The Synthesis of Prostaglandin E_1 and Related Substances

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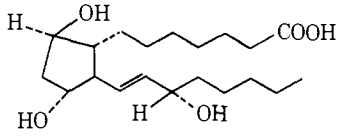
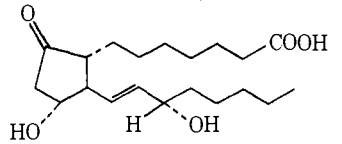
Abstract: The total synthesis of crystalline *dl*-prostaglandin E_1 and its methyl ester *via* bicyclo[3.1.0]hexanone intermediates is described. The same reaction sequence also produces *dl*-8-isoprostaglandin E_1, the 15-epimers of these prostaglandins, and also *dl*-PGA_1 and *dl*-PGB_1 methyl esters.

In an accompanying paper[1] 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 = CH_3). In this paper we give the details of the conversion of these intermediates to four prostaglandins of the "E" type[2] including crystalline *dl*-prostaglandin E_1 (PGE_1).[2]



$PGF_{1\beta}$



PGE_1

A communication[3] 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 solvolysis[3] 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 Simonovitch[4] gave good yields of a mixture of *vic*-glycols[5] (**3** from **1** and **4** from **2**) of unrearranged carbon skeleton. In neither case was unequivocal evidence found for the presence of *dl*-PGE_1 or *dl*-8-*iso*-PGE_1[6] 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 three-membered 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–threo* 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 PGE_1 when treated with base, and exhibited greater than 50% of the activity of natural PGE_1 methyl ester in the biological assays.[9] Approximately an equal

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

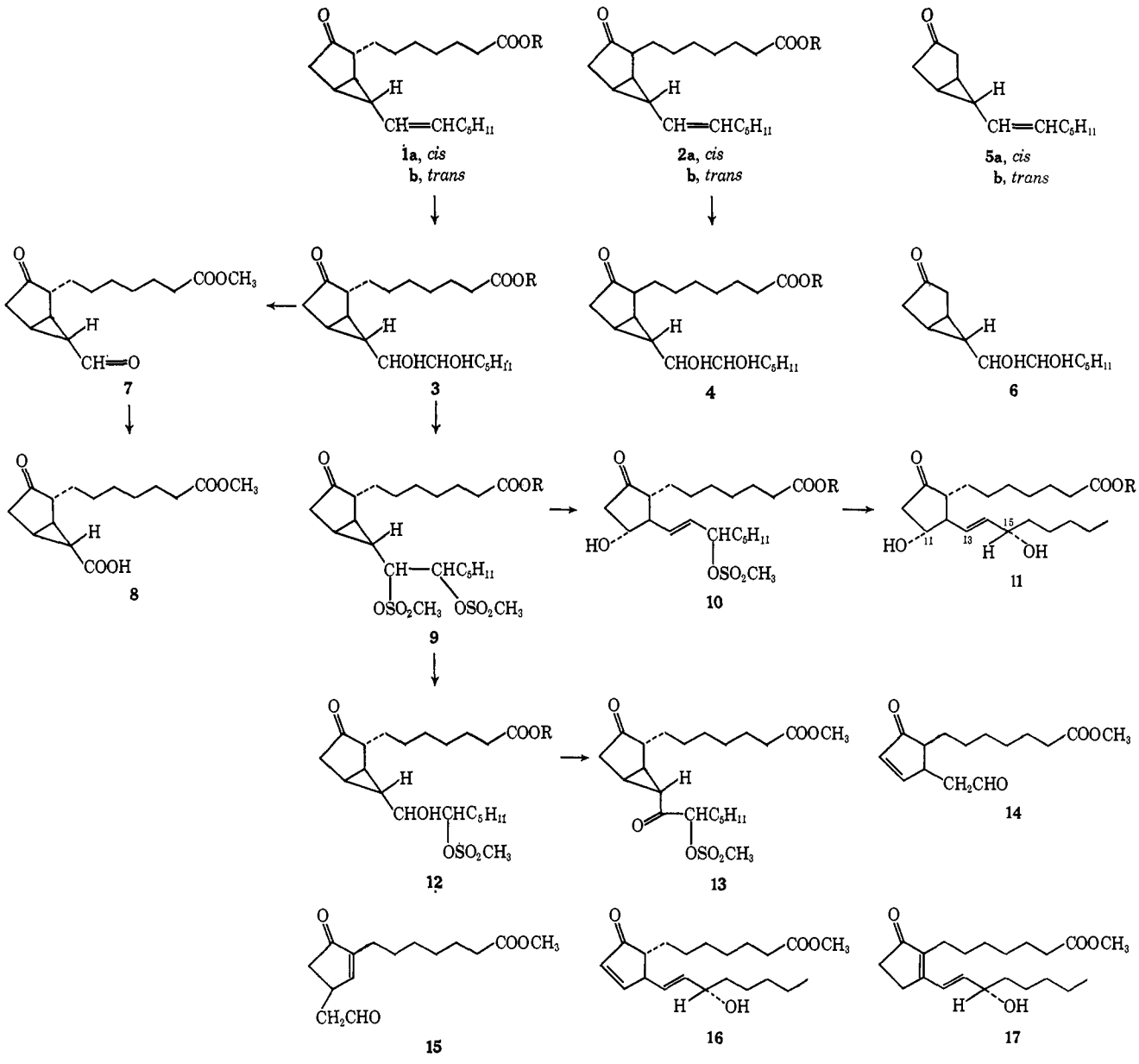


Figure 1.

amount of noncrystalline *dl*-15-*i*-PGE_1 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*-PGE_1 methyl ester in 5% yield.

Johnson[12] has recently used cyclopropylcarbinyl systems to produce stereoselectively *trans* olefins, and has rationalized the stereoselectivity on the basis of a concerted 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 *threo* 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*-PGE_1 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,

(10) J. E. Pike, F. H. Lincoln, and W. P. Schneider (*J. Org. Chem.*, in press) describes the preparation and characterization of 15(*R*)-PGE_1 made by epimerization of 15(*S*)-PGE_1 in formic acid.

(11) The use of the term "15-*i*-" is meant to designate the configuration at C_{15} opposite to that of natural PGE_1. 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).

(13) We are at present unable to make definite assignments of stereochemistry for glycols **3** and **4**, beyond the *erythro* or *threo* designation

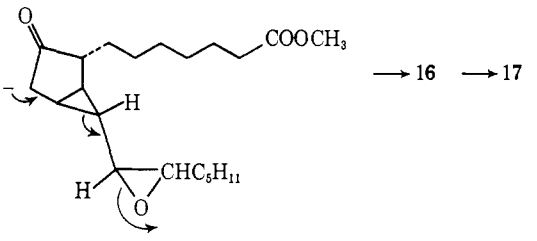
solvolysis of the cyclopropylcarbinyl mesylate does not take place by a completely concerted mechanism.

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*-PGE_1 trichloroethyl ester was obtained in 4% over-all yield. This was treated briefly with zinc in acetic acid[14] to remove the trichloroethyl group, giving *dl*-PGE_1, 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*-PGE_1 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*-PGE_1 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*-PGE_1. 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} α position. Since 8-*i*-PGE_1 can be isomerized to PGE_1 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 = CH_3). 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 bicarbonate, the main products (50% combined yields) were unsaturated ketones showing the same thin layer



→ **16** → **17**

18

chromatographic mobility on several systems as PGA_1 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 active[16] PGA-type compounds, rather than the PGB type, the end product of base-catalyzed isomerization.

Experimental Section[17]

6-*exo*-(*erythro*-1′,2′-Dihydroxyheptyl)-2α-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (3, R = CH_3). To a solution of 0.39 g of 6-*exo*-(*cis*-1′-heptenyl)-2α-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one[1] (**1a**, R = CH_3) 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 $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.46; H, 9.87.

The more polar isomer was also crystalline: ν = 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* isomer[1] **1b**, R = CH_3, 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 tlc 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).

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

(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 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)-2β-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (4, R = CH_3). In the same manner as above, 0.50 g of **2a** (R = 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 = CH_3): mp 42° from ether, Skellysolve B; R_f 0.40 on silica gel, developed with ethyl acetate.

Anal. Calcd for $C_{21}H_{36}O_5$: 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_f 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 (OCH_3), four-proton multiplet, δ 3.4–2.9 (carbinolic and hydroxylic protons), and the 6-*endo*-cyclopropyl hydrogen at δ 0.48.

6-*exo*-(*threo*-1′,2′-Dihydroxyheptyl)-2β-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (4, R = CH_3). 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 *threo* isomer and 129 mg (23%) of the more polar *threo* isomer of structure **4** (R = CH_3). 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 $C_{21}H_{36}O_5$: 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_f 0.23.

Anal. Found: C, 68.58; H, 10.11.

Thin layer chromatography of the four glycols of structure **4** (R = CH_3) on silica gel plates sprayed with 10% boric acid in methanol and dried 30 min at 70° gave the following R_f 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)-2β-(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 6-*exo*-(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 $NaHCO_3$, and 0.18 ml of 90% H_2O_2 which had been cooled to 0° and purged with N_2. 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 (~0 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, R_f 0.62 on silica gel plates developed with A-IX system,[18] but on a boric acid treated plate[7] 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 (OCH_3), 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 δ 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 − $2H_2O$), 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 PGE_1 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-one[1] 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 3-alcohols 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 reagent[19] 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: ν 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 $O-CH_3$ absorption. A small portion, esterified with ethereal diazomethane and compared on tlc (silica gel, 10% ethyl acetate–cyclohexane, 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 μl 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% methanol–ethyl 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 PGE_1 was seen in tlc's of these later fractions.

6-*exo*-Formyl-2α-(6′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (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 = CH_3), 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 OCH_3), 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_f *ca.* 0 on the same tlc system as above, methyl ester R_f 0.65), mp 106–107° after recrystallization from ethyl acetate–Skellysolve B.

Anal. Calcd for $C_{15}H_{22}O_5$: 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 OCH_3 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 tlc 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 min. The products were extracted with ether which was washed, 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 obtained[1] 6-*exo*-hydroxymethylbicyclo[3.1.0]-hexan-3α- and -β-ols.

B. 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, ν 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 2α-hydrogen at 2.69 (J = 21, 6, 2.5 cps), the 2β-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 E_1 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 E_1 methyl ester.

Fraction B, the two monomesylates, was characterized as follows: prominent ions in the mass spectrum at 350 (M − CH_3SO_2H), 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 (OCH_3), one proton as a doublet of doublets at 3.41 (J = 7.5 and 3.5 cps), a three-proton singlet at 3.1 (SCH_3), and the 6-*endo*-cyclopropyl hydrogen as a multiplet, δ 0.61 (J = 8 and 4 cps)

Fraction C, *dl*-15-isoprostaglandin E_1 methyl ester, had infrared and nmr spectra identical with those of the optically active 15(*R*)-PGE_1 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 behavior[17] were identical with those of natural PGE_1 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*-PGE_1 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*-PGE_1 methyl ester and 5.5% of its 15-epimer.

D. The less polar *threo*-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*-PGE_1 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 reagent[19] 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 (OCH_3) and a three-proton singlet at 3.15 (SCH_3); 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_3).** 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–Skellysolve 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 = CH_3.

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 tlc slightly faster than the methyl ester of 15-*i*-PGE_1, and undoubtedly consists of its corresponding trichloroethyl ester.

No. 43–47, 12 mg, moved slightly faster on tlc than the methyl ester of PGE_1 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 PGE_1.

In the same manner as above, 200 mg of the less polar *erythro–threo* 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*-PGE_1, identical with that above.

***dl*-Prostaglandin E_1.** 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 tlc 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 CC_4) 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 tlc[18] like PGE_1, 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 PGE_1. Biological activity was greater than 50% of natural PGE_1 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*-PGE_1 trichloroethyl ester fractions (*ca.* 6 mg) were hydrolyzed with zinc and acetic acid. In this way a further 2 mg of *dl*-PGE_1, mp 113–115°, was obtained, making the total yield of pure *dl*-PGE_1 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 acetate–cyclohexane were as follows: more polar *erythro-* and *threo*-bismesylates, R_f 0.47; less polar *erythro-* and *threo*-bismesylates, R_f 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), three-proton singlets at δ 3.65 and six-proton singlet at δ 3.1 (OCH_3 and SCH_3), 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.

The crude bismesylate from the more polar *erythro*-glycol was solvolyzed at 25° in 40 ml of acetone and 20 ml of water for 5 hr. After the usual work-up, the crude products were chromatographed on 60 g of silica gel, eluting with 10–100% ethyl acetate in cyclohexane. The following materials were eluted, in order of their polarity: A, 96 mg of a less polar monomesylate of glycol **4** (R = CH_3); B, 341 mg of an incompletely separated mixture of a more polar monomesylate of glycol **4**, R = CH_3, and *dl*-15-*i*-8-*i*-PGE_1 methyl ester; C, 50 mg (10% yield) of *dl*-8-*i*-PGE_1 methyl ester; D, 10 mg of *dl*-PGE_1 methyl ester. These were characterized as follows. A exhibited ν 3400, 1745, 1175, and 920 cm^{-1}; λ_{max}^{EtOH} 220 mn (ε 3,000), indicating some contamination by PGA_1-type compounds.

B. This monomesylate, contaminated (by tlc evidence) with *dl*-15-*i*-8-*i*-PGE_1 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 SCH_3 group.

Anal. Calcd for $C_{22}H_{38}O_7S$: 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*-PGE_1 methyl ester[6] and gave λ_{max}^{EtOH} 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 material[6] showing a broad multiplet, δ 5.0–5.8, for the C_{13},C_{14} 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**, R = CH_3, on solvolysis as above gave 5.4% yield of *dl*-8-*i*-PGE_1 methyl ester. From the more polar *threo*-glycol **4**, R = 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*-PGE_1 methyl ester. In each case 1–2% *dl*-PGE_1 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 (OCH_3 and SCH_3).

8-Isoprostaglandin E_1. 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 $NaHCO_3$ 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** (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 (H_{13} at δ 5.28, J = 15 and 9.5 cps, and H_{14} 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 E_1, 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–Skellysolve 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 A_1 and *dl*-Prostaglandin B_1 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*-PGA_1 and *dl*-PGB_1 methyl esters. These were not well separated by the column, but the early fractions of the main peak, 14 mg, consisted of pure *dl*-PGA_1 methyl ester, λ_{max}^{EtOH} 221 nm (ϵ 11,000), and identical mobility on several tlc systems[18] to natural material. The remainder of the material of the main peak, 56 mg (λ_{max} 219 (ϵ 7530), 278 nm (10,150), was a mixture consisting of 65% *dl*-PGA_1 methyl ester and 35% *dl*-PGB_1 methyl ester.

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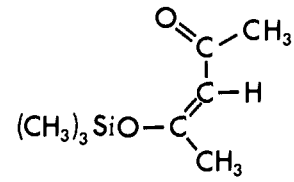
Communications to the Editor

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 open-chain enol ether structure in which the uncoordinated or "dangling" oxygen is ketonic. Such a structure has been assigned for trimethylsilicon acetylacetonate, $(CH_3)_3Si(acac)$.[3,4] In addition, the occurrence of isomers I and II has been claimed based on the coincidence 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.



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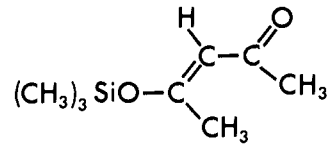

II

$(CH_3)_3Si(acac)$ 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).
(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.
(4) R. West, *J. Amer. Chem. Soc.*, 80, 3246 (1958).