a cyclic peroxysulfurane would force a phenyl ring into an apical position.
(11) Sulfurane 0.125 M and trapping agent 0.2 M.
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(13) k_{rel}: *p*-Cl, 1; *p*-Me, 2.2; *p*-MeO, 2.6. $R = 0.9996$. k_{rel} was calculated using the integrated rate equation: $k_{rel} = (\log [(A - X)/A])/(\log [(B - Y)/B])$, where A and B are the amounts of sulfides at the beginning of the reaction and X and Y are the amounts of sulfoxides at the end of the reaction. Product ratios were determined by GLC.
(14) k_{rel}: *p*-Cl, 0.45; H, 1; *p*-Me, 2.1; *p*-MeO, 3.2. $R = 0.9985$. The same procedure was followed as outlined in footnote 13.
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(16) The solution was 0.1 M in olefin and contained 140% excess (as a slurry) of sulfurane **4** and 1 equiv of H_2O_2/equiv of **4**.
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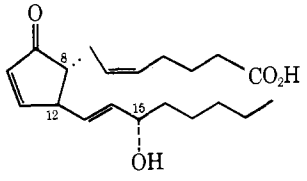
Larry D. Martin, J. C. Martin*
Department of Chemistry, Roger Adams Laboratory
University of Illinois
Urbana, Illinois 61801
Received January 17, 1977

Cyclopentanone Ring Formation with Control of Side Chain Stereochemistry. A Simple Stereoselective Route to the Prostaglandins[1,2,28]

Sir:

While much is known about the control of the relative stereochemistry of substituents directly attached to a carbocyclic ring, there are few methods[3] for directly controlling the relative stereochemistry of asymmetric centers remote from a ring. Recently, we developed a method[4] for the synthesis of cyclopentanone derivatives with control of acyclic asymmetric center directly attached to the ring. We have now extended this method to the control of a more distant center.

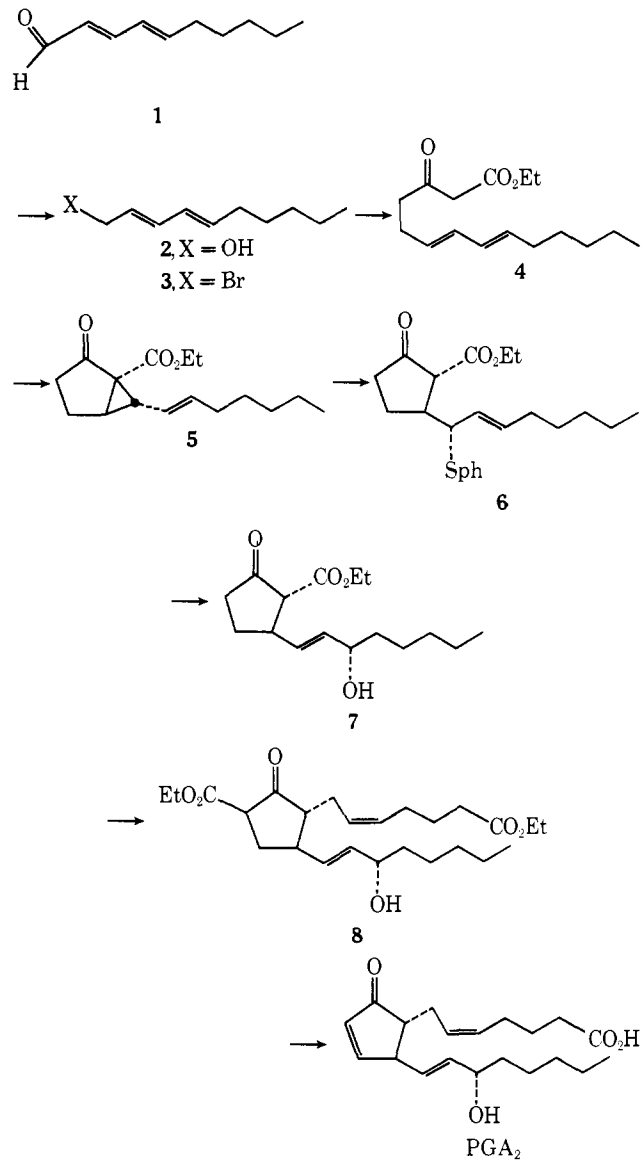
The problem of controlling the relative stereochemistry of a distal center is exemplified by prostaglandin A_2. Thus, it is easy to control the stereochemistry of C-12 relative to C-8, as the two side chains are more stable trans. Much more difficult is the control of the stereochemistry of C-15 relative to C-12. A great deal of effort has been directed toward the solution of this particular example of the general problem. A brief review of the published solutions may help delineate the strengths and weaknesses of current methods for controlling such a distal center. We limit our consideration to those methods which allow direct construction of the specific stereochemical relationship desired. Methods which depend on the combination of optically pure component fragments[5] or specialized selective reduction[6] do not fall within the scope of that consideration.



PGA_2

S_N2' cyclization[7] has been used to control relative stereochemistry. As recent work[8] has cast doubt on "1a relation syn des substitutions S_N2''",[7] this method must be explored more fully before its generality can be assessed. The conjugate addition of a chelated cuprate to an achiral enone[9] has also been used to effect such control. The generality of this method has similarly not been explored. Finally, a method based on the 1,2 to 1,4 transfer of relative stereochemistry by allylic rearrangement was recently published.[10] This method allows the rational control of absolute and therefore relative stereochemistry.

Scheme I



Modification of our cyclopentanone synthesis[4] to allow direct control of a distal side chain asymmetric center was accomplished by incorporation of such an allylic transfer of relative stereochemistry. The sulfoxide rearrangement developed by Evans[11] was particularly suited to this purpose (Scheme I).

As this approach starts with an allylic alcohol such as **2**, its flexibility extends to the many and varied methods for the synthesis of geometrically defined olefins. For this particular application, we were gratified to learn of the availability of aldehyde **1**, an autoxidation product of vegetable oil[12] which is separated in great quantity as a by-product of commercial margarine production.

The key cyclopropane **5** was readily prepared from **1**. Thus, reduction of the aldehyde[13] ($LiAlH_4$, NaOMe, ether, 0 °C, 30 min, 84%) gave the known[14] alcohol **2**, which was smoothly converted[15] to the unstable allylic bromide **3** (PBr_3, CaH_2, ether, 0 °C to room temperature, overnight, 81%). Alkylation of the dianion of ethyl acetoacetate[16] with crude bromide **3** led to the ketoester **4**[17] (0 °C to room temperature, 20 min, 55%). Diazo transfer[18] (1.1 equiv *p*-toluenesulfonyl azide, triethyl-

amine, CH_3CN, room temperature, 2 h) led to the diazoester, which was taken up in hexane and filtered through magnesium sulfate before cyclization[19] (1 wt equiv Cu bronze powder, toluene, reflux, 2 h, 50% based on ketoester **4**) to the key cyclopropane **5**.[21-23]

On the basis of literature precedent[12-23] we expected that **5** would react readily with thiophenoxide. While orbital overlap considerations made it likely that the opening would proceed to give a cyclopentanone rather than a cyclohexanone, it was not so clear that the opening would proceed in a 1,5 as opposed to a 1,7 sense. Further, if the reaction did not proceed at ambient temperature, we did not have the option of warming it up, as allylic sulfides are quite prone to thermal racemization.

In the event, opening of cyclopropane **5** with thiophenol proved facile (1.5 equiv of thiophenol, 0.2 equiv of potassium *tert*-butoxide, ethanol, room temperature, 5 min, 69%). Oxidation and reductive rearrangement[11] of sulfide **6**[17,24] (1.1 equiv of *m*-chloroperoxybenzoic acid, CH_2Cl_2, −78 °C, 5 min; trimethyl phosphite, methanol, reflux, 30 min; 63%) then lead smoothly to the hydroxy ester **7**,[17] identical with authentic material.[25,26]

Conversion of **7** to PGA_2 has been previously accomplished. Thus, alkylation followed by retro-Dieckmann cyclization[7] gives the ketoester **8**, which can be saponified and oxidized[10] to the natural product.[27]

The control of the relative stereochemistry of an asymmetric center distant from the cyclic portion of a molecule is a problem of general interest. The method outlined here offers a versatile and efficient approach to this problem. Application of this method to the synthesis of other complex natural products is currently under investigation.

References and Notes

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(20) The NMR spectrum of **5** displayed inter alia two vinyl protons, a multiplet centered at δ 5.76 and a doublet of doublets (J = 9, 16 Hz) at δ 5.24, thus confirming the trans stereochemistry of the double bond.
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(24) The sulfide **6** displayed inter alia a broad triplet (J = 7 Hz) at δ 3.52, thus confirming the 1,5 (as opposed to 1,7) sense of the opening.
(25) Hydroxy ester **7** was identical (TLC, GC/MS) with authentic material kindly supplied by Dr. J. Buendia of Roussel Uclaf.
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Douglass F. Taber
Department of Pharmacology, School of Medicine
Vanderbilt University
Nashville, Tennessee 37232
Received September 7, 1976

The Electronic Structure of Chromyl Chloride: a Functional Model for Cytochrome P-450

Sir:

In a brief note, Sharpless and Flood commented on the similarity of the chemistry of cytochrome P-450 and oxotransition metal complexes of chromium and manganese.[1] Although this observation received little attention, more recent work in several areas has again suggested the possibility of an active oxidant in cytochrome P-450 which has properties similar to these reagents. Several groups have found that various peroxides couple with complexes of ferric iron including purified preparations of P-450 to give hydroxylation products.[2] The postulated intermediate in these reactions is a ferryl ion, analogous to the compound I of various peroxidases, in which atomic oxygen is formally bound to ferric iron.[3] The analogy to oxotransition metal complexes of chromium and manganese in higher oxidation states is obvious.

One of the presumable objections to the chromium and manganese complexes as models for P-450 is the radical nature of many of their reactions. The mechanism of hydroxylation by chromyl chloride (CrO_2Cl_2), for example, as well as other Cr^{VI} species is thought to initially involve a hydrogen atom abstraction to give hydrocarbon radical and a Cr^{V} species.[4] This process appears to be rate limiting in the overall reaction, as indicated by primary kinetic isotope effects in the range of $k_H/k_D = 6-12$ for several organic compounds. P-450, on the other hand, is classically thought to hydroxylate carbon hydrogen bonds by an insertion mechanism, due to the existence of low primary kinetic isotope effects and retention of configuration.[5] Evidence presented elsewhere suggests that the low isotope effects observed thus far for P-450 may only reflect a partial expression of the rate of the hydroxylation step in the overall velocity of the enzymatic process.[6] Studies of the primary kinetic isotope effect by intramolecular competition at benzylic sites resulted in $k_H/k_D > 6$. This larger value of the isotope effect suggests that abstraction-recombination be considered a possible mechanism for hydroxylation by P-450, and consequently that compounds such as chromyl chloride and chromyl acetate be reconsidered as chemical models.

As part of a systematic study of the electronic structures of chemical models for P-450, we have investigated the ground state structure of chromyl chloride (CrO_2Cl_2) with ab initio and semiempirical molecular orbital theory. Our ab initio calculations employed the Cr(14s, 11p, 5d/8s, 6p, 2d) basis of Wachters,[7] an O(9s, 5p/4s, 3p) basis,[8] and a Cl(12s, 9p/6s, 5p) basis due to Veillard.[9] Integrals were calculated in C_{2v}