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(21) Melting points were taken on a micro-hot-stage apparatus and are uncorrected. Infrared (IR) spectra were run on a Beckman IR 9 infrared Spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 360 spectrometer at 60 MHz using tetramethylsilane as an internal standard. Abbreviations used: s = singlet, d = doublet, t = triplet, m = multiplet. Analyses were performed by Spang Microanalytical Laboratories.

Prostaglandins and Congeners. 21.[1] Synthesis of Some Cyclohexyl Analogues (11a-Homoprostaglandins)

M. Brawner Floyd* and Martin J. Weiss

Metabolic Disease Research Section, Lederle Laboratories, American Cyanamid Company, Pearl River, New York 10965

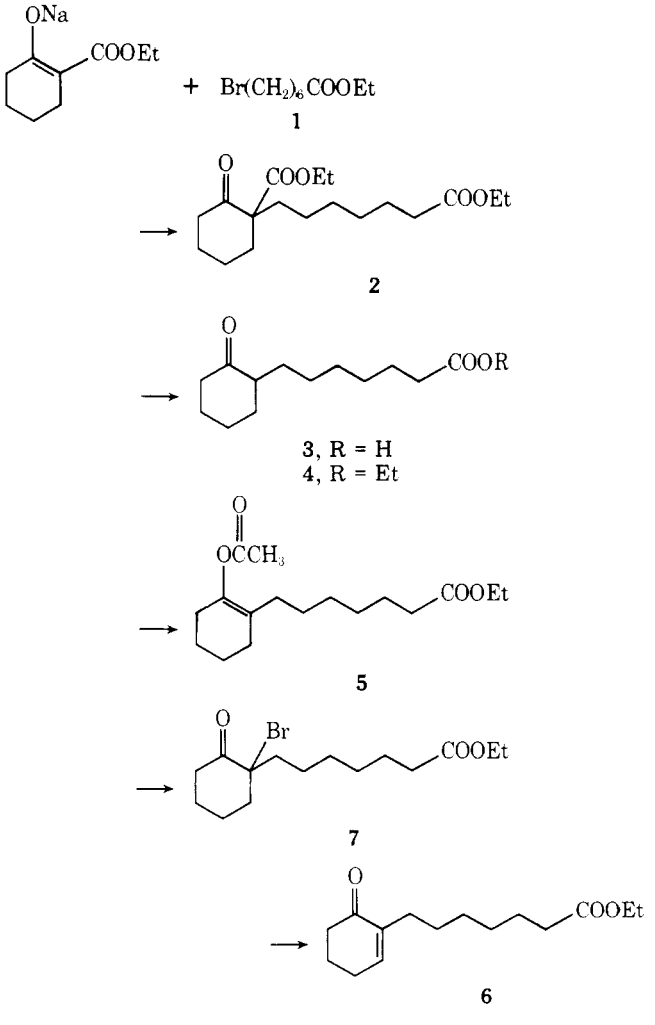
Received August 10, 1978

Several six-membered ring analogues of prostaglandin E_1 have been prepared. The compounds were all synthesized via conjugate addition of organometallic reagents to cyclohexenone **6**. A cyclohexenone analogue (**28**) of PGA_1 was prepared by a high-yield multistep net dehydrogenation of a cyclohexanone precursor (**18**). The PGA_1 analogue **28** was partially hydrated to the PGE_1 analogue **30** in aqueous base.

As part of an ongoing prostaglandin analogue synthesis program we wish to report the preparation of certain 11a-homoprostaglandins wherein the cyclopentanone ring has been replaced by the cyclohexanone ring.[2] Of particular interest was the preparation of 11a-homo-PGA_1, since this compound would not be expected to undergo the facile enzymatic or physiological medium-mediated biologically inactivating isomerization presumably characteristic of the PGA series. Thus the 11a-homo series provides a good approach to "frozen PGA" compounds.[3]

The synthetic scheme regularly utilized in our laboratories for prostaglandin synthesis is based upon the conjugate addition of a lithium 1-alkenylalanate[4] or lithium 1-alkenylcuprate reagent to an appropriate cyclopentenone. Accordingly, our first synthetic goal in the present study was the preparation of cyclohexenone **6**. All of the prostaglandin congeners reported herein are derived from this intermediate, which was prepared as follows.

The sodium enolate of commercially available 2-carbethoxycyclohexanone was alkylated with bromo ester **1** in DMF at 50 °C to give crude product **2**, which underwent hydrolysis, decarboxylation, and reesterification to ester **4** in ca. 50% overall yield. For the introduction of the required unsaturation the general method of Bedoukian,[5] which entails bromination of an enol acetate, was used to regiospecifically place bromine in the 2 position of the cyclohexanone ring. Other studies have shown that enolacetylation of 2-substituted cyclohexanones under equilibrating conditions results in predominant formation of the more substituted olefinic product.[6] Thus, reaction of **4** with refluxing acetic anhydride in the presence of PTSA with removal of acetic acid by distillation gave in 93% yield the desired enol acetate **5**, which on treatment with bromine in HOAc–pyridine[7] afforded crude bromo ketone **7**. The final step, dehydrobromination to the required cyclohexenone **6**, was accomplished with lithium bromide–lithium carbonate in hot DMF (82% overall yield from **5**).[8]



For the preparation of 11,15-dideoxyprostaglandins, of interest as specific prostaglandin antagonists,[9] the conjugate addition of lithium trialkyl-*trans*-1-alkenylalanates to cyclopentenones has been a particularly useful procedure.[10] Reaction of alanates **8** and **9** with cyclohexenone **6** by this method gave the desired conjugate addition products **10** and **11**, which were saponified to the corresponding acids **12** and **13**.

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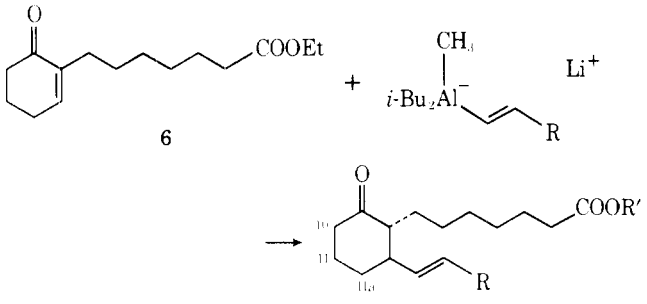
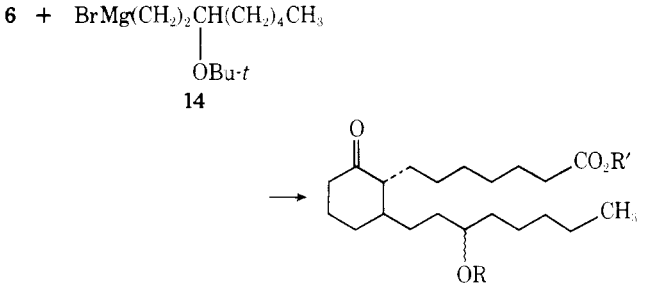


6

8, R = n-C_6H_{13}
9, R = n-C_3H_7
10, R = C_6H_{13}; R′ = Et
11, R = C_3H_7; R′ = Et
12, R = C_6H_{13}; R′ = H
13, R = C_3H_7; R′ = H

The 11-deoxy-13,14-dihydro derivative **16** was prepared via conjugate addition of Grignard reagent **14**[11] to cyclohexenone **6** in the presence of a catalytic amount of tri-n-butylphosphine–cuprous iodide complex. The blocked addition product **15,** obtained in only 14.5% yield, was deblocked in 71% overall

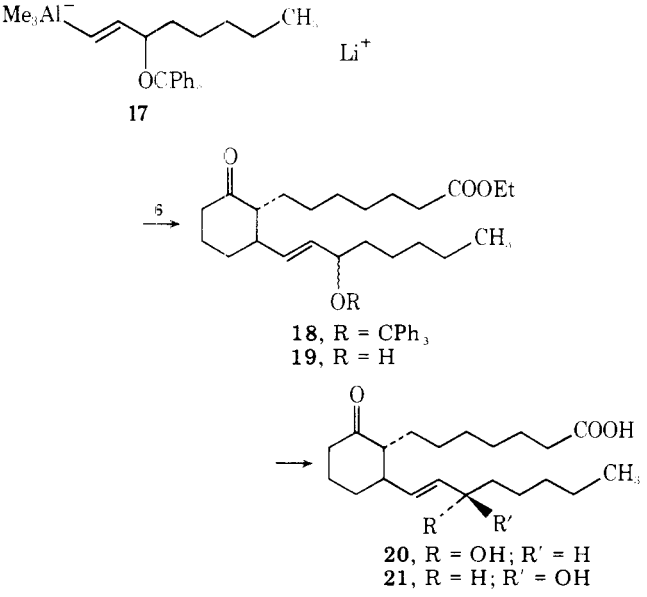


14

15, R = t-Bu; R′ = Et
16, R = R′ = H

yield by treatment with cold trifluoroacetic acid to remove the *tert*-butyl group, followed by saponification of the resulting crude product, which contained some 15-*O*-trifluoroacetyl ester. The 15-epimeric isomers were not separable chromatographically, as is usually the case with 13,14-dihydroprostaglandins.

Treatment of **6** with functionalized alanate reagent **17**[4] gave the conjugate addition product **18** in 35% yield. Detritylation with dilute acetic acid in tetrahydrofuran–water provided a separable mixture of the 15-epimeric esters **19,** which were saponified to the 11-deoxy-11a-homo analogues **20** and **21** of PGE_1 and its 15-epimer, respectively.



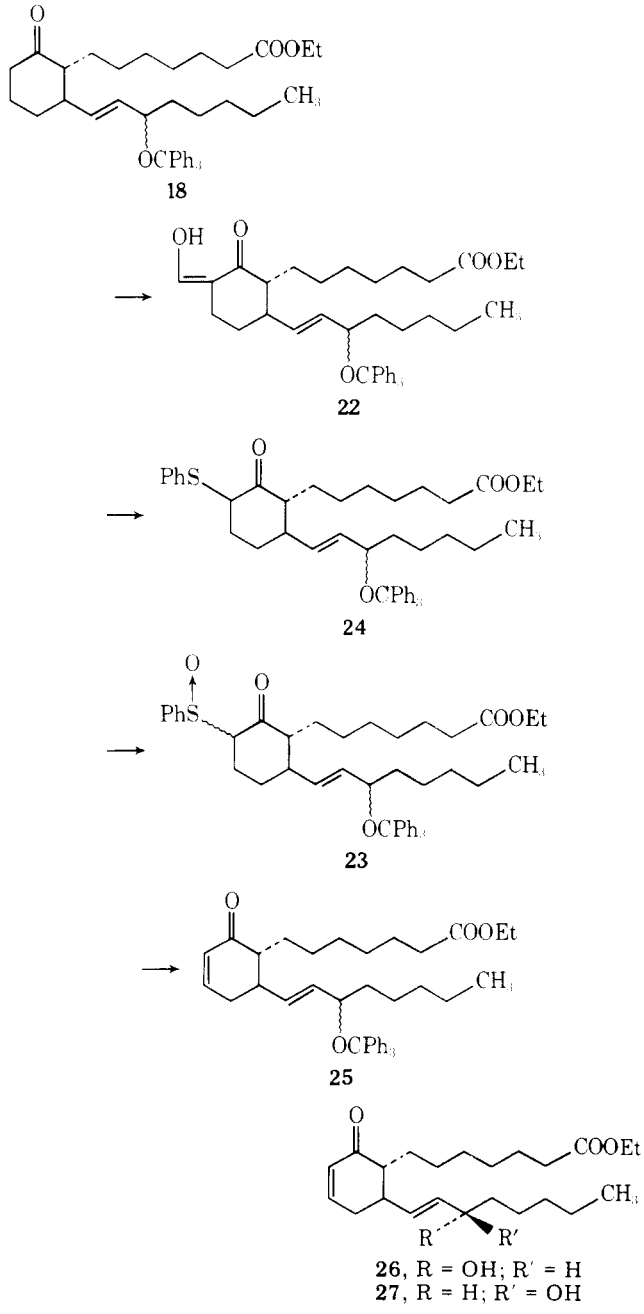
17

18, R = CPh_3
19, R = H

20, R = OH; R′ = H
21, R = H; R′ = OH

For the synthesis of the fully elaborated 11α-hydroxy-11a-homo congener **30,** an attractive approach involved hydration of the Δ^{10} analogue **26,** also of interest per se as an example of a "frozen PGA". In principle this approach had a reasonable chance of success since, in contrast to the cyclopentenones, cyclohexenones generally are capable of at least partial hydration at equilibrium in aqueous solution.[12]

Treatment of **18** with ethyl formate in the presence of sodium hydride gave the hydroxymethylene derivative **22** in high yield.[13] Reaction of the sodium enolate of **22** with benzenesulfenyl chloride in benzene solution followed by deformylation with ca. 0.01 N sodium ethoxide in EtOH at room temperature afforded the crude thioether **24,** also in high yield. After oxidation to sulfoxide **23** with a cold solution of *m*-chloroperoxybenzoic acid in chloroform,[14] thermal elimination of benzenesulfenic acid[15] (refluxing in benzene for 3 h) provided the desired Δ^{10}-derivative **25.** Detritylation then gave a separable mixture of the 15-epimeric (approximately equal amounts) esters **26** and **27** in 80% overall yield from **18.**[16]



18

22

24

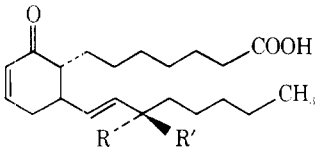
23

25

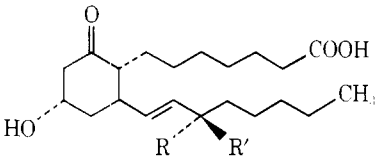
26, R = OH; R′ = H
27, R = H; R′ = OH

As anticipated, saponification and partial hydration of **26** with aqueous base furnished a 7:1 mixture of *dl*-11a-homo-

prostaglandin A_1 (**28**) and *dl*-11a-homoprostaglandin E_1 (**30**), which were separated chromatographically. Similarly, saponification of **27** gave the corresponding 15-epimers **29** and **31**.



28, R = OH; R′ = H
29, R = H; R′ = OH



30, R = OH; R′ = H
31, R = H; R′ = OH

The 11α-hydroxy configuration (equatorial) in **30** and **31** is supported by ^{1}H NMR analysis and is expected on steric grounds. The configuration at C-15 has not been proven and the assignments are based on relative chromatographic mobility with reference to natural prostaglandins (15-*epi*-PGE_1 more mobile than PGE_1) in all cases in this work.

The various 11a-homo analogues described in this paper were found to be less effective than the corresponding natural (five-membered ring) counterparts when tested for bronchodilator activity in the guinea pig[17] and for hypotensive activity by intravenous administration to the normotensive rat.

Experimental Section

General. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Boiling points are uncorrected. Dry column chromatography was carried out with Woelm Act. III silica gel, especially prepared for this purpose (ICN Pharmaceuticals, Inc.), loaded into Nylon tubing (Kontes Glass Co.). The columns were segmented, and fractions were eluted and combined after determination of zones by TLC. Proton magnetic resonance spectra (^{1}H NMR) were determined on a Varian HA-100 spectrometer. Chemical shifts (δ) refers to ppm downfield from internal Me_4Si. All reactions were conducted under nitrogen.

Ethyl (Methyl) 1-(6-Carbethoxyhexyl)-2-oxocyclohexanecarboxylate (2). To a stirred suspension of 51 g of sodium hydride (57% in mineral oil, 1.21 mol) in 675 mL of DMF was added 200 g of 2-cyclohexanonecarboxylate (60% ethyl, 40% methyl esters) during 1.5 h while maintaining a temperature of 25 °C. The mixture was stirred for 15 min, warmed to 50 °C, and treated with 300 g (1.27 mol) of ethyl 7-bromoheptanoate during 10 min. The mixture was stirred at 50–60 °C for 4 h, cooled, poured into water, and extracted with ether. The extract was washed with water and brine, dried, and evaporated.

A portion of the crude product was distilled to give a liquid: bp 151–155 °C (0.03 mm); IR (film) 5.76 and 5.85 μm.

Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 65.99; H, 9.06.

2-(6-Carbethoxyhexyl)cyclohexanone (4). A stirred mixture of 400 g of crude **2**, 202 mL of concentrated H_2SO_4, 971 mL of glacial HOAc, and 970 mL of water was refluxed for 22.5 h. The cooled mixture was treated with 380 g of sodium carbonate and 2 L of water and extracted with ether. The extract was washed with water and 2 × 1000 mL of 1.0 M Na_2CO_3. The alkaline extract was cautiously acidified with concentrated HCl and extracted with ether. The extract of acidic material was washed with water and brine and concentrated to give 232 g of viscous oil.

The crude **3** was dissolved in 2.5 L of ethanol with 3.8 g of *p*-toluenesulfonic acid monohydrate, and the solution was refluxed for 4.5 h. Benzene (200 mL) was added and heating was continued for 2 h while removing 200 mL of distillate. The solution was concentrated, diluted with ether, and washed successively with dilute $NaHCO_3$ and brine. After drying over magnesium sulfate the extract was concentrated and distilled to give 157 g (51% overall from 2-cyclohexanonecarboxylate ester) of colorless liquid: bp 123–126 °C (0.03 mm); IR (film) 5.75 and 5.84 μm.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.44; H, 10.34.

1-Acetoxy-2-(6-carbethoxyhexyl)cyclohex-1-ene (5). A stirred solution of 28.0 g of **4**, 170 mg of *p*-toluenesulfonic acid monohydrate, and 25.6 g of acetic anhdride was heated for 5 h while allowing 8 g of distillate, bp ≤ 118 °C, to escape from the mixture. The cooled solution was poured into a stirred, ice-cold mixture of 500 mL of saturated $NaHCO_3$ and 250 mL of hexane. After 1 h the hexane phase was separated, dried over magnesium sulfate, and concentrated. The product was distilled to give 30.3 g (93%) of colorless liquid: bp 130–135 °C (0.01 mm); IR (film) 5.68 and 5.75 μm.

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 67.94; H, 9.40.

2-(6-Carbethoxyhexyl)cyclohex-2-en-1-one (6). To a stirred solution of 24.3 g of enol acetate **5** in 750 mL of glacial HOAc and 125 mL of pyridine at 10 °C was added a solution of 13.8 g of bromine in 200 mL of glacial HOAc during 20 min. The resulting solution was allowed to stand at room temperature for 45 min and was then treated with sodium sulfite. The solution was diluted with brine and extracted with 1:1 hexane–ether. The extract was washed with water and brine, dried over potassium carbonate, and concentrated to give 32 g of crude bromo ketone **7**.

A stirred suspension of 17.2 g of lithium bromide monohydrate and 16.6 g of lithium carbonate in 200 mL of DMF was made anhydrous by boiling with benzene. After benzene had distilled, to the stirred suspension at 80 °C was added a solution of the above **7** in 50 mL of DMF in one portion. The stirred mixture was heated to reflux during 20 min and at reflux for 15 min, cooled, poured into 1.5 L of 0.3 N HCl, and extracted with ether. The extract was washed with water and brine, dried over magnesium sulfate, and concentrated. Distillation of the residue gave 17.1 g (82%) of colorless liquid: bp 117–121 °C (0.03 mm); ^{1}H NMR (CCl_4) δ 6.63 (m, vinyl-**H**); UV (MEOH) λ_{max} 236 nm (9050).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.04; H, 9.56.

Ethyl 9-Oxo-11a-homo-13-*trans*-prostenoate (10). To a stirred solution containing 72 mmol of diisobutyl-*trans*-1-octenylalane[10] in 15 mL of benzene and 35 mL of ether at 0 °C was added 41 mL of 1.6 M methyllithium in ether. The resulting solution of alanate **8** was stirred at ambient temperature for 20 min, recooled to 0 °C, and treated with a solution of 15.3 g (60 mmol) of **6** in 15 mL of ether during a 5-min period. The resulting mixture was stirred at 0 °C for 30 min and at 25 °C for 21 h. The resulting clear solution was diluted with ether and poured into a stirred mixture of ice and hydrochloric acid. The ether layer was washed with dilute hydrochloric acid and brine, dried over magnesium sulfate, and concentrated. Chromatography of the residue on silica gel with chloroform progressively enriched in ether gave 5.8 g (26%) of **10** as an oil: ^{1}H NMR ($CDCl_3$) δ 4.08 (2, q, CH_2O) and 5.31 (2, m, CH=CH).

Anal. Calcd for $C_{23}H_{40}O_3$: C, 75.78; H, 11.06. Found: C, 75.58; H, 10.98.

9-Oxo-11a-homo-13-*trans*-prostenoic Acid (12). A solution of 3.65 g (10 mmol) of ester **10** and 1.98 g of 85% potassium hydroxide in 65 mL of 10:1 methanol–water was allowed to stand at 25 °C for 22 h. The solution was acidified with hydrochloric acid and worked up with ether to give the crude acid. Chromatography on silica gel with benzene progressively enriched in ether gave 2.98 g (87%) of **12** as an oil: IR (film) 5.83 and 10.35 μm.

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.36; H, 10.91.

Ethyl 9-Oxo-11a-homo-18,19,20-trinor-13-*trans*-prostenoate (11). The alanate reagent **9** was prepared from 120 mmol of diisobutyl-*trans*-1-pentenylalane and reacted with 25.2 g (100 mmol) of **6** as described above for the preparation of **10**. The crude product was distilled to provide 9.67 g (30%) of colorless liquid: bp 143–147 °C (5 × 10^{-3} mm).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.44; H, 10.50.

9-Oxo-11a-homo-18,19,20-trinor-13-*trans*-prostenoic Acid (13). A solution of 4.84 g (15 mmol) of the ester **11** was saponified as described above for **10** to give 4.37 g (98%) of the acid **13** as an oil: MS 294.2195 (calcd for $C_{18}H_{30}O_3$, 294.2195).

Ethyl 9-Oxo-11a-homo-15ξ-*tert*-butoxyprostanoate (15). To a stirred solution of 200 mL of ca. 1 M 3-*tert*-butoxy-1-octyl magnesium bromide[11] in ether at 5 °C was added 3.82 g of tri-*n*-butylphosphine–Cu^II[18] followed by 60.8 g of cyclohexenone **6** during 25 min. After 1 h the cold mixture was quenched with 100 mL of saturated

ammonium chloride. The aqueous phase was extracted with additional ether and the combined ether phase was washed with brine, dried over magnesium sulfate, and concentrated. Most of the residual **6** and other volatile material was removed by short-path distillation. The residue was chromatographed on silica gel with benzene progressively enriched in ether to give 12.3 g (14.5%) of oil: IR (film) 5.73, 5.83, and 7.34 μm.

Anal. Calcd for $C_{27}H_{50}O_4$: C, 73.92; H, 11.49. Found: C, 73.69; H, 11.21.

9-Oxo-11a-homo-15ξ-hydroxyprostanoic Acid (16). A stirred, ice-cold sample of **15** (11.0 g) was treated with 50 mL of cold trifluoroacetic acid, and the resulting solution was stirred at 0 °C for 1 h. After evaporation in the presence of added chloroform, the residue was partitioned with 1:1 hexane–ether and water. The organic phase was concentrated, and the resulting oil was treated with a solution of 9.25 g of potassium hydroxide in 300 mL of 10:1 methanol–water. After standing at room temperature for 21 h the bulk of the methanol was evaporated, and the mixture was partitioned with ether and water. The aqueous phase was acidified with 40 mL of 4 N HCl and extracted with ether. The extract was diluted with hexane, washed with water and brine, and dried over magnesium sulfate. The residue obtained after solvent removal was chromatographed on silica gel with benzene progressively enriched in ether to give an oil: ^{1}H NMR ($CDCl_3$) δ 3.60 (m, C**H**OH).

Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.15; H, 10.80. Found: C, 71.03; H, 10.66.

Ethyl 9-Oxo-15ξ-trityloxy-11a-homo-13-*trans*-prostenoate (18). To a stirred solution of 32.3 g (62.5 mmol) of 96% pure 1-iodo-3-trityloxy-*trans*-1-octene[4] in 35 mL of toluene was added 32.5 mL (61.8 mmol) of 1.9 M *n*-butyllithium in hexane during 20 min at ca −65 °C. The resulting solution was stirred at −40 °C for 1 h and then treated during 10 min with 42 mL (61 mmol) of 1.446 M trimethylaluminum in hexane at −40 to −30 °C. The stirred solution was allowed to warm to 10 °C during 20 min, was recooled to 0 °C, and was treated during 30 min with a solution of 12.62 g of **6** (50 mmol) in 50 mL of ether. The resulting mixture was stirred at ambient temperature for 137 h,[19] diluted with ether, and poured into a stirred mixture of 750 g of ice and 25 mL of concentrated HCl. The organic phase was washed with water and brine and dried over magnesium sulfate. The residue obtained by evaporation of solvent was subjected to dry column chromatography on silica gel with benzene as developing solvent to afford **18** as a colorless oil in 35% yield: IR (film) 5.75, 5.83, and 10.65 μm; ^{1}H NMR (CCl_4) δ 3.74 (1, m, C**H**O).

Anal. Calcd for $C_{42}H_{54}O_4$: C, 80.99; H, 8.74. Found: C, 80.28; H, 8.69.

Ethyl 9-Oxo-15ξ-hydroxy-11a-homo-13-*trans*-prostenoate (19). A solution of 5.6 g (9.0 mmol) of **18** in 180 mL of 4:2:1 HOAc–THF–H_2O was heated under nitrogen for 4 h at 45 °C. The solvents were removed at reduced pressure. The resulting mixture was slurried with 100 mL of 20:1 petroleum ether–EtOAc and the mixture was cooled and filtered to remove triphenylcarbinol. The filtrate was concentrated and the residue was subjected to dry column chromatography on silica gel with 5:1 benzene–EtOAc as developing solvent. In this way the following components were separated:

The more polar component, ethyl 9-oxo-15-hydroxy-11a-homo-13-*trans*-prostenoate, was isolated as an oil: 995 mg; IR (film) 5.75, 5.84, and 10.33 μm.

The less polar component, ethyl 9-oxo-15-*epi*-hydroxy-11a-homo-13-*trans*-prostenoate, was isolated as an oil: 641 mg; IR (film) 5.75, 5.84, and 10.33 μm.

9-Oxo-15-hydroxy-11a-homo-13-*trans*-prostenoic Acid (20). To a stirred solution of 780 mg (2.05 mmol) of **19** (polar isomer) in 12 mL of 10:1 methanol–water was added 345 mg of potassium hydroxide. After solution was complete the solution was allowed to stand under nitrogen for 28 h at room temperature. The solution was diluted with 35 mL of water and extracted with ether. The aqueous phase was acidified with 2.0 mL of 4 N HCl, saturated with NaCl, and extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and evaporated to give 700 mg of crystalline product, mp 94–97 °C, after recrystallization from 1:1 ether–petroleum ether: IR (KBr) 5.78, 5.92, and 10.28 μm; ^{1}H NMR (acetone-d_6) δ 5.50 (2, m, C**H**=C**H**) and 4.04 (1, m, C**H**O).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.44; H, 10.39.

9-Oxo-15-*epi*-hydroxy-11a-homo-13-*trans*-prostenoic Acid (21). From 630 mg of **19** (mobile isomer) was obtained 446 mg of acid **21** as an oil after saponification as above and dry column chromatography with the system 4:1 benzene–ethyl acetate. The following are the R_f values for the system 60:40:2 heptane–EtOAc–HOAc on silica gel TLC: **20**, 0.39 and **21**, 0.48.

Ethyl 10-Hydroxymethylene-9-oxo-15ξ-trityloxy-11a-homo-13-*trans*-prostenoate (22). To a stirred suspension of sodium hydride (prepared by washing 195 mg of 57% dispersion with petroleum ether) in 3 mL of ethyl formate was added a solution of 721 mg (1.16 mmol) of **18** in 5 mL of glyme. Hydrogen gas evolved, and after 75 min the solution was poured into 10 mL of half-saturated aqueous ammonium chloride. The mixture was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and evaporated. The residual oil was used for the transformation to **23** without further purification. A portion of the residue was purified by preparative TLC to provide a viscous oil: UV (MeOH) λ_{max} 205 (16 500) and 300 nm (5200), (dilute KOH in MeOH) λ_{max} 205 (20 300) and 317 nm (15 000).

Ethyl 10-Phenylthio-9-oxo-15ξ-trityloxy-11a-homo-13-*trans*-prostenoate (24). To a stirred suspension of sodium hydride (prepared by washing 371 mg of 57% dispersion with petroleum ether) in 32 mL of benzene was added a solution of 5.27 g (maximum of 7.88 mmol) of crude **22** in 80 mL of benzene. Reaction was initiated by the addition of a trace of ethanol.

After 1 h at room temperature the stirred solution of the sodium salt was treated during 2 min with a solution of 1.25 g (8.67 mmol) of benzenesulfenyl chloride[20] in 8 mL of benzene. After 10 min the mixture was treated with sodium bicarbonate solution and diluted with ether. The organic phase was separated and washed successively with water and brine, dried over magnesium sulfate, and concentrated to give a mixture of the title compound and its 10-formyl derivative.

Deformylation was completed by dissolving the mixture in 75 mL of ethanol and treating the solution with 10 mL of 0.1 N sodium ethoxide in ethanol. After 4 h at room temperature the solution was treated with 90 mL (1.5 mmol) of HOAc, filtered, and evaporated with the aid of toluene to give 6.50 g of viscous amber oil; IR (film) 5.79 and 5.87 μm.

Ethyl 10-Phenylsulfinyl-9-oxo-15ξ-trityloxy-11a-homo-13-*trans*-prostenoate (23). To a stirred, ice-cold solution of 6.50 g of crude **24** in 85 mL of chloroform was added a solution of 1.71 g (8.42 mmol) of 85% *m*-chloroperoxybenzoic acid in 50 mL of chloroform during 60 min. After stirring at 0 °C for 15 min the solution was treated with 50 mL of half-saturated aqueous sodium sulfite. After 5 min the mixture was diluted with chloroform; the organic phase was separated, washed successively with sodium bicarbonate solution and water, and dried over magnesium sulfate. Evaporation gave 6.41 g of light amber gum: IR (film) 5.81, 5.90, and 9.7 μm.

Ethyl 9-Oxo-15ξ-trityloxy-11a-homo-10,13-*trans*-prostadienoate (25). A stirred solution of 6.40 g (maximum of 7.85 mmol) of crude **23** in 160 mL of benzene was refluxed for 3 h. The solution was concentrated and the residue was slurried with 125 mL of 30:1 petroleum ether–ethyl acetate. The filtrate was concentrated to give an oil: IR (film) 5.83, 6.03, and 6.35 μm.

Ethyl 9-Oxo-15ξ-hydroxy-11a-homo-10,13-*trans*-prostadienoates (26 and 27). A solution of 6.35 g (maximum of 7.85 mmol) of crude **25** in 160 mL of 4:2:1 HOAc–THF–H_2O was heated at 45 °C for 8 h. The solvents were removed at reduced pressure with the aid of toluene to give a mixture of oil and crystalline triphenylcarbinol.

This residue was dissolved in 10 mL of 30:20:1 heptane–ethyl acetate–HOAc and subjected to dry column chromatographic separation on silica gel using the same solvent.

The more polar component (**26**) was obtained as an oil: 1.058 g; IR (film) 5.77, 5.98, and 10.32 μm.

The less polar component (**27**) was obtained as an oil: 1.047 g; IR (film) 5.77, 5.98, and 10.32 μm.

In addition a mixture of the two epimers was obtained from some fractions, 275 mg (total yield = 80% from **18**), analyzed as follows.

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 73.10; H, 9.89.

9-Oxo-15-hydroxy-11a-homo-10,13-*trans*-prostadienoic Acid (28) and 9-Oxo-11α,15-dihydroxy-11a-homo-13-*trans*-prostenoic Acid (30). To a stirred solution of 1.058 g (2.79 mmol) of **26** in 20 mL of methanol and 10 mL of water was added 470 mg (8.4 mmol) of potassium hydroxide. The resulting solution was allowed to stand at room temperature for 19 h. The methanol was evaporated from the mixture at reduced pressure and replaced with water to give an aqueous solution. After 4 h reaction at room temperature the solution was acidified with 2.5 mL of 4 N HCl, saturated with sodium chloride, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated.

The residue was dissolved in 3 mL of 100:1 ethyl acetate–HOAc and subjected to dry column chromatographic separation on silica gel using the same solvent.

The less polar component (0.74 g), 9-oxo-15-hydroxy-11a-homo-

10,13-*trans*-prostadienoic acid (**28**), was obtained as white crystals, mp 86–92 °C, after recrystallization from ether–petroleum ether: IR (KBr) 5.78, 6.03, and 10.23 μm; ^{1}H NMR ($CDCl_3$) δ 6.86. (1, m, 11-**H**), 5.97 (1, d, 10-**H**), 5.58 (2, m, 13-**H**), and 4.08 (1, m, C**H**O); UV (MeOH) λ_{max} 223 nm (7700).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.76; H, 9.93.

The more polar component (0.10 g), 9-oxo-11α,15-dihydroxy-11a-homo-13-*trans*-prostenoic acid (**30**), was obtained as white crystals, mp 77–81 °C, after recrystallization from ethyl acetate–petroleum ether; ^{1}H NMR (acetone-d_6) δ 5.50 (2, m, 13-**H** and 14-**H**), 4.37 (1, m, 11β-**H**), and 4.06 (1, m, 15-**H**).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.45; H, 9.85. Found: C, 68.85; H, 9.94.

9-Oxo-15-*epi*-hydroxy-11a-homo-10,13-*trans*-prostadienoic Acid (29) and 9-Oxo-11α,15-*epi*-dihydroxy-11a-homo-13-*trans*-prostenoic Acid (31). From 0.83 g of **27** was obtained 523 mg of **29** and 84 mg of **31** after hydrolysis and chromatography as above. The following are the R_f values for the system 100:1 EtOAc–HOAc on silica gel TLC: **28**, 0.60; **29**, 0.63; **30**, 0.29; and **31**, 0.35.

Acknowledgments. The authors wish to express their gratitude to Mr. J. Nocera and Dr. P. Kohlbrenner for the preparation of some of the intermediates, to Messrs. W. Fulmor and G. Morton and staff for spectral data and interpretation, and to Mr. L. Brancone and staff for microanalytical data.

Registry No.—**1**, 29823-18-5; **2** methyl ester, 68184-84-9; **2** ethyl ester, 68184-85-0; **3**, 68184-86-1; **4**, 68184-87-2; **5**, 41432-44-4; **6**, 41301-80-8; **7**, 68184-88-3; **8**, 40964-30-5; **9**, 57756-57-7; **10**, 68224-66-8; **11**, 68224-67-9; **12**, 68184-89-4; **13**, 64122-53-8; **14** halide derivative, 68184-90-7; **15** isomer 1, 68184-91-8; **15** isomer 2, 68224-68-0; **16** isomer 1, 68295-61-4; **16** isomer 2, 68184-92-9; **17**, 55529-87-8; **18** isomer 1, 68224-69-1; **18** isomer 2, 68224-70-4; **19** isomer 1, 61557-46-8; **19** isomer 2, 61557-45-7; **20**, 61557-47-9; **21**, 61557-48-0; **22** isomer 1, 68224-71-5; **22** isomer 2, 68224-72-6; **23** isomer 1, 68224-73-7; **23** isomer 2, 68224-74-8; **24** isomer 1, 68224-75-9; **24** isomer 2, 68224-76-0; **25** isomer 1, 68224-77-1; **25** isomer 2, 68224-78-2; **26**, 61507-63-9; **27**, 61557-49-1; **28**, 61507-64-0; **29**, 61557-50-4; **30**, 61507-65-1; **31**, 61557-51-5; diisobutyl-*trans*-1-octenylalane, 40098-43-9; diisobutyl-*trans*-1-pentenylalane, 57716-76-4; 1-iodo-3-trityloxy-*trans*-1-octene, 52418-91-4; 1-lithio-3-trityloxy-*trans*-1-octene, 60950-73-4; trimethylaluminum, 75-24-1; benzenesulfenyl chloride, 931-59-9; methyl 2-cyclohexanonecarboxylate, 41302-34-5; ethyl 2-cyclohexanonecarboxylate, 1655-07-8.

References and Notes

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Stereochemistry of 14,22-Ethers Formed by Cyclization of Δ^7-22-Hydroxy Steroids[1]

D. John Aberhart and Eliahu Caspi*

The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Charles M. Weeks and William L. Duax*

Medical Foundation of Buffalo, Inc., Buffalo, New York 14203

Received July 12, 1978

The 14,22-ether **2c** produced by mild acid treatment of 3β-benzoyloxy-23,24-bisnor-5α-chol-7-en-22-ol (**1a**) is shown by X-ray crystallography to have the 8β(H),14β configuration.

In 1971, we reported the conversion of the Δ^7-22-hydroxy steroids **1a** or **1b** by very mild acid treatment into the corresponding 14β,22-ethers **2a** or **2b**, respectively.[2] Spectroscopic and chemical evidence fully supported structure **2**. The formation of **2** from **1** was postulated to proceed by an initial acid-catalyzed isomerization of the Δ^7 double bond to the $\Delta^{8(14)}$ position. This $\Delta^{8(14)}$ intermediate was then thought to undergo protonation at C-8 with capture of the resultant C-14 carbonium ion by the C-22 oxygen atom. The configuration at C-8 will naturally be determined by the stereochemistry of proton addition at this position. Although not specifically stated in our communication,[2] it had been assumed that the products had an 8β(H) configuration. Should the products have an 8α(H) configuration, ring B would have to assume a boat conformation. However, the formation of an 8β(H) product requires that the protonation at C-8 and capture of the C-14 carbonium ion occur on the same face of the double bond. Hence, by necessity the cyclization could not be a concerted process. An additional interpretive complication arose by recent observations on the backbone rearrangement of 17α(H)-$\Delta^{8(14)}$-sterols to 17β(H)-Δ^{14} products upon treatment with hydrogen chloride in chloroform.[3] The generality of the 17α(H) → 17β(H) rearrangement was confirmed with the use of 5α-ergosta-8(14),22-dien-3β-ol benzoate (**3**),[4] which, on

0022-3263/79/1944-0075$01.00/0