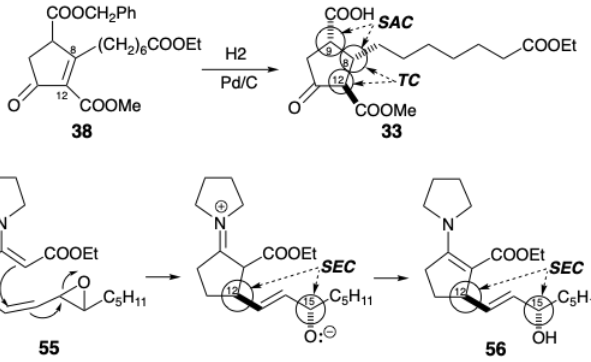
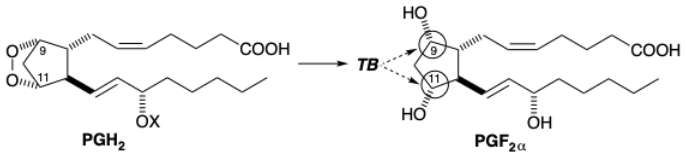
3.4: Syntheses of Prostaglandins from Polycyclic Precursors

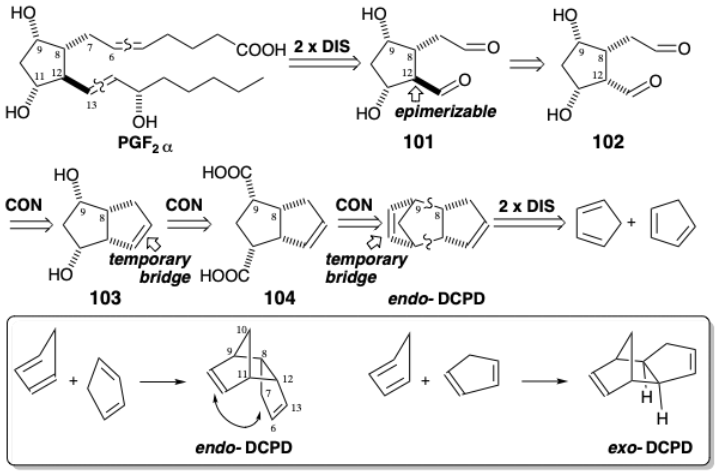
In the preceding syntheses of prostaglandins stereocontrol was achieved in several ways. For example, stereoselective generation of **33** from **38** depended on **steric approach control** (*SAC*) during catalytic hydrogenation to favor a *cis* relationship between substituents at positions 9 and 8.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



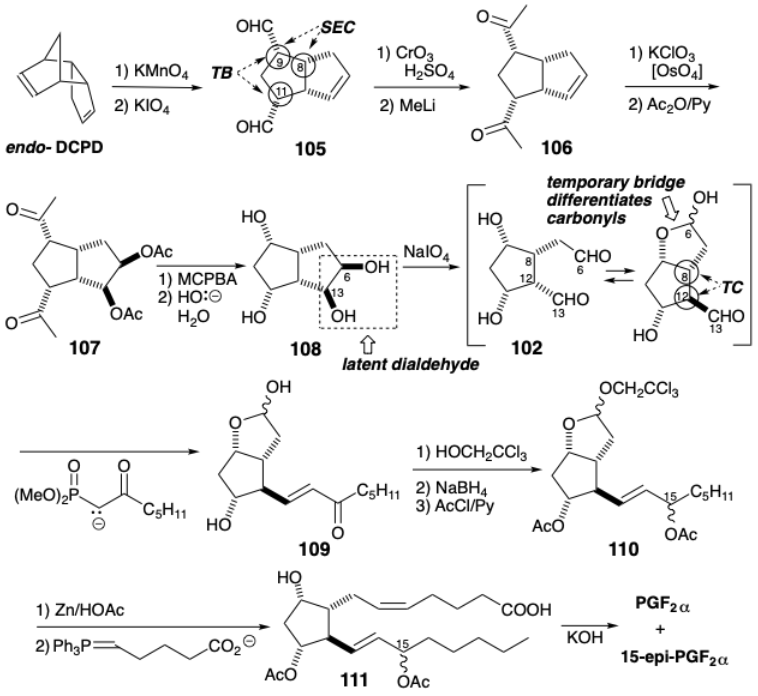
In this section, another technique for achieving stereocontrol will be considered. Thus, proximity of functional groups may be assured by the tactic of tying them together in a temporary ring which is ultimately cleaved. The biosynthesis of $PGF_{2\alpha}$ involves such a **temporary bridge** (*TB*)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



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

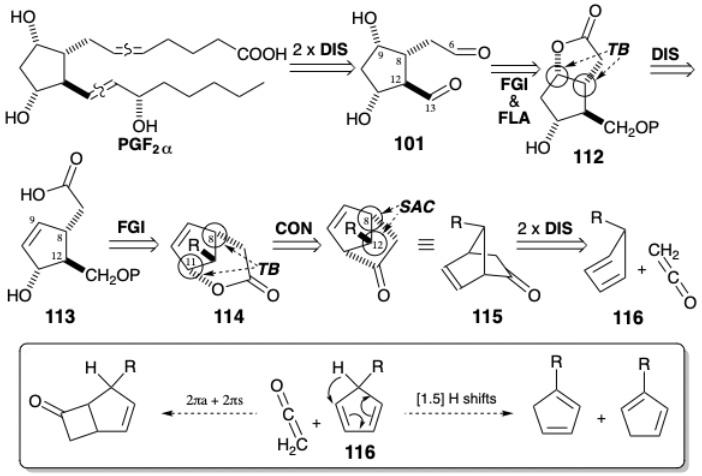


This synthesis exploits selective cleavage of one temporary bridge, the more strained C=C bond, to produce a dialdehyde **105**. After conversion to diketone **106**, the remaining C=C bond is partially oxidized to deliver **107** after acetylation. Baeyer-Villiger oxidation then produces a tetraacetate.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

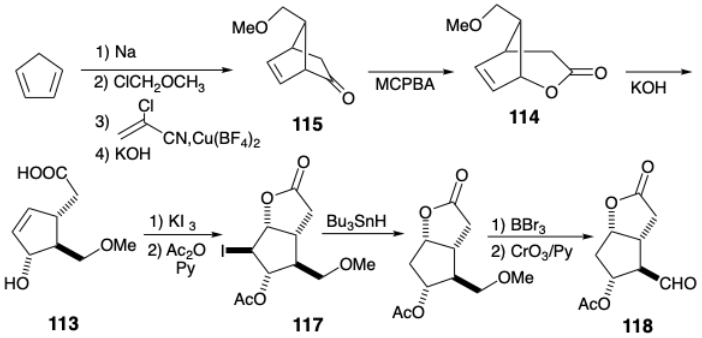


Corey's second strategy for total synthesis of prostaglandins[10] exploits two temporary bridges to assure the proper stereochemical relationships between the stereocenters at positions 9, 8, and 11. The *cis* relationship between the substituents at positions 8 and 9 in **101** is assured by a temporary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

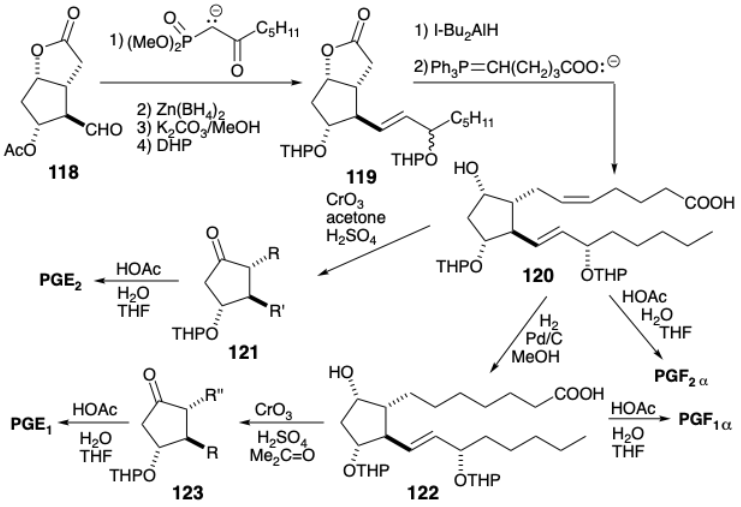
substituent at position 12 and the remaining stereocenters in the cyclopentane ring is ultimately the consequence of steric approach control during the cycloaddition of a 5-substituted 1,3-cyclopentadiene precursor **116** with ketene.



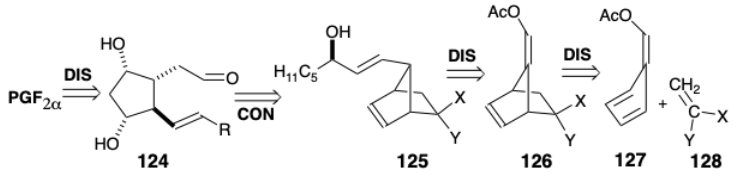
A potential flaw in this strategy arises from the instability of 5-substituted 1,3-cyclopentadienes that readily rearrange at room temperature, by [1.5]sigmatropic hydrogen migrations (see section 4.7), to generate mixtures of 1 and 2-substituted isomers. This isomerization was circumvented by using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



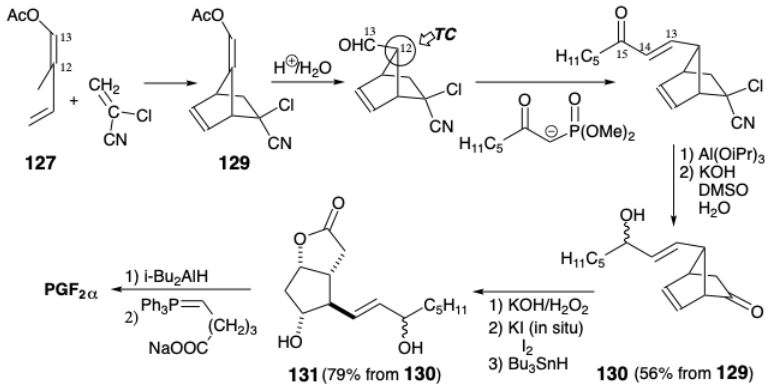
Appendage of the lower side chain to aldehyde **118** is achieved by olefination with a β-keto phosphonate. Reduction of an intermediate ketone followed by transesterification gives a lactone diol in which the hydroxyl at position 9 is differentiated from the remaining hydroxyls. The latter are then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



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



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

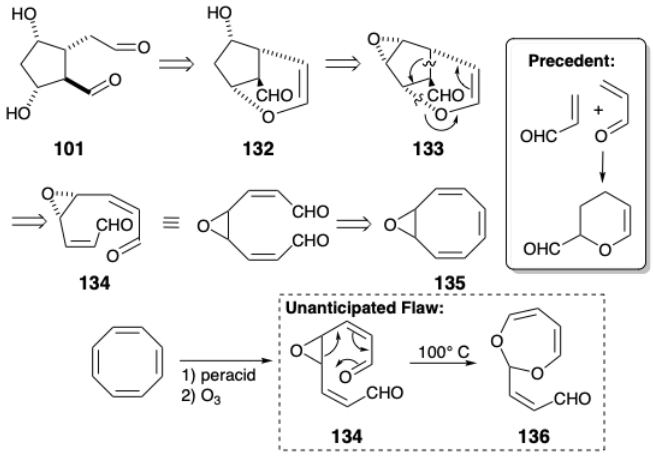


The strategies presented thus far all succeeded. Unfortunately, failed attempts are often not published. Sometimes they are described in doctoral theses. It would be a mistake to assume that synthetic planning for the total synthesis of complex molecules is

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

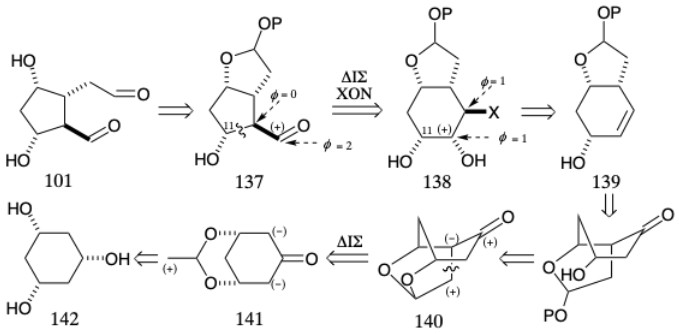
R. B. Woodward's Flawed Strategy

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



Ring Contraction Strategies

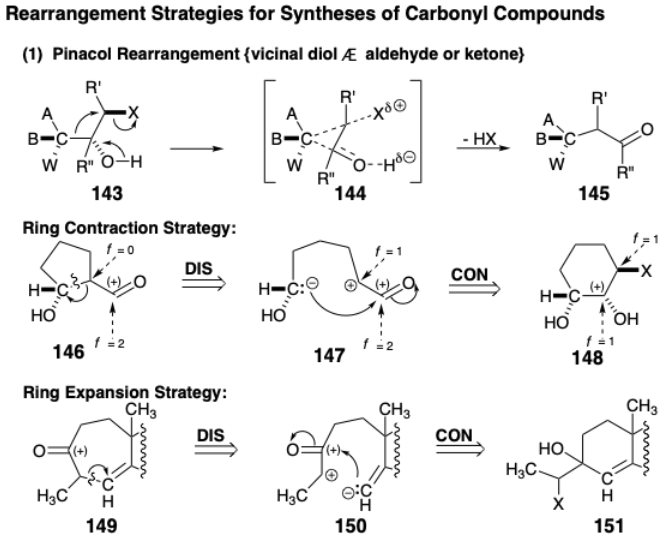
The mixed acetal **137** is another temporarily bridged precursor similar to Corey's aldehyde **118** (see above) except that the functionality level in **137** is identical with that in **101**. Therefore, the temporary bridge in 137, like that in 132, is an internally masked derivative of two functional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

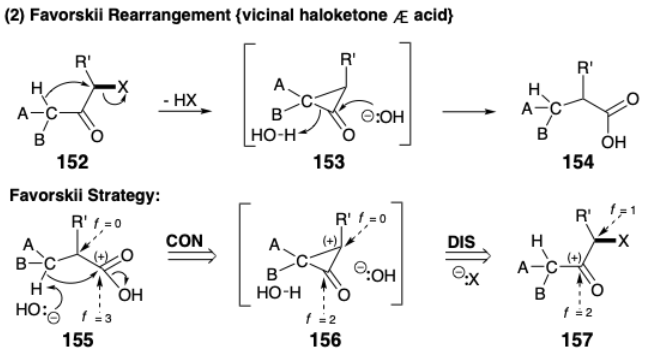


Stereospecific (the stereochemical configuration of the product isomer is determined by that of the reactant isomer) generation of the stereochemical relationships required in **137** is expected during the pinacol rearrangement of **138**. Thus, such rearrangements, i.e. **143** to **145**, generally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

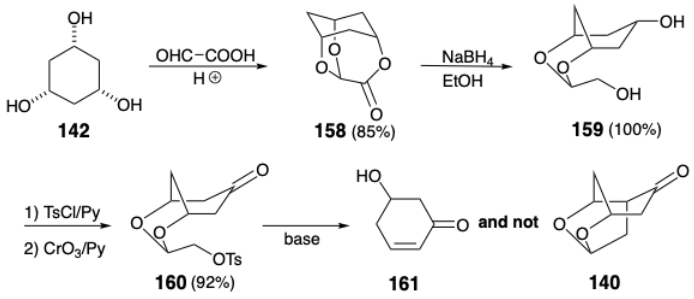
Two Step Reterosynthetic Analysis of Polar Rearrangements

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

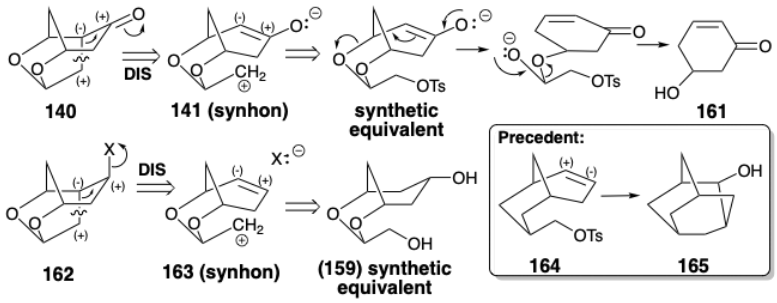




Although differentiation of the three hydroxyls in **142** was achieved by reaction with glyoxalic acid, the second Woodward strategy was also fatally flawed (see section 3.5). Reductive cleavage of **158** afforded diol **159** quantitatively, and the primary hydroxyl in **159** was readily activated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



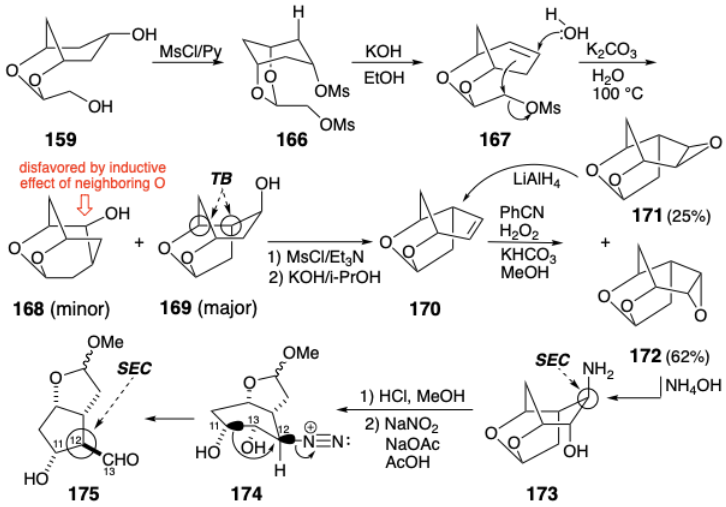
To obviate the necessity for enolate generation β to the alkoxy groups as in **141**, **162** was recognized as a direct precursor to olefin **139**. Polar disconnection of **162** suggests addition of a carbon electrophile to a C=C double bond as in **163**. The two dislocations, **140** to **141**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



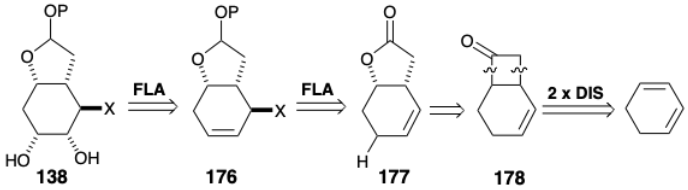
Synthetic equivalents of the unsymmetrical synthon **163** might be obtained from the available symmetrical diol **159** by β-elimination. Unfortunately, a precedent suggested that cyclization of **163** might not occur in the desired fashion. Thus, the carbocyclic analogue **164** produces the isomeric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

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

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



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



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