Geminal Prostanoids†

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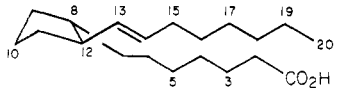
Received January 12, 1980

The synthesis and characterization of a new series of prostaglandin analogues is reported. These compounds are named "geminal" prostaglandins because both side chains are attached to the same ring carbon atom.

The "hairpin" conformation of prostaglandins (PG's) has been well documented for the solid state[1] and fairly well rationalized for aqueous solutions as well.[2] Importantly, the side chains prefer to be arranged more closely to the plane of the cyclopentane ring 1 than might be predicted



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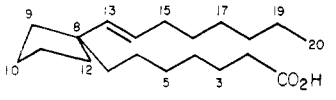

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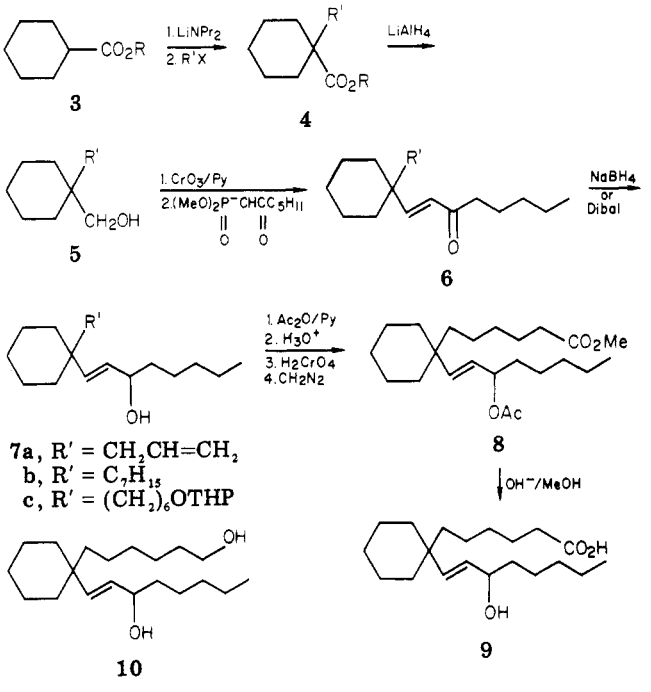
from simple steric interaction considerations. It occurred to us that another arrangement of the side chains on the cyclopentane ring existed which would maintain the trans relationship and perhaps not disturb the interchain atomic positions so much as to eliminate the biological activity. Such an arrangement would have the two chains on the same carbon atom of the ring in a geminal relationship as opposed to their being on adjacent ring carbons in a vicinal relationship. The resulting structure would perhaps look like **2**, in which the PG numbering is used as if the C-(13)–C(20) chain were moved from C-12 to C-8. The other possibility exists in which both chains are attached at C-12. Space-filling molecular models reveal significant similarities between the natural PG's and their geminal analogues.[3]

Our goal was to synthesize a wide variety of geminal PG analogues for testing in a variety of biological screens for PG-like activities. An analysis of the synthetic steps needed revealed three generalized problems: one, establishment of the side chains, or their synthons, at the potentially geminal carbon; two, arrangement of the ring carbons with proper functionality and, in fact, in a ring; three, unmasking and conversion of all synthons on the ring and the side chains to the proper PG functional groups.

From the beginning of our attempts we adopted the following strategy: one, form the ring with the ultimately desired functional groups protected and an activating group on the geminal carbon; two, attach one of the side chains at the geminal carbon as a synthon or with the functional groups protected; three, convert the activating group to the other side chain; four, remove the protective groups and perform other synthetic transformations to give the desired *gem*-PG. Although the aldehyde group was the first choice as the activating group because of the known[4] transformation into the 3-hydroxyoctenyl side chain and its analogues, practical considerations of stability and availability led to the choice of an ester as the best compromise.

Our first experiments were designed to demonstrate the feasibility of the basic synthetic approach, especially the

Scheme I

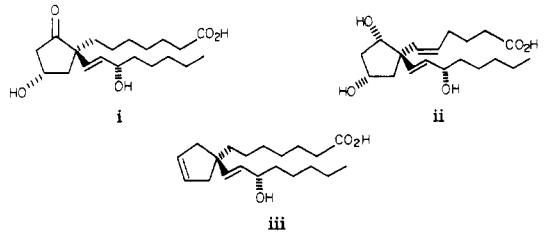


7a, R′ = $CH_2CH{=}CH_2$
b, R′ = C_7H_{15}
c, R′ = $(CH_2)_6OTHP$

possibility of converting a hindered carboxylic ester to a hindered aldehyde and then to an octenyl side chain. The actual sequence used is shown Scheme I. Initial alkylations were done on **3** with R = *tert*-butyl, because we wanted the extra reactivity control afforded by *tert*-butyl vs. lower alkyl groups (relatively resistant to reduction and base attack, easily cleaved by acid). However, subsequent

† Contribution no. 994.

(1) J. W. Edmonds and W. L. Duax, *J. Am. Chem. Soc.*, **97**, (1975).
(2) E. M. K. Leovey and N. H. Anderson, *J. Am. Chem. Soc.*, **97**, 4148 (1975).
(3) We propose the following nonsystematic nomenclature for these compounds. A structure is considered with the side chains extending to the right from the ring. The usual PG numbering is used with the carboxyl carbon numbered "1". Given a choice, the ring carbon to which both chains are attached (the "geminal carbon") is assigned as C-8, as in **2**. The positions of substituents on the ring and the side chains are numbered normally. For example, i is named 8-*gem*-PGE_1, ii is named 8-*gem*-PGF_2, and iii is named 9-deoxa-8-*gem*-PGA_1. With a full complement of substitution in the ring, the two possibilities would be enantiomeric for PGF analogues, and 8-*gem*-PGE would be enantiomeric with 12-*gem*-PGD.



i ii iii

(4) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971).

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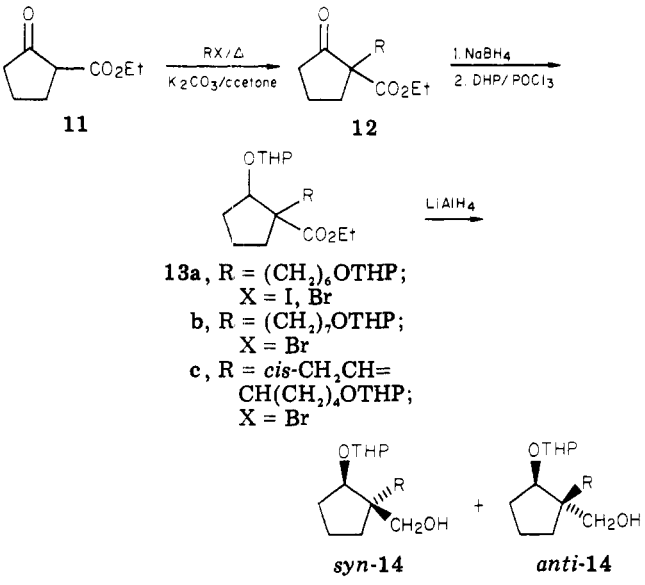
Scheme II



experiments showed that R = Me or Et gave equivalent, if not superior, results.

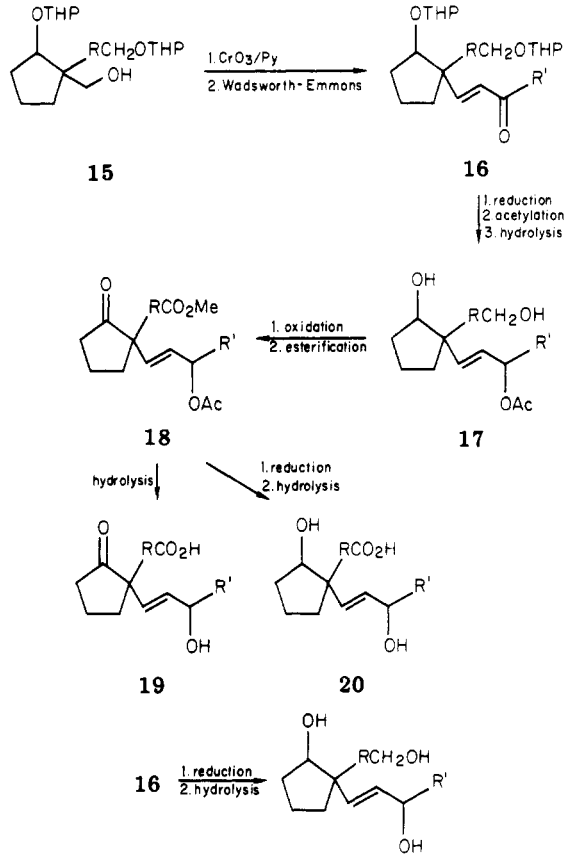
The only restrictions on the identity of R′X which we discovered were that X should be Br or preferably I. Successful, high-yield (>90%) alkylations were performed by using R′X = methyl iodide, heptyl bromide, and 6-(tetrahydropyranyloxy)hexyl iodide (from 6-chlorohexanol, dihydropyran, and sodium iodide). One attempt to use methyl 7-iodoheptanoate as R′X and R = *tert*-butyl in **3** gave as the only "new" product **3** with R = methyl, apparently arising via proton exchange and cyclization of R′X. All subsequent strongly basic alkylations with R′X containing a carboxyl synthon were done by using an alcohol protected as the tetrahydropyranyl ether.

Reduction of the hindered ester group of **4** directly to the aldehyde was unsuccessful despite literature precedents.[5] Full reduction to the alcohol **5** was best achieved with a commercially available solution of $LiAlH_4$ in ether, which gave quantitative reduction in a few minutes. Collins oxidation[6] was slow on the hindered alcohol but was successful. The aldehyde was not purified but was converted via the Wadsworth–Emmons alkylation to enone **6** in 70–80% yield (based on **5**) after chromatography. The hindered character of the aldehyde necessitated extra vigor for the alkylation to be completed. Of the many reagents tried, $NaBH_4$ in methanol or ethanol was the preferred reagent for 1,2-reduction of enones **6**.

Encouraged by the measurable[7] PG-like bioactivity shown by **7a** and **7b**, further synthetic manipulations were undertaken to provide other analogues. Several compounds (**10**, **21**, **30**, **41**) were tested in their reduced form. For others, protection of the enol as the acetate, THP ether cleavage, and chromic acid oxidation presented no particular problems. The acid–acetate was most conveniently isolated as its methyl ester (**8**), and final hydrolysis of the esters gave the *gem*-PG **9**. The overall yield from 6-(tetrahydropyranyloxy)hexyl iodide was 4%.

Having gained confidence that our general approach was sound, we proceeded to prepare PG analogues in which the five-membered rings more closely resembled those found in the natural compounds. Our first such targets were a series (**19**, **20**) named as *gem*-11-deoxy-PGE and -PGF compounds. Synthesis of these compounds began with the sequence outlined in Scheme II. The less polar isomer obtained from reduction of **13** is presumably *syn*-**14** in which hydrogen bonding can occur between the primary OH and ether oxygens of the THP group. The overall combined yield of **14** from RX ranged from 42 to 59%.

Scheme III[a]



[a] a, R = $(CH_2)_4$, R′ = C_4H_9; b, R = $(CH_2)_5$, R′ = C_5H_{11}; c, R = $(CH_2)_6$, R′ = C_5H_{11}; d, R = $(CH_2)_8$, R′ = C_7H_{15}; e, R = *cis*-$CH_2CH{=}CH(CH_2)_3$, R′ = C_5H_{11}.

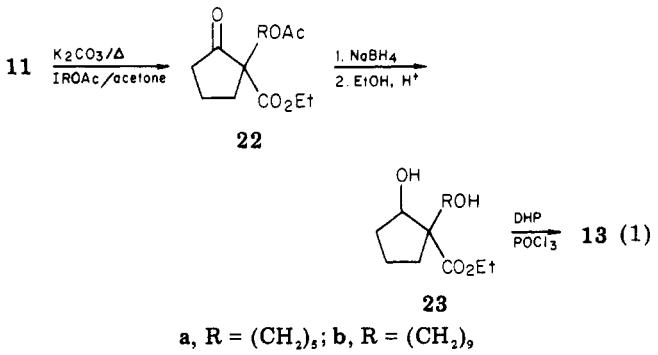
The next several steps of the synthetic sequence followed that already described in Scheme I, with the exception that acidic hydrolysis of **16** unmasked both ether-protected hydroxyls (Scheme III). Jones oxidation and diazomethane esterification then gave the corresponding keto ester **18**.

Diester **18** was hydrolyzed to 8-*gem*-11-deoxy-PGE derivatives **19**. Alternately, the ketone group was reduced by $NaBH_4$ before hydrolysis to 8-*gem*-11-deoxy-PFG compounds **20** which were obtained as mixtures of isomers, partially separable by column chromatography. Ketones **16** were reduced and the protecting groups removed to give triols **21**, analogous to **10**. Alternatively, **17** was hydrolyzed with base to yield **21** in similar overall yield.

Because convenient starting materials for synthesis of $X(CH_2)_nOTHP$ (X = Br, I; n = 5, 9) were unavailable, we devised routes to $X(CH_2)_nOAc$. Alkylation of **11** by these compounds was followed by reduction with $NaBH_4$ and then cleavage with acidic ethanol to preserve the ester on the ring (eq 1). Conversion of **23** to **13** was followed by the remaining sequence of Scheme II.

For the keto acid series of compounds, two stages in the synthetic sequence were suitable for isomer separations: primary alcohol **14**, as already mentioned, and esters of the product **19** itself. In our work we did not detect any

(5) J. Vit, U.S. Patent 3660416 (1972). L. I. Zakharin and I. M. Khorlina, *Tetrahedron Lett.*, 619 (1962).
(6) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(7) T. R. Williams and L. M. Sirvio, manuscript in preparation.



a, R = $(CH_2)_5$; b, R = $(CH_2)_9$

influence of the C-9 stereochemistry on the reduction of the C-15 ketone. Thus, *syn*-**14** and *anti*-**14** gave the same isomer mixture of **19** as determined by high-pressure LC separation of the diastereomers of the **19c** methyl ester.[8] Separation of diastereomers of the methyl esters of **19a,d,e** was also accomplished by high-pressure LC.

For the compounds with an oxygen function two carbons away from the geminal center (12-*gem*-PGE or -PGF derivatives), a different route was used and started with cyclopent-3-enoic acid.[9] The full synthetic sequence, essentially as in Scheme I, was carried out on **24** to give **29**, but in only 2.5% overall yield (Scheme IV). Another route to **29** which was successful but not as general involved hydrolysis of **26c** and oxidation and esterification to **44** (R = *cis*-$CH_2CH{=}CH(CH_2)_3$, Scheme VII). Reduction with $NaBH_4$ then yielded the **29c** methyl ester in 29% overall yield. From this reduction was also isolated a 15% yield of **30c**.

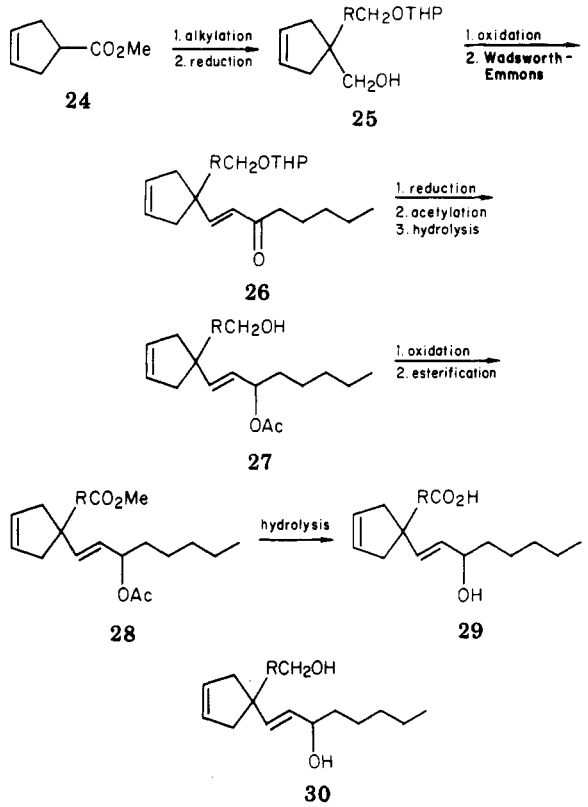
The 12-*gem*-PGE or -PGF analogues were available by three routes. First, hydroboration–oxidation[10] of **24** gave alcohol **31**. Then, after protection of the alcohol **31**, alkylation of the ester anion gave **33**. Note the similarity in functionality between **33** and **13**. In fact, the reaction sequence was the same for the two series from this point on (compare Schemes V and III). Hydroxy acids **40** were also obtainable by reduction of **38** followed by hydrolysis of the esters. Triols **41** were available from ketones **36**.

Alternately, **24** was alkylated first to give **35** which was then transformed into **33**, as shown in Scheme V. This second route gave a lower yield of **33** than the first route (15% vs. 51%, based on the valuable alkyl bromide). The third route to **40** is shown in Scheme VI and utilizes **28** (Scheme IV). Here, isoamylborane allowed selective attack of the desired ring functionality to give, after oxidation, **42** in 15% yield, with 25% recovered starting material. The remaining material was a complex mixture (by TLC) and was not purified further. Hydrolysis of the diester of **42** gave **40a**.

An interesting variation on our "standard" sequence (Scheme I) is shown in Scheme VI. The usual sequence proceeds from **36** through **32** and **37** to **39** (Scheme V). Alternatively, **36b** was carried through **43** to **42b** as shown. This route enjoyed the advantage of having fewer steps, but it suffered from slightly lower overall yield and the inability to produce **39** without further steps.

A final series of analogues was available from **24** via **26** (Scheme VII). Epoxidation of the cyclopentene ring of **44** was achieved regioselectively by reaction with *m*-chloroperbenzoic acid. Epoxide **45** was isolated in 52%

Scheme IV[a]



[a] a, R = $(CH_2)_5$; b, R = $(CH_2)_6$; c, R = *cis*-$CH_2CH{=}CH(CH_2)_3$.

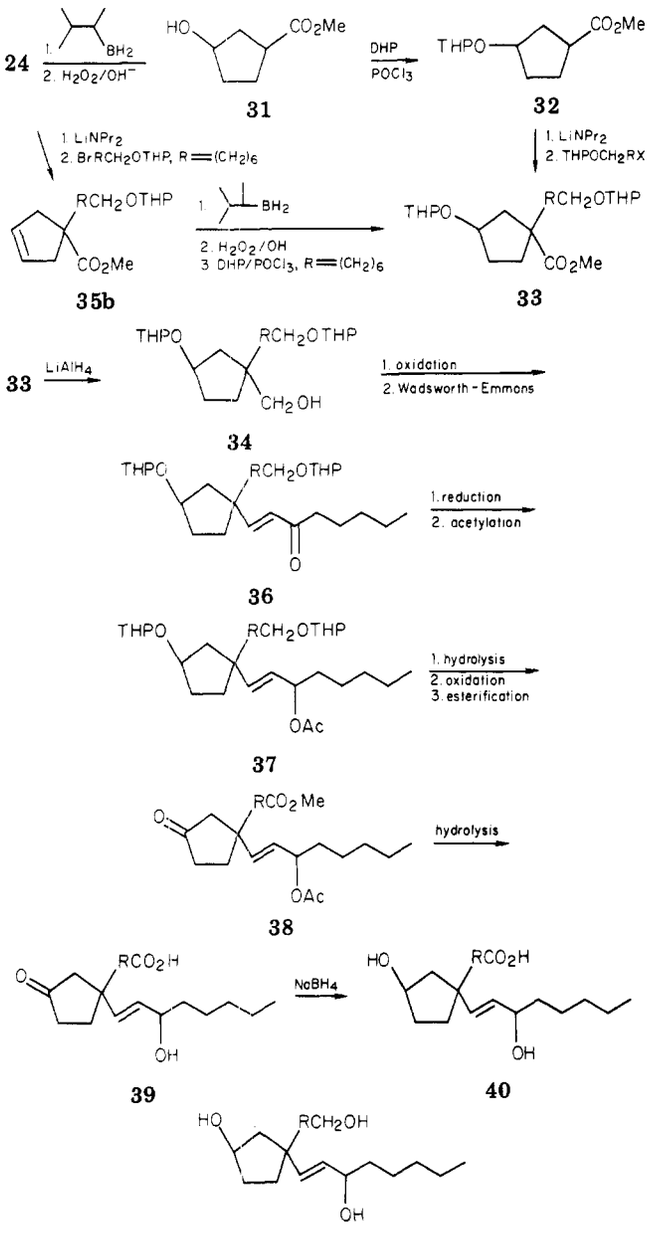
yield as a mixture of two isomers. Subsequent reduction and hydrolysis gave analogues **46**. Two pairs of diastereomeric methyl esters of **46** were separable by silica gel chromatography.

All of our compounds were prepared with achiral material, so no absolute configurations are shown in any of our synthetic schemes. Because of the presence in our compounds of asymmetric carbon atoms, diastereomeric mixtures were obtained in many cases. We attempted to separate isomers when possible, and we succeeded partly or fully in several instances: *syn*- and *anti*-**14** and the methyl esters of **19**, **20**, and **46**. With the exception of **46**, the only means of identifying the isomers was on the basis of chromatographic mobility. No differences in IR or NMR were interpretable as identifying relative stereochemistries.

In the case of the isomers of **46b**, we have been able to correlate the NMR spectra and relative chromatographic mobilities as follows. The methylene protons on the ring appear as an AB quartet. The chemical shifts of these protons are influenced by the stereochemical relationships between the protons, the epoxide group,[11] and the olefin group on the side chain.[12] The epoxide shields protons cis on the ring and deshields trans protons. The olefin in these compounds is oriented to exert a cis-shielding effect as well, with no effect on trans protons. Thus, the slower isomer of **46b** has the epoxide and olefin *cis*, which relationship yields both the most shielded and the least shielded protons. This assignment is consistent with the prediction that the cis isomer would be more polar and

(8) A homemade machine, using two Altex "prep" columns (5-μm microparticulate silica) in series and an Isco UA-5 ultraviolet detector at 254 nm, was satisfactory.
(9) G. H. Schmid and A. W. Wolkoff, *J. Org. Chem.*, **32**, 254 (1967).
(10) H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 7161 (1970).
(11) P. Sohar and G. Bernath, *Acta Chim. Acad. Sci. Hung.*, **87**, 285 (1975).
(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London, 1969, p 83.

Scheme V[a]



[a] a, R = $(CH_2)_5$; b, R = $(CH_2)_6$; c, R = *cis*-CH_2CH=$CH(CH_2)_3$.

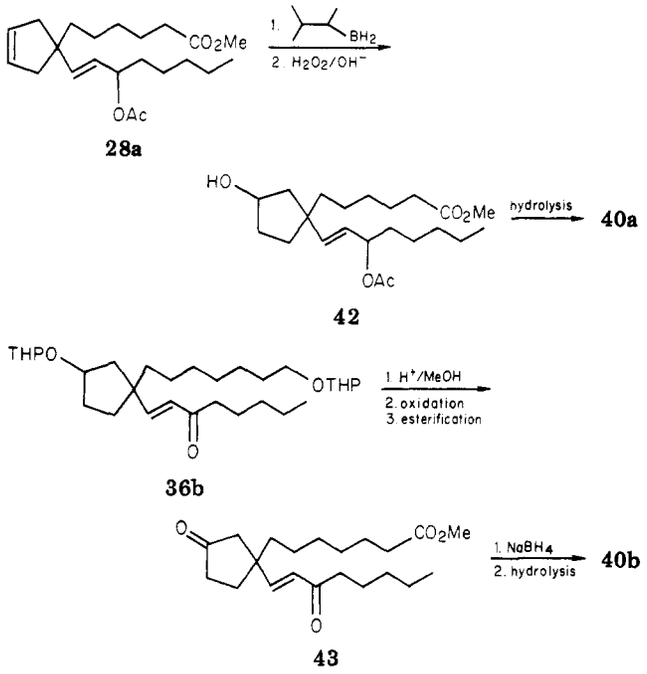
move more slowly in chromatography.

Experimental Section

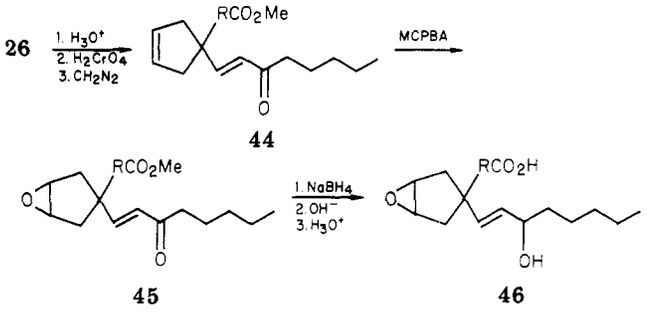
General Methods. All compounds isolated in the course of this investigation were characterized by infrared and proton magnetic resonance spectroscopy. Since only a few of our end products and none of the intermediates were obtained crystalline, elemental compositions of key compounds in the series were verified by high-resolution mass spectrometry. Spectral data were analyzed by the Analytical and Properties Research Laboratory of the Central Research Division of 3M Co. IR Spectra were obtained on neat samples (for oils) or on Nujol mulls (for solids); values reported are given in reciprocal centimeters. NMR spectra were obtained by using a Varian A-60 or XL-100 spectrometer on chloroform-*d* solutions containing tetramethylsilane as internal standard; values reported are in τ units. High-resolution mass spectra were done by using a CEC21-110C mass spectometer on underivatized samples.

Thin-layer chromatography (TLC) was performed by using Analtech "Uniplate" glass plates precoated with a 250-μm layer of silica gel GF. Column chromatography was conducted by using

Scheme VI



Scheme VII[a]



[a] a, R = $(CH_2)_5$; b, R = $(CH_2)_6$.

neutral silica gel (E. Merck, 70–230 mesh) or, when noted, acid-washed silica gel (Mallinckrodt SilicAR CC-4). All solvents were reagent grade or spectrograde and were used without further purification. Solvents for high-pressure liquid chromatography were reagent grade and were distilled from glass (Burdick and Jackson). Where mixed solvents were used for chromatography, the composition is expressed as a percent by volume of the former in the latter. The solvent system A-IX[13] is the upper layer from a mixture of 90 mL of ethyl acetate, 20 mL of acetic acid, 50 mL of 2,2,4-trimethylpentane, and 100 mL of water. All high-pressure LC separations were accomplished on two 10 mm i.d. × 25 cm long Lichrosorb SI 60 (5 μm) preparative columns (Altex) connected in series, with the effluent being monitored by a UV detector operating at 254 nm (ISCO, Model UA5).

Preparation of 32. Methyl cyclopent-3-enecarboxylate (5.0 g, 39.7 mmol) was hydroxylated by the standard method[10] to give 4.6 g (32 mmol, 81%) of liquid **31**: IR 3320, 1730, 1710; NMR 5.6 (p, 1 H), 6.3 (s, 3 H), 6.95 (m, 2 H), 7.7–8.5 (m, 6 H).

This crude hydroxy ester (2.0 g, 15 mmol) was protected by a known procedure[14] to give 1.6 g (7.5 mmol, 50%) of **32**: IR 1725, 1125 (d), 1075, 1025 (d); NMR 5.4 (m, 1 H), 5.6 (p, 1 H), 5.9–6.6 (m, 5 H), 6.7–7.2 (m, 1 H), 7.8–8.7 (m, 12 H).

General Procedure I. Preparation of 1-Substituted 1-Hydroxymethyl Carbocycles from Unactivated Esters. Preparation of 5c. A. To a solution of 16.5 mL of 1.5 M butyllithium (25 mmol) in 25 mL of dry tetrahydrofuran (THF) at 0 °C under an atmosphere of dry nitrogen was added 32 mmol

(13) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1965).
(14) G. Just, et al., *J. Am. Chem. Soc.*, **91**, 5364 (1969).

of diisopropylamine. After being stirred for 15 min, the solution was cooled to −70 °C, and 22 mmol of methyl cyclohexanecarboxylate was added. The solution was maintained at −70 °C for 30 min, and then a mixture of 24 mmol of 6-(tetrahydropyranyloxy)hexyl iodide in 4 mL of hexamethylphosphoramide was added. After being maintained at −70 °C for 10 min, the solution was warmed to 25 °C over 50 min, and the reaction was quenched by addition of water. Excess water was absorbed by sodium sulfate, the slurry was filtered, and the solvent was evaporated at reduced pressure to give 7.6 g of crude alkylated ester. The following alkyl halides were also used in this procedure: 1, $ICH_2CH{=}CH_2$; 2, $I(CH_2)_6CH_3$; 3, $I(CH_2)_6OTHP$, prepared in 85% yield from $Cl(CH_2)_6OH$;[14,15] 4, *cis*-$BrCH_2CH{=}CH(CH_2)_4OTHP$ and $Br(CH_2)_7OTHP$, prepared from $HOCH_2C{\equiv}CH$ and $Br(CH_2)_3Cl$ via $THPOCH_2C{\equiv}C(CH_2)_3CN$ in 13% and 40% yields respectively.[14,16-18]

B. The crude ester was dissolved in 15 mL of ether and the mixture was stirred under nitrogen while a solution of 0.9 M $LiAlH_4$ in ether was added at a rate to maintain a gentle reflux until the reaction subsided. After being stirred for 15 min more, the reaction was quenched by successive dropwise addition of 0.8 mL of water, 1.2 mL of 10% aqueous sodium hydroxide, and 2.4 mL of water. After 1 h of stirring, the slurry was filtered, and the filtrate was evaporated at reduced pressure. The resulting oil was purified by silica gel chromatography to give 3.6 g (12 mmol, 55%) of **5c**: NMR 5.35 (m, 2 H), 5.7 (m, 1 H), 6–6.7 (m, 8 H), 7.35 (m, 1 H), 8–8.9 (m, 28 H); IR 3450, 1120 (d), 1060 (d), 1025 (d).

General Procedure II. Preparation of 1-Substituted 1-Hydroxymethyl Carbocycles from Ethyl Cyclopentan-2-onecarboxylate. A. A mixture of 20 mmol of 6-tetrahydropyranyloxyhexyl iodide, 25 mmol of ethyl cyclopentan-2-onecarboxylate, and 40 mmol of potassium carbonate was refluxed with 125 mL of acetone for 18 h.[23] After the mixture cooled, 125 mL of ether was added, and the solids were filtered off. The filtrate was evaporated at reduced pressure, and an ether solution of the product was washed in succession with saturated sodium bicarbonate, water, and saturated sodium chloride. After the organic phase was dried with sodium sulfate and potassium carbonate, the residue was purified by silica gel chromatography. The following alkyl halides were also used in the procedure: 1, *cis*-$BrCH_2CH{=}CH(CH_2)_4OTHP$; 2, $Br(CH_2)_7OTHP$; 3, $I(CH_2)_5OAc$, prepared in 71% yield from $(CH_2)_5O$;[15,19] 4, $Br(CH_2)_9OAc$, prepared in 53% yield from $CH_2{=}CH(CH_2)_8COOH$.[20,21]

B. Compounds made from alkyl halides containing a terminal THPO group were carried directly to part C. Compounds made from alkyl halides containing an acetoxy group were refluxed in absolute ethanol with *p*-toluenesulfonic acid as a catalyst. This ethanol solution was treated directly with borohydride as in part C.

C. The ketone from part A was dissolved in 50 mL of methanol and stirred at 0 °C while a solution of 53 mmol of sodium borohydride in 50 mL of methanol was added over several minutes. For ketones treated in part B, the ethanol solution was stirred at 0 °C while the solid borohydride was added cautiously.

The resulting mixture was stirred at 0 °C for 15 min, and the reaction was then quenched by cautiously adding 20% aqueous acetic acid. Most of the solvent was removed at reduced pressure, the residue was partitioned between ether and water, and the organic phase was dried over sodium sulfate and potassium carbonate. Evaporation of the solvent gave crude oily product, which was used directly.

D. The crude alcohol from part C was converted[14] to the THP ether and purified by column chromatography to give 6.4 g (150 mmol) of **13a**.

E. By use of part B of general procedure I, the ester from part D was reduced with $LiAlH_4$, and the product was purified by column chromatography to give 4.5 g of **14a** (11.7 mmol, 58% yield based on starting alkyl halide): NMR 5.4 (m, 2 H), 5.8–6.8 (m, 9 H), 7.6–8.9 (m, 29 H); IR 3500, 1140 (d), 1075, 1035 (d).

General Procedure III. Conversion of Substituted Methanols to Oct-1-en-3-ones. Preparation of 6a. A. The alcohol 1-heptyl-1-(hydroxymethyl)cyclohexane was oxidized with CrO_3 and pyridine to the aldehyde, 1-heptyl-1-(oxomethyl)-cyclohexane, by following the procedure of Ratcliffe and Rodehorst.[6] This compound was isolated by ether extraction but not purified and was alkylated as described in part B below.

B. The crude aldehyde was converted to the enone by using known[4] procedures except that 10:1 dimethoxyethane–dimethyl sulfoxide was used as the solvent, and the reaction was kept at reflux for 24 h. Column chromatography gave 1.43 g (4.7 mmol, 62% for two steps) of the oily **6a**: NMR 3.6 (q, 1 H), 3.95–4.4 (m, 2 H), 4.9 (m, 2 H), 7.1–8.9 (m, 20 H), 9.1 (t, 3 H); IR 3020 (W), 1700, 1680, 1635, 990. Yields for other analogues in this sequence ranged from 23% to 72%. Dimethyl (2-oxohexyl)- and (2-oxononyl)phosphonate were prepared by modifying a known[22] procedure.

General Procedure IV. Preparation of Substituted Octenols and Octenol Acetates. Preparation of 17b. A. A solution of 1.05 g (2.19 mmol) of **16b** in 5 mL of toluene and 20 mL of benzene was cooled to 0 °C under a nitrogen atmosphere. Over 5 min was added 4.4 mmol of diisobutylaluminum hydride (1 M solution in hexane), and the resulting solution was maintained at 0 °C for 1 h. The reaction was quenched by addition of 50 mL of methanol, stirred for 1 h at 25 °C, and filtered through a Celite pad, and the filter cake was washed well with ether. The combined filtrates were evaporated at reduced pressure, and the residual oil was chromatographed on 100 g of neutral silica gel with 25% ethyl acetate/petroleum ether with 20-mL fractions. Product in fractions 15–40 was combined to give 1.04 g (2.16 mmol, 98%) of enol.

Alternatively, sodium borohydride could be used instead of diisobutylaluminum hydride. General procedure II, part C, was used.

B. At 0 °C, 5 mL of acetic anhydride and 5 mL of pyridine were added to 2.5 g (5.2 mmol) of the enol from part A. The solution was stirred for 5 h while it warmed to 25 °C. Ether was added, and the solution was washed in succession with 10% aqueous sodium hydroxide, 2 M hydrochloric acid, 10% aqueous sodium hydroxide, and saturated aqueous NaCl. After being dried over sodium sulfate, the solvent was removed at reduced pressure.

C. The enol acetate from part B (5.2 mmol) was stirred with 80% aqueous acetic acid (25 mL/g of alcohol) at 25 °C overnight to hydrolyze the tetrahydropyranyl groups. The homogeneous reaction mixture was diluted with ether, washed with saturated sodium bicarbonate, and dried over sodium sulfate. After removal of the solvent, the residue was chromatographed on neutral silica gel (100 g/g of product) with 50% EtOAc/petroleum ether/1% isopropyl alcohol eluent in 15-mL fractions. Fractions 50–80 were combined to give 1.55 g (4.4 mmol, 84%) of **17b**: NMR 4.4–5 (m, 3 H), 6–6.6 (m, 3 H), 7.8 (s, 2 H), 7.95 (s, 3 H), 8.1–8.9 (m, 24 H), 9.1 (t, 3 H); IR 3500, 1750 (d).

An alternative procedure for cleavage of the tetrahydropyranyl ethers is effected by using methanol and an acid catalyst such as oxalic acid or *p*-toluenesulfonic acid at room temperature for several hours. The procedure for isolation is the same as above. Yields for other analogues in this sequence ranged from 20% to 95%.

General Procedure V. Preparation of Geminal PG Esters and Acids. Preparation of 18a, 19a and 20a. A solution of 5.15 g (15.8 mmol) of **17a** in 250 mL of acetone was stirred at 0 °C while 17 mL of 2.8 M Jones reagent was added dropwise. The resulting mixture was stirred at 0 °C for 1 h and then further at room temperature for 0.5 h. The reaction was quenched by addition of 2 mL of isopropyl alcohol, and the resulting mixture was diluted with 100 mL of ether and then was filtered through

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Celite. The filter cake was treated with 125 mL of water to dissolve the chromium salts, the slurry was filtered, and the filtrate was acidified and subsequently extracted with ether. The ether solutions were washed with 2 N HCl and dried over Na_2SO_4. This solution was treated with excess diazomethane, the volatiles were removed at reduced pressure, and the residue was chromatographed on 400 g of neutral silica with 20% EtOAc/petroleum ether as eluent. A forefraction of 1000 mL was followed by 20-mL fractions. Product from fractions 31–84 was combined to give 5.1 g (14.5 mmol, 91%) of **18a**: NMR 4.3–4.9 (m, 3 H), 6.35 (s, 3 H), 7.8 (q, 4 H), 8.0 (s, 3 H), 8–8.9 (m, 16 H), 9.15 (t, 3 H); IR 1725.

This diester was stirred under nitrogen with 12 mL of 10% NaOH in water plus 50 mL of methanol. After 5.5 h the reaction mixture was acidifed with 2 N HCl to a pH of 1, diluted with 50 mL of saturated NaCl solution plus 25 mL of water, and extracted with ether. The combined ether extracts were washed sequentially with 2 N HCl and saturated NaCl and then dried over Na_2SO_4. Volatiles were removed at reduced pressure, and the residue was chromatographed on 250 g of acidic silica. A forefraction of 1000 mL of 30% EtOAc/petroleum ether was followed by 20-mL fractions of 50% EtOAc/petroleum ether. Fractions 51–94 were combined to give 2.9 g (9.8 mmol, 67%) of **19a**: NMR 3.7 (s, 2 H), 4.5 (d, 2 H), 5.9 (m, 1 H), 7.7 (q, 4 H), 7.9–8.9 (m, 16 H), 9.15 (t, 3 H); IR 3650–2300 (br), 1710 (br, s).

Fractions 26–34 gave 0.2 g (0.6 mmol) of the enol acetate of **19a**, and fractions 36–47 gave 0.2 g (0.6 mmol) of the methyl ester of **19a**.

To a solution of 0.41 g (1.4 mmol) of **19a** in 20 mL of methanol, stirred at 0 °C, was added 25% NaOH solution until a pH of 8 was achieved. Then 0.08 g (2.1 mmol) of solid $NaBH_4$ was added and general procedure II, step C, was followed. The residue was chromatographed on 40 g of acidic silica with 50% EtOAc/petroleum ether. Fractions 28–55 yielded 0.297 g (1.0 mmol, 77%) of **20a**: IR 3700–2300 (br), 1720.

General Procedure VI. Preparation of Diols and Triols. Synthesis of 21b from 17b. A solution of 0.207 g of enol **17b** (0.43 mmol) in 5 mL of 4:1 HOAc–H_2O was stirred at room temperature overnight. The resulting solution was diluted to 50 mL with ether, extracted with saturated $NaHCO_3$ solution until neutral in pH, and dried over Na_2SO_4. After removal of solvent at reduced pressure, the residue was chromatographed on 20 g of neutral silica with 5% isopropyl alcohol/ethyl acetate and 7-mL fractions. Fractions 9–14 were combined to give 0.04 g (0.13 mmol, 30%) of **21b**.

Synthesis of 21e from 17e. A solution of 0.425 g of **17e** in 4.7 mL of a solution of 0.5 N sodium hydroxide in 5:1 methanol–water was stirred under nitrogen for 4 h. Enough 2 N hydrochloric acid was added to bring the pH to 6, water was added to 25 mL, and the product was extracted with CH_2Cl_2. After the solvent was dried (Na_2SO_4) and evaporated, the residue was chromatographed as for **21b**. Fractions 9–14 again were combined to give 0.13 g (0.4 mmol, 33%) of **21e**: NMR 4.1–4.7 (m, 4 H), 5.85 (m, 1 H), 6.1 (m, 1 H), 6.3 (t, 2 H), 7.0 (s, 3 H), 7.6–8.9 (m, 22 H), 9.1 (t, 3 H); IR 3300, 1650 (w), 1100–1000 (br), 970.

Synthesis of the Methyl Ester of 29c and 30c. A solution of 1.3 g (3.4 mmol) of **26c** and 2 mg of *p*-toluenesulfonic acid in 50 mL of methanol was stirred overnight at room temperature. The methanol was replaced by 100 mL of acetone, and the solution was stirred vigorously at 0 °C while 3.2 mL of Jones reagent was added dropwise. The mix was stirred at 0 °C for 1 h, allowed to warm to ambient temperature over 30 min, and then diluted with water. Extraction with ether gave a solution which was dried over Na_2SO_4 and then was treated with excess diazomethane. After removal of volatiles, 0.99 g (3.0 mmol, 88%) of **44** (R = *cis*-$CH_2CH{=}CH(CH_2)_3$) was obtained. Of this, 0.9 g (2.7 mmol) was reduced by use of general procedure II, step C. The residue was chromatographed on 90 g of silica with 50% EtOAc/petroleum ether (20-mL fractions). From fractions 8–10 was collected 0.33 g (1.0 mmol, 31%) of the methyl ester of **29c**. From fractions 15–17 was collected 0.15 g (0.45 mmol, 15%) of **30c**.

Synthesis of 46a and 46b. General Procedure. A 3.0-g (7.7 mmol) sample of **26b** was hydrolyzed and oxidized to **44b** as outlined above. Chromatography of the crude product (200 g of silica, 20% EtOAc/petroleum ether, 20-mL fractions) gave the product in fractions 19–30 (1.7 g, 5.1 mmol, 66%).

This pure material in 25 mL of $CHCl_3$ was stirred at room temperature while 2.0 g (11.6 mmol) of *m*-chloroperbenzoic acid was added at once. After 15 min the reaction was quenched by the addition of 10% NaOH solution. The organic layer was evaporated, and the residue was dissolved in ether, washed with 10% NaOH solution, dried over Na_2SO_4, and chromatographed on 200 g of silica with 33% EtOAc/petroleum ether. Product **45b** was isolated from fractions 32–61 (20 mL each) as a mixture of isomers (0.9 g, 2.7 mmol, 52%).

To a solution of 0.19 g (5 mmol) of $NaBH_4$ in 20 mL of methanol was added with stirring a solution of 1.20 g (3.6 mmol) of **45b** in 10 mL of methanol. After 30 min at room temperature the reaction mixture was extracted with ether. The ether solution was evaporated at reduced pressure, and the addition of ether, separation of the phases, and evaporation was repeated. The residue was chromatographed on 125 g of silica with 50% EtOAc/petroleum ether and 20-mL fractions. Fractions 28–31 contained 0.28 g of the less polar isomer [NMR 8.02 (d, J = 15 Hz, 2 H), 8.22 (d, J = 15 Hz, 2 H)], fractions 36–45 contained 0.37 g of the more polar isomer [NMR 7.88 (d, J = 15 Hz, 2 H), 8.32 (d, J = 15 Hz, 2 H)], and fractions 32–35 contained 0.34 g of a mixture of the two isomers for a total yield of 0.99 g (2.9 mmol, 51%) of the methyl ester of **46b**.

A solution of 0.37 g (1.1 mmol) of this methyl ester in 25 mL of methanol was stirred at room temperature under nitrogen with 2 mL of 10% NaOH solution. After 6 h the mixture was acidified with cold 1 N HCl solution and extracted with ether. The organic layer was evaporated, ether was added, the phases were separated, and the ether layer was dried over Na_2SO_4. After removal of the solvent the residue was chromatographed on 45 g of acidic silica with 50% EtOAc/petroleum ether and 20-mL fractions. Fractions 12–21 contained 0.24 g (0.71 mmol, 68%) of **46b**. A small portion was esterified with diazomethane to give one spot on TLC, with an R_f value identical with that of the starting methyl ester of **46b**.

Preparation of 33b from 35. A sample (3.4 g, 10.5 mmol) of **35** was hydroxylated by using the procedure for the preparation of **31**. The crude product was chromatographed on 450 g of silica with 50% ether/petroleum ether and 20-mL fractions. From fractions 22–30 was isolated 0.7 g (2.2 mmol) of starting **35**. From fractions 32–45 was isolated 0.44 g (1.3 mmol) of desired product. From fractions 63–107 was isolated 1.0 g (3.9 mmol) of the diol derived from the product by loss of the primary alcohol protective group. These latter two compounds were combined and treated with dihydropyran and $POCl_3$ in the usual way. The resulting material was chromatographed on 290 g of silica with 25% EtOAc/petroleum ether and 20-mL fractions. From fractions 34–60 was isolated 1.0 g (2.3 mmol, 28%) of **33b**, identical in all respects with material prepared from **32**.

Preparation of 40a from 28a (Scheme VI). A sample of 1.1 g (3.0 mmol) of **28a** was hydroxylated as in the preparation of **31**. Chromatography of the crude product on 125 g of silica with 50% ether/49% petroleum ether/1% 2-propanol yielded 0.25 g (0.7 mmol, 22%) of **42** in fractions 24–36 (20 mL each). This diester was hydrolyzed with NaOH in aqueous methanol as described in general procedure V to give 0.24 g (0.7 mmol, 96%) of **40a**, identical in all respects with that obtained from Scheme V.

Preparation of 40b from 36b (Scheme VI). A sample of 0.73 g (1.5 mmol) of **36b** was hydrolyzed with methanol as in general procedure IV. The resulting crude product was oxidized with Jones reagent and esterified with diazomethane as in general procedure V. The crude product was chromatographed on neutral silica with 20% EtOAc/petroleum ether and 20-mL fractions. From fractions 37–43 was isolated 0.22 g (0.63 mmol, 42%) of **43**.

This diketo ester was reduced with $NaBH_4$ as in the procedure for the preparation of the methyl ester of **46b** given above. The crude product was chromatographed on 25 g of silica with 80% ether/petroleum ether and 8-mL fractions. Fractions 62–63 had 0.03 g of the less polar isomer, fractions 64–66 had 0.09 g of a mixture of isomers, and fractions 67–73 had 0.05 g of the more polar isomer, for a total yield of 0.17 g (0.48 mmol, 76%) of the methyl ester of **40b**. All fractions exhibited spectra indistinguishable from each other and from spectra of material obtained previously.

This ester was hydrolyzed with NaOH/aqueous methanol as described in general procedure V. A yield of 0.12 g (0.36 mmol,

73%) of **40b**, identical with that obtained by the alternate route (Scheme V), was obtained.

Registry No. 3 (R = CH_3), 4630-82-4; **4** (R = CH_3; R′ = *cis*-$CH_2CH{=}CH(CH_2)_4OTHP$), 75266-82-9; **4** (R = CH_3; R′ = $(CH_2)_7OTHP$), 75266-83-0; **4a** (R = CH_3), 67838-02-2; **4b** (R = CH_3), 75266-84-1; **4c** (R = CH_3), 75266-85-2; **5a**, 67838-03-3; **5b**, 67838-04-4; **5c**, 67838-05-5; **6a**, 75266-86-3; **6b**, 75266-87-4; **6c**, 75266-88-5; **9**, 75266-89-6; **11**, 611-10-9; **13a**, 75266-90-9; *syn*-**14a**, 75330-88-0; *anti*-**14a**, 75330-89-1; *syn*-**14b**, 75266-91-0; *anti*-**14b**, 75330-90-4; *syn*-**14c**, 75266-92-1; *anti*-**14c**, 75330-91-5; **16b**, 75330-92-6; **17a**, 75266-93-2; **17b**, 67838-39-5; **17e**, 67838-46-4; **18a**, 75266-94-3; **19a**, 75266-95-4; **20a**, 75266-96-5; **21b**, 67838-27-1; **21c**, 75266-97-6; **24**, 58101-60-3; **26b**, 75266-98-7; **26c**, 75266-99-8; **28a**, 75267-00-4; **29c** methyl ester, 75267-01-5; **30c**, 75267-02-6; **31**, 32811-76-0; **32**, 67838-07-7; **33b**, 75267-03-7; **35b**, 75267-04-8; **36b**, 75267-05-9; **40a**, 75267-06-0; **40b**, 75267-07-1; **42**, 75267-08-2; **43**, 75267-09-3; **44** (R = *cis*-$CH_2CH{=}CH(CH_2)_3$), 75267-10-6; **44b**, 75267-15-1; **45b** (isomer 1), 75267-11-7; **45b** (isomer 2), 75330-93-7; **46a**, 75267-14-0; **46b**, 75267-16-2; **46b** methyl ester, 75267-12-8; $ICH_2CH{=}CH_2$, 556-56-9; $I(CH_2)_6CH_3$, 4282-40-0; $I(CH_2)_6OTHP$, 65785-44-6; *cis*-$BrCH_2CH{=}CH(CH_2)_4OTHP$, 75267-13-9; $Br(CH_2)_7OTHP$, 10160-25-5; $I(CH_2)_5OAc$, 65921-65-5; $Br(CH_2)_9OAc$, 53596-82-0; 1-heptyl-1-(oxomethyl)cyclohexane, 67838-09-9.

Synthesis and Photochemistry of 17β-Hydroxy-*A*-homo-19-norpregn-5(10)-en-20α-yn-4-one. Synthesis of A,B Spiro Steroids[1,2]

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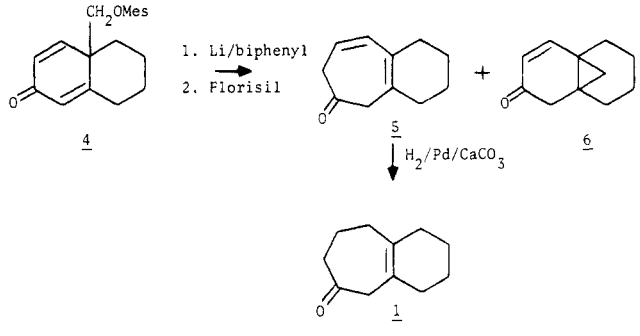
Received January 3, 1979

Bicyclo[5.4.0]undec-1(7)-en-3-one (**1**) and 17β-hydroxy-*A*-homo-19-norpregn-5(10)-en-20α-yn-4-one (**3**) were synthesized in good yield by processes which employed buffered acetolysis of the intermediate mesylates, 10-[(mesyloxy)methyl]-$\Delta^{1(9)}$-octalin (**7**) and 19-(methanesulfonoxy)androst-4-ene-3,17-dione 3-ethylene thioketal (**13**), respectively, for the ring-expansion steps. Photolysis of the β,γ-unsaturated ketones **1** and **3** gave the β,γ-unsaturated spiroketones **2** and **26a** via 1,3 acyl shifts. The structure of **26** was determined by X-ray analysis. These photoisomerizations are reversible, and quenching and sensitization studies showed that these photochemical rearrangements occurred from an excited singlet or short-lived triplet state. The stereochemistry of the photoproduct **26a** is that predicted on the basis of the ground-state conformation of **3**.

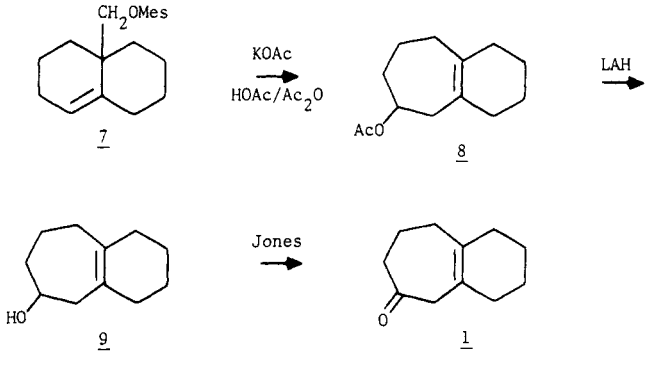
The observation that ground-state molecular conformations can control the mode of reaction for various photochemical reactions has been the topic of recent interest.[3-7] However, it has also been shown that if the lifetime of the excited-state intermediates is sufficiently long, then conformational transformations can sometimes occur, resulting in the formation of different photoproducts.[7,8] Hence it should be possible, knowing the ground-state conformation of a flexible molecule, to predict the stereochemistry of the photoproducts formed, provided no long-lived intermediates are involved.

In order to investigate this question in β,γ-unsaturated ketones, we investigated the photochemistry of the optically active steroid 17β-hydroxy-*A*-homo-19-norpregn-5-(10)-en-20α-yn-4-one (**3**). The A ring of this steroid contains a seven-membered ring incorporating a β,γ-unsaturated ketone whose conformation can be determined from optical rotatory dispersion (ORD).[9] A seven-membered cycloheptene ring is much more rigid than a cyclohexene ring, and Dreiding models indicate the presence of two stable chair conformations.[10] Furthermore, the bicyclo analogue of **3**, namely, bicyclo[5.4.0]undec-1(7)-en-3-one (**1**), has been shown to yield 6-methylenespiro[4.5]decan-

Scheme I



Scheme II



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