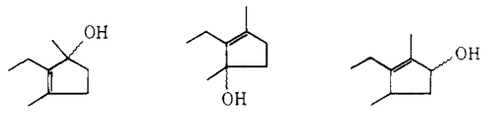
(90% yield) of pure **13**: mp 174–176 °C (lit.[5] mp 173–176 °C); NMR identical to reported data.[5]

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.

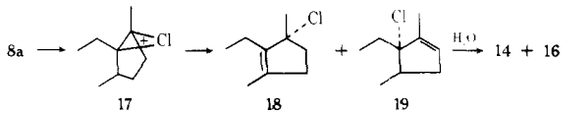
References and Notes

(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

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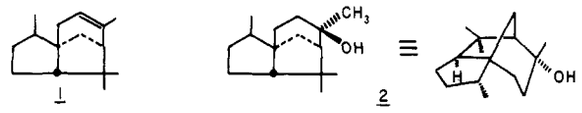
A total synthesis of racemic cedrol and cedrene is described in which a key step is the intramolecular Diels–Alder reaction of alkyl cyclopentadiene **3** to give the tricyclic olefin **4**. Oxidation of this material followed by ring expansion gives cedrone (**6**), which is converted to the sesquiterpenes.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

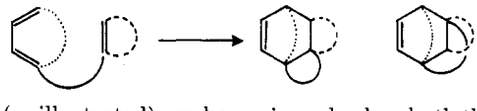
We report herein a total synthesis of (±)-cedrol (**2**) and (±)-cedrene (**1**) via an intramolecular Diels–Alder reaction



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

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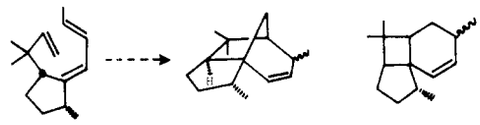
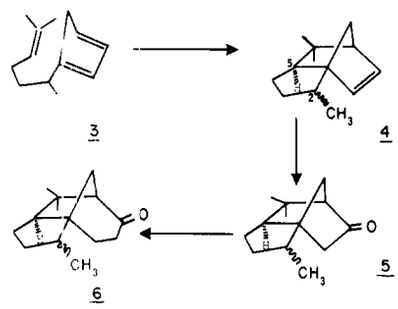
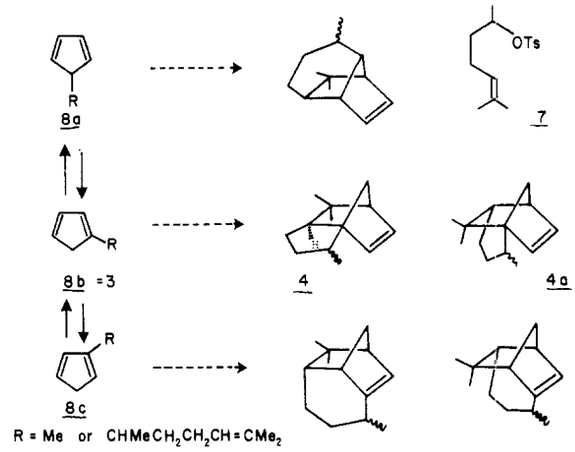
Scheme I



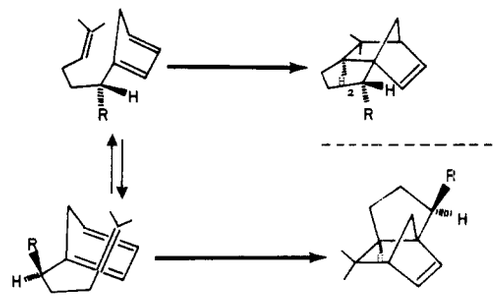
Scheme II



Scheme III



Scheme IV



appropriate ring systems the opportunity to prepare stereoselectively a variety of tricyclic sesquiterpenes is apparent.

Several possible approaches to the cedrene nucleus may be envisaged. Retrograde analysis of the cedrene skeleton reveals that a "paper" Diels–Alder route should be the sequence in Scheme I. The simplicity of this approach has certain appeal; however, our studies on other internal Diels–Alder systems, earlier work by House and Cronin[8] with acyclic dienes, and a careful examination of molecular models indicate that the unsaturated compound is too rigid to permit the required alignment of the π systems for the reaction to be successful. Indeed, it appears that to the extent that any monomeric product is formed the undesired cyclobutane compound will be favored due to the preferred orientation of the dienophile.

Thus, the approach selected (Scheme II) is based on the generation of a suitable tricyclo[5.2.1.$0^{1,5}$]dec-8-ene system (i.e., **4**) which by ring expansion and functional-group manipulation could be converted to cedrene. An attractive route to this intermediate is by internal cycloaddition of the alkyl cyclopentadiene **3**. The sequence takes advantage of the rapid isomerization of 5-alkyl- to 1-alkylcyclopentadienes at room temperature[9] and, although the double bond is trisubstituted, necessitating forcing conditions for the reaction, it was anticipated, due to the stereochemical constraints of the system, that the cyclopentane side chain would have the correct exo orientation[10] and that hydroboration would give the desired ketone **5** for ring expansion to cedrone (**6**).

Results and Discussion

A commercial sample of 6-methyl-5-hepten-2-one was reduced with lithium aluminum hydride in diethyl ether and the resulting alcohol[11] treated with tosyl chloride in pyridine to afford the tosylate **7** in 93% overall yield. Separate treatment of the alcohol with triphenylphosphine dibromide gave the corresponding bromide (74%). It is well established, from previous studies with methyl cyclopentadiene,[9] that the initial product from alkylation of sodium cyclopentadiene **8a** isomerizes rapidly at room temperature to **8b** and more slowly to **8c**. Thus, alkylation of sodium cyclopentadiene[12] with tosylate **7** in tetrahydrofuran at 0 °C for 30 min followed by 4 h at room temperature afforded, after workup, the isomer **8b** (85% yield).[13] Detectible amounts of the isomers **8a** and **8c** were not present based on the ^{1}H NMR spectrum. This spectrum displayed a multiplet at δ 2.80 due to the two allylic cyclopentyl hydrogens and a complex signal from δ 5.8 to 6.5 representing the three vinyl ring hydrogens consistent with structure **8b**.

Although the desired isomer **8b** had been obtained, the thermal conditions required for the Diels–Alder reaction will shift the equilibrium, and thus consideration of the possible intramolecular cycloaddition products which may result is warranted. These are depicted in Scheme III. It will be noted that monomeric tricyclic products from **8c** are unlikely, since both possible structures violate Bredt's rule. The desired product **4** from **8b** will clearly be favored, since the geometry of the system precludes the efficient overlap of the reacting centers required for the twistane structure **4a**. However, if sufficient **8a** is present it would cyclize to the undesired structure, although for this to occur the Diels–Alder reaction must be more rapid than isomerization to **8b** which seems unlikely under the temperature conditions found to be required.

Cyclization of **8** was effected by heating a dilute solution in hexamethylphosphoramide or tri-*n*-butylamine at 205 ± 5 °C for 7 h to give the tricyclic olefin **4** in 36% yield after column chromatography. Alternatively the reaction was conducted in a sealed tube in xylene at 155 °C for 50 h. Based on unreacted starting material this was the most efficient process affording the desired product in 74% yield, but attempts to push the reaction to completion including the use of metal catalysts were unsuccessful. It appears that the equilibrium position between the open precursor and the Diels–Alder adduct cannot be easily shifted under the temperature and pressure conditions available.

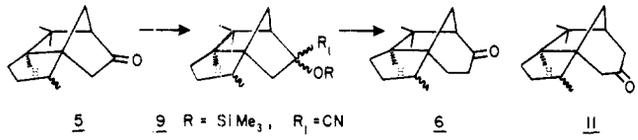
The isomeric internal Diels–Alder structures are excluded by the ^{1}H NMR spectrum of the cyclization product which is consistent with **4**. The olefinic signals appeared as an unsymmetrical multiplet at δ 6.01 representing the AB portion of an ABX system, while the single allylic bridgehead proton (X) gave rise to a broad resonance at δ 2.27 ($W_{1/2}$ = 6 Hz). The methyl signals appeared as singlets at δ 0.80 and 1.05 due to the endo and exo geminal group and as a doublet at δ 0.91 (J = 6.5 Hz) representing the secondary methyl function. Although **4** was homogeneous by both GLC and TLC, the proton noise-decoupled ^{13}C NMR spectrum indicated it was an epimeric mixture at C_2 (~1:1).[14] This spectrum confirmed the

single mode of attachment of the cyclopentane side chain, and the success of the synthesis indicated this was exo.

Unfortunately, there does not appear to be a simple method of controlling the stereochemistry at C_2 during the reaction. An unsubstituted alkyl cyclopentadiene (R = H) may react from either of the two conformations shown. These are equivalent except for the orientation of the double bond with respect to the cyclopentadiene methylene and cyclization will give rise to an enantiomeric mixture (the two products are nonsuperimposable mirror images). In our case (R = CH_3), since there is not a significant conformational energy difference due to the nonbonded interactions present in the precursor (between the methyl group and the methylene bridge), even optically active **8b** will afford a diastereomeric mixture.

Hydroboration of **4** in dimethoxyethane proceeded as expected to give after oxidative workup and treatment with Jones' reagent the desired ketone **5** whose infrared spectrum contained a strong carbonyl band at 1735 cm^{-1} typical of a cyclopentanone. No evidence for the positional isomer due to attack at the more hindered center was obtained. Previous work with norbornanone[15] suggested that ring expansion of this ketone should give predominantly the required ketone **6** as an epimeric mixture.

Ketone **5** was inert to diazomethane even under Lewis acid catalyzed conditions and, since conventional cyanohydrin formation failed, the trimethylsilylcyanohydrin **9** was prepared using the general procedure of Evans and co-workers[16] with trimethylsilylcyanide and zinc iodide at room temperature. The nitrile displayed a very weak infrared band at 2220 cm^{-1} in addition to intense absorptions at 860 and 1260 cm^{-1} due to the trimethylsilyl function. The primary amine **10** obtained upon lithium aluminum hydride reduction was treated with nitrous acid to give the ring-expanded ketones in 73% overall yield from **5**. This product contained a variable amount (15–25%) of the positional isomer **11** which was separated by TLC.[17]



5 **9** R = $SiMe_3$, R_1 = CN **6** **11**

10 R = H, R_1 = CH_2NH_2

Stereoselective addition of methyllithium[4] to the epimeric cedrone mixture **6** gave a 1:1 mixture of (±)-cedrol (**2**) and (±)-*epi*-cedrol. These alcohols were separated by GLC and the spectral (^1H NMR, IR, MS) and chromatographic properties (GLC, TLC) of the synthetic cedrol were indistinguishable from an authentic sample of the natural material. The cedrol was converted to (±)-α-cedrene (**1**) and (±)-β-cedrene in quantitative yield (ratio 80:20) by dehydration[19] in pyridine containing thionyl chloride at 5 °C to complete the synthesis.

Extension of this route using modified side chains should provide access to a variety of more highly oxygenated cedrenoids as well as the related tricyclo[6.2.1.$0^{1,6}$]undecane ring system possessed by isolongifolene.

Experimental Section

Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Georgia.

Infrared spectra were recorded neat, unless otherwise indicated, on a Perkin-Elmer 237B or 451 grating spectrophotometer and were calibrated with the 2850- and 1601-cm^{-1} bands of polystyrene film. Proton magnetic resonance spectra were measured using a Varian Model EM-360 spectrometer in carbon tetrachloride solutions, unless otherwise stated, containing tetramethylsilane as an internal standard. Band positions are reported in parts per million downfield from Me_4Si (δ scale). Mass spectra were determined on a Hitachi Perkin-Elmer EMU 6E instrument using a ionization energy of 70 eV.

The GLC analyses were conducted on a Varian Aerograph gas chromatograph Model 1720 with helium as a carrier gas on a 10 ft × 0.25 in. 13% SE-30 column supported on Chromosorb W (AW-DMCS) (70–80 mesh) (A) or on a 8 ft × 0.25 in. 20% Carbowax 20 M column supported on Chromosorb W (AW-DMCS) (70–80 mesh) (B).

Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Büchi rotary evaporator connected to a water aspirator.

6-Methyl-5-hepten-2-ol. A solution of 6-methyl-5-hepten-2-one (10 g, 68 mmol, Aldrich) in dry ether (50 mL) contained in a dropping funnel was added slowly to a 500-mL three-necked round-bottom flask, equipped with a reflux condenser fitted with a calcium chloride drying tube, containing a suspension of lithium aluminium hydride (2.66 g, 70 mmol) in anhydrous ether (110 mL). The resulting mixture was refluxed for 12 h and the excess reagent destroyed by the careful addition of aqueous ethyl acetate. The reaction mixture was diluted with cold 2 M sulfuric acid (150 mL). The organic layer was separated and the aqueous layer extracted with ether (2 × 45 mL). The combined ether extracts were washed with saturated aqueous sodium chloride solution and dried, the solvent was removed under reduced pressure, and the residual oil was purified by distillation [bp 33–35 °C (0.35 mm), lit.[11] bp 91 °C (34 mm)] to give the alcohol: 8.7 g (100%); IR (neat) 3320–3350 (br, OH) cm^{-1}; ^1H NMR δ 5.0 (1 H, br t, J = 7 Hz, CH=C), 4.16 (1 H, s, OH), 3.65 (1 H, sextet, J = 6.5 Hz, CHO), 1.64 (3 H, s, CH_3C=C), 1.55 (3 H, s, CH_3C=C), 1.09 (3 H, d, J = 6.5 Hz, CH_3CH) ppm; mass spectrum M* 128.

6-Methyl-5-heptene 2-*p*-toluenesulfonate (7). *p*-Toluenesulfonyl chloride (9.55 g, 50 mmol) was added in small increments to a cold solution (ice bath) of the methylheptenol (5.0 g, 39 mmol) in pyridine (22 mL), and stirring was continued for 21 h at ~5 °C (cold room). The white reaction mixture was transferred to a separatory funnel, ice-cold 40% aqueous hydrochloric acid (125 mL) was added, and the aqueous material was extracted with ether (2 × 100 mL). These combined extracts were washed with water and brine and then dried, and the solvent was removed under reduced pressure to give the tosylate **7**, 10.33 g (93.5%), as a clear light-yellow oil: IR (neat) 1597 (Ph) 1195, 1180 (–SO_3R) cm^{-1}; ^1H NMR δ 7.63 (2 H, d, J = 9 Hz, ArH α to SO_3), 7.18 (2 H, d, J = 9 Hz, ArH α to CH_3), 4.83 (1 H, br t, J = 7 Hz, CH=C), 4.47 (1 H, sextet, J = 6.5 Hz, CHO), 2.33 (3 H, s, CH_3Ar), 1.59 (3 H, s, CH_3C=C), 1.45 (3 H, s, CH_3C=C), 1.18 (3 H, d, J = 6.5 Hz, CH_3CH) ppm.

Anal. ($C_{15}H_{22}O_3S$) C, H, S.

2-Bromo-6-methyl-5-heptene. To triphenylphosphine (4.19 g, 16 mmol, BDH) suspended in cold (ice bath) dry acetonitrile (70 mL) a solution of bromine (2.56 g, 16 mmol) in acetonitrile (15 mL) was added dropwise followed by pyridine (1.3 mL, 16 mmol). The reaction, after stirring for 15 min in the ice bath, was warmed to room temperature, and a solution of 6-methyl-5-hepten-2-ol (2.0 g, 16 mmol) in acetonitrile (20 mL) was added over 15 min. The resulting clear solution was stirred at room temperature for 1 h, the solvent was removed and the resulting solid was extracted between ethyl acetate and water. The organic layer was dried and the residue after filtration and concentration distilled [bp 32–38 °C (0.75 mm)] to give the bromide: 2.3 g (74%); ^1H NMR δ 5.01 (1 H, br t, $J \approx 7$ Hz, CH=C), 4.00 (1 H, m, $J \approx 6.5$ Hz, CHBr), 1.60, 1.71 (9 H, CH_3) ppm; mass spectrum M* 190.

Preparation of 1,5-Dimethyl-4-hexenyl-2′-cyclopentadiene (8). (A) Sodium spheres (2.88 g, 0.125 mol, MCB) were refluxed in dry xylene (35 mL) under nitrogen until sodium sand had formed. After cooling to room temperature the xylene was decanted, and the sand was washed with dry tetrahydrofuran (2 × 25 mL) and suspended in tetrahydrofuran (75 mL). Freshly distilled cyclopentadiene (~10 mol) was added to the stirred mixture in four portions, resulting in a deep red-purple solution in which all the sodium had been consumed (~3 h).[12] The solution was cooled in an ice bath, and the tosylate **7** (31.3 g, 0.11 mol) in dry tetrahydrofuran (100 mL) was added dropwise over 0.5 h. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring continued for a further 4 h. The light-brown mixture was transferred to a separatory funnel, diluted with brine (100 mL), and extracted with ether (4 × 700 mL), the combined extracts were washed with brine and dried, and the solvent was removed to afford an oil which was purified by column chromatography on silica gel (10:1) elution with *n*-hexane to give the hydrocarbon **8**, 16.5 g (85%), as a clear oil: IR 1660, 1601 (C=C) cm^{-1}; ^1H NMR 5.8–6.5 (3 H, m, cyclopentadiene), 5.02 (1 H, br t, $J \approx 6$ Hz, CH=CMe_2), 2.80 (2 H, d of m $J \approx 5$, 1.3, 1 Hz, C=CCH_2C=C), 1.09 (3 H, d, J = 7 Hz, CH_3CH), 1.55, 1.63 [6 H, s, $(CH_3)_2C$=C] ppm; mass spectrum M* 176.

An analytical sample was obtained by preparative GLC (column A).

Anal. ($C_{13}H_{20}$) C, H.

(B) Similar reaction of sodium cyclopentadiene with the bromide required 104 h at room temperature in THF and after column chromatography afforded the triene **8** in 69% yield.

(C) Cyclopentadienylmagnesium bromide was prepared according to the method of Brieger[20] and reacted over 15 h at room temperature with tosylate in diethyl ether under nitrogen to give **8** in 65% yield after standard workup and chromatography.

(D) Lithium cyclopentadiene was generated from methyllithium and cyclopentadiene and reacted with the tosylate (4 h, 0–25 °C) to give a 57% yield of the alkyl cyclopentadiene after chromatography.

Preparation of 2,6,6-Trimethyltricyclo[5.2.1.0^{1,5}]dec-8-ene (4). (A) A solution of alkylcyclopentadiene **8** (18.41 g, 0.105 mol) in dry hexamethylphosphoramide (HMPA, 100 mL) was added over a 2-h period to a hot solution of HMPA (110 mL) maintained under N_2 in a silicone oil bath at 205 ± 5 °C in a 500-mL three-necked flask equipped with a condenser and pressure-equalizing dropping funnel. Heating was continued for a further 5 h, the reaction was cooled to room temperature, and the resulting black solution was diluted with brine (250 mL) and extracted with ethyl acetate (3 × 90 mL). The combined extracts were washed with water (5 × 100 mL), dried, and concentrated, and the oily residue was passed through a silica gel column (8:1) eluting with *n*-hexane. These fractions were combined and distilled [bp 53–56 (0.2 mm)] to give the tricyclic olefin **4:** 6.5 g (36%); IR (neat) 3040 (CH=C), 1550 (w, C=C) cm^{-1}; ^{1}H NMR δ 6.01 (2 H, m, CH=CH), 2.27 (1 H, br s, $w_{1/2}$ = 6 Hz, CH), 0.81 (3 H, s, CH_3), 1.07 (3 H, S, CH_3), 0.91 (3 H, d, J = 6.5 Hz, CH_3CH) ppm; ^{13}C NMR ($CDCl_3$) δ 139.56, 139.11, 136.03, 135.58 (C=C for each epimer); mass spectrum M* 176.

Anal. ($C_{13}H_{20}$) C, H.

(B) The triene **8** (0.161 g, 0.915 mmol) in dry xylene (4.5 mL) was sealed in a Carius tube and heated at 155 ± 3 °C for 51 h. The tube was opened, solvent was removed, and the product was isolated in 37% yield (74% based on unreacted starting material) by preparative GLC (column A).

(C) A solution of the triene **8** (0.271 g, 1.54 mmol) in dry tri-*n*-butylamine (15 mL) was added over a 0.5-h period to a hot solution of tri-*n*-butylamine (40 mL) maintained under N_2 in a silicone oil bath at 210 ± 5 °C in a 100-mL three-necked flask equipped with a condenser and pressure-equalizing dropping funnel. Heating was continued for a further 3.5 h, the cooled reaction mixture was poured into ice-cold 50% aqueous hydrochloric acid, and the product was extracted with ether (2 × 50 mL). The combined extracts were washed with dilute hydrochloric acid, 10% aqueous sodium bicarbonate solution (25 mL), and brine, dried, and concentrated to give an oily residue. The tricyclic olefin **4** was purified by preparative GLC, 0.079 g (29%, ~55% based on unchanged starting material) (column A).

Preparation of 2,6,6-Trimethyltricyclo[5.2.1.0^{1,5}]decan-8-one (5). To a cold (0 °C) solution of the alkene **4** (1.7 g, 9.7 mmol) in dry dimethoxyethane (12 mL) under nitrogen, in a 100-mL three-necked flask equipped with a reflux condenser and pressure-equallizing dropping funnel maintained in an ice bath, was added sodium borohydride (0.53 g, 14 mmol). Freshly distilled boron trifluoride etherate (1.97 mL, 16 mmol) in dimethoxyethane was added dropwise to the cold solution over a 10-min period. The reaction mixture was allowed to warm to room temperature, and stirring was continued for a total of 20 h. The reaction was then cooled in an ice bath and the excess reagent destroyed by careful addition of water (~1.5 mL) and this was followed by aqueous sodium hydroxide solution (3 M, 5 mL) and aqueous hydrogen peroxide (30%, 5 mL) dropwise. The reaction was refluxed gently for 45 min, aqueous 10% sodium sulfite solution was added to destroy the excess peroxide (negative starch/KI test), diluted with water, and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with brine (50 mL), dried, and concentrated to give an oil (1.7 g). This alcohol was dissolved in dry acetone and cooled to 0 °C (ice bath), and Jones' reagent was introduced dropwise to the stirred solution until a faint-yellow color persisted. A few drops of isopropyl alcohol were added to utilize excess oxidant, and the mixture was poured into ether–brine. The aqueous layer was extracted with ether (3 × 35 mL), and the combined extracts were washed with water and brine, dried, and concentrated to afford the ketone as an oil (1.59 g, 86%). This material was shown to be homogeneous by GLC analysis (column A) and was used without further purification: IR (neat) 1735, (CCl_4), 1745 cm^{-1}; NMR δ 0.96 (9 H, br s with two sharp shoulders), 1.03, 0.98 (CH_3); 75 mg of ketone plus 40 mg of Eu(fod)$_3$ resolved the methyl signals and confirmed that the diastereomeric ratio was 1:1; mass spectrum M* 192.

The ketone was further characterized as its 2,4-DNP derivative, crystallized from aqueous methanol, mp 164–166 °C.

Anal. ($C_{19}H_{24}N_4O_4$) C, H, N.

Preparation of Silyl Cyanohydrin (9). Anhydrous zinc iodide (10 mg) and trimethylsilylcyanide (0.92 g, 9.2 mmol) were added to the tricyclic ketone **5** (1.70 g, 8.85 mmol) maintained under nitrogen. The resulting solution was stirred at room temperature for 5.5 h and then concentrated under reduced pressure to give the cyanohydrin ether: 2.51 g (97%); IR (neat) 2220 (w, C≡N) cm^{-1}; ^{1}H NMR δ 0.30 [9 H, s, $(CH_3)_3Si$] ppm; mass spectrum M* 291.

Preparation of Amino Alcohol 10. Lithium aluminum hydride (10.4 g, 0.011 mol) was suspended in anhydrous ether (12 mL) under N_2 in a 50-mL three-necked flask equipped with a magnetic stirring bar, reflux condenser, and pressure-equalizing dropping funnel. An ether solution (10 mL) of the cyanohydrin ether **9** (2.66 g, 9.14 mmol) was added dropwise so that gentle reflux was maintained. Stirring was continued for 10 h at room temperature, excess hydride was destroyed by careful addition of water (~1 mL), 15% aqueous sodium hydroxide solution (1 mL), and water (1 mL), and the reaction was stirred until a granular white precipitate was formed. After filtration, the ether solution was washed with brine, dried, and concentrated to give the aminomethyl alcohol **10:** 1.81 g (89%); IR (neat) 3330 (br OH), 3120–3280 (br NH_2) cm^{-1}.

The amine hydrochloride was prepared by bubbling hydrochloric acid through an ether solution of the amine and collecting the precipitate: mp 205 °C, sublimed 250–260 °C; ^{1}H NMR (Me_2SOd_6) δ 8.10 (3 H, br s, NH_3^+), 4.95 (1 H, br s, OH), 2.80 (2 H. s, CH_2N) ppm. An analytical sample was recrystallized from methanol–diethyl ether (1:8).

Anal. ($C_{14}H_{26}ONCl$) C, H, N.

Preparation of 2,6,6-Trimethyltricyclo[5.3.1.0^{1,5}]undecan-8-one (6). An aqueous solution (3 mL) of sodium nitrite (0.38 g, 5.5 mmol) was added dropwise to a cold (ice bath) solution of the amino alcohol **10** (0.91 g, 4.08 mmol) in water (7 mL) containing glacial acetic acid (0.35 mL, 6.0 mmol). The reaction was stirred for 2 h at 0 °C and 6 h at room temperature, water was added, and the reaction was then extracted with ether (3 × 25 mL). The combined extracts were washed with aqueous 10% sodium bicarbonate solution and brine, dried, and concentrated to give the ketones as an oil (0.7 g, 83.3%). The analysis indicated that 15–25% (depending on run) of the positional isomer **11** was present. They were separated from the epimeric cedrones by TLC (six elutions with 20% chloroform–*n*-hexane). The upper band contained ketone **11:** IR (neat) 1706 (C=O) cm^{-1}; ^{1}H NMR δ 0.88 (3 H, d, J = 6.5 Hz, CH_3CH), 1.13 (3 H, s, CH_3), 1.02 (3 H. s, CH_3) ppm; mass spectrum M* 206.

The epimeric cedrones (**6**) were extracted from the lower band: IR (neat) 1705 (C=O) cm^{-1}; ^{1}H NMR δ 0.97 (9 H, br s with shoulders, CH_3) ppm; mass spectrum M* 206.

The diastereomer could be separated by preparative GLC (column B, 187 °C), the cedrone possessing the longer retention time.

Preparation of (±)-*epi*-Cedrol and (±)-Cedrol (2). A dry ether solution (5 mL) of the epimeric cedrones (0.33 g, 1.6 mmol) was added slowly to a methyllithium solution (10 mL, 11 mmol). The resulting solution was refluxed under nitrogen for 2 h, cooled, quenched carefully with water, diluted with ether, and extracted, and the combined ether extracts were washed with brine, dried, and concentrated to give the cedrols as a semicrystalline residue, 0.284 g (80%). The alcohols were separated by preparative GLC (column B, 177 °C), the (±)-*epi*-cedrol being eluted first.

(±)-*epi*-cedrol recrystallized from aqueous methanol: mp 107–109 °C; IR (Nujol) 3450 (br, OH); ^{1}H NMR δ 0.83 (3 H, d, J = 6 Hz, CH_3CH), 0.92 (3 H, s, *endo*-CH_3), 1.19 (3 H, s, *exo*-CH_3), 1.23 (3 H, s, CH_3COH) ppm; mass spectrum M* 222.

Anal. ($C_{15}H_{26}O$) C, H, O.

(±)-Cedrol recrystallized from aqueous methanol; mp 94–96 (lit.[4] (+)-cedrol mp 86–87 °C); IR (nujol) 3330 (br, OH) cm^{-1}; ^{1}H NMR δ 0.82 (3 H, d, J = 6 Hz, CH_3CH), 0.97 (3 H, s, *endo*-CH_3), 1.18 (3 H, s, *exo*-CH_3), 1.26 (3 H, s, CH_3COH) ppm; mass spectrum M* 222. These spectral features were the same as an authentic sample of commercial cedrol.

The total ketone mixture from the ring expansion was also treated with methyllithium and the resulting alcohols were separated by GLC (column B), or alternatively the positional isomers were first separated from the cedrols by TLC eluting with 50% chloroform–*n*-hexane.

Preparation of (±)-α-Cedrene (1) and (±)-β-Cedrene.[19] Thionyl chloride (0.1 mL) was added to a cold (0 °C) pyridine solution (1 mL) of (±)-cedrol (15 mg, 0.07 mmol), and the reaction was stirred under nitrogen for 1.5 h. Water was added and the mixture was extracted with ether (3 × 15 mL); these extracts were washed with cold aqueous 10% hydrochloric acid and brine, dried, and concentrated

to afford a quantitative conversion to (±)-α- and (±)-β-cedrene (80:20). They could be separated by GLC (column B, 146 °C): ^{1}H NMR δ 0.82 (3 H, d, J = 6.5 Hz, CH_3CH), 0.92 (3 H, s, *endo*-CH_3), 0.98 (3 H, s, *exo*-CH_3), 5.15 (0.8 H, br s, HC=C, α), 4.49 (0.2 H, br s, CH_2=C, β) ppm; mass spectrum M* 204.

These results compared favorably with an authentic sample of cedrol, which under the conditions described above afforded the α- and β-cedrenes in an 83:17 ratio. The spectral features of the synthetic cedrene were in excellent agreement with an authentic sample of α-cedrene (Aldrich) shown by GLC and NMR analysis to contain 14% of the β isomer

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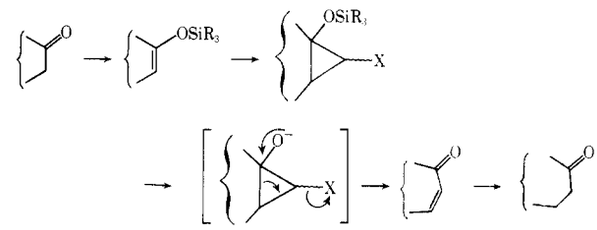
Registry No.—**1**, 22567-43-7; **2**, 22567-44-8; **4** epimer 1, 65391-62-0; **4** epimer 2, 65391-63-1; **5** epimer 1, 65391-64-2; **5** epimer 2, 65391-65-3; 5-DNP, 65442-01-5; **6** epimer 1, 50896-63-4; **6** epimer 2, 50896-62-3; **7**, 4582-61-0; **8b**, 65378-59-8; **9**, 65378-60-1; **10**, 65378-61-2; **10** HCl, 65378-62-3; **11**, 65378-63-4; 6-methyl-5-hepten-2-one, 110-93-0; 6-methyl-5-hepten-2-ol, 1569-60-4; *p*-toluenesulfonyl chloride, 98-59-9; 2-bromo-6-methyl-5-heptene, 4434-77-9; cyclopentadiene, 542-92-7; sodium cyclopentadiene, 4984-82-1; cyclopentadienyl bromide, 41851-49-4; lithium cyclopentadiene, 16733-97-4; trimethylsilylcyanide, 7677-24-9; (±)-*epi*-cedrol, 65391-66-4; (±)-β-cedrene, 65450-98-8.

References and Notes

(1) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291, 3292 (1953); Pl. A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Klau, St. Meyer, and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953); Pl. A. Plattner, A. Fürst, St. Meyer, and W. Keller, *ibid.*, **37**, 266 (1954).
(2) P. Yates and G. F. Field, *J. Am. Chem. Soc.*, **82**, 5764 (1960).
(3) R. Kaiser and P. Naegeli, *Tetrahedron Lett.*, 2009 (1972); A. N. Singh, A. D. Upadhye, V. V. Mhasker, S. Dev, A. V. Pol, and V. G. Naik, *Tetrahedron*, **30**, 3689 (1974).
(4) G. Stork and F. H. Clarke, Jr., *J. Am. Chem. Soc.*, **77**, 1073 (1955); **83**, 3114 (1961).
(5) E. J. Corey, N. N. Girotra, and C. T. Mathew, *J. Am. Chem. Soc.*, **91**, 1557 (1969); T. G. Crandall and R. G. Lawton, *ibid.*, **91**, 2127 (1969); E. Demole, P. Enggist, and C. Borer, *Helv. Chim. Acta*, **54**, 1845 (1971); N. H. Anderson and D. D. Syrdal, *Tetrahedron Lett.*, 2455 (1972); E. J. Corey and R. D. Balanson, *Tetrahedron Lett.*, 3153 (1973); P. T. Lansbury, V. R. Haddon, and R. C. Stewart, *J. Am. Chem. Soc.*, **96**, 896 (1974).
(6) A portion of our work has appeared in preliminary form: E. G. Breitholle and A. G. Fallis, *Can. J. Chem.*, **54**, 1991 (1976); presented in part at the International Symposium on Stereochemistry, Abstract M1, Kingston, Ontario, Canada, June 27–July 2, 1976. At the outset it appeared that α-pompene was also a member of this tricyclic family; however, its structure has been revised; A. Matsuo, T. Maeda, M. Nakayama, and S. Hayashi, *Tetrahedron Lett.*, 4131 (1973); A. Matsuo, H. Nozak, M. Nakayame, Y. Kushi, S. Hayashi, and N. Kaminjo, *Tetrahedron Lett.*, 241 (1975).
(7) R. G. Carlson, *Annu. Rep. Med. Chem.*, **9**, 270 (1974); W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977).
(8) H. O. House and T. H. Cronin, *J. Org. Chem.*, **30**, 1061 (1965).
(9) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965); see also J. Backes, R. W. Hofmann, and F. W. Steuber, *Angew. Chem., Int. Ed. Engl.*, **14**, 553 (1975).
(10) Cf. E. J. Corey and R. S. Glass, *J. Am. Chem. Soc.*, **89**, 2600 (1967); A. Krantz and C. Y. Lin, *ibid.*, **95**, 5662 (1973).
(11) O. Wallach, *Justus Liebigs Ann. Chem.*, **275**, 171 (1893); J. Mori, *Tetrahedron*, **31**, 3011 (1975).
(12) R. B. King and F. G. A. Stone, *Inorg. Synth.*, **7**, 99 (1963).
(13) Attempted use of thallium cyclopentadiene was unsuccessful.
(14) We are grateful to A. W. McCulloch and J. A. Walter, National Research Council of Canada, Halifax, Nova Scotia, for obtaining this spectrum.
(15) G. Fachinett, F. Pictra, and A. Marsili, *Tetrahedron Lett.*, 393 (1971); M. A. McKinney and P. P. Patel, *J. Org. Chem.*, **38**, 4059 (1973).
(16) D. A. Evans, G. L. Carroll, and L. K. Truesdale, *J. Org. Chem.*, **39**, 914 (1974).
(17) This sequence would be improved if formation of the unwanted ketone could be suppressed. This should be feasible as outlined, since the carbon bearing oxygen is locked in position in the starting ketone and final product. After completion of the synthesis but before this was a workable alternative, others reported a closely related ring expansion for the system X = H using ferric chloride which should be applicable to the present case.[18]



(18) Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2073 (1976); cf. G. Stork and T. L. MacDonald, *J. Am. Chem. Soc.*, **97**, 1264 (1975).
(19) E. V. Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).
(20) G. Brieger, *J. Am. Chem. Soc.*, **85**, 3783 (1963).

Synthesis of Garosamine and of Related Amino Sugars. An Efficient Tetrahydrooxazine Ring Opening

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Garosamine, a component of the antibiotic gentamicin, and a series of related amino sugars have been synthesized from glucose by a stereospecific route involving a versatile tricyclic intermediate. A new oxidative tetrahydrooxazine ring-opening reaction is also reported.

The synthesis of branched chain amino sugars has been the focus of attention of a number of research groups in recent years because of the common occurrence of these compounds in nature in association with antibiotics. Synthetic approaches to these compounds have usually employed the addition of organometallic reagents, diazoalkanes, and enolate salts to cyclic ketones with varying degrees of stereochemical control. Such an approach was used in a previous synthesis of the methyl glycoside of garosamine (**1**),[1] a component monosaccharide of the gentamicin antibiotics.[2] Because of our interest in synthetic approaches to aminoglycoside antibiotics,[3] we required an efficient and stereospecific synthesis of garosamine and of structurally related amino sugars. We wish to report such a synthesis and also the development in the course of this work of a novel tetrahydrooxazine ring-opening reaction.

We had observed in a related study that the aldehyde **2** is prone to undergo aldol condensations leading, for example, after borohydride reduction of the initially formed aldol condensation product, to the dimeric compound **3**, of undetermined stereochemistry at position 4 of both furanosyl rings. Exploitation of the reactivity of a related aldehyde in the synthesis of apiose has been reported.[4] Our planned synthesis is outlined in Scheme I.

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