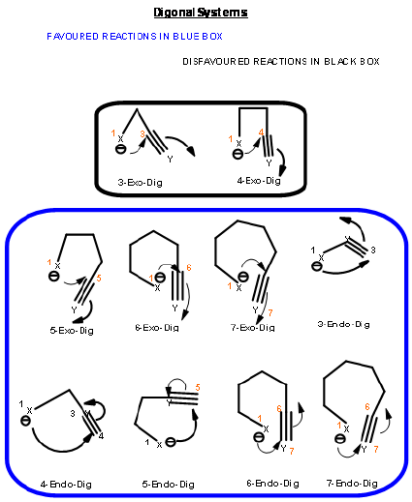
Based on this criterion, Baldwin suggested the following rules. The number (3 to 7) in the nomenclature refers to the number of atoms in the chain that leads to the proposed cyclic transition state.

## Baldwins Rules

1. All Exo-Tet reactions are favored reactions
2. All Endo-Tet are disfavored reactions
3. All Exo-Trig reactions are favored reactions
4. 3 to 5-Endo-Trig reactions are disfavored reactions
5. 6 and 7-Endo-Trig reactions are favored reactions
6. 3 to 7-Endo-Dig reactions are favored reactions
7. 3 to 4-Exo-Dig reactions are disfavored reaction
8. 5 to 7-Exo-Dig are favored reactions






These complex rules are simple to apply, but difficult to remember without a suitable 'memory aid'. E. Juaristi [2] (in his web page http://www.relaq.mx/RLQ/EusebioJuaristi_vitae.htm) suggests the following mnemonics for all the Disfavored Reactions (the Stop sign). A modified version is presented here **(Fig 2.2.4).** Note that the numbers are progressively increasing. The STOP sign and the wagon would probably be easier to remember.

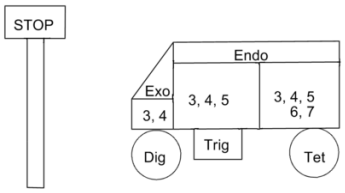



Figure 2.2.4

An alternate summary of the Baldwin's Rules is provided by Clayden et. al., in their inimitable text book. This table is now easy to remember **(Fig 2.2.5).** You have to remember 5-Endo-trig and 4-Exo-Dig as key points for Disfavored reactions.

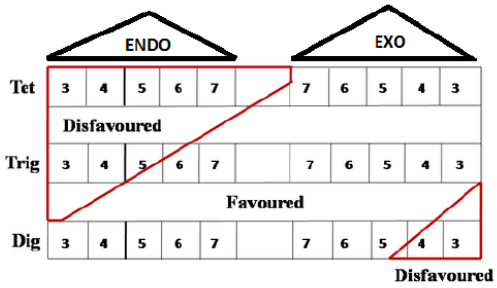



Figure 2.2.5

Baldwin cited several examples in support of these rules. Scientists soon attempted to validate the proposed rules. Steric and electronic factors appear to modify these conclusions. In most of the studies, the rules were generally applicable. Let us look at the following interesting study **(Fig 2.2.6).** A 6-endo-Tet reaction should be disfavored. Such reactions do not form a ring, but appear to pass through a cyclic transition state leading to the cleavage of a sigma bond, while a new sigma bond is formed.

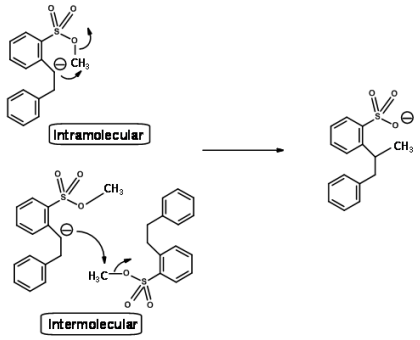



Figure 2.2.6

Using an ingenious double labeling experiment shown below, Eschenmoser clearly established that this reaction is *intermolecular* **(Fig 2.2.7).** He took an equimolar mixture of hexadeutero- and normal starting materials and conducted the reaction. If the reaction were only intramolecular, the product would be both hexadeutero- and no deutero- products only. The actual product distribution was as shown in Figure 2.2.7, *which is in keeping with intermolecular mechanism only.*

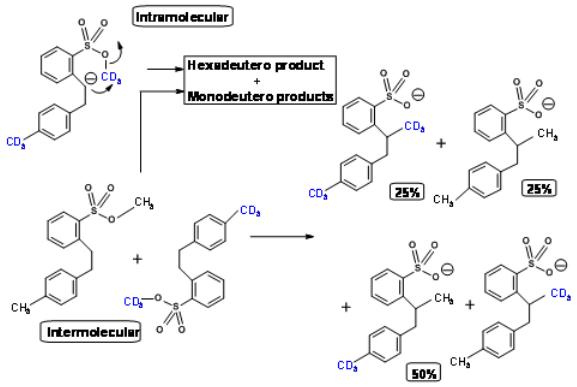



Figure 2.2.7

The constraint in such cases lies obviously in the length of the chain bearing the reactive groups. The angle of attack of $180^0$ is not attainable in a six-membered ring. King *et al.*,showed that as the length of the chain (tether) increased, intramolecular reaction became more feasible as shown in Figure 2.2.8. An intramolecular reaction became feasible only when the teather allowed a ten-membered ring transition state.

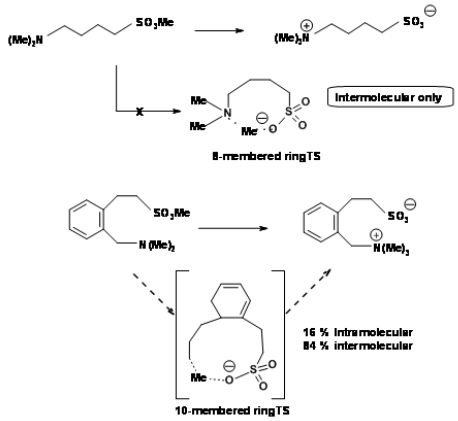



Figure 2.2.8

Another Disfavored cyclization is 5-Endo-Trig. The following Michael-type cyclization is of considerable interest **(Fig 2.2.9).** The base catalyzed intramolecular addition does not proceed as expected. However, the acid catalyzed reaction proceeds. A close look at an alternate mechanism suggests that a 5-Exo-Trig path becomes available under acid catalyzed conditions .

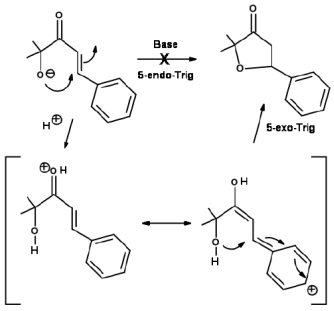



Figure 2.2.9

Baldwin sites three closely related reactions **(Fig 2.2.10)** to support his rules. The oxygen analogue failed to cyclize as anticipated for 5-Endo-Trig reactions. However, the thiol analogue cyclized readily to give the thiophene ring. This is attributed to the fact that the larger atom requires entirely different bond angles not envisaged in Baldwin's Rules. The nitrogen analogue investigated preferred an alternate path. Why does the nitrogen prefer amidation and not Michael-type cyclization? Could it be due to an unreactive olefin? This question was answered through an intermolecular *'control reaction'* shown in Fig 2.2.11. The amine moiety preferred a Michael-type addition to amidation.

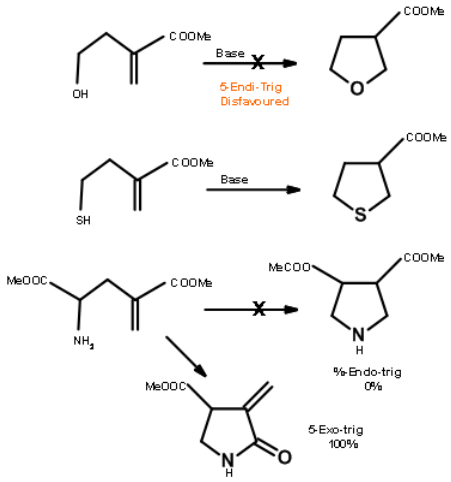



Figure 2.2.10

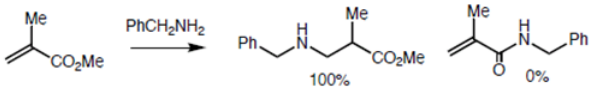



Figure 2.2.11

This lack of cyclization was therefore attributed to the fact that the lone pair cannot attack the pi-orbitals due to wrong orientation in one conformation and the distances involved in the other conformation (see Figure 2.2.12).

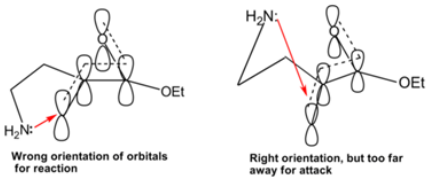



Figure 2.2.12

Applicability of Baldwin's 5-Endo-Trig restriction was verified through a carefully planned retro-reaction **(Fig 2.2.13).** The Deuterium labeling experiment proved the fact that anion formation was effective. Lack of cleavage reaction proved that the above conclusions (5-Endo-Trig restriction) are valid in reverse reactions as well.

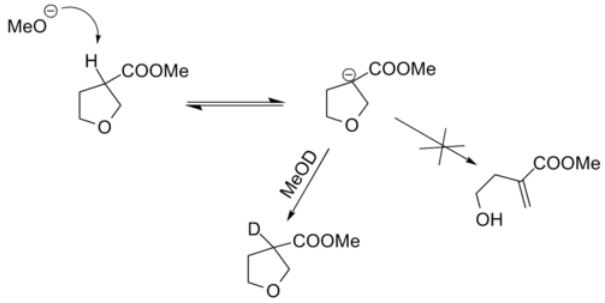



Figure 2.2.13

The fact that 5-Exo-Trig is favored is seen in several reactions. The fact that 6-Endo-Trig reactions are favored is also well documented **(Fig 2.2.14).**

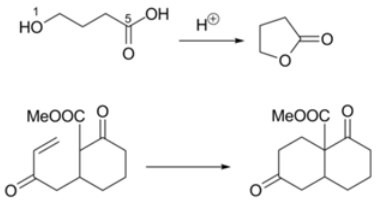



Figure 2.2.14

The 5-Endo-Dig cyclization looks awkward on paper **(Fig 2.2.15).** But the reaction proceeds to completion. A close look at the orbitals concerned explains the reaction. The orientation of one of the pi-orbitals is just right for the reaction to occur. Compare this with the orientation shown in Figure 2.2.12.

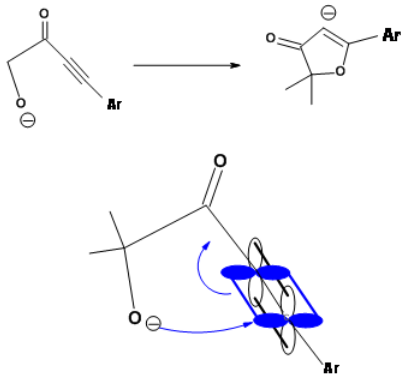


Figure 2.2.15

How about the acetal formation reaction of ketones with ethylene glycol **(Fig 2.2.16)**? Is this a case of failure of Baldwin's Rules as in several carbonium ion reactions?

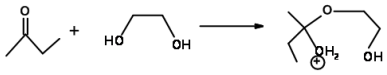


Figure 2.2.16

These rules are generally applicable. However, there are several exceptions as well. A proper approach would be to use these 'thumb rules' as a guideline while planning synthetic schemes and not use them as inviolable rules. The following points may be kept in mind while applying these rules.

1. The rules suggest only the 'favored paths'. This expression 'favored / disfavored' should not be read as 'allowed / disallowed'. Under suitable conditions, the alternate high-energy path may be opened, either partially or exclusively.

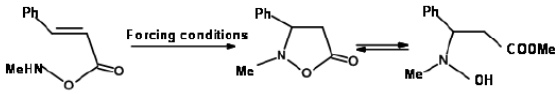



Figure 2.2.17

2. When a large atom from the Second Group of the periodic table is involved, the angle requirements of these atoms may vary. In such cases, the rules may not be applicable. See Fig 2.2.10 for one such example.

3. Special modified Baldwin's Rules have been evolved for enolate anions.

## References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3. Organic Chemistry by Clayden, Greeves, Warren and Wothers: Page 1144.
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5. King et. al., Chem. Commun., 175 (1982); Tetrahedron Lett., 23, 4465 (1982). and Peter Beak, Acc. Chem. Rec., 25, 215 (1992).

## 2.2: Bredt's Rule

In its original form, **Bredt's Rule** stated that bridged ring systems (like camphane (Figure 1.2.1.1A) and pinane (Figure 1.2.1.1B)) (Fig 1.2.1.1) cannot have a double bond at the bridgehead position (the points marked by bold dots in structures 'A' and 'B'). This rule came from observations on dehydration of alcohols in these ring systems. When you look at these molecules carefully, you could see that the bridged rings are made out of a larger ring (shown by thick lines in the Figure s) bearing a bridge at specified points. Most of the rings studied by Bredt had six-membered ring as the largest ring. The constraint dictated by Bredt's Rule has now been attributed to the fact that the small and common rings can accommodate only a cis- double bond. A bridgehead olefin demands a trans- geometry at the olefin. Hence the rule was applicable to almost all naturally occurring bridged ring systems known at that time.

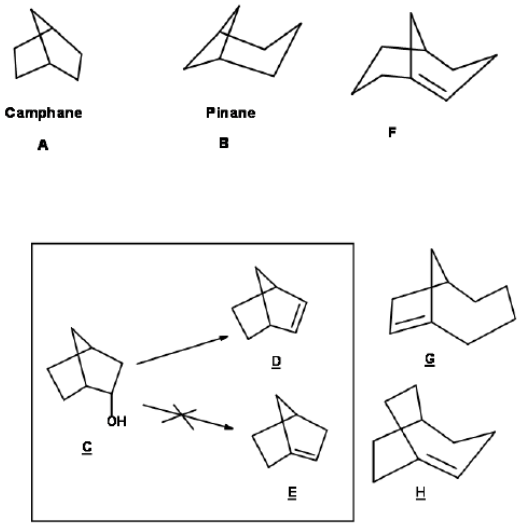



Fig 1.2.1.1

The scope of this rule has been investigated in detail. Medium sized rings are large enough to accommodate a trans- double bond. Hence the bicyclic rings 1.2.1.1F and 1.2.1.1G, bearing a cyclooctane ring as the outer ring, were synthesized and were indeed found to be stable. On the other hand, the isomeric cycloheptene ring system 1.2.1.1H was unstable. Faweet (1950) suggested that the S value, which is a summation of the numbers found in the nomenclature (m + n + o = S), would determine the stability of the ring system. Bicyclic ring systems with a bridgehead double bond having S value less than 9 would be highly strained. As the S value increases, the strain decreases.

Bretd's Rule cautions us on the type of rings that could bear a double bond. When a synthetic intermediate or a transition state in a mechanism demands such an intermediate, one should exercise caution on the position of the olefin. For example, Prelog (1948, 1949) attempted an aldol condensation on the ring systems shown (Fig 1.2.1.2). When n = 5, both products bicyclo[6,4,0]alkene (S = 10) (C), and

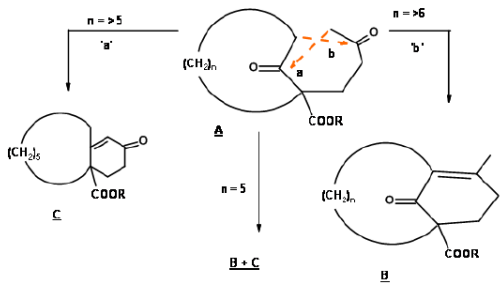



***Fig 1.2.1.2***

bicyclo[5,3,1]alkene (S=9) (B) were formed. On the other hand, when n=>6, the main product was a bicyclo[6,3,1]alkene system (B) (S=10). When n = <5 product B was not observed. Note that these models were based on reversible aldol condensation reactions (equilibrium reactions) and therefore correspond to the thermodynamic stability of the product. Under forced conditions however, the rule may not hold, as seen in the following example (Fig 1.2.1.3).

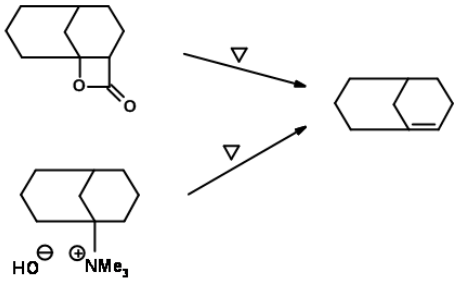



***Fig 1.2.1.3***

# 2.3: Cram's Rule and Prelog's Rule

A carbonyl carbon is $sp^2$ hybridized. This means that the carbonyl carbon and the three other atoms attached to it would be in one plane. A nucleophile attacking the carbonyl carbon in molecules like **1A** in Figure 1.2.1 could attack from either side of this plane with equal ease. Have a close look at the aldehyde shown in Figure 1.2.1.The phenyl group is also flat. Nucleophilic attack on benzaldehyde could take place from either side with equal ease. Since a new asymmetric center is now created by this reaction, both enantiomers could be formed with equal ease, resulting in a racemic mixture.

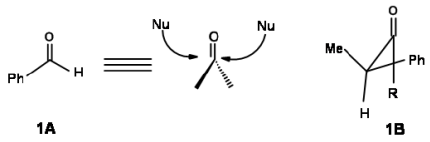



Figure 1.2.1

In complex organic molecules, this seldom happens. When the $\alpha$ - carbon is asymmetric (see **1B**), the nucleophile would experience more steric hindrance from one side, leading to unequal synthesis of the two enantiomers. This fact was first recognized by D. Cram in 1952. After analyzing several published reactions, he put forth an explanation based on one proposed conformation. **He set forth to first define a *Reactive conformation,* as the least energy conformation in which the chemical reaction takes place.** Thus, for **1B** there could be several conformations, out of which chemical reactions prefer to proceed **via** the conformation having the least steric strain **(Fig 1.2.2).**

Studies in Stereochemistry. X. The Rule of "Steric Control of Asymmetric Induction" in the Syntheses of Acyclic Systems Donald J. Cram, Fathy Ahmed Abd Elhafez, J.Am. Chem. Soc. **74,** 5828(1952).

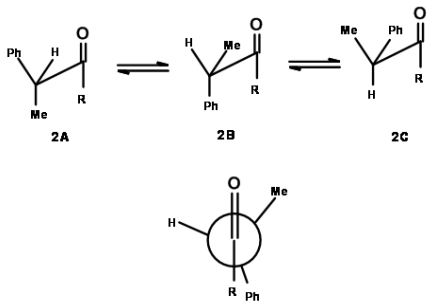



Figure 1.2.2

**Cram's Rule**

- The existing asymmetric center would have a Small, Medium and Large group, denoted **S,M** and **L** respectively.
- *In the reactive conformation, the carbonyl group would orient itself in such a way that it will rest between the Small group and the Medium group.*
- The attacking nucleophile would prefer to attack from the side of the small group, resulting in the predominant formation of one diastereomer in the product.

This is now known as **Cram's Rule.** When the starting material is a pure enantiomer, the product mixture would show predominance of one enantiomer. He supported his argument with a set of his own experiments shown in Figure 1.2.3

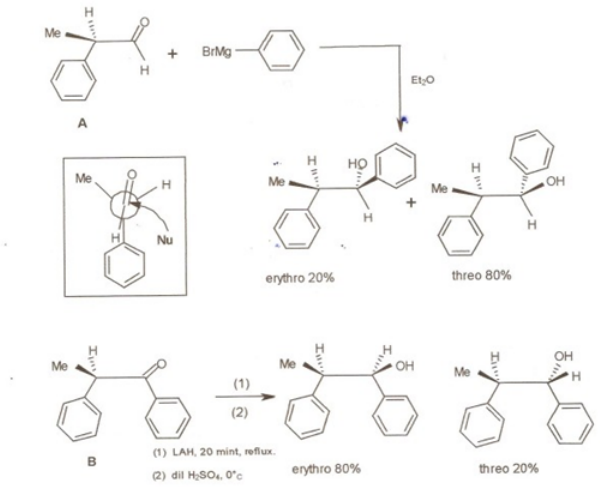
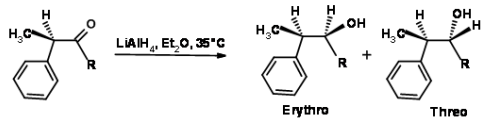



Figure 1.2.3

The predominance of one diastereomer in such reactions could be explained on the basis of Cram's Rules. This rule proved to be effective in predicting the major product in most of the asymmetric syntheses. However, several exceptions were soon observed. They were explained on the basis of further conformational arguments.

*Felkin* pointed out that the reactive conformations of Cram had severe eclipsing strain between **R** group on carbonyl center and **L** group on the alpha\! - carbon (see **2B** in Figure 1.2.2). He progressively increased the bulk of the R group and observed that the diastereomeric excess could swing from erythro 74% to threo 96% as the bulk increased **(Fig 1.2.4).**

Torsional strain involving partial bonds. The stereochemistry of the lithium aluminium hydride reduction of some simple open-chain ketones. Marc Cherest, Hugh Felkin and Nicole Prudent Tetrahedron Letters, 9, 2199 (1968).




| R | Erythro : Threo |
|---|---|
| Me | 74 : 26 |
| Et | 76 : 24 |
| i-Pr | 83 : 17 |
| t-Bu | 98 : 2 |

Fig 1.2.4

He proposed a staggered conformation, wherein the nucleophile approached the carbonyl carbon from the least hindered side. The major difference in these two approaches is depicted in Figure 1.2.5.

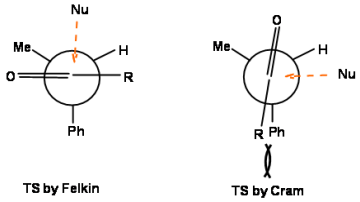



Figure 1.2.5

The flaw in the Felkin's model is that it is not true for aldehydes, where R=H. An improvement over Felkin's model was the Felkin-Nguyen (Felkin-Anh) model, which suggested that the nucleophile would attack the $sp^2$ center of the carbonyl at $95^0$ to $105^0$ angle relative to the carbonyl bond axis, favoring an attack from the least hindered direction (Figure 1.2.6). This differed from the earlier models that suggested a perpendicular attack.

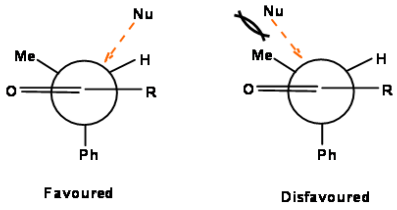



Figure 1.2.6

What happens when the alpha\!- carbon bears atoms like 'O','N' or 'S'? The first thought would be that the nucleophile would prefer the side opposite to the electronegative group. This would lead to a Felkin-Anh transition state. This would be true only when the reagent does not have additional complexing site. For example, in sodium borohydride the sodium ion cannot from a bivalent complex. On the other hand, zinc borohydride could form a divalent chelation complex between the carbonyl oxygen and the electronegative atom. This is called **Cram-chelation complex,** which leads to a **Cram-chelate product**. The three arguments discussed so far are shown in Figure 1.2.7.

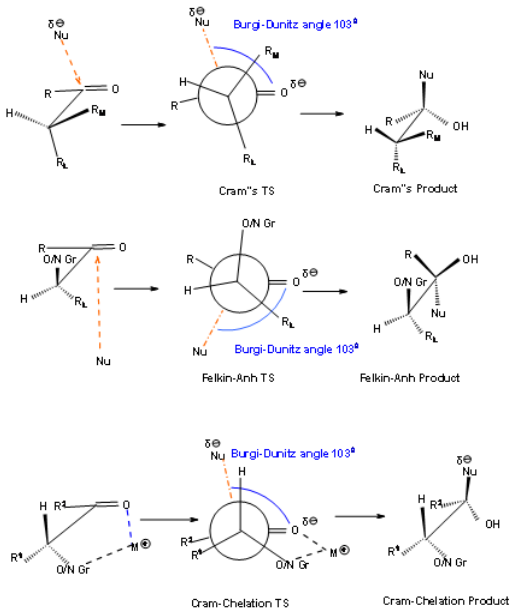



Figure 1.2.7

Two examples are shown in Figure 1.2.8 to depict that *Cram's chelation control* could lead to a reversal in selectivity. Notwithstanding these refinements to the original Crams's Rule, the fact remains that this line of extending conformational arguments to *reactive conformations* suggested by Cram has resulted in greater understanding of nucleophilic additions to aldehydes and ketones.

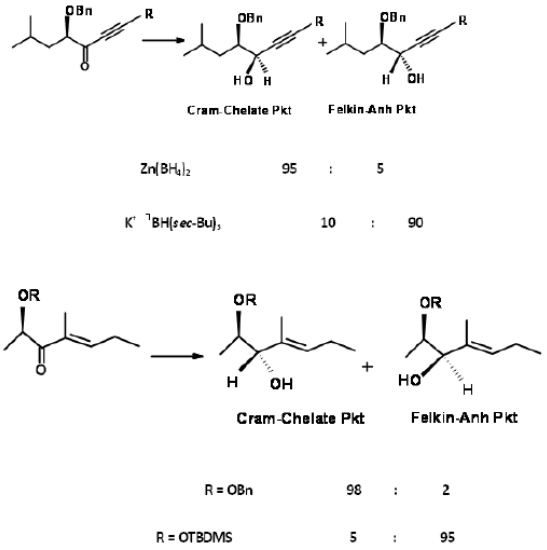



Figure 1.2.8

## Prelog's Rule

An extension of Cram's idea of reactive conformation to chiral esters of $\alpha$-ketoesters(pyruvates) is the **Prelog's Rule** reported in 1953[3]. It generally relates to Grignard addition to chiral pyruvates made using chiral alcohols **(Fig 1.2.9).**

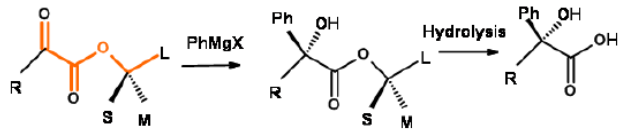



Figure 1.2.9

The rule has been applied for asymmetric synthesis of $\alpha$-hydroxyacids and for assigning the configuration of secondary and tertiary alcohols. The *anti* configurational arrangement of the two $\alpha$-carbonyl moieties could be rationalized. The negative end of these dipoles would prefer to be as far removed as possible. The two lone pairs would sit on ether oxygen like the 'Rabit Ears'. The keto-carbonyl would orient between the two ears. This will place the bonds shown in red in the same plane as thr keto-carbonyl group. The attack from the side of the small (S) group is an extension of Cram's Rules. The asymmetric induction could be at times poor due to the large distance between the reaction center and the asymmetric center inducing asymmetry at the developing chiral center.

## References

1. Prelog V, Helv. Chim. Acta, **36,** 308(1953)

# 2.4: Hofmann's Rule and Zaitsev's Rule

In reactions like Hofmann's Exhaustive Methylation – Elimination reactions, the least substituted olefin is generally formed as a major product. This is called the **Hofmann's Rule**. All such reactions bear charged leaving groups like $–NR_3^+$ or $–SR_2^+$ and involve strong bases. The **Zaitsev's Rule** (**or Saytzeff rule**) draws our attention to the alternate possibility. On elimination of HX, the more stable olefin is obtained **(Fig 2.3.1).** The apparent contradiction in this set of rules is easily resolved through a critical look at the mechanisms involved in these two sets of reaction conditions.

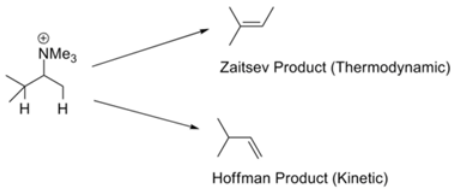



Fig 2.3.1

There could be two reasons for such preferences. Ingold (1960) and Bunnett (1969) suggested that a positively charged leaving group increases the acidity of the β-protons. A substituent at the β-position could hyperconjugatively decrease the acidity of the β-proton. Consequently, a terminal methyl group (this has no alkyl substituent) is more acidic than the internal methine proton (bearing at least one alkyl substituent). When the leaving group is a halogen, the mechanism shifts *towards E1*. Under these conditions, the stability of the developing double bond becomes important and this leads to the thermodynamically more stable product. The school of H.C Brown had suggested (1956) that steric factors govern such elimination reactions. The charged leaving groups are large compared to neutral leaving groups.

The larger leaving groups like $–NR_3^+$ and $–SR_2^+$ give more Hoffmann product than smaller groups like halogens. The bulkiness of the base also increases the Hoffmann product at the cost of the Zaitsav product. The situation appears to be more complex. When the base strength was increased without increasing the bulk at the reaction site ($X\text{-}C_6H_4\text{-}O^-$), the Hoffmann product increased at the cost of the Zaitsav product (Froemsdorf (1966,67)). This suggests an E1cB mechanism, where the acidity of the β proton is important. Thus the mechanism (and therefore the products composition) could be altered by factors such as the size of the leaving group, size of the base, nature of the leaving group and the strength of the base.

# 2.5: Markovnikov Rule

Polar addition of HBr to olefins proceeds in such a way, the carbon that is rich in hydrogen becomes richer. In mechanistic terms, we could restate the rules as follows: Polar addition of $H^+X^-$ to olefins proceed in such a way that the negative component adds to the more stable carbonium ion intermediate **(Fig 2.4.1).**

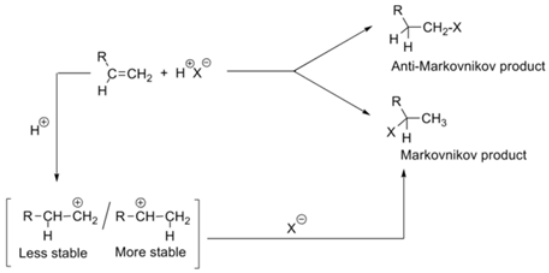



Fig 2.4.1

HBr and HI easily undergo free radical addition, promoted by light or heat. Free radical additions give the anti-Markovnikov product. Clean Markovnikov products are obtained when such reactions are carried out in polar solvents and care is taken to avoid light.

# 3: Criteria for Selection of the Synthetic Route

Once a Target Molecule is chosen for synthesis, one could sit down and device several routes for its synthesis. On what criteria do you select a Target and how do you arrive at a synthetic route? The answer depends on the overall goal of your project.

For a natural product chemist, he might have isolated and determined the structure of a new molecule. He may need to synthesize the molecule to prove the structure. While working on structure elucidation, the route chosen for synthesis should unambiguously establish the part of the structure you are working on. Each step is chosen on this structure-criterion alone. Here the length of the route and the cost of the chemicals are not important.

An elegant (enantiopure) synthesis of some complex structure is the dream of an academician working in the university laboratory. He is often more concerned with developing new routes, new reactions and new mechanistic principles. His concern is to develop new horizons and give good training to the young chemists. He is seldom worried about the cost of his research. He has time at his command and hopefully enough money to pursue his passion. He is judged by the quality (and quantity) of his research publications and the quality of training he has imparted to the students. Having a patent is an added feather to his cap.

A pharmaceutical chemist and a material chemist are more interested in developing versatile and fast synthetic routes for a chosen molecule. Their efforts are directed towards the synthesis of a large number of closely related molecules, within a short time. Such a chemist is looking into Structure-Activity Studies, aimed at developing new drug molecules or molecules with special properties. He is often judged by the number of such active molecules that he has discovered and patents held in his name and not just by the number of new molecules synthesized by him or the elegance of the synthetic route. A publication to his credit is an added feather to his cap. In his endeavours, the cost and the efficiency of the synthetic routes are not the criteria for research. He believes that once the ‘right molecule’ is discovered, more efficient routes could always be generated at a suitable date. His art is directed towards fast discovery of molecules with the right properties.

An industrial chemist is most concerned with the ‘cost’ of synthesis of the molecule. His efforts are directed towards development of economical synthetic procedures, which includes not only the cost of the chemicals but also the cost of waste treatment, recycling and environmental cleaning. He selects the molecules on the basis of their economic value (net profit for his company). He should be concerned about eco-friendly reactions and procedures. In general, a development chemist in an industrial R&D laboratory looks at very large-scale (typically several kilogram batch) reactions, their reproducibility, safety and cost parameters. His focus is on the commercial value of his product, the profitability and the patents.

Therefore, the target molecule and the route chosen depend of the hat the chemist is wearing. We do have examples of amazing chemists who efficiently juggle with more than one hat at the same time. We take our proverbial hats off for those versatile and multifaceted chemists. This is because, for an efficient operation, different tasks demand different skill-sets and use of different sets of databases. Nonetheless, the underlying chemistry is same in all these activities. Of course, occasionally one could be creative, versatile and cost-effective at the same time. In the following pages we would look into the broad principles governing the art of organic syntheses. We have already discussed some ‘rules’ that govern synthesis. We would now explore guidelines that concern the logic of organic syntheses. We would then discuss several interesting syntheses to illustrate these principles.

# 4: The Logic of Synthesis

‘There could be ART in Organic Synthesis’ declared the inimitable monarch of organic synthesis, Professor R.B. Woodward. His school unveiled several elegant approaches covering a variety of complex structures and broke new grounds to define the art of organic synthesis. ‘If organic synthesis is a branch of science, what is the LOGIC of organic synthesis?’ marveled several others. The development of the concept of logical approaches towards synthesis has been evolving over the past several decades. A few stalwarts focused their attention on this theme and attempted to evolve a pattern to define this logic. There is no doubt that all of us who dabble with synthesis contribute our small bit in the magnificent direction. A few names stand out in our minds for their outstanding contributions. Notable contributions came from the schools of J.A. Marshal, E.J. Wenkert, G. Stock, S Hanessian, E.E. van Tamalen, S. Masamune, R.B. Woodward, E.J. Corey and several others. More focused on this theme were the contributions from the school of E.J. Corey.

The period 1960 – 1990 witnessed the evolution of this thought and the concept bloomed into a full-fledged topic that now merits a separate space in college curriculum. Earlier developments focused on the idea of *ANTITHETIC APPROACHES* and perfected the art of DISCONNECTION via RETROSYNTHESIS. This led to logical approaches for the construction of *SYNTHETIC TREES* that summarized various possible approaches for the proposed Target structure. All disconnections may not lead to good routes for synthesis. Once the synthetic tree was constructed, the individual branches were analyzed critically. The reactions involved were looked into, to study their feasibility in the laboratory, their mechanistic pathways were analyzed to understand the conformational and stereochemical implications on the outcome of each step involved and the time / cost factors of the proposed routes were also estimated. The possible areas of pitfall were identified and the literature was critically scanned to make sure that the steps contemplated were already known or feasible on the basis of known chemistry. In some cases, model compounds were first constructed to study the feasibility of the particular reaction, before embarking on the synthesis of the complex molecular architecture. Thus a long process of logical planning is now put in place before the start of the actual synthetic project. In spite of all these careful and lengthy preparations, an experienced chemist is still weary of the Damocles Sword of synthesis viz., the likely failure of a critical step in the proposed route(s), resulting in total failure of the entire project. All achievements are 10% inspiration and 90% perspiration. For these brave molecular engineers, sometimes also called chemists, these long-drawn programs and possible perils of failures are still worth, for the perspiration is enough reward.

A sound knowledge of mechanistic organic chemistry, detailed information on the art and science of functional group transformations, bond formation and cleavage reactions, mastery over separation and purification techniques and a sound knowledge of spectroscopic analysis are all essential basics for the synthesis of molecules. A synthetic chemist should also be aware of developments in synthetic strategies generated over the years for different groups of compounds, which include Rules and guidelines governing synthesis. Since organic chemistry has a strong impact on the development of other sister disciplines like pharmacy, biochemistry and material science, an ability to understand one or more of these areas and interact with them using their terminologies is also an added virtue for a synthetic chemist. With achievements from synthesis of strained molecules (once considered difficult (if not impossible) to synthesize, to the synthesis of complex, highly functionalized and unstable molecules, an organic chemist could now confidently say that he could synthesize any molecule that is theoretically feasible. This is the current status of the power of organic synthesis. Based on the task assigned to the chemist, he would select a Target molecule for investigation and devise suitable routes for synthesis.

## Protection and Deprotection Strategies in Organic syntheses

For the manipulation of functional groups and formation of new covalent bonds we make use of a large number of Reagents and Name Reactions. In complex organic syntheses, the starting materials and intermediates in the synthetic scheme often have more than one reactive functional group. A few such multifunctional building blocks are shown below to illustrate this point **(Fig 4.1.1 )**. While working on such complex

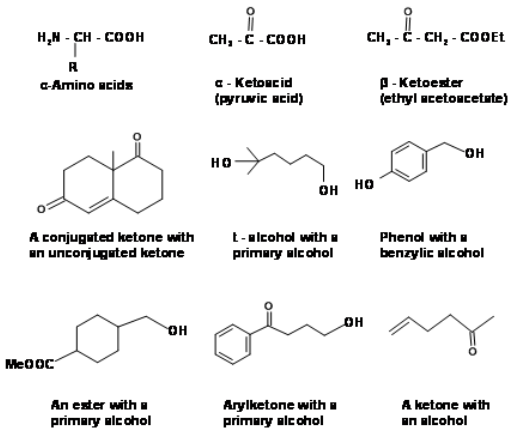



Fig 4.1.1

molecules, it is often necessary to *protect* some groups to enable selective working at the desired locations only. Organic chemists have heavily relied on such protection / deprotection strategies and have diligently developed protecting (masking) and deprotection (unmasking) protocols. We would discuss some of the important protecting groups in this chapter.

Before proceed further, it must be emphasized here that this protocol should be applied only after alternate options have been critically analyzed. This is because protection / deprotection strategy involves an increase of at least two more critical steps, adding to the length of the synthesis and consequent drop in overall yields of the desired compound. In large-scale reactions, this leads to a huge impact to the Atom Economy and pollution cost of the synthetic process. All this translates into an increase in the overall cost of the final drug molecule.

## Protection Strategies

Group / Site Selective Reagent: Protection / deprotection is not always required whenever you see a multiplicity of functional groups. You could solve the selectivity issue by using site selective reactions / reagents. By choosing an appropriate selective reagent to suit the scheme on hand, you could selectively attack only one of the reactive sites. Consider an olefinic ketone **(Fig 4.1.2)**. Sodium borohydride reduction in methanol as solvent could selectively reduce the keto- group to a secondary alcohol

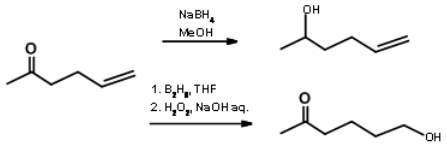



Fig 4.1.2

leaving the olefin undisturbed. On the other hand, diborane reagent in THF as solvent would be a reagent of choice when the selective reduction at the olefin moiety is desired. Diborane reduction of an olefin is several times faster than reduction of ketones. The oxidative cleavage of borane product is also selective. Thus, you can avoid the protection / deprotection strategy by employing a selective reagent. In C – C bond formation reactions we come across several such site-selective reagents. One such reagent widely used in research is the Wittig reagent. They attack the aldehyde or ketone selectively in the presence of ester, nitrile. olefin etc..

## Selective Protection

In the case of a molecule like **4.1.3A (Fig 4.1.3)** bearing an olefin and a carboxylic acid, the –COOH group is several times more reactive than the olefin towards diborane reduction.

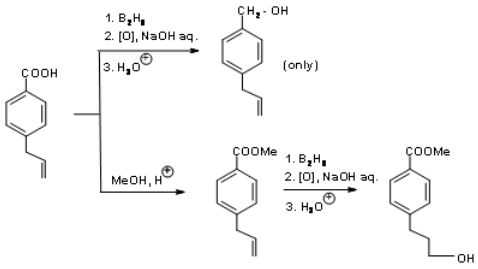



Fig 4.1.3

Hydroboration / oxidation reduces the acid to a primary alcohol, leaving the olefin unaffected. On the other hand, if you need a selective reduction of olefin, the acid group has to be processed through a selective protection / deprotection sequence as shown in **(Fig 4.1.3)**

Compound **4.1.4A** illustrates several important points in Protection / Deprotection protocol. Both the functional groups could react with a Grignard Reagent. Carboxylic acid group would first react with one mole of the Grignard Reagent to give a carboxylate anion salt. This anion does not react any further with the reagent. When two moles of Grignard Reagent are added to the reaction mixture, the second mole attacks the ketone to give a tertiary alcohol. On aqueous work-up, the acid group is regenerated. Thus, the first mole of the reagent provides a selective transient protection for the –COOH group. Once the acid group is esterified, such selectivity towards this reagent is lost. The reagent attacks at both sites. If reaction is desired only at the ester site, the keto- group should be selectively protected as an acetal. In the next step, the grignard reaction is carried out. Now the reagent has only one group available for reaction. On treatment with acid, the ketal protection in the intermediate compound is also hydrolyzed to regenerated the keto- group.

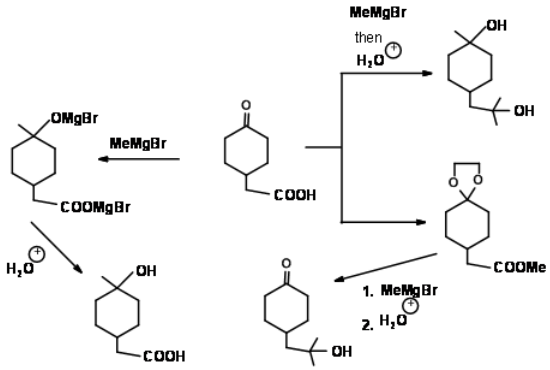


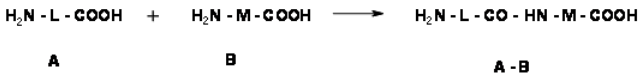

Fig 4.1.4

## Orthogonal Protection or Differential Protection

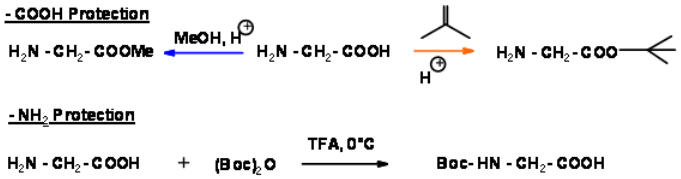
Orthogonal protection is a strategy that allows deprotection of multiple protective groups one at a time, each with a dedicated set of reagents and / reaction conditions without affecting the other. This technique is best illustrated with peptide bond formation and associated deprotection reactions. An amino acid has two functional groups $-NH_2$ and –COOH. When two amino acids (A and B) react under conditions for the peptide bond condensation reaction, a mixture of 4 dipeptides (at least) could be formed as shown below.

$$A + B \rightarrow A-A + A-B + B-A + B-B \tag{4.1}$$

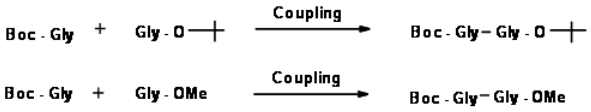
If we are interested in only one product A – B, we have to do selective protections and selective deprotections in a proper sequence. Consider the following peptide bond formation reaction.



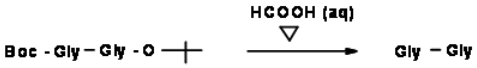

In order to get only one product A – B, we should protect the N – terminal of 'A' and C – terminal of 'B'. Let us look closely at two different dipeptide formation schemes. In the following sequence, the C – terminal is protected in two different ways for one amino acid. For the second amino acid, the N – terminal is protected with an acid labile Boc- protection.



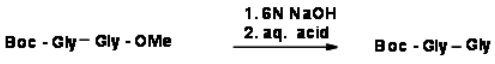

In the next step, the two monoprotected amino acids are coupled as shown below.




Take a close look at both the products. In the first product, both protections are acid sensitive. If the final product desired is the protection-free dipeptide, this is indeed a short route.




If the desired product is a mono-protected dipeptide, then selective deprotection is the preferred reaction. This is feasible only when we use starting compounds that are differentially protected. This is called **Orthogonal Protection**.




Similar techniques are available for other functional groups as well. Let us now learn more on Protection / Deprotection for some important functional groups.

## Protection of R – COOH Group

In the introduction, we have seen that carboxylate ion lends protection to an attack of Grignard reagents at this carbonyl carbon. However, this is not sufficient for a vast variety of reagents. Meyer's 2-oxazolines mask an acid function while activating the α-position for lithiation reaction. The use of this group as protection for –COOH group is rare.

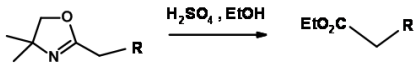



Fig 4.1.5). Methyl esters are readily prepared by two procedures. The diazomethane procedure is suitable for methyl esters (small scale) only. The alcohol esterification procedure is common for all alcohols except tert-butanol. Note that only t-butyl esters proceed through the O – alkyl fission mechanism. All other esters proceed via O – acyl fission mechanism. The t-butyl group being bulky, the acyl carbonyl is shielded from nucleophilic attacks. This is of great value in peptide synthesis. Also note that the benzyl esters are labile with base catalysed hydrolysis as well as hydrogenolysis which is another fission involving the ether oxygen bond.

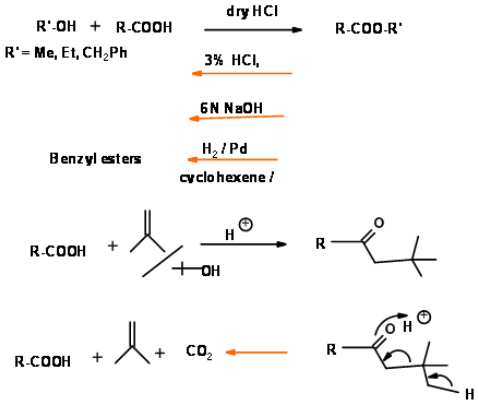



Figure 4.1.5

## Protection of Aldehydes and Ketones

Since alcohols, aldehydes and ketones are the most frequently manipulated functional groups in organic synthesis, a great deal of work has appeared in their protection / deprotection strategies. In this discussion let us focus on the classes of protecting groups rather than an exhaustive treatment of all the protections.

### Acetals

There are two general methods for the introduction of this protection. Transketalation is the method of choice when acetals (ketals) with methanol are desired. Acetone is the by-product, which has to be removed to shift the equilibrium to the right hand side. This is achieved by refluxing with a large excess of the acetonide reagent. Acetone formed is constantly distilled. In the case of cyclic diols, the water formed is continuously removed using a Dean-Stork condenser **(Fig 4.1.6)**.

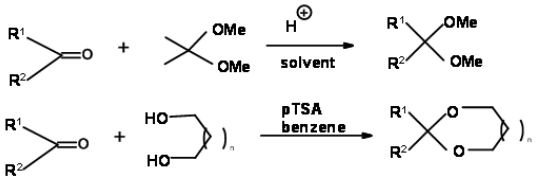



Fig 4.1.6

The rate of formation of ketals from ketones and 1,2-ethanediol (ethylene glycol), 1,3-propanediol and 2,2-dimethyl-1,3-propanediol are different. So is the deketalation reaction. This has enabled chemists to selectively work at one center. The following examples from steroid chemistry illustrate these points **(Fig 4.1.7)**.

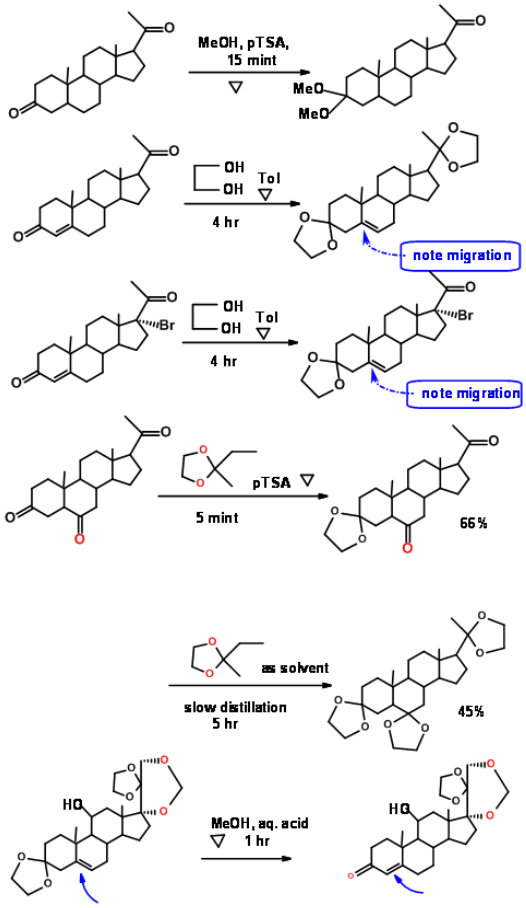



Fig 4.1.7

The demand for **Green Chemistry processes** has prompted search for new green procedures. Some examples from recent literature are given here **(Fig 4.1.8)**.

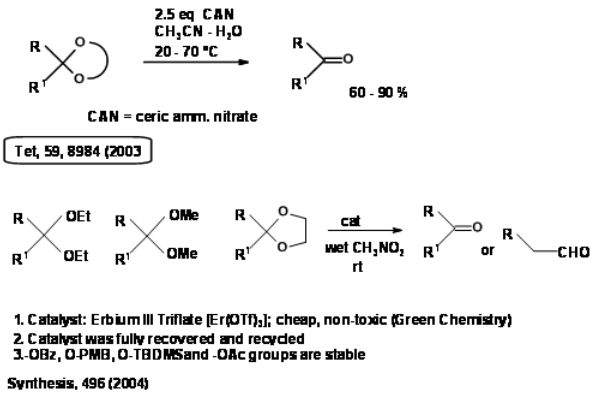



Fig 4.1.8

## Thioketals

Compared with their oxygen analogues, thioketals markedly differ in their chemistry. The formation as well as deprotection is promoted by suitable Lewis acids. The thioacetals are markedly stable under deketalation conditions, thus paving way for selective operations at two different centers. When conjugated ketones are involved, the ketal formation (as well as deprotection) proceeds with double bond migration. On the other hand, thioketals are formed and deketalated without double bond migration **(Fig 4.1.9)**.

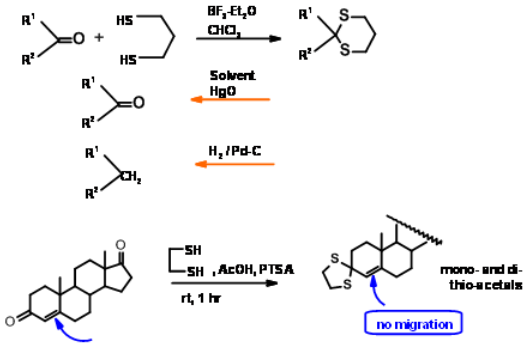



Figure 4.1.9

## Protection of Amino groups (-NH2 &–NH)

N-Acetyl (N – COC$H_3$), N – Benzoyl (N – COPh) Protections

These are the classical protecting groups for primary and secondary amines. The reagents are cheap and the protocol is simple. Such amides generally need drastic conditions for deprotection, though the yields are generally good **(Fig 4.1.10)**. A standard procedure is refluxing in aqueous alkali or aqueous mineral acid. Due to the drastic conditions, care should be exercised in this procedure to ensure racemi zation is avoided. Amides are generally crystalline solids that are easily purified by crystallization. When the protection is introduced at the early stages of a long synthetic scheme and a very stable protection is desired (as in nucleotide synthesis) an amide is the most preferred protection.

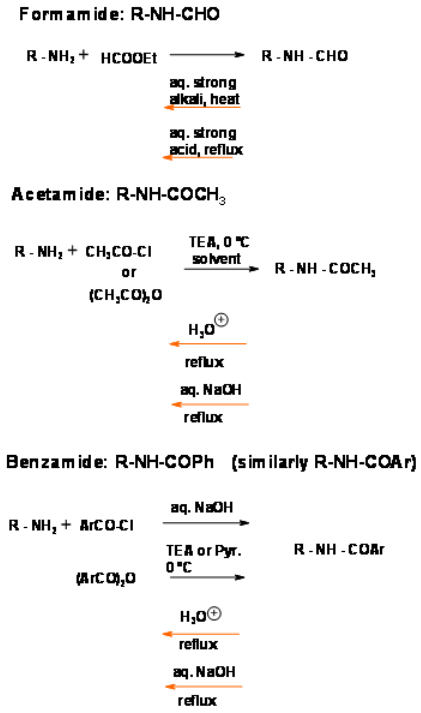



Figure 4.1.10

Several more labile amide bonds have been investigated. The amides of trifluoroacetic acid are of special interest. The introduction as well as cleavage is simple and mild **{Fig 4.1.11)**.

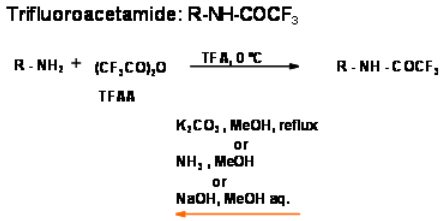
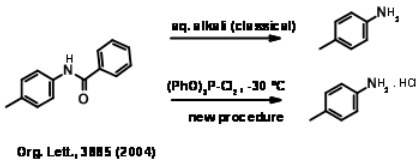



Figure 4.1.11

A recent report in amide hydrolysis is given below.




N – **Phthaloyl Protection** (N – **Pht**)

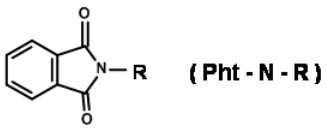



Fig 4.1.13).

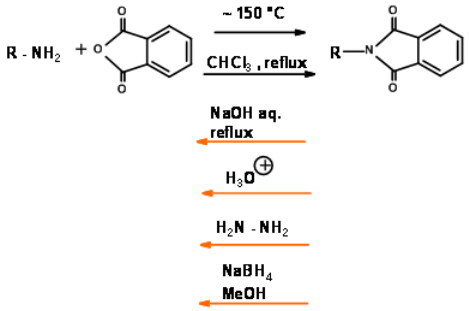



Figure 4.1.12

## Mechanism for $NaBH_4$ Reduction of N – Pht

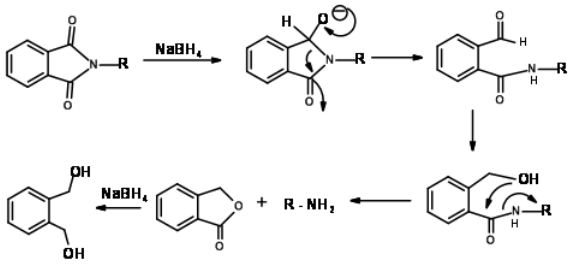
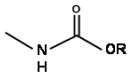



Figure 4.1.13

**N – Carboxylic acid Esters as protective groups**




As described above, the amide bonds are very strong. On the other hand, the ester bonds are easily cleaved by mild base conditions. A carboethoxy protection on amine has an amide bond as well as an ester bond. Since N – COOH groups obtained on hydrolysis are very unstable, this protection provides a large family of protective groups for primary and secondary amines.

**N – Carboethoxycarbonly (N – COOEt) and Carbobenzyloxycarbonyl (N – COOCH2Ph) (N – Cbz or N – Z) Protections:**

These groups are easily introduced using the corresponding chloroformate esters. Anhydrides or mixed anhydrides under mild basic conditions. Both these protections could be removed under prolonged stirring with base at room temperature. Though mild, some racemisation is sometimes observed. The N – Cbz protection has an added advantage in that it could be easily cleaved under

hydrogenolysis conditions **(Fig 4.1.14)**. N – Cbz Protection is however stable to acidic conditions. Compare this with –Boc protection discussed below.

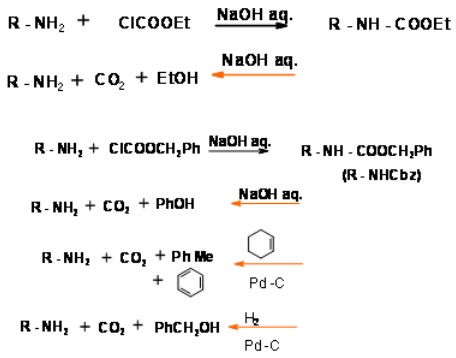



Figure 4.1.14

**Tert-Butyloxycarbonyl Protection ( N – COOBut, N – Boc)**

The Tert-Butyloxycarbonyl Protection could be introduced and removed under very mild acid conditions. This protection is stable to alkali and hydrogenolysis **(Fig 4.1.15)**. Thus, N – Z and N – Boc are complimentary as protective groups.

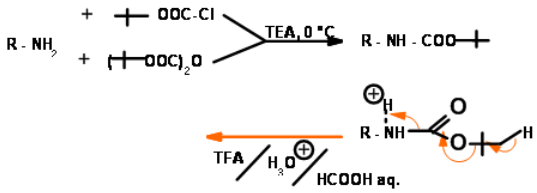



Figure 4.1.15

**N – Fluoromethyleneoxycarbonyl Protection (Fmoc)**

This UV active protecting group is very popular in Solid Phase Peptide Synthesis (SPPS) protocols. Protection as well as deprotection steps proceed under mild conditions in good yields **(Fig 4.1.16)**.

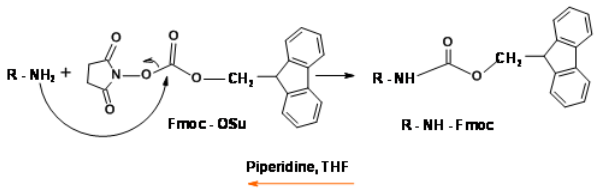



Figure 4.1.16

The mechanism for Fmoc deprotection is shown in **(Fig 4.1.17)**

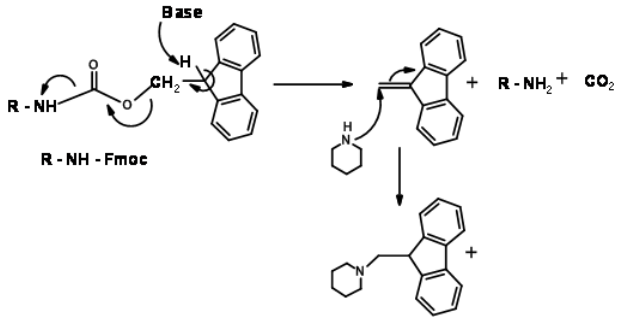



Figure 4.1.17

**N – Silylation**

Silylation is a common protection for active hydrogen on heteroatoms. In the case of N – Si bond, quaternary ammonium fluorides cleave this bond **(Fig 4.1.18)**.

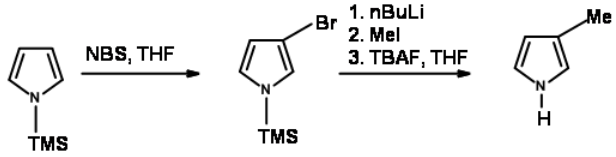



Figure 4.1.18

**N – Tosylation (N – Tos)**

This protection is very stable. N – Tosylation is easily carried out through acid chloride procedure. It is cleaved by solvated electron cleavage reaction. When this group is attached to a primary amine, the –NH group becomes very acidic **(Fig 4.1.19)**.

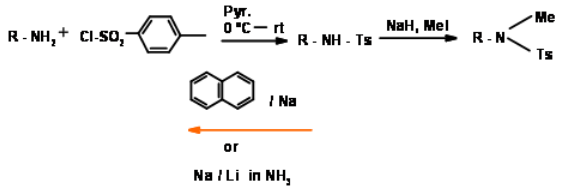



Figure 4.1.19

## Protection of – OH Groups

**Acetates ( – Ac) and benzoates (– Obz)):**

The – OH group protection chemistry has been extensively investigated. The classical protection is the formation of esters of aliphatic and aromatic carboxylic acids. Aromatic esters are comparatively difficult to hydrolyze under mild base condition. This provides an opportunity for selective deprotection protocols **(Fig 4.1.20)**. Note that this protection is sensitive to acid as well as base conditions.

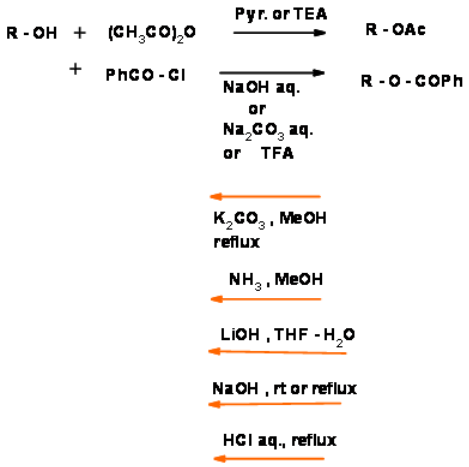



Figure 4.1.20

**Methyl (– OMe) and Benzyl (R – OBn) Ethers**

An ether group is one amongst the most stable functional groups. Hence, this group has been the most favored protecting group. Deprotection was a problem. In the early part of the twentieth century, the only procedure was refluxing with aqueous HI or HBr. In recent years several new procedures have appeared for effective removal under mild conditions. The special feature of the benzyl ethers is that this protection is readily removed under neutral hydrogenolysis conditions **(Fig 4.1.21)**. Substituents like – OMe or – NO2 could be introduced on the benzene ring to modify the reactivity at the protection site.

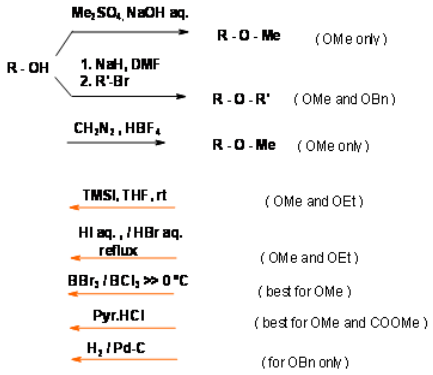
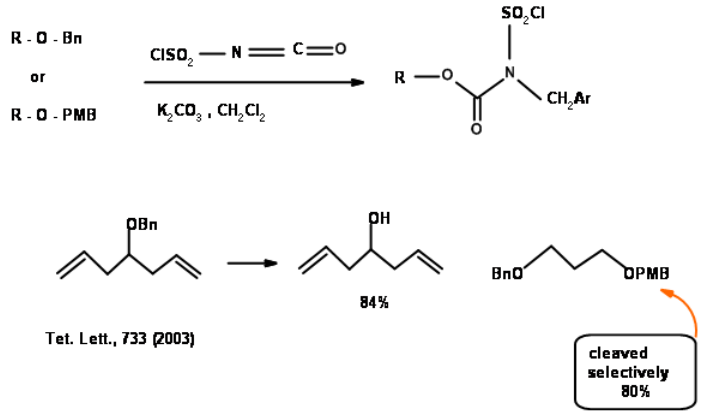



Figure 4.1.21

When an olefin could compete at the hydrogenolysis procedure, the following sequence appears to be an alternate procedure **(Fig 4.1.22)**.




**Bz = Benzyl; PMB = p-Methoxybenzyl**

Figure 4.1.22

Allyl ether is a recent introduction in – OH protection. The versatility of this protection could be seen in the following examples **(Fig 4.1.23)**.

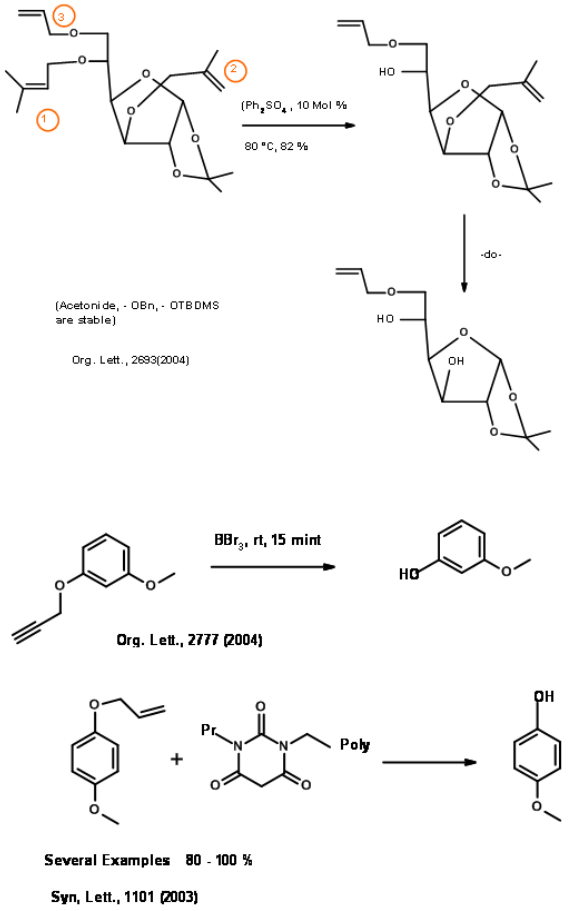



Figure 4.1.23

**Silyl Ethers (R – OSi$R_3$)**

The oxygen – silicon sigma bond is stable to lithium and Grignard reagents, nucleophiles and hydride reagents but very unstable to water and mild aqueous acid and base conditions. A silyl ether of secondary alcohol is less reactive than that of a primary alcohol. The O – trimethylsilyl (O – SiMe3) was first protection of this class. **(Fig 4.1.24)**.

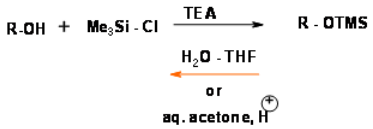



Figure 4.1.24

Replacement of methyl group with other alkyl and aryl groups gives a large variety of silyl ether with varying degrees of stability towards hydrolysis **(Fig 4.1.25)**.

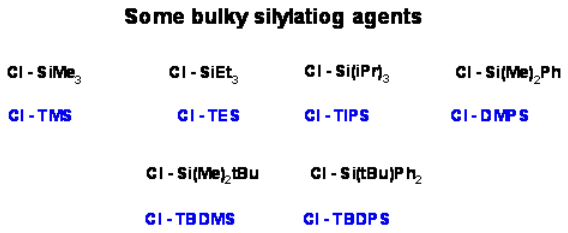



Figure 4.1.25

The following examples illustrate the selectivity in formation and hydrolysis of this group **(Fig 4.1.26)**.

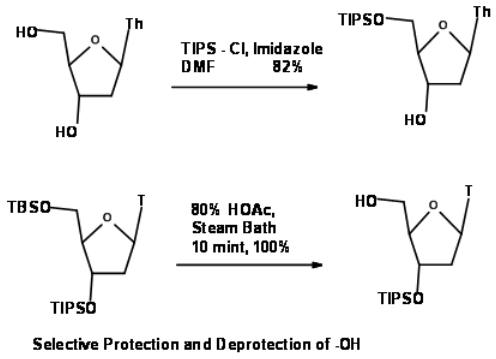



Figure 4.1.26

**Tetrahydropyranyl ether (– OTHP) and Tetrahydrofuranyl ether (– OTHF)**

These protective groups for alcohols are in fact acetals. They are synthesized using the dihydropyran (DHP) and dihydrofuran (DHF) respectively. They behave like acetals in their stability and cleavage **(Fig 4.1.27)**. The rate of formation and cleavage for these two groups differ, which finds application for differential protection of alcohols.

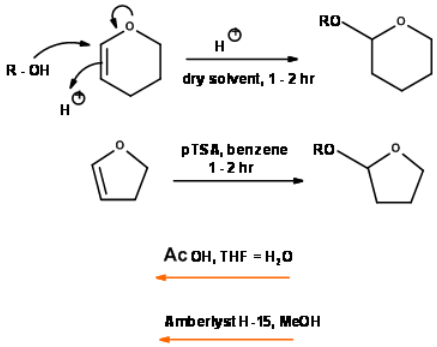



Figure 4.1.27

These protective groups found extensive use in synthesis. However, two major drawbacks were soon observed.

1. A new stereopoint is generated while introducing this protection. Though it is not relevant from the point of view of the target molecule, in chiral molecules this created diastereomer problems in spectroscopy (NMR and MS) and chromatography.
2. These ethers occasionally caused explosions in hydroboration procedures due to peroxide formation. The diastereomer problem was solved by the introduction of O-methyleneoxymethyl ether ( – O – MOM) and O – methyleneoxybenzyl ether (R – O – MOB) *(Fig 4.1.28)*. Several other modifications are now available.

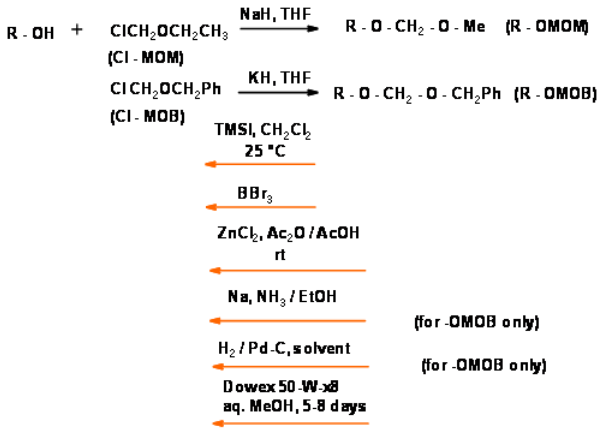



Figure 4.1.28

**Protection of vic – Diols**

On reaction with benzaldehyde or acetone with suitable acid catalyst, vic-diols form cyclic acetals. This in fact is a proof for the existence of vic-diols in the molecule. They are acetal protections and therefore behave as acetals in their chemistry **(Fig 4.1.29)**

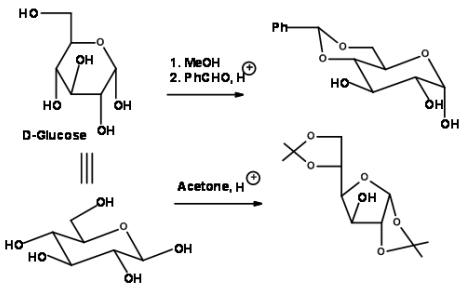



Figure 4.1.29

## Conclusion

The above discussions are just a glimpse of the vast literature on this topic. When more than one competing functional groups are present in a molecule, it may be necessary to introduce at least one protection and one deprotection step in the synthetic scheme. This adds not only to the length of the synthetic scheme, but also to the cost of the final compound. With growing awareness in **Green Chemistry**, chemists have been trying to reduce this protocol to a minimum or preferably avoid this altogether. Several protection free syntheses of natural products are known in the literature. We would discuss this topic at the end of this chapter.

## Further Reading

1. Greene T. W., Protective Groups in Organic Synthesis. Wiley. N. Y., (1980), (1991).
2. Smith M. B., Organic Synthesis, McGraw-Hill Inc, N. Y., (1994).
3. Djerassi C., Steroid Reactions –An Outline for Organic Chemists, Holden-Day nc. San Francisco )1963).
4. Advanced Organic Chemistry: Principles Tools and Logic of Synthesis, R. Balaji Rao, Vishal Publishing Co., Jalandhar, India (2012).
5. Amino Acids, Peptides and Proteins in Organic Chemistry, Vol 4, Ed by Andrew B. Hughes (2011) Wiley-VCH; Protection Reactions, V.V. Sureshbabu and N. Narendra page 1 – 97.

# 4.2 Disconnection of bonds

Having chosen the TARGET molecule for synthesis, the next exercise is to draw out synthetic plans that would summarize all reasonable routes for its synthesis. During the past few decades, chemists have been working on a process called RETROSYNTHESIS. Retrosynthesis could be described as a logical Disconnection at strategic bonds in such a way that the process would progressively lead to easily available starting material(s) through several synthetic plans. Each plan thus evolved, describes a ‘ROUTE’ based on a retrosynthesis. Each disconnection leads to a simplified structure. The logic of such disconnections forms the basis for the retroanalysis of a given target molecule. Natural products have provided chemists with a large variety of structures, having complex functionalities and stereochemistry. This area has provided several challenging targets for development of these concepts. The underlining principle in devising logical approaches for synthetic routes is very much akin to the following simple problem. Let us have a look of the following big block, which is made by assembling several small blocks **(Fig 4.2.1)**. You could easily see that the large block could be broken down in different ways and then reassembled to give the same original block.

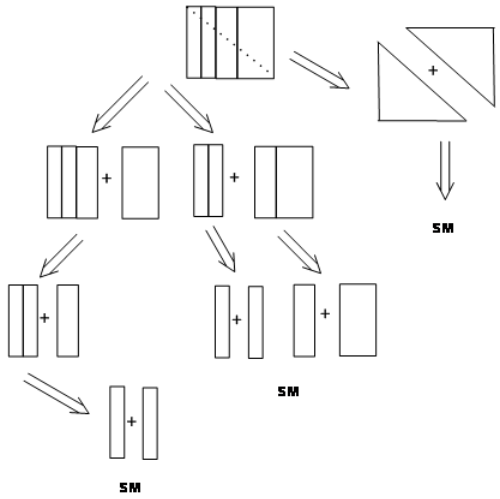



Figure 4.2.1

Now let us try and extend the same approach for the synthesis of a simple molecule. Let us look into three possible 'disconnections' for a cyclohexane ring as shown in Figure 4.2.2.

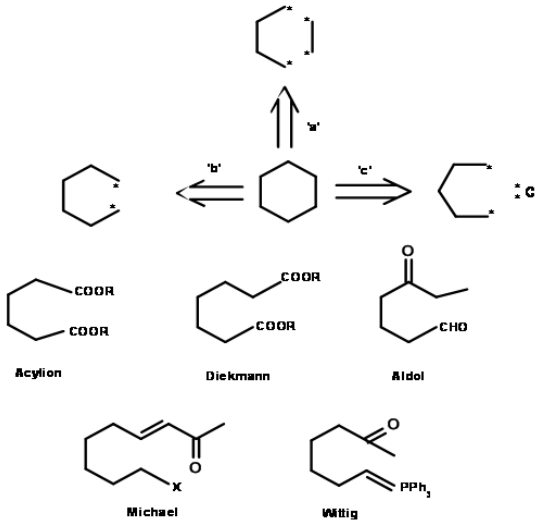



Figure 4.2.2

In the above analysis we have attempted to develop three ways of disconnecting the six membered ring. Have we thus created three pathways for the synthesis of cyclohexane ring? Do such disconnections make chemical sense? The background of an organic chemist should enable him to read the process as a chemical reaction in the reverse (or 'retro-') direction. The dots in the above structures could represent a carbonium ion, a carbanion, a free radical or a more complex reaction (such as a pericyclic reaction or a rearrangement). Applying such chemical thinking could open up several plausible reactions. Let us look into path b, which resulted from cleavage of one sigma bond. An anionic cyclisation route alone exposes several candidates as suitable intermediates for the formation of this linkage. The above analysis describes only three paths out of the large number of alternate cleavage routes that are available. An extended analysis shown below indicates more such possibilities **(Fig 4.2.3)**. Each such intermediate could be subjected to further disconnection process and the process continued until we reach a reasonably small, easily available starting materials. Thus, a complete 'SYNTHETIC TREE' could be constructed that would summarize all possible routes for the given target molecule.

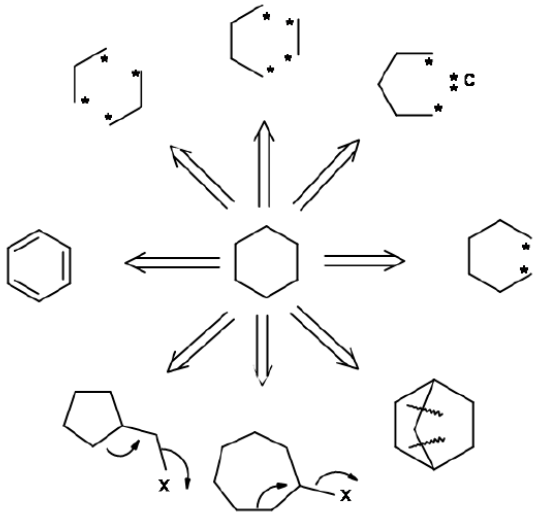



Figure 4.2.3

## 4.3 Efficiency of a route

A route is said to be efficient when the ‘overall yield’ of the total process is the best amongst all routes investigated. This would depend not only on the number of steps involved in the synthesis, but also on the type of strategy followed. The strategy could involve a ‘linear syntheses’ involving only consequential steps or a ‘convergent syntheses’ involving fewer consequential steps. Figure 4.3.1 shown below depicts a few patterns that could be recognized in such synthetic trees. When each disconnection process leads to only one feasible intermediate and the process proceeds in this fashion

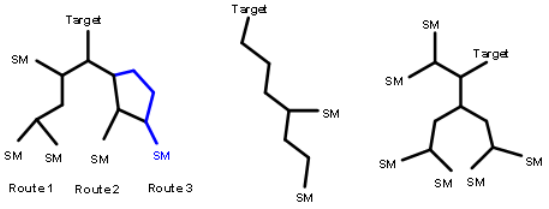



Figure 4.3.1

all the way to one set of starting materials (SM), the process is called a **Linear Synthesis**. On the other hand, when an intermediate could be disconnected in two or more ways leading to different intermediates, branching occurs in the plan. The processes could be continued all the way to SMs. In such routes different branches of the synthetic pathways converge towards an intermediate. Such schemes are called **Convergent Syntheses**.

The flow charts shown below **(Fig 4.3.2)** depicts a hypothetical 5-step synthesis by the above two strategies. Assuming a very good yield (90%) at each step (this is rarely seen in real projects), a linier synthesis gives 59% overall yield, whereas a convergent synthesis gives 73% overall yield for the same number of steps..

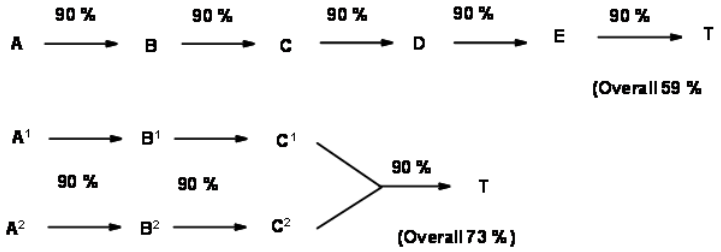



Figure 4.3.2

## 4.4 Problem of substituents and stereoisomers

The situation becomes more complex when you consider the possibility of unwanted isomers generated at different steps of the synthesis. The overall yield drops down considerably for the synthesis of the right isomer. Reactions that yield single isomers (Diastereospecific reactions) in good yields are therefore preferred. Some reactions like the Diels Alder Reaction generate several stereopoints (points at which stereoisomers are generated) simultaneously in one step in a highly predictable manner. Such reactions are highly valued in planning synthetic strategies because several desirable structural features are introduced in one step. Where one pure enantiomer is the target, the situation is again complex. A pure compound in the final step could still have 50% unwanted enantiomer, thus leading to a drastic drop in the efficiency of the route. In such cases, it is desirable to separate the optical isomers as early in the route as possible, along the synthetic route. This is the main merit of the Chiron Approach, in which the right starting material is chosen from an easily available, cheap 'chiral pool'. We would discuss this aspect after we have understood the logic of planning syntheses. Given these parameters, you could now decide on the most efficient route for any given target.

Molecules of interest are often more complex than the plain cyclohexane ring discussed above. They may have substituents and functional groups at specified points and even specific stereochemical points. Construction of a synthetic tree should ideally accommodate all these parameters to give efficient routes. Let us look into a slightly more complex example shown in Figure 4.4.1 . The ketone **4.4.1A** is required as an intermediate in a synthesis. Unlike the plain cyclohexane discussed above, the substitution pattern and the keto- group in this molecule impose some restrictions on disconnection processes.

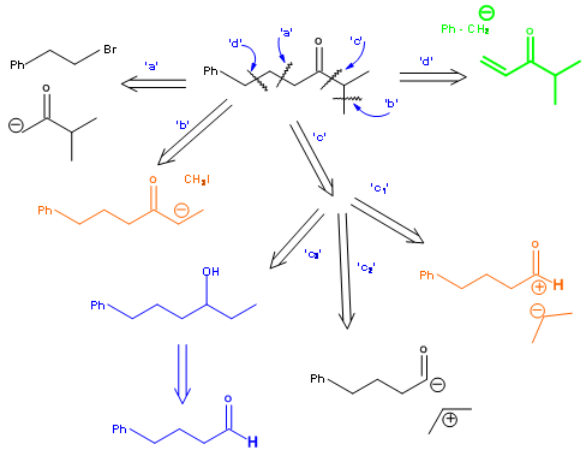



Figure 4.4.1

*Cleavage a:* This route implies attack of an anion of methylisopropylketone on a bromo-component. *Cleavage b:* This route implies simple regiospecific methylation of a larger ketone that bears all remaining structural elements. *Cleavage c:* This route implies three different possibilities. Route C-1 envisages an acylonium unit, which could come from an acid halide or an ester.

Route C-2 implies an umpolung reaction at the acyl unit. Route C-3 suggests an oxidation of a secondary alcohol, which could be obtained through a Grignard-type reaction. *Cleavage d:* This implies a Micheal addition.

Each of these routes could be further developed backwards to complete the synthetic tree. These are just a few plausible routes to illustrate an important point that the details on the structure would restrict the possible cleavages to some strategic points. Notable contributions towards planning organic syntheses came from E.J. Corey's school. These developments have been compiles by Corey in a book by the title LOgIC OF CHEMICAL SYNTHESIS. These and several related presentations on this topic should be taken as guidelines. They are devised after analyzing most of the known approaches published in the literature and identifying a pattern in the logic. They need not restrict the scope for new possibilities. Some of the important strategies are outlined below.

## 4.5 Preliminary scan

When a synthetic chemist looks at the given Target, he should first ponder on some preliminary steps to simplify the problem on hand. Is the molecule polymeric? See whether the whole molecule could be split into monomeric units, which could be coupled by a known reaction. This is easily seen in the case of peptides, nucleotides and organic polymers. This could also be true to other natural products. In molecules like C-Toxiferin 1 **(4.5.1A) (Fig 4.5.1)**, the point of dimerisation is obvious. In several other cases, a deeper insight is required to identify the monomeric units, as is the case with Usnic acid **(4.5.1B)**. In the case of the macrolide antibiotic Nonactin **(4.5.1C)**, this strategy reduces the possibilities to the synthesis of a monomeric unit **(4.5.1D)**. The overall structure has S4 symmetry and is achiral even though assembled from chiral precursors. Both (+)-nonactic acid and (−)-nonactic acid **(4.5.1D)** are needed to construct the macrocycle and they are joined head-to-tail in an alternating (+)-(−)-(+)-(−) pattern. (see J. Am. Chem. Soc., 131, 17155 (2009) and references cited therein).

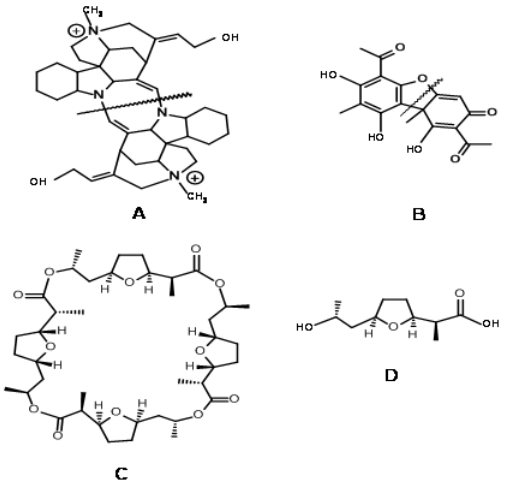



Figure 4.5.1

Is a part of the structure already solved? Critical study of the literature may often reveal that the same molecule or a closely related one has been solved. R.B. Woodward synthesized **(4.5.2C)** as a key intermediate in an elegant synthesis of Reserpine **(4.5.2A)**. The same intermediate compound **(4.5.2C)** became the key starting compound for Velluz et.al., in the synthesis of Deserpidine **(4.5.2B) (Fig 4.5.2)**.

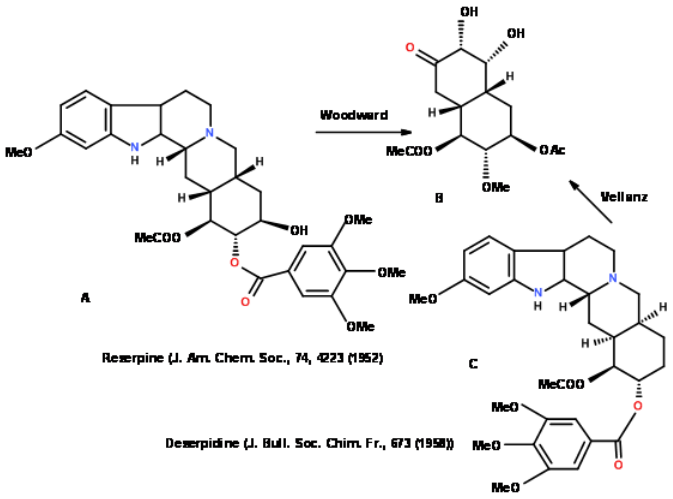



Figure 4.5.2

Such strategies reduce the time taken for the synthesis of new drug candidates. These strategies are often used in natural product chemistry and drug chemistry. Once the preliminary scan is complete, the target molecule could be disconnected at Strategic Bonds.

## 4.6 Strategic Bonds, Retrons and Transforms

STRATEGIC BONDS are the bonds that are cleaved to arrive at suitable Starting Materials (SM) or SYNTHONS. For the purpose of bond disconnection, Corey has suggested that the structure could be classified according to the sub-structures generated by known chemical reactions. He called the sub-structures RETRONS and the chemical transformations that generate these Retrons were called TRANSFORMS. A short list of Transforms and Retrons are given below (TABLE 4.6.1). Note that when Transforms generate Retrons, the product may have new STEREOPOINTS (stereochemical details) generated that may need critical appraisal.

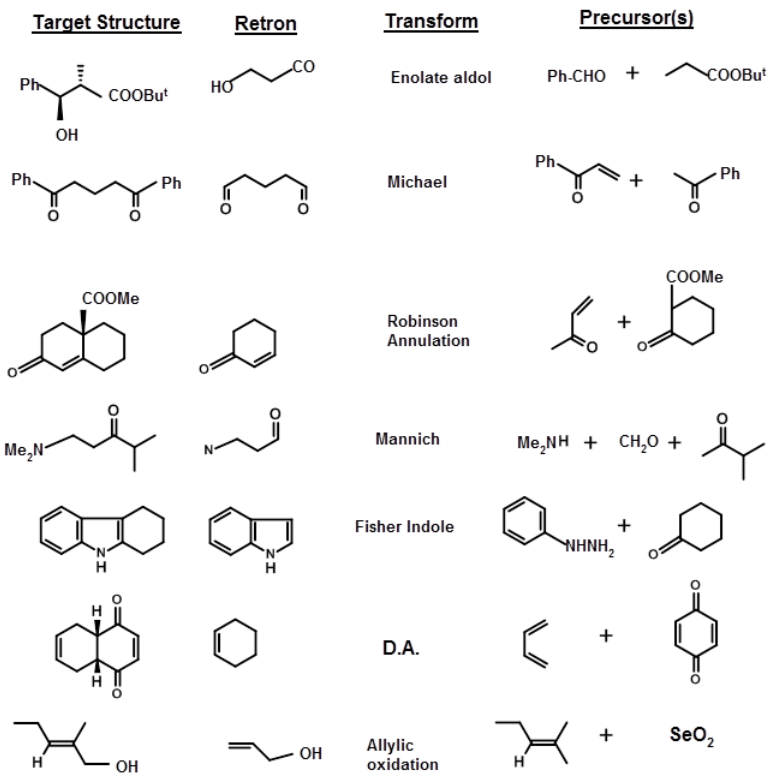



Figure 4.6.1

The structure of the target could be such that the Retron and the corresponding Transforms could be easily visualized and directly applied. In some cases, the Transforms or the Retrons may not be obvious. In several syntheses, transformations do not simplify the molecule, but they facilitate the process of synthesis. For example, a keto- group could be generated through modification of a -CH-$NO_2$ unit through a **Nef reaction**. This generates a new set of Retron / transforms pair. A few such transforms are listed below, along with the nomenclature suggested by Corey **(Fig 4.6.2)**.

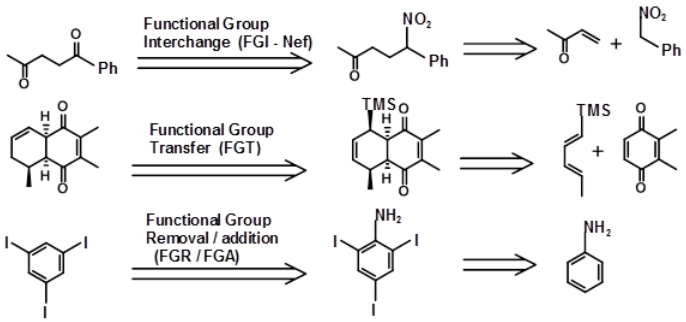



Figure 4.6.2

A Rearrangement Reaction could be a powerful method for generating suitable new sub-structures. In the following example, a suitable Pinacol Retron, needed for the rearrangement is obtained through an acyloin transform **(Fig 4.6.3)**. Such rearrangement Retrons are often not obvious to inexperienced eyes.

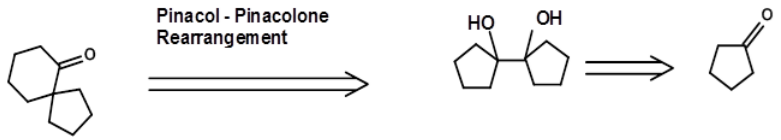



Figure 4.6.3

Some transforms may be necessary to protect (acetals for ketones), modify (reduction of a ketone to alcohol to avoid an Aldol condensation during a Claisen condensation) or transpose a structural element such as a stereopoint (e.g. $S_N2$ inversion, epimerization etc.,) or shifting a functional group. Such transforms do not simplify the given structural unit. At times, activation at specific points on the structure may be introduced to bring about a C-C bond formation and later the extra group may be removed. For example, consider the following retrosynthesis in which an extra ester group has been introduced to facilitate a Dieckmann Retron. In complex targets, combinations of such strategies could prove to be a very productive strategy in planning retrosynthesis. Witness the chemical modification strategy shown below for an efficient stereospecific synthesis of a trisubstituted olefin **(Fig 4.6.4)**

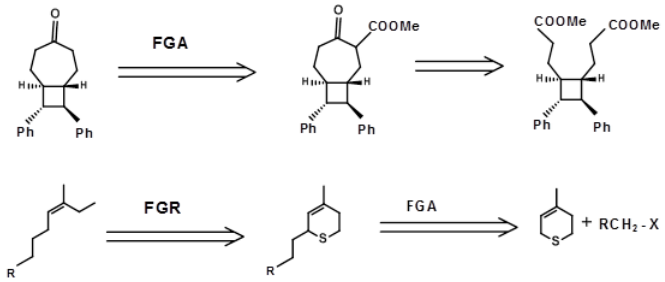



Figure 4.6.4

Figure 4.6.4 Examples for FGA / FGR strategies for complex targets

Amongst the molecular architectures, the bridged-rings pose a complex challenge in Structure-Based disconnection procedures. Corey has suggested guidelines for efficient disconnections of strategic bonds.

A bond cleavage for retrosynthesis should lead to simplified structures, preferably bearing five- or six-membered rings. The medium and large rings are difficult to synthesize stereospecifically. Amongst the common rings, a six-membered ring is easily approached and manipulated to large and small rings. Simultaneous cleavage of two bonds, suggesting cycloaddition – retrons are often more efficient. Some cleavages of strategic bonds are shown in Figure 4.6.5, suggesting good and poor cleavage strategies based on this approach. However, these guidelines are not restrictive.

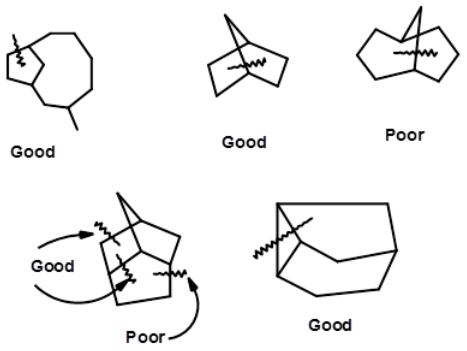



Figure 4.6.5: Some cleavages at strategic bonds on bridged-ring systems.

Identifying Retron – Transform sets in a given target molecule is therefore a critical component in retrosynthesis. Such an approach could often generate several synthetic routes. The merit of this approach is that starting materials do not prejudice this logic. Retrosyntheses thus developed could throws open several routes that need further critical scrutiny on the basis of known facts.

Identification of Retrons / Transforms sets provided the prerequisite for computer assisted programs designed for generating retrosynthetic routes. A list of Retrons and the corresponding transforms were interlinked and the data was stored in the computer. All known reactions were thus analyzed for their Retron / Transform characteristics and documented. The appropriate literature citations were also documented and linked. Based on these inputs, computer programs were designed to generate retrosynthetic routes for any given structure. Several such programs are now available in the market to help chemists generate synthetic strategies. Given any structure, these programs generate several routes. Once the scientist identifies the specific routes of interest for further analysis, the program generates detailed synthetic steps, reagents required and the appropriate citations. In spite of such powerful artificial intelligence, the intelligence and intuitive genius of a chemist is still capable of generating a new strategy, not yet programmed. Again, human intelligence is still a critical input for the analysis the routes generated using a computer. Based on the experience of the chemists' team, their projected aim of the project and facilities available, the routes are further screened.

## 4.7 Elaboration of the concepts

Short lists of syntheses that exemplify retroanalysis strategies devised through powerful transforms are given below. Several syntheses from natural product chemistry are later discussed in this chapter, which further illustrates these points.

Retrosynthesis based on Diels-Alder Transform; (E.J. Corey et.al., J.A.C.S. (1972), 94, 2549). Fumagillol **(4.7.1A)** presents 4 stereocentres and sensitive functionalities.

Simplification of the functional groups first exposed a vic-diol. This site could come from an olefin D. Further retroanlysis led to a structurally simplified target sequence B to F. A cyclohexene ring system is suitable for a powerful DA Transform. This step generated two stereocentres in one reaction and also an olefin in the correct position for hydroxylation. The key intermediate C could also be generated through a functional group transform leading to G. This provided scope for a new set of starting materials using another DA Transform. The Retrosynthetic analysis and the actual synthesis are shown in Figure 4.7.1.

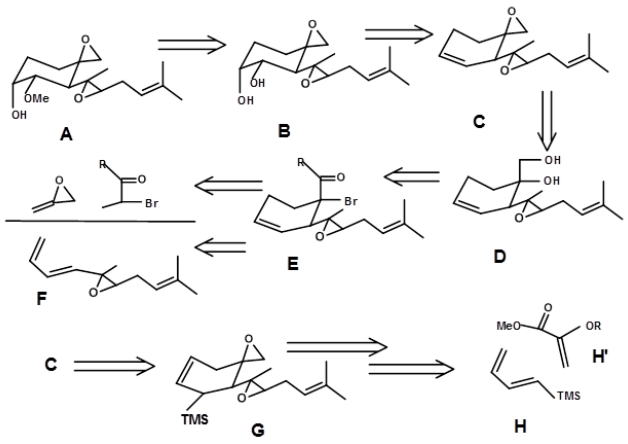



Figure 4.7.1

Synthetic protocol reported by Corey is outlined in Figure 4.7.2

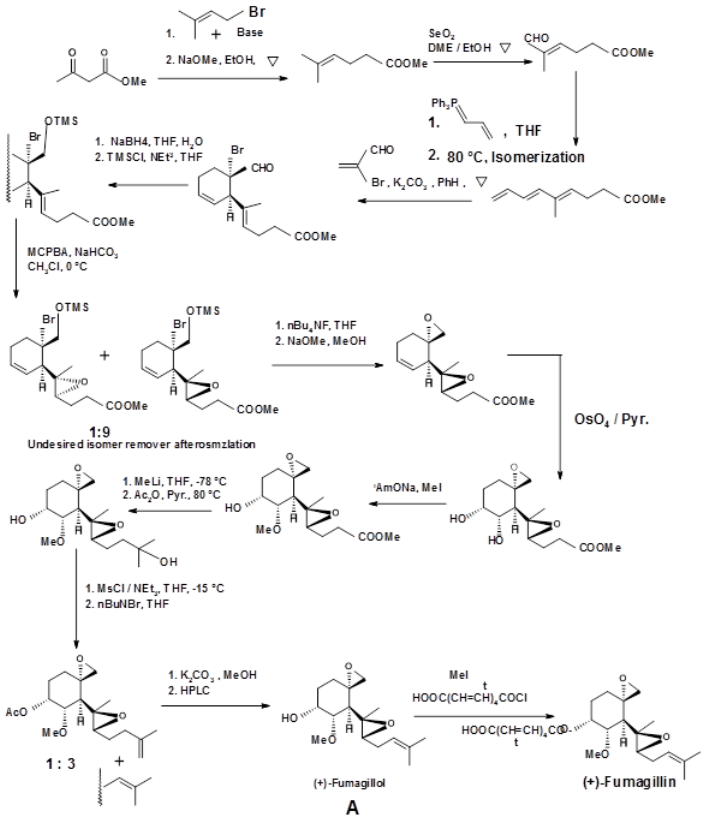



Figure 4.7.2

For the synthesis of Estrone, an interesting DA Transform strategy was devised by Kametani et.al.. The retrosynthetic strategy is depicted in Fig 4.7.3. The required diene precursor was generated via cyclo-reversion reaction of a cyclobutene unit (T. Kametani et.al., Tetrahedron, (1981), 37, 3).

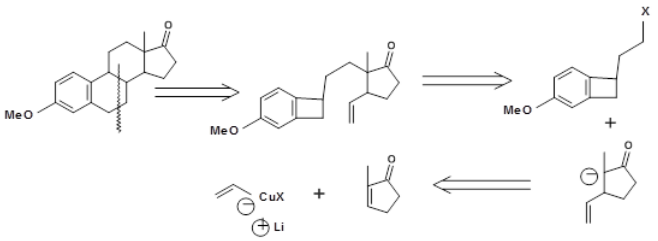



Figure 4.7.3 : DA approach to Estrone

The crucial stereospecific trisubstituted olefins on Squalene **(4.6.4B)** were synthesized using a Claisen Retron **4.7.4A (Fig 4.7.4)**. Note the double Claisen approach in this strategy.

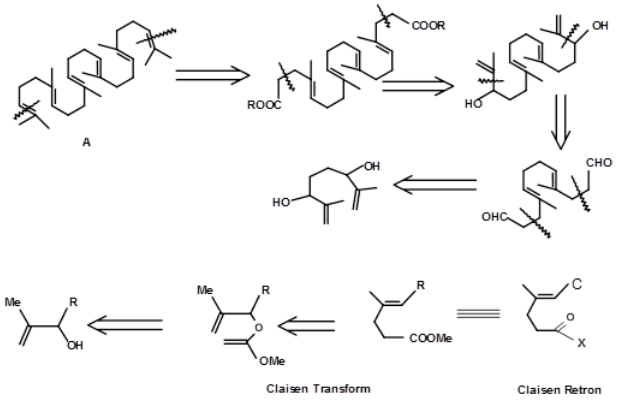



Figure 4.7.4

The biogenetic-type cyclisation of olefins provides scope for application of Mechanistic Transform or transforms based on mechanistic considerations. A cleaver introduction of a chiral centre provided an efficient route for generating several enantiopure chiral centres in one step using this strategy **(Fig 4.7.5)**.

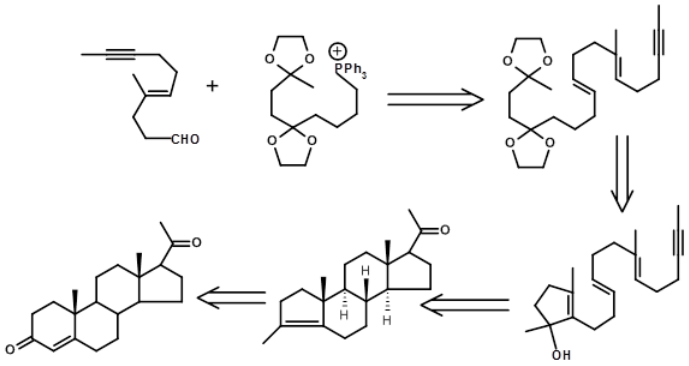



Figure 4.7.5 Mechanism based Transform strategy for Estrone; W.S. Johnson, J. Am. Chem. Soc., 93, 4333 (1971).

## 4.8 The problem of enantiomers

In these lengthy discussions above, we learnt about disconnection approaches. We said that stereocentres could introduce special challenges in planning efficient synthetic routes. Let us look at the molecule Biotin to understand disconnection strategies and problem of stereocentres.

Baker established the structure of Biotin in 1947 through an unambiguous synthesis of the molecule. A retroanalysis of the synthetic scheme is as shown below **(Fig 4.8.1)**.

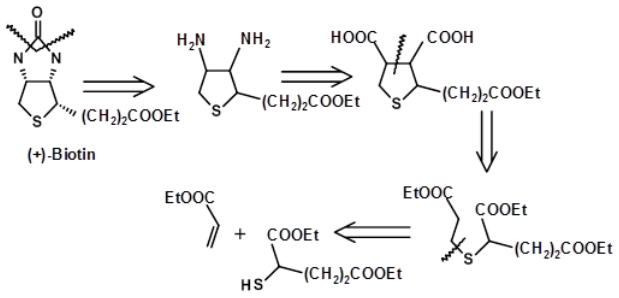



Figure 4.8.1

The SM chosen and the synthetic approach clearly established the atom connectivities and the overall structure of the compound. However, the route made not attempt to synthesize one pure isomer because the actual stereochemistry was not established at that time. The route yielded all the eight stereoisomers (3 asymmetric centers). These isomers were carefully separated. In 1952 the biologically active isomer was identified as the all cis- enantiomer (+)-Biotoin. At this stage, several groups reported the stereospecific synthesis of the all cis- isomer exclusively **(Fig 4.8.2)**. The following retroanalysis depicts three such attempts. Note that these efforts were directed towards the synthesis of the racemate and not the pure (+)- isomer of Biotin.

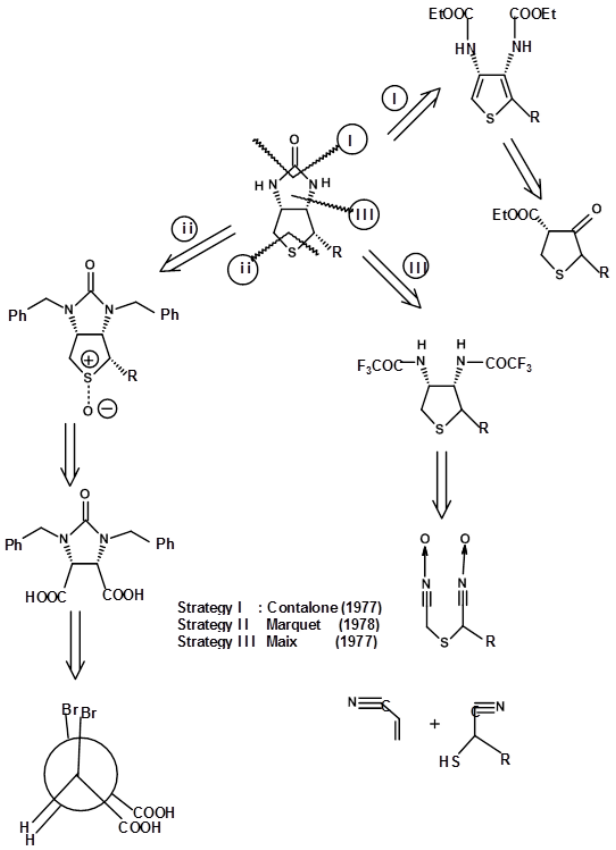



Figure 4.8.2

These approaches solved the problem of diastereomeric purity. But they still left a mixture of two unresolved enentiomer viz., (±)-Biotin. To obtain a pure enantiomer in excellent yields, you have to resolve the racemic mixtures at appropriate stages. Alternately one could resort to asymmetric synthesis at all crucial stages. A still better approach would be to start from a chiral SM, which has most of the stereocentres in the correct fashion. This elegant approach is called the **Chiron approach**. When carefully executed, such procedures yield very pure enantiomer as the final product. Two such approaches for (+)-Biotin is shown below. In the first approach a chiral amino acid cysteine is chosen because it has one key asymmetric center, the sulphur moiety and a carboxylic acid

in the correct positions **(Fig 4.8.3)**. In this example the choice of the SM is quite obvious. Note the cleaver introduction of the second nitrogen and the cyclisation step leading to the formation of the tetrahydrothiophene ring. Also note that the yield of Cram vs anti-Cram (chelation) products could be influenced by a choice of the reagent. These kinds of insights come only through a thorough knowledge of this particular reaction.

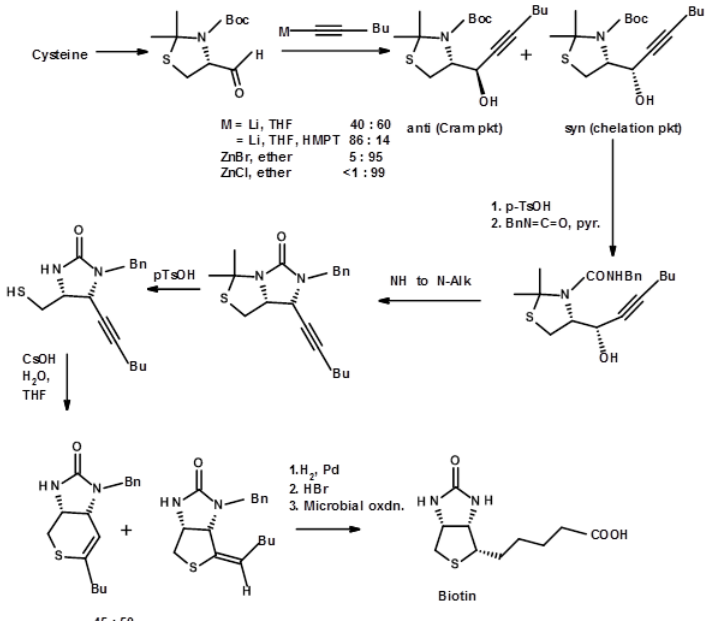



**Fig. 4.8.3**

In the second example chosen here, the choice of the SM as the appropriate chiron is not obvious but hidden. Such an analysis demands a more critical insight into the concerned stereocentres.

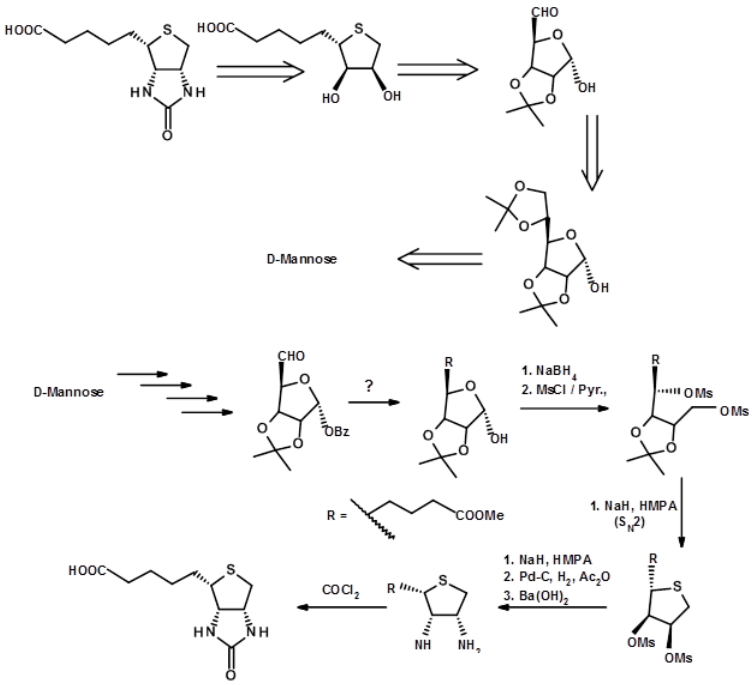



Figure 4.8.4

## Conclusion

An emerging concept in the Logic In Synthesis is deliberate planning of Green Synthetic Pathways. The logic of retroanalysis is same as discussed above. The only differentiating point is that the criteria for selection of synthetic route discussed earlier would now analyses the same synthetic tree through a Green Chemistry window to select only those routes that have maximum Green aspects. The green chemistry goal is enforced through inclusion the Twelve Principles of Green Chemistry. This could be done by embracing one or more of the following techniques - Use of Green Energy Sources like Microwave, Sonochemistry, Photochemistry etc., solvent free syntheses, using easily recoverable new solvent and eco-friendly solvents, reusable catalysts in syntheses and schemes that avoid protecting group chemistry. Most of the chemistry used in Green Chemistry is not really new to chemists. Chemistry is now revisited due to the environment consciousness that has now crept into industrial chemistry and society at large. Most of the chemistry is buried in two centuries of chemical literature. Several new discoveries in reagents have appeared in recent years. Now Chemists have to become more alert to this awakening to environmental damages caused by chemical activities on this globe.

The above discussions are meant only to illustrate the major steps involved in retrosynthetic analysis of a molecule. Thorough knowledge of synthetic tools, mechanisms and stereochemistry are essential prerequisites for a chemist to venture into the synthesis of complex molecules. Needless to add that all these efforts have to be suitably backed up by a team of chemists, having a rigorous training in laboratory techniques, a first-hand experience on several organic reactions / reagents and thorough knowledge of purification techniques, spectroscopic techniques and not the least, a good knowledge of search techniques to scan and retrieve requisite information from the vast chemical literature accumulated since the dawn of modern chemistry.

## Retroanalysis of Some Interesting Molecules

Let us now dwell deep into a few select structures chosen from natural product chemistry and see how these structures have been tackled through different synthetic strategies. We would start with a simple molecule – Disparlure – with only two asymmetric centers. The course would end with a flovour of some Green Chemistry based syntheses to draw the attention of students to this newly emerging concepts and concerns.

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# 5: Strategies in Disparlure Synthesis

The gypsy moth (*Porthytria dispar*) is a serious pest of the forests. In 1976 B.A. Bierl et.al., (Science, 170,88 (1970)) isolated the sex pheromone from extracts of 78,000 tips of the last two abdominal segments of female moths. The structure was assigned as **5.1.** Later, the precursor molecule – the cis-olefin was also isolated from the same source.

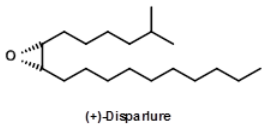


Figure 5.1

A laboratory bioassay from synthetic materials showed that just 2 pg of 5.1 was enough to elicit bioactivity. Since the availability of the molecule from natural sources was very minute even for structure elucidation problems and study its anticipated role as pest control molecule, there was intense interest in an efficient synthesis of this molecule. Some disconnections for this simple molecule are depicted in Figure 5.2.

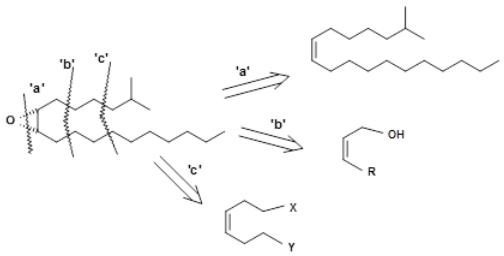


Figure 5.2

Epoxides could be made from corresponding olefins. In this case, the olefin should be Z-olefin. When synthesis of such olefins are not stereospecific, direct epoxidation using peroxides would yield a mixture of α- and β-epoxide from both isomeric olefins. To avoid such mixtures at the last stage, one should introduce selectivity at an early stage of the synthesis.

The first attempt was directed towards synthesis of the appropriate olefin and epoxidation (B.A. Bierl et.al., (Science, 170, 88 (1970)). The stereoselectivity was unsatisfactory (Fig 5.3). This necessitated extensive purification.

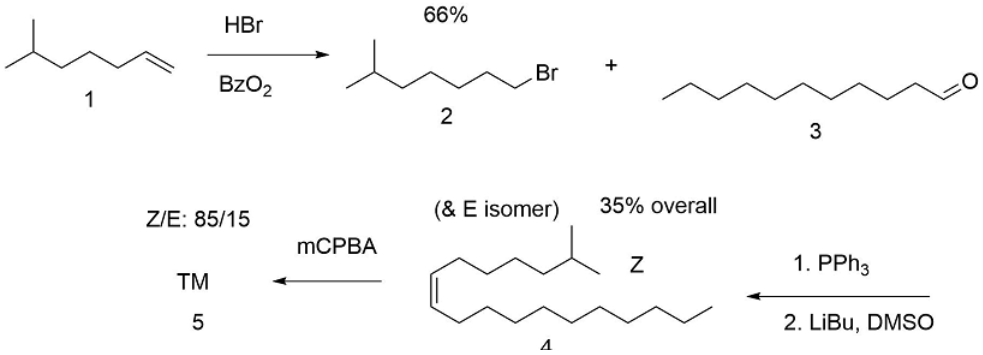


Figure 5.3. Image constructed by Toby Hoch.

The ratio of cis- / trans- isomers in Wittig Olefination reaction could be altered by modification of reagents and reaction parameters. H.T. Bestmann et.al., (Chem. Ber., 109, 3375 (1976)) were able to improve the synthesis by modifying the Wittig reaction conditions **(Fig 5.4)**.

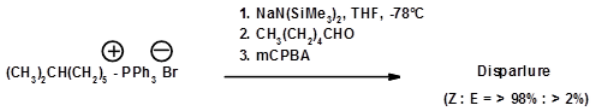


Figure 5.4

Pure cis- olefins could be obtained by catalytic reduction of acetylenes (Angew. Chem., Int. Ed., 11, 60 (1972). Klunenberg et.al., (Angew. Chem., Int. Ed., 17, 47 (1978) took advantage of the cis- olefin moieties in 1,5-cyclooctadiene by selective oxidation of one double bond. The chains were introduced by sequential Kolbe electrolysis **(Fig 5.5)**.

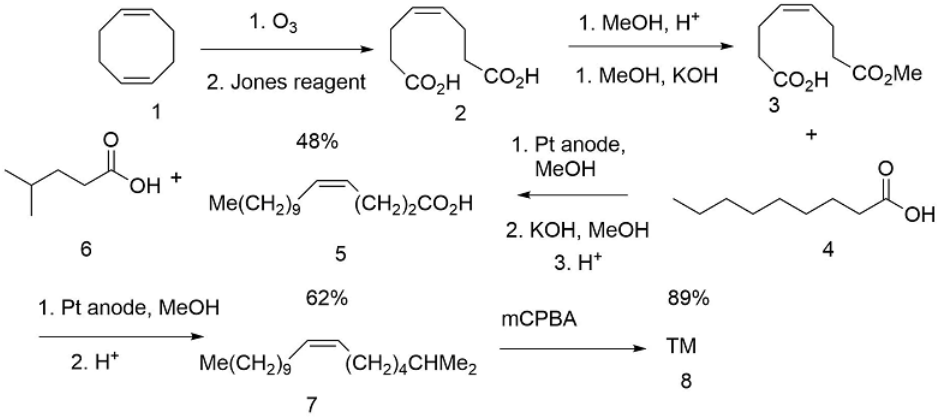


Figure 5.5. Image constructed by Toby Hoch.

## Synthesis of Optically pure Disparlures

Epoxidation of olefins yield only racemates unless the epoxidation step involves an asymmetric synthesis. Synthesis of pure (+)- and (-)- isomers could be achieved in three ways.

1. Resolution of a racemate: This could be a method of choice when both enantiomers are needed for SAR studies. All antipodes of the compound would be available through identical synthetic pathways.
2. Asymmetric synthesis of appropriate intermediates: When only one of the antipodes is desired, this process provides a wide range of synthetic possibilities for investigation. When a large number of closely related compounds are the targets, this method is a better choice.
3. Sourcing the chiral intermediate from a suitable chiral pool: Once the chiral target is clear, this could be a method of choice. In the case of Disparlure, the amount that could be isolated from gypsy moth was so small that even the optical rotation could not be determined. Several workers have reported synthesis of optically pure (+)- and (-)- Disparlure and its structural isomers. The first report came from S. Iwaki et.al., (J. Am. Chem. Soc., 96, 7842 (1974)). They started with L-(+)-Glutamic acid and resolved the intermediate diastereomeric alcohol-lactones by repeated crystallization technique **(Fig 5.6)**. Their synthesis was not stereospecific. SAR studies revealed that the cis-(+)- isomer was most effective.

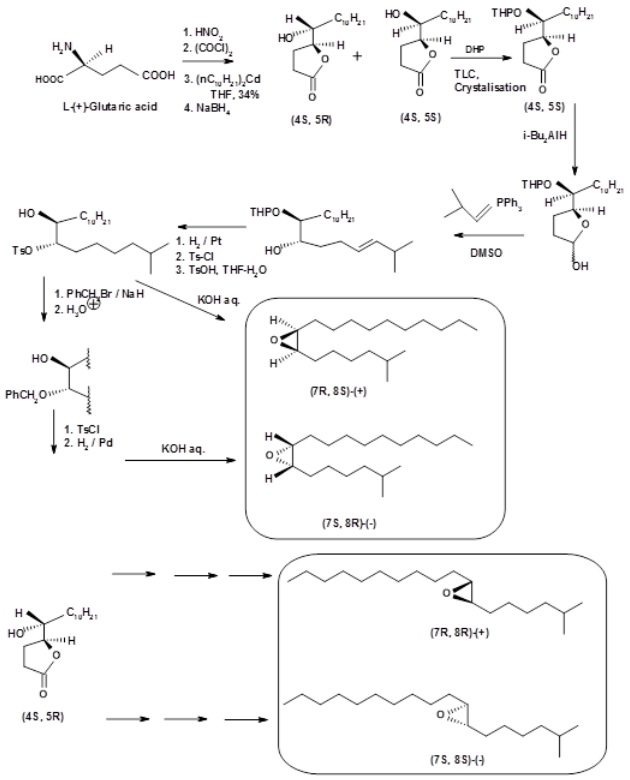


Figure 5.6

Mori et.al.,( Tet. Lett., 3953 (1976); Tetrahedron, 53, 833 (1979)) soon followed with a synthesis of (+)- and (-)- Disparlures starting from L-(+)-tartaric acid **(Fig 5.7)**.

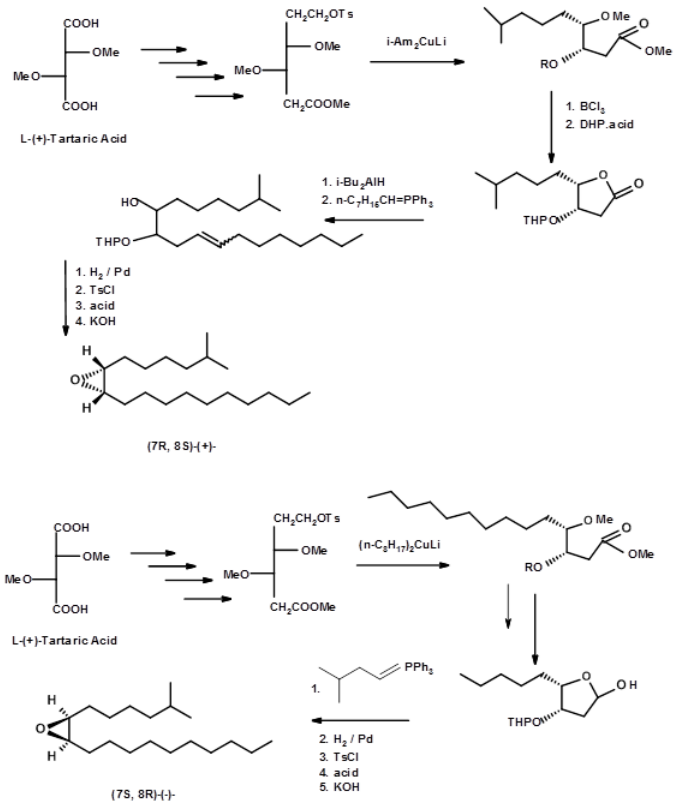


Figure 5.7

This synthesis had the merit that some of the chiral intermediated were crystallisable and therefore amenable for easy purification to very pure intermediates and pure final products. Their intermediates were subjected to critical spectral analysis to assess their purity. Thus, their bio-assays gave more reliable data. A synthesis of (+)- and (-)- Disparlure from another chiral synthon - isopropylidene D- and L- erythroses - was reported by Alexandros E. Koumbis et.al., (Tetrahedron Letters, 46, 4353 (2005)) **(Fig 5.8)**.

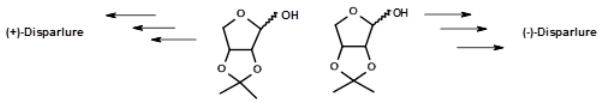


Figure 5.8

A successful synthesis of (+)- Disparlure by the application of Sharpless epoxidation was reported by Kossier B. E.. et.al., (J. Am. Chem. Soc., 103, 464 (1981)) **(Fig 5.9)**.

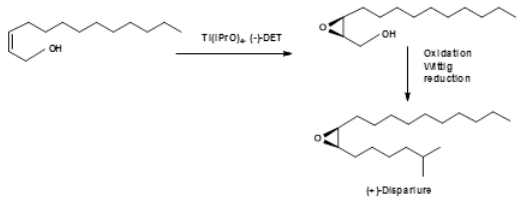


Figure 5.9

Synthesis of all four isomers in a very pure form came from the school of Sharpless E. B. ( Tet. Lett., 6411 (1992)). Using both the chiral hydroxylation agents, they reported an efficient synthesis of all enantiomers **(Fig 5.10)**. The efficiency of the asymmetric synthesis was as high as 95% and gave 100% pure intermediated by crystallization. The overall process was very efficient.

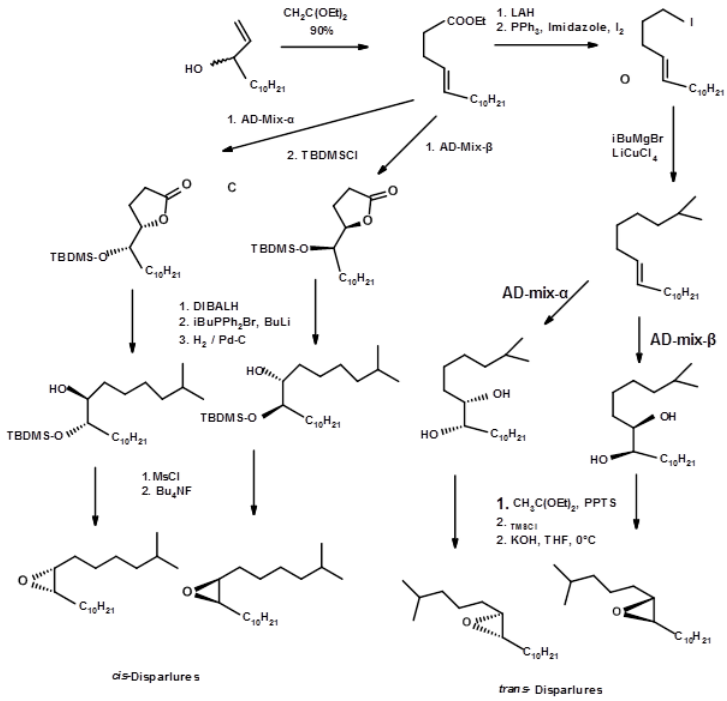


Figure 5.10

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# 6: Strategies in (-)-Menthol Synthesis

(-)-Menthol is amongst the most important perfume / flavor chemical, extensively used in pharmaceuticals, cosmetics, toothpastes, chewing gums and toiletries. Out a the estimated total production of about 20,000 m.tons, natural menthol accounts to about 13 m.tons, the rest coming from synthetic sources. The natural source - oil of Mentha Arvensis - being erratic due to dependence on monsoon, the demand for synthetic menthol is on the increase. The manufacturing processes chosen for discussions here demonstrate three important methodologies used in industry for the synthesis of chiral compounds. A summary of some of the known processes is provided in Figure 6.1.

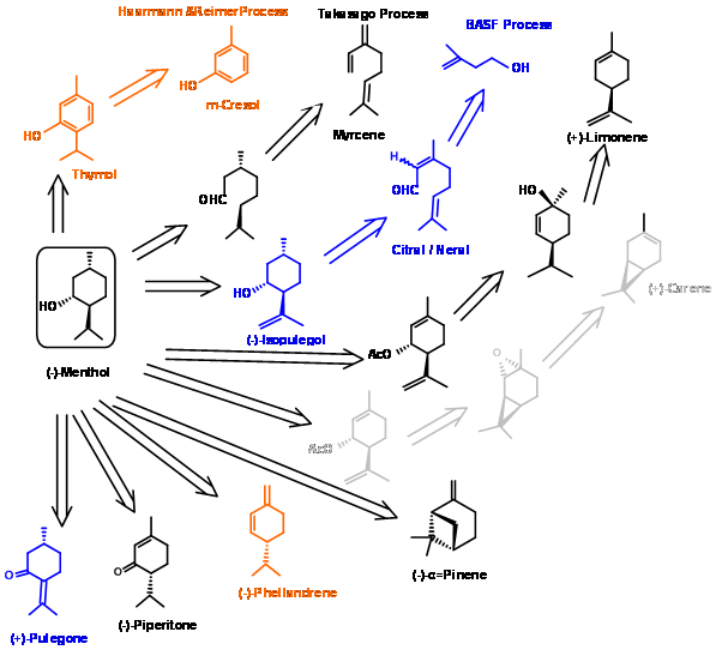



Fig 6.1

**Symrise Process** (formerly know as Haarmann & Reimer process) (US Patent 3,943,181 (Mar 9 1976)) – In this process **(Fig 6.2)**, thymol is synthesized from m-cresol. Catalytic hydrogenation gave a mixture of Menthols from which menthols were first obtained as a racemic mixture by careful fractional distillation. The residual mixture was epimerised to increase the content of racemic menthol using a patented catalytic process. The breakthrough in the process is the resolution of the benzoate ester of the racemate by recrystallization by a process of seeding the concentrate with one pure epimer. The mother liquor that was now rich in the (+) isomer was recycled by taking it back to the distillation cycle. In this process, overall yield of (-)-menthol is about 90%.

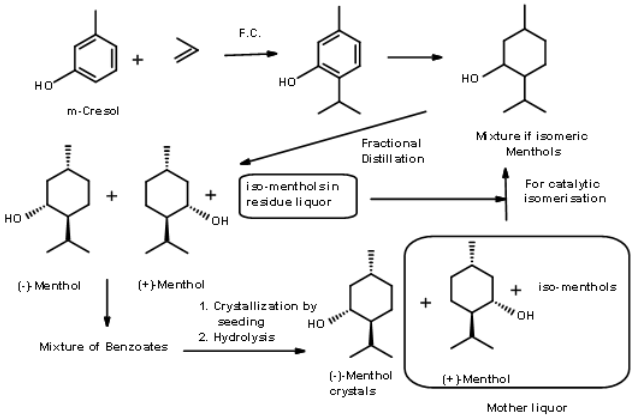



Fig 6.2

**Takasago Process:** In this process a (S)-DINAP catalysed isomerization is the key step **Fig 6.3**. Addition of lithium amide to Myrcene gave an addition compound that was isomerised using a chiral ruthenium catalyst. Hydrolysis of the resulting enamine gave an aldehyde citronellal in high enantiomeric purity. This was cyclized by Lewis catalyst. Catalytic reduction of the olefin gave (-)-Menthol1.

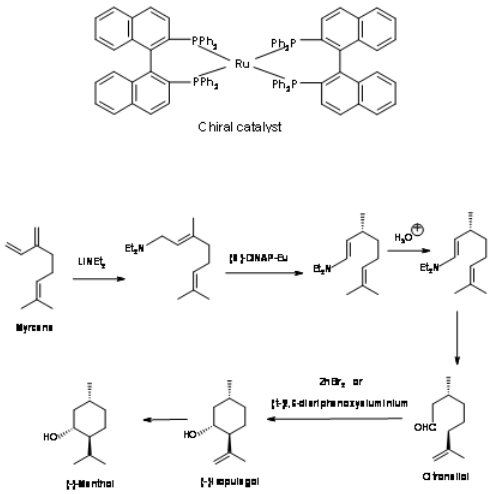



Fig 6.3

**BASF Process:** BASF has already set up processes for the synthesis of a series of terpenes starting from butene. In view of the high demand for (-)-Menthol, they extended the product chain to (-)-Menthol as well. The scheme for the synthesis of the product chain is shown in Figure 6.4.

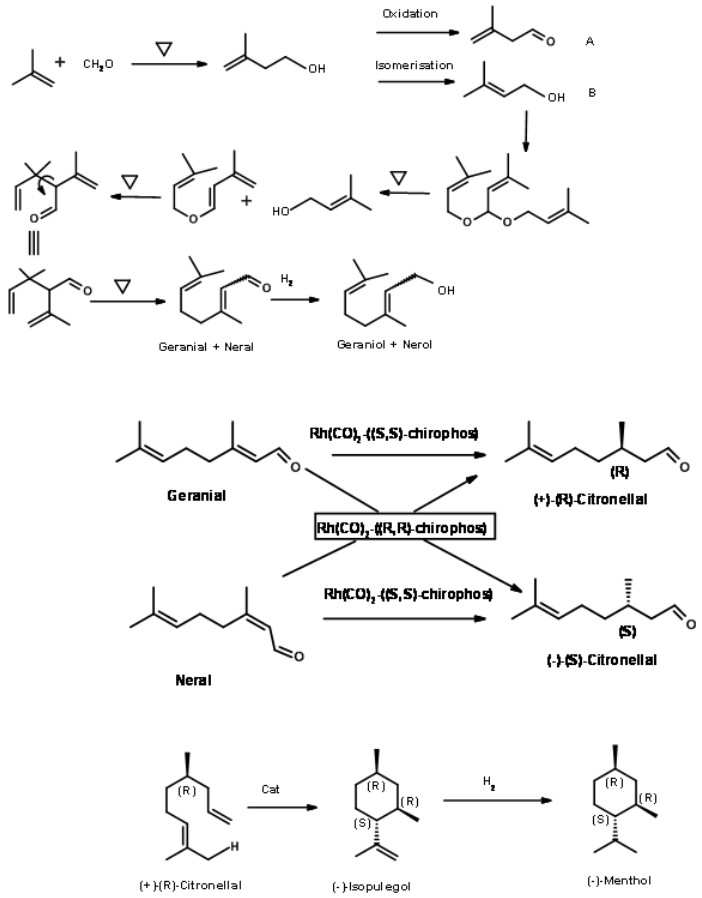



Fig 6.4

Extention of the Citral value chain to (+)-Citronellal, (-)-Isopulegol and finally to (-)-Menthol gave a range of value added products. Note that these processes have taken advantage of the developments in catalytic processes in recent years. Details of the catalysts are not made public.

## References


1. Preparation of citral, United States Patent 4288636 (09/08/1981)
2. Method for the production of menthol, United States Patent 7709688 (05/04/2010);
3. Enantioselective hydrogenation of allylic and homoallylic alcohols, J. Am. Chem. Soc., 1987, 109 (5), pp 1596–1597
4. Norbert; Method for the production of isopulegol, United States Patent 7550633 (06/23/2009);
5. Diarylphenoxy aluminum compounds, United States Patent 7608742 (10/27/2009)
6. CONTINUOUS PROCESS FOR PREPARING MENTHOL IN PURE OR ENRICHED FORM, WIPO Patent Application WO/2009/033870 (03/19/2009).


**(-)-Menthol from (+)-Limonene(Fig 6.5):** Limonene is abundantly available from peels of citrus fruits. On selective catalytic reduction with Ra-Ni, it could be reduced to (+)-1-Menthene, which on epoxidation and hydrolysis gave (+)-1-hydroxyneocarvomenthol. Acylation followed by pyrolysis gave (-)-trans-menth-2-ene-1-ol as the major product. The crude product was solvolysed to give a mixture of piperityl actates as the allylic migration products. The crude product was distilled at this stage to separate the cis- and trans piperitols. The minor ring contraction product was useful as perfume intermediate elsewhere. The final reduction was achieved by H2 / Pd-C to give 75% yield of (-)-Menthol after fractional distillation.

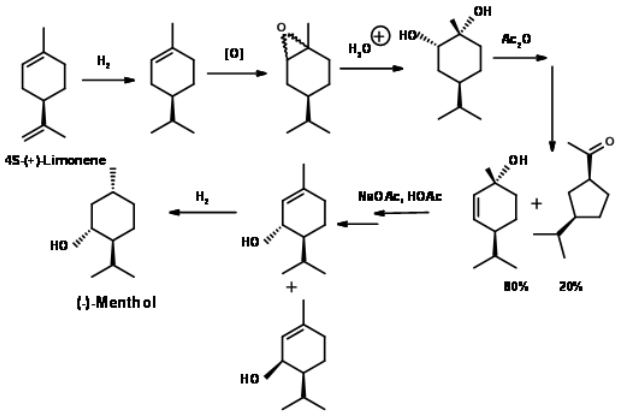



Fig 6.5

**(-)-Menthol from (+)-Pulegone(Fig 6.6):** The Starting material has the correct configuration at C1. The problem is to reduce the double bond enantioselectively. The double bond is first reduced by catalytic hydrogenation to give a mixture of (-)-Menthone and (+)-Isomenthone. The all-equatorial configuration of (-)-menthol is best attained by dissolving metal reduction. The enolate intermediate is protonated to the thermodynamically stable (-)-menthol.

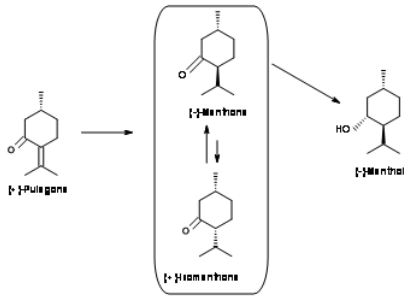


Fig 6.6

**(-)-Menthol from (-)-Piperitone (Fig 6.7):** Look closely at the stereochemistry at the asymmetric center of (-)-Piperitone. The isopropyl is in the wrong configuration for (-)-Menthone. The challenge here is (1) isomerise this center and (2) enantioselectively reduce the double bond. All attempts to produce (-)-Menthol produce only mixtures as shown in Figure 6.7. Hence this process has not been very successful.

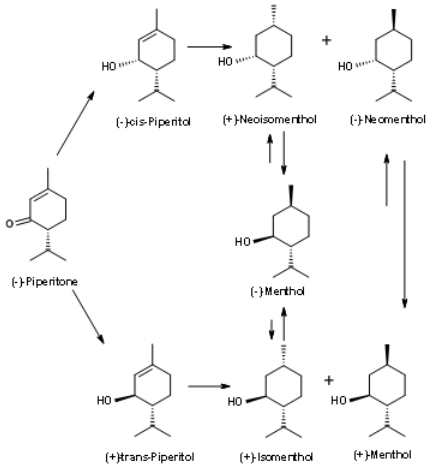



Fig 6.7

**(-)-Menthol from (-)-β-Pinene (Fig 6.8):**(-)-β-Pinene offers a good route because the requisite structural features are present and is available in sufficient optical purity. Hydrogenation of (-)-β-Pinene gave cis-Pinane is a major product. On pyrolysis, the strained bridged ring system cleaved to give optically pure 2,6-dimethyl-2,7-octadiene. It was converted to (+)-Citronellol in good yields by direct oxidation. Alternately the more substituted olefin was first subjected to a Markovnikov addition of HCl followed by an anti-Markovnikov addition of HBr. Solvolysis reaction provided a mixture of citronellols. Catalytic oxidation of the alcohol provided (+)-Citronellal. This could be converted to (-)-Menthol by known procedures. The product was however contaminated with trace amounts of (+)-Menthol arising from trans-Pinane generated in the first step.

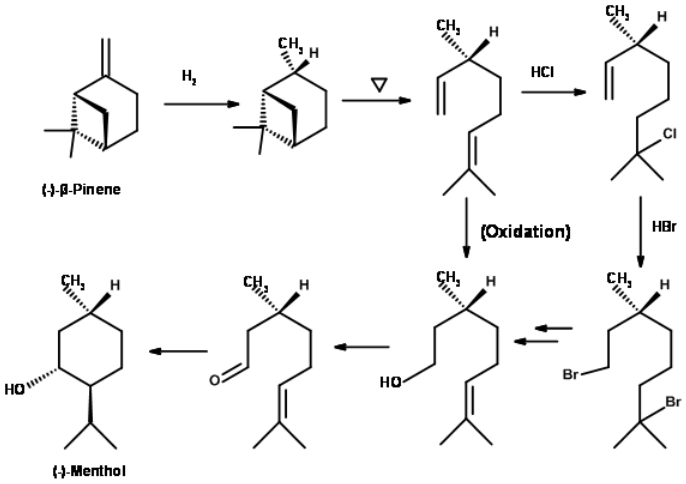



Fig 6.8

**(-)-Menthol from (+)-δ-3-Carene (Fig 6.9):** δ-3-Carene is another chiral synthon that has the required structural features to serve as a starting material for (-)-Menthol. Catalytic isomerization of δ-3-Carene gave (+)-δ-2-Carene. Two different routes were investigated. In the first route (+)-δ-2-Carene was pyrolysed to cleave the cyclopropane ring. The resultant diene had the right stereochemistry at C1 and C4. The latter did not matter because this asymmetry is lost soon and regenerated in the process. Treatment of the unconjugated diene with HCl and dehydrohalogenation led to a conjugated diene. Addition of HCl led to an allyl chloride. Solvolysis with acetic acid-sodium acetate provided an S$N^2$' displacement causing an allylic rearrangement. The resulting piperitol acetates gave (+)-cis and (-)-trans-piperitols which could be fractionally distilled. Pure(-)-trans-piperitols yielded (-)-menthol on hydrogenation.

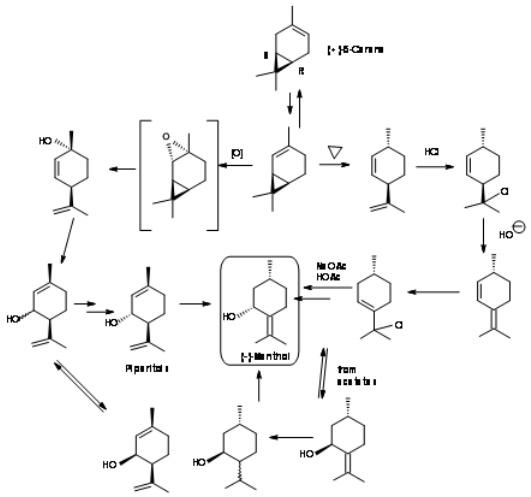


Fig 6.9

In the second route (+)-δ-2-Carene was epoxidised to yield (+)-cis-2,8-p-menthadienol directly. On buffering with formic acid – acetic acid mixture, allylic rearrangement occurred to give a mixture of formate and acetate of piperityl esters. The corresponding alcohols could be fractionally distilled. The cis-isomer could be isomerised to improve the yield of pure (-)-trans-piperitol. Hydrgenation gave (-)-Menthol.

Conclusion: In this section we were focused on development of commercially viable routes for (-)-Menthol. Note the way modern reagents have influenced industrial processes.

## References


1. Leffingwell, J.C. & R.E. Shackelford, Laevo-Menthol - Syntheses and organoleptic properties, Cosmetics and Perfumery, 89(6), 69-89, 1974
2. Hopp, R., Menthol: its origins, chemistry, physiology and toxicological properties, Rec. Adv. Tobacco Science, Vol. 19, 3-46 (1993).

# 7: Strategies in Longifolene Synthesis

The synthesis of Longifolene has held the fascination of synthetic organic chemists for several decades. Since the compound was available in a pure form from natural sources in sufficient quantities, the fascination was purely academic. During structure elucidation studies, it was observed that this bridged structure underwent a host of migration reactions. These rearrangements were of interest both from theoretical and practical points of view. The concept of 'disconnection' and 'retrosynthesis' that was evolving around 1960' led to the development of Logic in Organic Synthesis during this period. The structure of Longifolene was a happy exploration ground for those grand masters who were involved in these developments. For this reason synthesis of Longifolene has been closely associated with these developments. While analyzing such structures, Corey had suggested a few 'strategic bond disconnection'

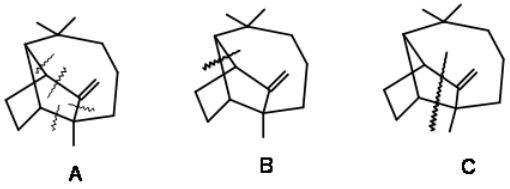



Fig 7.1

for logical approaches towards synthesis (Fig 7.1). Please note that these suggestions were meant to provide guidelines and therefore need not restrict any further innovations. It was further pointed out that any one of these disconnections could lead to several paths for the construction of synthetic trees. For example, let us consider one such disconnections at bond 'a' shown in Fig 7.2. This could throw open four branches on the synthetic tree. Out of these, Corey first selected the Michael strategy because one such cyclisation was already known in the chemistry of Santonin.

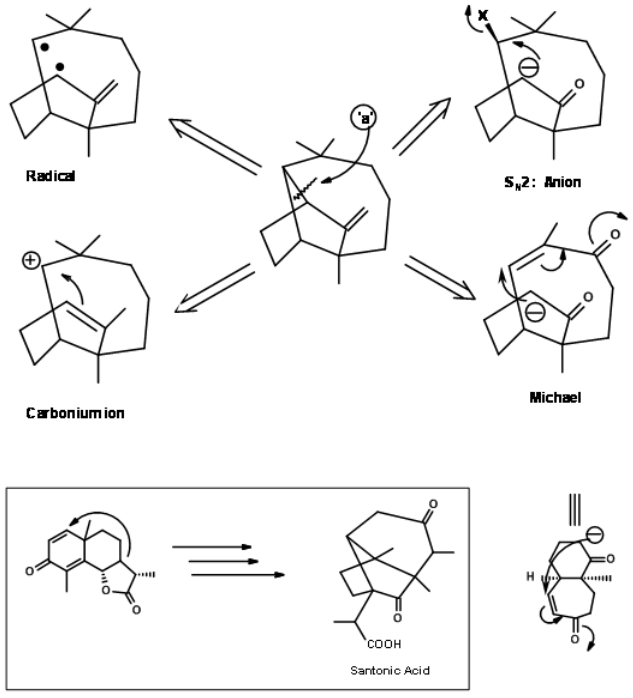



Figure 7.2

Execution of this concept by Corey ( J. Am. Chem. Soc., 83, 2151 (1961); ibid.,86, 478 (1964)) is shown in Fig 7.3.

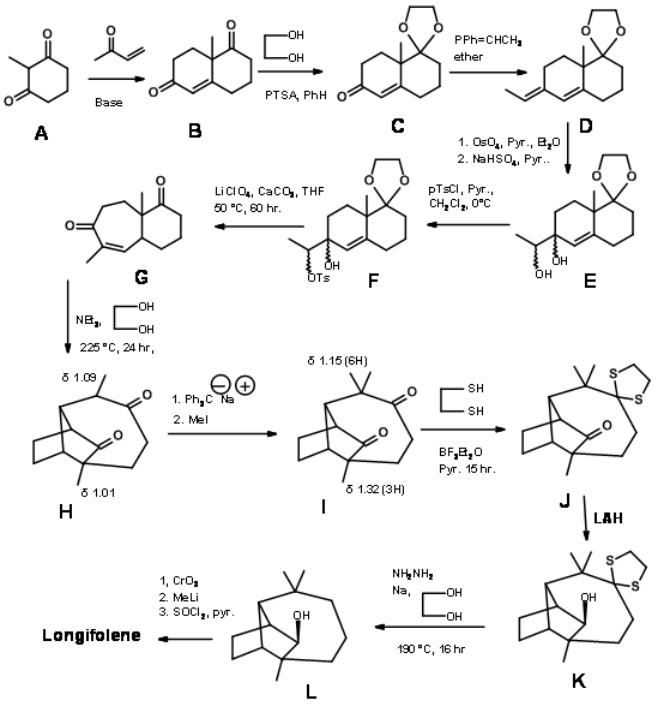



Figure 7.3

L.W. Oppolzer et.al., set up the longifolene ring system through a rearrangement transform. He made use of De Mayo reaction, which is a photocyclisation – retroaldol sequence shown below **(Fig 7.4)**.

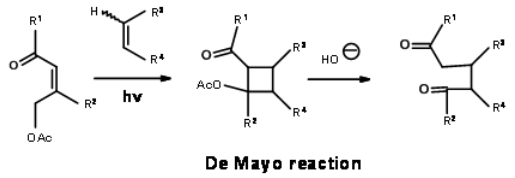



Figure 7.4

As shown in the synthetic scheme Figure 7.5, a [2+2] cycloaddition reaction on C gave D, which exposed the retroaldol components after an hydrogenolysis. Another useful feature of this synthesis is the utilization hydrogenolysis reaction on cyclopropane to expose a gem-dimethyl group. A chiral starting material A yielded (+)-Longifolene in 25% overall yield.

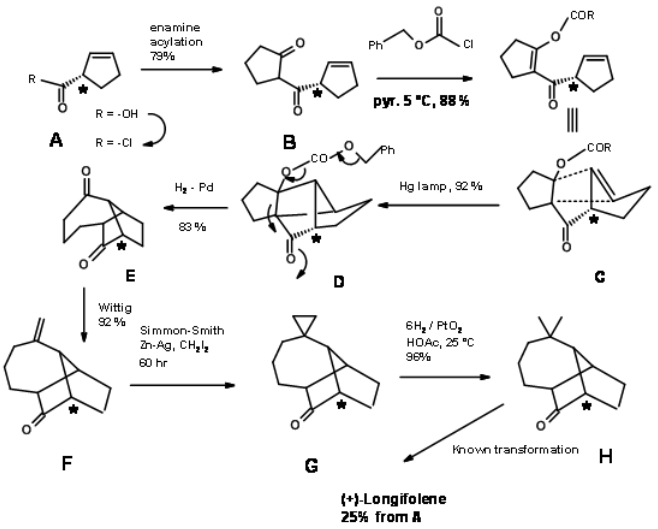



Figure 7.5

A carbene insertion strategy was reported by A.G. Schutz et.al., (J. Org. Chem., 50, 915(1985)). The retroanalysis is shown in Figure 7.6.

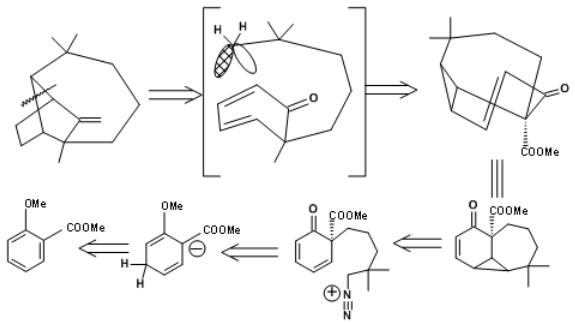



Figure 7.6

The synthetic scheme is shown in Figure 7.7.

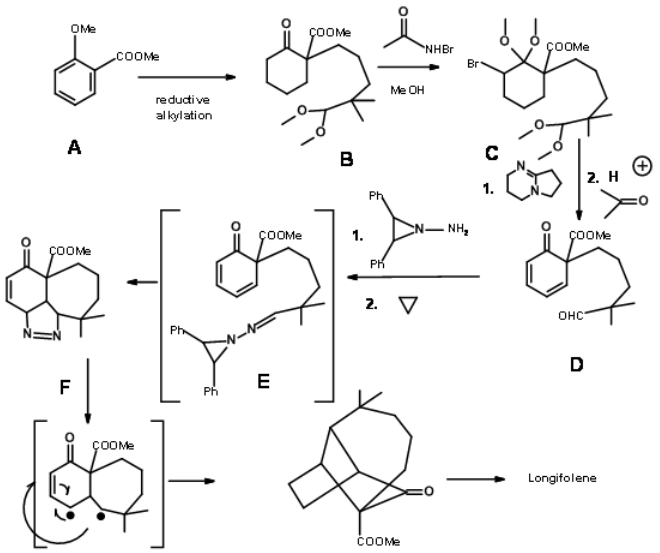
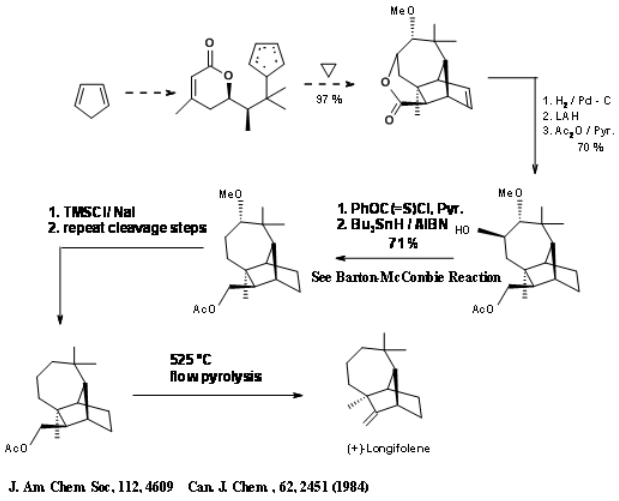



Figure 7.7

The Diels-Alder strategy indicated in the introduction to this section on Longifolene was demonstrated by Fallis et.al., **(Fig 7.8)**




J. Am. Chem. Soc, 112, 4609 Can. J. Chem., 62, 2451 (1984)

Figure 7.8

Another Diels-Alder strategy came from Ho and Liu **(Fig 7.9)**. Note the utilization of the exo- cyclic olefin by converting this unit to the required seven membered ring moiety.

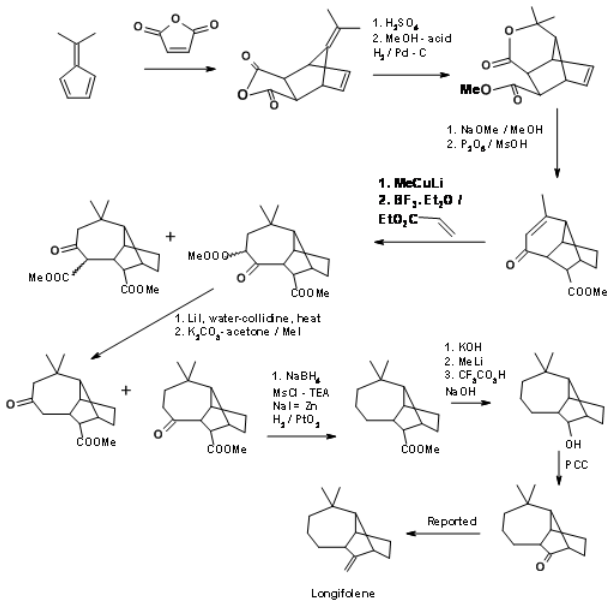



Figure 7.9

A cationic cyclisation strategy for Longifolene skeleton reported by Johnson's school has some interesting features. Figure 7.10 depicts the cyclisation reaction that forms the key step in this scheme.

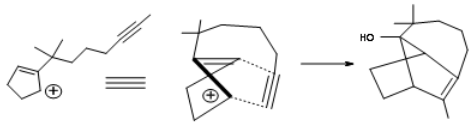



Figure 7.10

The detailed synthetic plan is shown in Figure 7.11.

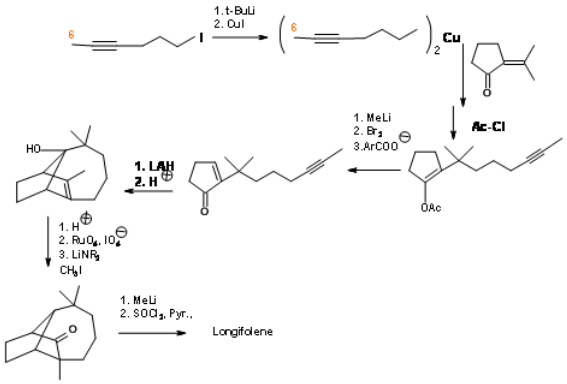



Figure 7.11

Note that this cyclization still leaves the methyl group on the wrong carbon. The unwanted –OH group was removed via a Lewis acid complexed hydride transfer reaction. The acid catalyzed isomerisation of the double bond is followed by a hydroxylation-oxidation sequence to expose a carbonyl group. The quaternary methyl group was then introduced via., an enolate. The exocyclic methylene was reintroduced to complete the synthesis.

# 8: Strategies in Cedrene Synthesis

Cedrene represents a very complex tricyclic sesquiterpene. Such complexity called for ingenious approaches for the total synthesis of the ring system. There are several syntheses reported for this ring system. We would discuss a few approaches. Some strategic bond cleavages are shown as broken lines in **Figure 8.1**.

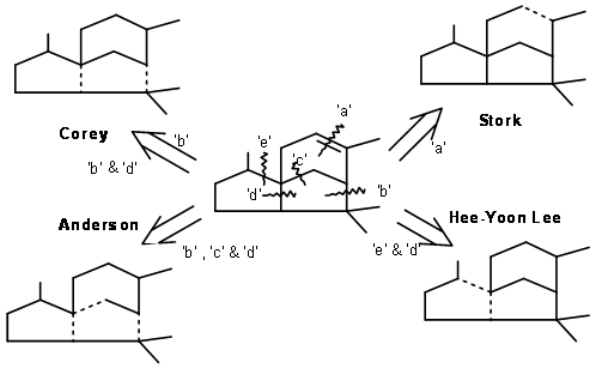



Figure 8.1

**Disconnection at 'a':** G. Stork et.al., (J. Am. Chem. Soc., 77, 1078 (1955); ibid, 83, 3114 (1961)) took advantage of the fact that fused five membered rings would be cis- fused. Such a system would have a crowded 'concave phase'. These two features formed the basis for Stork's synthesis of Cedrene. Their synthetic scheme is shown in **Figure 8.2**. The first alkylation set in motion the steric out come of the remaining steps.

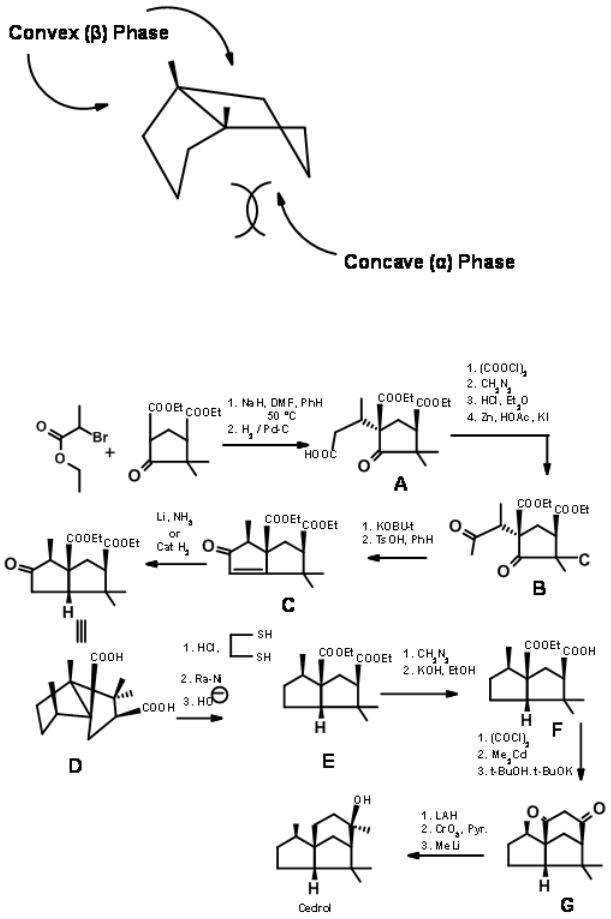



Figure 8.2

**Disconnection at 'b':** For his 1969 Cedrene synthesis (J. Am. Chem. Soc., 91, 1557 (1969)), Corey set up the spiro-ring system (cleavage of bond 'b'). A p- alkylation of phenolate gave the spiro ring (J. Am. Chem. Soc., 84, 788 (1962)). Lewis catalyzed cylisation of the enolate completed the skeleton **(Figure 8.3)**.

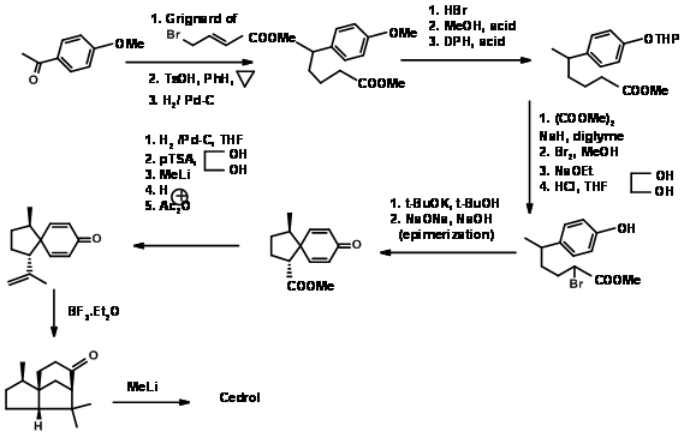



Figure 8.3

**Disconnection at 'b' and 'd':** Based on biogenetic cyclization concept, Corey achieved a one-step cyclization of the A and B rings **(Figure 8.4)** onto a preformed C ring (Tet. Lett., 2455 (1972)). The key for success in this scheme is the prior formation of bond 'd' followed by the formation of the 'b' bond. Note the role of a cyclopropyl ketone that orchestrated the development of a carbonium ion followed by an incipient carbanion to complete the A and B rings in this order.

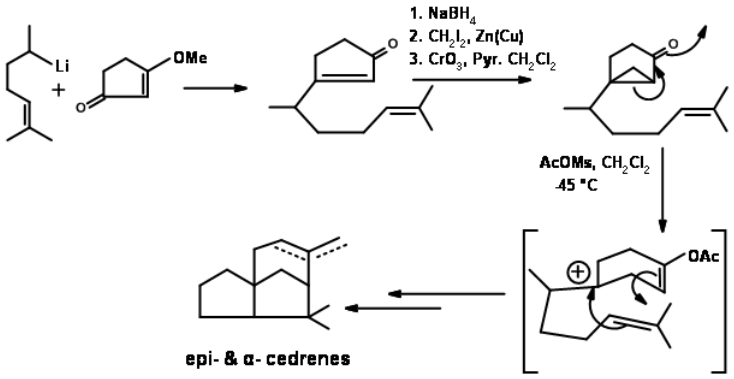



Figure 8.4

**Biogenetic type cyclization:** A remarkable biogenetic type cyclization of Nerolidol to Cedrene was reported by Anderson et.al., (Tet. Lett., 2455 (1972). The cyclizations could be accomplished in two steps. With formic acid a six membered ring is first formed. Further treatments with triflouroacetic acid completed the synthesis. The overall yield was very moderate **(Figure 8.5)**.

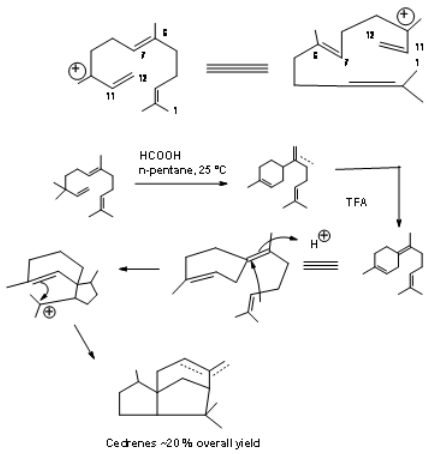



Figure 8.5

**Disconnection at 'e' and 'd' bonds:** In Anderson's biogenetic-type cyclization, formation of the six membered C ring was first realized. A six membered ring system also served as a key step for free radical cyclization reported by Hee-Yoon Lee. Tandem radical cyclization was their central theme. Such radical cyclizations have been reported for the synthesis of natural products. Hee-Yoon Lee reported application of this strategy to the synthesis of α-Cedrene (Ter. Lett., 7713 (1998)). The success of this scheme hinged on two factors.

1. Selective formation of a radical for formation of 'd' bond to accomplish the B ring
2. The acceptor carbon should generate a new free radical in the process to complete the A ring. The first task was achieved through incorporation of a xanthane unit and the second crucial task was accomplished via., N-aziridinylimine group. The synthetic scheme is shown in **Figure 8.6**.

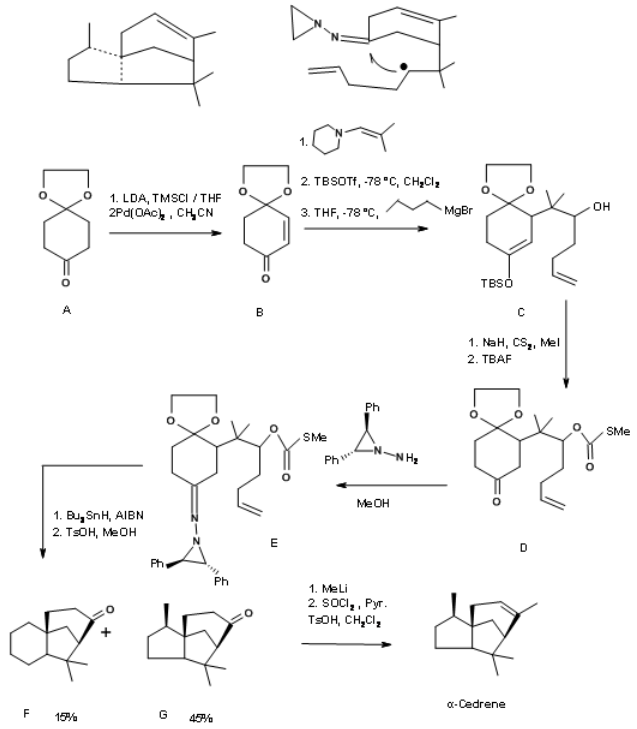


Figure 8.6

**Disconnection at 'b' and 'd':** An approach by Chen et.al., (Tet. Lett., 2961 (1993)) relied on the free radical cyclization reaction on a suitably fuctionalized C ring **(Figure 8.7)**. The synthesis of C ring is achieved via., a DA reaction. Knoevenagal reaction placed the required chain for completing the A and B rings. Tin hydride reduction generated a free radical at the site of the nitro group, which underwent a tandem cyclization to complete the A and B rings in that order.

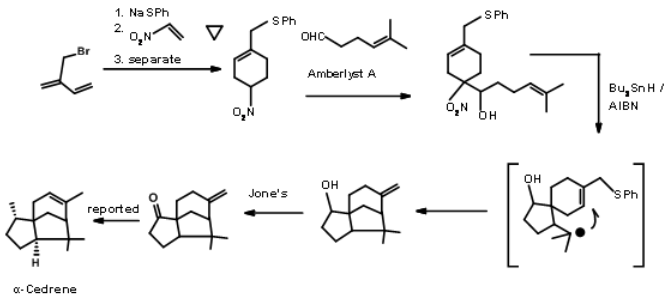


Figure 8.7

A Diels-Alder approach to to tricyclic cedrene skeleton was reported by Breitholle et.al., (Can. J. Chem., 54, 1991 (1976) **(Figure 8.8)**. Alkylation of cyclobutadiene to the requisite chain gave 8.8A after equilibration. The DA reaction proceeded in 36% yield to give a mixture of isomers. The ketone 8.8B did not undergo ring expantion with diazomethane. The ring expansion was finally achieved via the methylene amine 8.8C via diazotisation. The fact that two ring expansion products 8.8D and 8.8E were formed with 8.8D as the major product suggests that the amine 8.8F was the major isomer.

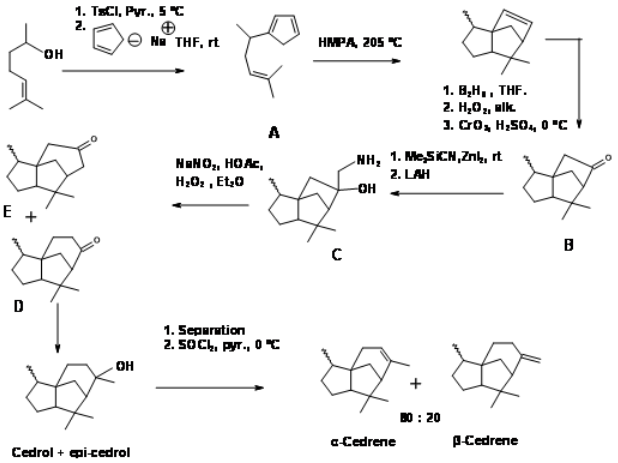



Figure 8.8

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# 9: Strategies in Reserpine Synthesis

The structure of Reserpine was solved by 1953. R.B. Woodward's group reported the first synthesis of Reserpine in 1956 (J. Am. Chem. Soc., 78, 2023, 2657 (1956); Tetrahedron, 2, 1 (1958)). His scholarly analysis clearly displayed aspects of retroanalysis, which was just evolving at that time. This synthesis commands admiration for the way he used conformational analysis and stereoelectronic effects to precisely develop the stereopoints in this exceedingly complex problem for that time. He recognized that the E-ring has a dense array of 5 asymmetric centers in a six membered E ring. His disconnection of reserpine led him to the key intermediate C. We could formalize his retroanalysis as shown in Figure 9.1.

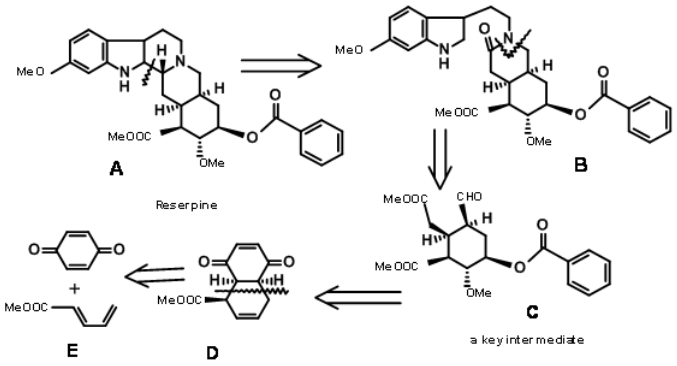



Figure 9.1

Another brilliant piece of conformational analysis could be seen in the way he converted Isoreserpine to Reserpine by introducing conformational strain in an otherwise comfortable molecule.

**Synthesis of Woodward's Aldehyde (9.1C):** In a cleaver execution by Woodward's group **(Fig 9.2)**, all the required carbons for the D/E rings and three of the five asymmetric centers were created by one Diels-Alder reaction **(9.2B)**. Note the simple dissymmetry in one component – methyl acrylate – could precisely place three asymmetric centers in a row in a correct fashion. This cycloaddition reaction developed a concave phase and a convex phase1 in the product that guided further modifications on this intermediate. The hydride reagent in the next step delivered the hydride from the less hindered convex phase, placing the –OH group in the concave phase. This facilitated the formation of a five-membered lactone ring **(9.2C)**. The alternate six-membered lactone ring was presumably more strained. Bromination on **9.2C** with molecular bromine formed the bromonium ion complex from the convex phase, while the –OH group could enter from the concave phase to form an ether **(9.2D)**. Treatment with sodium methoxide displaced the bromine from the convex phase, possibly via elimination – addition route **(9.2E)**. The next bromonium ion complex again proceeded from the convex phase, with the water molecule entering from the concave phase to enable a trans-diaxial opening of the bromonium complex **(9.2F)**. After one oxidation step, the molecule was now set for a complex double elimination reaction, with the zinc attacking two centers. An attack at the bromide center opened the ether ring while another attack at the carbonyl group opened the lactone ring. This complex Tandem Reaction placed all the five asymmetric centers. Opening the unsaturated ring gave the key intermediate **9.2I**.

**Completion of the A, B, C, D and E rings:** Condensation of **9.2I** with o-methoxytryptamine followed by Pictet-Spengler condensation led to the formation of Isoreserpine and not Reserpine. Woodward reasoned that this was due to the fact that the C, D and E rings in all-trans geometry, had all substituents in the stable equatorial orientation in Isoreserpine. Woodward executed the isomerisation at C3 in an ingenious way. Aqueous alkali hydrolyzed the acetate – ester functions, which was than lactonised under DCC conditions. Thus, an unstable all-axial E ring was locked in as a lactone **(9.2M)**. This forced the molecule in a crowded unstable state. On acid catalyzed isomerisation with the high boiling carboxylic acid, the C3 position isomerized to the reserpine configuration. On transesterification, the correct isomer was formed with a free –OH ready for final acylation.

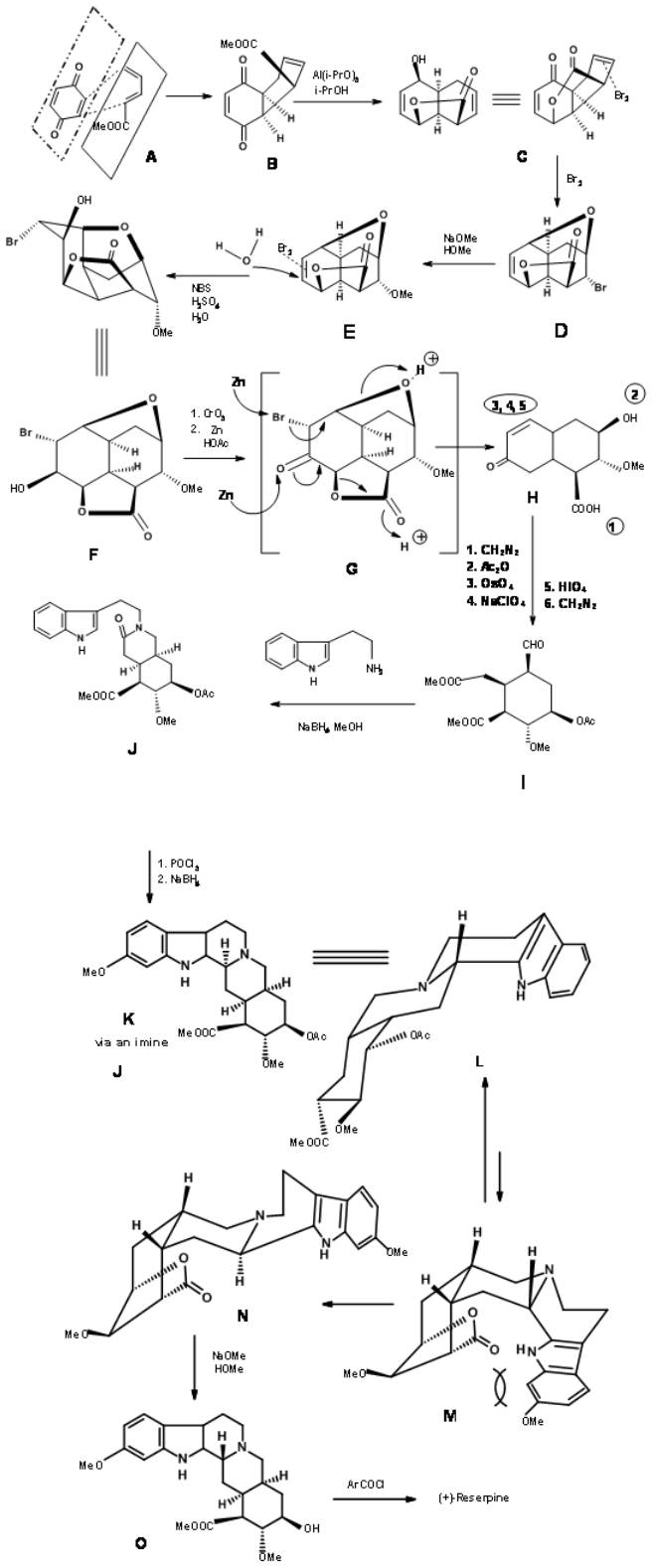


Figure 9.2

**G. Metha's Synthesis of E ring:** G. Metha et.al., (J. Chem. Soc., Perkin Trans. 1, 1319 (2000)) controlled the stereochemistry on the E ring through a bicyclo[2.2.1]heptane system as shown in Figure 9.3.

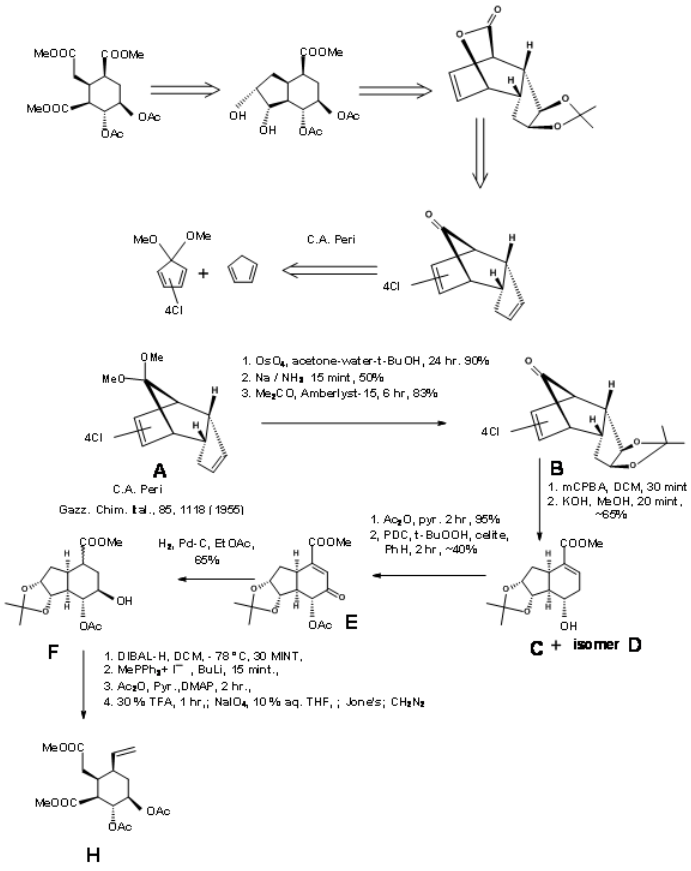
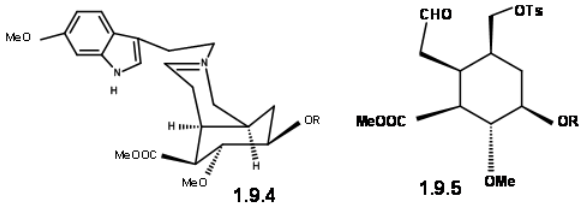



Figure 9.3

**Stork's synthesis:** Gilbert Stork (J. Am. Chem. Soc., 127, 16255 (2005) reasoned that the stereochemistry at C3 in the (AB  ABDE  ABCDE) cyclisation route of Woodward could be controlled if an iminium intermediate **9.4** could be formed first. This would then orient a chair-like folding of the tether chain (potential C ring) for an axial attack on the iminium ion to give a stereoselective C/D ring closure to form reserpine. They reasoned that the intermediate **9.5** would serve as the key intermediate.




**9.4 (left) and 9.5 (right)**

After some unsuccessful attempts, Stork's school completed the synthesis of **9.5** using a route shown in Figure 9.6. Condensation of the hexynal **9.6A** with the lithium enolate of methyl methoxy acetate followed by benzenesulphonyl chloride and further heating with DBU gave the conjugated methoxy ester with the (Z) isomer **9.6B** as the dominant product. Trimethylsilyl chloride trapped the diene ketene acetal **9.6C** without purification of the intermediate product. D.A reaction with maleic anhydride followed with aqueous THF gave the decarboxylated acid that was esterified to give **9.6E**. A free-radical cyclisation with tributylstannane in refluxing t-butanol and subsequent workup led to an epimeric mixture that was equilibrated with base to the desired isomer **9.6G**. Reduction of the keto- group with L-Selectride gave the axial alcohol. This alcohol was the inverted via mesylation and treatment with cesium acetate to give **9.6I**. Reduction with LAH, selective tosylation of the primary alcohol and silylation of the secondary alcohol and ozonolysis gave **9.6L** via **9.6K**. Opening of the 5-membered ring was achieved by trapping the kinetic enolate as TMS

derivative **9.6M** and ozonolysis and final esterification gave **9.6N**. This key intermediate was also synthesized via an alternate more efficient route.

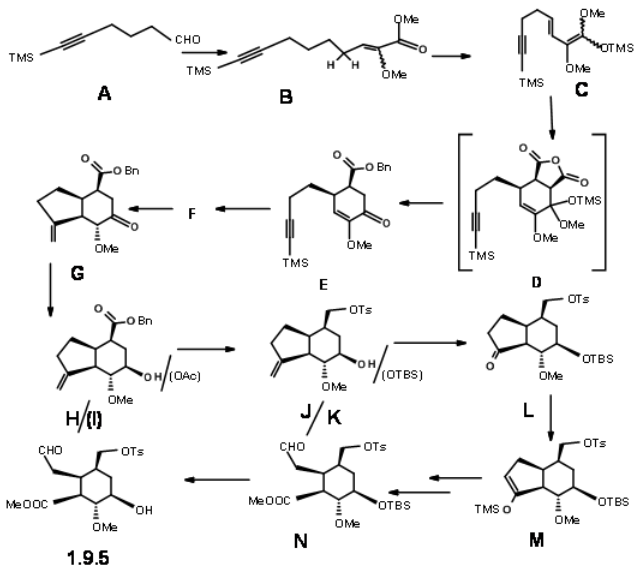


Fig 9.6

Unfortunately, condensation of **9.5** with the indole precursor gave isoreserpine as the major product **(Fig 9.7)**. The researchers reasoned that this unexpected result was most probably due to formation of the

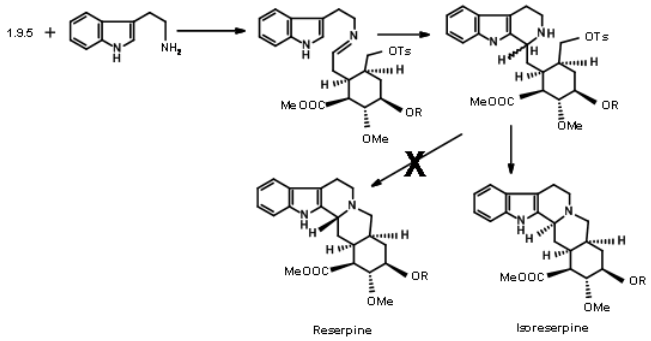


Fig 9.7

C ring prior to cyclisation. In order to drive the reaction towards a DE ring formation, they decided to trap the intermediate imine as the cyanoamine **9.8A**. This was achieved by adding an excess of potassium cyanide to the reaction mixture

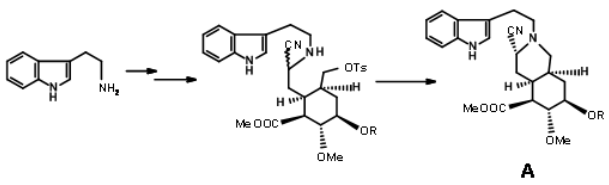


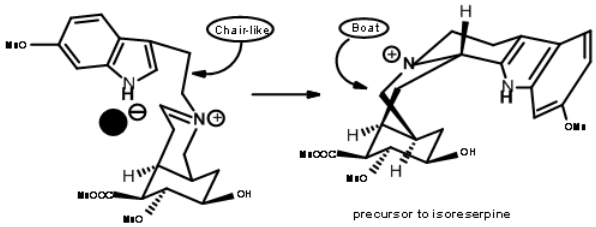
Figure 9.8

The expected product **9.8A** with an axial cyano- group was the sole product. Refluxing the aminonitrile in acetonitril as solvent again gave (±) methyl isoreserpine precursor as the major product **(Fig 9.9)**.**Since the expected chair-like folding and an axial**

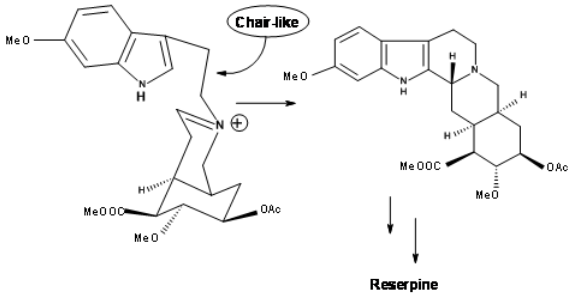
**attack of the indole moiety on the iminium ion moiety appeared to be on sound srereoelectronic grounds,** the authors reasoned that the cyanide anion on the α- phase of the molecule formed a tight ion pair with the immonium ion


Figure 9.9

under these conditions.This anion prevented axial attack on a chair-like folding of the chain, forcing a boat like conformation prior to cyclisation followed by an axial attack to give isoreserpine as a major product.




In such an event, allowing the cyanide counter ion to escape from the influence of the iminium ion by the use of a polar solvent should clean the reaction site for a chair-axial attack. When the nitrilamine **9.8A** was treated 10%




solution of 1 N HCl in THF solvent, the precursor for (±) methyl reserpine was the product in 90% yield. This was eventually converted to reserpine by known procedures. Based on these results, another very short chiral route has been reported by the authors. Thus, persistence and critical mechanistic reasoning at every point of failure led to a successful direct synthesis of the correct isomer.

S. Hanessean et.al., (J.Org. Chem.,62, 465 (1997) applied the Chiron approach to the key intermediate **9.10B** suitable for the CD ring formation in a E  ABE  ABCDE approach discussed so far.

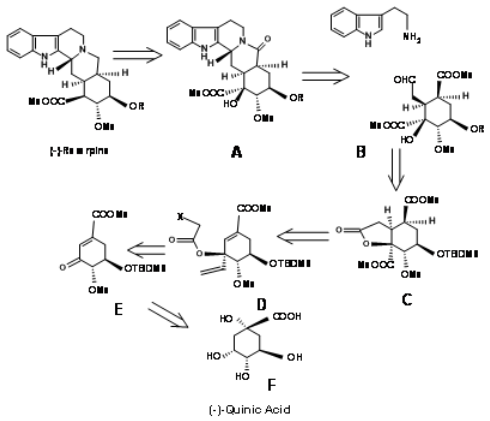



Figure 9.10

Quinic acid **9.10F** had most of the chiral centers in the proper orientation. However it needed modification at the potential C20, C15 and C16 centres. Retroanalysis of Hanessian is shown in Figure 9.10. The actual synthesis is shown in Figure 9.11. Lactonisation, followed by selective benzyl protection and methylation of the remaining OH groups gave the compound B. Oxidation was followed by methanolysis of lactone ring led to elimination to give the conjugaten ketone D. Protection of the C18 – OH as TBDMS followed by vinylation using Grignard reagent placed the potential carboxylic acid function. The t-alcohol thus generated provided an anchor the stereospecific introduction of the needed two carbon chain. A reductive free radical cyclisation placed the carbon chain in the correct stereochemistry. The correct isomer at C20 (I) was then moved to the next step. This key intermediate L led to the reserpine and isoreserpine precursors **9.11M** and **9.11M**' in the ratio 1.4 : 1 respectively. These steps are shown in Figure 9.11.

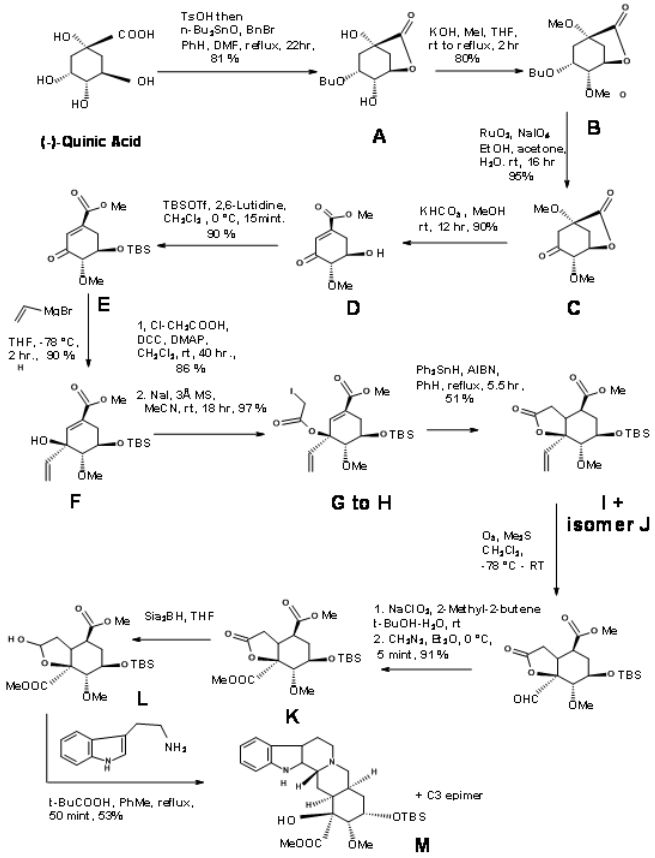



Figure 9.11

# 10: Strategies in Prostaglandins Synthesis

Chemical Synthesis of Prostaglandins witnessed phenomenal activity during the 1960's and 70's. During this period, organic chemistry saw intensive development in 'disconnection' and 'Logic' as primary tools for synthesis. This period also saw development of several new reagents for stereoselective synthesis. The complexity of the structure of PG skeleton posed a great challenge for synthesis. The fact that molecules belonging to this family held great potential as drug candidates but were available only in minute quantities from natural sources was the main reason for the intense activity in the chemical synthesis and skeletal modifications for SAR studies. The numbering system on the skeleton and the main structural features of this family of molecules could be seen in Figure 10.1

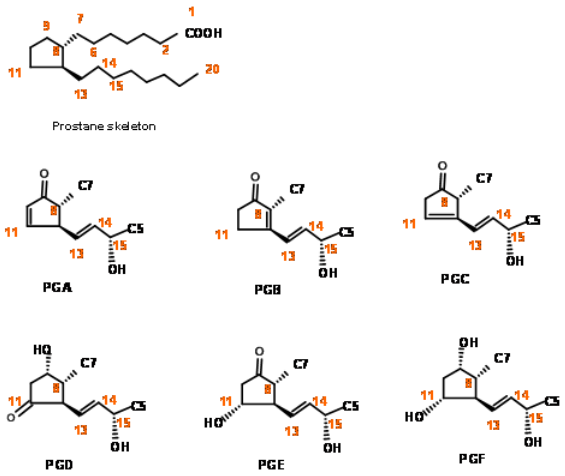



Figure 10.1

Placing a keto- group at C9 is a delicate operation because such β- hydroxy ketones would readily undergo dehydration to give a PGA skeleton. On a five membered ring, PGA system could again undergo ready isomerisation to PGB, a stable ring system, probably via a PGC skeleton. On reduction with sodium borohydride, the keto- group at C9 is reduced to a mixture 9α- and the unnatural 9β- epimers. The natural PGF skeleton has an 9α- configuration for the –OH group. In the natural PGF skeleton we have four asymmetric centers on a five membered ring. As you know well, a five membered ring is conformationally very flexible. Hence setting up precise stereochemistry on this ring posed a great challenge during the 60's. There could be three main strategies for the construction of five membered ring systems **(Fig 10.2)**.

1. An open chain could be cyclized to a ring.
2. A suitable cycloalkane ring could be ring expanded or contracted to a five membered ring.
3. A suitable bicyclo[l,m,n]ring system could be opened to give a five membered ring.

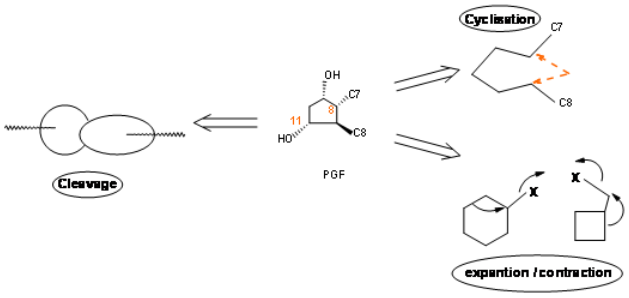



Figure 10.2

Let us look at a few outstanding synthetic efforts that successfully met these challenges in Prostaglandin chemistry.

## Cyclization of open chain precursors

Setting up a series of asymmetric centers on an open chain is as great a challenge as setting them up on a five membered ring. Corey's early attempt in 1968 was to design a suitable six membered ring, open up the ring to a chain and then cyclize the chain regiospecifically to the required five membered ring ( J. Am. Chem. Soc., 90, 3245 (1968)). Their retroanalysis and synthesis are shown in Figure 10.3. The first DA reaction set two crucial stereocentres that guide the remaining stereopoints on the five membered ring formed by aldol reaction. This synthesis is a good example for **convergent synthesis**. The starting materials come by two different routes shown in Figure 10.4.

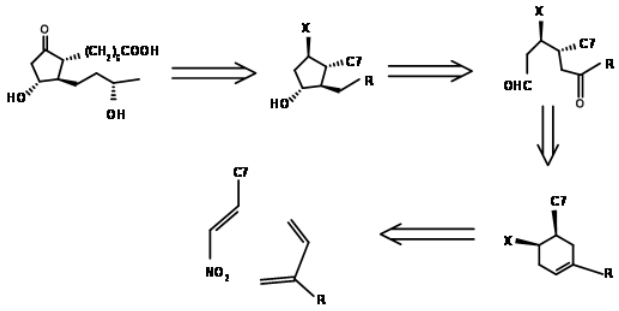


Figure 10.3

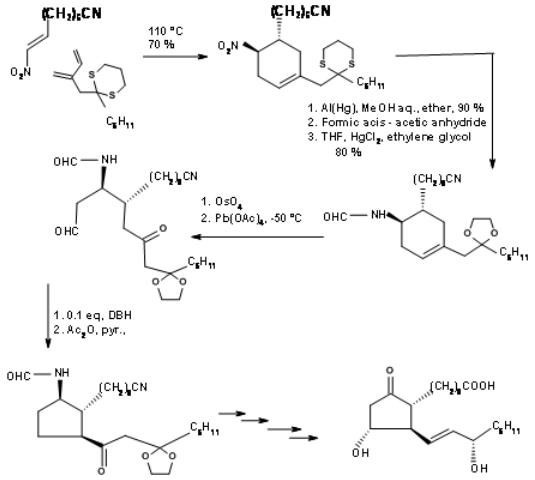



Figure 10.4

The Kojima's disconnection of the cyclopentane ring at C8 – C12 bond provided an open chain. Careful planning of the functional groups on the proposed chain enabled his group to plan the stereocentres in a more direct way. Their retroanalysis and synthetic route are shown in Figure 10.5.

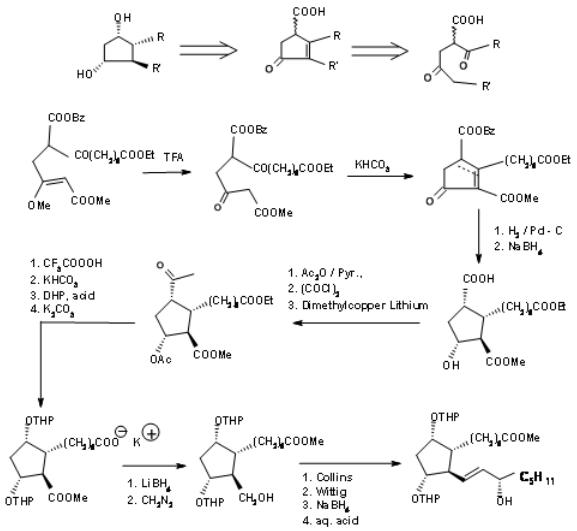


Figure 10.5

## Cyclopentane ring precursor

The difficult problem of setting up stereocentres on a five membered ring was solved elegantly by Corey et.al.,(Tet. Lett., 311 (1970)) **(Fig 10.6)**. Observe the artistic precision with which the substituents are woven into a five membered ring with the aid of iodolactonisation and epoxide ring formation reactions. An example for mastery in the Art of Synthesis.

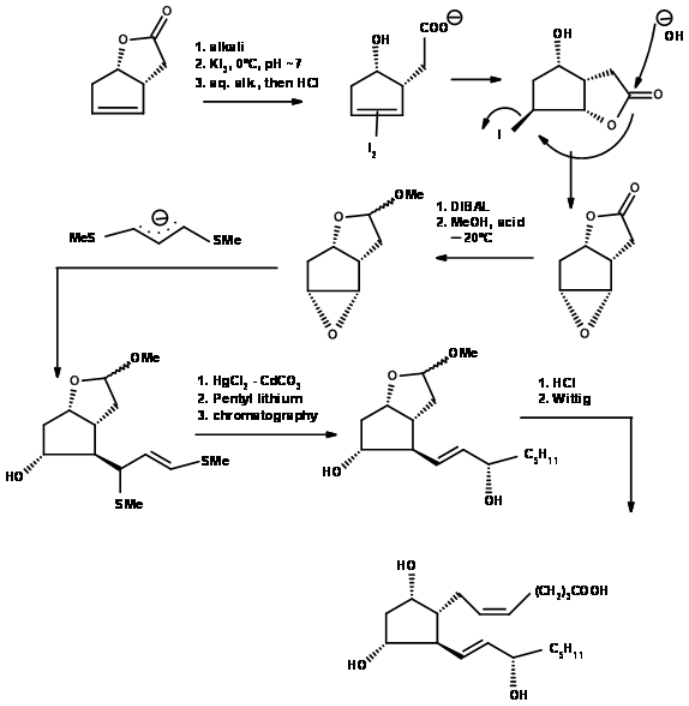


Figure 10.6

F.S. Alvarez et.al., took advantage of the steric constraints due to eclipsing strains in five membered rings and wove three asymmetric centers in a row on a five membered ring (J. Am. Chem. Soc., 94, 7823 (1972)) **(Fig 10.6)**.

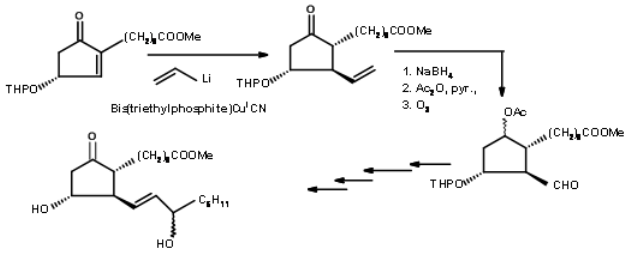


Figure 10.7

## Cyclohexane ring Precursor

Starting from all cis-cyclohexan1,3,5-triol, Woodward's school demonstrated their excellence in the Art of Organic Synthesis. The first step is the differential protection with glyoxalic acid **(Fig 10.8)**. Note an interesting architectural design aspect. This chain of two carbon protecting group is eventually incorporated into the main structure. Note that this also accomplishes another very difficult task viz., placing a reactive 2 carbon chain into the crowded concave phase. The solvolysis of the mesylate is assisted by the neighbouring olefin. Note the elegant planning of the ring contraction step.

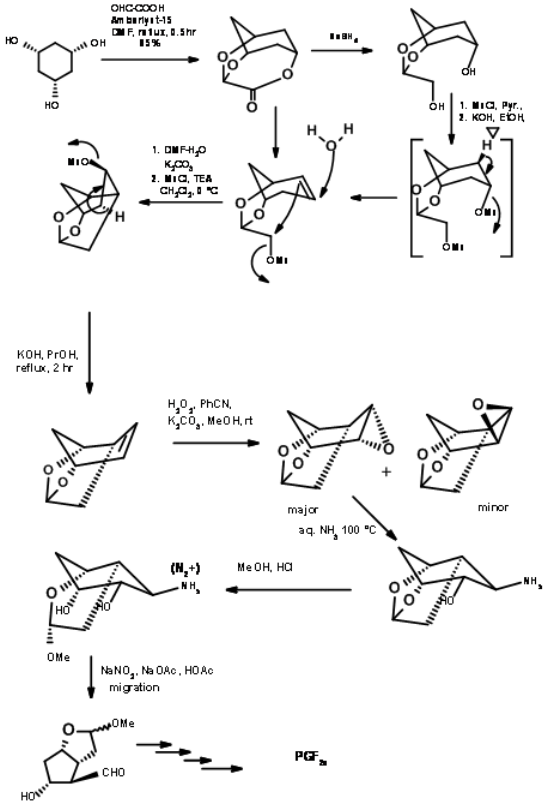


Figure 10.8

In 1973, Corey revealed a synthesis (Tet. Lett., 309 (1973)) based on six membered ring involving a ring expansion and a ring contraction to achieve the goal **(Fig 10.9)**.

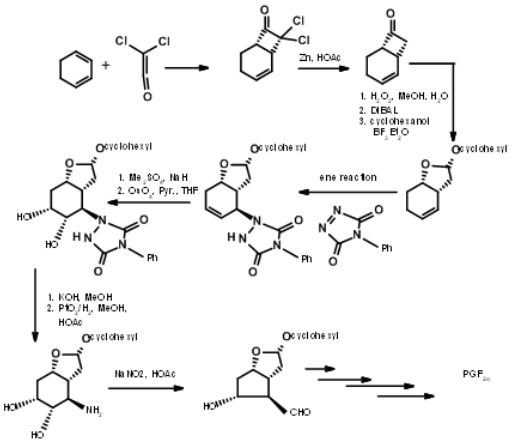


Figure 10.9

## Bicycloalkane Approaches

There are several syntheses based on such strategy to derive the stereochemical advantage of a bicycloalkane ring system. Here we shall discuss the Bicycloheptane strategy of Corey (J. Am. Chem. Soc., 91, 5675 (1969): Ann. N.Y. Acad. Sci., 180, 24 (1971)). This route provides entry to all natural and unnatural PGs. It provides facility for separation of enantiomers at a very early stage using Amphetamine salt procedure on the first chiral acid-alcohol. This scheme has been scaled up to multigram-scales. Corey's retroanalysis is shown in Figure 10.10. This retroanalysis led to DA reaction.

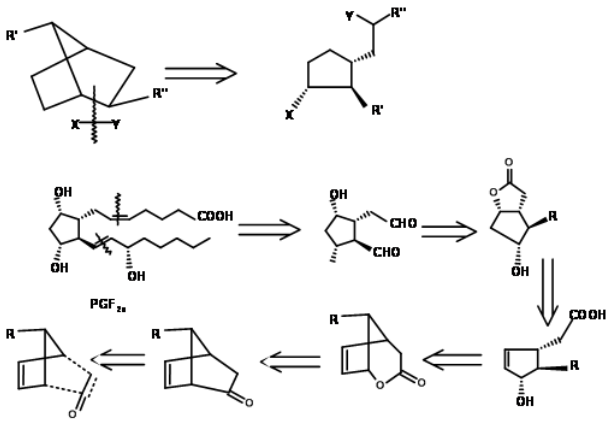


Figure 10.10

The first problem was the synthesis of a cyclopentadiene with the alkyl group at the methylene carbon. Anion routes for alkylation of cyclopentadiene mostly led to a mixture of cyclopentadienes, due to easy isomerisation of the olefin. The problem was solved by alkylation with thallium anion **(Fig 10.11)**. The desired cyclopentadiene was obtained in about 97% yield. The next challenge was in the DA reaction.

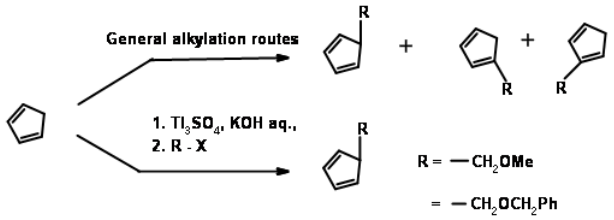



Figure 10.11

Ketenes do not undergo Diels-Alder cycloaddition. They give cyclobutane products even with dienes. Using a 'masked ketene precursor' this problem was solved as shown in Figure 10.12. The bicyclo[2.2.1]heptane thus formed underwent Baeyer-Villiger oxidation as expected. Saponification of the lactone gave a five membered ring with three asymmetric centers in place. The fourth center was generated through an iodolactonisation reaction.

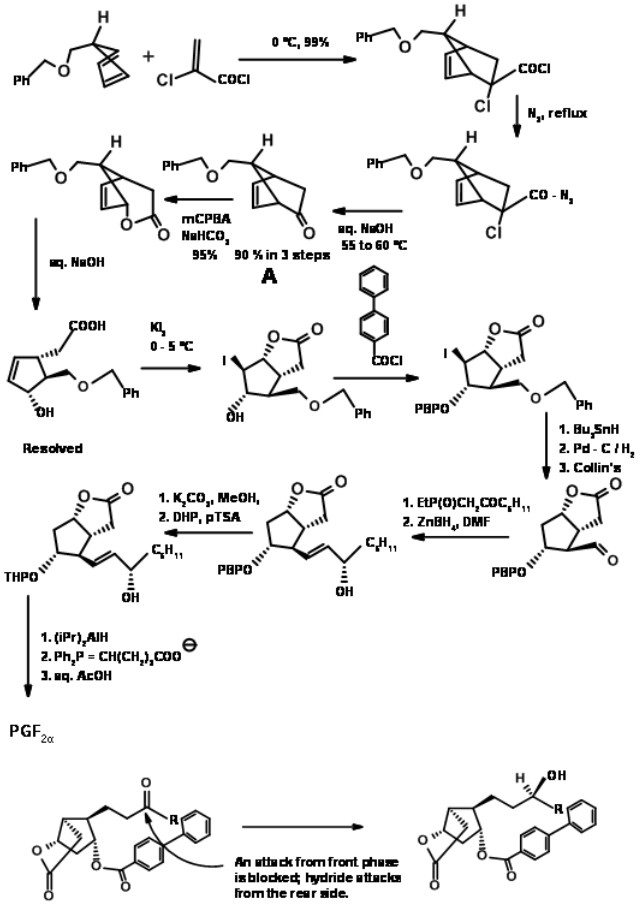



Figure 10.12

Note the stereochemistry of this iodolactonisation step. After removal of the halogen, the –OH at C11 was protected as p-phenylbenzoyl ester. This ester not only gave a crystalline derivative for purification (a useful feature during large scale reactions) but also served as a shielding agent to induce C15-(S)– OH at a later stage. Hydrogenolysis of the C13 – OR to – OH followed by Collins oxidation gave the C13 aldehyde suitable for a Wittig reaction. The α,β-unsaturated ketone was reduced selectively to C15-(S)– OH using Zinc borohydride. This selectivity has been attributed the shielding effect of the bulky aroyl group from the front side, allowing the hydride to enter stereoselectively. Reduction of the ester group with trialkylaluminium hydride gave the hemiacetal for the final Wittig. Note the differential protections used in this synthesis at different stages.

# 11: Strategies in Steroids Synthesis

The main skeletal features in steroid rings are depicted by the two figures shown in Figure 11.1. The same numbering system is maintained even while describing part structures obtained as synthetic intermediates.

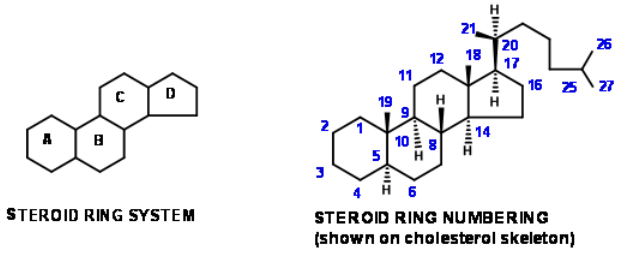



Figure 11.1

This convention helps us to follow the development of structural features through long synthetic schemes. Students should also become familiar with another convention followed by chemists to categorize synthetic schemes, originally evolved for steroids. Similar descriptions are also found in alkaloid chemistry. 'An $AB \rightarrow ABC \rightarrow ABCD$ Approach' would mean that a naphthalene skeleton (either aromatic or suitable perhydro- skeleton) is chosen as SM. The C ring is then constructed on the AB rings. The D ring is then formed by ring closure. An example to this strategy is Bechmann's synthesis (1940). Such descriptions do not indicate any details like the substitution patterns on the SM or synthetic intermediates nor do they spill light on stereochemical details. These details are discussed in the synthetic schemes.

## Bechmann's Synthesis (1940) of Equilenin

This classical synthesis exploits the chemistry of the naphthalene ring. 1-naphthylamine-2-sulphonic acid was chosen as the AB ring **(Fig 11.2)**. The sulphonic

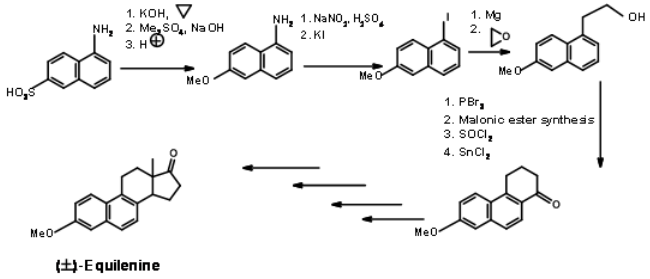



Figure 11.2

acid moiety was converted to a phenol and protected as the methyl ether. The amine moiety was converted to iodide through diazotisation. The C and D rings were then built on the AB rings

## Woodward's synthesis of Cholesterol:

Woodward's synthesis of Cholesterol (J. Am. Chem. Soc., 73, 2403, 3547, 3548 (1951); ibid, 74, 4223 (1952) **(Fig 11.3)** could be described as $C \rightarrow CD \rightarrow BCD \rightarrow ABCD$ Approach. Since the D ring remains D-homo until the last step of ring construction and the required 5-membered ring was obtained only after a ring contraction, it could also be termed as $C \rightarrow BC \rightarrow ABC \rightarrow ABCD$ Approach. Remember that this molecule has 8 asymmetric centers and could therefore have 28 (256) optical isomers. This synthesis envisaged the synthesis of just one set of diastereomers. This stereospecific synthesis incorporated all the stereopoints in a stereo- and regiospecific manner. The D ring provides an anchor for variations in the chain. The double bond on the C ring allowed an opening for the synthesis of cortisone. The legends on the arrows show the reactions.

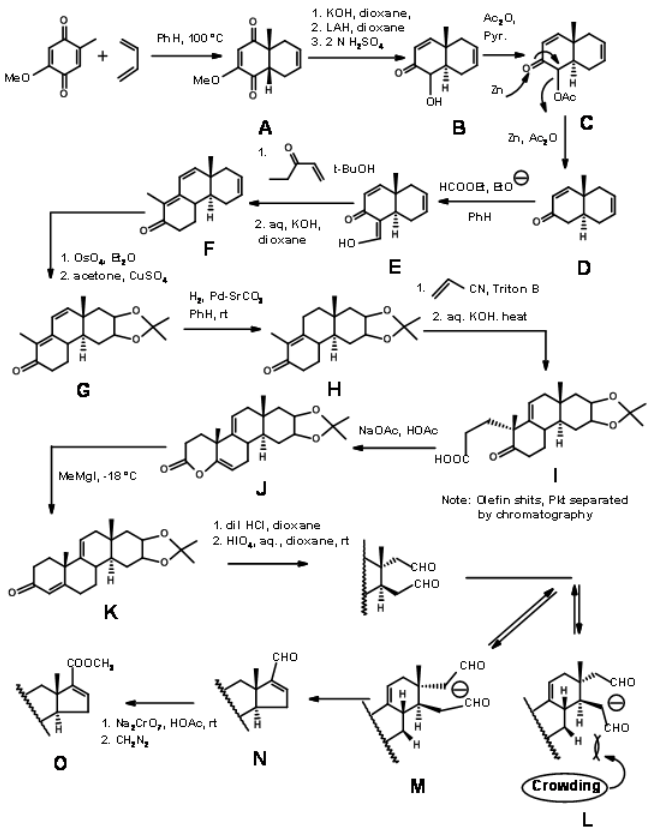



Figure 11.3

## Synthesis of Estrone

Estrone has attracted several chemists as a target for executing new methodologies on this complex yet useful steroid. A very popular method for the introduction of the D ring, followed by cyclization of the C ring in steroid synthesis was introduced by Torgov (1950, 63). His synthesis of Estrone is shown in Figure 11.4. His procedure for $AB \rightarrow ABD \rightarrow ABCD$ Approach became very popular. Several modifications were later developed to further improve this methodology.

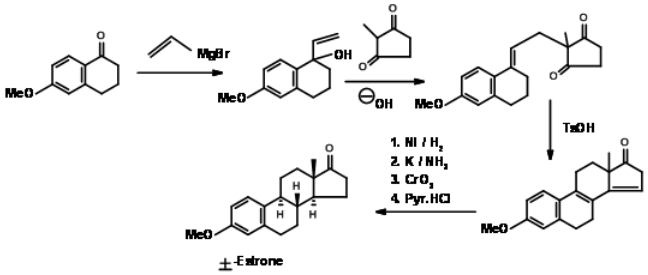



Figure 11.4

Bartlet used a mechanistic transform in his synthesis of Estrone. He applied a biogenetic-type cyclisation for his A $\longrightarrow$ AD $\longrightarrow$ ABCD approach shown in Figure 11.5. A furan ring served as a masked 1,4-diketone needed for the D ring. Also note the rearrangement transform used for the stereospecific introduction of the angular methyl group at C13 position in the last step of the synthesis.

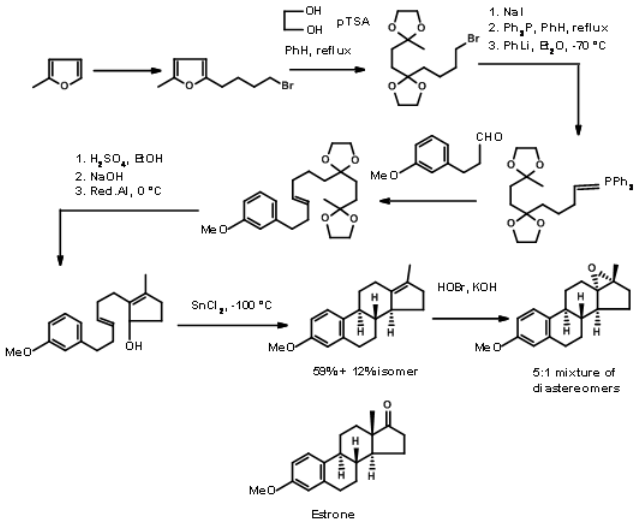



Figure 11.5

Hughes (1960) relied on aldol transforms for his A  AD  ABCD Approach. Here he made use of the reliable reduction protocols developed by several workers for controlling the stereochemistry at ring junctions **(Fig 11.6)**

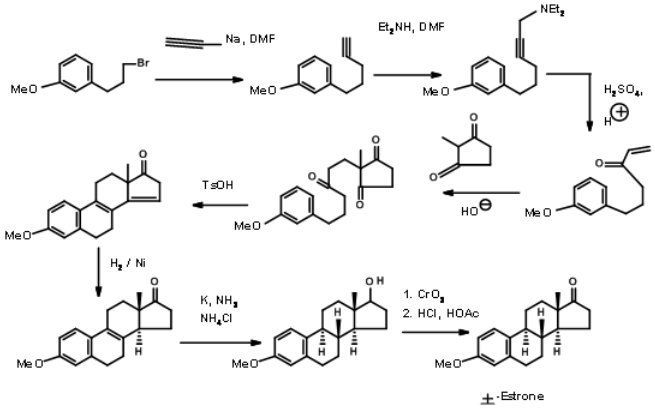



Figure 11.6

P. Hermann et.al., (J. Org. Chem., 73, 6202 (2008)) had attempted a sequential Media:Ring Closure Reactions (RCR) strategy for the stereospecific synthesis of Estrone. These workers relied on the $CP_2ZrBU_2$ catalyst studied extensively in their laboratory and developed a short 9-step synthesis from known diene (A  AB  ABC  ABCD Approach)**(Fig 11.7)**. Cyclisation of the B ring proceeded satisfactorily. Cylisation of the C ring was sensitive to the halogen. After several attempt, cyclisation proceeded well with the vinyl fluoride. The formation of the D ring using Zr catalyst was unsuccessful. The ring closure of the D ring was finally accomplished using the second-generation Media:Grubbs catalyst. The final modification of the D-ring has been already reported by Bartlett P.A et.al., ( J. Am. Chem. Soc., 95, 7501 (1973) thereby completing a formal synthesis of Estrone.

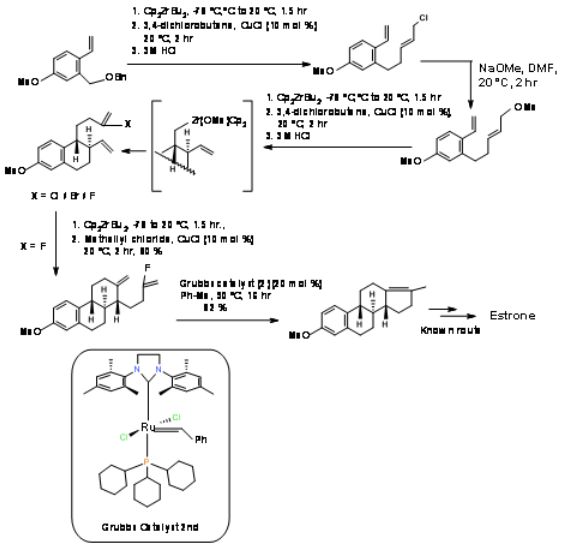



Figure 11.7

Marko Weimar et.al., (J. Org. Chem., 75, 2718 (2010)) have reported a very successful DA Transform for the formation of CD ring from Dane's diene as AB ring and a D ring as dienoplile **(Fig 11.8)** (AB  ABCD Approach; see references cited for similar approaches).

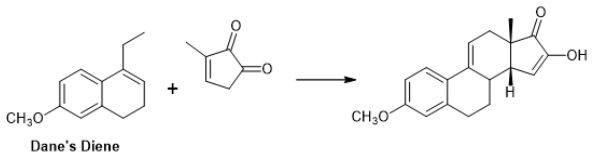



Figure 11.8

Key for the success of this strategy was the metal-free chiral catalyst, which they successfully tailored by the introduction of three H-bonding sites. The catalyst that worked efficiently was the Media:axially chiral amidine salt **11.9**.

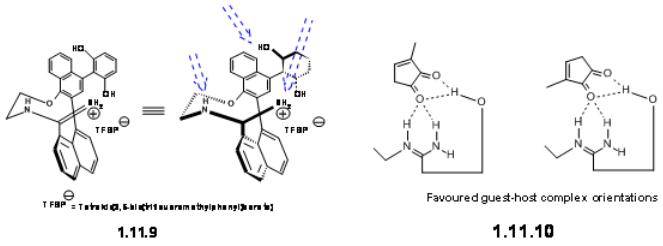



Figure 11.9

They have suggested that this ligand formed a Host-Guest complex with the dienoplile as depicted in **11.10.**

Under these conditions, the Diels-Alder reaction proceeded in excellent yield. This compound was converted to Estrone as shown in Figure 11.11

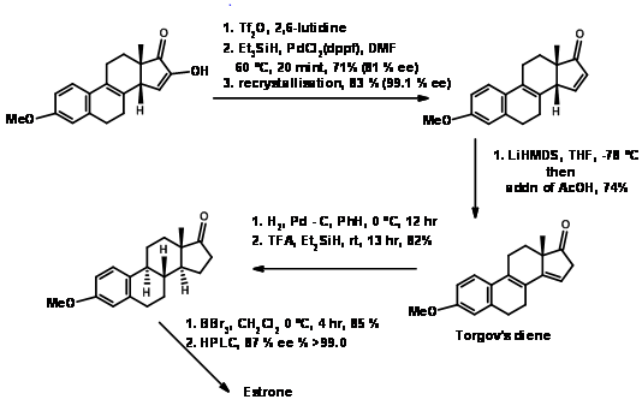
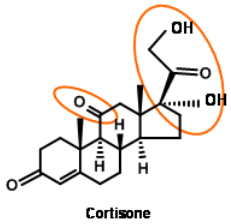



Figure 11.11

## Synthesis of Cortisone

Cortisone attracted the attention of several synthetic chemists, because this wonder drug was available only in minute quantities from animal sources. Two challenging features in the structure of cortisone were the keto- group at C11 and the 1,2,3- oxygenation pattern at the two-carbon side chain at C17.




Cortisone

Sarrett (J. Am. Chem. Soc., 74, 4974 (1952); J. Am. Chem. Soc., 76, 5031 (1954)) used an ABC  ABCD Approach. His starting molecule had all the features needed for the A, B and C rings of Cortisone. It had a C11 –OH group and a conveniently placed ketone for building the D ring. They exploited the known stereoelectronic constraints of anion reactions on a rigid 6-membered ring to construct the C/D trans ring junction **(Fig 11.12)**. This cyclisation has two noteworthy features. The olefin served as a masked ketone. Unlike Woodward's Cholesterol synthesis **(Fig 11.3)**, which had a competing site for anion formation, in this scheme only one anion is feasible leading to predictable product.

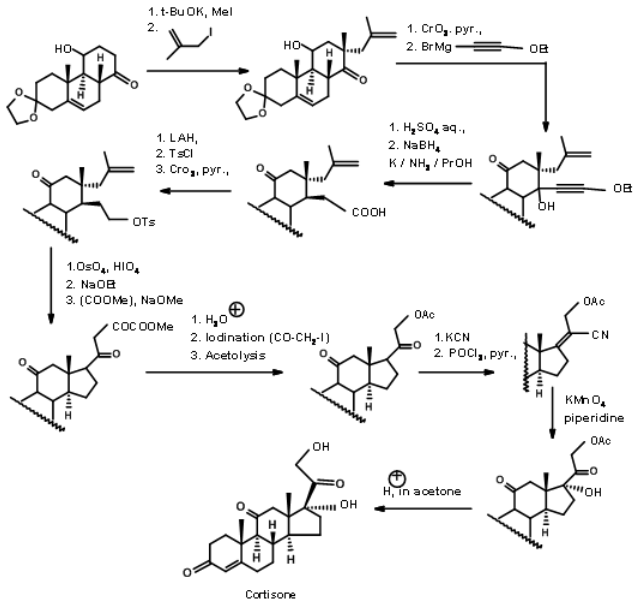



Figure 11.12

An interesting new approach in steroid synthesis came from Y. Horiguchi (J. Org. Chem., 51, 4325 (1986)). This could be described as CD  BCD  ABCD Approach. Note that the C11 oxygenation and the carbons needed for the A ring came through a single oxidation step, as envisaged in their retroanalysis shown in Figure 11.13.

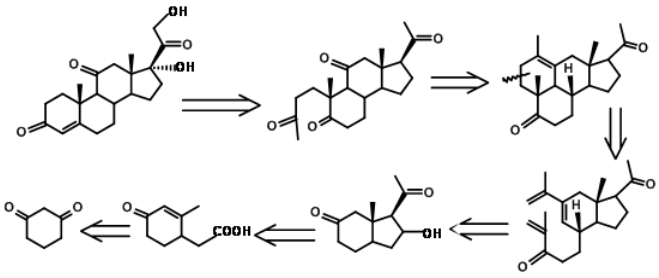



Figure 11.13

A detailed synthetic scheme of Horiguchi is shown in Figure 11.14. The strategy for formation of A as well as the D ring is of interest in this synthesis.

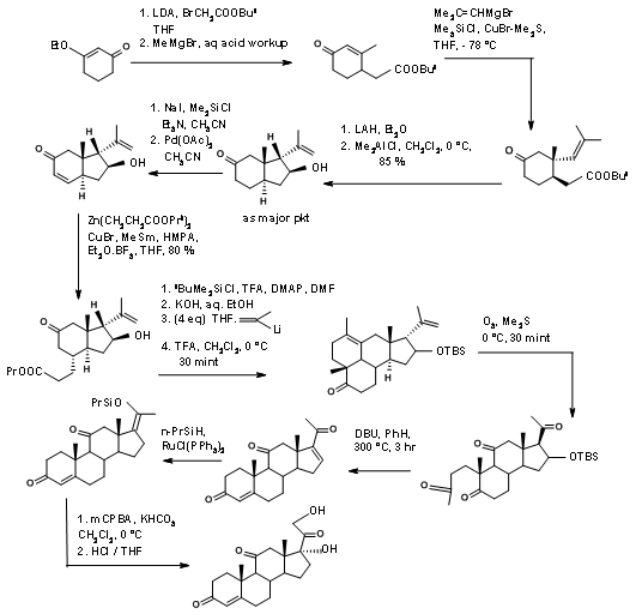


Figure 11.14

Nemoto's retroanalysis (J. Org. Chem., 55, 5625 (1990)) provided an interesting electrocyclic ring opening – cycloaddition strategy for a B  BCD  ABCD Approach **(Fig 11.15)**.

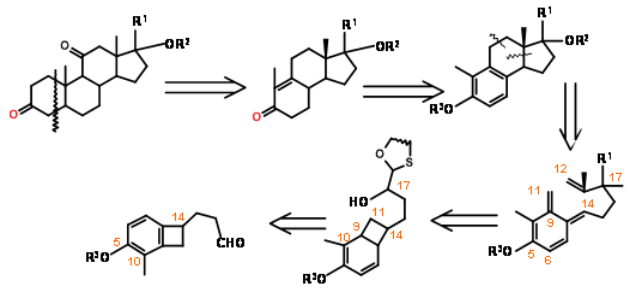


Figure 11.15

The synthetic scheme is shown in Figure 11.16. Note the versatile chiral auxiliary in the first step that serves several useful bond-forming purposes in addition to guiding three asymmetric center on C/D rings.

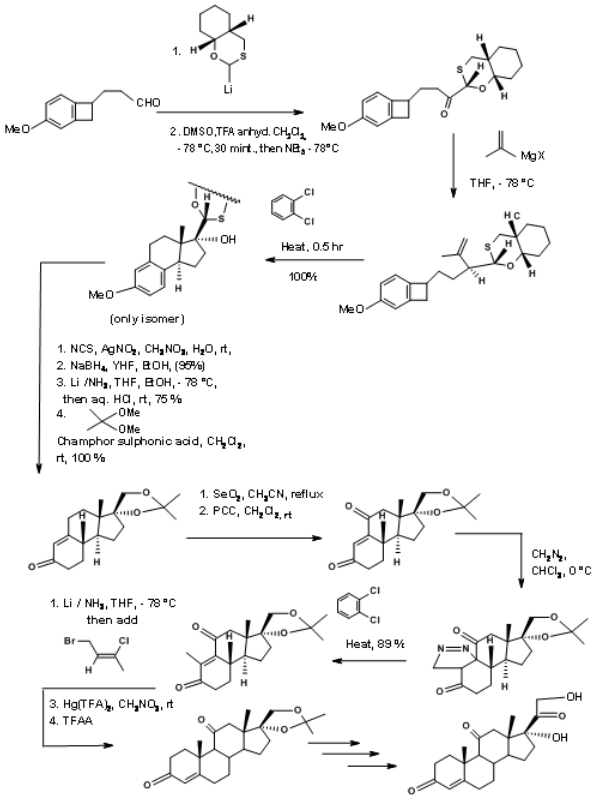



Figure 11.16

The fascination for mastering the steroid skeleton still continues unabated.

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# 12: Woodward's Synthesis of Chlorophyll

Chlorophyll, the most conspicuous of natural products, has held the fancy of organic chemists for more than two century, not only for its complex structure but also for its photochemical roll in the production of food that sustains all living things on this planet. Isolation and structure elucidation work began during the end of nineteenth century. This monumental activity that started with Willstätter, culminated in elucidation of the complete structure for Chlorophyll 'a' only by the middle of twentieth century. Most of these outstanding works, stretched over half a century, took place when modern organic chemistry was at its infancy. The synthesis of Chlorophyll 'a' by R. B. Woodward[1] is acclaimed was an outstanding achievement in organic synthesis and ranks amongst the shinning gems in synthesis. The preliminary analysis for the synthesis, the persistent planned attach on this complex, delicate chemistry by his school and the logic of the famous Woodwardian approach are all good lessons for any discerning student of Organic Synthesis.

## Analysis before initiating the synthesis

In the cited lecture, Woodward starts his discussions on synthesis with a series of questions that delineates not only the critical features of the structure under attach, but also arrives at a plausible target and approach for synthesis of this complex molecule. The structure of Chlorophyll 'α' is shown in **(Fig 12.1)**.

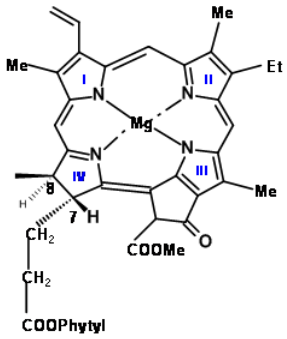
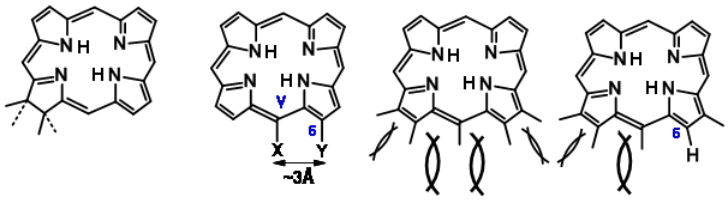



Figure 12.1

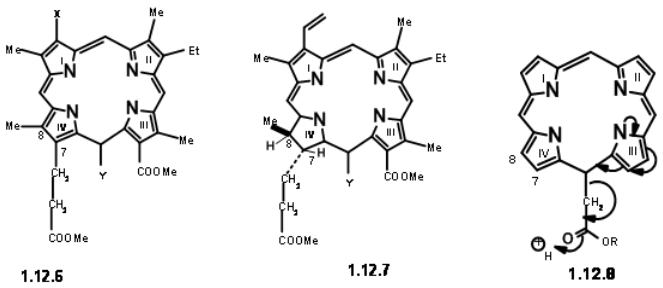
Earlier work had established that the magnesium atom and the phytyl group were easy to remove and put in place through well established chemistry. Chlorophyll 'α' belongs to the green coloured pigment family **chlorins (12.2)**. Simple chlorins are readily oxidized (lost their 'extra' hydrogens) to give the more conjugated porphyrins **(12.3)**. But some chlorins like chlorophyll do so only under drastic conditions. The second feature that drew their attention is the carbocyclic five membered fused ring attached to ring III. A close study of the molecular models suggested that a porphyrin, which had a string of substituents on C5, C6, Cγ, C7 and C8 positions, would be highly crowded as shown in **(12.3)** and **(12.4)**. They noted that chlorins and porphyrins that had a substitution at Cγ and a carboxyl group at C6, loose $CO_2$ with ease, while absence of Cγ subsitution




**1.12.2** **1.12.3** **1.12.4** **1.12.5**

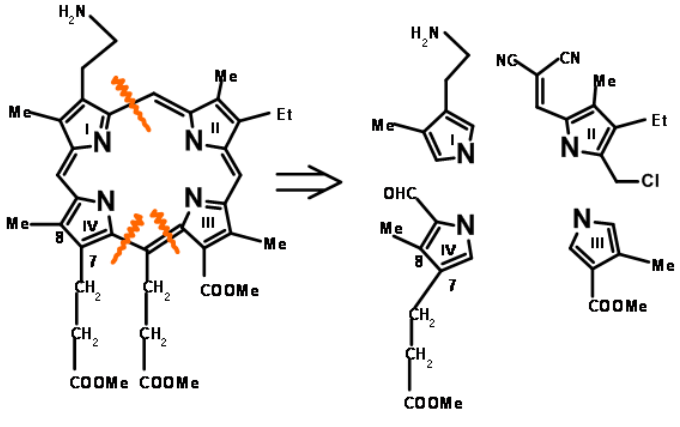
endeared the C6 carbonyl increased stability. All these features led them to conclude that in porphyrins, the space at C7 / Cγ and Cγ / C6 are most crowded. Decarboxylation reduces this strain partially**(12.5)**. Presence of substituent at Cγ increases the strain for C7 / Cγ space as well. This crowding is perhaps partly relieved by formation of the carbocyclic ring at Cγ / C6. Furthermore, the strain at C7 / Cγ could be relieved by introduction of the 'extra' hydrogen at C7 and C8. The same strain factors would influence the trans- arrangement for substituents at C7 and C8. Such detailed analysis of the given structure not only helped them to understand

the given structure but also suggested that the 'Target' for synthesis could be a porphylin like **(12.6)**. Once it is synthesized, such a structure could be coerced to move on to take up the 'extra' hydrogens and move to **(12.7)**. Some questions remained. The vinyl group on the first ring was considered as very sensitive to withstand the rigour of the projected synthesis.



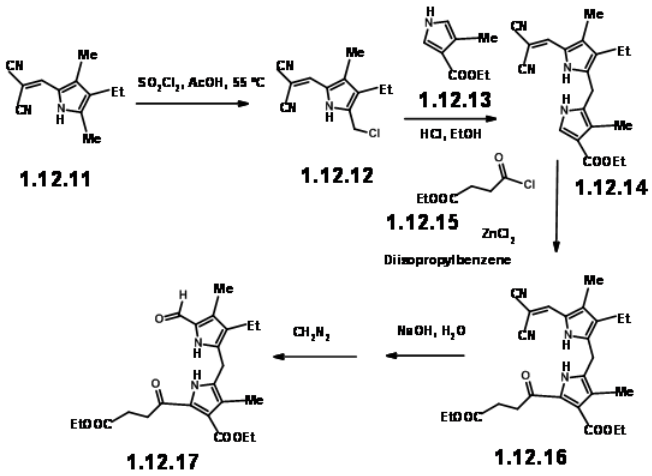
1.12.6 1.12.7 1.12.8

Hence, it was replaced with an equivalent aminopropane chain. As shown in structure **(12.7)**, the residue needed at Cγ is an acetic acid moiety. However, mechanistic analysis of such a porphyrin **(12.8)**suggested that such a unit would readily eliminate due to an expected 'electronic factor' (actually, we would now say 'enamine-like activity'). They decided to make this unit a propionic acid residue to avoid this instability. We have now arrived at a target structure **(12.9)**. Based on the known pyrrole chemistry, they decided to make the ***Right Hand Side and the Left Hand Side*** of the molecule independently and condense these units into a tetramer. Thus, they arrived at the following four monomer units **(12.10)**.

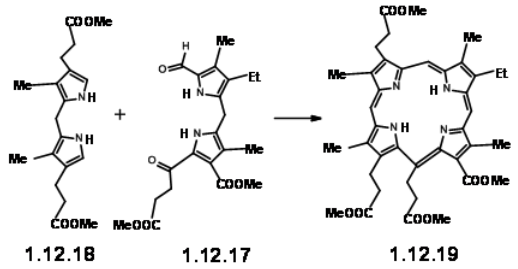


1.12.9 1.12.10

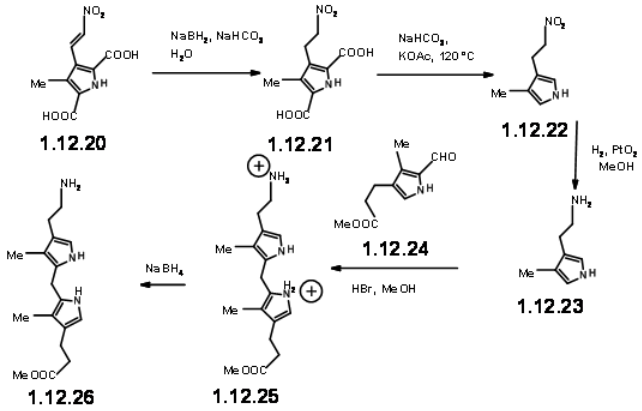
**RHS Unit:** The pyrrole units II and III were combined to give the expected dimer unit in good yields. Acylation with β-carbomethoxypropionyl chloride gave the RHS unit **(12.17)**.



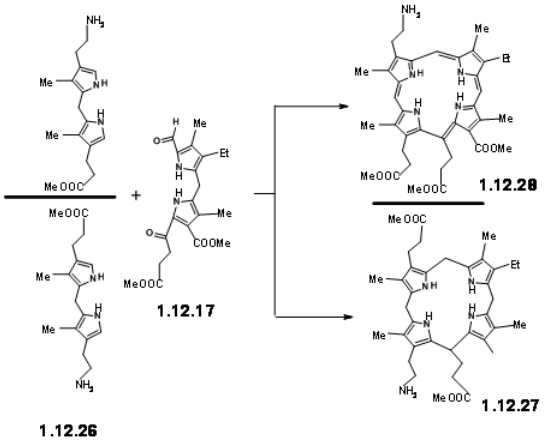
With this RHS unit **(12.17)** on hand, they tried the crucial cyclisation with a readily available model LHS unit **(12.18)**. On condensation under acid conditions, followed by oxidation with iodine, the required porphyrin **(12.19)** could be obtained in acceptable 25% yield.



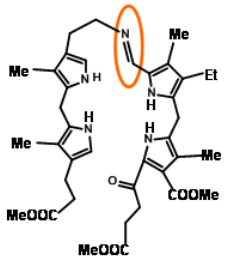

Encouraged with this result, they went ahead to synthesize the actual LHS unit **(12.26)**.




With the LHS unit ready at hand, they looked at the cyclisation of these two units. They realized that this condensation could give two products due to two different orientations of the reactants. Though the yield of this condensation product was comparable to previous condensation, they saw some drawbacks.

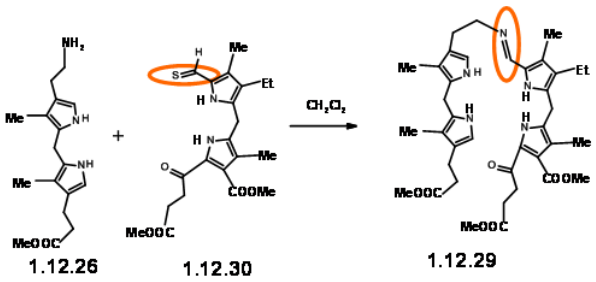



The yield was not acceptable for their projected purpose. Furthermore, this route resulted in the formation of isomeric products, whose structure assignment posed problems. Such ‘inelegance’ (an expression used by RBW in his lecture) was not acceptable for their group. Hence, they decided to freeze the mobility of the two units by linking the amine and the aldehyde units into a Schiff base **(12.29)**.



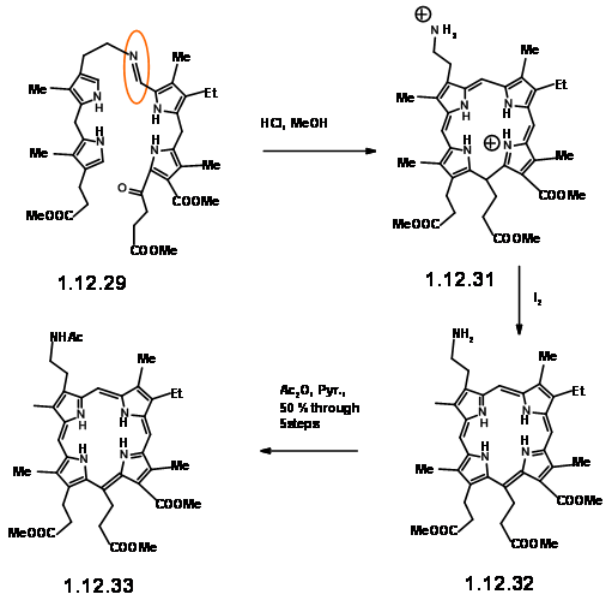
1.12.29

This masterly defined craftsmanship in molecular engineering was, however, not easy to achieve in practice. Pyrrole aldehydes were generally unreactive and could be converted to Schiff bases only under acid catalysis or buffered conditions. The problem arose from the LHS unit that proved to be very sensitive to such reaction conditions. No trace of the expected condensation product was observed. After several experiments, activation at aldehyde unit via Schiff bases followed by condensation with LHS unit via base exchange became a viable approach. But the discovery that such Schiff bases could be

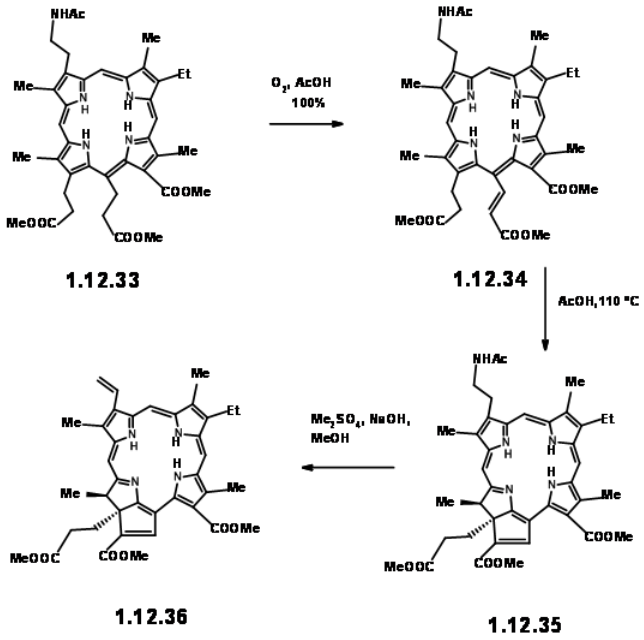


1.12.26 1.12.30 1.12.29

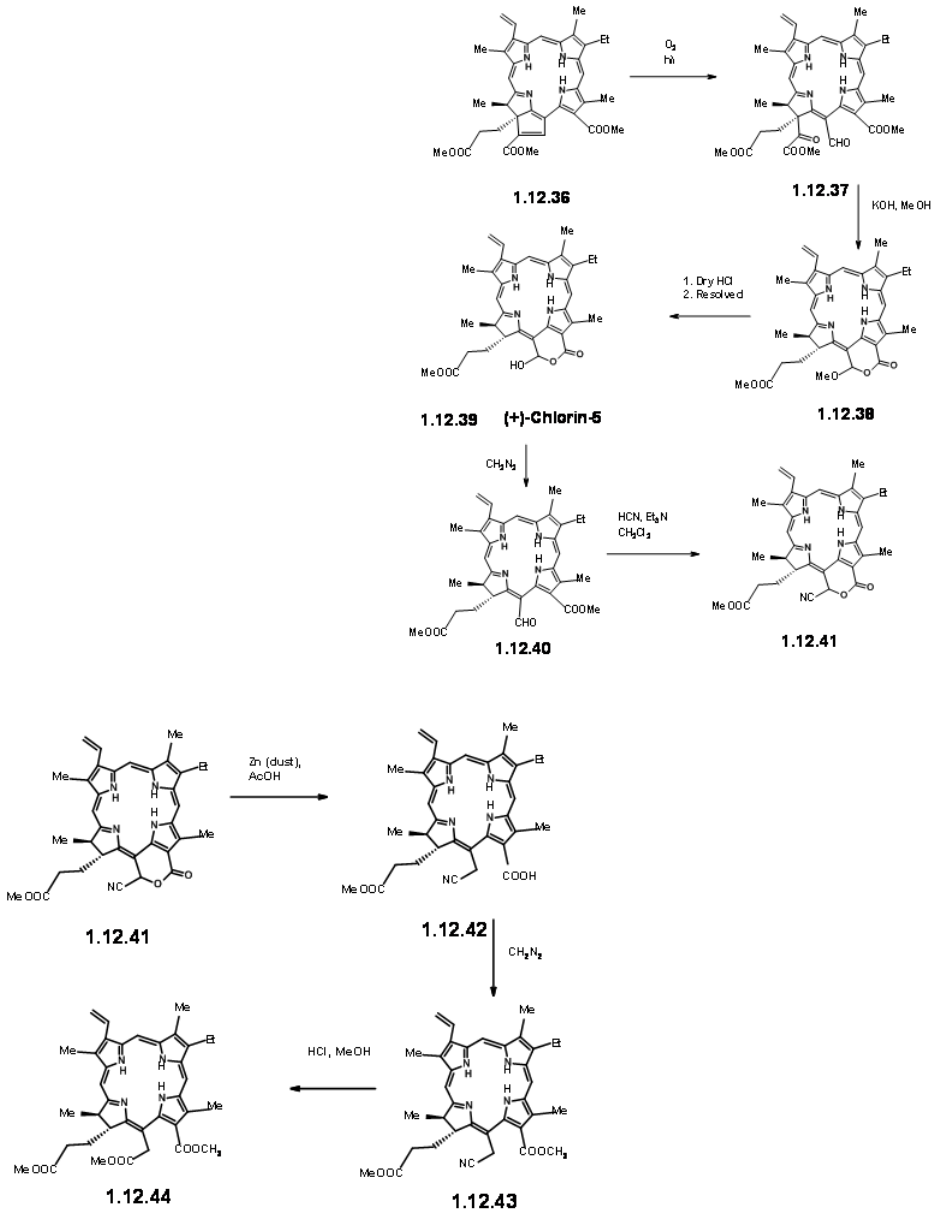
smoothly converted to thioaldehyde **(12.30)** provided a breakthrough. This thioaldehyde smoothly condensed with the LHS unit under neutral conditions in good yield. This 'extraordinarily sensitive' Schiff base, on acid treatment gave the cation **(12.31)**, which was isolated as the dibromide. This dication was immediately oxidized with iodine to **(12.32)** and isolated as the acetamide **(12.33)** on acylation with acetic anhydride. In spite of the sensitivity of the intermediates and quick subsequent steps, the porphyrin **(12.33)** could be obtained in good yield and could be scaled up to several gram scale.



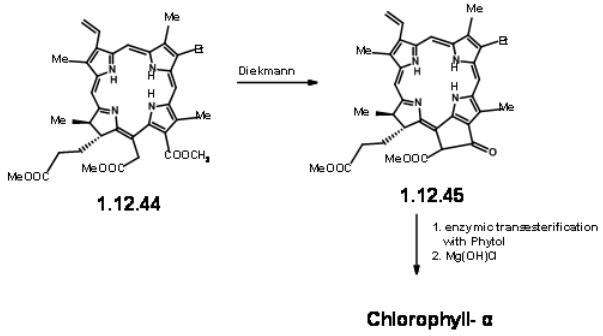

When the porphyrin **(12.33)** was heated in acetic acid in air, migration of the first hydrogen occurred to give **(12.34)**. On heating in acetic acid at 110 0C, the chain at Cγ cyclised at C7 to give the reduced ring unit IV . Note the orientation of the two chains on ring IV is trans as expected. At this stage, attention was shifted to the vinyl group on ring I . This was readily achieved by Hoffmann exhaustive methylation-elimination sequence shown above **(12.36)**.




On exposure to light and air, the extra ring readily cleaved to give a pyruvic ester and a formyl group **(12.37)**. The extra pyruvyl moiety was readily cleaved in methanolic KOH, which led to a methoxy lactone **(12.380**. Dry HCl gave the hamiacetal that could be resolved using quinine salt method to give (+)-Chlorin-5 **(12.39)**. Diazomethane esterification exposed the aldehyde unit **(12.40)**. Treatment of the formyl compound **(12.40)** with HCN in triethyl amine gave the cyanolactone **(12.41)**, which on reduction, esterification and hydrolysis with methanolic HCl gave **(12.44)**, the precursor for a Dieckmann cyclisation product.




From here to (-)-Clorophyll α was already known. A Diekmann followed by introduction of the phytyl group by enzymztic methods completed the synthesis (Fortchr. Chem. Forsch., 2, 538 (1952)).



To this day, this masterpiece in organic synthesis has several feature that hold the interest for lovers of Art and Logic in organic synthesis.

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# 13: Synthesis of Vitamin $B_{12}$

The total synthesis of Vitamin $B_{12}$ was accomplished in 1973 by a grand collaboration between R. B. Woodward's group at Harvard University (USA) and A. Eschenmoser's group, Swiss Federal Institute of Technology (ETH), Zürich, Switzerland. It took about twelve years and more than two dozen senior scientists to complete this gigantic task. The achievement is variously eulogized by organic chemists – monumental achievement in the annals of organic synthetic chemistry; a breakthrough; a mile stone in organic synthesis; unrivaled even after 40 years; a task no less adventurous than concurring Mount Everest. At the time the adventure started it was the most formidable challenge in synthetic chemistry, which few would have dared. The announcement of its synthesis marked the coming of age of synthetic organic chemistry. Woodward and Eschenmoser worked in close collaboration and in competition during this historic pace. In the process, they achieved not only an astounding synthesis, but also opened several new fields for future investigations. Woodward Hoffmann Rule is the most famous of the offshoots. While studying this synthesis, a student should also ponder over the thoroughness in their planning of all aspects of the scheme and initiation of suitable basic studies well in advance to facilitate the main scheme at appropriate junctures. This long introduction is just in tune with the length of the scheme, time taken and magnificent achievements.

## Retroanalysis of Vitamin $B_{12}$ synthesis

**Figure 13.1** shows the structure of Vit $B_12$ and the main structural features / challenges of the complex molecule.

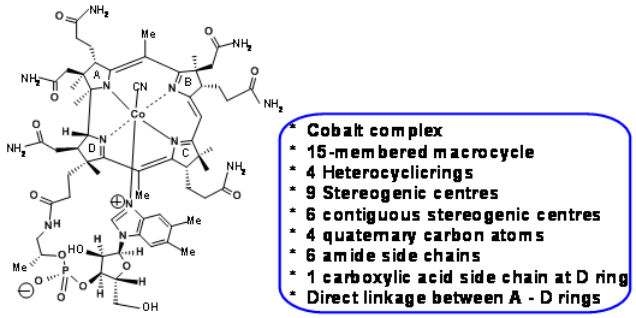


Figure 13.1

In his inimitable style, R. B. Woodward draws attention to these challenges in the beginning of his lectures and to the fact that it took close to 50 years to establish the structure of Vit $B_12$ by chemical degradation and finally by X-Ray diffraction studies by Dorothy Hodgkin in 1956. One should note that most of the chemical degradation studies, remarkable as they might be, happened during the early years of the twentieth century, when modern organic chemistry was in its making. Spectroscopic data, if any, were conspicuous by their absence and most of the degradation and synthetic chemistry were too harsh by modern (meaning 1960s) standards for this delicate molecule. Hence, this was a daunting scenario. This meant that a whole lot of synthetic chemistry had to be reinvented to suit these challenges. Such aspects were thoroughly planned in and contingency plans were put in place well in advance. Discerning students could see a glimpse of this planning in this short presentation. The ideas on retroanalysis, as we understand today, were in the developing stages during the sixties. The retroanalyses we use here are later-day additions by other scientists, based on the facts (lectures, papers etc.,) published by the two groups. All such citations are included at the end of the write-up.

The synthetic target was identified as Cobyric Acid, because this compound was a natural product and had been converted to Vit $B_12$ by Bernhauer K., et.al., (1960)**(Figure 13.2)**. Hence total synthesis of Cobyric Acid would amount to a formal synthesis of Vit $B_12$.

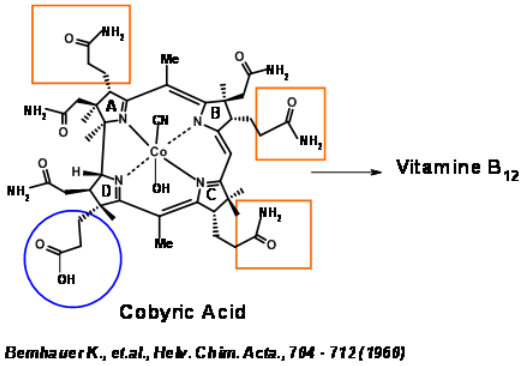


Figure 13.2

Cobyric acid had seven carboxylic acid side chains, out of which four were propionic acid moieties, one on each heterocyclic ring. The main challenge was to differentiate the propionic acid chain on the D ring from the other acetic acid and propionic acid moieties. It was therefore decided that this odd acid moiety would be masked as nitrile **(Figure 13.3)**. That still leaves a daunting task of differentiation, which we could address later. It was first decided to view the molecule as made up of two halves – the **Eastern Side and the Western Side**. The first disconnection was at the A/B ring junction at the methylene bridge **(1.13.3A)**. Cleavage of the second bridge at C/D ring junctions gave the Eastern Half as **Thiodextrolin** in charge of Eschenmoser's group at Zurich and the Western Half as **Cyanobromide** in charge of Woodward's group at Harvard (US).

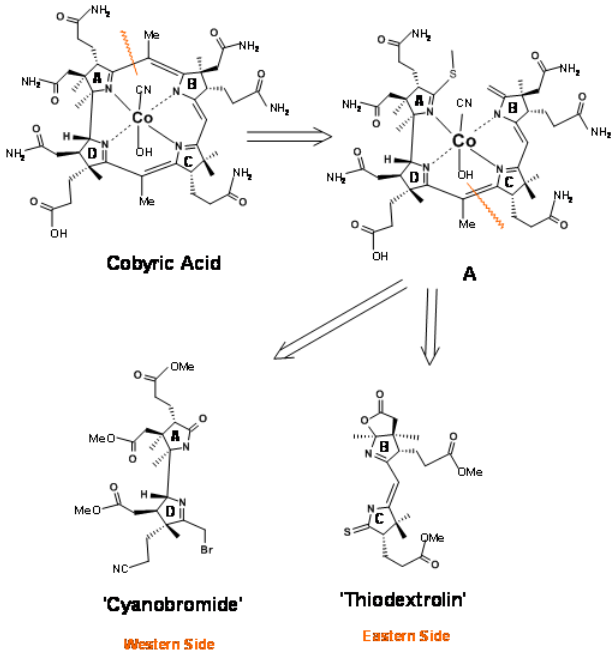


Figure 13.3

## Retroanalysis of cyanobromide

This western half has a formidable array of *six contiguous stereocentres* on an eight-carbon frame. Note that the stereocentres were planned on the basis of known stereoselectivities and the six membered rings were built to provide the propionic acid chains **(Figure 13.4)**. The nitrogen for the A ring came from an indole, whose benzene ring gave the side chains for the A ring. The D ring

nitrogen came via a Beckmann rearrangement. Cornorsterone **(1.13.4A)** was the key intermediate (corner stone) that held all the stereocentres and chains on the Western Half.

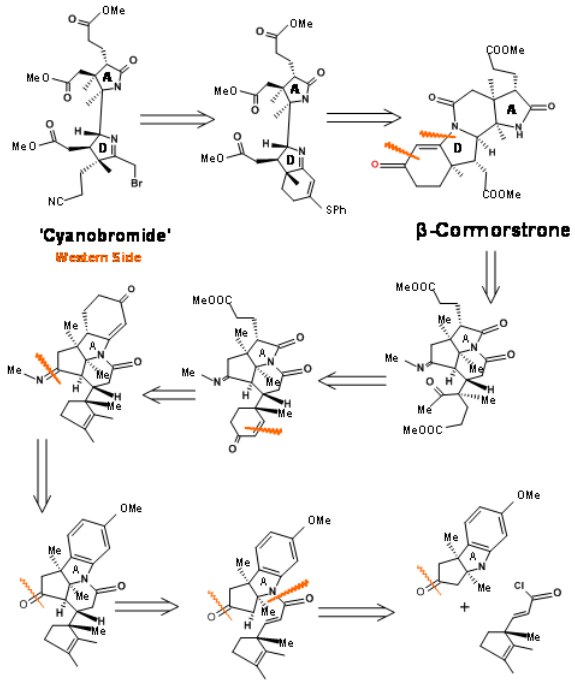


Figure 13.4

## Synthesis of Western Half

The required enantiopure 1,2,3-trimethylyclopentene unit came from camphorquinone as shown in **Figure 13.5**.

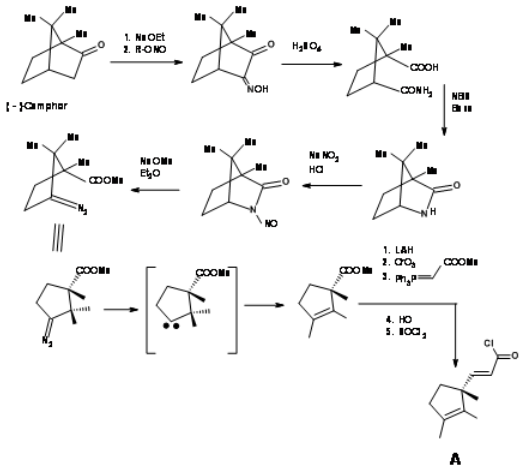


Figure 13.5

Through another convergent synthesis, a five membered ring was fused to indole at C2 – C3 bond and resolved as shown in **Figure 13.6**.

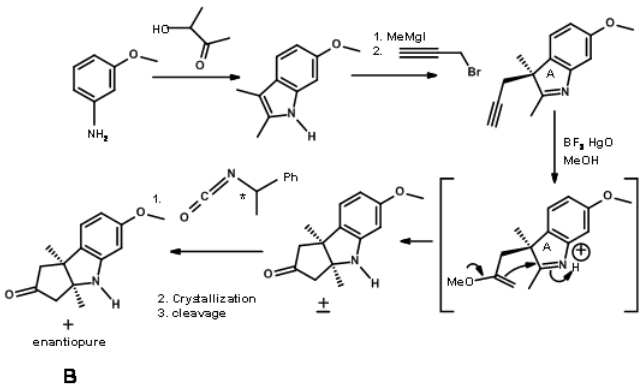


Figure 13.6

The (+)- enantiomer was actually needed for target synthesis. The useless (-)- enentiomer was used as a model compound (for this was "just about the only kind of model study which we regard as wholly reliable" – RBW).

Fragments **A** and **B** were combined and then processed to Corrnorsterone as shown in **Figure 13.7**.

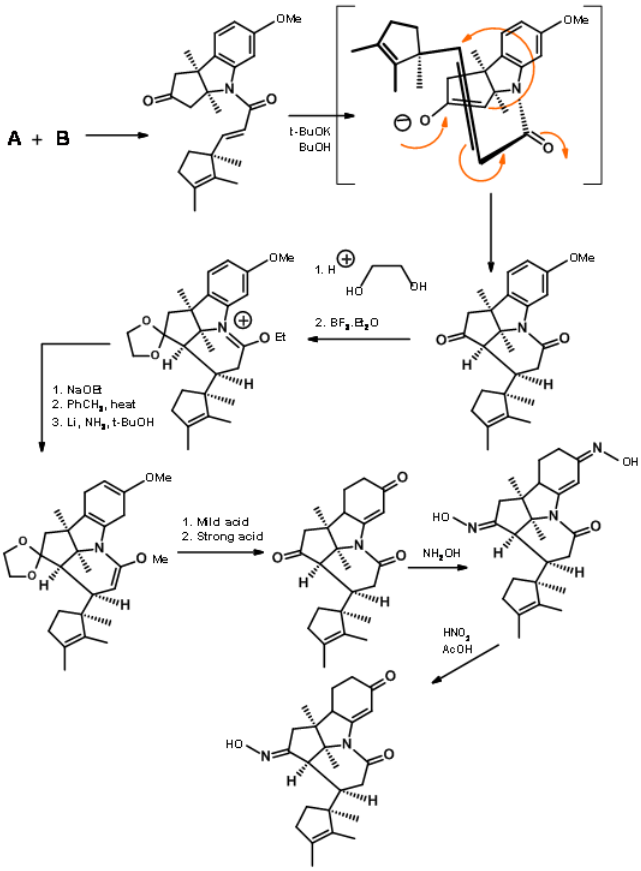


Figure 13.7

Note that the Beckmann ring expansion process set in motion a cascade of reaction, leading to a Claisen condensation and D ring formation, all in one step. The six membered imide carbonyl was also cleaved and placed an acetate chain on the D ring. In spite of this elaborate planning and execution, the process yielded a mixture of epimers at propionic acid side chain on the A ring, the required isomer being a minor component of the mixture. The major undesired product does not cleave at the amide bond due to unfavourable steric compression at the developing side chains **(Figure 13.8)**.

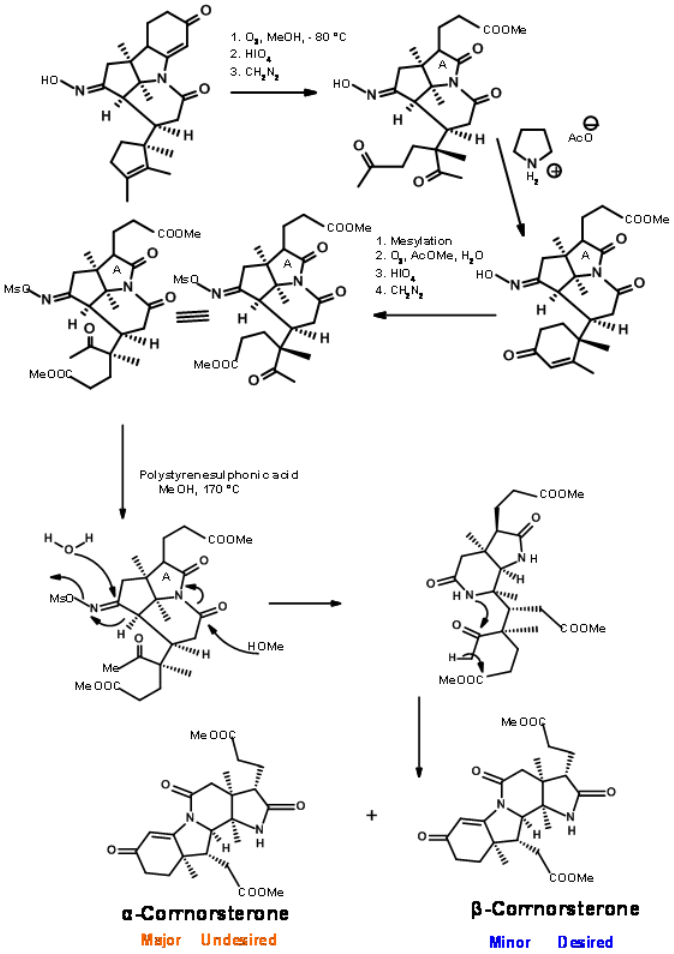


Figure 13.8

This unfavorable steric problem was however soon solved. On hydrolysis under strong base conditions, the amide ring opened and the propionic acid side chain isomerised to the less strained isomer. This could be then be acidified and esterified to β-cornorsterone, with a recovery of 90% of the desired isomer **(Figure 13.9)**.

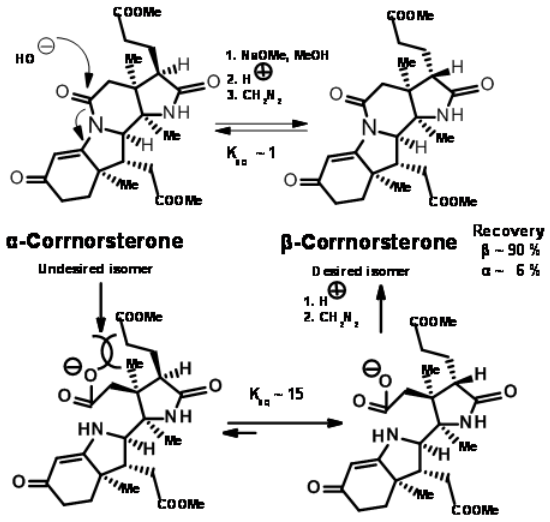


Figure 13.9

This correct isomer was treated with a mixture of methanol and thiophenol under acid conditions **(Figure 13.10)**. This set two processes in motion. The thiophenol attacked the ketone and activated this center, while the methanol oxygen attacked the amide bond leading to an ester and a thioenol ether.

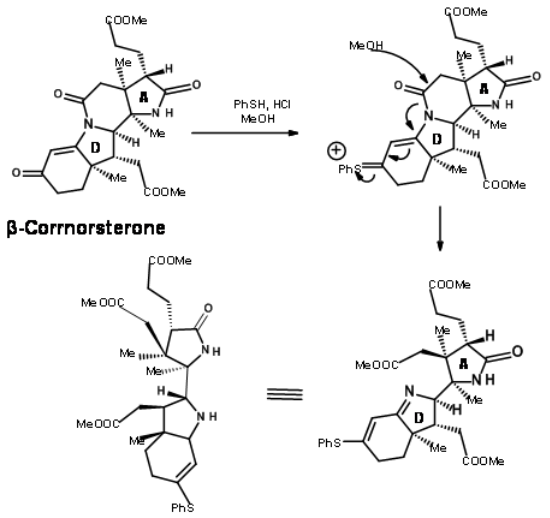


Figure 13.10

Ozonolysis of the thioenol ether at – 90°C cleaved the olefin unit to the aldehyde-thioester compound **(Figure 13.11)**. An interesting new chemistry evolved here. While thioesters are less reactive to acid hydrolysis and showed comparable reactivity with oxygen nucleophiles, nitrogen nucleophiles were unique. The thioester reacted much faster then normal oxyesters to give amides. Thus, the thioester was exclusively cleaved to amide with ammonia, leaving three methyl esters untouched. The aldehyde moiety was then selectively converted to alcohol and then mesylated under mixed anhydride / pyridine conditions. This sequence also converted the amide moiety to nitrile. The mesylate was then converted to bromide to give the key intermediate cyanobromide.

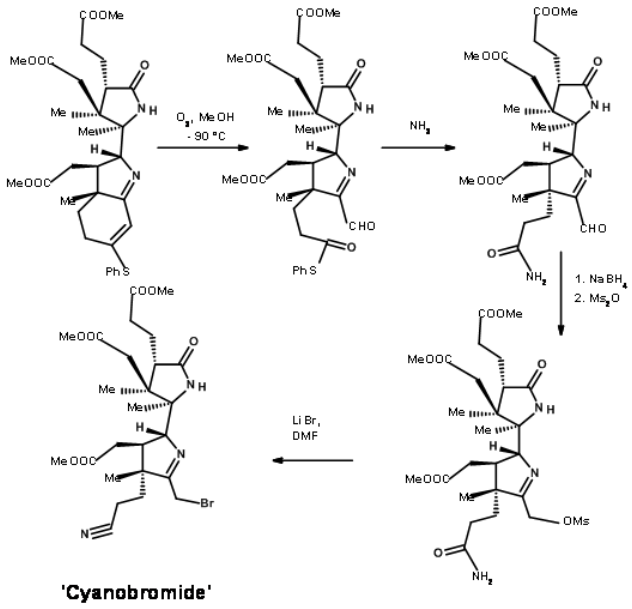


Figure 13.11

The Zurich group was simultaneously working on the synthesis of the Eastern Half named **Thiodextrolin**. The fragments for B and C rings were planned via., a single intermediate **(1.13.12)**.

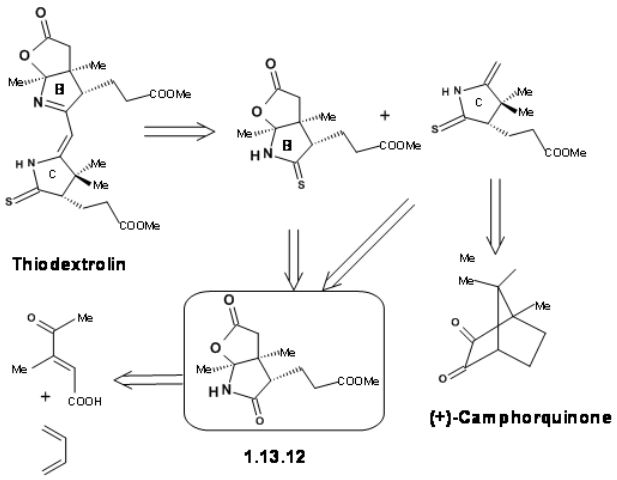


Figure 13.12

The synthesis started with a Diels-Alder reaction to secure two asymmetric centers properly and the racemate was resolved. The pure enantiomer was followed through the scheme to obtain the B ring segment. The same intermediate yielded the C ring fragment as well **(Figure 13.13)**.

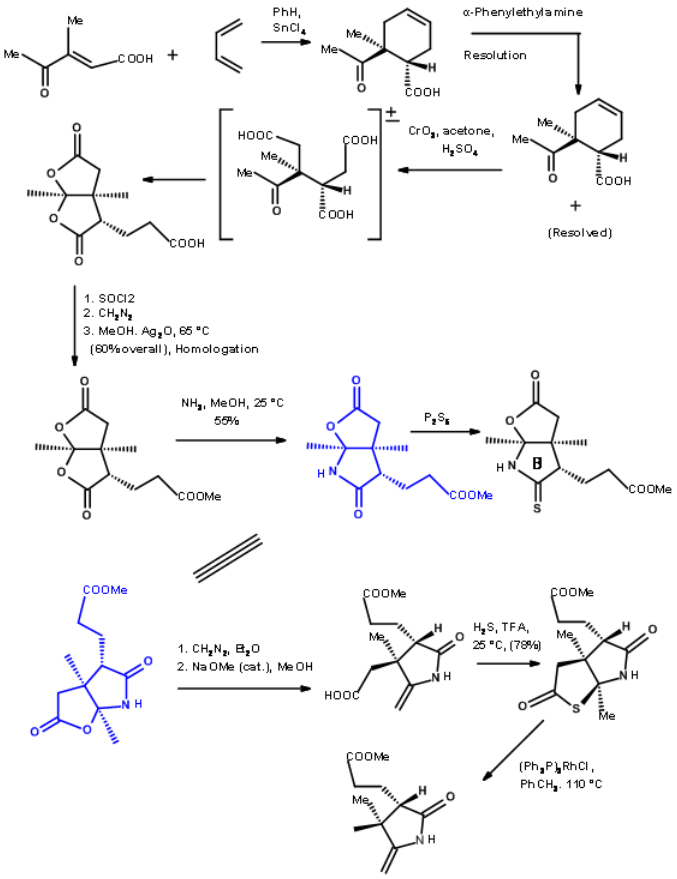

Figure 13.13

To connect two such fragments Eschenmoser had developed two sulphide contraction procedures. The mechanisms of the processes are shown below.

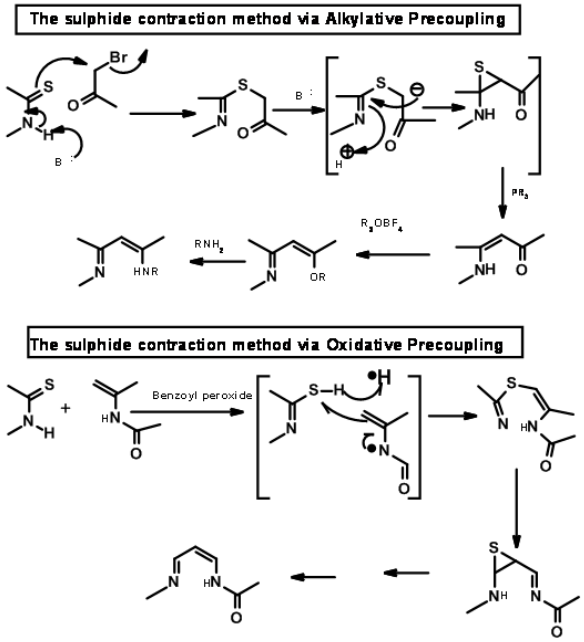


Figure 13.14

Using the oxidative coupling / sulfur extrusion procedure, they coupled the B and C rings as shown in **Figure 13.15**.

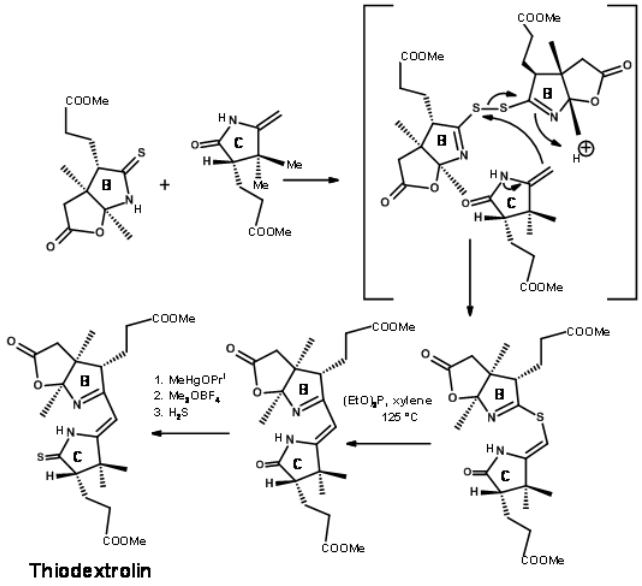


Figure 13.15

Woodward's group also developed a new synthesis for the C ring starting from (+)-Camphorquinone. The scheme is shown in **Figure 13.16**.

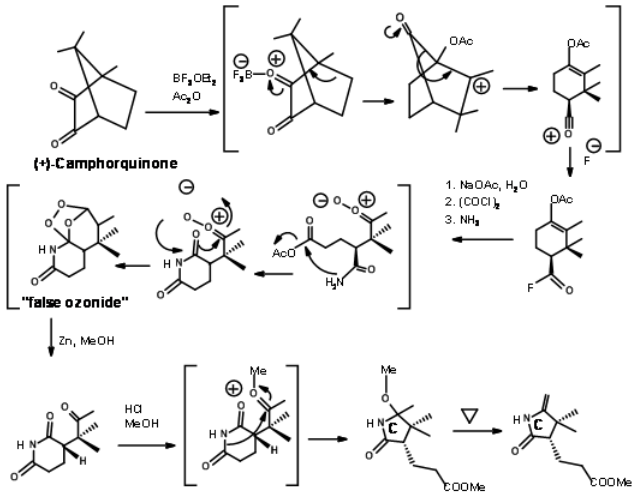


Figure 13.16

Though great care had been spared for the stereocentres at all points, the problem of stereoisomers could not be avoided. The crystalline thiodextrollin that was synthesized was actually a mixture of two stereoisomers at the propionic acid moiety of the B ring. Though they had purified the mixture at this point, it was of no value because this stereocentre was due for further disturbances at later stages. The mixture was taken forward for the first coupling at C / D bridge. After considerable effort that lasted over a year, they were first coupled at the Southern end using the alkylation / extrusion procedure **(Figure 13.17)**. Note that the first product of alkylation was a thioether Type I, which readily isomerised to thioether Type II. The product was named Cyanocorrigenolide. This isomerisation disturbed the stereocentre at the C ring.

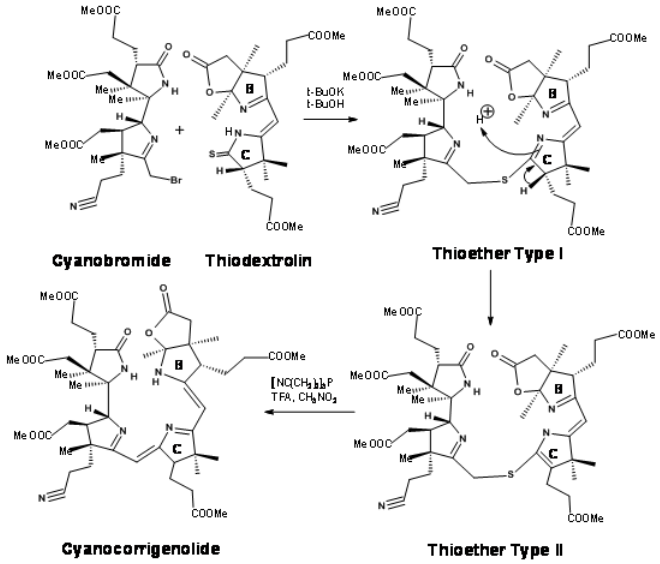


Figure 13.17

The next phase was the formation of A / B bridge. The C / D coupled compound was first treated with phosphorous pentasulphide followed by trimethyloxonium fluoroborate ($Me_3OBF_4$) **(Figure 13.18)**. This procedure replaced the oxygens on the A and B rings by sulfur and finally to the S-methyl derivative. Dimethylamine in methnol cleaved the thiolactone ring selectively to a dimethylacetamide chain and a terminal olefin. The olefin was rather unstable. This was to be converted immediately to the cobalt complex. This procedure was not easy. Under several conditions, the cobalt metal ion catalyzed further reactions leading to extensive “destruction” of the compound. After several experiments it was observed that cobalt chloride or iodide in THF was unique for smooth cobaltation. The complexation process brought the A and B rings in close proximity. A base catalysed reaction then enabled formation of the bridge and removal of the sulfur moiety the best condition being DBN catalysed cyclization.

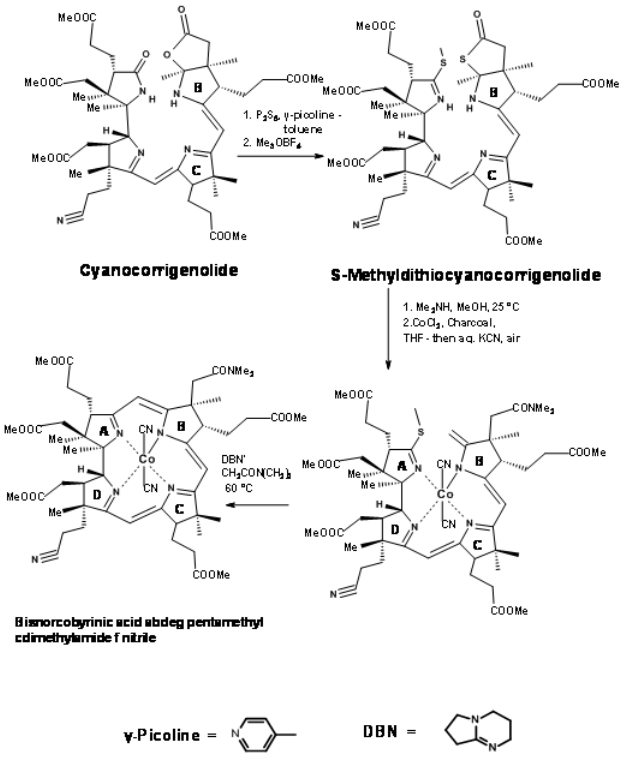


Figure 13.18

Note that the overall transformation interfered with the asymmetric center at C ring. Nonetheless, the A / B bridge was finally in place.

The Zurich group also came up with an alternate Zn-complex procedure along the same lines. All these manipulations were indeed harsh to the (three) epimerisable propionic acid chains on the A, B and C rings. The final product was purified by TLC ("plate chromatography") and critically analyzed by HPLC (a new chromatographic tool at that time). The UV chromophores in all the products were of great help in this chromatography.

The synthesis has now two major milestones to pass. There are three active methine bridges in the molecule. The bridge at B / C rings had to be 'protected' from methylation. This was achieved by an oxidative lactone formation reaction at the B ring (I2, AcOH) **(Figure 13.19)**. This new quaternary center and the existing quaternary carbon at C12 together exerted a steric congestion around C10. The chloromethyl ether entered the C5 and C15 centres exclusively. Ra-Ni hydrogenolysis cleaved the thioethers and the lactone ring in one step. This step was followed by esterification.

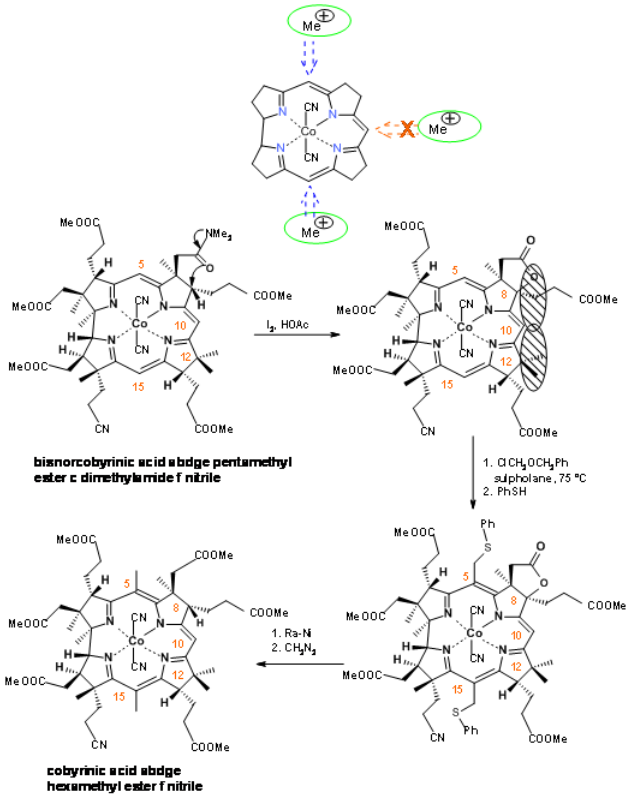


Figure 13.19

Conc. sulfuric acid converted the nitrile to amide **(Figure 13.20)**.At this stage, they faced the difficult task of selective cleavage of amide, in the presence of six esters in the molecule. After extensive parallel experimentations, the Harvard group rediscovered an efficient selective cleavage of the amide moiety in $N_2O_2$ reagent.

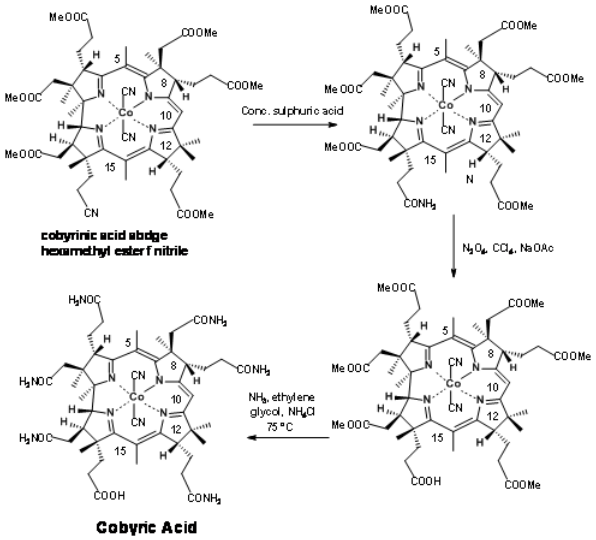


Figure 13.20

The Zurich group also came out with a “diabolically cleaver scheme” for selective hydrolysis of the amide group in the presence of ester groups. This scheme is shown in **Figure 13.21**. However the former was preferred due to its simplicity and better yields. Nonetheless, Eschenmoser’s solution stands testimony to human ingenuity.

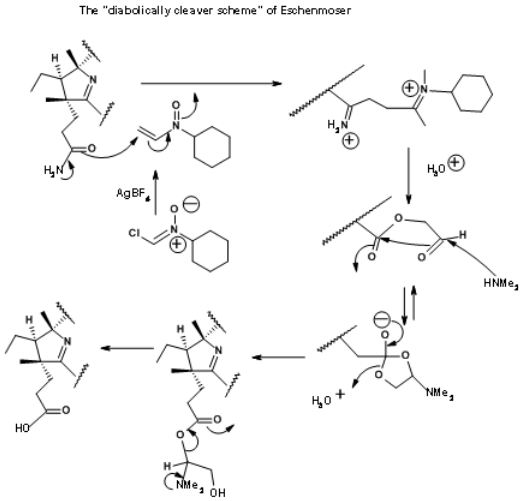


Figure 13.21

The very last step of this long synthesis posed a major problem that needs special mention. Amidation of esters with ammonia was the only remaining step for the final assault on the synthesis of Cobyric acid. A closer look reveals that the task may not be that easy. The ester moieties (in particular the acetate units) were in crowed environments. Parallel to these developments, model studies on very similar molecules were in progress. Based on these studies, when the hexamethylester 1 acid was treated with ammonia in ethylene glycol at 75°C for 30 hours, the product obtained was not cobyric acid but a pseudocobyric acid, whose structure was established as dehydrocobyric acid. This product could be purified only by HPLC. This was one among the products obtained by earlier workers. But they had no idea about such a complication. This mystery took several critical studies to solve. Throughout all these studies, great care was exercised to see that the solvents were well deoxygenated before use. Oxygen was strictly avoided from the reaction atmosphere. The source for this oxidative cyclization was attributed to cobalt, which was suspected to oxidatively bond to the C9 position, facilitating the amide anion to cyclise. This unwanted reaction took a long time to solve. Several studies were aimed at ammonialysis under reducing conditions and also to open the lactam ring under reduction conditions.

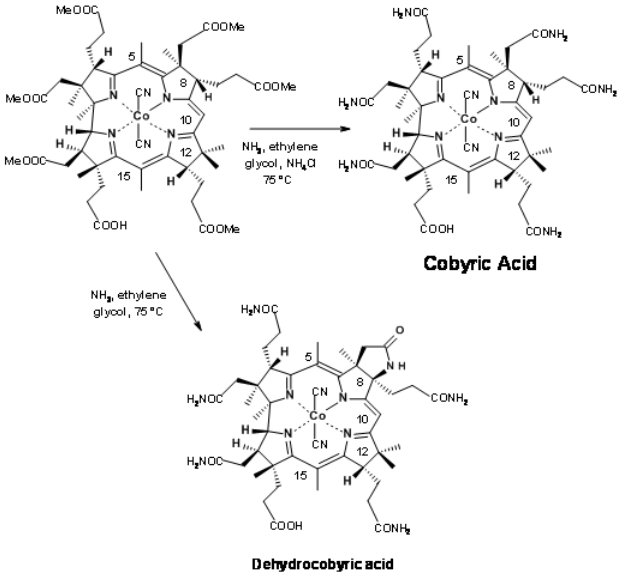


Figure 13.22

Finally a few milligrams of ammonium acetate were added to the reaction mixture to prevent the formation of amide anion, which was suspected to be the culprit for cyclization **(Figure 13.22)**. This trick helped. The reaction was complete within 10 hours, with cobyric acid as the only product in good yields. This cobyric acid was identical in all respects, particularly in HPLC, with the natural product, thus ending this long journey for the formal synthesis of Vitamin $B_{12}$.

This extraordinary adventure in organic synthesis is noted for several most significant achievements.

- Developments in Corrin chemistry
- Synthetic strategy
- Development of several new methodologies
- Woodward-Hoffmann Rules

Even after half a century this Vit $B_{12}$ synthesis remains unrivaled and continues to inspire generations of chemists.

## Further Reading


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# 14: Green Chemistry - Protection-Free Organic Synthesis

During the past two centuries, the art organic synthesis has seen enormous progress in several disciplines of organic chemistry. Soon after the strides made by stalwarts like Kekule, Fischer and Robison during late 19th century and early 20th century, chemistry witnessed the dawn of mechanistic organic chemistry. The era of spectroscopy and reagents soon followed to compliment and advance mechanistic organic chemistry and synthesis to new heights. During the middle of twentieth century, advances in Separation Science took over the classical art of purification. The last three decades of the century saw the birth of Logic in Synthesis. All these developments augured well for new developments in drug discovery leading to large-scale synthesis of several complex organic molecules. However, this hectic pace of developments in industrial chemistry has taken place at the cost of environment that is so vital for survival of life on earth. In chemical industry, this realization came about only after disasters like the one witnessed at Bhopal, India jolted the chemical world. The onus of development of new molecules rests on us (chemists) and therefore the onus of *responsible development* is once again on our shoulders. Clean Chemistry (meaning Green Chemistry) depends on several factors – clean starting materials, clean reagents, clean solvents, clean product, clean energy and (not the least) clean processes. While all these subtitles are discussed under Green Chemistry, we would restrict our present discussions to one aspect of the Green Process viz., protection free syntheses because this falls under our present discussions 'Logic of Synthesis'.

- *Advanced Organic Chemistry: Principles Tools and Logic of Synthesis, Vishal Publishing Co.,* Jalandhar, India (2012).

The Logic of Synthesis opens up a systematic methodology for the development of Synthetic Trees. When properly devised, a synthetic tree contains all plausible routes for the synthesis of the **Target** compound. The route chosen depends on the need and constraints of the developer scientist. Hence, the choice of clean chemistry starts here. The routes should be analyzed from the windows for Green Chemistry. One such green window is the lookout for a Protection Free synthetic route. **Why Protection Free Route?** An industrially feasible route has to be very efficient to be economical. By imposing such a condition - Protection Free - to the choice of routes, it should possible to arrive at such routes. Each protection / deprotection sequence adds two steps to the scheme. Thus, more the protecting groups, less is the overall yield. In addition, each protection / deprotection step adds to the byproduct load released into the environment. Thus, protection based planning has a double-edged sword hidden at every such step. To minimize loss (of precious final product) protection / deprotection sequence should therefore be treated as an avoidable technique to be used only sparingly. Always remember that protection methodology provides such a sense of security, one tends to abuse and over use such a facility. Once a chemist settles in such a comfort zone, one tends to spend less time / effort to look for alternate approaches.

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***Is it possible to avoid it?*** It should be possible to deliberately select such routes from the Synthetic Tree or device such a tree based on this additional criteria. One could select only those routes that do not call for protection or has a minimum of such techniques.

- One could add filtration criteria while devising synthetic trees to avoid such conflicting groups. This would indeed greatly shrink the size of the tree and thus limit the number of choices.
- The scheme could be devised with a minimum of conflicting groups. This would enhance the number of synthetic schemes and thus provide more choice to the scientist.
- Wherever such conflicts arise, one should first look for suitable reagents that are chemoselective and / or regioselective, instead of resorting to the comfort of protection. Advances in reagents / reactions are such that we now have several selective reagents and their number is increasing by each passing day.

Once a conscious decision is taken that protection free syntheses are ***'elegant'*** in addition to being ***economical***, one is more likely to come up with suitable schemes. Since industrial scale syntheses are mainly guided by cost factors, it is not surprising to find several industrial processes that are protection free syntheses. Protection / deprotection should be treated as a case of mind set rather than limitations of chemistry. Having said this in such strong terms, let us also concede that it may not be feasible to completely avoid protection / deprotection strategies. In support of these statements, we would soon look at some successful protection free synthesis in this chapter. In 2007, Phil S. Baran *et.al.*, reported the total synthesis of some marine natural products

*without* using protecting groups. While discussing the synthesis, the authors suggest that the following guidelines would be helpful while planning retro-analysis under this philosophy.

1. Redox reactions that do not lead the C – C bond formation should be minimized.
2. The percentage of C – C bond formation events in the synthetic steps should be maximized.
3. Disconnections should be made to maximize convergence.
4. The overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework.
5. Wherever possible *cascade or tandem reactions* should be designed.
6. The *innate reactivity* of the functional groups should be exploited to avoid protection strategies.
7. If necessary one should *invent new methodologies* to discover new aspects of chemical reactivities.
8. *Biomimectic* chemistry could provide useful guidelines when dealing with natural products.

In an effort to prove their point, they have reported an efficient route for the synthesis of (+)-Ambiguine H. This synthesis is shown below **(Fig 14.1)**. The strategic bond disconnections envisaged by these workers were guided on the above guidelines.

*Since a route chosen is a deliberate choice of the researcher, it may not be fair to compare research publications based on different motives. I would be like comparing apples and oranges.*Nature 446, 404 *(2007) and references cited therein.*

The proposed strategic disconnections for ambiguine H are shown below **(Fig 14.1)**.

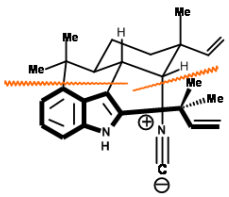


Figure 14.1

The first target was (-)-Hapalindole U for which the t-prenyl unit is not required. The top six membered ring unit came from the well-known terpene through four steps shown in **(Fig 14.2)**

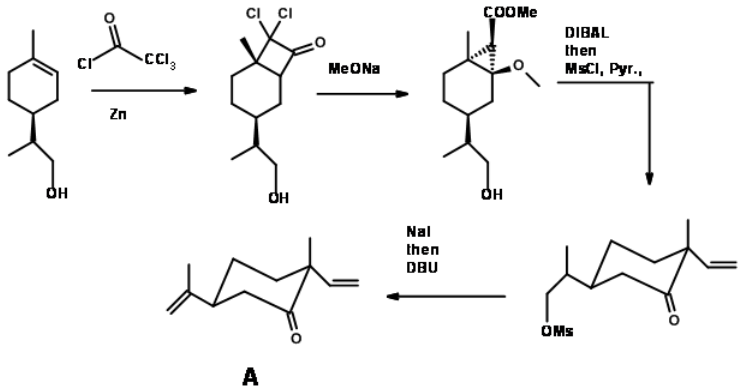


Figure 14.2 See J. Chem. Soc. Chem. Commun., 2759 (1994)

The α- position to the ketone in A was linked the C3 of indole without protection, using a reaction developed in their laboratory (J. Am. Chem. Soc., 127, 7459 (2004)) **(Fig 14.3)**. The second coupling was attempted with several catalysts. The free radical Heck conditions failed. They led mainly to cyclisation at C2 of indole unit. Probing further, the reaction succeeded by using the technique of slow addition of Herrman's catalyst. In the absence of NH group on indole, such reactions failed to give this coupling. Now conversion to the natural product (-)-Hapalindole U (A) needed stereoselective transformation of the carbonyl unit to isonitrile unit. This was achieved by stereocontroled, microwave assisted reductive amination followed by formylation and

dehydration reactions to give (-)-Hapalindole U (A). All these reactions could be scaled up to the level of several grams. (-)-Hapalindole U was made in sufficient quantities and stored.

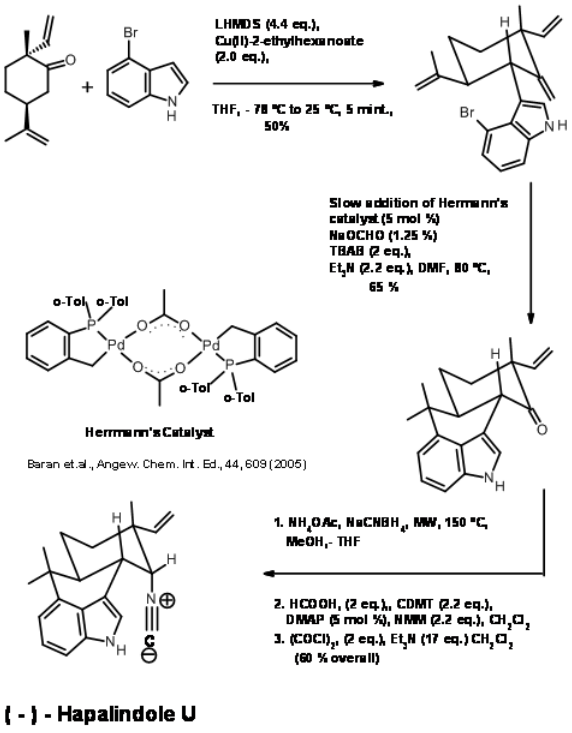


Figure 14.3

The next target (+)-Ambiguine H was a very unstable compound, which was made as and when needed, using the following reactions.

(-)-Hapalindole U had several very reactive units in proximity. Introducing a prenyl unit into the crowded C2 region of the indole unit was very difficult **(Fig 14.4)**. Treatment of t-BuOCl followed by prenyl-9-BBN led to a complex series of reaction, resulting in a crystalline product B. The formation of this product was rationalized by a cascade reaction mechanism shown in figure. Photolysis of B led to a Norrish-type cleavage, followed by rearrangement that got rid of all the extra groups on the skeleton to yield Ambiguine H. The reaction was not allowed to reach completion because the product was also sensitive to photolysis. The reported yield is based on recovered B.

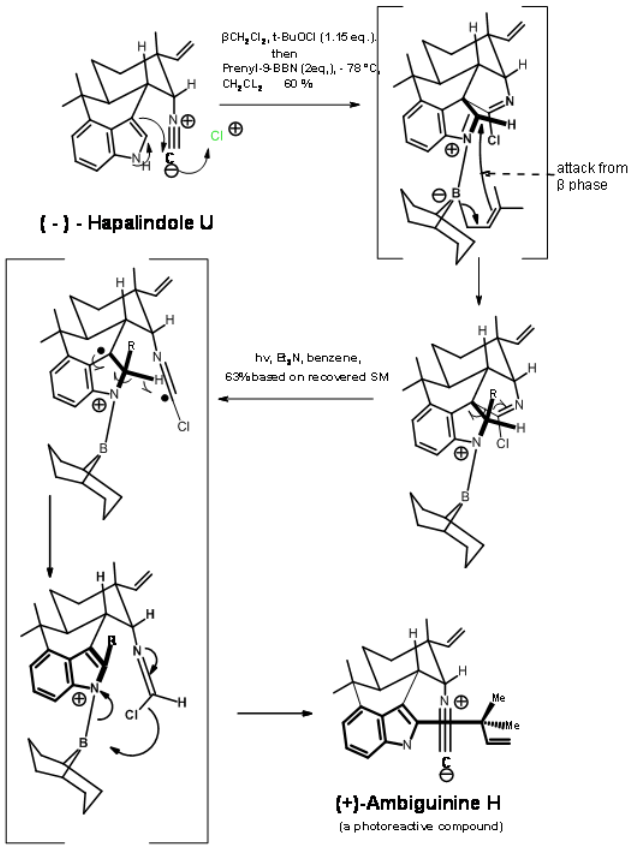


Figure 14.4

The insistence that no protection protocols would be permitted in the scheme gave not only a short route to the target compound, but also led to the use of Rearrangement Transforms, use of Cascade Reactions and led to new discoveries in chemical reactivities.

In old chemistry, you would come across several such complex targets (for that time), whose synthesis were achieved without (or with very few) protection / deprotection sequences. There are other syntheses reported in recent years that have followed a 'no protection' barrier in planning the syntheses . We could visit two more such synthesis in this chapter.

Kessane, a constituent of Japanese Valarian root is of interest due to its sedative and anxiolitic effect. In 2003, Booker-Milburn K. I. and co-workers reported an industrial synthesis of this compound in 8 steps following the theme 'no protection / deprotection'. The outline of the synthesis is presented in **(Fig 14.5)**

- *Chem. Int. Ed. Engl., 34, 1370 (1995); Hoffman R. W, Synthesis, 21, 3531 (2006)*
- *Booker-Milburn K.I.; Jenkins H.; Charmant J. P. H.; Mohr Peter Org. Lett., 5, 3309 (2003).*

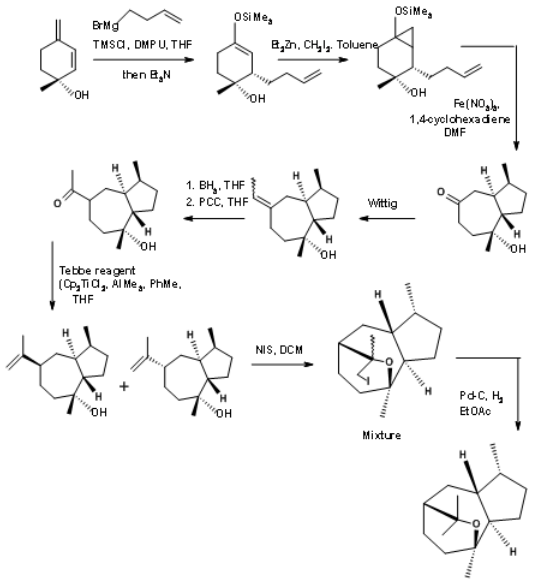


Figure 14.5

The use of transition metal reagents could aid in the construction of C – C bonds without the need for protective groups, as demonstrated by Baldwin's group in 2006 **(Fig 14.6)**. This synthesis of Aureothin was achieved in 7 steps with no protection protocol.

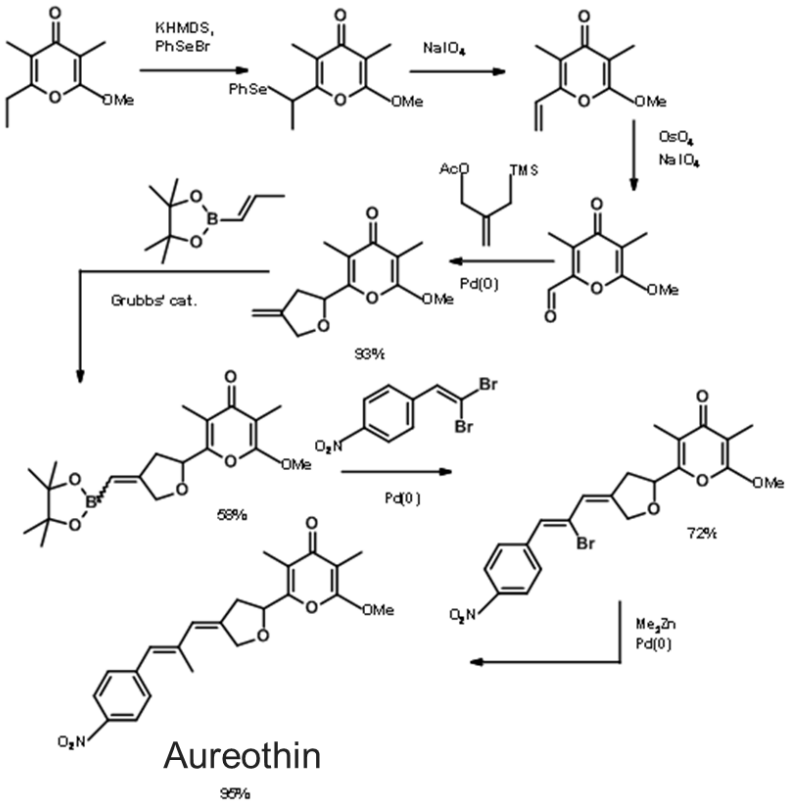


Figure 14.6

- Jacobson, M. F., Moses, J. E., Adlington, R. M. and Baldwin, J. E., Tetrahedron, 62, 1675 (2006).

Some rare molecular engineering marvels like R.B. Woodward's synthesis of PGF **(Fig 1.10.7)** open up new concepts on 'Protection' in molecular synthesis. Note the way he incorporated a protecting group scaffold into the molecular mainframe. Unlike

the usual way of thinking of protection / deprotection as an isolated operation, these workers subsequently incorporated this protecting unit into the molecular frame, thereby achieving ‘carbon economy’ well ahead to his time. These concepts of green chemistry came decades later. Also revisit some of the biogenetic type cyclization reaction discussed earlier in the light of Green Chemistry.

## Conclusion

Any doubt on feasibility of protection free synthesis could be laid to rest. However, at the present state of developments in common synthetic methodologies, the protection free methodology has its limitations too. At present, it appears inconceivable to bring about a medium sized peptide or nucleotide with such a protection free protocols. This could also be true to several other syntheses of complex molecules. The main thesis of this essay is that it is practical to conceive such protection free synthetic protocols. This falls within the call of Green Chemistry. Though this has been the watchword in industrial synthesis, Baran’s 2007 paper coined the idiom “Protection-free synthesis’ and drew attention to such a possibility. Since then several papers have appeared with this idiom. One can be assured that such a basic green concept cannot be a passing fade. It is more likely to mark a corner stone in the logic of organic synthesis.

## Further Readings


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# Index

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