Condensed Cyclic and Bridged-ring Systems. Part 6.[1] Stereochemically Defined Synthesis of (±)-3-Methoxy-17,18,19,20-tetranor-B-homophylloclada-1(10),2,4-triene-16-one through Intramolecular Alkylation of a γδ-Unsaturated α'-Diazomethyl Ketone

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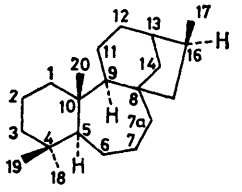
A stereochemically defined synthesis of (±)-3-methoxy-17,18,19,20-tetranor-B-homophylloclada-1(10),2,4-triene-16-one (7) is described. The key intermediate, 1,2,3,4,6,7-hexahydro-9-methoxy-5*H*-dibenzo[*a*,*c*]cycloheptene-3-carboxylic acid (3), is converted into the corresponding 3-diazomethyl ketone (4) and subjected to intramolecular oxo-carbenoid addition and boron trifluoride–ether-catalysed cyclisation, leading to the cyclopropyl ketone, (±)-3-methoxy-9β,15-cyclo-17,18,19,20-tetranor-B-homophylloclada-1(10),2,4-trien-16-one (5) and the tetracyclic unsaturated ketone, (±)-3-methoxy-17,18,19,20-tetranor-B-homophylloclada-1(10),2,4,9(11)-tetraen-16-one (6), respectively. Catalytic hydrogenation of the cyclopropyl ketone (5) and of the unsaturated ketone (6) gave the product (7) in high yield.

We have reported previously [2] the development of two simple synthetic routes to the bicyclo[3.2.1]octan-6-one unit fused within reduced fluorene, phenanthrene, and other systems, by intramolecular alkylation of γδ-unsaturated α'-diazomethyl ketones. Some potential intermediates in syntheses of complex diterpenoids have thus been obtained. We now describe a stereospecific synthetic route to a tetracyclic bridged-ring ketone (7) related to the B-homophylllocladane system (A).



(A)

The tricyclic carboxylic acid (3) was prepared by way of the vinyl alcohol (2) [3] by a Diels–Alder reaction analogous to earlier work in this [2c,d] and other laboratories.[4] The diene generated *in situ* from the vinyl alcohol (2) [prepared by the condensation of vinylmagnesium bromide with the methoxytetrahydrobenzocycloheptenone (1) [5]] underwent a cycloaddition with methyl acrylate in boiling benzene in the presence of catalytic amounts of iodine, quinoline, and hydroquinone to afford a liquid ester, which was treated directly with dry hydrogen chloride in benzene to isomerise the double bond. Alkaline hydrolysis then afforded a solid acidic product, difficult to crystallise and with a wide m.p. range, from which the desired acid (3) could be isolated in *ca.* 25% overall yield [based on (1)] through formation of the dicyclohexylamine salt, followed by regeneration of the free acid. The pure acid could be only partly separated by fractional crystallisation of the crude acid. All attempts at isolation of any other characterisable product from the reaction mixture failed. The tetrasubstituted nature of the double bond in the acid (3) was confirmed by the absence of olefinic proton signals in the n.m.r. spectrum of the corresponding methyl ester. The u.v. spectrum of this acid showed a single styrenoid band at 253 nm (log ε 4.26), in conformity with the reported [3] u.v. absorption [$\lambda_{max.}$ 254 nm (ε 11 900)] for the analogous tetrasubstituted styrene system in 3-methoxy-B-homo-1,3,8,5(10)-estratetraen-17-ol. Although the overall yield of the acid (3) is not high, the Diels–Alder reaction provides a simple route to this tricyclic system with proper functionality.

Through the usual sequence of reactions (see Experimental section) the acid (3) was converted into the crystalline diazo-ketone (4). Decomposition of the diazo-ketone in the presence of ' activated copper oxide ' [2c] in boiling cyclohexane–tetrahydrofuran under irradiation with tungsten lamps, and chromatographic purification of the reaction product afforded the cyclopropyl ketone (5) in 50% yield. Repeating the oxo-carbenoid addition reaction without irradiation gave the cyclopropyl ketone in slightly lower yield (*ca.* 40%). Acid-induced cleavage of the cyclopropyl ketone (5) gave the unsaturated bridged ketone (6) in high yield. Direct boron trifluoride–ether-catalysed cyclisation of the diazo-ketone (4) also afforded the unsaturated ketone (6) in 50% yield. Hydrogenolysis of the cyclopropane bond conjugated with the aromatic system in the cyclopropyl ketone (5) over palladium–charcoal (10%) in ethanol gave a single saturated ketone (7) in 93% yield. The stereochemistry of this ketone was assigned by analogy with the other systems studied in our laboratory.[2,6] Catalytic hydrogenation of the styrenoid ketone (6) also proceeded with high stereoselectivity and produced the same ketone in high yield. Further transformations of this bridged ketone are being studied.

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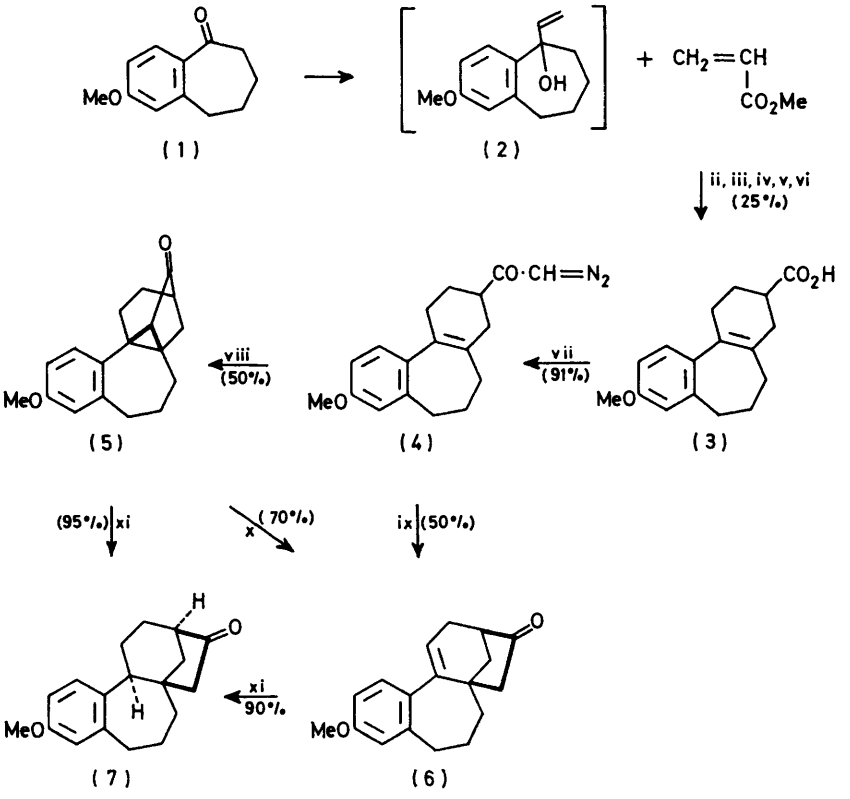
EXPERIMENTAL

For general procedures see Part 4.[2a]

1,2,3,4,6,7-Hexahydro-9-methoxy-5H-dibenzo[a,c]*cycloheptene-3-carboxylic Acid* (3).*—6,7,8,9-Tetrahydro-2-methoxybenzocyclohepten-5-one (1), m.p. 61° (lit.,[5] m.p. 62°), was prepared in 63% yield according to the procedure of Khan and Proctor.[5] To an ice-cold stirred solution of vinylmagnesium bromide [from magnesium (0.9 g, 38 mg atom) and vinyl bromide (3.6 g) (freshly generated [2a] from 1,2-dibromoethane) in tetrahydrofuran (7 ml)] a solution of the benzocycloheptenone (1) (2.5 g, 13 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was stirred for 1 h at 0 °C, then 1.5 h at 25 °C, and finally refluxed for 2 h. After removal of the tetrahydrofuran, the Grignard complex was chilled in ice, treated with benzene (50 ml), and decomposed with ice-cold aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with benzene. The combined extracts were washed with water and dried (Na_2SO_4). A small portion of the solution was evaporated under reduced pressure to afford a light yellow semisolid which showed a broad i.r. absorption at 3 450 cm^{-1} (OH) and no trace of a C=O band. This solution of the vinyl alcohol (2) was mixed with freshly distilled methyl acrylate (3 g, 34 mmol), a crystal of iodine, quinoline (0.05 ml), and hydroquinone (10 mg) and refluxed for 10 h under a Dean–Stark water separator. The cooled mixture was washed with aqueous 5% sodium thiosulphate followed by water, dried (Na_2SO_4), and concentrated, and the residue was distilled to separate the adduct (2.45 g), b.p. 150—155° at 0.2 mmHg, as a pale yellow oil, $\nu_{max.}$ 1 725s cm^{-1}. This was stirred for 30 min at 0 °C in benzene saturated with dry hydrogen chloride. The usual work-up gave a light yellow viscous liquid (2.44 g), $\lambda_{max.}$ 254 nm (log ε 4.24); $\nu_{max.}$ 1 725s cm^{-1}. This ester was hydrolysed by refluxing for 4 h with potassium hydroxide (2.5 g) in 90% ethanol (25 ml) under nitrogen. After dilution with water and concentration under reduced pressure the neutral material was removed by extraction with ether. The alkaline layer was acidified with hydrochloric acid (6N) and the precipitated acid was extracted with ether. The ether layer was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford a light yellow solid (1.75 g), m.p. 110—123°. An ethereal solution (10 ml) of the acid (1.75 g) was mixed with freshly distilled dicyclohexylamine (1.5 ml) and kept overnight at 0 °C. The separated crystalline dicyclohexylamine salt (1.9 g) on recrystallisation thrice from methanol–ether gave needles (1.7 g), m.p. 149° (Found: C, 76.5; H, 9.5. Calc. for $C_{29}H_{43}NO_3$: C, 76.8; H, 9.5%). The recrystallised salt (1.7 g) was dissolved in methanol (5 ml) and hydrochloric acid (6N) (10 ml) was added with stirring at room temperature. The mixture was extracted with ether and the extract washed with water, dried (Na_2SO_4), and evaporated to afford the acid (3) (910 mg), m.p. 154°; $\lambda_{max.}$ 254 nm (log ε 4.24); $\nu_{max.}$ 1 700s and 1 600m cm^{-1}; single spot on t.l.c. [benzene–methanol (9 : 1)] (Found: C, 74.7; H, 7.7. Calc. for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4%). The acid (3) (100 mg) was esterified with an excess of diazomethane in ether. The ester was obtained as a faintly



SCHEME Reagents: i, CH_2:CHMgBr–THF; ii, I_2–quinoline–hydroquinone–C_6H_6; iii, HCl–C_6H_6; iv, KOH–H_2O–EtOH; v, $(C_6H_{11})_2$-NH; vi, HCl–MeOH; vii, NaOMe–MeOH, $(COCl)_2$–C_5H_5N–C_6H_6, CH_2N_2–Et_2O; viii, 'activated CuO'–THF–C_6H_{12}($h\nu$); ix, BF_3–Et_2O–Cl_2CH_2; x, HCl–$CHCl_3$; xi, Pd–C (10%) in EtOH

* We thank B. C. Ranu for the initial experiments towards the preparation of this compound.

yellow liquid; $\nu_{max.}$ 1 725s cm^{-1}; δ (CCl_4) 1.8—2.6 (13 H, m), 3.66 (3 H, s, CO_2Me), 3.76 (3 H, s, OCH_3), and 6.6—7.3 (3 H, m, ArH). Decomposition of the residual dicyclohexylamine salt in the mother liquors gave a gummy solid from which no other crystalline product was isolated. However, the pure acid (3) could be isolated from the crude product after repeated crystallisation from ether–petroleum in 8—10% yield; m.p. and mixed m.p. 154°.

3-Diazoacetyl-1,2,3,4,6,7-hexahydro-9-methoxy-5H-dibenzo-[a,c]*cycloheptene* (4).—The acid (3) (1.1 g, 4 mmol) in methanol (10 ml) was neutralised with *ca.* 10% sodium methoxide in methanol (phenolphthalein as indicator). The solvent was evaporated off under reduced pressure. To the sodium salt, dry benzene (3 × 25 ml) was added and distilled off (3 times) to remove traces of methanol. To a rapidly stirred, ice-cold suspension of the sodium salt in dry benzene (50 ml) and pyridine (0.2 ml), oxalyl chloride (2.5 ml) was added dropwise. The mixture was stirred at room temperature for 30 min and finally warmed at *ca.* 60 °C for 1.5 h. The precipitate was filtered off and the filtrate concentrated under reduced pressure. The brown solid residue was dissolved in anhydrous ether (60 ml) and added to a stirred solution of an excess of cold ethereal diazomethane [from *N*-methyl-*N*-nitrosourea (5 g)]; the mixture was left overnight at room temperature. Evaporation yielded a dark yellow solid which was dissolved in ether and filtered through a short column of neutral alumina (15 g). Evaporation gave the *diazo-ketone* (4) as a pale yellow solid (1.10 g, 91%), m.p. 118—119° (decomp.); $\nu_{max.}$ 2 120s and 1 635m cm^{-1}; δ ($CDCl_3$) 1.73—2.50 (13 H, m, complex), 3.76 (3 H, s), 5.30 (1 H, s, $CO{\cdot}CHN_2$), and 6.70—7.03 (3 H, m, complex) (Found: C, 72.8; H, 7.0. $C_{18}H_{20}N_2O_2$ requires C, 73.0; H, 6.8%).

Carbenoid Decomposition of the Diazo-ketone (4): (±)-*3-Methoxy-9β,15-cyclo-17,18,19,20-tetranor-*B*-homophyllocladа-1(10),2,4-trien-16-one* (5).—*Method A: thermal decomposition under irradiation.* The diazo-ketone (4) (500 mg, 1.6 mmol) in cyclohexane–tetrahydrofuran (7 : 3; 95 ml) was stirred and refluxed with ' activated copper oxide catalyst ' [2c] (2 g; 25 mmol) under irradiation by two 200 W tungsten lamps. The time required for complete decomposition of the diazo-ketone was 3 h. The cooled mixture was filtered and the solvent was distilled off *in vacuo*. The resultant semisolid (500 mg) was dissolved in benzene (10 ml) and chromatographed on neutral alumina (20 g). Benzene–petroleum (1 : 3; 1 l) eluted the bridged ketone (5) (226 mg, 50% after recrystallisation from ethyl acetate–petroleum), m.p. 124°; $\nu_{max.}$ 1 710s and 1 600m cm^{-1}; single spot on t.l.c. [benzene–ethyl acetate (4 : 1)]; δ ($CDCl_3$) 1.28br (2 H, s, 14-H_2), 1.71—2.80 (12 H, m), 3.75 (3 H, s, OCH_3), and 6.66—7.10 (3 H, m, ArH) (Found: C, 80.5; H, 7.6. $C_{18}H_{20}O_2$ requires C, 80.5; H, 7.5%). Elution with benzene–petroleum (1 : 1) and benzene yielded only an intractable gum.

Method B: thermal decomposition. The diazo-ketone (4), under the above conditions but without irradiation, afforded the bridged ketone (5) in *ca.* 40% yield; m.p. and mixed m.p. 124°. The reaction was complete in 5 h.

(±)-*3-Methoxy-17,18,19,20-tetranor-*B*-homophyllocladа-1(10),2,4,9(11)-tetraen-16-one* (6).—*Method A: acid-catalysed fragmentation of the bridged ketone* (5). Through a solution of the bridged ketone (5) (200 mg) in dry chloroform (100 ml) was bubbled a stream of dry hydrogen chloride at ice-bath temperature for 2 h; the colour gradually turned red. Removal of solvent *in vacuo* left a solid, which was crystallised from petroleum to obtain the styrenoid *ketone* (6) (140 mg, 70%), m.p. 109°, as long needles; $\nu_{max.}$ 1 735s cm^{-1}; $\lambda_{max.}$ 237 nm (log ε 4.12); δ ($CDCl_3$) 1.23—2.71 (13 H, m), 3.76 (3 H, s, OCH_3), 5.28br (1 H, t, *J* 6 Hz, CH=C), and 6.63—7.18 (3 H, m, ArH); M^+ 268 (Found: C, 80.7; H, 7.6. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%).

Method B: boron trifluoride–ether-catalysed intramolecular alkylation of the diazo-ketone (4). To a stirred solution of the diazo-ketone (4) (300 mg) in anhydrous methylene chloride (70 ml), cooled in an ice-salt bath (*ca.* −10 °C), freshly distilled boron trifluoride–ether (0.3 ml) was added. After 1 h, the solution was washed with water, 5% sodium carbonate solution, and water, and dried (Na_2SO_4). Removal of solvent under reduced pressure and chromatography of the residue on neutral alumina (20 g) with benzene–petroleum (1 : 5) as eluant afforded the ketone (6) (120 mg, 50%), m.p. and mixed m.p. 109°, identical with the sample described above (i.r. spectrum).

(±)-*3-Methoxy-17,18,19,20-tetranor-*B*-homophyllocladа-1(10),2,4-trien-16-one* (7).—(A) *Catalytic hydrogenolysis of the cyclopropyl ketone* (5). The ketone (5) (200 mg) in ethanol (25 ml) was hydrogenolysed over palladium–charcoal (10%; 100 mg) (uptake complete within 10—15 min). The usual work-up gave a solid which on recrystallisation from light petroleum afforded the saturated *ketone* (7) (200 mg, 95%), m.p. 125—126°; $\lambda_{max.}$ 228 (log ε 3.8) and 278 nm (3.5); $\nu_{max.}$ 1 740 cm^{-1}; δ ($CDCl_3$) 1.25—2.9 (16 H, m), 3.76 (3 H, s, OCH_3), and 6.6—7.1 (3 H, m, ArH); M^+ 270 (Found: C, 79.7; H, 8.1. $C_{18}H_{22}O_2$ requires C, 80.0; H, 8.2%).

(B) *Catalytic hydrogenation of the unsaturated ketone* (6). The styrenoid ketone (6) (250 mg) in ethanol (25 ml) was hydrogenated as above (uptake complete within 10 min). The crude product (7) (240 mg, 90%) had m.p. and mixed m.p. 125—126°.

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