Facile and Efficient Constructions of the Carbocyclic Frameworks of Four Kinds of Terpenoids from a Common Precursor[1]

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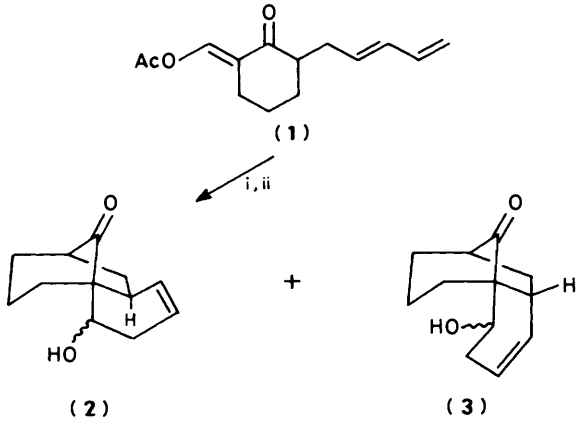
Facile and efficient syntheses of the basic carbocyclic frameworks of stemodane [(**7**)], cedrane [(**14**) and (**17**)], perhydroazulene [(**21**)], and himachalene [(**26**)] terpenoids are described. The key features of the synthetic study were the use of the 2-hydroxytricyclo[6.3.1.$0^{1,6}$]dodec-4-en-12-one (**2**), which was readily obtained by a stereoselective intramolecular Diels–Alder reaction of the trienone (**1**), as a common precursor and use of simple manipulations for the construction of these terpenoid skeletons.

The intramolecular Diels-Alder reaction[2] has found an increasing utility in the total synthesis of natural products. They usually give complex polycyclic molecular structures in a stereo- and regio-selective manner in a single step. In connection with our investigation toward total syntheses of some complex natural products by cycloaddition reactions,[3] we became interested in the development of a new methodology for preparation of some kinds of basic carbocyclic frameworks of terpenoids from a common cycloadduct. Although many elegant methods have been reported for terpenoid synthesis, preparations of several kinds of skeleton from a common compound are few.

We report herein the details of the synthesis of four types of terpenoid carbocyclic frameworks, *viz.* stemodane,[4] cedrane,[5] hydroazulene,[5] and himachalene,[5] from 2-hydroxytricyclo-[6.3.1.$0^{1,6}$]dodec-4-en-12-one (**2**),[6]† which was prepared in excess over the C-3 epimer (**3**) by means of an intramolecular Diels–Alder reaction of the trienone (**1**) followed by basic hydrolysis as shown in Scheme 1; enone (**2**) was used as a common precursor in our synthetic studies.



Scheme 1. *Reagents and conditions:* i, 220 °C, mesitylene; ii, LiOH, aq. MeOH, CH_2Cl_2, $Bu^n_4NHSO_4$

Results and Discussion

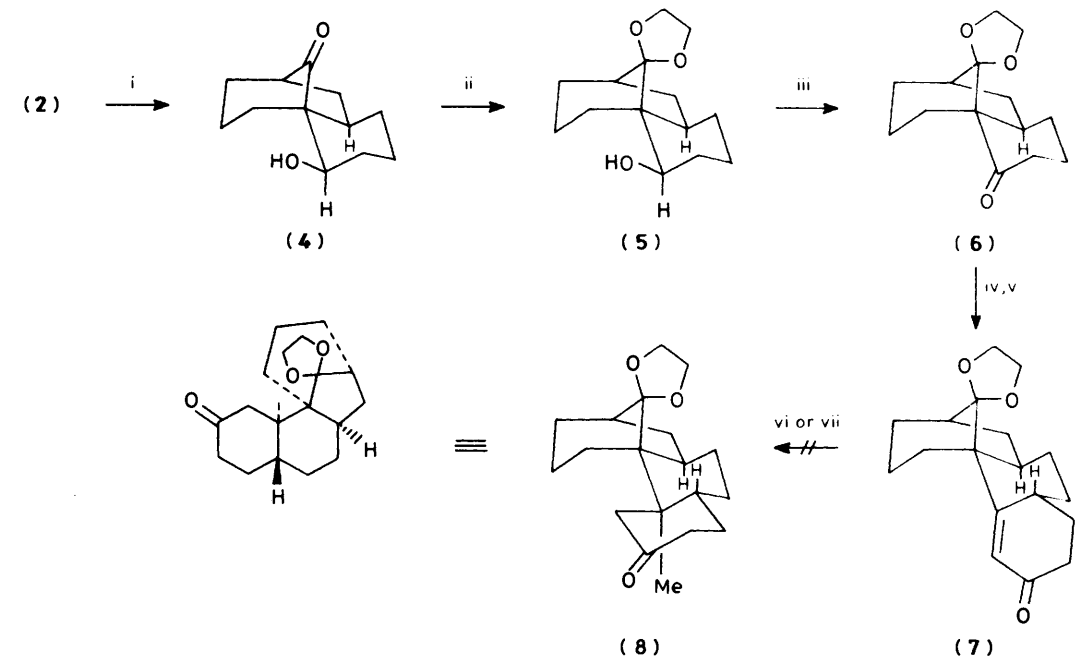
Synthesis of the Stemodane Skeleton (**7**).—Hydrogenation of the β-hydroxy isomer of (**2**) with 10% palladium–carbon gave the ketol (**4**), which was submitted to acetalization followed by Swern oxidation[7] of the resulting alcohol (**5**) to afford the keto acetal (**6**) in 88% overall yield from (**2**). From the α-isomer, the same keto acetal was obtained by the same sequence as above in 86% overall yield. Attempted Robinson-type annulation could be achieved *via* a two-step sequence according to the procedure of Stork.[8] Thus, treatment of compound (**6**) with 3-trimethylsilylbut-3-en-2-one[9] in the presence of lithium di-isopropylamide (LDA) at −78 °C, followed by heating with sodium methoxide in methanol, gave the tetracyclic enone (**7**), with the skeleton of stemodane-type terpenoids, as the sole product in 76% yield. The β configuration of the 5-H (steroid numbering) in (**7**) could be deduced on the basis of a thermodynamic equilibration condition[10] for the aldol condensation step. With the tetracyclic enone (**7**) synthesized, we attempted to introduce a methyl group onto the β position of this compound *via* conjugate addition (Scheme 2). In the event, several attempts were made to achieve the methylation of enone (**7**) with Me_2CuLi[11] or $MeCuBF_3$;[12] unfortunately, no adduct (**8**) could be obtained because of the highly steric congestion around the reaction centre of the molecule.

Syntheses of the Cedrane Skeletons (**14**) *and* (**17**).—For assembly of the cedrane skeleton, it is necessary to contract the cyclohexene ring to a five-membered ring with retention of the configuration at C-3. In pursuing this objective, we carried out two different approaches for the contraction, *i.e.*, the first one was sequential ozonolysis of the double bond and aldol condensation of the resulting dialdehyde, the second approach was the use of the photochemical Wolff rearrangement[13] of the cyclic diazoketone.

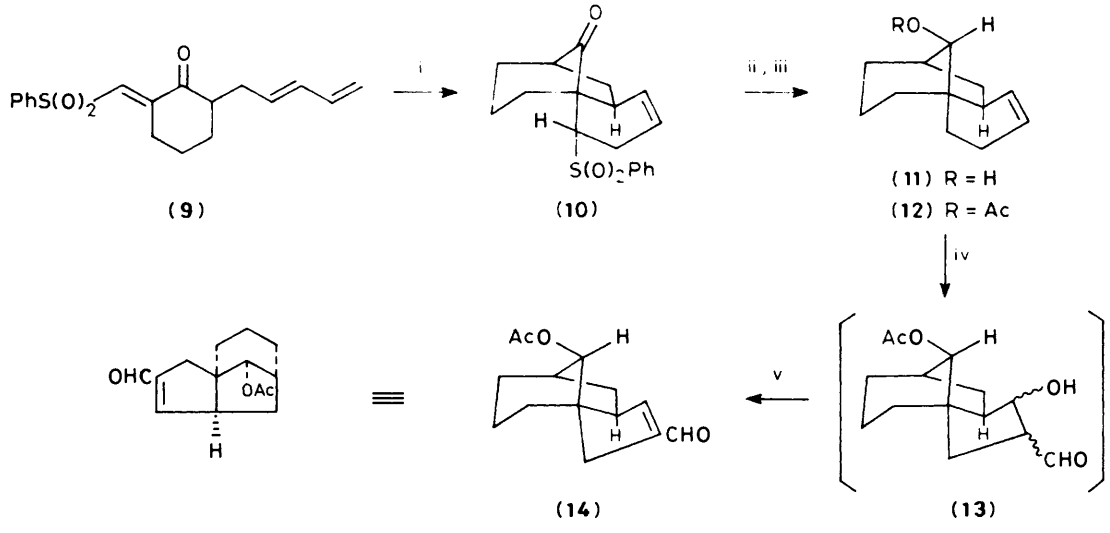
Thus, Birch reduction of the keto sulphone (**10**), prepared by stereoselective thermolysis of the trienone (**9**), gave the single alcohol (**11**) *via* the simultaneous desulphonylation and stereoselective reduction of the carbonyl group at C-12.[6] After acetylation, ozonolysis of the acetate (**12**) in methylene dichloride at −78 °C, followed by treatment with triethylamine,[14] furnished the aldol (**13**) which, without further purification, was then refluxed with a catalytic amount of toluene-*p*-sulphonic acid (PTSA) in benzene to afford the α,β-unsaturated aldehyde (**14**) in 33% yield from acetate (**12**). Examination of the ^{1}H n.m.r. spectrum of compound (**14**) revealed the olefinic proton of 4-H as a broadened singlet at δ_H 6.63, and the i.r. spectrum exhibited the conjugated carbonyl absorption at 1 670 cm^{-1}, which was indicative of the structure shown in Scheme 3.

The second route for the cedrane skeleton construction commenced with formylation of compound (**6**) with ethyl formate and sodium hydride in dimethoxyethane (DME). The

† All compounds reported in this paper are racemic. For convenience, only one enantiomer is shown.



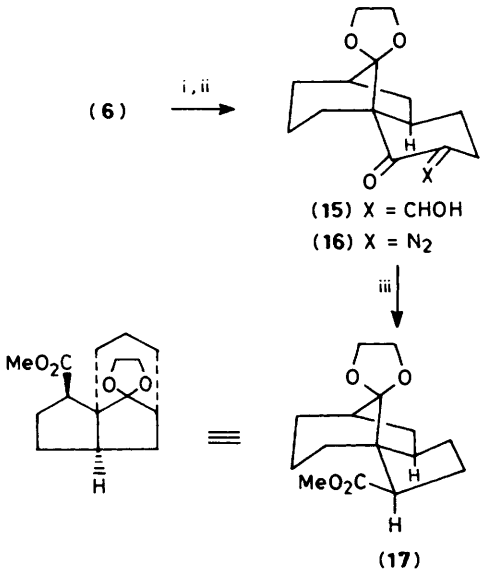
Scheme 2. *Reagents:* i, H_2, 10% Pd–C; ii, $HOCH_2CH_2OH$, CSA; iii, $(COCl)_2$, DMSO, NEt_3; iv, LDA, $Me_3SiC(=CH_2)COMe$; v, 5% NaOMe, MeOH; vi, Me_2CuLi; vii, $MeCuBF_3$



Scheme 3. *Reagents and conditions:* i, 180 °C, toluene; ii, Li, liq. NH_3, THF, EtOH; iii, Ac_2O, pyridine, DMAP; iv, O_3, CH_2Cl_2 then NEt_3; v, PTSA, benzene

hydroxymethylene derivative (**15**) thus obtained was treated with tosyl azide[15] in the presence of triethylamine to give the diazo ketone (**16**) in 70% yield from (**6**). Photochemical Wolff rearrangement in methanol solution led to the formation of the ring-contracted methyl ester (**17**) in 81% yield as a single product. At this point, although the configuration of the methoxycarbonyl function was not known with certainty, the eventual conversion of ester (**17**) into the acetonide (**23**) (*vide infra*) in the next section established its orientation as shown (Scheme 4).

Synthesis of the Perhydroazulene (**21**).—With successful synthesis of the ester (**17**) behind us, we were ready to effect the conversion of this ester into the perhydroazulene (**21**). Thus, hydrolysis of the acetal group in compound (**17**) under acidic conditions provided the ketone (**18**). Baeyer–Villiger oxidation[16] of compound (**18**) with *m*-chloroperbenzoic acid (MCPBA) in the presence of lithium carbonate in chloroform gave the lactone (**19**) in 83% yield as the sole product. The cleavage of the lactone ring was achieved reductively with lithium aluminium hydride to give the triol (**20**), which was then immediately acetylated to furnish the perhydroazulene diacetate (**21**) in 65% yield. The orientation of the hydroxymethyl group at C-10 in (**20**) was strongly supported by the fact that the triol (**20**) could be converted into the acetonide (**23**) *via* sequential acetonide formation[17] with 2,2-dimethoxypropane (DMP) in the presence of (+)-camphor-10-sulphonic acid in dimethylformamide (DMF), and acetylation of the intermediate (**22**) under standard conditions (Scheme 5).

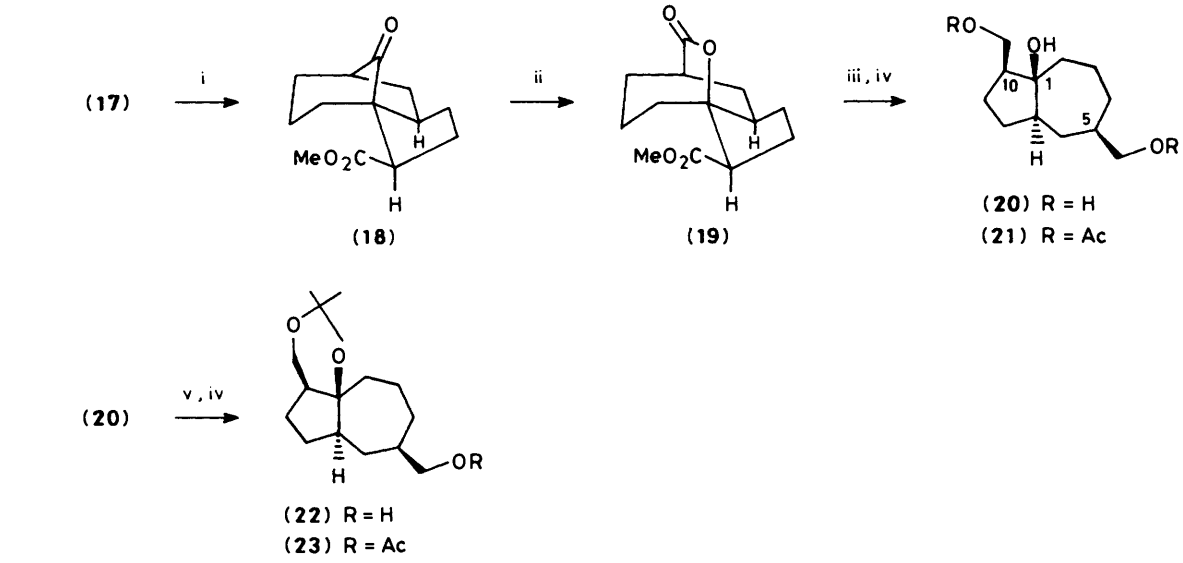


Scheme 4. *Reagents:* i, HCO_2Et, NaH, DME; ii, *p*-TsN_3; iii, *hv*, MeOH

efficiently transformed into four kinds of terpenoid carbon skeletons by use of simple manipulations, and the tricyclic system can serve as a synthetically useful synthon. The methodology should provide a basis for the total synthesis of natural products.

Experimental

General Methods.—M.p.s were determined on a Yanako micro melting point apparatus and are uncorrected. I.r. spectra were recorded on a Hitachi 260—10 spectrophotometer. N.m.r. spectra were measured on a JEOL JNM-PMX-60 and JEOL PS-100 spectrometers. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Mass spectra were taken on a Hitachi M-52G spectrometer and a JEOL-TMS-OISG-2 spectrometer. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue when the organic layer was separated, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. All new compounds described in this Experimental section were homogeneous on t.l.c.



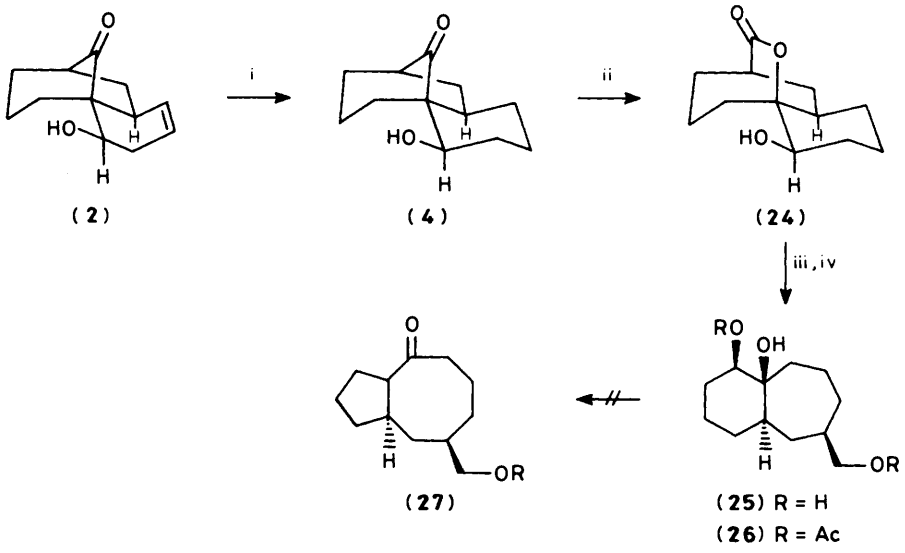
Scheme 5. *Reagents:* i, H_3O; ii, MCPBA; iii, $LiAlH_4$; iv, Ac_2O, pyridine, DMAP; v, $Me_2C(OMe)_2$, CSA

Synthesis of the Himachalene Skeleton (**26**).—The strategy of the conversion is the same as in the case of the perhydroazulene, *i.e.*, involving a cleavage of the bond between C-1 and C-12 in compound (**2**) *via* Baeyer–Villiger oxidation. In the event, treatment of ketol (**4**), derived from enone (**2**) by catalytic hydrogenation, with MCPBA afforded solely the lactone (**24**), which was treated with lithium aluminium hydride followed by acetic anhydride in pyridine. Thus was obtained the desired bicyclic diacetate (**26**) in 69% overall yield from (**2**). Attempted pinacol–pinacolone-type rearrangement of the triol (**25**), aimed at synthesis of the fused 5- and 8-membered-ring system (**27**) (Scheme 6), found in the sesquiterpene precapnelladiene[18] isolated from soft coral, afforded none of the expected rearranged products even under various reaction conditions.

In conclusion, we have demonstrated that the functionalized 2-hydroxytricyclo[6.3.1.$0^{1,6}$]dodec-4-en-12-one (**2**), readily derivable *via* an intramolecular Diels–Alder reaction, can be

(6α*H*)-12,12-*Ethylenedioxytricyclo*[6.3.1.$0^{1,6}$]*dodecan*-2-*one* (**6**).—*Method A. From the* β-*hydroxy isomer.* A solution of the 2β-hydroxy isomer (**2**)[6] (260 mg, 1.4 mmol) in anhydrous ethanol (10 ml) was hydrogenated over a catalytic amount of 10% palladium–carbon under atmospheric pressure at room temperature for 30 h. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to leave the alcohol (**4**) (260 mg) which was refluxed for 1.5 h with ethylene glycol (330 mg, 5.4 mmol) and a catalytic amount of (+)-camphor-10-sulphonic acid (CSA) in benzene (10 ml) in a Dean–Stark water separator. The reaction mixture was diluted with benzene and washed successively with water and saturated aqueous sodium chloride. The residue upon work-up gave the alcohol (**5**) (310 mg) as an oil, which was used in the next reaction without further purification.

To a solution of oxalyl chloride (200 mg, 1.6 mmol) in anhydrous methylene dichloride (8 ml) at −78 °C were added



Scheme 6. *Reagents:* i, H_2, 10% Pd–C; ii, MCPBA; iii, $LiAlH_4$; iv, Ac_2O, pyridine

dropwise dimethyl sulphoxide (DMSO) (230 mg, 3.0 mmol) and a solution of the alcohol (**5**) (310 mg) in anhydrous methylene dichloride (7 ml), and the mixture was stirred for 15 min at the same temperature. After addition of triethylamine (0.91 ml, 6.5 mmol), the mixture was stirred at −78 °C for 5 min and the reaction temperature was then allowed to rise to ambient. After being stirred for 1 h at room temperature, the mixture was diluted with water and the aqueous layer was separated, and extracted with chloroform. The combined extracts were washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed with n-hexane–ethyl acetate (7:3 v/v) as eluant to give the *keto acetal* (**6**) (280 mg, 88%) as an oil (Found: C, 71.45; H, 8.05. $C_{14}H_{20}O_3$ requires C, 71.15; H, 8.55%); $\nu_{max.}$($CHCl_3$) 1 690 cm^{-1} (C=O); δ_H (100 MHz; $CDCl_3$) 3.87 (4 H, m, OCH_2CH_2O); *m/z* 236 (M^+).

Method B. From the α-hydroxy isomer. A solution of the 2α-hydroxy isomer (**2**)[6] (160 mg, 0.83 mmol) in anhydrous ethanol (7 ml) was hydrogenated over a catalytic amount of 10% palladium–carbon under atmospheric pressure at room temperature for 14 h. After removal of the catalyst by filtration through Celite, the filtrate was evaporated to leave the alcohol (**4**) (170 mg), which was refluxed for 3.5 h with ethylene glycol (220 mg, 3.50 mmol) and a catalytic amount of CSA in benzene (9 ml) in a Dean–Stark water separator. The reaction mixture was diluted with benzene and washed successively with water and saturated aqueous sodium chloride. The residue upon work-up gave the alcohol (**5**) (180 mg) as an oil which was used in the next reaction without further purification.

To a solution of oxalyl chloride (110 mg, 0.83 mmol) in anhydrous methylene dichloride (3 ml) at −78 °C were added dropwise DMSO (130 mg, 1.66 mmol) and a solution of the alcohol (**5**) (180 mg) in anhydrous methylene dichloride (6 ml), and the mixture was stirred for 15 min at the same temperature. After addition of triethylamine (0.53 ml, 3.78 mmol), the mixture was stirred at −78 °C for 5 min and the reaction temperature was allowed to elevate to ambient. After being stirred for 1 h at room temperature, the mixture was diluted with water and the aqueous layer was separated, and extracted with chloroform. The combined extracts were washed with saturated aqueous sodium chloride. The residue upon work-up was chromatographed with n-hexane–ethyl acetate (7:3 v/v) as eluant to give the keto acetal (**6**) (170 mg, 86%), identical with the authentic material.

(7β*H*,10α*H*)-16,16-*Ethylenedioxytetracyclo*-[10.3.1.0^{1,10}.0^{2,7}]*hexadec-2-en-4-one* (**7**).—To a stirred solution of di-isopropylamine (43 mg, 0.42 mmol) in anhydrous DME (1.0 ml) was added dropwise n-butyl-lithium (1.515M-n-hexane solution; 0.26 ml) at −78 °C and the mixture was stirred for 30 min at −10 °C. To the solution, cooled to −78 °C, was added a solution of the keto acetal (**6**) (62.7 mg, 0.26 mmol) in anhydrous DME (1.0 ml), and the mixture was stirred at the same temperature for 3.5 h, after which a solution of 3-trimethylsilylbut-3-en-2-one (37.8 mg, 0.27 mmol) in anhydrous DME (1.0 ml) was added to the mixture and the mixture was then stirred for another 3.5 h, during which time the reaction temperature was allowed to reach ambient. After dilution of the mixture with ether, a small amount of saturated aqueous ammonium chloride was added. The residue upon work-up gave the diketone (72.0 mg), which was used in the next reaction without further purification.

To a solution of sodium methoxide in methanol [from sodium (30.5 mg, 1.33 mmol) and anhydrous methanol (0.30 ml)] was added a solution of the diketone (72.0 mg) in anhydrous methanol (0.30 ml), and the mixture was stirred at 60 °C for 1.5 h, and was then diluted with saturated aqueous ammonium chloride and most of methanol was removed under reduced pressure. The resulting mixture was extracted with ether and the residue upon work-up was chromatographed with n-hexane–ethyl acetate (3:2 v/v) as eluant to afford the starting keto acetal (**6**) (35.0 mg) and then the *tetracyclic enone* (**7**) (25.7 mg, 76%) as a yellow oil, $\nu_{max.}$($CHCl_3$) 1 660 cm^{-1} (conj. C=O); δ_H (100 MHz; $CDCl_3$) 3.80 (4 H, m, OCH_2CH_2O) and 6.16 (1 H, d, *J* 2.7 Hz, >C=CHCO) (Found: M^+, 288.1759. $C_{18}H_{24}O_3$ requires *M*, 288.1726).

(5α*H*)-11β-*Acetoxytricyclo*[5.3.1.0^{1,5}]*undec-3-ene-3-carbaldehyde* (**14**).—Ozone was passed through a solution of the acetate (**12**)[6] (84 mg, 0.38 mmol) in anhydrous methylene dichloride (5.0 ml) at −78 °C until the colour of the solution changed to blue. After the excess of ozone had been purged with nitrogen gas, triethylamine (154 mg, 1.53 mmol) was added at the same temperature, and the mixture was stirred at room temperature for 10 h. The mixture was washed with ice-cold water, and the residue upon work-up gave the aldol (**13**) (67 mg) as an oil, which was used in the next reaction without further purification.

A solution of the crude aldol (**13**) (67 mg) and a catalytic amount of PTSA in benzene (5.0 ml) was refluxed for 7 h in a Dean–Stark water separator. After removal of the solvent, the residue was chromatographed with n-hexane–ethyl acetate (4:1 v/v) as eluant to afford the *cedrane-skeleton acetate* (**14**) (29 mg, 33%) as an oil, $\nu_{max.}$($CHCl_3$) 1 725 (ester) and 1 670 cm^{-1} (conj. C=O); δ_H (60 MHz; $CDCl_3$) 2.10 (3 H, s, $OCOCH_3$), 4.46 (1 H, d, *J* 5.0 Hz, >C*H*OAc), 6.63 (1 H, br s, C*H*=CCHO), and 9.66 (1 H, s, CHO) (Found: M^+, 234.1252. $C_{14}H_{18}O_3$ requires *M*, 234.1254).

(6α*H*)-3-*Diazo*-12,12-*ethylenedioxytricyclo*[6.3.1.0^{1,6}]-*dodecan*-2-*one* (**15**).—To a stirred suspension of sodium hydride (60% in oil; 240 mg, 5.9 mmol) in anhydrous DME (6.0 ml) at room temperature was added a solution of the keto acetal (**6**) (280 mg, 1.2 mmol) in anhydrous DME (8.0 ml). After the mixture had been stirred for 1 h, ethyl formate (439 mg, 5.9 mmol) was added and the mixture was stirred at the same temperature for 15 h; ice–water was added and the solvent was removed under reduced pressure. The residue was washed with ether, acidified with 10% aqueous sulphuric acid, and extracted with ether. The combined extracts were washed with saturated aqueous sodium chloride and the residue upon work-up gave the hydroxymethylene compound (**15**) (260 mg), which was used in the next reaction without further purification.

To a solution of the hydroxymethylene compound (**15**) (260 mg) and triethylamine (219 mg, 2.2 mmol) in anhydrous methylene dichloride (4.0 ml) at −5 to −10 °C was added a solution of toluene *p*-sulphonyl azide (190 mg, 9.8 mmol) in anhydrous methylene dichloride (1.0 ml) and the mixture was stirred for 15 h, during which time it attained room temperature. The reaction mixture was then diluted with 5% aqueous sodium hydroxide and the aqueous layer was extracted with chloroform. The combined extracts were washed successively with 2.5% aqueous sodium hydroxide and saturated aqueous sodium chloride. The residue upon work-up was chromatographed with n-hexane–ethyl acetate (17:3 v/v) as eluant to give the α-*diazo ketone* (**16**) (218 mg, 70%) as a yellow oil, $\nu_{max.}$($CHCl_3$) 2 090 (N_2) and 1 610 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$) 3.87 (4 H, m, OCH_2CH_2O) (Found: M^+, 262.1322. $C_{14}H_{18}N_2O_3$ requires *M*, 262.1317).

Methyl (5α*H*)-11,11-*Ethylenedioxytricyclo*[5.3.1.0^{1,5}]-*undecane*-2β-*carboxylate* (**17**).—A solution of the α-diazo ketone (**16**) (60.0 mg, 0.23 mmol) in anhydrous methanol (4.0 ml) at 0 °C was irradiated using a Riko 400 W high-pressure mercury lamp for 3 h. After removal of the solvent, the residue was chromatographed with n-hexane–ethyl acetate (9:1 v/v) as eluant to afford the *ester* (**17**) (49.1 mg, 81%) as an oil (Found: C, 67.4; H, 8.4. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%); $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1} (ester); δ_H (100 MHz; $CDCl_3$) 3.59 (3 H, s, CO_2CH_3) and 3.74 (4 H, m, OCH_2CH_2O); δ_C (25 MHz; $CDCl_3$) 19.491 (t), 28.180 (t), 29.061 (t), 33.112 (t), 34.227 (t), 36.106 (t), 42.858 (t), 45.500 (d, C-7), 51.078 (q, CO_2CH_3), 51.430 (d, C-2), 58.416 (s, C-1), 63.466 (t, OCH_2CH_2O), 64.170 (t, OCH_2CH_2O), 117.421 (s, C-11), and 174.253 (s, CO_2Me); *m*/*z* 266 (M^+).

Methyl(5α*H*)-12-*Oxo*-11-*oxatricyclo*[5.3.2.0^{1,5}]*dodecane*-2β-*carboxylate* (**19**).—A solution of the acetal (**17**) (35.6 mg, 0.13 mmol) and 10% aqueous hydrochloric acid (0.5 ml) in acetone (10 ml) was stirred at room temperature for 2 h. After removal of the solvent the residue was extracted with chloroform and the extracts were washed with saturated aqueous sodium chloride. The residue upon work-up gave the ketone (**18**) (27.5 mg) which was used in the next reaction without further purification.

A solution of the ketone (**18**) (27.5 mg), a catalytic amount of lithium carbonate, and MCPBA (70%; 25.9 mg, 1.4 mmol) in chloroform (1 ml) was stirred at room temperature for 18 h. The reaction mixture was diluted with both chloroform and saturated aqueous sodium hydrogen carbonate, and was then extracted with chloroform, and the extracts were washed successively with saturated aqueous potassium carbonate and saturated aqueous sodium chloride. The residue upon work-up was chromatographed with n-hexane–ethyl acetate (3:2 v/v) as eluant to give the *lactone* (**19**) (24.3 mg, 83%) as an oil (Found: C, 65.65; H, 7.4. $C_{13}H_{18}O_4$ requires C, 65.55; H, 7.6%); $\nu_{max.}$($CHCl_3$) 1 735 cm^{-1} (lactone); δ_H (60 MHz; $CDCl_3$) 3.72 (3 H, s, CO_2CH_3); *m*/*z* 238 (M^+).

(7α*H*)-5β,10β-*Bis*(*acetoxymethyl*)*bicyclo*[5.3.0]*decan*-1β-*ol* (**21**).—To a stirred solution of the lactone (**19**) (20.0 mg, 0.084 mmol) in anhydrous tetrahydrofuran (THF) (0.5 ml) at room temperature was added dropwise a suspension of lithium aluminium hydride (10 mg) in anhydrous THF (0.5 ml). The mixture was then quenched with saturated aqueous ammonium chloride, at 0 °C. The precipitate was filtered through Celite and washed with ether. The residue obtained upon work-up of the filtrate was used in the next reaction without further purification.

A solution of the crude triol (**20**) (13.2 mg), anhydrous pyridine (0.1 ml), and acetic anhydride (0.1 ml) in anhydrous methylene dichloride (0.5 ml) was stirred at room temperature for 5 h. After removal of the solvent, the residue was chromatographed with n-hexane–ethyl acetate (7:3 v/v) as eluant to give the *perhydroazulene* (**21**) (38.4 mg, 65%) as an oil, $\nu_{max.}$($CHCl_3$) 3 500—3 700 (OH) and 1 720 cm^{-1} (ester); δ_H (100 MHz; $CDCl_3$) 2.03 (6 H, s, 2 × $OCOCH_3$), 3.85 (2 H, d, *J* 6.0 Hz, CH_2OAc), 4.04 (1 H, dd, *J* 6.0 and 12.0 Hz, C*H*OAc), and 4.30 (1 H, dd, *J* 8.0 and 12.0 Hz, C*H*OAc) (Found: M^+, 238.1557. $C_{14}H_{22}O_3$ requires *M*, 238.1567).

(6α*H*,9α*H*)-11β-*Acetoxymethyl*-3,3-*dimethyl*-2,4-*dioxatricyclo*[7.5.0.0^{1,6}]*tetradecane* (**23**).—A solution of the crude triol (**20**) (7.9 mg, 0.037 mmol), a catalytic amount of CSA, and DMP (0.1 ml) in DMF (0.5 ml) was refluxed for 2 h. After removal of the solvent, the residue was treated with a mixture of anhydrous pyridine (0.2 ml) and acetic anhydride (0.1 ml) at room temperature for 10 h. After removal of the solvent, the residue was chromatographed with n-hexane–ethyl acetate (9:1 v/v) as eluant to afford the *acetonide* (**23**) (2.7 mg, 19%) as an oil, $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1} (ester); δ_H (100 MHz; $CDCl_3$) 1.24 (3 H, s, *Me*CMe), 1.36 (3 H, s, MeC*Me*), 1.96 (3 H, s, $OCOCH_3$), 3.42 (1 H, dd, *J* 3.0 and 12.0 Hz, C*H*OCMe_2O), 3.76 (2 H, d, *J* 8.0 Hz, CH_2OAc), and 3.94 (1 H, dd, *J* 3.5 and 12.0 Hz, C*H*OCMe_2O) (Found: M^+, 296.1990. $C_{17}H_{28}O_4$ requires *M*, 296.1987).

(6α*H*)-2β-*Hydroxy*-12-*oxatricyclo*[6.3.2.0^{1,6}]*tridecan*-13-*one* (**24**).—To a solution of the keto alcohol (**4**) (77 mg, 0.40 mmol) in anhydrous methylene dichloride (3.0 ml) were added MCPBA (70%; 135 mg, 0.63 mmol) and a catalytic amount of lithium carbonate, and the mixture was refluxed for 15 h. The mixture was then diluted with saturated aqueous sodium thiosulphate and stirred for 10 min. The aqueous layer was separated and extracted with chloroform. The combined extracts were washed successively with aqueous potassium carbonate, water, and saturated aqueous sodium chloride. The residue upon work-up was chromatographed with n-hexane–ethyl acetate (7:3 v/v) as eluant to afford the *lactone* (**24**) (75 mg, 90%) as an oil, $\nu_{max.}$($CHCl_3$) 3 100—3 500 (OH) and 1 725 cm^{-1} (CO–O); δ_H (60 MHz; $CDCl_3$) 6.93 (1 H, m, 2-H) (Found: M^+, 210.1262. $C_{12}H_{18}O_3$ requires *M*, 210.1257).

(7α*H*)-11β-*Acetoxy*-5β-*acetoxymethylbicyclo*[5.4.0]*undecan*-1β-*ol* (**26**).—To a stirred solution of the lactone (**24**) (30.8 mg, 0.146 mmol) in anhydrous THF (0.5 ml) at room temperature

was added dropwise a suspension of lithium aluminium hydride (15 mg) in anhydrous THF (1 ml). Then, the reaction mixture was quenched, at 0 °C, with saturated aqueous ammonium chloride. The precipitate was filtered off on Celite and washed with ether. The residue upon work-up of the filtrate gave the triol (**25**) (31.2 mg, 99%) as an oil, which was used in the next reaction without further purification.

A solution of the triol (**25**) (56 mg, 0.26 mmol), a catalytic amount of 4-(dimethylamino)pyridine (DMAP), and acetic anhydride (267 mg, 2.61 mmol) in anhydrous pyridine (1.0 ml) was stirred at room temperature for 19 h. After removal of the solvent, the residue was chromatographed with n-hexane–ethyl acetate (4:1 v/v) as eluant to give the *diacetate* (**26**) (61 mg, 78%) as an oil (Found: C, 64.35; H, 9.0. $C_{16}H_{26}O_5$ requires C, 64.4; H, 8.8%); $\nu_{max.}$($CHCl_3$) 3 300—3 700 (OH) and 1 730 cm^{-1} (OCOMe); δ_H (100 MHz; $CDCl_3$) 1.55 (1 H, s, disappears on D_2O shake, OH), 1.97 (3 H, s, $OCOCH_3$), 1.98 (3 H, s, $OCOCH_3$), 3.76 (2 H, d, *J* 7 Hz, CH_2OAc), and 4.58 (1 H, t, *J* 3 Hz, 11-H); *m/z* 298 (M^+).

Acknowledgements

We thank Miss K. Mushiake, Miss K. Koike, Miss E. Kurosawa, and Mr. K. Kawamura, Pharmaceutical Institute, Tohoku University for microanalyses and spectral measurements. This work was financially supported in part by a Grant-in-Aid Special Project Research (5821006) of the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

References

1 A preliminary communication of a part of this work has appeared: K. Shishido, K. Hiroya, K. Fukumoto, and T. Kametani, *Chem. Lett.*, 1985, 87.
2 For a recent review, see A. G. Fallis, *Can. J. Chem.*, 1984, **62**, 183.
3 K. Shishido, T. Saitoh, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2139.
4 E. Piers, B. F. Abeysekera, D. J. Herbert, and I. D. Suckling, *J. Chem. Soc., Chem. Commun.*, 1982, 404; P. R. Kanjilal, M. Sarkar, S. K. Patra, S. Ghosh, and U. R. Ghatak, *J. Org. Chem.*, 1985, **50**, 857.
5 For an excellent review of the total synthesis of sesquiterpenes, see C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White, 'The Total Synthesis of Natural Products,' ed. J. Apsimon, Wiley, New York, 1983, vol. 5.
6 K. Shishido, K. Hiroya, Y. Ueno, K. Fukumoto, T. Kametani, and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, preceding paper.
7 A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
8 G. Stork and B. Ganem, *J. Am. Chem. Soc.*, 1973, **95**, 6152; G. Stork and J. Singh, *ibid.*, 1974, **96**, 6181.
9 R. K. Boeckman, Jr., D. M. Blum, B. Ganem, and N. Halvey, *Org. Synth.*, 1978, **58**, 152.
10 R. K. Boeckman, Jr., D. M. Blum, and S. D. Arthur, *J. Am. Chem. Soc.*, 1979, **101**, 5060.
11 H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31**, 3128.
12 Y. Yamamoto, S. Yamamoto, H. Yatagai, and K. Maruyama, *J. Org. Chem.*, 1982, **47**, 119.
13 M. Regits and J. Rüter, *Chem. Ber.*, 1968, **101**, 1263; K. B. Wiberg, B. L. Furtek, and L. K. Olli, *J. Am. Chem. Soc.*, 1979, **101**, 7675; K. B. Wiberg, L. K. Olli, N. Golembeski, and R. D. Adams, *ibid.*, 1980, **102**, 7467; W. G. Dauben and D. M. Walker, *Tetrahedron Lett.*, 1982, **23**, 711.
14 M. Kitamura, M. Isobe, Y. Ichikawa, and T. Goto, *J. Am. Chem. Soc.*, 1984, **106**, 3252.
15 T. Curtius and G. Kraemer, *J. Prakt. Chem.*, 1930, **125**, 303.
16 K. Narasaka, T. Sakakura, T. Uchimaru, and D. G. Vuong, *J. Am. Chem. Soc.*, 1984, **106**, 2954.
17 M. Tanabe and B. J. Bigley, *J. Am. Chem. Soc.*, 1961, **83**, 756; C. H. Robinson, L. E. Finckenor, R. Tiberi, and E. P. Oliveto, *J. Org. Chem.*, 1961, **26**, 2863.
18 E. Ayanoglu, T. Gebreyesus, C. M. Beechan, and C. Djerassi, *Tetrahedron*, 1979, **35**, 1035.

Received 10*th September* 1985; *Paper* 5/1550