Communications to the Editor

Stereospecific Total Synthesis of the Natural and Racemic Prostaglandins of the E and F Series

Sir:

The limited availability of the prostaglandins[1] from natural sources places total synthesis into a strategic position with regard to the procurement of these important substances. Although several imaginative and practical syntheses have been reported[2-4] this problem merits continuing attention, not the least so because of the opportunities offered by each individual synthesis for unique structural alterations, to be reflected, hopefully, in modified biological properties.

We wish to report a novel stereospecific synthesis of all the prostaglandins of the F and E series, both natural and racemic, from a common intermediate **6**, a salient feature of which is the introduction of the fully functionalized eight-carbon side chain in optically active form into a racemic moiety containing all the remaining chiral centers, creating two diastereomers, the separation of which constitutes the desired resolution. This principle had previously been applied to the synthesis of 7-oxa-$PGF_{1\alpha}$.[5]

Benzylation of the dianion of *cis*-cyclopentene-3,5-diol (NaH) with benzyl chloride in DMF at 25° for 48 hr (95%), followed by epoxidation with *m*-chloroperbenzoic acid in carbon tetrachloride at 25° for 100 hr (73%), gave the epoxide **1**, mp 50–51°.[6] Reaction of **1** with lithium diallyl cuprate[7,8] in ether for 2 hr afforded in 95% yield the *trans*-allyl alcohol **2**, mp 76–77°, which was tosylated (TsCl in pyridine) at 25° for 48 hr to form **3a**, mp 57–58°, in 95% yield. Ozonolysis of **3a** in methylene chloride at −78° (crystallized ozonide, mp 98.5–99.5°) and reduction with zinc and acetic acid at 25°, followed by acetalization of the resulting aldehyde with ethylene glycol in benzene in the presence of BF_3 etherate at room temperature, afforded in 92% yield the acetal tosylate **4**, mp 74–75°. Hydrogenolysis of the benzyl groups was achieved with an equal weight of 10% Pd/C in 95% ethanol containing 10% acetic acid and 2 equiv of potassium acetate, and the crude diol **5** was converted to the epoxide **6** with 2% KOH in methanol at 25° for 2 hr (75% overall for both steps). The trimethylsilyl ether[9] of **6** was treated with (*S*)-(−)-3-silyloxy-1-octynyldimethylalane (**7**) (10 equiv)[10] in toluene at 40° for 2 hr.[11,12] After hydrolysis of the trimethylsilyl groups (5% K_2CO_3, 25°, 4 hr) the material was subjected to column chromatography on silica gel to yield two major fractions: (1) a mixture[13] of **8** and its diastereomer, the latter possessing the opposite unnatural configuration in the chiral centers of the cyclopentane ring, $[\alpha]_D$ −0.2° (26%), and (2) a similar mixture of the products of reverse opening of the epoxide ring, $[\alpha]_D$ +5.6° (42%).[14] This unfavorable product ratio represents a weakness of this synthesis paralleling the experience of Corey and Noyori[15] with a related sequence. A solution to this problem of directing the epoxide opening *regiospecifically* in the desired manner has been found, which forms the subject of the following communication.[16] Reduction of the mixture of **8** and its diastereomer with $LiAlH_4$ (10 mol equiv) in boiling THF for 3 hr produced a mixture (84%) of **9** ($[\alpha]_D$ +0.2°) and the corresponding diastereomeric olefin ($[\alpha]_D$ +5.2°) which in contrast to their acetylenic precursors were readily separated by high-pressure chromatography. Hydrolysis of the more polar isomer **9** with 0.03 *N* HCl in acetonitrile–water (2:1) for 24 hr at 25° afforded the hemiacetal **10**, which was subjected to a Wittig reaction with the ylide salt prepared from 5-triphenylphosphoniovaleric acid (6 equiv) with NaH (11 equiv) in dimethyl sulfoxide at 50° for 3 hr[17] to form $PGF_{2\alpha}$ (**11**), $[\alpha]^{THF}_D$ +22.1°, in 55% yield from **9**. This material was identical with natural $PGF_{2\alpha}$ by tlc in four systems,[18] glc, ir and nmr spectra, and the mass spectrum of its tristrimethylsilyl ether methyl ester.[19]

(1) "Prostaglandins," *Ann. N. Y. Acad. Sci.*, **180** (1971).

(2) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1491 (1971), and references cited therein.

(3) U. Axen, J. L. Thompson, and J. E. Pike, *Chem. Commun.*, 602 (1970), and earlier papers.

(4) D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawsky, and N. L. Wendler, *ibid.*, 1258 (1970).

(5) J. Fried, M. M. Mehra, and W. L. Kao, *J. Amer. Chem. Soc.*, **93**, 5594 (1971).

(6) All products were characterized by elemental analysis, ir, nmr (Varian A60), and mass spectra (Finnigan 1015 with glc inlet). Rotations were performed in chloroform unless indicated otherwise. All chromatography was performed on silica gel.

(7) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969).

(8) In contrast to the procedure of ref 7 we have prepared lithium allyl cuprate in the absence of dibutyl sulfide. Reproducible yields of **2** were obtained when allyllithium (0.625 *M*, 400 ml) was added under N_2 to CuI (0.4 *M*, 250 ml) at −78°, followed by the epoxide (0.2 *M*, 250 ml), all in ether, and allowing the temperature to rise to 25°.

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 427.

(10) Prepared from (*S*)-(−)-3-hydroxy-1-octynol (resolved according to J. Fried, C. H. Lin, M. M. Mehra, W. L. Kao, and P. Dalven, *Ann. N. Y. Acad. Sci.*, **180**, 38 (1971)) by silylation (bp 76–78°, $[\alpha]^{Et_2O}_D$ −56°) followed by lithiation (*n*-BuLi in hexane) in toluene at −35° for 10 min and subsequent reaction with dimethylchloroalane in toluene at 0° for 1 hr.

(11) J. Fried, C. H. Lin, and S. H. Ford, *Tetrahedron Lett.*, 1379 (1969).

(12) Excess 3-silyloxy-1-octyne was recovered for reuse by fractional distillation of the trapped volatiles.

(13) This mixture could not be further separated by chromatography. When allowed to crystallize prior to chromatography, the diastereomer of **8** (chiral centers of the ring opposite to those of **8**) was obtained in pure form, mp 102–103°, $[\alpha]_D$ −2.0°. After chromatography a 1:1 mixture of the latter and **8** was obtained, mp 70–73°, $[\alpha]_D$ −0.7°, as well as an amorphous fraction containing mainly **8**. When the epoxide opening reaction was performed with *rac*-1-octyn-3-ol the mixture of diastereomeric racemates corresponding to **8**, mp 58–62°, crystallized after silica gel chromatography.

(14) The two sets of position isomers are easily distinguished by the nmr signals of their respective C-12 protons, which in the "normal" series, *e.g.*, **8**, gives rise to a multiplet centered at δ 2.55, while in the "iso" series this signal appears at 3.05.

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

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

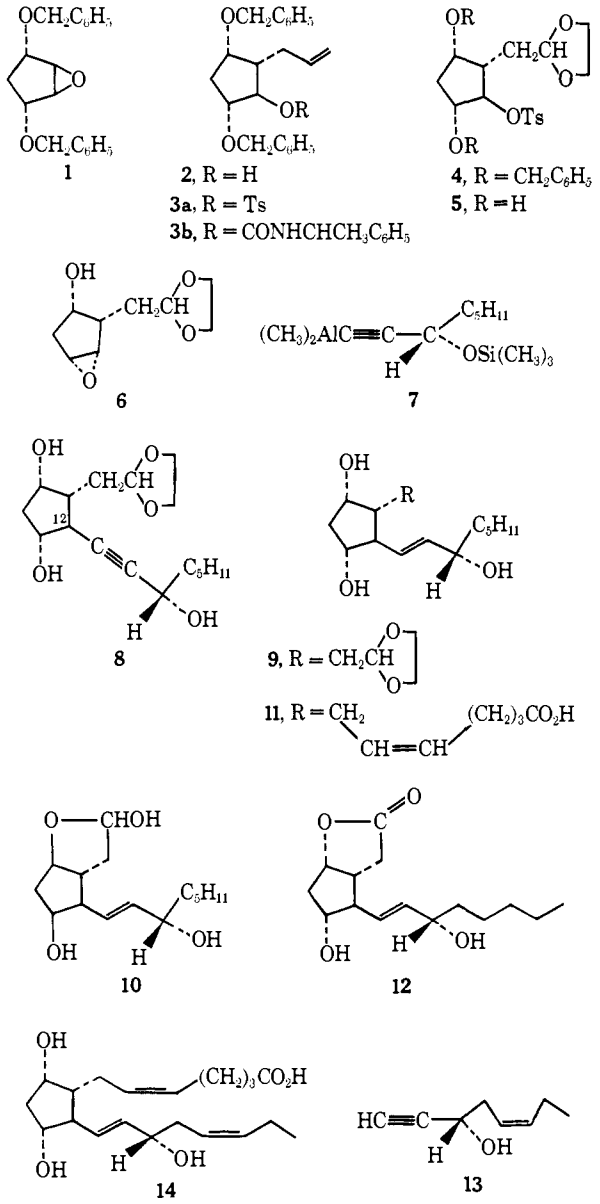
(17) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(18) N. H. Andersen, *J. Lipid Res.*, **10**, 316 (1969).

(19) *rac*-$PGF_{2\alpha}$ prepared in a parallel sequence with *rac*-octyn-3-ol had mp 55–56°. Subjecting the diastereomer of **9** ($[\alpha]_D$ +5.2°) to acid hydrolysis followed by Wittig reaction afforded the enantiomer of 15 epi-$PGF_{2\alpha}$, $[\alpha]^{THF}_D$ −11°, identical by spectral criteria with *nat*-15-epi-$PGF_{2\alpha}$. Alternatively, the Wittig product derived from the mixture of **9** and its diastereomer can be separated by high-pressure chromatography.

When the acid hydrolysis of **9** was preceded by acetylation and the resulting aldehyde oxidized with Jones reagent followed by alkaline hydrolysis, there was isolated after acidification in 90% yield the lactone **12**, identical with an authentic sample[17] by tlc, glc, and mass spectrum of its bistrimethylsilyl ether. Conversion of **12** into PGE_2 has been described,[17] and so has the conversion of PGE_2 into PGE_1 and $PGF_{1\alpha}$.[20] The preparation of **12**, therefore, also constitutes a synthesis of these three prostaglandins.

By an analogous sequence *rac*- and *nat*-$PGF_{3\alpha}$ (**14**) and their 15-epimers can be prepared in equivalent



yields using *rac*- or (*S*)-*cis*-oct-5-en-1-yn-3-ol (**13**) in place of octyn-3-ol. *rac*-**13** was prepared from *cis*-3-hexenal[21] with ethynylmagnesium bromide in THF at 0° in 62% yield: bp 67–67.5° (6–7 mm). Resolution of **13** was achieved *via* the hemiphthalate ester (*S*)-(−)-α-phenethylamine salt:[10] mp 120–122°; $[\alpha]_D$ −27.2°. Pure (*S*)-**13** had $[\alpha]^{Et_2O}_D$ −3.7°.[22] *rac*-$PGF_{3\alpha}$ (**14**) prepared by the above procedure was shown to be identical with an authentic sample by its tlc mobility in three systems,[18] glc, and ir and nmr spectra, as well as the mass spectrum of its tristrimethylsilyl ether methyl ester. It is clear from the foregoing that by our method the intermediate corresponding to **9** but possessing a 17,18-cis double bond can be converted into the lactone corresponding to **12** and thence into PGE_3.[23]

Greater economy may be achieved by utilizing optically active **2** in the above syntheses. Resolution was performed with (+)-α-phenethylamine isocyanate, which yielded the (+)-urethane (**3b**), mp 102.5–103°, $[\alpha]_D$ +12°, from ether–hexane in 70% yield. On alkaline hydrolysis (+)-**3b** reverted to (+)-**2**, mp 70–71°, $[\alpha]_D$ +44°, possessing the absolute configuration shown.[24]

Acknowledgments. We are grateful for the generous support of this work by the National Institutes of Health (research grants AM 11499 and K6-AM-21846). Our thanks are due to Dr. John Pike of the Upjohn Co. for authentic samples of $PGF_{2\alpha}$, its racemate, and $PGF_{3\alpha}$, to Dr. Ned M. Weinshenker of the Alza Corp. for 15-epi-$PGF_{2\alpha}$, to Professor E. J. Corey for a sample of the lactone **12**, and to Drs. G. Ohloff and M. Winter of Firmenich and Co. for generous supplies of *cis*-3-hexenal dimethyl acetal.

ster's rules has the *R* configuration. (−)-**13** therefore possesses the *S* configuration.

(23) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **93**, 1490 (1971).

(24) The absolute configuration of (+)-**2** was established as follows. Catalytic reduction of the tosylate (+)-**3a**, $[\alpha]_D$ +17°, with Pd/C afforded the corresponding dihydrodiol tosylate, $[\alpha]_D$ +59°, which was converted to the hydroxy epoxide, $[\alpha]_D$ −8.4°, with KOH in methanol, and thence into the keto epoxide, $[\alpha]_D$ −91°. The latter was related to the known (*S*)-2-methylcyclopentanone, *a* = +23(CH_3OH), by its negative Cotton effect, *a* = −23(CH_3OH); *cf.* ref 1, p 42. We thank Dr. M. M. Mehra for this resolution.

*Address correspondence to this author at the Department of Chemistry.

Josef Fried,* C. H. Lin, J. C. Sih
P. Dalven, G. F. Cooper
Department of Chemistry and The Ben May Laboratory for Cancer Research
University of Chicago
Chicago, Illinois 60637

Received March 6, 1972

Regiospecific Epoxide Opening with Acetylenic Alanes. An Improved Total Synthesis of E and F Prostaglandins

Sir:

In the preceding communication[1] we have described a total synthesis of the prostaglandins, which suffered from a single low-yield reaction (25–30%), caused by lack of regioselectivity in the epoxide opening of the trimethylsilyl ether of **6**[2] with (*S*)-(−)-3-trimethylsilyloxy-1-octynyldimethylalane (**7**). Similar problems were encountered by Corey and Noyori[3] in the reaction of the epoxide I with 1,3-bis(methylthio)allyllithium,

(20) E. J. Corey and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 7319 (1971).

(21) M. Winter, *Helv. Chim. Acta*, **46**, 1792 (1963).

(22) The absolute configuration of **13** was determined by catalytic reduction (Pd/C) to 3-octanol, $[\alpha]_D$ −9.5°, which according to Brew-

(1) J. Fried, C. H. Lin, J. C. Sih, P. Dalven, and G. F. Cooper, *J. Amer. Chem. Soc.*, **94**, 4342 (1972).

(2) The arabic boldface numerals refer to the formulas of the preceding communication, the Roman numerals to those of the present one.

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