the rate constants of the exchange at various temperatures, using the INVERS EXII program[12] and the parameters as above. The Arrhenius plot yielded the activation energy of 14.1 ± 0.6 kcal/mol. Then the enthalpy, entropy, and free energy of activation at 25° were obtained as 13.5 ± 0.6 kcal/mol, 9.8 ± 3.0 eu, and 10.6 ± 1.0 kcal/mol, respectively.[13]

To the best of our knowledge, this is the first example of observing the nonequivalence of the methyl protons in high resolution nmr spectroscopy.[14]

(13) The large entropy of activation was critically commented by a referee. The careful redetermination of the spectra and simulation using the INVERS EXII program, which takes not only the rotating motion of the methyl group in one direction but also the to-and-fro motion into consideration, gave a little smaller $\Delta S^{\ddagger}$ but the value is still large. This value may include some intractable systematic errors.

(14) Another referee gave a comment that we should be very careful in interpreting the results because even the line broadening in a differential way had been observed by the prevention of isotropic tumbling of the large molecule due to the increase in solvent viscosity. We believe, however, that the cause is the slow rotation of the methyl group for the following two reasons. (1) The computed spectra by assuming the AB_2 pattern are in good agreement with the observed ones and (2) the signal of the bridgehead proton has the line width of less than 1.5 Hz at −71.9°, where the splitting of the methyl signal is seen as shown in Figure 1.

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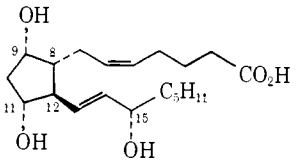
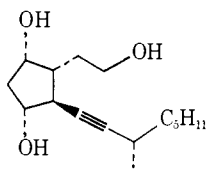
Asymmetric Synthesis of Prostaglandin Intermediates

Sir:

The salient structural features of the primary prostaglandin $F_{2\alpha}$ (**1**) include the five chiral centers, 8*R*, 9*S*, 11*R*, 12*R*, and 15*S*, four of which are situated on the cyclopentane ring.[1] In this communication we report the asymmetric formation of the intermediates **11**[2] and **13**[3,4] which possess the four nuclear chiral centers needed to prepare this natural prostaglandin. The addition of (3*S*)-*tert*-butoxy-1-octynyldimethylalane to epoxydiol **13** is an efficient process[5] and leads to triol **2**, which contains all five asymmetric centers



1 ($PGF_{2\alpha}$)

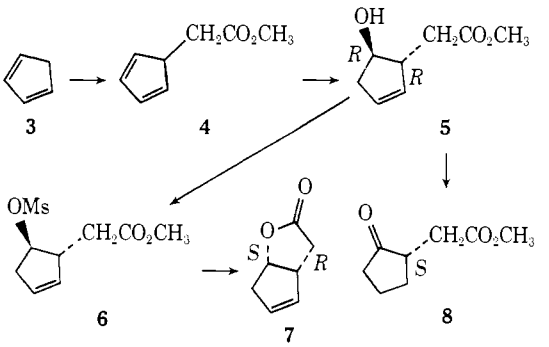


2

needed for prostaglandin $F_{2\alpha}$. Previously, Fried and coworkers had converted racemic triol **2** to *dl*-prostaglandin $F_{2\alpha}$.[3]

The sodium salt of cyclopentadiene (**3**) was stirred with methyl bromoacetate in tetrahydrofuran solution at −78° to generate *in situ* diene **4**. This substance was immediately treated with (+)-di-3-pinanylborane followed by alkaline hydrogen peroxide oxidation[6] to yield hydroxy ester **5**,[7] $[\alpha]_D$ −136°, in 45% yield (Scheme I). Similar treatment of diene **4** with (−)-di-

Scheme I[a]



3 4 5 6 7 8

[a] While the structures depicted above correspond to the absolute configuration of the natural prostaglandins, all reactions were carried out with both optical antipodes as well as the racemates.

3-pinanylborane yielded the antipode of **5**, $[\alpha]_D$ +136°. To determine the optical purity of **5** and its antipode, the corresponding (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetates were prepared.[6] The 100-MHz nmr spectra of these substances showed chemical-shift differences in the methyl ester region and indicated that the alcohols were at least 92% optically pure.[6] However, comparison of the above optical rotations with those of the optically pure hydroxy esters ($[\alpha]_D$ −141 and +141°, obtained by resolution) indicated that the asymmetric hydroboration products were at least 96% optically pure.

The hydroxy ester **5** was quantitatively converted into mesylate **6**, $[\alpha]_D$ −85°, which afforded the crystalline optically pure lactone **7**, mp 46–47°, $[\alpha]_D$ −106°, in 92% yield on treatment with aqueous sodium hydroxide in tetrahydrofuran at 0°. The crystalline lactone **7** could also be prepared by saponification of hydroxy ester **5** to the corresponding crystalline hydroxy acid, mp 56–57°, $[\alpha]_D$ −148°, which was exposed to methanesulfonyl chloride in pyridine. Thus, lactone **7** or its antipode could be readily prepared in optically pure form in over 40% yield from cyclopentadiene (**3**) without resorting to chemical resolution.

The absolute stereochemistry of the hydroxy ester

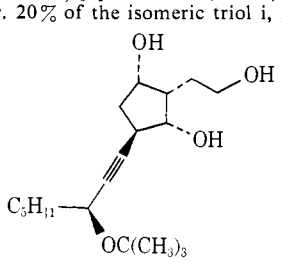
(1) For recent reviews on prostaglandin synthesis, see: G. L. Bundy, *Ann. Rep. Med. Chem.*, 7, 157 (1972); U. Axen, J. E. Pike, and W. P. Schneider in "The Total Synthesis of Natural Products," Vol. 1, J. ApSimon, Ed., Wiley-Interscience, New York, N. Y., 1973, pp 81–142; P. H. Bentley, *Chem. Soc. Rev. (London)*, 2, 29 (1973); N. M. Weinshenker and N. H. Andersen in "The Prostaglandins," Vol. 1, P. W. Ramwell, Ed., Plenum Press, New York, N. Y., 1973, pp 5–82.

(2) E. J. Corey and R. Noyori, *Tetrahedron Lett.*, 311 (1970).

(3) J. Fried, J. C. Sih, C. H. Lin, and P. Dalven, *J. Amer. Chem. Soc.*, **94**, 4343 (1972).

(4) J. Fried and C. H. Lin, *J. Med. Chem.*, **16**, 429 (1973).

(5) We obtained triol **2**, $[\alpha]_D$ −40.9° (*c* 1.07, $CHCl_3$), in 55–60% yield along with *ca.* 20% of the isomeric triol **i**, $[\alpha]_D$ −1.4° (*c* 1.01,



$CHCl_3$), when epoxydiol **13** was treated with 5–10 equiv of (3*S*)-*tert*-butoxy-1-octynyldimethylalane in toluene at 60°. The optimum conditions for forming triol **2** are discussed in a forthcoming publication by J. Fried and J. C. Sih (personal communication).

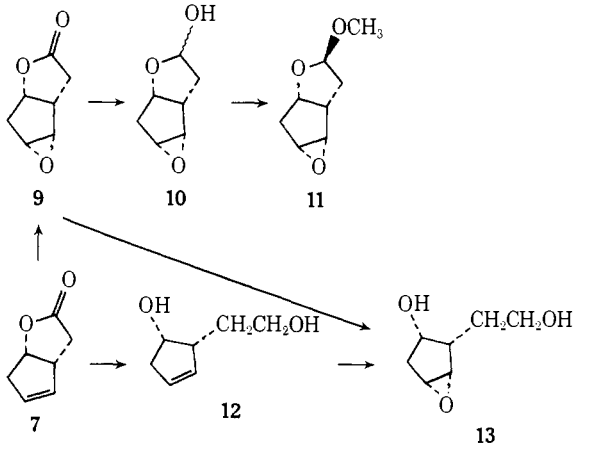
(6) *Cf.* J. J. Partridge, N. K. Chadha, and M. R. Uskokovič, *J. Amer. Chem. Soc.*, **95**, 532 (1973), and references therein.

(7) Optical rotations were taken in 1% methanol solutions at 25° unless otherwise indicated. All substances were completely characterized spectrally and gave acceptable combustion analyses.

5 and its antipode was established by catalytic hydrogenation to the dihydro derivatives which were oxidized with standard Jones reagent[8] to yield ketone **8**, $[\alpha]D$ $-122°$ and its antipode, $[\alpha]D$ $+123°$. Ketone **8** exhibited a strong negative Cotton effect (ORD amplitude $a = -91$, centered at 296 nm) and was assigned the *S* absolute configuration whereas the antipodal ketone showed a strong positive Cotton effect (ORD amplitude $a = +94$, centered at 296 nm) and was assigned the *R* absolute configuration.[6]

Lactone **7** formed the *cis*-epoxy lactone **9**, mp 76–77°, $[\alpha]D$ $-115°$ ($CHCl_3$), in 80% yield on exposure to commercial 40% peracetic acid[2] in sodium acetate–acetic acid buffer (Scheme II). The prostaglandin in-

Scheme II[a]



[a] See footnote *a* of Scheme I.

termediate **11**, $[\alpha]D$ $-180°$ ($CHCl_3$), was prepared by treating epoxy lactone **9** with diisobutylaluminum hydride[2] at $-78°$ to yield epoxy lactol **10**, mp 65–66°, $[\alpha]D$ $-4.4°$ ($CHCl_3$, rotation at equilibrium), which was immediately exposed to methanolic boron trifluoride[2] (75% overall yield). Racemic epoxy acetal **11** has been converted into *dl*-prostaglandin $F_{2\alpha}$ by Corey and Noyori.[2]

Lactone **7** also yielded the optically active form of the Fried prostaglandin intermediate **13**,[3,4] $[\alpha]D$ $-5.0°$, in greater than 90% overall yield by reduction ($LiAlH_4$, ether, 25°) to diol **12**, $[\alpha]D$ $-74°$, which was cleanly epoxidized with *m*-chloroperbenzoic acid in methylene chloride containing sodium bicarbonate at 0°. Epoxy diol **13** was homogeneous in a wide variety of chromatographic systems and yielded a single epoxy diacetate with acetic anhydride. The relative stereochemistry of **13** was initially assigned on the basis of its 100-MHz nmr spectrum and the known hydroxy-directing effect of epoxidation of homoallylic alcohols.[8] This assignment was confirmed by reducing the *cis*-epoxy lactone **9** directly to epoxy diol **13** ($LiAlH_4$, THF, 0°, 33% yield).

In conclusion, short asymmetrically induced syntheses were devised for several key prostaglandin intermediates beginning with cyclopentadiene (**3**). These results open additional routes for the facile preparation of optically active prostaglandins in substantial quantities.

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Solvent Effect in the Photoreduction of Decafluorobenzophenone by 2-Propanol. Reinterpretation of the Light-Intensity Effect in the Benzophenone–2-Propanol System

Sir:

Aromatic ketones in the $^3(n_1\pi^*)$ state abstract hydrogen[1] from solvents and yield pinacols by a ketyl radical recombination reaction. Decafluorobenzophenone (**1**) reacts in the $^3(n_1\pi^*)$ state;[2,3] however, the ketyl radical[4] formed in 2-propanol, cyclohexane, and alkyl aromatics does not lead to the formation of eicosafluorobenzopinacol (**2**).[2,5] This anomaly has been explained by the importance of competitive radical cross-combination reactions[2] in cyclohexane and alkyl aromatics. Evidence is presented in this paper to show that a quantitative yield of **2** is obtained when **1** is photolyzed in perfluoroalkane containing 2-propanol.[6] The earlier conclusion[7] that triplet quenching by radicals was occurring in the benzophenone–2-propanol system appears unjustified;[8] therefore, further studies are reported to clarify the existing ambiguity.

Experimental techniques were similar to those used previously.[2] When degassed solutions of **1** (0.01 and 0.02 *M*) in perfluoromethylcyclohexane containing 2-propanol (0.005–to 0.04 *M*) were irradiated with 366-nm light, the principal products were **2** and acetone. Typical results are shown in Table I. Decafluorobenzhydrol (**3**), which is the principal product[5] when

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(2) J. Dedinas and T. H. Regan, *J. Phys. Chem.*, 76, 3926 (1972).
(3) Phosphorescence spectrum reported by J. Simpson and J. Offen, *J. Chem. Phys.*, 55, 4832 (1971).
(4) (a) A. Singh, M. G. Jonasson, F. C. Sopchyshyn, and F. P. Sargent, XXXIIIrd International Congress of Pure and Applied Chemistry, Boston, Mass., July 25–30, 1971, reported the identification of the ketyl radical generated by flash photolysis of **1** in 2-propanol. (b) The esr spectrum of the decafluorobenzophenone ketyl radical has been reported by F. P. Sargent and M. G. Bailey, *Can. J. Chem.*, 49, 2350 (1971).
(5) N. Filipescu, J. P. Pinion, and F. L. Minn, *Chem. Commun.*, 1413 (1970).
(6) Surprisingly, there was no photoreduction of **1** in the presence of decafluorobenzhydrol. Aromatic ketones in the $^3(n_1\pi^*)$ state usually react with the corresponding alcohols:[1g] W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Amer. Chem. Soc.*, 83, 2789 (1961).
(7) N. C. Yang and S. Murov, *J. Amer. Chem. Soc.*, 88, 2852 (1966).
(8) Estimates based on triplet lifetime,[1f,2] radical rate constants,[1f] and quenching by ground-state benzophenone, $k_q = 1.2 \pm 0.2 \times 10^8$ M^{-1} sec^{-1},[9a] indicate that at 0.1 *M* concentration used by Yang and Murov,[7] the latter type of quenching was more probable than quenching by radicals.
(9) (a) M. B. Ledger and G. Porter, *J. Chem. Soc., Faraday Trans. 1*, 68, 539 (1972); (b) S. A. Weiner, *J. Amer. Chem. Soc.*, 93, 6978 (1971).