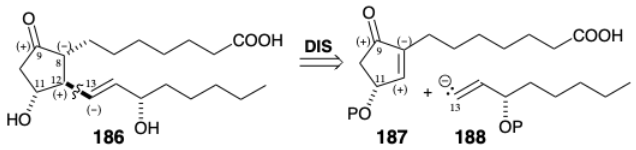
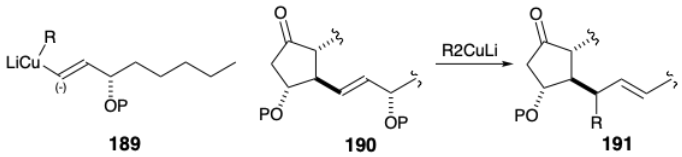
3.5: Syntheses of Prostaglandins from Cyclopentanes

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



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

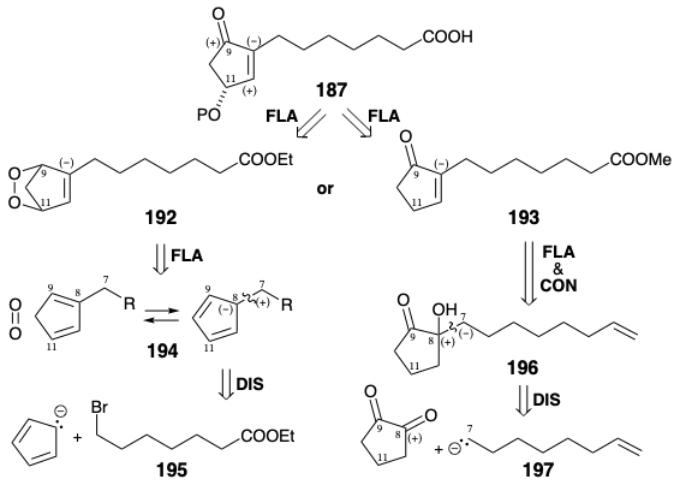


(6) *Favor potentially flawed strategies* only if the effort involved in further examination of the possible flaw is offset by the potentially great reward of an especially elegant and efficient synthesis.

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

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

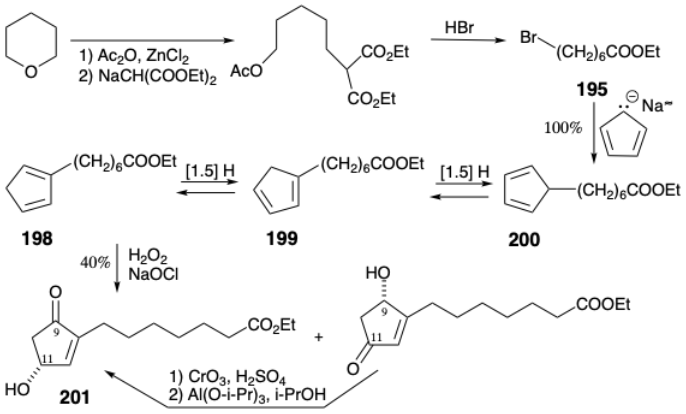
The 9,8,12,11-circuit in **187** is dissonant. One strategy for generation of this dissonant functional array (see page 88) involves 1,4-dioxidative addition (4πs + 2πs cycloaddition) of singlet oxygen to a monosubstituted 1,3-cyclopentadiene precursor **194** to generate an endoperoxide **192** that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



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

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

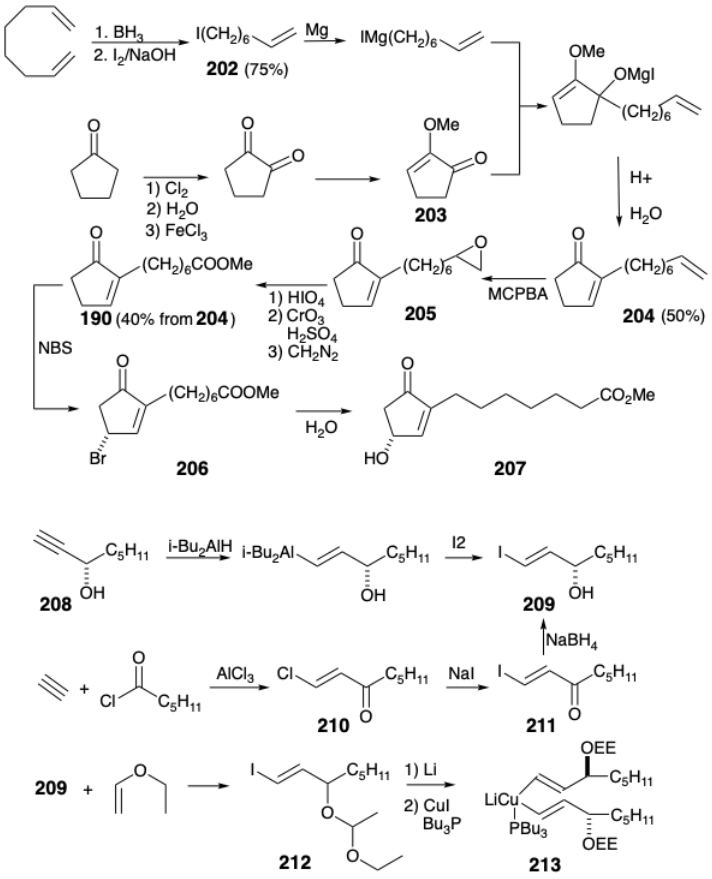
Bromoester **195** was prepared from tetrahydropyran and diethyl malonate. Singlet oxygen, generated chemically, reacts with the monosubstituted cyclopentadienes **198**-**200** under basic conditions to deliver hydroxycyclopentenone **201** and its isomer having a hydroxyl at the 9-position and a carbonyl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



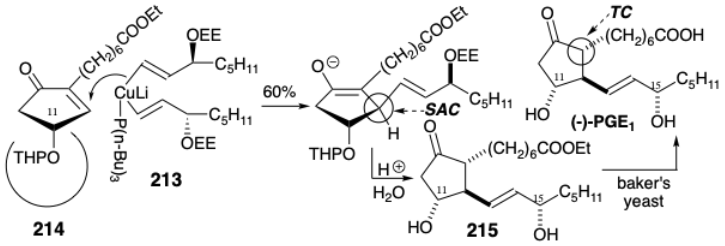
A Grignard reagent synthetic equivalent of nucleophilic synthon **197** was prepared by monohydroboration of 1,7-octadiene followed by iodo-deborination and reaction of the resulting iodide **202** with magnesium. Oxidation of cyclopentanone provides 1,2-cyclopentanedione whose methyl enol ether **203**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

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

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

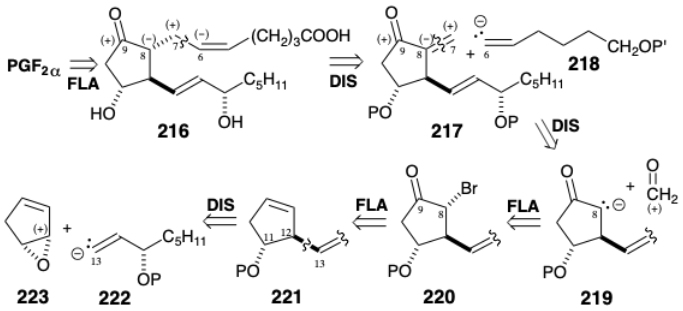


The key 1,4-addition of optically pure divinylcuprate **213** to the THP derivative **214** of racemic hydroxycyclopentenone **201**, followed by removal of THP and EE protecting groups, delivers an almost 1:1 mixture of (-)-PGE_1 ethyl ester **215** with the absolute stereochemistry of the natural product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

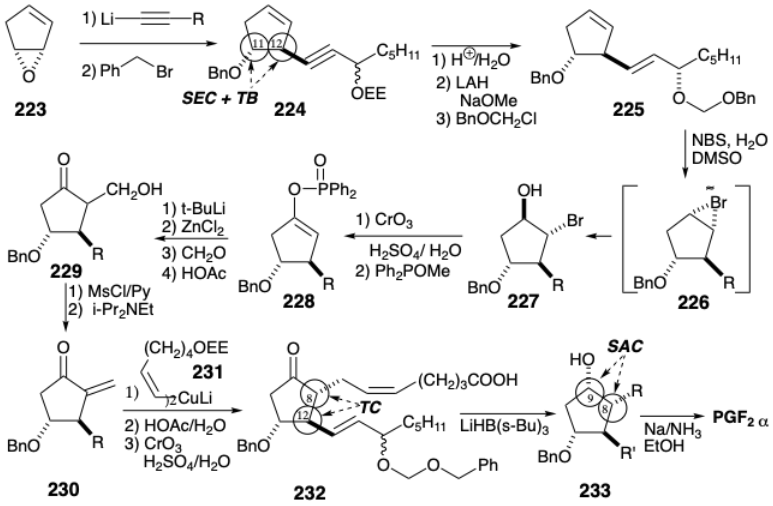


Another strategy for synthesis of prostaglandins from cyclopentane precursors[17] exploits steric approach control during hydride reduction of a PGE_2 derivative **216** to provide the correct configuration at the 9-position in $PGF_{2\alpha}$. Polar analysis of **216** suggests that the upper side chain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

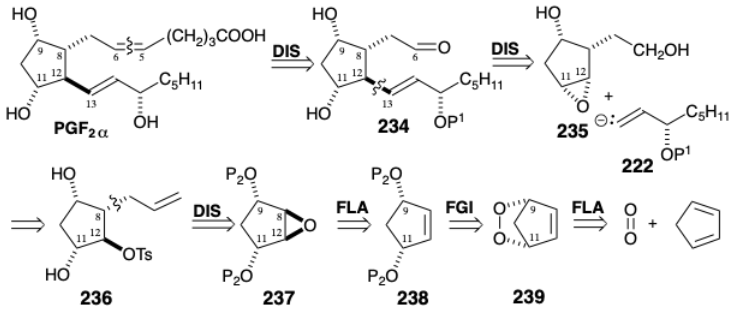
terminus leading to a *trans* relationship between the nucleophile and nucleofuge groups which become the substituents at positions 12 and 11 respectively.



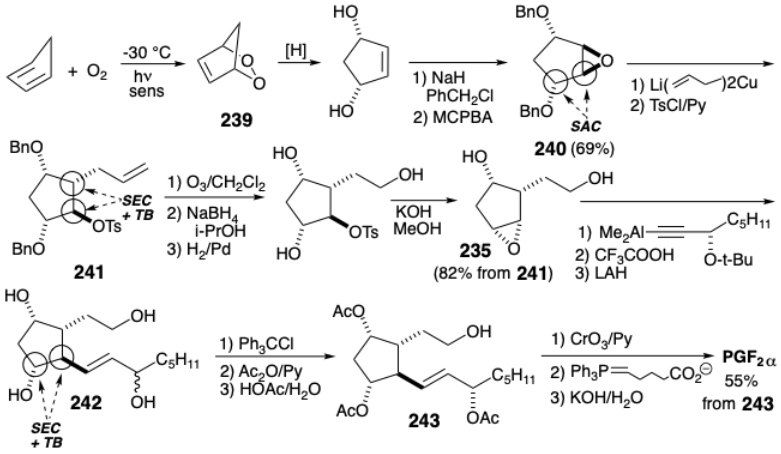
The lithium acetylide from 3-(α-ethoxyethoxy)-1-octyne can serve as a terminal vinyl carbanion equivalent. Thus, reacts with epoxide **223** to afford **224** after benzylation of an intermediate alkoxide. Hydrolysis of the EE protecting group followed by *trans* stereoselective hydride reduction of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



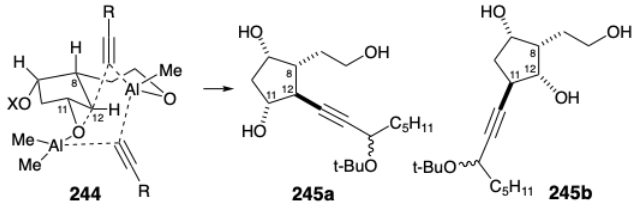
Stereospecific opening of epoxides by carbon nucleophiles can be exploited to introduce both prostanoid side chains onto a cyclopentane nucleus. A remarkable strategy for the total synthesis of $PGF_{2\alpha}$ from cyclopentadiene[18] first simplifies the target by disconnection of the upper side chain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



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



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



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

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

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