The Synthesis of Prostaglandin E₁ and Related Substances

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Abstract: The total synthesis of crystalline dl-prostaglandin E₁ and its methyl ester via bicyclo[3.1.0]hexanone intermediates is described. The same reaction sequence also produces dl-8-isoprostaglandin E₁, the 15-epimers of these prostaglandins, and also dl-PGA₁ and dl-PGB₁ methyl esters.

n an accompanying paper¹ details are given for the synthesis of a number of prostaglandins of the F type, e.g., prostaglandin $F_{1\beta}$ (PGF_{1\beta}), via bicyclo[3.1.0]hexane intermediates. In that paper we described the preparation of four isomeric exo-substituted bicyclo-[3.1.0]hexanones 1a, 1b, 2a, and 2b (R = CH₃). In this paper we give the details of the conversion of these intermediates to four prostaglandins of the "E" type² including crystalline *dl*-prostaglandin E₁ (PGE₁).²



A communication³ by Just and Simonovitch claimed that a mixture of undisclosed composition containing compounds of structure 1 (R = H and also CH_3) gave impure PGE_1 and its methyl ester when treated with a mixture of hydrogen peroxide and sodium formate in formic acid. Our first efforts were to repeat this. Oxidative solvolysis³ of the keto esters 1a and 2a (R = CH_3) and also of the desired keto acids 1a and 2a (R = H) essentially as described by Just and Simonovitch⁴ gave good yields of a mixture of vic-glycols⁵ (3 from 1 and 4 from 2) of unrearranged carbon skeleton. In neither case was unequivocal evidence found for the presence of dl-PGE₁ or dl-8-iso-PGE₁⁶ or their methyl esters in the more polar products, and, if present, the yield must have been less than 1%. We also investigated the unalkylated ketones 5a and 5b under the same and other conditions, and found unrearranged vic-glycols 6 as essentially the only products.

Four *dl* pairs of glycols of structure 3 and another four pairs of structure 4 are possible. We found that the performic acid hydroxylation (Just and Simonovitch conditions) was quite nonstereospecific. For example, pure cis 1a ($R = CH_3$) gave a mixture of glycols which was easily separated by silica gel chromatography into two vic-glycol fractions of quite different polarity, and each of these was further separated on boric acid treated thin layer plates^{7a} into erythro and threo isomers in nearly equal amounts. These glycols were cleaved by periodate to a noncrystalline aldehyde 7 which slowly oxidized in air to a crystalline acid 8, mp 106-107°. Stereochemistry of these glycols will be discussed further below. The nonstereospecific nature of this hydroxylation^{7b} presumably demonstrates the considerable carbonium-ion character of the cyclopropylcarbinyl carbon in the epoxide-opening step, yet the reaction proceeds almost exclusively without opening of the threemembered ring. This is quite different from the behavior of some other cyclopropylcarbinyl systems,⁸ where often the predominant reaction involves ring opening.

Other conditions were sought for inducing the desired rearrangement of the cyclopropylcarbinyl system. The vic-glycols 3 ($R = CH_3$) were converted to their bismethanesulfonates, e.g., 9, and these were solvolyzed in a variety of aqueous-organic solvent mixtures. We assumed that solvolysis of the cyclopropylcarbinyl mesylate would be the most rapid,8 and that, to whatever extent solvolysis occurred with ring opening, the resulting intermediate 10 would then be an allylic mesylate, which would also solvolyze very rapidly. The less polar erythro-threo pair and also the more polar erythro-three pair of glycols $3 (R = CH_3)$ from the performic acid hydroxylation gave rather unstable bismesylates which on solvolysis in acetone-water at room temperature each gave about 5% yields of crystalline (mp 55–57°) dl-prostaglandin E_1 methyl ester (11, $R = CH_3$). This material had infrared, nmr, and mass spectra identical with those of the natural material, gave the 278-nm ultraviolet absorption (ϵ 26,000) characteristic of PGE₁ when treated with base, and exhibited greater than 50 % of the activity of natural PGE₁ methyl ester in the biological assays.⁹ Approximately an equal

⁽¹⁾ G. Just, C. Simonovitch, F. H. Lincoln, W. P. Schneider, U. Axen,

<sup>G. B. Spero, and J. E. Pike, J. Am. Chem. Soc., 91, 5364 (1969).
(2) A preliminary account of some of this work has been published:
W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson,</sup> *bid.*, **90**, 5895 (1968). The synthesis of crystalline prostaglandins has also been communicated by another group: E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *ibid.*, **90**, 3245 (1968); E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, ibid., 90, 3247 (1968).

⁽³⁾ G. Just and C. Simonovitch, Tetrahedron Lett., 2093 (1967).

⁽⁴⁾ C. Simonovitch, private communication.

⁽⁵⁾ See also K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock,

M. Harman, and J. A. Weisbach, *Tetrahedron Lett.*, 1569 (1968). (6) E. G. Daniels, W. C. Krueger, F. P. Kupiecki, J. E. Pike, and W. P. Schneider, *J. Am. Chem. Soc.*, **90**, 5894 (1968).

^{(7) (}a) L. J. Morris, *Lipids*, 1, 41 (1966); *J. Chromatog.*, 12, 321 (1963); (b) see also G. Berti, B. Macchia, and F. Macchia, *Tetrahedron*, 24, 1755 (1968).

⁽⁸⁾ K. B. Wiberg and A. J. Ashe, III, Tetrahedron Lett., 1553 (1965); J. Am. Chem. Soc., 90, 63 (1968). Also see P. von R. Schleyer and G. W. Van Dine, ibid., 88, 2321 (1966), and references therein, and G. Ohloff and W. Giersch, Helv. Chim. Acta, 51, 1328 (1968).

⁽⁹⁾ The effects on smooth muscle (gerbil colon) and rat blood pressures were determined in the laboratory of Dr. J. R. Weeks, Pharmacology Research, The Upjohn Co.



Figure 1.

amount of noncrystalline dl-15-*i*-PGE₁ methyl ester^{10,11} was also formed in the solvolysis. The major products were a mixture of isomeric monomesylates of unrearranged structure 12. That the surviving mesylate group was at C-15 (prostanoic acid numbering system) was proved by oxidation to the keto mesylate 13, where spectrally it was clear that the keto group was adjacent to the cyclopropyl ring. The monomesylates 12 could be reconverted to bismesylates and solvolyzed, again giving dl-PGE₁ methyl ester in 5% yield.

Johnson¹² has recently used cyclopropylcarbinyl systems to produce stereoselectively *trans* olefins, and has rationalized the stereoselectivity on the basis of a con-

(10) J. E. Pike, F. H. Lincoln, and W. P. Schneider (J. Org. Chem., in press) describes the preparation and characterization of 15(R)-PGE₁ made by epimerization of 15(S)-PGE₁ in formic acid.

made by epimerization of 15(S)-PGE₁ in formic acid. (11) The use of the term "15-*i*." is meant to designate the configuration at C₁₅ opposite to that of natural PGE₁. The designations of substituents on the ring system as " α " or " β " are meant to refer to groups below and above the plane of the ring, respectively, as written.

(12) S. F. Brady, M. A. Ilton, and W. S. Johnson, J. Am. Chem. Soc., 90, 2882 (1968); M. Julia, S. Julia, and S. Y. Tchen, Bull. Soc. Chim. France, 1849 (1961). certed process. To test the possible concertedness of the above mesylate solvolysis reaction, we prepared the four pure glycol racemates of structure $3 (R = CH_3)$. Since the performic acid hydroxylation was nonstereospecific, we used cis hydroxylation via osmium tetroxide and found that 1a ($R = CH_3$) gave cleanly the two *dl*erythro-glycols and 1b ($R = CH_3$) the two three isomers, each pair readily separated by silica gel chromatography. These were all chromatographically distinct on boric acid treated tlc plates and corresponded to the four components of the mixture produced by the performic acid hydroxylation above. The two erythro isomers were obtained crystalline, mp 41-42.5 and 70-71°. Conversion of each of these glycols to its bismesylate and subsequent solvolysis under identical conditions gave nearly the same distribution of products containing 4-8% dl-PGE₁ methyl ester in each case. No evidence was found for the formation of 13,14-cis-prostaglandins.¹³ We thus conclude that under these conditions,

5373

(13) We are at present unable to make definite assignments of stereochemistry for glycols 3 and 4, beyond the erythro or three designation solvolysis of the cyclopropylcarbinyl mesylate does not take place by a completely concerted mechanism.

Because of the instability of PGE_1 to basic or strongly acidic hydrolytic conditions, we elected to make *dl*- PGE_1 by modification of the above route, rather than by hydrolysis of its methyl ester. A mixture of the two more polar *erythro* and *threo* racemates of structure 3 (R = H) was converted to the trichloroethyl ester and this was then carried through the stages of bismesylation and solvolysis as above. The oily dl-PGE1 trichloroethyl ester was obtained in 4% over-all yield. This was treated briefly with zinc in acetic acid¹⁴ to remove the trichloroethyl group, giving dl-PGE1, mp 113.5-115°. While this is about the same melting point as that of the natural isomer, the mixture melting point was slightly depressed. The synthetic material showed no optical rotation between 475 and 230 nm (where natural PGE_1 shows a negative Cotton effect) and identity with natural material was established by the same spectral and biological criteria as used above for the methyl ester.

We next turned to the β -alkylated bicyclo[3.1.0]hexanones 2a and 2b ($R = CH_3$). These were separately hydroxylated with osmium tetroxide and the products chromatographed, giving the four possible glycol racemates of structure 4 ($R = CH_3$). All were obtained in crystalline form. Each of these was converted to its bismesylate which was solvolyzed as above. Again a similar ratio of products was formed from each. The yields of dl-8-*i*-PGE₁ methyl ester (mp 52–53°) ranged from 6 to 10%, and the amount of dl-15-i-8-i- PGE_1 methyl ester was about the same, but difficult to quantitate, since it was not completely separated from the major products of the reactions, the unrearranged glycol monomesylates, by chromatography. In addition, 1-2% of *dl*-PGE₁ methyl ester was formed by epimerization at C-8. The free acid, dl-8-isoprostaglandin E_{1} ,¹⁵ mp 101–102°, was prepared by a parallel series of reactions, but using the trichloroethyl ester protecting group, as was done above to prepare dl-PGE₁. The yields of ring-opened solvolysis products from the β alkylated series seem to be uniformly higher than those of the α -alkylated series, perhaps because of less steric hindrance to nucleophilic approach at the $C_{11} \alpha$ position. Since 8-*i*-PGE₁ can be isomerized to PGE₁ in 70% yield, ¹⁰ the β -alkylated series also serves as a source for this important natural product.

One further difference between the α - and β -alkylated series is shown by the periodate cleavage of the glycols **4** (R = CH₃). Instead of obtaining the β -alkylated analog of the bicyclo[3.1.0]hexanone 7, the major products were the two unsaturated cyclopentanones **14** and **15**.

The above solvolyses of bismesylates, e.g., **9**, were carried out in acetone-water or tetrahydrofuran-water at or below room temperature. When bismesylates **9** were refluxed in acetone-water containing sodium bi-

(15) This acid was first prepared in these laboratories by Dr. C. Simonovitch using another reaction sequence, which will be reported later.

carbonate, the main products (50% combined yields) were unsaturated ketones showing the same thin layer



chromatographic mobility on several systems as PGA₁ and PGB_1 methyl esters (16 and 17, respectively). The ultraviolet absorption spectrum of this mixture indicated it consisted of 75% PGA-type material (λ_{max}^{EtOH} 219 nm) and 25% PGB type (λ_{max}^{EtOH} 278 nm). These materials probably do not arise entirely by dehydration of initially formed prostaglandins of the E type, but by base-catalyzed conversion of monomesylates 12 to 14.15-epoxides, followed by ring opening via the anion 18 above. Separate experiments showed that epoxides of this type and monomesylates 12 rapidly generate ultraviolet absorption at 278 nm on treatment with strong base. Holden, et al.,⁵ have earlier observed this reaction with such epoxides. It is an important finding, however, that the conditions above allow the preparation, in good yields, of the less stable, but more biologically active¹⁶ PGA-type compounds, rather than the PGB type, the end product of base-catalyzed isomerization.

Experimental Section¹⁷

6-exo-(erythro-1',2'-Dihydroxyheptyl)- 2α -(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (3, R = CH₃). To a solution of 0.39 g of 6-exo-(cis-1'-heptenyl)- 2α -(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one¹ (1a, R = CH₃) in 8 ml of pyridine was added 0.32 g of osmium tetroxide. After stirring at 25° for 15 hr, a solution of 1.0 g of sodium bisulfite in 16 ml of water and 10 ml of pyridine was added and stirring was continued for 5 hr. The dark solution was diluted with water and extracted with chloroform, and the extracts were washed several times with water, dried, and evaporated. The residue was chromatographed on 50 g of silica gel, eluting with 50-100% ethyl acetate in Skellysolve B. The less polar erythro-glycol isomer obtained amounted to 0.150 g (35%), the more polar, 0.180 g (42%).

The less polar *erythro* isomer was crystalline (mp 70–71° from ethyl acetate–Skellysolve B): ν 3460, 1730, 1715, 1250, 1215, 1190, 1175, 1095, 1065, 1055 cm⁻¹, and mass spectral ions at 368 (M⁺), 350, 337, 319, 267, 250, and 235 mass units.

Anal. Calcd for $C_{21}H_{36}O_3$: C, 68.44; H, 9.85. Found: C, 68.46; H, 9.87.

The more polar isomer was also crystalline: $\nu = 3430, 3340, 1735, 1710, 1260, 1250, 1220, 1195, 1175, 1165, 1110, 1075, 1055, 1035 cm⁻¹ The mass spectrum was the same as for the less polar isomer. The melting point was 41-42.5° after recrystallization from ether-Skellysolve B.$

Anal. Found: C, 68.63; H, 9.79.

6-exo-(threo-1',2'-Dihydroxyheptyl)- 2α -(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one. In the same manner as above, the trans isomer¹ 1b, R = CH₃, 500 mg, gave 180 mg (32.5%) of a less polar glycol and 110 mg (20%) of more polar glycol. These were not obtained crystalline, but corresponded in the behavior to two of

based on the method of preparation. We have found among prostanoic acids we have studied that the 15(R) isomers are uniformly less polar on silica gel than the natural 15(S) epimers. If it is assumed that this holds for structures 3 and 4, then the less polar member of each pair could be considered to have the 15-i or 15(R,S) configuration.

⁽¹⁴⁾ R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrueggen, J. Am. Chem. Soc., 88, 852 (1966).

⁽¹⁶⁾ S. Bergstrom, L. A. Carlson, and J. R. Weeks, *Pharmacol. Rev.*, 20, 1 (1968).
(17) Ir spectra were recorded with a Perkin-Elmer Model 221 spec-

⁽¹⁷⁾ Ir spectra were recorded with a Perkin-Elmer Model 221 spectrometer on Nujol mulls or on methylene chloride solutions. The nmr spectra were run on a Varian 60 spectrophotometer operating at 60 Mc and employing tetramethylsilane as an internal standard. Mass spectra were recorded on an Atlas CH-4 instrument equipped with a TO-4 source (ionization voltage 70 eV). Uv spectra were taken on 95% ethanol solutions using a Cary Model 14 spectrophotometer.

the glycols obtained by performic acid hydroxylation of 1a. R = CH_3 (see below) (R_f 0.62 and 0.46 on boric acid treated plates).

6-exo-(erythro-1',2'-Dihydroxyheptyl)-2\beta-(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (4, $R = CH_3$). In the same manner as above, 0.50 g of 2a ($\mathbf{R} = \mathbf{CH}_{3^{1}}$) was treated with 0.42 g of osmium tetroxide in 10 ml of pyridine. Chromatography of the crude products gave 283 mg (51%) of the less polar erythro isomer 4 (R = CH₃): mp 42° from ether, Skellysolve B; R_i 0.40 on silica gel, developed with ethyl acetate.

Anal. Calcd for C21H36O5: C, 68.44; H, 9.85. Found: C, 68.21; H, 9.80.

The more polar erythro isomer consisted of 148 mg (27%) of crystalline material, mp 58–59°, from ether, R_i 0.19.

Anal. Found: C, 68.27; H, 9.97.

These two glycols had nearly identical infrared and nmr spectra: ν 3400, 1735, 1745, 1240, 1200, 1170, 1060, 735 cm⁻¹ and δ 3.65, three-proton singlet (OCH₂), four-proton multiplet, δ 3.4-2.9 (carbinolic and hydroxylic protons), and the 6-endo-cyclopropyl hydrogen at $\delta 0.48$.

6-exo-(threo-1',2'-Dihydroxyheptyl)- 2β -(6''-carbomethoxyhexyl)bicyclo[3.1.0] hexan-3-one (4, R = CH₃). In the same manner as above, 0.50 g of 2b (R = $CH_{3^{1}}$) was hydroxylated with osmium tetroxide to give 219 mg (39.5%) of the less polar three isomer and 129 mg (23%) of the more polar three isomer of structure 4 (R = CH₃). The less polar material was crystallized from ether-Skellysolve B: mp 46–47°; $R_f 0.40$ (silica gel plate, developed with ethyl acetate).

Anal. Calcd for C21H36O5: C, 68.44; H, 9.85. Found: C, 68.31; H, 9.75.

The more polar threo isomer was recrystallized from ether: mp 77-78°; R_t 0.23. Anal. Found: C, 68.58; H, 10.11.

Thin layer chromatography of the four glycols of structure 4 $(\mathbf{R} = \mathbf{CH}_3)$ on silica gel plates sprayed with 10% boric acid in methanol and dried 30 min at 70° gave the following R_i values: less polar erythro, 0.75; less polar threo, 0.70; more polar threo, 0.60; and more polar erythro, 0.46.

The infrared and nmr spectra of the threo isomers were very similar to those of the erythro isomers above.

6-exo-(erythro- and-threo-1',2'-Dihydroxyheptyl)-2\beta-(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (3, $R = CH_3$). A. Via Performic Acid Hydroxylation of 1a ($R = CH_3$). To 1.90 g of 6exo-(1'-cis-heptenyl)- 2α -(6''-carbomethoxyhexyl)bicyclo[3,1,0]hexan-3-one (1a) at 0° was added a mixture of 50 ml of 98% formic acid, 650 mg of NaHCO₃, and 0.18 ml of 90% H₂O₂ which had been cooled to 0° and purged with N₂. The solution was stirred at 0° for 0.5 hr and then allowed to warm to room temperature over 2 hr. Formic acid was removed under vacuum and benzene was added. This was also removed under vacuum and the residue was extracted with ethyl acetate. This was washed with water and bicarbonate, saturated salt, and dried with sodium sulfate. Evaporation gave a residue consisting of formates of the glycol. These were hydrolyzed with 50 ml of methanol and 10 ml of saturated sodium bicarbonate at 25° for 2 hr. Water (40 ml) was added, the methanol removed under vacuum, and the aqueous suspension was acidified to pH 3 and extracted with ethyl acetate. This was washed with water and saturated salt, dried with sodium sulfate, and evaporated. The residue was chromatographed on 150 g of silica gel and eluted with 750 ml each of 25, 35, 50, 75% ethyl acetate-Skellysolve B, collecting 150-ml fractions. Fractions 12-15, 789 mg (38%), consisted of a mixture of two isomeric glycols of structure 3a, $R = CH_3$. This material showed a single spot, Rf 0.62 on silica gel plates developed with A-IX system, 18 but on a boric acid treated plate⁷ it showed two spots of nearly equal intensity at R_f 0.62 and 0.52. The upper spot corresponds to the less polar threo-glycol (characterized above). The nmr spectrum showed a three-proton singlet at δ 3.67 (OCH₃), about four protons, multiplet, between δ 2.7 and 3.6, for carbinolic and hydroxylic protons, five protons as multiplet, δ 1.9-2.7, for protons adjacent to carbonyls, and one cyclopropyl proton was evident at $\delta 0.6$. Fractions 16-21, 685 mg (33%), were also one spot on silica gel plates, but showed two spots with R_f 0.46 and 0.36 on boric acid treated plates and consisted of the more polar erythro- and threo-glycols (above). The less polar of the two had the same mobility on boric acid treated plates as the more polar threo isomer. Its ir and nmr spectra were very similar to that of fractions 12-15 above. The mass spectrum showed 350 (M - 18), 332 (M - 2H₂O), 292 (350 -58), 267 (M - 101), 235 (267 - 32). Investigation of the small amount of more polar material (1-2% yield) eluted from the column by tlc showed no definite evidence for the presence of PGE₁ methyl ester.

B. Via Performic Acid Oxidation of cis 1a (R = H). A solution of 440 mg of 6-exo-(cis-1'-heptenyl)- 2α -(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one¹ in 48 ml of isopropyl alcohol was cooled in an ice bath. While stirring, a solution of 480 mg of sodium borohydride in 4.8 ml of water was added. The mixture was stirred 2.5 hr while the ice gradually melted and the temperature rose toward room temperature. Then 2 ml of acetone was added, followed by 2.4 ml of acetic acid in 24 ml of water. The organic solvent was removed in vacuo and the residue extracted with ethyl acetate. This was washed with bicarbonate, saturated salt, dried over sodium sulfate, and evaporated. The crude mixture of 3alcohols was dissolved in 16 ml of methanol and 8 ml of 1 N sodium hydroxide was added. The mixture was stirred 2 hr under nitrogen at 25°, then the clear solution was acidified by adding 5 ml of water and 12 ml of 1 N hydrochloric acid. Methanol was removed in vacuo and the product was extracted with ethyl acetate. The extracts were washed with water and saturated salt, dried with sodium sulfate, and evaporated. The residue had an nmr spectrum consistent with the structure, 6-exo-(1'-heptenyl)- 2α -(6''-carboxyhexyl)bicyclo[3.1.0]hexan-3-ol.

This crude product was dissolved in 100 ml of acetone, cooled to 0°, and treated with 1 ml of Jones reagent¹⁹ for 10 min. Then 4 ml of isopropyl alcohol was added, followed by 40 ml of water, and the acetone was removed in vacuo. The product was extracted with ethyl acetate, which was washed with 1 N hydrochloric acid and saturated salt, dried with sodium sulfate, and evaporated. The crude product was chromatographed on 50 g of Mallinckrodt Silicar CC-4. and eluted with 4, 7.5, 10, 15, 25, and 50% ethyl acetate-Skellysolve B. Fractions 9-12 contained 303 mg of product: v 2500-3500 (COOH), 1745, 1720, 1040, 845, 725 cm⁻¹. The nmr absorption spectrum was very similar to starting keto ester except for absence of O-CH₃ absorption. A small portion, esterified with ethereal diazomethane and compared on tlc (silica gel, 10% ethyl acetatecyclohexane, developed twice), was identical with starting ketone.¹ Only about 20 mg of later fractions contained some of the β alkylated ketone (2) by this test.

To 100 mg of the above keto acid (1a, R = H) cooled to 0° under nitrogen was added a solution made up of 8 ml of dry formic acid (distilled from boric anhydride) to which had been added 10 μ l of 90% hydrogen peroxide and 65 mg of dry sodium bicarbonate, all nitrogen purged before the addition. After 30 min, the ice bath was removed and the mixture was stirred 1.5 hr at room temperature. The formic acid was removed at 25° in vacuo and benzene was then added and removed in vacuo to complete removal of formic acid. To the residue was added 10 ml of methanol and 2.5 ml of saturated sodium bicarbonate. This stood at 5° overnight, then was acidified to pH 4. The methanol was removed in vacuo: the solution was adjusted to pH 3 and extracted with ethyl acetate. The extracts were washed, dried, evaporated, and chromatographed on 15 g of acid-washed silica gel. Elution was with 25, 35, 50, 75, and 100% ethyl acetate-Skellysolve B and 1 and 10% methanolethyl acetate. The first material eluted, 7 mg, had tlc mobility like starting material. Then 100 mg of a mixture of two materials, one with uv absorption, was eluted. This was followed by 35 mg of partly crystalline material showing infrared and nmr spectra consistent with structure 3, R = H. The mass spectrum of this material showed the molecular ion (354) and also 253 (cleavage between the glycol hydroxyls) as a strong ion peak. The next material eluted (with ethyl acetate) was 50 mg of noncrystalline material, also having nmr and ir spectra very similar to the glycol above, and a mass spectra virtually identical. In both of these glycols, the 6-endo-cyclopropyl hydrogen was seen in the nmr spectra at δ 0.4–0.8 (multiplet, J = 3.5 and 7 cps), and no olefinic protons were present. Esterification of these glycol fractions with diazomethane gave the same two pairs of erythro- and threo-glycol methyl esters (tlc on boric acid treated silica gel plates) as were obtained in A above. Later fractions from the column, ca. 3 mg, were more polar mixtures, but no distinct spot like PGE1 was seen in tlc's of these later fractions.

6-exo-Formyl-2α-(6'-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3one (7) and 6-exo-Carboxy- 2α -(6'-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (8). A mixture of the more polar glycols (3, R = CH₃), 187 mg from the preceding experiment, was treated with 210 mg of sodium periodate in 9 ml of water and 10 ml of methanol at

⁽¹⁸⁾ M. Hamberg and B. Samuelsson, J. Biol. Chem., 241, 257 (1966).

⁽¹⁹⁾ K. Bowden, J. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, J. Chem. Soc., 39 (1946).

25° for 20 min. Extraction with ether and chromatography of the crude product on 15 g of silica gel (elution with 10–100% ethyl acetate in Skellysolve B) gave 80 mg (57%) of aldehyde 7, showing nmr absorptions at 564 cps (doublet, J = 4 cps for the aldehydic proton), 221 cps (three-proton singlet for OCH₃), and a five-proton multiplet (120–170 cps for protons adjacent to carbonyl groups). This aldehyde, on standing in air, slowly deposited crystals of acid 8 (R_i ca. 0 on the same tlc system as above, methyl ester R_i 0.65), mp 106–107° after recrystallization from ethyl acetate–Skellysolve B.

Anal. Calcd for $C_{13}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.67; H, 7.90.

The less polar glycol mixture $(3, R = CH_3)$ obtained in the preceding experiment gave the same aldehyde and acid as above after cleavage with sodium periodate.

1-(6-Carbomethoxyhexyl)-3-formylmethylcyclopent-2-en-1-one (15). To a solution of 203 mg of a mixture of the less polar erythro- and threo-glycols of structure 4 ($R = CH_3$) in 12 ml of methanol was added a solution of 254 mg of sodium periodate in 11 ml of water. After stirring 20 min at 25°, it was extracted with ethyl acetate, washed with water and saturated salt, dried, and evaporated. The residue was chromatographed on 15 g of silica gel, eluting with 75 ml each of 10, 20, 35, 50, 75, and 100%ethyl acetate in Skellysolve B. One major peak, 103 mg (70%), was eluted with 50% ethyl acetate-Skellysolve B, as a colorless oil, ν 2700, 1745, 1710, 1640 cm⁻¹, showing ultraviolet absorption at 229 mµ. In the nmr, an aldehyde proton was evident at δ 9.82 (triplet, J = 1.5 cps), one olefinic proton at δ 7.23, three OCH₃ protons as a singlet at δ 3.65, and no cyclopropyl protons were evident. The mass spectrum showed prominent peaks at 266, 235, 222, and 190 mass units.

A small amount of material was also obtained from the column which showed two olefinic protons as doublets of doublets at δ 6.17 and 7.7, characteristic of the alternate mode of ring opening to give structure **14**.

In the same way, the more polar *erythro-* and *threo-*glycols of structure $4 (R = CH_3)$ gave the same unsaturated aldehyde, identical in nmr and ir spectra and tlc behavior with that obtained above.

6-exo-(erythro- and threo-1',2'-Dihydroxyheptyl)bicyclo[3.1.0]hexan-3-one (6). A. To 480 mg of $5a^{1}$ in 30 ml of formic acid at 0° was added 0.24 ml of 30% hydrogen peroxide. The mixture was allowed to warm to room temperature and stir for 3 hr. Formic acid was removed under vacuum and the residue was treated with 20 ml of dioxane and 20 ml of saturated aqueous sodium bicarbonate for 2.5 hr. The mixture was extracted with chloroform, washed, dried, and evaporated. The residue was chromatographed on silica gel, eluting with increasing ratios of ethyl acetate in Skellysolve B. The following fractions were identified by their nmr spectra: 310 mg of diformates of structure 6, 170 mg of monoformates of structure 6, and 15 mg of the diol 6. No material was obtained which showed olefinic protons in the nmr. The mono- and diformates above were hydrolyzed in 1:1 dioxane-20% aqueous sodium carbonate for 4.5 hr at 25°, giving material identical in the mobility (2:1 cyclohexane-ethyl acetate on silica gel) with the glycol (6) obtained below. A sample, 80 mg, of the combined glycol fractions 6 were treated with 4 ml of methanol and 3.9 ml of aqueous sodium periodate (0.1 mmole/ml) at 25° for 20 The products were extracted with ether which was washed, min. dried, and evaporated. The residue, in 20 ml of ether, was treated with 250 ml of lithium aluminum hydride for 30 min and then worked up. The product was identical in nmr and tlc behavior with the previously obtained¹ 6-exo-hydroxymethylbicyclo[3.1.0]hexan-3 α - and - β -ols.

A solution of 2.92 g of 5a in 58 ml of pyridine was treated with 2.46 g of osmium tetroxide and stirred overnight. The dark solution was diluted with a solution of 7 g of sodium bisulfite in 117 ml of water and 77 ml of pyridine and stirred 5 hr. After the addition of more water, the products were extracted with methylene chloride, which was washed, dried, and evaporated. The residue was chromatographed on 250 g of silica gel, eluting with 25-100%ethyl acetate in Skellysolve B. The main peak of material eluted, 1.157 g (34%), was crystalline, mp 63-64° after recrystallization from ethyl acetate-Skellysolve B, and consisted of the erythro isomer of 6, v 3300, 3020, 1750, 1120, 1110, 990, 975, 890, 840, 785, and 725 cm⁻¹. In the nmr, the 2'-hydrogen occurred as a broad multiplet at δ 3.9–3.6, the 1'-hydrogen as a doublet of doublets, δ 3.15 (J = 3.5 and 8 cps), and the 6-endo-cyclopropyl hydrogen as two triplets between δ 0.9 and 0.5 (J = 3.5 and 8 cps). It showed prominent ion peaks at 226, 208, 198, and 125 mass units.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.92; H, 9.67.

C. In the same way as above, 1.97 g of the *trans* isomer **5b** gave 746 mg (32%) of noncrystalline *threo* isomer of **6**, ν 3350, 3020, 1750, 1050, 970, 935, 815, and 790 cm⁻¹. The nmr spectrum showed the 2'-hydrogen, multiplet centered at δ 3.5, the 2 α -hydrogen at 2.69 (J = 21, 6, 2.5 cps), the 2 β -hydrogen at δ 2.15 (J = 21, 1.5 cps), and the 6-*endo*-hydrogen at δ 0.52 (J = 8, 3.5 cps).

dl-Prostaglandin E₁ Methyl Ester (11) and dl-15-Isoprostaglandin E_1 Methyl Ester. A. A solution of 509 mg of the more polar erythro isomer of $3 (R = CH_3)$ in 9 ml of pyridine was cooled to 0° and treated with 1.3 ml of methanesulfonyl chloride. After 1 hr at 0°, the ice bath was removed and the mixture was stirred 1 hr additional. It was then cooled again to 0° , ice was added, and the products were extracted with methylene chloride. This was washed with cold, dilute hydrochloric acid, dried, and evaporated. This crude dimesylate residue showed essentially one spot on tlc, strong infrared absorptions at 1740, 1350, 1175, and 910 cm⁻¹, and prominant ion peaks in the mass spectrum at 332 (M $- 2CH_3SO_3H$), 301 (332 - 31), and 300 (332 - 32) mass units. It was rather unstable to the usual chromatographic purifications. It was dissolved in 27 ml of acetone and diluted with 13.5 ml of water and the resulting solution stored at 25° for 6 hr. The mixture was concentrated under vacuum, extracted with methylene chloride, and was washed, dried, and evaporated. Chromatography on 50 g of silica gel and elution with increasing proportions of ethyl acetate in Skellysolve B gave the following materials: A, 75 mg of unknown, least polar products; B, 389 mg (63%) of a mixture of two glycol monomesylates of structure 12 ($R = CH_3$); C, 27 mg (5.3%) of dl-15-isoprostaglandin E_1 methyl ester; and D, 34 mg (6.7%) of crystalline *dl*-prostaglandin E₁ methyl ester.

Fraction B, the two monomesylates, was characterized as follows: prominent ions in the mass spectrum at 350 (M – CH₃-SO₂H), 332 (350 – 18), 301 (323 – 31), 300 (332 – 32), 319 (350 – 31), 318 (350 – 32); infrared absorptions at ν 3500, 1745, 1340, 1170, 920 cm⁻¹; and in the nmr, one proton as a broad multiplet at δ 5.0–4.6, three-proton singlet at 3.7 (OCH₃), one proton as a doublet of doublets at 3.41 (J = 7.5 and 3.5 cps), a three-proton singlet at 3.1 (SCH₃), and the 6-endo-cyclopropyl hydrogen as a multiplet, δ 0.61 (J = 8 and 4 cps)

Fraction C, dl-15-isoprostaglandin E₁ methyl ester, had infrared and nmr spectra identical with those of the optically active 15(R)-PGE₁ methyl ester (see ref 10). The mass spectrum showed the molecular ion, 368, and other prominent ions at 350, 332, and 297 mass units. It was not obtained crystalline.

Fraction D was recrystallized from ether-Skellysolve B, mp 55-57°. The nmr and infrared spectra and tlc behavior¹⁷ were identical with those of natural PGE₁ methyl ester. The mass spectrum showed peaks at 368, 350, 332, and 297 mass units, and ultraviolet absorption at 278 nm (ϵ 26,000), developed after adding 20 µl of 50% aqueous KOH to a sample in 3 ml of ethanol.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.08; H, 9.92.

B. The less polar *erythro* isomer of structure **3**, $R = CH_3$, treated as above gave 5% *dl*-PGE₁ methyl ester and an equal amount of its 15-epimer.

C. The more polar *threo* isomer of structure 3, $R = CH_3$, similarly gave 5% *dl*-PGE₁ methyl ester and 5.5% of its 15-epimer.

D. The less polar *threa*-glycol of 3, $R = CH_3$, was not obtained in as pure a form as the above isomers, so the yields of prostaglandins, while similar to the above, are not known with such certainty.

E. In the same way as above, the mixture of monomesylates (12, $R = CH_3$) obtained from the above solvolysis reactions was reconverted to the bismesylate and solvolyzed, giving 5% yield of *dl*-PGE₁ methyl ester and an equal amount of its 15-epimer.

6-exo-(1'-Keto-2'-mesyloxyheptyl)- 2α -(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (13). About 70 mg of fraction B, the monomesylates, above was dissolved in 12 ml of acetone, cooled to 0°, and treated with 0.15 ml of Jones reagent¹⁹ for 10 min. Then 1 ml of isopropyl alcohol and 5 ml of water were added, and the mixture was concentrated under vacuum and extracted with ethyl acetate. The extracts were washed, dried, and evaporated. The nmr spectrum of the residue showed the proton on carbon bearing the mesyloxy group as a triplet at δ 5.06, J = 6 cps; a three proton singlet at 3.67 (OCH₃) and a three-proton singlet at 3.15 (SCH₃); the 6-endo-cyclopropyl proton had been shifted downfield below δ 1.0. The mass spectrum showed prominent ions at 444, 413, 348, 317, 316, 206, and 205 mass units.

dl-Prostaglandin E_1 Trichloroethyl Ester (11, $R = CH_2CCl_2$). To a dried sample, 329 mg of the glycol acid 3, R = H, consisting of

the more polar *erythro* and *threo* isomers, was added 20 ml of methylene chloride, 3.3 ml of trichloroethanol, 1.8 ml of pyridine, and then 0.33 g of dicyclohexylcarbodiimide. After stirring 2 hr at 25°, the entire reaction mixture was poured onto a column of 100 g of silica gel. Elution with 2 l. of 25-75% ethyl acetate-Skelly-solve B, gradient, gave 300 mg (67% yd) of the desired trichloroethyl ester above, contaminated with a little crystalline dicyclohexylurea. This material had a two-proton singlet at δ 4.76 for the protons of the trichloroethyl group but the nmr spectrum was otherwise similar to that of the corresponding methyl ester, 3, R = CH₃.

The 300 mg of glycol trichloroethyl ester obtained above was treated at 0° under nitrogen in 7.5 ml of pyridine with 0.8 ml of methanesulfonyl chloride. After 5 min at 0°, it was allowed to warm to room temperature and stir 2 hr total. It was again cooled in ice, and 5 ml of water was added. After stirring 5 min at 0°, ethyl acetate was added, and it was washed twice with water, twice with 1 N hydrochloric acid, then with bicarbonate, saturated salt, dried over sodium sulfate, and evaporated. The residue, 348 mg, by thin layer chromatography consisted largely of a material less polar than the starting glycol. To this was added 8 ml of acetone and 2 ml of water, and the resulting solution stood at 5° under nitrogen for 68 hr. Water was then added, acetone was removed in vacuo, and the products were extracted with ethyl acetate. This was washed with bicarbonate, saturated salt, dried over sodium sulfate, and evaporated, crude weight 315 mg. Chromatography on 50 g of silica gel and gradient elution with 1 l. of 25-100% ethyl acetate-Skellysolve B, followed by 5% methanol-ethyl acetate gave four peaks.

No. 9–15, 88 mg, and no. 17–26, 117 mg, consisted of monomesylates of the general structure 12, $R = CH_2CCl_3$, the infrared spectrum showing absorption for OH (3500 cm⁻¹), C=O (1745 cm⁻¹), 1340, 1170, 920, 800, 720 cm⁻¹.

No. 32-40, 15 mg, moved on the slightly faster than the methyl ester of 15-*i*-PGE₁, and undoubtedly consists of its corresponding trichloroethyl ester.

No. 43–47, 12 mg, moved slightly faster on the than the methyl ester of PGE₁ and showed in the nmr two olefinic protons centered at δ 5.65 and two protons of the trichloroethyl ester group as a singlet at δ 4.76 and was otherwise consistent with the trichloroethyl ester of PGE₁.

In the same manner as above, 200 mg of the less polar *erythrothreo* pair of glycols of structure 3, R = H, was converted to the trichloroethyl esters, the bismesylates, and solvolyzed, giving 8.5 mg of the trichloroethyl ester of *dl*-PGE₁, identical with that above.

dl-Prostaglandin E1. Fractions 43-47, 12 mg, of the preceding experiment were dissolved in 1 ml of 90% acetic acid and stirred with about 100 mg of zinc dust at 25° for 2 hr, when the showed no ester remaining. Ethyl acetate was added; the solution was decanted into a separatory funnel and washed several times with water, then saturated salt, dried with sodium sulfate, and evaporated. The residue was chromatographed on 3 g of silica gel (Mallinckrodt Silicar CC₄) eluting with 50 ml each of 50, 75, 100% ethyl acetate-Skellysolve B, and 5% methanol-ethyl acetate. Fractions 7-9, 6.5 mg, were largely crystalline, moved on tlc18 like PGE1, and after two recrystallizations from ethyl acetate-Skellysolve B, melted at 113.5–115°, wt 3.5 mg. Mixture melting point with natural PGE_1 (mp 114-115°) was 109-114°. The optical rotatory dispersion curve showed no optical activity between 475 and 230 nm (sensitive 0.001°), and the mass spectrum was identical with that of natural PGE₁. Biological activity was greater than 50% of natural PGE₁ in two systems.9

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.73; H, 9.96.

The recovered monomesylate fractions from the preceding experiment, 205 mg, were remesylated and solvolyzed as above, and the *dl*-PGE₁ trichloroethyl ester fractions (*ca.* 6 mg) were hydrolyzed with zinc and acetic acid. In this way a further 2 mg of *dl*-PGE₁, mp 113–115°, was obtained, making the total yield of pure *dl*-PGE₁ 5.4 mg, or 1.6% over-all from the glycol acid.

dl-8-Isoprostaglandin E_1 Methyl Ester. A solution of 0.50 g of the more polar *erythro*-glycol of structure 4, $R = CH_3$, mp 58–59°, in 10 ml of pyridine was cooled to 0° and treated with 1.25 ml of methanesulfonyl chloride. The solution was stirred at 0° for 1 hr, and then allowed to warm to room temperature over an additional 1-hr period. Then the mixture was cooled, ice was added, and the product extracted with methylene chloride. The extracts were washed with cold 5% hydrochloric acid, dried, and evaporated to leave 0.71 g of a brown oil.

In the same way, the other three racemates of structure 4, $R = CH_3$, were also converted to bismesylates. The mobilities of these

products on silica gel plates developed with 50% ethyl acetatecyclohexane were as follows: more polar *erythro*- and *threo*-bismesylates, R_t 0.47; less polar *erythro*- and *threo*-bismesylates, R_t 0.57. All four gave similar infrared and nmr spectra: 1745, 1360, 1180, 970, 915, 740 cm⁻¹; one-proton multiplets at about δ 4.8 and 4.3 (proton on carbon bearing a mesyloxy group), threeproton singlets at δ 3.65 and six-proton singlet at δ 3.1 (OCH₃ and SCH₃), and a distorted triplet at δ 0.9 consisting of the terminal methyl partially obscuring the 6-*endo*-cyclopropyl hydrogen. The bismesylate from the less polar *threo*-glycol crystallized as needles from ethyl acetate–Skellysolve B, mp 86–87°.

Anal. Calcd for $C_{23}H_{40}O_9S_2$: C, 52 65; H, 7.68; S, 12.22. Found: C, 52.32; H, 7.74; S, 12.21.

B. This monomesylate, contaminated (by tlc evidence) with *dl*-15-*i*-8-*i*-PGE₁ methyl ester, was partially crystalline, and was recrystallized from acetone-Skellysolve B to give the pure monomesylate: mp 93-94°; ν 3510, 3450, 3030, 3010, 1745, 1340, 1205, 1175, 1170, 1030, 990, 920, and 810 cm⁻¹. In the nmr, a three-proton singlet at δ 3.05 showed the presence of one SCH₃ group.

Anal. Calcd for $C_{22}H_{38}O_7\hat{S}$: C, 59.17; H, 8.58; S, 7.18. Found: C, 59.39; H, 8.77; S, 7.00.

C. This material exhibited the same mobility ($R_f 0.40$) on silica gel plates developed in ethyl acetate as did authentic 8-*i*-PGE₁ methyl ester⁶ and gave λ_{max}^{EiOH} 278 nm (ϵ 23,400) on treatment with base. After recrystallization from ether–Skellysolve B, it melted at 52–53°, ν 3400, 1740, 1240, 1200, 1175, 975 cm⁻¹. The nmr spectrum was like authentic material⁶ showing a broad multiplet, δ 5.0–5.8, for the C₁₃,C₁₄ olefinic protons. Prominent ions at 350, 332, and 277 were present in the mass spectrum.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 67.99; H, 10.06

The bismesylate prepared from the less polar *threo*-glycol 4, $\mathbf{R} = \mathbf{CH}_3$, on solvolysis as above gave 5.4% yield of *dl*-8-*i*-PGE₁ methyl ester. From the more polar *threo*-glycol 4, $\mathbf{R} = \mathbf{CH}_3$, the yield was 11%, and from the less polar *erythro* 8.0%. Solvolysis of the less polar *erythro*-bismesylate in 2:1 tetrahydrofuran-water, otherwise as above, gave 10% *dl*-8-*i*-PGE₁ methyl ester. In each case 1-2% *dl*-PGE₁ methyl ester was also formed. From the more polar *threo*-bismesylate solvolysis, one of the monomesylates was obtained crystalline, mp 85-87° from acetone–Skellysolve B.

Anal. Calcd for $C_{22}H_{38}O_7S$: C, 59.17; H, 8.58; S, 7.18. Found: C, 58.95; H, 8.71; S, 7.01.

6-exo-(1'-Keto-2'-mesyloxyheptyl)- 2β -(6''-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one. A solution of 75 mg of the monomesylate of fraction B of the preceding experiment in 12 ml of acetone was treated at 0° with 0.15 ml of Jones reagent. After 10 min the product was isolated in the usual way. The nmr spectrum showed a triplet, δ 4.0, J = 6 cps, for the hydrogen on carbon bearing the mesyloxy group and three-proton singlets at δ 3.65 and 3.1 (OCH₃ and SCH₃).

8-Isoprostaglandin E₁. To 1.2 g of keto acid 2a (R = H) under nitrogen was added a cold (0°) solution of 325 mg of sodium bicarbonate and 0.1 ml of 90% hydrogen peroxide in 25 ml of 98%formic acid. After stirring at 0° for 0.5 hr, the ice bath was removed and stirring was continued a further 1.5 hr. The formic acid was removed in vacuo, 25 ml of benzene was added, and this was also removed in vacuo. The residue was extracted with ethyl acetate which was washed with water and saturated salt, dried with sodium sulfate, and evaporated. To the residue was added 45 ml of methanol and 15 ml of saturated aqueous sodium bicarbonate. This was stirred at 25° 2 hr, concentrated in vacuo to remove methanol, and acidified to pH 2-3. The products were extracted with ethyl acetate which was washed with water, dried, and evaporated, leaving 1.38 g of a mixture of epimeric glycol acids 4 (R = H). These were esterified in 140 ml of methylene chloride with 23 ml of trichloroethanol, 12.6 ml of pyridine, and 2.31 g of dicyclohexylcarbodiimide at 25° for 2 hr. Then 5 ml of water was added, and

after stirring 5 min the mixture was washed with 1 N HCl and NaHCO₃ solution, dried, and evaporated. The residue was dissolved in benzene, filtered to remove some dicyclohexylurea, and chromatographed on 150 g of silica gel. Elution with 20–100% ethyl acetate in Skellysolve B gave major peaks corresponding to epimeric glycols of structure 4 ($\mathbf{R} = CH_2CCl_3$). The less polar, 700 mg, showed one spot on tlc—silica gel, 50% ethyl acetate–cyclohexane; the more polar, 800 mg, showed two very close spots on the same tlc system. The R_f values of these trichloroethyl esters were similar but slightly greater than those of the corresponding methyl esters, above.

To 667 mg of the less polar glycol 4 ($R = CH_2CCl_3$) above was added 16.5 ml of pyridine and then, at 0°, 1.67 ml of methanesulfonyl chloride. The mixture was stirred at 0° for 10 min, and 1.75 hr longer with the ice bath removed. It was then again cooled to 0°, 15 ml of water was added, and the mixture was extracted with ethyl acetate. This was washed several times with cold dilute hydrochloric acid and aqueous sodium bicarbonate, dried, and evaporated. The crude bismesylate was stirred in 53 ml of acetone and 26 ml of water under nitrogen at 25° overnight. The solution was concentrated *in vacuo* and extracted with ethyl acetate, which was washed, dried, and evaporated. The residue was chromatographed on 75 g of silica gel and eluted with increasing amounts of ethyl acetate in Skellysolve B. After two main peaks of material, 276 and 103 mg, of unrearranged glycol monomesylates was eluted 34 mg of dl-8-isoprostaglandin E_1 trichloroethyl ester showing two olefinic protons between δ 5.0 and 6.0 (H₁₃ at δ 5.28, J = 15 and 9.5 cps, and H₁₄ at δ 5.7, J = 15 and 7 cps), two protons of the trichloroethyl group as a singlet, δ 4.8, and two carbinolic protons as multiplets between δ 3.9 and 4.5. This was followed by 12 mg of the trichloroethyl ester of dl-prostaglandin E₁, the nmr spectrum of which was identical with that obtained above.

The 34 mg of *dl*-8-isoprostaglandin E_1 trichloroethyl ester was dissolved in 1 ml of 90% acetic acid and stirred with 100 mg of zinc dust for 2 hr. It was then diluted with ethyl acetate which was washed several times with water, dried, and evaporated. The residue was chromatographed on 5 g of Silicar CC4 (Mallinckrodt) acid-washed silica gel and eluted with 50–100% ethyl acetate–Skelly-

solve B. The fractions corresponding in tlc mobility to 8-isoprostaglandin E_1^6 on the A IX system,¹⁸ 15 mg, were combined and crystallized from ethyl acetate–Skellysolve B, mp 101–102°. This material showed no optical rotation between 475 and 230 nm, and the nmr and mass spectra were identical with those of the "natural" isomer.⁶

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.56; H, 9.60.

dl-Prostaglandin A1 and dl-Prostaglandin B1 Methyl Esters. A mixture (150 mg) of the less polar erythro- and threo-glycols (3) $(R = CH_3)$ was treated in 4 ml of pyridine with 0.4 ml of methanesulfonyl chloride at 0° and then allowed to warm to room temperature over 2 hr. Ice was then added; the product was extracted with ethyl acetate and was washed with cold dilute hydrochloric acid, sodium bicarbonate, dried, and evaporated. The crude bismesylate was dissolved in 15 ml of acetone to which was added 2 ml of water and 4 ml of saturated sodium bicarbonate solution, and the resulting mixture was refluxed under nitrogen for 4 hr. After acidification, the mixture was extracted with ethyl acetate, and the extracts were washed, dried, and evaporated. The crude residue was briefly treated with excess ethereal diazomethane and chromatographed on 20 g of silica gel. Elution with increasing proportions of ethyl acetate in cyclohexane gave a total of 71 mg (50% yield) of a mixture of *dl*-PGA₁ and *dl*-PGB₁ methyl esters. These were not well separated by the column, but the early fractions of the main peak, 14 mg, consisted of pure dl-PGA₁ methyl ester, λ_{max}^{EtoH} 221 nm (ϵ 11,000), and identical mobility on several tlc systems¹⁸ to natural material. The remainder of the material of the main peak, 56 mg $(\lambda_{max} 219 \ (\epsilon 7530), 278 \ nm \ (10,150), was a mixture consisting of$ 65% dl-PGA₁ methyl ester and 35% dl-PGB₁ methyl ester.

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Communications to the Editor

A Novel Stereochemical Rearrangement Process for an Isomer of Trimethylsilicon Acetylacetonate, a Silyl Enol Ether

Sir:

Nearly every element possessing metallic character is known to form compounds with acetylacetonate and other β -diketonates. In the majority of compounds, the metal is bonded to both donor oxygen atoms on the ligand, resulting in a cyclic chelate structure. In certain mercury(II)^{1,2} and silicon(IV)^{3,4} β -diketonates, however, the central atom is bonded to only one donor oxygen atom. Thus these compounds possess an openchain enol ether structure in which the uncoordinated or "dangling" oxygen is ketonic. Such a structure has been assigned for trimethylsilicon acetylacetonate, (CH₃)₃Si(acac).^{3,4} In addition, the occurrence of isomers I and II has been claimed based on the coinci-

(2) G. S. Hammond, D. C. Nonhebel, and C. S. Wu, Inorg. Chem., 2, 73 (1963).

(3) W. H. Knoth, Ph.D. Thesis, The Pennsylvania State University, University Park, Pa., 1954; cf., L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 14.



dence of infrared absorption bands for the compound and the carbonyl stretching frequencies for the *cis* and *trans* isomers of the methyl enol ether of acetylacetone.³ This communication reports some nmr studies of $(CH_3)_3Si(acac)$ which confirm the existence of the expected isomers and, more important, which show that one of the isomers undergoes a novel stereochemical rearrangement process.

 $(CH_3)_3Si(acac)$ was prepared and purified according to the method described by West.⁴ Anal. Calcd for $C_8H_{16}O_2Si$: C, 55.77; H, 9.36; Si, 16.30; mol wt, 172. Found: C, 55.70; H, 9.21; Si, 16.51; mol wt $(C_6H_5NO_2)$, 184. Vibrational frequencies $\nu_{C=O}$, $\nu_{C=C}$, and ν_{Si-O} were in agreement with the reported values and verify the previously assigned enol ether structure.^{3,4}

⁽¹⁾ D. C. Nonhebel, J. Chem. Soc., 738 (1963).

⁽⁴⁾ R. West, J. Amer. Chem. Soc., 80, 3246 (1958).