Bicyclo[2.2.1]heptanes as Intermediates in the Synthesis of Steroids. Total Synthesis of Estrone

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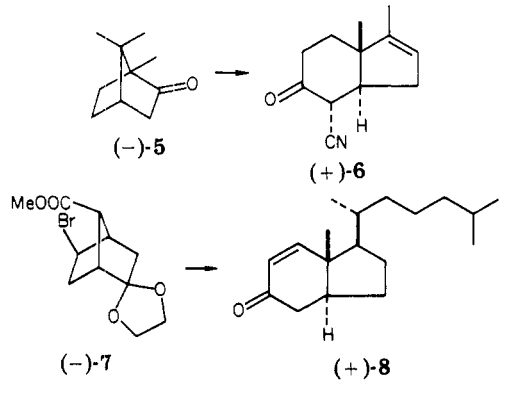
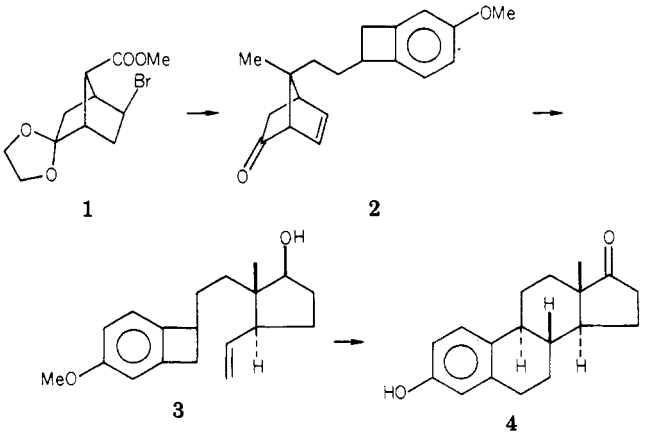
A synthesis of *dl*-estrone has been accomplished by employing the key bicyclo[2.2.1]heptene intermediate **2** prepared from ketal ester **16** via a series of reactions featuring the remarkable stereospecific alkylation of **16** with 2-(4-methoxybenzocyclobutenyl)ethyl iodide. Intermediate **2** provided direct access to benzocyclobutene derivative **3** which upon thermolysis underwent intramolecular cycloaddition via the corresponding *o*-quinodimethane.

The synthesis of steroids and related polycyclic substances continues to receive considerable attention. Numerous ingenious schemes have been developed over the years since the pioneering work of Bachmann and coworkers during the thirties.[2] We report a total synthesis of *dl*-estrone (**4**)[3] which (1) employs the rigid carbocyclic bicyclo[2.2.1]heptene derivative **2**, readily available from bromo ketal ester **1**,[4] for elaboration of ring D and (2) involves the use of the intramolecular cycloaddition of *o*-quinodimethanes developed independently by Oppolzer[5] and Kametani[6] for generation of the BC ring system (cf. Scheme I).

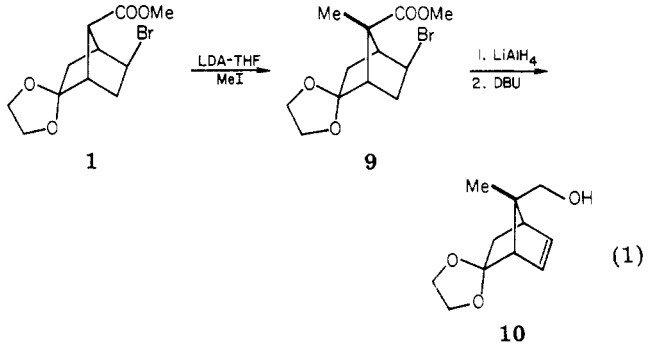
The potential of conformationally rigid bicyclo[2.2.1]heptanes for steroid total synthesis has recently been demonstrated. In an elegant series of experiments, Stevens and Gaeta took advantage of the topology and natural chirality of (−)-camphor (**5**) and prepared the ring system CD intermediate (+)-**6**.[7] Our own efforts in this area have resulted in the transformation of the chiral bicyclo[2.2.1]heptane derivative (−)-**7** into the CD ring system (+)-**8**, possessing the fully elaborated sterol side chain of cholesterol.[8]



Scheme I



Of critical importance to the success of Scheme I was the ability to stereospecifically introduce the benzocyclobutenyl moiety into the C(7) position of the bicyclo[2.2.1]heptane 1. This appeared at first glance not to be a difficult task since bicyclo[2.2.1]heptenol **10** had previously been prepared from bromo ketal ester **1**[4] via a highly stereoselective methylation reaction[9] (eq 1), thereby ensuring the configuration about the eventual C(13) position of estrone. It was anticipated that alkylation of the anion derived from 1-cyano-4-methoxybenzocyclobutene **12** with the mesylate **11b**, in principle readily available from **10**,[10] would provide, after reductive decyanation and hydrolysis, intermediate **2** (Scheme I). Unfortunately, all of our attempts to prepare the required mesylate **11b** were unsuccessful. Only products arising from loss of the mesylate with π-bond participation were observed.



(1)

This problem was conveniently solved by taking advantage of some observations made previously in our

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(2) Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.*, **1939**, *61*, 974.

(3) For recent syntheses of estrone see: (a) Bartlett, P. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 7501. (b) Danishefsky, S.; Cain, P. *Ibid.* **1976**, *98*, 4975. (c) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Matsumoto, H.; Fukumoto, K. *Ibid.* **1977**, *99*, 3461. (d) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *Tetrahedron Lett.* **1978**, 2425. (e) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1979**, *101*, 215.

(4) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.

(5) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833, 3834. Oppolzer, W.; Keller, K. *Ibid.* **1971**, *93*, 3836. Oppolzer, W. *Tetrahedron Lett.* **1974**, 1001; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(6) (a) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 29. (b) Kametani, T.; Kato, Y.; Honda, T.; Fukumoto, K. *Ibid.* **1976**, *4*, 241. (c) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 3378. (d) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *Ibid.* **1978**, *100*, 6218.

(7) Stevens, R. V.; Gaeta, F. C. A. *J. Am. Chem. Soc.* **1977**, *99*, 6105.

(8) Grieco, P. A.; Takigawa, T.; Moore, D. R. *J. Am. Chem. Soc.* **1979**, *101*, 4380. See also: Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *Ibid.* **1979**, *101*, 4378.

(9) Grieco, P. A.; Masaki, Y. *J. Org. Chem.* **1975**, *40*, 150.

(10) The one carbon homologated alcohol **11a** was prepared from **10** in ca. 70% overall yield [(1) TsCl, Py; (2) NaCN, Me_2SO, 80 °C; (3) 40% KOH, triethylene glycol, 130 °C; (4) $LiAlH_4$, THF, 0 °C].

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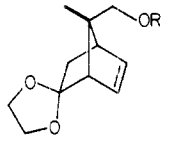
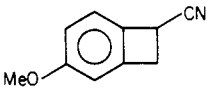
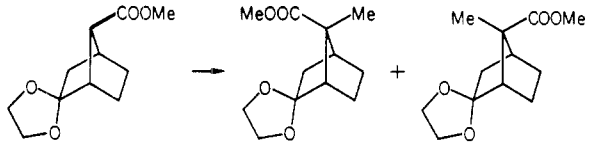


11a, R = H
b, R = $MeSO_2$



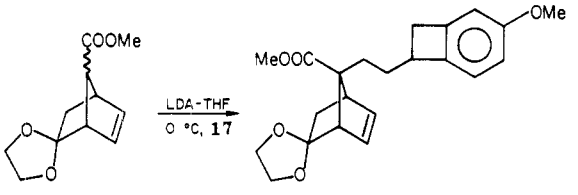
12

laboratory.[11] Whereas the bromo ketal ester 1 undergoes essentially exclusive syn (with respect to the ketal) alkylation (cf. 1 → 9, eq 1),[9] the corresponding debrominated bicyclo[2.2.1]heptane derivative 13 affords upon alkylation with methyl iodide a 4:1 ratio of 14 and 15, respectively, in high yield. On the basis of this result we examined the



13 14 15

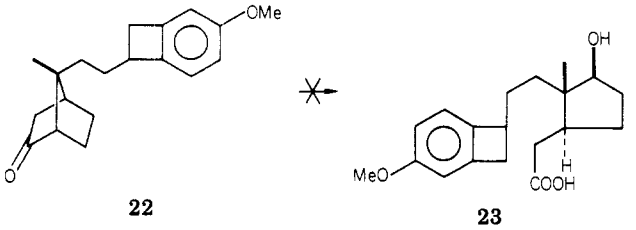
alkylation of ester 16 (obtained by treatment of 1 with diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing dimethylformamide) with 2-(4-methoxybenzocyclobutenyl)ethyl iodide (17).[3c] Somewhat to our surprise, alkylation of the enolate derived from 16 gave in 91% isolated yield a single product possessing structure 18.



16 18

Although the conversion of 18 into *dl*-estrone confirms the assignment of configuration at C(7) [C(13) steroid numbering], initial confirmation of stereochemistry was achieved by transformation of 18 into 20 via the bicyclo[2.2.1]heptene 19 (Scheme II). The spectra of 20 were found to be identical in all respects with those of a sample of 20 prepared by an alternate route (Scheme III).

Ketal 20 constitutes a potential precursor to estrone. However, initial attempts to carry out a Baeyer–Villiger oxidation on the ketone 22, which was obtained from 20 by hydrolysis, did not lead to any of the desired hydroxy carboxylic acid 23 or the corresponding lactone. Efforts



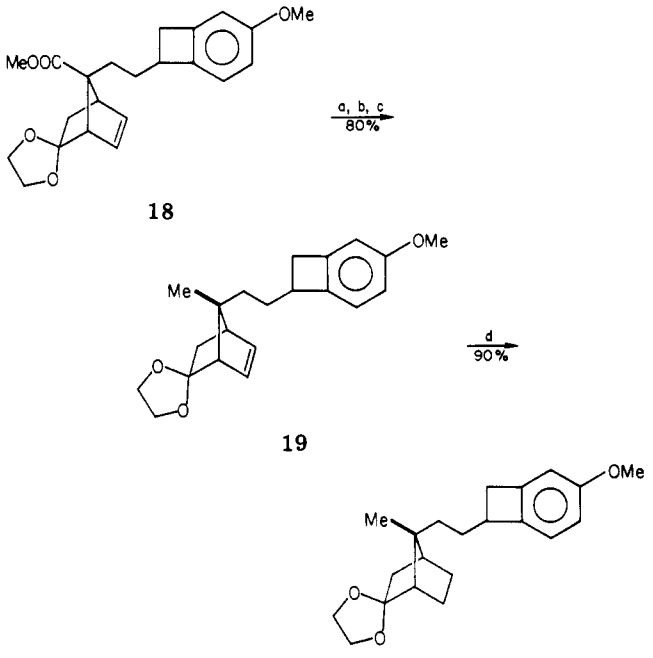
22 23

along these lines were abandoned in favor of the bicyclo[2.2.1]heptene derivative 19 (Scheme II).

With all of the carbon atoms needed for construction of estrone now assembled in the form of 19, we proceeded to elaborate ring D bearing a C(14) β-oriented vinyl group (Scheme IV). Deketalization of 19 generated (95%) the bicyclic ketone 2 in 95% yield. Baeyer–Villiger oxidation of 2, which unleashed the five-membered D ring, and subsequent esterification of the resultant hydroxy carboxylic acid gave rise to cyclopentenol 24. Transformation

(11) Unpublished results of D. R. Moore, University of Pittsburgh.

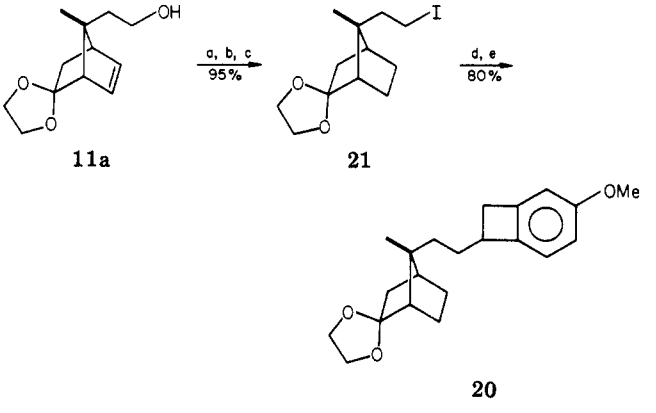
Scheme II[a]



18 19 20

[a] (a) $LiAlH_4$, THF, 60 °C; (b) MsCl, Py, CH_2Cl_2; (c) $LiEt_3BH$, THF; (d) H_2, 5% Pd-C.

Scheme III[a]



11a 21 20

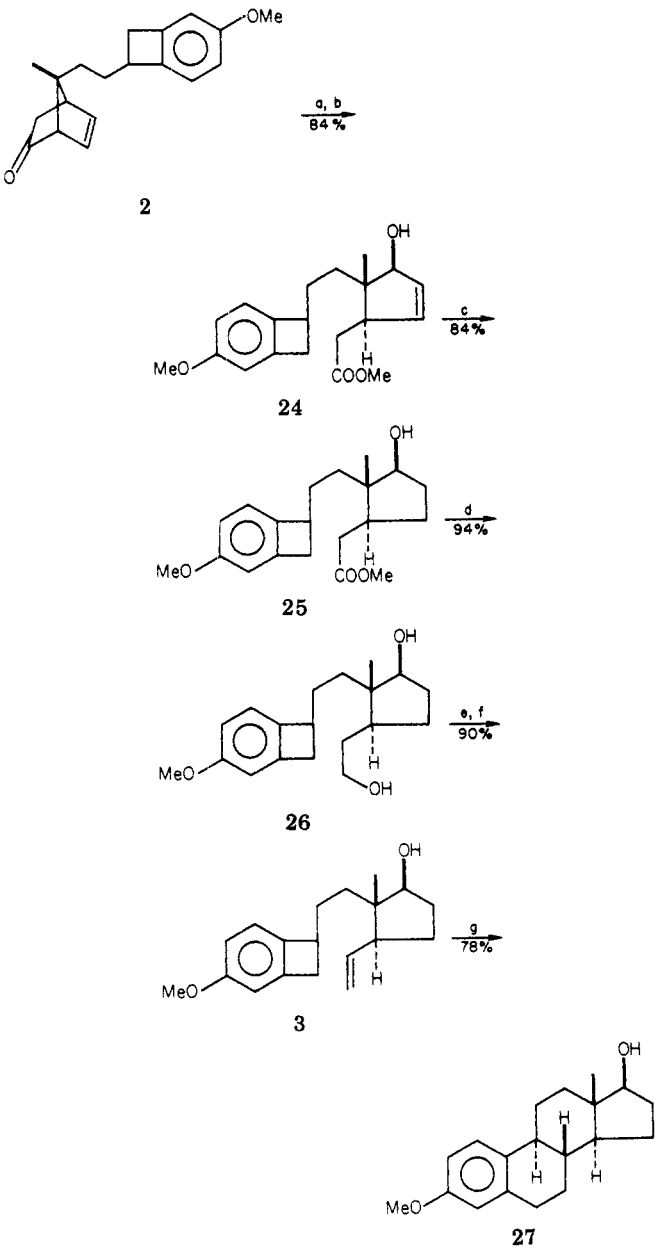
[a] (a) H_2, 5% Pd-C; (b) MsCl, Py, CH_2Cl_2; (c) NaI, acetone, reflux; (d) LDA, THF, −78 °C, 1-cyano-4-methoxybenzocyclobutene (12); (e) Na, NH_3, THF, *i*-PrOH, −78 °C.

of 24 into 26 proceeded in a straightforward fashion in high overall yield as indicated. Introduction of the C(14) (steroid numbering) vinyl substituent was accomplished in the presence of the free hydroxyl at C(17) by using selenium-based methodology.[12] Treatment of diol 26 with a 50% excess of *o*-nitrophenyl selenocyanate in tetrahydrofuran containing excess freshly distilled tri-*n*-butylphosphine produced a near-quantitative yield of primary monoselenide without any complications due to the hindered C(17) hydroxyl. Elimination of *o*-nitrobenzeneselenenic acid proceeded smoothly at room temperature upon treatment with 50% hydrogen peroxide.

Thermolysis of 3 at ca. 200 °C in *o*-dichlorobenzene according to Kametani's procedure[3c] generated in situ the sterically favored E-oriented *o*-quinodimethane which underwent cycloaddition via the sterically less congested exo transition state, giving rise to a 78% yield of crystalline

(12) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

Scheme IV[a]



[a] (a) 10% NaOH, 30% H_2O_2, 2:2:1 MeOH-THF-HOH; (b) CH_2N_2; (c) H_2, PtO_2, EtOAc; (d) $LiAlH_4$, THF; (e) o-$NO_2C_6H_4SeCN$, Bu_3P, THF, 0 °C; (f) 50% H_2O_2, THF; (g) o-dichlorobenzene, 200 °C.

racemic 3-methoxyestra-1,3,5(10)-triene-17β-ol (**27**), mp 134–135 °C (lit.[13] mp 132–133 °C). The transformation of **27** into estrone was carried by using well-established procedures.[14] Oxidation of **27** with Jones' reagent afforded a 95% yield of (±)-estrone methyl ester, mp 144–145 °C (lit.[15] mp 143.2–144.0 °C), which upon demethylation (BBr_3, CH_2Cl_2, 0 °C) provided pure racemic estrone (**4**), mp 254.5–256.0 °C (lit.[15] mp 252.8–254.7 °C).

The ready availability of bromo ketal ester **1** in optically pure form[16] permits direct asymmetric synthesis of estrone and related steroids employing the synthetic methodology described above.

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz (T-60 spectrometer). Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} 0.0) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran was distilled from sodium–benzophenone, and pyridine was distilled from calcium hydride. Methylene chloride was passed through a column of alumina prior to use.

Methyl 7-[2-(3-Methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-carboxylate (18). To a stirred solution of lithium diisopropylamide (0.62 mmol), prepared from 0.09 mL of diisopropylamine and 0.39 mL of n-butyllithium (1.6 M in hexane) in 0.5 mL of anhydrous freshly distilled tetrahydrofuran at −78 °C, was added a solution of 100 mg (0.48 mmol) of ketal ester **16**[17] in 1.0 mL of dry tetrahydrofuran over a 5-min period. After the addition was complete, the reaction mixture was warmed to 0 °C over 30 min and treated with 274 mg (0.95 mmol) of 2-(4-methoxybenzocyclobutenyl)ethyl iodide (**17**)[3c] in 1.0 mL of tetrahydrofuran. Stirring was continued at 0 °C for 1.5 h. The reaction was quenched by the addition of 10 mL of saturated ammonium chloride solution, and the product was isolated by extraction with ether. The combined ethereal extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo left a residue which was chromatographed on 8.0 g of silica gel. Elution with 10:1 hexane–ether gave 120 mg of recovered iodide. Continued elution with 3:1 hexane–ether provided 161 mg (91%) of pure ester **18** as a colorless oil which was homogeneous by TLC analysis (1:1 hexane–ether; R_f 0.28): IR (CCl_4) 3065, 2990, 2945, 2905, 2875, 2824, 1732, 1605, 1589, 1475, 1462, 1453, 1440, 1434, 1335, 1300, 1273, 1241, 1221, 1214, 1195, 1165, 1129, 1109, 1080, 1046, 1025, 1011, 950, 908, 861, 718 cm^{-1}; NMR (CCl_4) δ 6.87–6.45 (m, 3 H, aromatic protons), 6.25–5.81 (m, 2 H, CH=CH), 4.0–3.6 (m, 4 H, OCH_2CH_2O), 3.70 (s, 3 H, OCH_3), 3.58 (br s, 3 H, $COOCH_3$). Anal. ($C_{22}H_{26}O_5$) C, H.

7-[2-(3-Methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]-spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol. To a stirred suspension of 176 mg (4.64 mmol) of lithium aluminum hydride in 10 mL of anhydrous tetrahydrofuran was added 429 mg (1.16 mmol) of ketal ester **18** in 5.0 mL of tetrahydrofuran. After 18 h at 60 °C, the reaction mixture was cooled to 0 °C, treated slowly with water over 30 min, and filtered. The aluminum salts were washed with tetrahydrofuran several times and the combined organic layers were concentrated in vacuo. The residue was chromatographed on 8.0 g of silica gel. Elution with 1:1 ether–hexane gave 334 mg (84%) of pure alcohol as a colorless oil: R_f 0.44 (ether); IR ($CHCl_3$) 3550, 3070, 3000, 2975, 2950, 2920, 2890, 2830, 1605, 1591, 1478, 1457, 1440, 1424, 1395, 1340, 1320, 1300, 1275, 1245, 1170, 1119, 1085, 1070, 1042, 1025, 951, 910, 895, 861, 840, 820 cm^{-1}; NMR ($CDCl_3$) δ 7.01–6.60 (m, 3 H, aromatic protons), 6.30–6.02 (m, 2 H, CH=CH), 3.90 (m, 4 H, OCH_2CH_2O), 3.75 (s, 3 H, OCH_3). Anal. ($C_{21}H_{26}O_4$) C, H.

7-[2-(3-Methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]-7-methylspiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane] (19). A solution of 376 mg (1.10 mmol) of the above ketal alcohol in 7.0 mL of methylene chloride containing 0.36 mL (4.48 mmol) of pyridine was treated at 0 °C with 0.17 mL (2.24 mmol) of methanesulfonyl chloride. After 15 h at ~5 °C, the temperature was raised to 25 °C where stirring was continued for 3 h. The

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(14) Cf.: Ponsold, K.; Wagner, H. *Z. Chem.* **1977**, *17*, 61.
(15) Johnson, W. S.; Banerjee, D. K.; Schneider, W. P.; Gutsche, C. D.; Shelberg, W. E.; Chinn, L. J. *J. Am. Chem. Soc.* **1952**, *74*, 2832.
(16) Grieco, P. A.; Wang, C.-L. J.; Owens, W.; Williams, E.; Sugahara, T.; Yokoyama, Y.; Okuniewicz, F. J.; Withers, G. "Chemistry and Biochemistry of Prostanoids"; Pergamon Press: Elmsford, NY, 1979; p 87.
(17) Ester **16** as a mixture at C(7) was prepared in 85% overall by treatment of bromo ketal ester **1** with 4.0 equiv of DBU in refluxing DMF.

reaction mixture was diluted with 50 mL of benzene, and the solvent was removed under reduced pressure. The residue was chromatographed on 8.0 g of silica gel. Elution with 1:2 hexane–ether gave 460 mg (100%) of pure mesylate [R_f 0.67 (ether); IR (CCl_4) 1370, 1180 cm^{-1}; NMR (CCl_4) δ 2.84 (s, 3 H, OSO_2CH_3)] which was used directly in the next reaction.

To a solution of 124 mg (0.30 mmol) of the above mesylate in 2.5 mL of dry tetrahydrofuran was gradually added dropwise at 25 °C 1.18 mL (1.18 mmol) of a 1 M solution of lithium triethylborohydride (Super-Hydride) in tetrahydrofuran. After 3 h at 25 °C, the reaction was quenched by the slow addition of water. The product was isolated by extraction with ether. The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The residue was chromatographed on 8.0 g of silica gel. Elution with 5:1 hexane–ether provided 91 mg (95%) of pure ketal **19** as a colorless oil: R_f 0.47 (1:1 hexane–ether); IR (CCl_4) 3075, 2950, 2920, 2880, 2850, 2825, 2802, 1604, 1688, 1475, 1465, 1381, 1340, 1322, 1295, 1275, 1242, 1220, 1205, 1165, 1120, 1110, 1091, 1049, 1022, 950, 915, 895, 718 cm^{-1}; NMR (CCl_4) δ 6.83–6.43 (m, 3 H, aromatic protons), 6.10–5.80 (m, 2 H, CH=CH), 3.65 (s, 3 H, OCH_3), 3.90–3.50 (m, 4 H, OCH_2CH_2O), 1.11 (s, 3 H). Anal. ($C_{21}H_{26}O_3$) C, H.

7-[2-(3-Methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]-7-methylbicyclo[2.2.1]hept-5-en-2-one (2). A solution of 322 mg (0.99 mmol) of ketal **19** in 10 mL of tetrahydrofuran was treated with 3.3 mL of 10% hydrochloric acid solution. After 5 h at room temperature, the product was isolated by extraction with ether (3 × 30 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was chromatographed on 8.0 g of silica gel. Elution with 5:1 hexane–ether gave 266 mg (95%) of the desired ketone: R_f 0.49 (1:1 hexane–ether); IR (CCl_4) 3070, 3000, 2980, 2950, 2920, 2895, 2855, 2840, 1750, 1607, 1595, 1480, 1470, 1431, 1390, 1348, 1320, 1280, 1252, 1230, 1178, 1150, 1135, 1091, 1060, 1035, 920, 875, 725 cm^{-1}; NMR (CCl_4) δ 6.85–6.50 (m, 3 H, aromatic protons), 6.40 (m, 1 H), 5.97 (m, 1 H), 3.70 (s, 3 H, OCH_3), 1.09 (s, 3 H). Anal. ($C_{19}H_{22}O_2$) C, H.

Methyl 4-Hydroxy-5-[2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]-5-methyl-2-cyclopenteneacetate (24). A solution of 245 mg (0.87 mmol) of ketone **2** in 8.5 mL of methanol, 8.5 mL of tetrahydrofuran, and 4.5 mL of water was treated at 0 °C with 3.0 mL of a 10% sodium hydroxide solution and 1.5 mL of 30% hydrogen peroxide. After 12 h at room temperature an additional 2.0 mL of 10% sodium hydroxide solution and 1.0 mL of 30% hydrogen peroxide were added to the reaction flask. Stirring was continued at room temperature for 22 h. The reaction mixture was acidified with concentrated hydrochloric acid and the excess peroxide destroyed by the addition of solid sodium bisulfite. Reacidification followed by isolation of the product by extraction with ethyl acetate (4 × 30 mL) gave crude hydroxy acid [IR (CCl_4) 3600–2300, 1712 cm^{-1}] which was esterified with ethereal diazomethane. Removal of the solvent in vacuo left a residue which was chromatographed on 8.0 g of silica gel. Elution with 2:1 hexane–ether gave 241 mg (84%) of pure hydroxy ester **24**: R_f 0.22 (1:1 hexane–ether); IR (CCl_4) 3625, 3500, 3060, 3000, 2950, 2935, 2900, 2855, 2830, 2810, 1741, 1606, 1595, 1479, 1470, 1455, 1440, 1425, 1390, 1375, 1348, 1281, 1261, 1250, 1229, 1200, 1175, 1130, 1090, 1032, 1009, 920 cm^{-1}; NMR (CCl_4) δ 6.90–6.48 (m, 3 H, aromatic protons), 5.70 (s, 2 H, CH=CH), 4.18 (br s, 1 H, CHOH), 3.70, (s, 3 H, OCH_3), 3.60 (s, 3 H, $COOCH_3$), 0.86 (s, 3 H, CH_3). Anal. ($C_{20}H_{26}O_4$) C, H.

Methyl 3-Hydroxy-2-[2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]-2-methylcyclopentaneacetate (25). A solution of 228 mg (0.69 mmol) of cyclopentenol **24** in 10 mL of dry ethyl acetate containing 5 mg of platinum oxide was stirred at room temperature under an atmosphere of hydrogen for 1.5 h. The catalyst was removed by filtration and the solvent was evaporated in vacuo. Chromatography of the residue on silica gel with 2:1 hexane–ether gave 193 mg (84%) of the saturated cyclopentanol **25**: R_f 0.26 (1:1 hexane–ether); IR (CCl_4) 3630, 3500, 3080, 3000, 2950, 2925, 2895, 2875, 2850, 2825, 2805, 1740, 1604, 1590, 1475, 1465, 1450, 1441, 1438, 1421, 1378, 1340, 1320, 1278, 1245, 1223, 1195, 1168, 1154, 1145, 1100, 1082, 1045, 1025, 1010, 995, 975, 920, 890, 845 cm^{-1}; NMR (CCl_4) δ 6.91–7.48 (m, 3 H, aromatic protons), 3.70 (s, 3 H, OCH_3), 3.59 (s, 1.5 H, CO_2CH_3), 3.56 (s, 1.5 H, CO_2CH_3), 0.70 (s, 3 H). Anal. ($C_{20}H_{28}O_4$) C, H.

3-Hydroxy-2-[2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]-2-methylcyclopentaneethanol (26). To a stirred solution of 151 mg (0.48 mmol) of hydroxy ester **25** in 5.0 mL of anhydrous tetrahydrofuran cooled to 0 °C was added 76 mg (2 mmol) of lithium aluminum hydride. After 2 h at room temperature, excess reducing reagent was destroyed by the addition of ethyl acetate. The reaction mixture was cooled to 0 °C and treated with water. The product was isolated in the usual manner by washing and extracting with ethyl acetate. The crude diol was chromatographed on 8.0 g of silica gel. Elution with 1:1 benzene–ether gave 137 mg (94%) of diol **26** as a colorless oil: R_f 0.46 (ether); IR ($CHCl_3$) 3625, 3450, 3000, 2960, 2925, 2895, 2875, 2850, 2840, 2810, 1604, 1590, 1478, 1465, 1455 1445, 1429, 1400, 1380, 1343, 1312, 1275, 1248, 1170, 1126, 1105, 1085, 1049, 1026, 990, 912 cm^{-1}; NMR ($CDCl_3$) δ 7.03–6.62 (m, 3 H, aromatic protons), 3.72 (s, 3 H, OCH_3), 0.75 (s, 3 H). Anal. ($C_{19}H_{28}O_3$) C, H.

3-Ethenyl-2-[2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]-2-methylcyclopentanol (3). To a solution of 120 mg (0.40 mmol) of diol **26** and 135 mg (0.60 mmol) of *o*-nitrophenyl selenocyanate in 5.0 mL of tetrahydrofuran cooled to 0 °C was added 120 mg (0.60 mmol) of tri-*n*-butylphosphine. After 2 h at 0 °C, the reaction mixture was concentrated in vacuo and the residue was chromatographed on 25 g of silica gel. Elution with 1:1 hexane–ether gave 188 mg (98%) of the desired selenide as a yellow oil: R_f 0.33 (1:2 hexane–ether); IR (CCl_4) 3640, 3400, 3080, 3000, 2950, 2925, 2900, 2875, 2850, 2835, 1595, 1570, 1520, 1478, 1468, 1455, 1435, 1339, 1305, 1277, 1249, 1225, 1175, 1125, 1095, 1080, 1050, 1040, 1025, 850, 725, 700 cm^{-1}; NMR (CCl_4) δ 8.21 (m, 1 H), 7.37 (m, 3 H), 6.94–6.48 (m, 3 H), 3.71 (s, 3 H), 0.70 (s, 3 H).

A solution of the above selenide (186 mg, 0.38 mmol) in 7.5 mL of tetrahydrofuran was treated at 0 °C with 0.25 mL of 50% hydrogen peroxide solution. Upon completion of the addition of hydrogen peroxide, the reaction was warmed to room temperature. After 2.5 h, the reaction mixture was diluted with water and the product was isolated by extraction with ether. The combined organic layers were washed with sodium bisulfite solution, water, and brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on 30 g of silica gel. Elution with 1:1 methylene chloride–ether gave 99 mg (91%) of olefin **3** as a colorless oil: R_f 0.58 (1:2 hexane–ether); IR (CCl_4) 3625, 3450, 3080, 2995, 2950, 2910, 2890, 2870, 2845, 2825, 2800, 1635, 1600, 1582, 1470, 1460, 1450, 1440, 1420, 1390, 1375, 1340, 1275, 1245, 1220, 1215, 1185, 1166, 1122, 1096, 1081, 1025, 995, 915, 860, 845 cm^{-1}; NMR (CCl_4) δ 6.91–6.48 (m, 3 H, aromatic protons), 5.97–5.40 (m, 1 H), 5.00–4.70 (m, 2 H), 3.70 (s, 3 H, OCH_3), 0.74 (s, 3 H). Anal. ($C_{19}H_{26}O_2$) C, H.

3-Methoxyestra-1,3,5(10)-trien-17β-ol (27). A solution of 97 mg (0.34 mmol) of olefin **3** in 10 mL of *o*-dichlorobenzene was heated at 200 °C under an atmosphere of nitrogen for 7.5 h. The cooled reaction mixture was chromatographed on 8.0 g of silica gel. Elution with 2:1 hexane–ether provided 97 mg of crystalline 3-methoxyestra-1,3,5(10)-trien-17β-ol, R_f 0.44 (1:2 hexane–ether). Recrystallization from hexane–methanol gave 76 mg (78%) of pure **27**, mp 134–135 °C (lit.[13] mp 132–133 °C).

***dl*-Estrone Methyl Ether.** A stirred solution of 43 mg (0.15 mmol) of 3-methoxyestra-1,3,5(10)-trien-17β-ol in 3 mL of acetone was treated at 0 °C with 0.06 mL of Jones' reagent. After 10 min, the reaction mixture was quenched at 0 °C with excess 2-propanol, and stirring was continued for 10 min. The reaction mixture was diluted with water, and the product was isolated by extraction with chloroform. The combined organic layers were washed with saturated sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded crude estrone methyl ether in quantitative yield. Chromatography on 6.0 g of silica gel with 5:1 hexane-ether gave 40.4 mg (95%) of pure crystalline racemic estrone methyl ether: R_f 0.53 (1:1 hexane–ether); mp 144–145 °C (methanol–acetone) [lit.[15] 143.2–144.0 °C (methanol–acetone)].

***dl*-Estrone.** To a solution of 20 mg (0.07 mmol) of *dl*-estrone methyl ether in 1.0 mL of methylene chloride cooled to −30 °C was added 0.1 mL of boron tribromide. After 2 h at 5 °C the

reaction was quenched by the addition of methanol followed by dilution with water. The product was isolated by extraction with chloroform. The combined organic layers were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the crude product was chromatographed on 6.0 g of silica gel. Elution with 2:1 hexane–ether gave 1.0 mg of recovered methyl ether and 14.5 mg (80% based on recovered starting material) of pure crystalline racemic estrone: R_f 0.31 (1:1 hexane–ether); mp 254.5–256.0 °C (acetone) [lit.[15] mp 252.8–254.7 °C (acetone)].

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Registry No. **2**, 73178-94-6; **3**, 73178-95-7; **4**, 19973-76-3; **4** methyl ether, 1091-94-7; **16**, 73178-96-8; **17**, 60100-25-6; **18**, 73178-97-9; **19**, 73178-98-0; **24**, 73178-99-1; **24** hydroxy acid, 73179-00-7; **25**, 73179-01-8; **26**, 73179-02-9; **26** selenide, 73179-03-0; **27**, 3855-62-7; 7-[2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]spiro[bicyclo-[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol, 73193-02-9; 7-[2-(3-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)ethyl]spiro[bicyclo-[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol mesylate, 73179-04-1.

Notes

An Improved Route to a Key Hydroazulenone Intermediate for Helenanolide Synthesis

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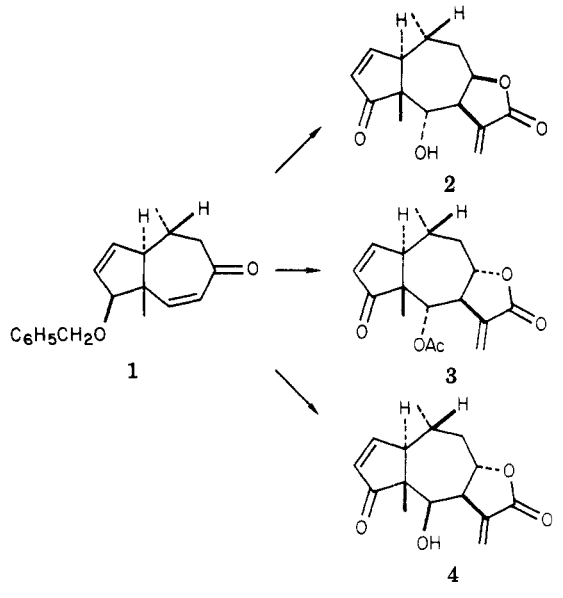
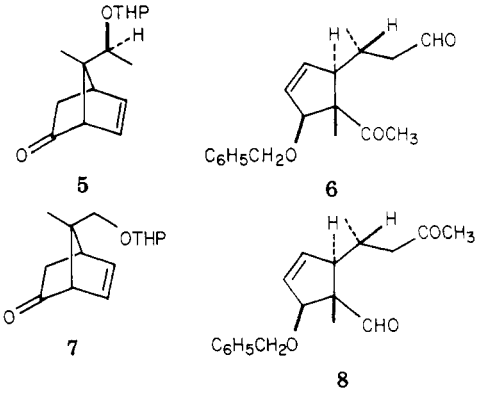
Considerable progress in the total synthesis of ambrosanolides (e.g., ambrosin,[2] confertin,[3] damsin,[2,3d,4] hymenin,[5] parthenin,[5] and stramonin-B[6]) has been recorded during the past 4 years. In contrast, progress in helenanolide total synthesis has been limited due to problems encountered in elaborating the six chiral centers located on the flexible seven-membered ring [cf. helenalin (**2**)].[7]

We have recently reported total syntheses of helenalin (**2**),[7a] bigelovin (**3**),[7b] and mexicanin I (**4**)[7c] which proceeded via the common intermediate hydroazulenone **1**. Enone **1** was synthesized previously from keto aldehyde **6**[7a] by employing a lengthy sequence of reactions starting from the bicyclo[2.2.1]heptenone derivative **5**.[2] We detail below a shorter, more efficient route to **1** which (a) utilizes as a starting material the known bicyclo[2.2.1]heptenone **7**[8] and (b) proceeds via the intermediacy of keto aldehyde **8**, a direct precursor to hydroazulenone **1**.





The C(3) endo-methylated bicyclo[2.2.1]heptenone **9** was readily prepared in 94% yield upon treatment of the lithium enolate of **7**[8] in tetrahydrofuran cooled to 0 °C with methyl iodide. As anticipated, the bulky C(7) *syn*-methyl group completely blocks exo approach to the enolate. During the course of the base-catalyzed Baeyer–Villiger oxidation (H_2O_2, OH^-, 1:1 HOH–MeOH)[9] and subsequent esterification,[10] which unravels the bicyclo[2.2.1]heptenone

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