Soc., 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(9) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **29**, 123 (1964).
(10) No attempt was made to separate these epoxides. The stereochemistry was assigned on the basis of precedent and the epoxide ring opening was expected to generate (after oxidation) easily separable enone **9b** as the major product; see ref 6.
(11) J. K. Crandall and L. C. Crawley, *Org. Synth.*, **53**, 17 (1973); C. L. Kissel and B. Rickborn, *J. Org. Chem.*, **37**, 2060 (1972); R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, **92**, 2064 (1970).
(12) J. C. Collins and W. W. Hess, *Org. Synth.*, **52**, 5 (1972); R. Ratcliffe and R. Rodehorst, *ibid.*, **55**, 84 (1976); N. H. Andersen and H. Uh, *Synth. Commun.*, **3**, 115 (1973).
(13) E. Roman, A. J. Frey, P. A. Stadler, and A. Eschenmoser, *Helv. Chem. Acta*, **40**, 1900 (1957); R. W. Skeean, G. L. Trammell, and J. D. White, *Tetrahedron Lett.*, 525 (1976).
(14) D. F. MacSweeney and R. Ramage, *Tetrahedron*, **27**, 1481 (1971).
(15) R. D. Rieke and P. M. Hudnall, *J. Am. Chem. Soc.*, **94**, 7178 (1972); R. D. Rieke and S. E. Bales, *J. Chem. Soc., Chem. Commun.*, 879 (1973).
(16) R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Am. Chem. Soc.*, **94**, 2056 (1972).
(17) A. Maercker, *Org. React.*, **14**, 270 (1965).
(18) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970); *Aust. J. Chem.*, **25**, 1719, 1713 (1972).
(19) I. T. Harrison, *Chem. Commun.*, 616 (1969).
(20) R. Mechoulan and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965).
(21) We are grateful to Professor W. Fenical for providing natural samples of zonarone and isozonarone which were converted to the respective methyl ethers (**1a** and **1b**) by reduction ($NaBH_4$, CH_3OH) and *O*-alkylation (CH_3I, CaO, Me_2SO, room temperature, 24 h).
(22) The names of each of the compounds were obtained from Professor Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, Columbus, Ohio, 43210.

Stereoselective Biomimetic Total Synthesis of 6α-Methyl-19-norsteroids

Marinus B. Groen and Filippus J. Zeelen*

Organon Scientific Development Group, Oss, The Netherlands.

Received November 1, 1977

Cyclization of the chiral substrate 3-methyl-2-[(*E*)-6′-(*m*-methoxyphenyl)-3′-heptenyl]-2-cyclopenten-1-ol (**6**) was investigated. In addition to high stereo- and regioselectivity almost complete optical induction by the methyl substituent was observed: with stannic chloride at −70 °C ~75% of the tetracyclic products consisted of 3-methoxy-6α,17-dimethyl-1,3,5(10),13(17)-gonatetraene (**8a**). This compound was converted into the 3-methyl ethers of *dl*-6α-methylestrone (**11**) and *dl*-6α-methylestradiol-17β (**13**), thus giving access to 6α-methyl-19-norsteroids.

In the last decade the biomimetic polyene cyclization reaction has proved to be a fruitful approach to the total synthesis of polycyclic natural products.[1] Practical applications for the synthesis of steroids were most extensively explored by Johnson and co-workers.[1a,b] One of the many contributions by this group was a stereospecific total synthesis of *dl*-estrone.[2]

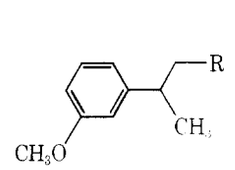
In this paper we report an extension of the latter synthesis, starting with a polyolefinic substrate which carries a methyl substitutent at the pro-C-6 atom.[3] The purpose of this modification was (a) to see whether the newly introduced chiral center would effect asymmetric induction in the cyclization and (b) to examine the practicality of this synthesis as a route to 6α-methyl-19-norsteroids.[17]

The substrate used in the *dl*-estrone synthesis[2] lacks a stable chiral center, leading to racemic products.[4] The presence of a stable chiral center in the substrate allows early resolution (an important condition for an efficient steroid synthesis) and formation at will of the steroid with the natural or unnatural configuration depending on which enantiomer of the substrate is used, *provided a high degree of optical induction by the chiral center takes place.* Examples of optical induction in the biomimetic synthesis of 11α-methyl- and 11α-hydroxyprogesterone were reported by the Stanford group.[3a,b] In the present case the chiral center is further removed from the reaction center so that optical induction is not an a priori obvious matter.

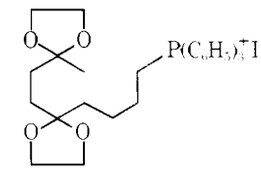
6α-Methyl-19-norsteroids were shown to be compounds with potent hormonal activity.[5] They have been prepared by partial synthesis via a somewhat troublesome route[6] and in racemic form via a Smith–Torgov type total synthesis.[5] Interestingly the latter synthesis produces 6β-methylestradiol derivatives as the major initial products, whereas the 6α isomers are the biologically more active ones.[7]

Synthesis of the Substrate

Methyl 3-(*m*-methoxyphenyl)butyrate (**1**) was prepared in 68% yield by addition of lithium dimethylcuprate to methyl *m*-methoxycinnamate. This synthesis is shorter than the published one[5] and more versatile allowing the introduction of alkyl groups other than methyl by a proper choice of the organometallic reagent. It should be noted that **1** is an asymmetric compound and therefore, at least in principle, resolvable.

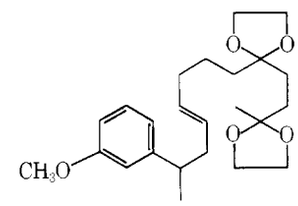


1, R = $COOCH_3$
2, R = CHO

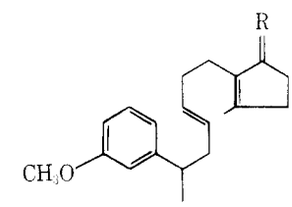


3

Elegant asymmetric syntheses of β-substituted acids[8a] and aldehydes[8b] have been reported. The aldehyde **2**, obtained by reduction of **1** with diisobutylaluminium hydride in 72% yield, was condensed with the phosphorane derived from **3**[9] employing Wittig–Schlosser conditions.[10] The olefin **4** was



4



5, R = O
6, R = H(OH)

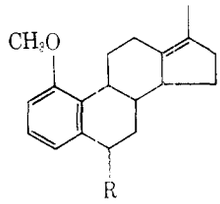
isolated in 80% yield (over 95% trans isomer by NMR analysis). Acid-catalyzed hydrolysis followed by base-catalyzed cyclodehydration produced the cyclopentenone **5** in 84% yield.

The ketone **5** was reduced with lithium aluminum hydride to the substrate **6** in quantitative yield. Due to its instability **6** was subjected to cyclization immediately after workup.

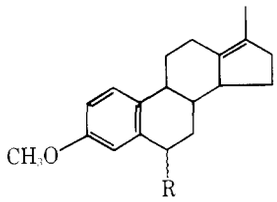
0022-3263/78/1943-1961$01.00/0

Cyclization Studies

The substrate **6** was cyclized with stannic chloride (3–5 equiv) in dichloromethane (30 min, −70 °C). The reaction mixture showed essentially two spots on TLC. These corresponded with a less and a more polar fraction isolated in 12 and 64% yield by column chromatography, consisting of the 1-methoxy (**7a, 7b**) and 3-methoxy isomers (**8a, 8b**), respectively.



7a, R = α-CH_3
b, R = β-CH_3



8a, R = α-CH_3
b, R = β-CH_3

Crystallization of the less polar fraction from methanol afforded its major component (9.5% yield based on **6**), mp 94.5–96.5 °C, which was assigned structure **7a.** The proton NMR spectrum showed inter alia a doublet at δ 1.27 (J = 6.8 Hz) for the 6α-CH_3 group and a doublet of doublets at δ 6.94 (J = 8 and 2.5 Hz) for the proton at C-4. The latter represents a downfield shift of over 0.2 ppm with respect to the 6-unsubstituted case. This shift is characteristic for a 6α-methyl substituent.[5]

Examination of the NMR spectrum of the mother liquor revealed the presence of a second methyl signal centered at δ 1.30 (d, J = 7 Hz), attributed to the 6β-isomer **7b.** Integration and taking into account the amount of **7a** isolated showed that the **7a/7b** ratio originally must have been ca. 9:1.

Crystallization of the more polar fraction from methanol afforded nearly pure **8a,** mp 37–42 °C, in 53% yield based on **6.** The proton NMR spectrum showed inter alia a doublet at δ 1.31 (J = 7 Hz) for the 6α-CH_3 group and a broadened doublet (J = 2.5 Hz) at δ 6.83 for the proton at C-4. These values compare well with reported data.[5] The stereochemistry was proven unambiguously by the conversion of **8a** into compounds with known structure (vide infra). The NMR spectrum of the mother liquor showed an additional doublet centered at δ 1.28 attributed to the 6β-isomer **8b** (cf. ref 5). The original mixture was determined to be a 9:1 mixture of **8a** and **8b.**

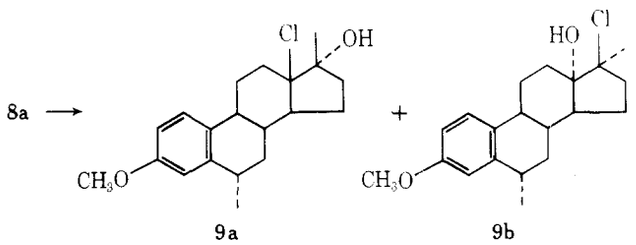
The cyclization of **6** was also carried out with formic acid at ca. 5°C. This afforded **7a** plus **7b** in 19% yield and **8a** plus **8b** in 52.5% yield. As in the previous experiment the **7a/7b** and **8a/8b** ratio's were ca. 9:1.

Pure **8a** was converted into a mixture of chlorohydrins (**9a, 9b**) by reaction with N-chlorosuccinimide in 2:1 *tert*-butyl alcohol/water. In situ treatment with KOH afforded the α-epoxide **10** in 54% yield, mp 149–151 °C.

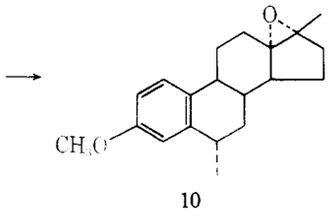
The somewhat disappointing yield could be traced to the first step. A sample of pure chlorohydrin[11] was isolated by chromatography over deactivated alumina (ca. 50% yield). Subsequent treatment with base employing the same conditions as above afforded **10** in practically quantitative yield.

The epoxide **10** was converted into the methyl ether of *dl*-6α-methylestrone (**11**) in 64% yield with boron trifluoride in toluene or dichloromethane. This compound, mp 110–112 °C, was spectroscopically (NMR, IR) identical to authentic **11** (*d* enantiomer),[12] but different from authentic **12.**[13] Thus the structure of **11** and hence that of **8a** were unequivocally established.

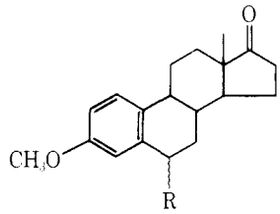
The mother liquor of **8a** (enriched in **8b**) was also carried through the reaction sequence described above. The NMR spectrum of the reaction product clearly showed the presence



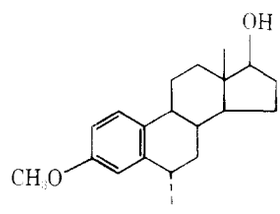
9a 9b



10



11, R = α-CH_3
12, R = β-CH_3



13

of both **11** (13-CH_3 at δ 0.89) and **12** (13-CH_3 at δ 0.92), but the latter product could not be obtained in a pure state.

Reduction of **11** with lithium aluminum hydride afforded the known racemic estradiol derivative **13,** whose physical data agreed with those reported.[5]

Discussion

The synthesis of the substrate **6** closely follows the reported procedure[2] and requires no comment. The low-temperature cyclization of **6** with $SnCl_4$ showed high regioselectivity, the para/ortho ratio (=**8a** + **8b**/**7a** + **7b**) being ca. 5 at −70 °C. As expected this ratio was affected by temperature and catalyst decreasing to 2.7 at 5 °C with formic acid. No doubt the para/ortho ratio can be improved by conducting the cyclization at lower temperature and by the use of bulkier ether substituents as was demonstrated by Johnson.[2]

More significant for our purpose is the great preponderance of 6α- over 6β-methyl-substituted cyclization products (9:1 ratio). This implies that cyclization of the (*S*) enantiomer of **6,** which can be obtained from (*S*)-**1,** must lead predominantly to products with the natural steroid configuration. It can be deduced that in that case the 6α-substituted products **7a** and **8a** will have the natural configuration and those with the 6β-methyl substituent **7b** and **8b** the unnatural one. Since the latter products can easily be removed by crystallization it follows that the work described here lends itself to the *total asymmetric synthesis of steroids with natural configuration* by the simple expedient of resolution (or asymmetric synthesis) at a *very early stage.*[14]

Whereas generally good yields were obtained in the synthesis leading to **8a** further conversion into **11** suffered from relatively low yields. This was especially so for the formation of the chlorohydrins (**9a, 9b**). It was found that in this reaction step considerable amounts of polar by-products (up to 30% yield) were formed. We believe that these products[15] arise by initial α attack of the Cl^+ ion followed by proton elimination and hydrolysis.[16]

In spite of these complications, which need further exploration, already the overall yield of the total synthesis described here compares favorably with the previously reported Smith–Torgov route.[5] Moreover it complements the latter in that 6α- rather than 6β-methylestrone derivatives are ob-

tained as the principal products. In fact apart from a single reference in the patent literature[7] no satisfactory synthesis for this class of compounds appears to have been reported (for an alternative unpublished synthesis, ref 12).

Experimental Section

Boiling points and melting points, determined in capillary tubes, are uncorrected. Infrared spectra were recorded in dichloromethane solution on a Perkin-Elmer 357 grating spectrometer. Proton NMR spectra were recorded in deuteriochloroform solution with tetramethylsilane as internal standard on a Varian A 60 D or a Bruker HX-90E instrument.

Microanalyses were performed by Dr. W. McMeekin, Analytical Department, Organon Laboratories, Newhouse, Scotland. For column chromatography Woelm silica gel 90–230 mesh and Woelm aluminum oxide were used.

Unless stated otherwise reaction mixtures were worked up by addition of water followed by three extractions with ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. After filtration solvents were removed in vacuo on a rotary evaporator. The residues were chromatographed over 20–30-fold by weight silica gel.

***dl*-3-(*m*-Methoxyphenyl)butanal (2).** A solution of lithium dimethylcuprate was prepared by addition of 40 mL of methyllithium (2 M solution, 0.080 mol) in ether to 7.6 g (0.040 mol) of cuprous iodide in 70 mL of dry ether under nitrogen at 0 °C.

A solution of 4.8 g (0.025 mol) of methyl *m*-methoxycinnamate in 20 mL of ether was added dropwise and the resulting mixture was stirred for 1 h at 0 °C. The crude product was chromatographed with 8:2 hexane–ethyl acetate to give 3.65 g (68% yield) of methyl 3-(*m*-methoxyphenyl)butyrate (1). This was dissolved in 36 mL of dry toluene and cooled to −78 °C under nitrogen. A solution of diisobutylaluminum hydride in toluene (17.5 mL, 1.2 M, 20% excess) was added dropwise at <−70 °C. The reaction mixture was stirred for 25 min at −70 °C and then poured onto 70 mL of 2 N sulfuric acid. The mixture was allowed to warm up to room temperature and the organic layer was separated, dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was chromatographed with 9:1 hexane–ethyl acetate and distilled in vacuo to give 2.25 g of **2** (72% yield): bp 92–94 °C (0.8 mm); NMR δ 1.32 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 2.67 (m, 2 H, CH_2CHO), 3.35 (m, 1 H, $ArCH$–), 3.80 (s, 3 H, OCH_3), 6.6–7.4 (m, 4 H, aromatic H's), 9.70 (t, *J* = *2 Hz, 1 H, CHO*); IR 2839 (OCH_3), 1725, 2720, 2821 cm^{-1} (CHO). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.96. Found: C, 74.24; H, 7.79; O, 18.19.

***dl*-(*E*)-2-(*m*-Methoxyphenyl)-9,12-bis(ethylenedioxy)-4-tridecene (4).** A suspension of 6.32 g (0.01 mol) of the phosphonium salt **3** in 20 mL of dry THF was cooled in an ice bath under nitrogen, while 11 mL of a 1.0 M solution of phenyl lithium in ether was added dropwise (a red coloration indicating formation of the ylid started after addition of ca. 1 mL). The resulting red solution was stirred for 15 min without cooling and then cooled to −70 °C. A solution of 1.6 g (9 mmol) of aldehyde **2** in 5 mL of dry THF was added dropwise and after 5 min 18 mL of 1 M phenyllithium in ether was added. The resulting red solution was warmed to −30 °C. After 5 min at −30 °C the reaction was quenched with 1 mL of methanol. Normal workup and chromatography with 8:2 hexane–ethyl acetate afforded 2.9 g (79% yield) of **4** as a colorless oil: NMR δ 1.22 (d, *J* = 7 Hz, 3 H, protons at C-1), 1.31 (s, 3 H, protons at C-13), 1.70 (s, 4 H, protons at C-10 and C-11), 2.7 (m, 1 H, $ArCH$–), 3.80 (s, 3 H, OCH_3), 3.92 (br s, 8 H, OCH_2CH_2O), 5.36 (m, 2 H, olefinic protons), 6.6–7.4 (m, 4 H, aromatic protons), 1.3–2.4 (m, 8 H); IR 971 cm^{-1} (trans CH=CH). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; O, 19.78. Found: C, 71.09; H, 9.07; O, 19.89.

***dl*-3-Methyl-2-[(*E*)-6′-(m-methoxyphenyl)-3′-heptenyl]-2-cyclopenten-1-one (5).** A solution of 2.9 g (7.2 mmol) of **4** in 130 mL of 2:1 95% ethanol–0.2 N hydrochloric acid was heated at 55–60 °C for 1.5 h. Subsequently 11.5 mL of 2 N aqueous potassium hydroxide was added and the resulting mixture was heated at reflux for 2 h. The reaction mixture was concentrated in vacuo to ca. 50 mL and was further worked up in the normal manner. Chromatography with 8:2 hexane–ethyl acetate gave 1.8 g (84% yield) of **5** as a viscous colorless oil: NMR δ 1.20 (d, *J* = 7 Hz, 3 H, $ArCHCH_3$), 1.98 (br s, 3 H, allylic methyl), 3.78 (s, 3 H, OMe), 5.32 (m, 2 H, CH=CH), 6.5–7.3 (m, 4 H, aromatic protons), 1.9–2.9 (m, 11 H); IR 1699, 1645 (cyclopentenone), 969 cm^{-1} (trans CH=CH). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.60; H, 8.86; O, 10.50.

***dl*-3-Methyl-2-[(*E*)-6′-(*m*-methoxyphenyl)-3′-heptenyl]-2-cyclopenten-1-ol (6).** A solution of 1.8 g (6 mmol) of **5** in 60 mL of dry ether was cooled to −20 °C. Lithium aluminum hydride (0.45 g, 12 mmol) was added in portions, with stirring. The mixture was allowed to warm up to 0 °C over 30 min. The excess of hydride was destroyed by addition of saturated sodium sulfate solution. The ether layer was decanted from precipitated salts, which were extracted with two more portions of ether. The combined ether solutions were dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo (<25 °C). This left 1.8 g (99% yield) of **6** as a colorless oil, which was immediately used in the next step.

***dl*-1- and -3-Methoxy-6α,17-dimethyl-1,3,5(10),13(17)-gonatetraene (7a and 8a). a. With Stannic Chloride.** A solution of stannic chloride (2.8 mL, 5 equiv) in 150 mL of dry dichloromethane was cooled to −70 °C under nitrogen. A solution of 1.80 g (6.0 mmol) of **6** in 60 mL of dichloromethane was added dropwise with stirring over 1 h and the resulting red solution was stirred for another 30 min at −70 °C. A solution of 6.0 g of NaOH in 30 mL of 80% ethanol was added dropwise (temperature <−60 °C) followed by water. The mixture was allowed to warm up to room temperature; the organic phase was separated and dried over anhydrous K_2CO_3. The solvent was stripped off and the residue was chromatographed with 9:1 hexane–toluene. First 1-methoxy isomers (**7a, 7b**) were eluted (0.198 g, 12% yield). Crystallization from methanol gave 0.133 g of **7a,** mp 94.5–96.5 °C, and a second crop of 0.027 g, mp 87–91 °C (9.5% yield). The mother liquor contained about equal amounts of **7a** and **7b.** Further elution produced the 3-methoxy isomers (**8a, 8b**) as an oil (1.08 g, 64% yield). Crystallization from methanol gave 0.90 g (53% yield) of crystalline **8a,** mp 37–42 °C. Repeated crystallization afforded an analytically pure sample, mp 45–46 °C. The mother liquor consisted of **8a** and **8b,** which could not be separated.

b. With Formic Acid. A solution of 0.85 g (2.83 mmol) of **6** in 50 mL of dichloromethane was added dropwise with stirring to 25 mL of 98% formic acid at ca. 5 °C After the addition was completed (ca. 1 h) the pale yellow reaction mixture was stirred for 15 min at 5 °C and then diluted with water. The organic phase was separated, washed with water and aqueous sodium bicarbonate, and dried over anhydrous K_2CO_3. The products were isolated and purified as in a. Thus were obtained **7a** + **7b** (9:1 mixture) in 19% yield (0.15 g) and **8a** + **8b** in 52.5% yield (0.42 g) also as a 9:1 mixture. **7a:** NMR δ 1.27 (d, *J* = 6.8 Hz, 3 H, 6α-CH_3), 1.65 (br s, 3 H, 17-CH_3), 3.80 (s, 3 H, OCH_3), 6.71 (dd, *J* = 7.5 and 2 Hz, H at C-2), 6.94 (dd, *J* = 8 and 2.5 Hz, H at C-4), 7.15 (t, *J* = 7.5 Hz, H at C-3), 0.5–3.3 (m, 14 H). **8a:** NMR δ 1.31 (d, *J* = 7 Hz, 3 H, 6α-CH_3), 1.63 (br s, 3 H, 17-CH_3), 3.77 (s, 3 H, OCH_3), 6.72 (dd, *J* = 8.5 and 2.5 Hz H at C-2), 6.83 (d, *J* = 2.5 Hz, H at C-4), 7.23 (d, *J* = 8.5 Hz, H at C-1), 0.7–3.2 (m, 14 H). Anal. Calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28; O, 5.67. Found for **7a:** C, 84.98; H, 9.15; O, 5.70. Found for **8a:** C, 85.07; H, 9.42; O, 5.76.

***dl*-3-Methoxy-6α,17-dimethyl-13α,17α-epoxy-1,3,5(10)-gonatriene (10).** To a solution of 0.282 g (1.0 mmol) of **8a** in 10 mL of *tert*-butyl alcohol was added with stirring and cooling in ice 5 mL of water, 0.50 g of powdered calcium carbonate, and 0.54 g (4 mmol) of *N*-chlorosuccinimide. The mixture was stirred for 1 h at 5 °C. In one experiment the reaction mixture was worked up at this point and chromatographed over neutral alumina (activity grade IV) to give **9a** and **9b** in ca. 50% yield. Otherwise 3 mL of 40% aqueous KOH was added and the resulting mixture was stirred for 30 min at 5 °C. Water and dichloromethane were added and the organic phase was separated and dried over anhydrous K_2CO_3. The solvent was stripped off and the residue was chromatographed over base-washed alumina (activity grade IV) with 2:1 hexane–dichloromethane. A small amount of starting material was eluted followed by 0.161 g of **10** (54% yield) and 0.10 g of more polar by-products. Analytically pure **10,** mp 149–151 °C, was obtained by recrystallization from methanol. The mixture of **9a** and **9b** redissolved in 2:1 *tert*-butyl alcohol–water and treated as above afforded **10** in quantitative yield: NMR δ 1.36 (s, 3 H, 17-CH_3), 1.32 (d, *J* = 7 Hz, 3 H, 6α-CH_3), 3.83 (s, 3 H, OCH_3), 6.7–7.4 (m, 3 H, aromatic protons), 0.85–3.3 (m, 14 H). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.50; H, 8.88; O, 10.94.

***dl*-3-Methoxy-6α-methyl-1,3,5(10)-estratrien-17-one (11)** A solution of 0.217 g (0.73 mmol) of **10** in 23 mL of toluene was treated with 0.2 mL of boron trifluoride etherate and shaken for 1 min. The purple reaction mixture was shaken with aqueous K_2CO_3 until the color had disappeared. Normal workup and chromatography with 9:1 hexane–ethyl acetate afforded 0.138 g (64% yield) of **11** as an oil which crystallized on standing. An analytical sample had mp 110–112 °C (from methanol): NMR δ 0.89 (s, 3 H, 13-CH_3), 1.34 (d, *J* = 7 Hz, 3 H, 6α-CH_3), 3.79 (s, 3 H, OCH_3), 6.6–7.3 (m, 3 H, aromatic protons), 0.8–3.3 (m, 14 H). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.53; H, 8.61; O, 10.77.

***dl*-3-Methoxy-6α-methyl-1,3,5(10)-estratrien-17β-ol (13).** A 20-mg sample of **11** was reduced with lithium aluminum hydride in ether. Normal workup and crystallization from ether afforded 18 mg

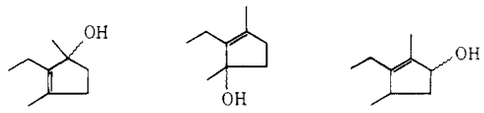
(90% yield) of pure **13**: mp 174–176 °C (lit.[5] mp 173–176 °C); NMR identical to reported data.[5]

Acknowledgment. We thank Professor W. S. Johnson for stimulating discussions. He guided us on the way which led to the initiation of this study. We acknowledge the assistance of Mr. B. Hindriken.

Registry No.—1, 65452-45-1; **2**, 65452-46-2; **3**, 33548-59-3; **4**, 65452-47-3; **5**, 65452-48-4; **6**, 65452-49-5; **7a**, 65452-50-8; **7b**, 65484-12-0; **8a**, 65452-51-9; **8b**, 65452-52-0; **9a**, 65452-53-1; **9b**, 65452-54-2; **10**, 65452-55-3; **11**, 65452-56-4; **12**, 65452-57-5; **13**, 5753-83-3; lithium dimethylcuprate, 15681-48-8; methyl *m*-methoxycinnamate, 15854-56-5.

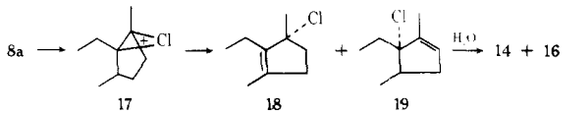
References and Notes

(1) For recent reviews on this subject see: (a) W. S. Johnson, *Bioorg. Chem.*, **5**, 51 (1976); (b) W. S. Johnson, Angew. Chem., **88**, 33 (1976); (c) E. E. van Tamelen, *Acc Chem. Res.*, **8**, 152 (1975).
(2) (a) P. A. Bartlett and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 7501 (1973); (b) P. A. Bartlett, J. I. Brauman, W. S. Johnson, and R. A. Volkmann, *ibid.*, **95**, 7502 (1973).
(3) Pro-C-6 referes to the carbon atom which is to become C-6 (steroid numbering) following Johnson's nomenclature: (a) W. S. Johnson and G. E. DuBois, *J. Am. Chem. Soc.*, **98**, 1038 (1976); (b) W. S. Johnson, S. Escher, and B. W. Metcalf, *ibid.*, **98**, 1039 (1976).
(4) A chiral center is present in the form of an allylic alcohol or its derivative, which is lost upon cyclization. It was suggested[2a] that optical induction by this chiral center might take place, but investigations to that effect showed only minimal retention of optical activity: W. S. Johnson, J. A. M. Peters, N. P. van Vliet, and F. J. Zeelen, to be published.
(5) G. H. Douglas, G. C. Buzby, Jr., C. R. Walk, and H. Smith, *Tetrahedron*, **22**, 1019 (1966)
(6) C. C. Bolt, A. J. van den Broek, G. H. Visser, H. P. de Jongh, and C. M. Siegmann, *Recl. Trav Chim, Pays-Bas*, **90**, 849 (1971).
(7) Japanese Patent Publication 2282 (1963), Teikoku Horm. Manufacturing Comp.; *Chem. Abstr.*, **59**, 11607 (1963).
(8) (a) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, **97**, 6266 (1975); (b) S. Hashimoto, S. Yamada, and K. Koga, *ibid.*, **98**, 7450 (1976).
(9) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Am. Chem. Soc.*, **93**, 4332 (1971).
(10) Reaction conditions for this and the following steps in the synthesis were taken with some modifications from Johnson's work.[2,9]
(11) The NMR spectrum of this sample showed inter alia singlets at δ 1.49 and 1.64 (ca. 4:1 ratio) which tentatively may be assigned to the 17-CH_3 group of **9a** and **9b**, respectively.
(12) Authentic *d*-11, mp 89–90 °C, was prepared from 6α-methyl-4-estrene-3,17-dione[6] by microbiological aromatization (Arthrobacter Simplex) followed by methylation.
(13) Authentic *d*-**12**, mp 106–107 °C, was prepared by methylation of 6β-methylestrone: E. Velarde, J. Iriarte, H. J. Ringold, and C. Djerassi, *J. Org. Chem.*, **24**, 311 (1959).
(14) By the same token steroids with the unnatural configuration may be obtained by starting with (*R*)-**6**.
(15) NMR evidence suggest the following partial structures:



14 15 16

The NMR spectrum showed inter alia signals at δ 1.7 (br s, allylic methyl in **15** and **16**), 1.34 (s, CH_3CO in **14**), and 4.56 (br d, J = 5 Hz, HCOH in **16**).
(16) We propose the following mechanism:



17 18 19

(17) A similar total synthesis of thiophene analogues of 6α-alkyl-19-norsteroids was reported recently: A. A. Macco, R. J. de Brouwer, and H. M. Buck, *J. Org. Chem.*, **42**, 3196 (1977).

Total Synthesis of (±)-Cedrol and (±)-Cedrene via an Intramolecular Diels–Alder Reaction

Edward G. Breitholle and Alex G. Fallis*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7

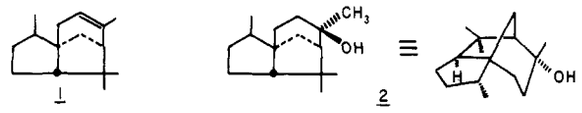
Received September 21, 1977.

A total synthesis of racemic cedrol and cedrene is described in which a key step is the intramolecular Diels–Alder reaction of alkyl cyclopentadiene **3** to give the tricyclic olefin **4**. Oxidation of this material followed by ring expansion gives cedrone (**6**), which is converted to the sesquiterpenes. Modification of the functionality of the starting materials will permit the application of this general route to diverse tricyclic systems.

Cedar-wood oil contains the interesting sesquiterpenes α-cedrene (**1**) (accompanied by ~15% of the β isomer) and its crystalline hydration product cedrol (**2**), both of which possess the relatively rare tricyclo[5.3.1.$0^{1,5}$]undecane skeleton.[1] In addition, several related more highly oxygenated members of this family such as shellolic acid[2] and other lac resin and vetiver oil components[3] are known. Interest in these tricyclic sesquiterpenes is widespread and a number of diverse syntheses have been reported since the original total synthesis of Stork and Clarke.[4] However, all of these recent synthetic studies[5] have attempted to mimic, to some extent, the bio-

synthesis of cedrene and, thus, have utilized a series of carbonium ion intermediates of the general type illustrated.

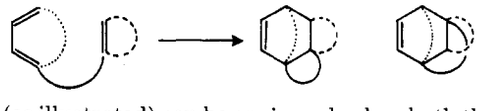
We report herein a total synthesis of (±)-cedrol (**2**) and (±)-cedrene (**1**) via an intramolecular Diels–Alder reaction



1 2

of an alkyl cyclopentadiene. The stereoselective route is direct and should be suitable for the construction of related compounds.[6]

The Diels–Alder reaction occupies a position of prominence in the arsenal of the synthetic organic chemist as a consequence of its good yields, mild reaction conditions, predictability, and high stereoselectivity. In view of both the steric and electronic requirements for this cycloaddition, intramolecular applications provide access to diverse systems which are otherwise difficult to prepare.[7] Thus, complex multicyclic



arrays (as illustrated) can be envisaged, when both the diene and dienophile components are themselves cyclic, and with

0022-3263/78/1943-1964$01.00/0