Synthesis of Sesquiterpene Antitumor Lactones. 8.[1] An Approach to the Synthesis of Pseudoguianolides Based on Oxy-Cope Rearrangement

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Enone alcohol **2** has been prepared and subjected to base-catalyzed rearrangement. Isomeric product **6** or **7** is produced, depending on the reaction conditions. Tricyclic dione **6** results from the use of more than 1.5 equiv of KH in THF; bicyclic enedione **7** results from the use of KOH in aqueous methanol. The structures of **6** and **7** are proven by unambiguous synthesis. A mechanistic rationale is advanced wherein compounds **6** and **7** are produced by a series of aldol and oxy-Cope rearrangement steps.

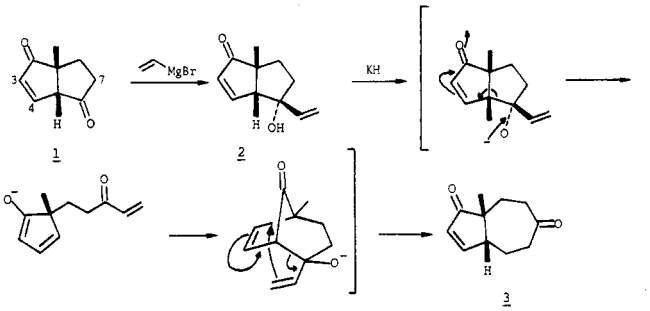
As a possible general synthesis of the pseudoguianolide skeleton, we have considered the hypothetical sequence of reactions shown in Scheme I. If this scheme could be reduced to practice, an economical construction of both 10α- and 10β-methylpseudoguaianolides would be possible by using the appropriate stereoisomeric 1-lithio-1-propene. Furthermore, appropriate substitution at C_7 in the starting enedione **1** would allow for the typical three-carbon side chain of the pseudoguaianolides. As will be seen, the approach is unsuccessful, not because **3** is not formed but because it reacts further to give a tricyclic product.

Compound **1** is prepared from 2-methylcyclopentanone as outlined in Scheme II. The initial Michael addition to produce **4** was done by using a modified version of the published procedure,[2] and none of the other regioisomer was detected in the crude product. Several methods were examined for dehydrobromination of the bromo ketone obtained from **4**. The procedure of Green and Long[3] provides **5** in superior yield and higher purity than LiBr–Li_2CO_3–DMF,[4] Li_2CO_3–DMF,[4] or refluxing quinoline.[5] Many conditions were examined for accomplishing the vinylogous Claisen condensation **5** → **1**. Base-catalyzed methods are uniformly unsuccessful. The best results are obtained when the keto acid, obtained by saponification of **5**, is treated with 1.5 equiv of boron trifluoride etherate in a refluxing mixture of acetic anhydride and acetic acid. Although yields are variable, we have obtained **1** in an overall yield of 10–17%, based on 2-methylcyclopentanone.

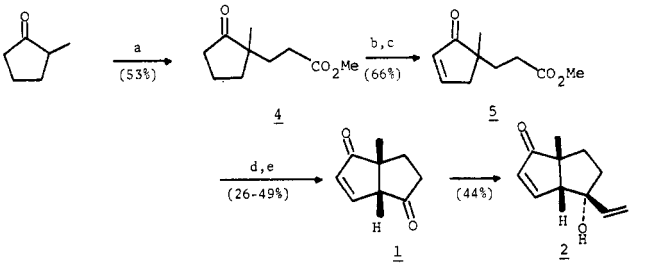
Addition of 1 equiv of vinylmagnesium bromide to enedione **1** affords vinyl carbinol **2** in a reproducible 44% yield. It is assumed that the organometallic reagent attacks **1** from the more accessible convex face of **1** and that **2** has the indicated stereostructure. It is clear from the ^1H NMR and IR spectra of **5** that the enone system is intact.

Treatment of **2** with excess KH in THF affords crystalline tricyclic dione **6** in 42% yield (Scheme III). When KOH in aqueous methanol is employed, crystalline bicyclic enedione **7** is obtained in 46% yield. By use of shorter reaction times, epimeric alcohol **8** can be observed spectroscopically and may be isolated by preparative GLC. Finally, when *catalytic* amounts of KH are used in THF (0.2–0.5 equiv), isomeric products **6** and **7** are produced in a ratio of 1:1.

Scheme I

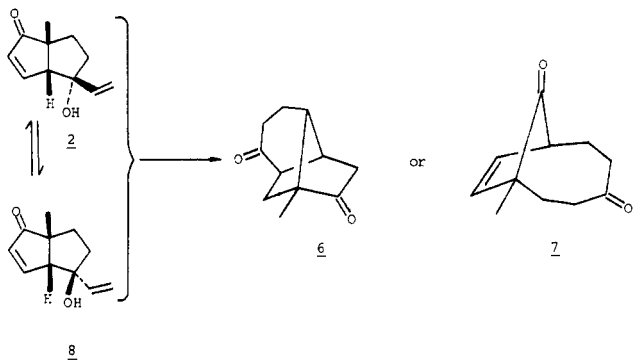


Scheme II



[a] Methyl acrylate, THF, NaOMe. [b] Br_2, $CHCl_3$. [c] $CaCO_3$, DMAC. [d] KOH, MeOH. [e] $BF_3 \cdot Et_2O$, Ac_2O, AcOH.

Scheme III



The structures of **6** and **7** were initially assigned on the basis of their IR, ^1H NMR, and ^{13}C NMR spectra and/or reasonable mechanistic arguments (vide infra). For confirmation of these assignments, both were prepared by alternate routes. The unambiguous synthesis of **6** is outlined in Scheme IV. The starting material, keto ester **10a** or **10b**, was prepared in connection with another project and was available in quantity.[6,7] Attempts to

(1) For paper 7 see F. Plavac and C. H. Heathcock, *Tetrahedron Lett.*, 2115 (1979).
(2) H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).
(3) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).
(4) H. O. House and R. W. Bashe, *J. Org. Chem.*, **30**, 2942 (1965).
(5) E. W. Warnhoft and D. R. Marshall, *J. Org. Chem.*, **32**, 2000 (1967).

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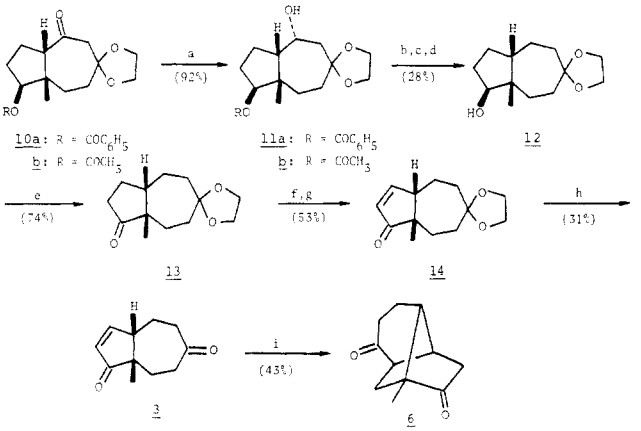
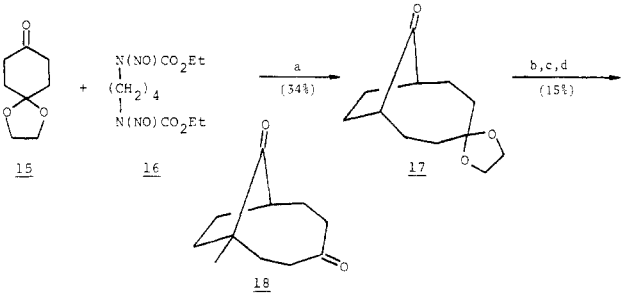
Scheme IV



[a] $NaBH_4$, EtOH. [b] NaH, THF, CS_2, MeI. [c] n-Bu_3SnH, $PhCH_3$. [d] KOH, MeOH. [e] PCC, NaOAc, CH_2Cl_2. [f] LDA, THF, Me_3SiCl. [g] $Pd(OAc)_2$, $C_6H_4O_2$, CH_3CN. [h] HOAc, H_2O. [i] KH, THF.

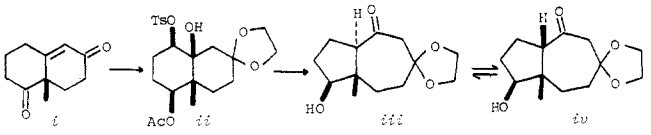
Scheme V



[a] K_2CO_3, MeOH, CH_2Cl_2. [b] LDA, DME. [c] CH_3I. [d] H_3O^+.

deoxygenate **11** by reduction of the derived methanesulfonate were not successful. The primary product is a mixture of alkenes resulting from *elimination* of the methanesulfonate. However, the Barton process[9] served admirably. After introduction of the cyclopentenone double bond,[10] the cycloheptanone carbonyl was unmasked to obtain enedione **3**. Treatment of **3** with KH in THF affords tricyclic isomer **6**, identical in all respects with the material obtained by the similar treatment of **2**. The dihydro derivative of enedione **7** was prepared from the monoketal of 1,4-cyclohexanedione[11] by Gutsche's method[12] as outlined in Scheme V.

(6) The synthesis of **10** will be reported in another paper. In brief, it is prepared by solvolytic rearrangement of keto tosylate *ii*, which is prepared from *i* by standard methods.[7] The initial rearrangement product is the trans-fused hydroazulenone *iii*, which may be equilibrated by base to a 4:1 mixture of *iii* and the cis-fused isomer *iv*. Pure cis-fused product is obtained by preparative high-pressure LC separation of the mixture of benzoates or acetates.[8]



(7) Eric Delmar, Ph.D. Dissertation, University of California, Berkeley, 1978.

(8) We thank Mr. Samuel Graham for a supply of esters **10a** and **10b**.

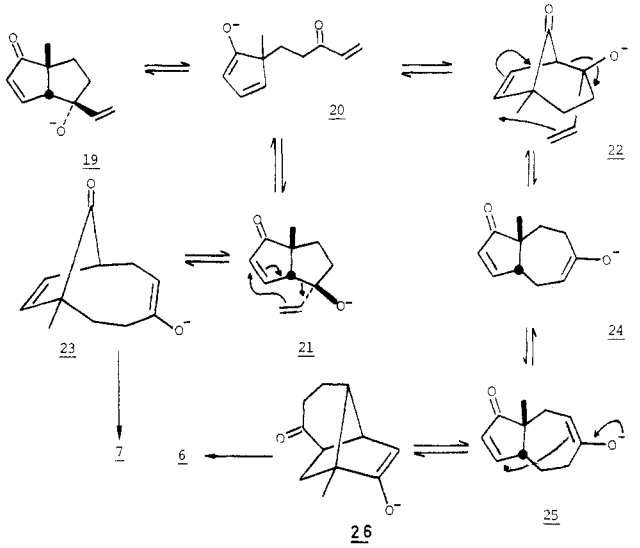
(9) D. H. R. Barton and S. W. McOmbie, *J. Chem. Soc., Perkin Trans. 1*, 1574 (1975).

(10) Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, **43**, 1011 (1978).

(11) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Am. Chem. Soc.*, **74**, 1401 (1952).

(12) J. W. Baum and C. D. Gutsche, *J. Org. Chem.*, **33**, 4312 (1968).

Scheme VI



An attractive mechanistic rationale for our results is outlined in Scheme VI. We reason that **19**, the alkoxide of **2**, undergoes reverse aldolization to give enolate **20**, which can close at the γ-position to give **21**, the alkoxide of isomer **8**. Alkoxide **21** is geometrically disposed for oxy-Cope rearrangement[13] to afford **23**, the enolate ion corresponding to product **7**. In protic medium, **23** is protonated, and enedione **7** is the only observed product. However, in aprotic medium, we argue that **23** equilibrates with **21** and hence **20**. Aldol closure of **20** on the α-carbon of the dienolate system provides **22**, which can isomerize by the oxy-Cope path to **24**, which undergoes equilibration to isomeric enolate **25**, followed by intramolecular Michael closure to **26**, the enolate corresponding to tricyclic dione **6**. The final closure is obviously supported by our finding that **3** isomerizes readily to **6** under similar conditions.

Clearly both **6** and **7** could be formed directly by Michael reactions of **20**; however, it is felt that this pathway is less likely, particularly for **6**, where an eight-membered ring is formed. Similar rearrangements have been studied previously by Dauben and Hart[14] and by Srinivasan et al.[15]

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Ether, 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Boiling points and melting points (Pyrex capillary) are uncorrected. IR spectra were determined with a Perkin-Elmer Model 297 infrared recording spectrophotometer. ^1H NMR spectra were determined on the following spectrometers: Varian T-60, Varian EM 390, or UCB 180 (a superconducting, 180-MHz, Fourier transform instrument). Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz. ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer or at 45.28 MHz on the

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(14) W. G. Dauben and D. J. Hart, *J. Org. Chem.*, **42**, 3787 (1977).

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UCB 180. Mass spectra were obtained with Atlas MS-12 and Consolidated 12-110B mass spectrometers. Mass spectral data are tabulated as m/e (intensity expressed as percent of total ion current). Gas–liquid partition chromatography (GLC) was done with Varian Aerograph A-90P, 920, and 940 gas chromatographs. High-pressure liquid chromatography (LC) was done with a Waters PrepLC/System 500 (preparative). μ-Porasil columns were used unless otherwise noted. Elemental analyses were performed by the Microanalytical Laboratory operated by the College of Chemistry of the University of California at Berkeley.

Methyl 1-Methyl-2-oxocyclopentanepropanoate (4). To a stirred solution of 90 g (0.92 mol) of 2-methylcyclopentanone in 1000 mL of dry THF, cooled in an ice bath, was added 5.0 g (93 mmol) of sodium methoxide, followed by 83 mL (79 g, 0.92 mmol) of methyl acrylate in 100 mL of dry THF dropwise over 2 h. Stirring was continued for a further 5 h, the reaction mixture was poured into 2000 mL of 5% aqueous HCl and extracted with three 500-mL portions of ether, and the combined ethereal extracts were washed with 500 mL of brine and dried over $MgSO_4$. The solvent was removed at reduced pressure, and distillation of the residue at 0.1 μmHg afforded 91 g (53%) of the desired product, bp 85–90 °C.

Methyl 1-Methyl-2-oxo-3-cyclopentenepropanoate (5). To a mechanically stirred solution of 52 g (0.29 mol) of methyl 1-methyl-2-oxocyclopentanepropanoate (4) in 1000 mL of chloroform was added 16.5 mL (51.5 g, 0.32 mol) of bromine in 300 mL of chloroform dropwise over 5 h. The reaction was followed by ^1H NMR. The reaction mixture was washed with two 1000-mL portions of saturated aqueous $NaHCO_3$ and 1000 mL of brine and then dried over $MgSO_4$, and the solvent was removed at reduced pressure to leave 82 g of crude bromo ketone. This crude bromo ketone was dissolved in 50 mL of DMAC (*N,N'*-dimethylacetamide) and added over 5 min to a well-stirred, refluxing slurry of 43 g (0.43 mol) of calcium carbonate in 700 mL of DMAC. After 5 min more, the reflux condenser was replaced with a distillation head and DMAC removed as rapidly as possible by judicious reduction of pressure until ~200 mL remained. The residue was cooled, diluted with 2000 mL of ether, and filtered to remove $CaCO_3$, and the ether solution was washed with four 800-mL portions of water and 800 mL of brine and dried over $MgSO_4$. Removal of ether at reduced pressure left 34 g of crude product which was distilled at 30 μmHg to give 26.1 g (51%) of a colorless liquid, bp 70–95 °C.

More product was isolated as follows. The calcium carbonate was washed with ethyl acetate which afforded 8.9 g of material upon evaporation. The combined aqueous washes were extracted twice with chloroform which afforded 15.3 g of material heavily contaminated with DMAC. The combined residues were distilled at aspirator pressure to remove DMAC and then vacuum distilled at 50 μmHg to give 8.5 g (15%) of a colorless liquid: bp 90–105 °C; total yield 66%; ^1H NMR ($CDCl_3$) δ 1.13 (3 H, s), 1.6–2.5 (4 H), 2.55 (2 H, dd, J = 2, 3), 4.65 (3 H, s), 6.1 (1 H, dt, J = 2, 6), 7.65 (1 H, dt, J = 3, 6); ^{13}C NMR ($CDCl_3$) δ 22.8, 29.0, 32.1, 42.6, 51.0, 132.2, 161.7; IR (thin film) 1740, 1700 cm^{-1}; mass spectrum, 182 (0.15), 150 (2.06), 95 (3.98), 79 (2.88), 67 (3.13), 55 (2.68).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 65.68; H, 7.78.

3aβ-Methyl-3,3a-dihydro-1,4(2*H*,6aβ*H*)-pentalenedione (1). A solution of 34.0 g (0.19 mol) of enone ester **5** in 1750 mL of methanol containing 1% KOH (0.27 mol) was stirred overnight at room temperature. The reddish solution was poured into 4000 mL of water, extracted with two 1500-mL portions of ether to remove neutral material, acidified to pH 1 with 10% HCl, and extracted with three 1000-mL portions of chloroform. The combined chloroform extracts were dried over $MgSO_4$ and evaporated to leave 23.8 g (75%) of crude enone acid as a yellowish oil. No further purification was attempted: ^1H NMR ($CDCl_3$) δ 1.15 (3 H, s), 1.6–2.5 (4 H), 2.55 (2 H, dd, J = 2), 6.07 (1 H, dt, J = 2, 6), 7.55 (1 H, dt, J = 6); IR (thin film) 3600–2500, 1700, 1590 cm^{-1}.

A solution of 5.82 g (30 mmol) of enone acid in 10 mL of acetic anhydride and 100 mL of acetic acid was refluxed for 30 min, and 6 mL (49 mmol) of boron trifluoride etherate was added. Refluxing was continued for 4.5 h, after which the reaction mixture was poured into 500 mL of brine and allowed to stand overnight to hydrolyze excess acetic anhydride. The solution was extracted with three 150-mL portions of CH_2Cl_2, and the combined CH_2Cl_2 extracts were washed with three 200-mL portions of saturated aqueous $NaHCO_3$ and 200 mL of brine and dried over $MgSO_4$. The aqueous washes were extracted with 400 mL of CH_2Cl_2, and the organic extracts were washed with saturated aqueous $NaHCO_3$ and with brine before being dried over $MgSO_4$. Removal of solvent gave a total of 4.86 g of crude product which was purified by bulb to bulb distillation at 30 μmHg to afford 2.87 g of colorless liquid: ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.6–2.5 (4 H), 3.18 (1 H, dd, J = 2, 3), 6.25 (1 H, dd, J = 2, 6), 7.55 (1 H, dd, J = 3, 6); ^{13}C NMR ($CDCl_3$) δ 22.0, 29.9, 36.8, 63.5, 133.6, 158.3; IR (thin film) 1740, 1710, 1580, 820 cm^{-1}; mass spectrum, 150 (3.91), 122 (1.40), 55 (8.67).

Anal. Calcd for $C_9H_{10}O_2$: C, 72.00; H, 6.67. Found: C, 71.86; H, 6.71.

4β-Ethenyl-4α-hydroxy-6aβ-methyl-5,6-dihydro-1-(3aβ*H*)-pentalenone (2). To a stirred solution of 1.57 g (10.5 mmol) of bicyclic keto enone **1** in 100 mL of dry ether at room temperature was added over 90 min 20 mL of ca. 0.5 M (10 mmol) freshly prepared vinylmagnesium bromide in THF. After being stirred for 1 h further at room temperature, the reaction mixture was poured into 200 mL of saturated aqueous NH_4Cl and 50 mL of 5% aq HCl and extracted with two portions of ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and after removal of solvent afforded 1.80 g of crude product. The desired vinyl alcohol was obtained by chromatography over 80 g of silica, eluting with 1:1 ether–hexanes: 0.78 g (44%) of an oil was obtained; ^1H NMR ($CDCl_3$) δ 1.15 (3 H, s), 1.3–2.1 (4 H), 2.9 (1 H, dd, J = 2, 3), 5.1–6.3 (4 H), 7.65 (1 H, dd, J = 3, 6); ^{13}C NMR ($CDCl_3$) δ 22.4, 32.4, 38.1, 53.0, 62.6, 79.2, 112.9, 133.5, 143.1, 163.1; IR (CCl_4) 3610, 3450 (br), 1710, 1590, 925, 830 cm^{-1}; mass spectrum, 178 (1.95), 108 (2.69), 96 (8.45), 83 (6.00), 55 (5.75).

The analytical sample was obtained by preparative GC.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.89; H, 7.71.

1-Methyl-3a,6,7,7a-tetrahydro-1,4-methanoindan-2,5-dione (6). A 0.494-g (2.7 mmol) sample of a 22% oil dispersion of potassium hydride was washed with three 10-mL portions of hexane, and 60 mL of dry THF was added. To the well-stirred suspension was added 0.342 g (1.92 mmol) of vinyl alcohol **2** in 10 mL of THF in one portion, and the reaction mixture was stirred for 2 h before being poured into 250 mL of saturated aqueous NH_4Cl. Extraction with three 100-mL portions of ether was followed by combination of the ethereal extracts which were washed with 100 mL of brine, dried over $MgSO_4$, and evaporated to afford 0.393 g of crude product. Chromatography over 18 g of silica, eluting with hexanes–ether (3:2), gave 0.143 g (42%) of a white solid which was recrystallized from ether to give the analytical sample: mp 106–107 °C; ^1H NMR ($CDCl_3$) δ 1.2 (3 H, s), 1.3–2.8 (14 H); ^{13}C NMR ($CDCl_3$) δ 11.1, 20.0, 32.5, 33.0, 41.1, 41.9, 45.7, 52.8; IR (CCl_4) 1750, 1720 cm^{-1}; mass spectrum, 178 (5.21), 149 (1.34), 134 (2.22), 105 (2.08), 93 (5.89), 80 (4.76), 55 (2.36).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.14; H, 7.84.

1-Methylbicyclo[5.2.1]dec-8-ene-4,10-dione (7). A solution of 401 mg (2.25 mmol) of vinyl alcohol **2** in 15 mL of methanol was prepared and 44 mg (0.79 mmol) of KOH in 5 mL of water was added. After being stirred for 30 h at room temperature, the reaction mixture was poured into 80 mL of saturated aqueous NH_4Cl and extracted with three 20-mL portions of ether. The combined ether layers were washed with 20 mL of brine and dried over $MgSO_4$, and solvent was removed to afford 304 mg of crude product which was chromatographed over 11 g of silica, eluting with hexanes–ether (2:1), to give 184 mg (46%) of white crystals which were recrystallized from benzene–hexane: mp 60–62 °C; ^1H NMR ($CDCl_3$) δ 1.03 (3 H, s), 1.5–3.0 (9 H), 6.1 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 22.7, 30.4, 39.1, 40.7, 41.2, 51.1, 131.0, 139.0; IR (CCl_4) 1750, 1705 cm^{-1}; mass spectrum, 178 (0.36), 150 (0.90), 134 (1.19), 119 (1.67), 106 (5.59), 93 (4.95), 79 (3.97), 55 (4.90).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.89; H, 7.75.

4α-Ethenyl-4β-hydroxy-6aβ-methyl-5,6-dihydro-1-(3aβ*H*)-pentalenone (8). A 1-mL (0.11 mmol) sample of 0.11 M aqueous KOH was added to a solution of 64 mg (0.36 mmol) of vinyl alcohol **2** in 3 mL of methanol, and the solution was stirred

for 6 h at room temperature. The reaction was worked up by being poured into 60 mL of saturated aqueous NH_4Cl and extracted with two 30-mL portions of ether. The combined ether extracts were washed with 30 mL of brine, dried over $MgSO_4$, and evaporated to afford 56 mg of crude product which was chromatographed over 9 g of silica, eluting with hexanes–ether (2:1), to give 34 mg of a 3:1 mixture of alcohol 8 and bicyclic diketone 7. A pure sample of 8 was obtained by preparative GLC and gave the following spectral data: ^1H NMR ($CDCl_3$) δ 1.3 (3 H, s), 1.3–2.1 (4 H, m), 2.85 (1 H, dd), 5.0–6.0 (3 H, m), 6.1 (1 H, dd, J = 2, 6), 7.4 (1 H, dd, J = 3, 6); ^{13}C NMR ($CDCl_3$) δ 22.6, 33.9, 36.7, 53.9, 66.2, 82.0, 114.1, 134.2, 140.9, 162.8; IR (CCl_4) 3600, 1700 cm^{-1}; mass spectrum, 178 (0.24), 160 (0.35), 117 (2.08), 96 (2.18), 91 (1.63), 83 (1.29), 55 (1.99); high-resolution mass spectrum, calcd for $C_{11}H_{14}O_2$ m/e 178.0993, obsd m/e 178.0985.

1β-(Benzoyloxy)-8aβ-methyl-1,2,3,3aβ,8-pentahydro-4,6-(5H,7H)-azulenedione 6-Ethylene Ketal (10a). Hydroazulenic ketone **10a** was separated from its ring-junction stereoisomer by preparative high-pressure LC, eluting with 40% ether in hexanes, to afford **10a** of high purity: ^1H NMR ($CDCl_3$) δ 1.3 (3 H, s), 1.5–3.0 (11 H), 3.85 (4 H, s), 4.8 (1 H, dd, J = 8), 7.1–8.0 (5 H); ^{13}C NMR ($CDCl_3$) δ 21.3, 28.0, 31.6, 33.2, 52.0, 58.9, 64.1, 82.4, 128.0, 129.1, 132.6; IR (CCl_4) 1720 cm^{-1}.

The analytical sample was obtained by recrystallization from ether; mp 141–2 °C.

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.97; H, 7.09.

1β-(Benzoyloxy)-4α-hydroxy-8aβ-methyl-1,2,3,3aβ,4,7,8-heptahydro-6(7H)-azulenone 6-Ethylene Ketal (11a). To a solution of 620 mg (1.8 mmol) of ketone **10a** in 45 mL of absolute ethanol at 5 °C was added 110 mg (2.9 mmol) of solid sodium borohydride. The cooling bath was removed, and the reaction was stirred for 30 min, poured into 150 mL of brine, and extracted with three 50-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and afforded 706 mg (114%) of an oil upon removal of solvent. Crystallization from ether afforded 571 mg (92%) of a white crystalline solid: mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 1.15 (3 H, s), 1.3–2.4 (11 H), 3.0 (1 H), 3.85 (5 H), 5.1 (1 H, dd, J = 8), 7.2–8.0 (5 H); ^{13}C NMR ($CDCl_3$) δ 23.6, 23.8, 28.5, 31.0, 33.0, 42.8, 53.0, 63.9, 64.5, 70.2, 83.0, 128.2, 129.5, 132.7.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.12; H, 7.43.

1β-Hydroxy-8aβ-methyl-1,2,3,3aβ,4,7,8-heptahydro-6-(7H)-azulenone 6-Ethylene Ketal (12). Method I. A 40-mg (0.83 mmol) sample of a 50% oil dispersion of sodium hydride was washed with three 3-mL portions of pentane and suspended in 5 mL of THF. A solution of 137 mg (0.4 mmol) of alcohol **11a** in 5 mL of THF was added. The reaction was stirred at room temperature for 3 h, 1.5 mL (25 mmol) of carbon disulfide and 0.5 mL (8 mmol) of methyl iodide were added, and stirring was continued for 60 h. The solvent was removed by heating the mixture in a stream of nitrogen, and the residue was partitioned between 150 mL of water and 50 mL of ether. The ether layer was separated, and the aqueous layer was extracted with 50 mL of ether. The combined ether extracts were washed with 50 mL of brine and dried over $MgSO_4$, and the solvent was removed to afford 148 mg (85%) of crude xanthate: ^1H NMR ($CDCl_3$) δ 1.15 (3 H, s), 1.4–2.4 (11 H), 2.5 (3 H, s), 3.8 (4 H, s), 5.1 (1 H, dd), 5.9 (1 H, m), 7.2–8.0 (5 H).

To a refluxing solution of 0.1 mL (0.38 mmol) of n-Bu_3SnH in 2 mL of dry toluene was added 98 mg (0.23 mmol) of crude xanthate in 2 mL of toluene over 1 h. Refluxing was continued for 24 h, after which toluene was removed by heating the mixture in a stream of nitrogen. The residue was chromatographed over 10 g of silica gel, eluting first with 5% ether in hexanes until all the nonpolar material had been separated and then with 20% ether in hexanes, to afford 29 mg of the desired reduction product: ^1H NMR ($CDCl_3$) δ 1.1 (3 H, s), 1.3–2.4 (13 H), 3.8 (4 H, s), 4.85 (1 H, dd, J = 9, 6), 7.2–8.0 (5 H).

Without further purification, this crude material was heated on a steam bath in 5 mL of methanol with 111 mg (1.8 mmol) of KOH for 1 h. The reaction mixture was poured into 80 mL of brine and extracted with two 30-mL portions of ether and 30 mL of CH_2Cl_2. The ether and CH_2Cl_2 extracts were each washed with 30 mL of brine and then combined for drying over $MgSO_4$. Removal of the solvent left 20 mg (38% from xanthate) of alcohol **12**: ^1H NMR ($CDCl_3$) δ 0.9 (3 H, s), 1.2–2.0 (13 H), 3.55 (1 H, dd, J = 9, 6), 3.8 (4 H, s); ^{13}C NMR ($CDCl_3$) δ 22.1, 28.1, 28.4, 31.1, 31.6, 33.0, 38.2, 44.7, 48.8, 64.1, 64.2, 81.8; IR (thin film) 3450 cm^{-1}; mass spectrum, 226 (1.32), 99 (33.97); high-resolution mass spectrum calcd for $C_{13}H_{22}O_3$ m/e 226.1570, obsd m/e 226.1576.

Method II. Alcohol **12** was also prepared from 1.09 g (3.9 mmol) of acetate **10b** in an overall yield of 38% by the same series of steps used above.

8aβ-Methyl-3,3aβ,4,5,8-pentahydro-1,6(2H,7H)-azulenedione 6-Ethylene Ketal (13). To a well-stirred suspension of 505 mg (2.31 mmol) of PCC[16] and 49 mg (0.6 mmol) of anhydrous sodium acetate in 5 mL of dry CH_2Cl_2 was added 332 mg (1.48 mmol) of alcohol **12** rapidly. After being stirred for 8 h, the reaction mixture was diluted with 50 mL of ether and filtered through a short column of 5 g of Florisil. Evaporation of the eluate afforded 266 mg of crude ketone **13** which was purified by column chromatography over 10 g of silica gel, eluting with 50% ether in hexanes, to afford 244 mg (74%) of ketone **13**: ^1H NMR ($CDCl_3$) δ 1.0 (3 H, s), 1.3–2.4 (13 H), 3.8 (4 H, s); ^{13}C NMR ($CDCl_3$) δ 24.7, 26.5, 26.7, 27.5, 32.5, 35.7, 36.9, 47.6, 51.2, 63.9, 64.0, 111.0; IR (CCl_4) 1735 cm^{-1}; mass spectrum, 224 (2.03), 99 (30.56); high-resolution mass spectrum calcd for $C_{13}H_{20}O_3$ m/e 224.1413, obsd m/e 224.1410.

8aβ-Methyl-4,5,8-trihydro-1,6(3aβH,7H)-azulenedione 6-Ethylene Ketal (14). To a solution of 0.07 mL of diisopropylamine (0.5 mmol) in 5 mL of THF at 5 °C was added 0.35 mL (0.49 mmol) of a 1.4 M solution of n-BuLi in hexane dropwise over 2 min. After 30 min, the solution was cooled to −70 °C, and 102 mg (0.45 mmol) of ketone **13** in 2 mL of THF was added over 2 min. The reaction was stirred for 2 h at −70 °C, 0.06 mL (0.5 mmol) of chlorotrimethylsilane was added, and the cooling bath was removed. After being stirred for 2.5 h, the reaction mixture was poured into 100 mL of water and 100 mL of ether. The ether layer was separated and washed with 100 mL of water and 100 mL of brine and dried over $MgSO_4$. Removal of the solvent left 134 mg (100%) of crude silyl enol ether: ^1H NMR ($CDCl_3$) δ 0.2 (9 H, s), 1.0 (3 H, s), 1.2–2.5 (11 H), 3.8 (4 H, s), 4.3 (1 H, m).

To a solution of 59 mg (0.26 mmol) of $Pd(OAc)_2$ and 25 mg (0.23 mmol) of benzoquinone in 2 mL of dry acetonitrile was added 134 mg (0.45 mmol) of crude silyl enol ether in 2 mL of dry acetonitrile. The dark reaction mixture was stirred for 19 h and then poured into 100 mL of ether and 100 mL of water. The organic layer was separated and the aqueous phase extracted with 100 mL of ether. The combined ether layers were washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine and dried over $MgSO_4$. Removal of the solvent left 121 mg of an orange oil which was purified by column chromatography over 10 g of silica gel, eluting with 40% ether in hexanes, to afford 53 mg (53%) of enone **14** as an oil: ^1H NMR ($CDCl_3$) δ 1.1 (3 H, s), 1.3–2.2 (8 H), 2.65 (1 H, m), 3.8 (4 H, s), 6.1 (1 H, dd, J = 6, 2), 7.4 (1 H, dd, J = 6, 3); IR (CCl_4) 1710, 910 cm^{-1}.

8aβ-Methyl-4,5,8-trihydro-1,6(3aβH,7H)-azulenedione (3). To a solution of 57 mg (0.26 mmol) of ketal **14** in 2 mL of glacial acetic acid was added water dropwise until the solution appeared slightly cloudly. After being stirred for 20 h at room temperature, the reaction mixture was poured into 150 mL of water and extracted with four 50-mL portions of ether. The combined ether extracts were washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine and dried over $MgSO_4$. Removal of solvent left 20 mg of crude **3** which was purified on the Chromatotron (2-mm layer of SiO_2), eluting with ether, to afford 14 mg (31%) of **3**: ^1H NMR ($CDCl_3$) δ 1.05 (3 H, s), 1.4–2.6 (8 H), 2.8 (1 H, m), 6.1 (1 H, dd, J = 6, 2), 7.4 (1 H, dd, J = 6, 3); IR (CCl_4) 1710, 910 cm^{-1}; mass spectrum, 178 (7.52), 163 (0.92), 150 (4.85), 121 (3.84), 108 (3.91), 93 (3.27), 79 (3.92), 55 (7.65); high-resolution mass spectrum calcd for $C_{11}H_{14}O_2$ m/e 178.0994, obsd m/e 178.1000.

1-Methyl-3a,6,7,7a-tetrahydro-1,4-methanoindan-2,5-dione (6). An 11-mg (0.06 mmol) sample of a 22% oil dispersion of potassium hydride was washed with 2 mL of hexane and then stirred in 1 mL of THF. A solution of 14 mg (0.08 mmol) of enone **3** in 1.5 mL of THF was added rapidly, and the reaction was stirred at room temperature for 3 h, poured into 150 mL of water, and extracted with three 50-mL portions of ether. The combined ether extracts were washed with 50 mL of brine and dried over $MgSO_4$.

Solvent was removed to leave 8 mg of a crude solid, which was purified by column chromatography over 5 g of silica gel, eluting with 60% ether in hexanes, to afford 6 mg (43%) of **6** identical in all respects with material obtained by rearrangement of **2**.

Bicyclo[5.2.1]decane-4,10-dione 4-Ethylene Ketal (17). A solution of 0.641 (4.1 mmol) of keto ketal **15** in 15 mL of dry methanol was stirred under dry nitrogen at ice bath temperature with 0.134 g (0.97 mmol) of powdered anhydrous K_2CO_3. A solution of 1.183 g (4.1 mmol) of dinitrosocarbamate **16** in 20 mL of CH_2Cl_2 was added dropwise over 1 h and the resulting solution stirred for 3 h, during which time it warmed to room temperature. The reaction mixture was poured into 150 mL of water and 50 mL of brine and extracted with three 50-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with 50 mL of aqueous Na_2CO_3 and 50 mL of brine, dried over $MgSO_4$, and evaporated to leave 0.884 g of crude product which was chromatographed over 70 g of silica, eluting with hexane–ether (5:2), to give 0.251 g (34%) of an oil: ^1H NMR ($CDCl_3$) δ 1.4–2.5 (14 H), 3.8 (4 H, s); ^{13}C NMR ($CDCl_3$) δ 24.8, 27.1, 33.8, 44.7, 63.2, 64.4; IR (CCl_4) 1735 cm^{-1}; mass spectrum, 210 (0.17), 182 (5.68), 99 (10.59), 55 (11.61); high-resolution mass spectrum calcd for $C_{12}H_{18}O_3$ m/e 210.1255, obsd m/e 210.1249.

1-Methylbicyclo[5.2.1]decane-4,10-dione (18). Method I. A solution of 131 mg (0.74 mmol) of unsaturated bicyclic diketone **7** in 13 mL of 95% ethanol was hydrogenated at atmospheric pressure over 20 mg of 10% Pd on carbon. When 1 equiv of hydrogen had been absorbed, the solution was filtered to remove the catalyst, and the solvent was removed at reduced pressure to leave 134 mg of crude product which was chromatographed over 8 g of silica, eluting with hexane–ether (2:1), to afford 95 mg of pure saturated diketone.

Method II. To a solution of 0.13 mL (94 mg, 0.93 mmol) of diisopropylamine in 10 mL of dry DME at ice bath temperature was added dropwise over 15 min 0.7 mL (0.97 mmol) of a 1.38 M solution of *n*-BuLi in hexane. After the mixture was stirred for a further 10 min, 184 mg (0.87 mmol) of ketal ketone **17** in 7 mL of DME was added dropwise over 30 min, and stirring was continued for an additional 30 min before addition of 1 mL (16 mmol) of methyl iodide. After 90 min the reaction mixture was poured into 300 mL of 5% aqueous HCl before extraction with three 100-mL portions of ether. The combined ether extracts were washed with 100 mL of 5% aqueous HCl and 100 mL of brine and dried over $MgSO_4$. Removal of solvent at reduced pressure left 73 mg of crude product which was chromatographed over 9 g of silica, eluting with hexane–ether (3:2), to afford 31 mg of the title compound.

Both samples gave identical spectral data: ^1H NMR ($CDCl_3$) δ 1.05 (3 H, s), 1.5–3.0 (13 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 23.4, 29.1, 34.0, 36.2, 38.0, 39.7, 45.3; IR (CCl_4) 1740, 1710 cm^{-1}; mass spectrum, 180 (0.75), 162 (0.66), 152 (1.25), 110 (2.51), 97 (5.63), 55 (6.34).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.01; H, 8.96.

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Registry No. **1**, 75400-29-2; **2**, 75400-30-5; **3**, 75400-31-6; **4**, 7424-82-0; **5**, 75400-32-7; **6**, 75400-33-8; **7**, 75400-34-9; **8**, 75400-35-0; **10a**, 75400-36-1; **10b**, 75400-37-2; **11a**, 75400-38-3; **11a** xanthate, 75400-39-4; **12**, 75400-40-7; **13**, 75400-41-8; **14**, 75400-42-9; **15**, 4746-97-8; **16**, 19935-89-8; **17**, 75400-43-0; **18**, 75400-44-1; 2-methylcyclopentanone, 1120-72-5; methyl acrylate, 96-33-3; methyl 3-bromo-1-methyl-2-oxocyclopentanepropanoate, 75400-45-2; 1-methyl-2-oxo-3-cyclopentenepropanoic acid, 75400-46-3; vinyl bromide, 593-60-2; 1β-(benzoyloxy)-8aβ-methyl-1,2,3,3aβ,4,7,8-heptahydro-6(7*H*)-azulenone 6-ethylene ketal, 75400-47-4; 8a-methyl-3,3a,4,5,8-pentahydro-2-(trimethylsilyloxy)-1,6(2*H*,7*H*)-azulenedione 6-ethylene ketal, 75400-48-5.

Reactions of Steroid Salts with Hexachlorocyclotriphosphazene[1]

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The sodium salts of the steroids desoxoestrone (VI), estrone (VII), β-estradiol (VIII), 17α-ethynylestradiol (IX), estradiol 3-methyl ether (XIV), and 1,4-dihydroestradiol 3-methyl ether (XV) were found to react with hexachlorocyclotriphosphazene (III) to yield species of the general formula $N_3P_3Cl_5(OR)$ (IV). The remaining halogen atoms were replaced by methylamine to yield hydrolytically stable derivatives of formula $N_3P_3(NHCH_3)_5(OR)$ (V). These are model compounds for the analogous steroid-substituted phosphazene linear high polymers. Aliphatic steroids such as cholesterol (X), dihydrocholesterol (XI), pregnenolone (XII), estradiol 3-methyl ether (XIV), or 1,4-dihydroestradiol 3-methyl ether (XV) underwent dehydration as well as substitution in contact with III. Mestranol (XVII) as its 17-sodium salt did not react rapidly with III, presumably for steric reasons. At elevated temperatures, estrone 3-methyl ether (XVI) interacted with III by a complex process that involved elimination of hydrogen chloride. All the chlorine atoms in III could be replaced by a reaction with the sodium aryloxide salt of estrone (VII). The replacement followed a nongeminal pathway. The significance of these results for the synthesis of the related high polymers is discussed.

Considerable interest exists in the synthesis of high molecular weight polymers that may function as carrier molecules for chemotherapeutic agents.[2-8] Phosphazene high polymers with steroidal side groups could be potentially useful drugs or prodrugs, assuming that a slow hydrolytic release of the steroid could occur in vivo. Moreover, the possibility exists that steroidal phosphates might be released during hydrolysis, species that have themselves been used in steroid therapy.[9-11] However, effective

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