A Formal Total Synthesis of (±)-Herbertene

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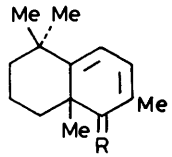
Methylation of the α,β-unsaturated ketone (**2**) in presence of lithium di-isopropylamide and hexamethylphosphoramide complex yielded the methylated ketone (**3**). Reduction of ketone (**3**) with sodium borohydride yielded the alcohol (**4**) whose tosyl derivative (**5**) on heating with dimethylformamide and lithium bromide afforded the diene (**18**). Oxidation of (**18**) with chromic acid produced the dienone (**19**) and the alcohol (**23**). Treatment of the dienone (**19**) with TosMIC (tosylmethyl isocyanide) and potassium t-butoxide yielded the nitrile derivative (**20**) which on reduction with di-isobutylaluminium hydride (DIBAL) followed by further reduction with sodium borohydride adsorbed on alumina yielded the alcohol (**22**). Oxidation of the α,β-unsaturated ketone (**2**) with dichlorodicyanobenzoquinone in dioxane afforded the dienone (**15**) which on hydrocyanation afforded principally the nitrile derivative (**6**) which was converted into the alcohol (**22**) by a seven-step sequence (reduction, oxidation, tetrahydropyranylation, methylation, reduction, tosylation, and detosylation).

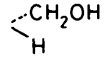
Matsuo *et al.*[1] isolated, from the liverwort *Herberta aduna*, a new sesquiterpene, (−)-herbertene (**1**) which possesses a 1,1,2-trimethyl-2-*m*-tolycyclopentane structure. It is of interest to note that sesquiterpenes such as cuparene and cuparenol, isolated from the liverwort *Bazzanlia pompeana*, contain a *p*-tolyl residue.[2] Frater[3] observed that the alcohol (**22**) on treatment with perchloric acid in formic acid underwent rearrangement yielding the aromatic sesquiterpene (±)-herbertene (**1**). In the course of our investigation of the synthesis of natural products related to terpenes, an attempt was made to realize an alternative synthesis of the alcohol (**22**) and the present paper decribes the results obtained.

Discussion

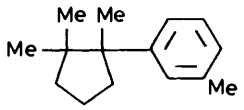
The α,β-unsaturated ketone (**2**),[4] chosen as starting material, was considered a suitable synthon for the present work since this readily available compound would permit various routes for its elaboration to the target molecule (**22**). The enol ether of ketone (**2**), generated by treatment with trimethylsilyl chloride and potassium hydride,[5] was subjected to cyclopropanation with methylene di-iodide and zinc–silver couple.[6] The resulting product gave, on treatment with boiling alcoholic sodium hydroxide, the methylated ketone (**3**) only in 20% yield. The stereochemistry of the newly introduced methyl group was assigned on the basis of analogy.[6] Several modifications were made to improve the yield of the methylated ketone (**3**) but no notable improvement was observed. Thus an alternative method was tried. Methylation of the enolate derived *via* addition of the ketone (**2**) to the lithium di-isopropylamide–hexamethylphosphoramide (LDA–HMPA) complex[7] proceeded smoothly, yielding the methylated ketone (**3**) in 67% yield and this was completely identical, as evidenced by spectroscopic comparison, with the ketone (**3**) prepared by the aforementioned procedure. This identity indicated that the stereochemistry of the newly introduced methyl group in ketone (**2**) prepared by distinctly separate procedures had the same configuration. Reduction of the ketone (**3**) with sodium borohydride and cerium(III) chloride[8] yielded the alcohol (**4**) in 80% yield. The configurational assignment of the hydroxy group was made on the basis of ^{1}H n.m.r. spectroscopy which showed a multiplet at δ 3.84 with half-band width ($w_{\frac{1}{2}}$) 16 Hz, thus indicating the axial nature[9] of the proton at C-7 of the alcohol (**4**). The most satisfactory method for the synthesis of compound (**18**) was achieved by subjecting the alcohol (**4**) to tosylation followed by detosylation. Treatment of the alcohol (**4**) with tosyl chloride and pyridine yielded the tosyl ester (**5**) in excellent yield, which on heating with lithium bromide and dimethylformamide (DMF) afforded the diene (**18**). Dehydration of the alcohol (**4**) with phosphorus trichloride oxide and pyridine, iron(III) chloride on silica gel,[10] iodine and benzene, and dimethyl sulphoxide did not produce the diene (**18**) in satisfactory yield.

The final stage of the synthesis demanded the stereoselective introduction either of an aldehyde or a carboxy group at C-4† of the diene (**18**) and the resulting product on reduction would yield the target molecule (**22**). In order to realize this objective, the diene (**18**) was oxidized with chromium trioxide. The desired dienone (**19**) was obtained in 36% yield and despite variations in experimental conditions the yield could not be improved. The low yield of the dienone (**19**) might be abscribed to the high steric hindrance to attack at C-9 occasioned by the C-10 and C-8 methyl groups. Oxidation of the diene (**18**) also afforded alcoholic material (10%) which was assigned the structure (**23**) on the basis of spectral analysis. The mechanism for the formation of the alcohol (**23**) is depicted in Scheme 1. The acyloin exhibited a molecular ion peak at *m/z* 222 in the mass spectrum.

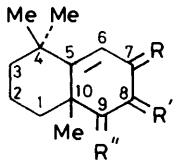


(**18**) R = H,H
(**19**) R = O
(**20**) R = 
(**21**) R = 
(**22**) R = 

† Throughout this Discussion, the arbitrary numbering scheme shown for structures (**2**)—(**14**) is used. It does not coincide with the systematic numbering schemes used in the Experimental section.



(1)



(2) R = O, R′ = R″ = H,H

(3) R = O, R′ =  , R″ = H,H

(4) R =  , R′ = , R″ = H,H

(5) R =  , R′ = , R″ =

(6) R = O, R′ = H,H, R″ = 

(7) R = O, R′ = H,H, R″ = 

(8) R = O, R′ = H,H, R″ = 

(9) R = O, R′ = H,H, R″ =

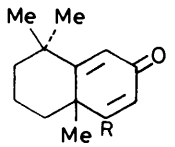
(10) R = O, R′ = , R″ =

(11) R = O, R′ = Me,Me, R″ =

(12) R = O, R′ = H,H, R″ =

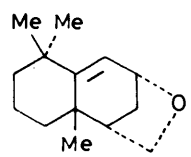
(13) R = O, R′ = H,H, R″ =

(14) R = O, R′ = H,H, R″ =



(15) R = H

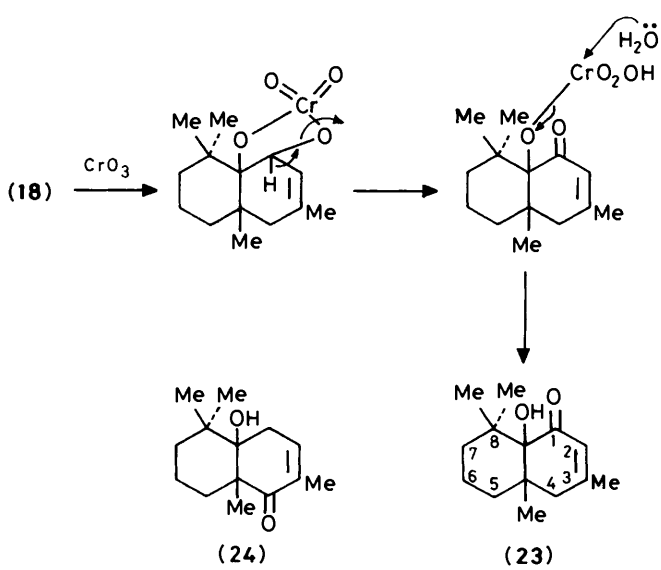
(16) R = Me



(17)

Ts = 

THP = 



Scheme 1.

I.r. absorptions for the hydroxy and α,β-unsaturated ketone were observed. In the ^{1}H n.m.r. spectrum the product exhibited broad signals for the two allylic protons at δ 3.25 and 2.83. The signal at δ 5.70, which appeared as a multiplet with a very small *J*-value, indicated the presence of an α-vinyl proton and thus supported the assigned structure of the alcohol (**23**). If the alcohol were to be assigned structure (**24**) instead of (**23**), the β-vinyl proton would have had to appear within the range δ 6.00—7.00 in the ^{1}H n.m.r. spectrum. Irradiation of the signal at δ 1.85 (vinyl methyl group) sharpened the vinyl proton signal at δ 5.70. The signal at δ 2.35, which corresponded to the hydrogen of the hydroxy group, was exchangeable with D_2O. Unequivocal confirmation of the structure of the alcohol (**23**) was not sought.

With the synthesis of the dienone (**19**) we were ready to address the final problem, that of the transformation of the C-9 carbonyl to the C-9 hydroxymethylene group. In planning this objective it occurred to us that compound (**21**) would be a particularly valuable intermediate for the above mentioned transformation. The direct conversion of C-9 carbonyl into C-9 aldehyde by the published procedures[11,12] was not successful. Therefore it was hoped to attain this transformation by converting the dienone (**19**) into compound (**20**) which would easily

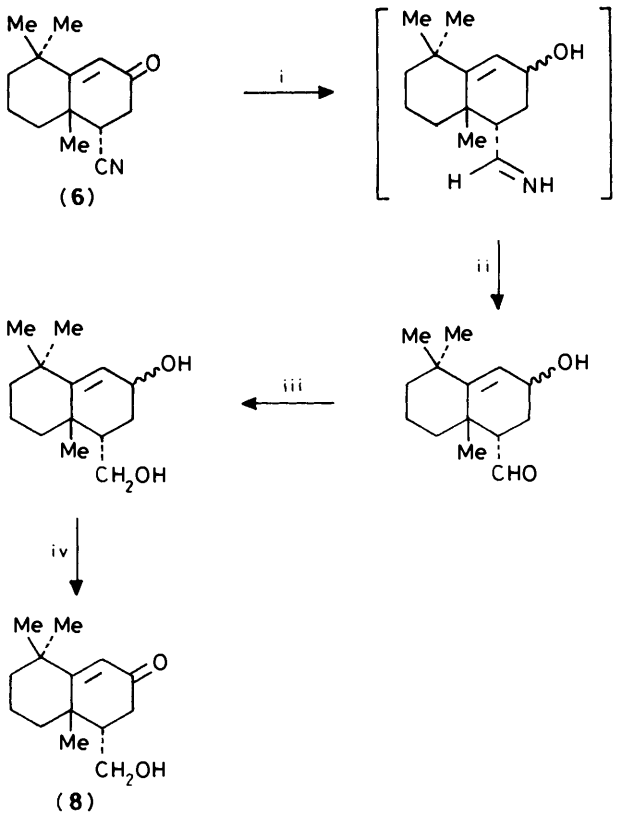
produce the aldehyde (**21**). The dienone (**18**) on treatment with TosMIC (tosylmethyl isocyanide) in potassium t-butoxide[13] yielded the nitrile (**20**) in mediocre yield. Because of the steric hindrance of the carbonyl group, a satisfactory yield of compound (**20**) was not obtained. Reduction of nitrile (**20**) with DIBAL[14] yielded the aldehyde (**21**) which was found to be unstable, as evidenced by its rapid change of colour, and this, on reduction with sodium borohydride adsorbed on alumina,[15] produced the alcohol (**22**). The identity of the alcohol (**22**) was confirmed by direct comparison (i.r. and t.l.c.) with an authentic specimen.[3] The ^{1}H n.m.r. spectroscopic data of our synthetic alcohol (**22**) and the authentic specimen, both taken in our laboratory, were identical. The identity of the alcohol (**22**) also confirmed the configuration of the nitrile and aldehyde groups of compounds (**20**) and (**21**) respectively.

An alternative approach was also sought for the synthesis of the alcohol (**22**) and we believe that it is worthwhile to publish our results. The α,β-unsaturated ketone (**2**) on oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) yielded the dienone (**15**) in 58% yield, which was subjected to hydrocyanation by heating with potassium cyanide, ammonium chloride, and DMF. The major product (63%) obtained was assigned the structure (**6**) on the basis of literature analogy.[16] The spectral data also lent strong support in favour of the structure (**6**). Another product (27%) obtained during hydrocyanation was identified as a cyanated product on the basis of spectral data and therefore there was no alternative except to assign the structure (**7**) for the second product.

The ketone (**6**) on reduction with DIBAL afforded an oily material which presented in its i.r. spectrum the characteristic absorptions for the carbonyl and hydroxy groups. As the resulting material could not be purified owing to its tendency to decomposition it was subjected to reduction with sodium borohydride adsorbed on alumina. The product isolated was subjected to selective oxidation[17] with cerium(IV) ammonium nitrate and sodium bromate to obtain an oily material (26%) whose spectroscopic data led us to assign the structure (**8**). The possible mechanism for the formation of compound (**8**) is depicted in Scheme 2. This mechanism will also be helpful in explaining the transformation of compound (**20**) to alcohol (**22**). Protection of the hydroxy function through the remainder of the planned sequence seemed advisable and thus the alcohol (**8**) was converted into its pyranyl derivative (**9**), whose conversion into the alcohol (**22**) was accomplished by methylation, reduction, tosylation, and detosylation without isolation or purification of any intermediates. The identity of compound (**22**) was confirmed on the basis of ^{1}H n.m.r., i.r., and t.l.c. comparisons with a sample of compound (**22**) prepared by the already mentioned procedure. We observed that the alcohol (**22**) has a tendency to polymerize within two or three days.

Several alternative routes were attempted in order to synthesize the alcohol (**22**) with a view to improving its yield. Though none of them proved rewarding, we will discuss the two approaches which afforded novel information. The first approach consisted of methylation[7] of the cyanated ketone (**6**) with the hope of obtaining compound (**10**), a suitable candidate for its transformation to alcohol (**22**). Instead of the desired compound, three products were isolated, the compounds (**11**) (25%) as solid material, (**12**) (16%) as an oil, and (**16**) (12%) as solid. The structures of these compounds were tentatively assigned on the basis of spectral data (see Experimental section). We believe that the formation of dienone (**16**) takes place through the partial dehydrocyanation of nitrile (**12**).

In the second approach the conjugated methylation of dienone (**15**) followed by its transformation to the tricycle (**17**) was attempted. Treatment of compound (**15**) with lithium dimethylcuprate[18] yielded two methylated products (**13**) and (**14**) in unequal proportions. Neither from a comparison of the spectral data of the methylated products nor from the basis of the reference cited[18] was it possible to ascertain which methylated product (major or minor isomer) possesses structure (**13**), a useful intermediate for the preparation of the tricycle (**17**). The reduction of the carbonyl group of the two methylated products (**13**) and (**14**), carried out separately, with DIBAL, followed by oxidation with lead tetra-acetate in benzene using a 250 W incandescent lamp, returned most of the starting material (**13**) and (**14**) unchanged and we had to abandon our efforts to synthesize the cyclic ether (**17**).



Scheme 2. *Reagents:* i, DIBAL; ii, water; iii, BH_4^-

In conclusion, the synthesis of the alcohol (**22**) has been realized by two distinct routes and since the alcohol (**22**) has been converted into (±)-herbertene (**1**), our method for the preparation of the alcohol (**22**) constitutes an alternative method for the synthesis of (±)-herbertene.

Experimental *

M.p.s were determined on a Kofler hot-stage and are uncorrected. Unless otherwise stated, i.r. spectra were taken on a Perkin-Elmer 337 spectrometer for KBr discs or liquid films, and ^{1}H n.m.r. spectra, recorded on a Varian A-90 spectrometer, were measured in CCl_4 with tetramethylsilane as internal standard. Mass spectra were recorded on DuPont 21-492B and Hitachi Perkin-Elmer RMU-6H at 70 eV using a direct inlet system. Column chromatography was carried out with Neutral Brockmann alumina or silica gel (BDH). T.l.c. plates were coated with silica gel having a thickness of *ca.* 0.2 mm and the spots were located by exposing the dried plates to iodine vapour. Unless otherwise stated, all organic extracts were

* ^{1}H N.m.r. data in this section are in accordance with the systematic nomenclature used.

washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Microanalyses were carried out in Mikroanalytisches labor Pascher, Germany. All compounds described herein are racemic although the prefix (±) is omitted and only one enantiomer is depicted in the structural formula.

Dry solvents were distilled immediately before use. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride. Diethyl ether was distilled from sodium metal. Ethereal extracts were dried over Na_2SO_4.

Preparation of Zinc–Silver Couple.—To a hot solution of silver acetate (200 mg) in acetic acid (200 ml) was added, all at once, granular zinc (34 g) and the mixture stirred for 45 s. The zinc–silver couple formed was separated by decantation and washed with acetic acid (150 ml) and then with ether (50 ml). Dry ether (200 ml) was then poured into the product and silver wool (2 or 3 small batches) was added.

3α,4a,8,8-*Tetramethyl*-4,4a,5,6,7,8-*hexahydronaphthalen*-2(3H)-*one* (**3**).—*Method A.* Potassium hydride (400 mg of 40% slurry in oil) was washed thrice by decantation from dioxane and was then covered with dioxane (6 ml). To the suspension were added trimethylsilyl chloride (1 ml) and the ketone (**2**) (550 mg). The resulting mixture was heated at reflux for 7 h, cooled to room temperature, and then quenched with triethylamine (5 ml). The reaction mixture was diluted with water and extracted with ether several times. The combined extract was dried and concentrated to obtain a thick oily material (820 mg).

To a stirred ethereal suspension of Zn–Ag couple (1.2 g) was added methylene di-iodide (900 mg) dropwise at a sufficient rate to maintain gentle reflux. After the mixture had been stirred at room temperature for a further 1 h, the trimethylsilyl enol ether of the ketone (**2**) (820 mg) was added dropwise during 15 min and the resulting mixture was refluxed for 18 h. To the mixture cooled to 0 °C (ice-bath) were added ether (100 ml) and pyridine (6 g) and the mixture was stirred vigorously for 1 h. The precipitated material was removed by filtration and washed with ether. The filtrate and washings were combined and a little pyridine was added dropwise until no more precipitate was formed. After filtration, the solvent was removed under pressure to obtain a dark brown oily material (1.02 g).

The crude product, dissolved in methanolic potassium hydroxide (20 ml; 8%), was heated under reflux for 8 h. After acidification of the alkaline extract, the organic material was taken up in ether and the ethereal extract was washed, dried, and evaporated. The resulting material on chromatographic purification over silica gel (eluant hexane–ether 95:5) yielded the oily ketone (**3**) (112 mg, 20%), *m/z* 206 (M^+); $\nu_{max.}$(film) 1 660 cm^{-1} (CO); δ 1.14 (d, 3 H, *J* 6 Hz, 3-Me), 1.15 (s, 3 H, 8-Me), 1.20 (s, 3 H, 8-Me), 1.35 (s, 3 H, 4a-Me), and 5.95 (s, 1 H, 1-H) (Found: C, 81.5; H, 10.8. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%).

Method B. To a stirred solution of di-isopropylamine (6 ml) in dry THF (70 ml) cooled to 0 °C was added butyl-lithium (1.6M; 18 ml). To the mixture cooled to −70 °C was added HMPA (6 ml) followed, after the mixture had been stirred for another 30 min, by a solution of the ketone (**2**) (3 g) in dry THF (30 ml). The reaction mixture was stirred for 30 min and was then treated with methyl iodide (3 ml). The alkylation mixture was stirred for another 1 h at between −60 and −70 °C and was then allowed to attain room temperature, diluted with saturated aqueous ammonium chloride, and extracted with ether; the extract was washed and dried. Removal of the solvent followed by chromatographic purification over silica gel (eluant hexane–ether 95:5) yielded the ketone (**3**) (2.15 g, 67%), identical (i.r., t.l.c., and n.m.r.) with an authentic specimen prepared by Method A.

3α,4a,8,8-*Tetramethyl*-2,3,4,4a,5,6,7,8-*octahydronaphthalen*-2α-*ol* (**4**).—To a solution of the ketone (**3**) (2.15 g) in methanolic cerium(III) chlorohydrate (27 ml; 0.4M) was added sodium borohydride (408 mg) and then the mixture was stirred for 10 min. Excess of sodium borohydride was destroyed with acetone (2 ml) and the reaction mixture was diluted with water and then extracted with ether. The extract was washed, dried, and evaporated. The resulting material obtained on rapid filtration on silica gel (eluant hexane–ether 1:1) yielded the alcohol (**4**) (1.74 g, 80%), *m/z* 208 (M^+) and 190 ($M^+ - H_2O$); $\nu_{max.}$(film) 3 280 cm^{-1} (OH); δ 1.14 (d, 3 H, *J* 6 Hz, 3-Me), 1.16 (s, 3 H), 1.20 (s, 3 H), 1.35 (s, 3 H) (8-, 8-, and 4a-Me), 3.84 (1 H, m, $w_{\frac{1}{2}}$ 16 Hz, 2-H), and 5.43 (d, 1 H, *J* 2.3 Hz, 1-H). Its attempted purification by column chromatography was not successful owing to its tendency to decompose.

1,1,4a,6-*Tetramethyl*-1,2,3,4,4a,5-*hexahydronaphthalene* (**18**).—To a solution of the alcohol (**4**) (2 g) in dry pyridine (20 ml) was added freshly crystallized toluene-*p*-sulphonyl chloride (6.75 g) and the mixture was stirred for 20 h. The reaction mixture was treated with ice–water and then extracted with ether. The extract was washed successively with hydrochloric acid (5%), aqueous sodium hydrogen carbonate (5%), and brine, dried, and evaporated to obtain the tosyl derivative as a yellow oil, which was homogeneous on t.l.c. and exhibited complete disappearance of the hydroxy group peak in the i.r. spectrum. The tosyl derivative (**5**) was directly used for the next step without further purification.

To a solution of the tosyl ester (**5**) (3.85 g) in dry DMF (30 ml) was added anhydrous lithium bromide (1 g) and the mixture was heated for 2 h at 125 °C, then cooled, diluted with water, and extracted with ether. The extract was washed, dried, and evaporated to obtain an oily material, which on chromatographic purification over silica gel (eluant hexane) yielded the oily diene (**18**) (1.21 g, 60%), *m/z* 190 (M^+); δ 1.01 (s, 3 H), 1.21 (s, 6 H) (1-, 1-, and 4a-Me), 1.76 (s, 3 H, 6-Me), 5.63 (m, 1 H, 8-H), and 5.81 (d, 1 H, *J* 6 Hz, 7-H) (Found: C, 88.4; H, 11.7. $C_{14}H_{22}$ requires C, 88.35; H, 11.65%).

2,5,5,8a-*Tetramethyl*-6,7,8,8a-*tetrahydronaphthalen*-1(5H)-*one* (**19**).—To an ice-bath-cooled and stirred solution of dry pyridine (18 ml) in dry chloromethane (200 ml) was added chromium trioxide (10 g) (dried over phosphorus pentaoxide). After the deep yellow solution had been stirred at 0 °C for 5 min, a solution of the diene (**18**) (1 g) in methylene dichloride (8 ml) was added and the mixture was stirred for an additional 10 min at 0 °C, and at room temperature for 20 h. The reaction mixture was decanted and the residue was washed several times with methylene dichloride. The combined extract was washed successively with dil. hydrochloric acid (5%), aqueous sodium hydrogen carbonate (5%), and brine, and was dried. Evaporation of the solvent yielded an oily brown material, which on chromatographic purification over silica gel (eluant hexane) afforded the title dienone (**19**) (36 mg, 36%), m.p. 56—57 °C (from hexane); *m/z* 204 (M^+); $\nu_{max.}$(film) 1 660 cm^{-1} (C=O); δ 1.20 (s, 3 H), 1.26 (s, 3 H), and 1.30 (s, 3 H) (5-, 5-, and 8a-Me), 1.86 (s, 3 H, 2-Me), 6.25 (s, 1 H, 4-H), and 6.46 (s, 1 H, 3-H) (Found: C, 82.3; H, 9.9. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%).

Further elution with hexane–ether (9:1) yielded 8-hydroxy-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1(4*H*)-one (**23**) (108 mg, 10%), m.p. 65—67 °C (from ether–hexane); *m/z* 222 (M^+); $\nu_{max.}$(film) 3 425 (OH) and 1 660 cm^{-1} (C=C–C=O); δ 1.12 (s, 3 H), 1.20 (s, 3 H), 1.22 (s, 3 H) (8-, 8-, 4a-Me), 1.85 (s, 3 H, 3-Me), 3.25 and 2.83 (m, 2 H), and 5.70 (s, 1 H, 2-H) (Found: C, 75.6; H, 9.9. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%).

(2,5,5,8a-*Tetramethyl*-1,5,6,7,8,8a-*hexahydro*-1-*naphthyl*)-*methanol* (**22**).—To a stirred mixture of potassium t-butoxide (1.75 g) [prepared from potassium (600 mg) in t-butyl alcohol

(5 ml)] and the ketone (**19**) (110 mg) in dimethoxyethane (DME) (8 ml) was added, at room temperature under dry nitrogen, a solution of TosMIC (250 mg) in dry DME (5 ml). The reaction mixture, after being stirred for 3 h, was treated with water and extracted with ethyl acetate. The extract was washed, dried ($CaCl_2$), and evaporated to obtain an oily material, which on chromatographic purification on neutral alumina (eluant hexane–ether 9:1) yielded the nitrile (**20**) (54 mg), $\nu_{max.}$(film) 2 225 cm^{-1} (C≡N).

To a solution of the nitrile (**20**) (50 mg) in dry toluene (6 ml), cooled to 0 °C was added DIBAL (0.5 ml of a solution in toluene; 1.75M) (Aldrich). The solution was stirred for 1 h at room temperature. To the reaction mixture were added ether (12 ml) and acetic acid (3 ml; 10%) The aqueous layer was extracted with ether, the combined extracts were washed successively with aqueous sodium hydrogen carbonate (5%) and brine, and dried. Elimination of the solvent yielded a dense liquid, which on purification by preparative t.l.c. afforded the aldehyde (**21**) (33 mg), $\nu_{max.}$ 1 710 cm^{-1} (CO). In repeated experiments the isolation of the aldehyde (**21**) by chromatographic purification was considered worthwhile owing to its tendency of rapid decomposition and therefore in subsequent steps the crude material was used directly. The reaction was repeated four times to accumulate more material.

To the sodium borohydride–Alox complex (1 g), prepared by the literature procedure,[15] suspended in ether (10 ml), was added a solution of the reduction product (125 mg) in ether (10 ml). After the reaction mixture had been stirred at room temperature for 30 min, the solid material was filtered off and washed with ether. The combined filtrate and washings were evaporated to afford an oily material, which on chromatographic purification over silica gel (eluant hexane–ether 7:3) yielded the alcohol (**22**) (59 mg, 50%), *m/z* 220 (M^+); $\nu_{max.}$(film) 3 300 cm^{-1} (OH); δ 1.15 (s, 9 H) (5-, 5-, and 8a-Me), 1.56 (s, 1 H, OH, exchangeable by D_2O), 1.86 (s, 3 H, 2-Me), 3.72 (d, 2 H, *J* 5 Hz, CH_2OH),and 5.75 (s, 2 H, 3- and 4-H) (Found: C, 81.8; H. 11.0. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%).

4a,8,8-*Trimethyl*-5,6,7,8-*tetrahydronaphthalen*-2(4aH)-*one* (**15**).—To a solution of the α,β-unsaturated ketone (**2**) (300 mg) in dry distilled dioxane (70 ml) was added DDQ (400 mg) and the resulting solution was refluxed under nitrogen for 72 h. The reaction mixture was cooled, filtered, and concentrated to yield a dark oily material, which was chromatographed over silica gel. Evaporation of the ether–hexane (60:40) eluate afforded *dienone* (**15**) (171 mg, 58%), m.p. 38—40 °C (from hexane–ether); *m/z* 190 (M^+); $\nu_{max.}$(KBr) 1 660 cm^{-1} (CO); δ 1.23 (3 H, s), 1.30 (3 H, s), and 1.33 (3 H, s) (together 3 × Me), 5.96—6.09 (m, 2 H), and 6.56 (1 H, d, *J* 6 Hz) (Found: C, 81.15; H, 10.4. $C_{13}H_{18}O$ requires C, 82.06; H, 9.54%).

Hydrocyanation of the Dienone (**15**).—A solution of the dienone (300 mg) in DMF (4 ml) was treated with a solution of potassium cyanide (120 mg) and ammonium chloride (84 mg) in water (0.5 ml) and the mixture was stirred at 100 °C for 3 h. It was then cooled, and diluted with ether (50 ml); the organic phase was washed, dried, and evaporated to obtain an oily material (350 mg), which was chromatographed over alumina. On elution with hexane–ether (90:10), 30 fractions were collected (each fraction 15 ml). Fractions (10—18) were combined and worked up to give the cyano ketone 5,5,8-*trimethyl*-3-*oxo*-1,2,3,5,6,7,8,8a-*octahydronaphthalenecarbonitrile* (**6**) (215 mg, 63%), m.p. 90 °C (from ether); *m/z* 217 (M^+) and 202 (M^+ − Me); $\nu_{max.}$(KBr) 2 225 (CN) and 1 650 cm^{-1} (CO); δ 1.26 (s, 6 H) and 1.42 (s, 3 H) (together 3 × Me), and 6.12 (s, 1 H, 4-H) (Found: C, 77.3; H, 8.8. $C_{14}H_{19}NO$ requires C, 77.38; H, 8.81%).

Fractions (23—30) were combined and evaporated to give the epimeric 1β-*carbonitrile* (**7**) (92 mg, 27%), m.p. 152 °C (from ether); *m/z* 217 (M^+) and 202 (M^+ − Me); $\nu_{max.}$(KBr) 2 220 (CN) and 1 660 cm^{-1} (CO); δ 1.21 (6 H, s), 1.43 (3 H, s) (together 3 × Me), and 6.13 (1 H, s, 4-H) (Found: C, 77.3; H, 8.8%).

4α-*Hydroxymethyl*-4a,8,8-*trimethyl*-4,4a,5,6,7,8-*hexahydronaphthalen*-2(3H)-*one* (**8**).—To a solution of the cyanated ketone (**6**) (100 mg) in toluene (10 ml) was added, *via* syringe, DIBAL (25% solution in toluene; 1 ml). The reaction mixture was stirred at room temperature for 3 h. Dil. hydrochloric acid was added and the product was extracted with chloroform. Evaporation of the dried ($CaCl_2$) extract gave an oil (180 mg), $\nu_{max.}$ 3 450 (OH) and 1 710 cm^{-1} (CO).

To the sodium borohydride–Alox complex (1 g), prepared by the procedure already described,[15] suspended in ether (3 ml) was added a solution of the above reduction product (176 mg) in ether (5 ml). After being stirred for 1 h at room temperature the reaction mixture was filtered and the solid material was washed with ether several times. The combined filtrate and washings were evaporated to afford an oily alcohol (120 mg), $\nu_{max.}$ 3 470 cm^{-1} (OH).

To a suspension of sodium bromate (79 mg) in acetonitrile (4 ml) were added the oily alcohol (115 mg) and cerium(IV) ammonium nitrate (29 mg). The mixture was heated under reflux for 40 min. The resulting solution was diluted with ether and washed successively with saturated aqueous sodium hydrogen carbonate and brine. Evaporation of the dried extract yielded a dark red material, which on preparative t.l.c. over silica gel (eluant hexane–ether 1:1) yielded the *hydroxymethyl compound* (**8**) (27 mg, 26%); *m/z* 222 (M^+); $\nu_{max.}$ 3 400 (OH) and 1 640 cm^{-1} (CO); δ 1.16, 1.20, 1.23 (3 s, 9 H, 4a-, 8-, and 8-Me), 3.65 (m, OH, exchangeable by D_2O), 3.95 (m, 2 H, CH_2OH), and 5.95 (s, 1 H, 1-H) (Found: C, 75.55; H, 9.9. $C_{14}H_{22}O_2$ requires, C, 75.63; H, 9.97%).

(2,5,5,8a-*Tetramethyl*-1,5,6,7,8,8a-*hexahydro*-1-*naphthyl*)-*methanol* (**22**) (*Alternative Preparation*).—A solution of compound (**8**) (50 mg) in dihydropyran (3 ml) containing toluene-*p*-sulphonic acid (1 mg) was stirred for 35 min at room temperature, and then to it was added anhydrous potassium carbonate (1 g). After this mixture had been stirred for 2 min, water (10 ml) was added and the mixture was extracted with ether. The dried extract on evaporation yielded the pyranyl derivative (**9**) (62 mg), $\nu_{max.}$ 1 680 cm^{-1}.

To a stirred solution of di-isopropylamine (1 ml) in dry THF (8 ml) cooled to 0 °C was added butyl-lithium (1.6M; 3 ml). To the mixture cooled to −70 °C was added HMPA (1 ml) and, after the mixture had been stirred for another 30 min, a solution of the pyranyl derivative (**17**) (60 mg) in dry THF (5 ml) was added. The reaction mixture was stirred for an additional 30 min, and then treated with methyl iodide (0.5 ml). The alkylated product mixture was stirred for another 1 h, at between −60 and −70 °C, allowed to attain room temperature, diluted with aqueous ammonium chloride, and extracted with ether; the extract was washed and dried. Removal of the solvent yielded a reddish oil (72 mg) which contained a mixture of three products (t.l.c.).

To a solution of the methylated product (72 mg) in methanolic cerium(III) chlorohydrate (3 ml; 0.4M) was added sodium borohydride (60 mg) and the mixture was stirred for 10 min. The usual work-up as described already in the synthesis of compound (**4**) yielded an alcoholic material (75 mg), which was dissolved in dry pyridine (3 ml); freshly crystallized toluene-*p*-sulphonyl chloride (200 mg) was added and the mixture was stirred for 20 h at room temperature. The reaction mixture was treated with ice–water and extracted with ether. The dried extract on evaporation yielded the tosyl derivative as a yellow

oil (102 mg), which showed the absence of any hydroxy group (i.r.).

To a solution of the tosyl ester (70 mg) in dry DMF (5 ml) was added anhydrous lithium bromide (85 mg) and the mixture was heated for 2 h at 125 °C, then cooled, diluted with water, and extracted with ether. The extract was washed, dried, and evaporated to obtain an oily material, which on chromatographic purification over silica gel (eluant hexane–ether 7:3) afforded the title alcohol (**22**) (20 mg, 20%), identical (i.r., ^{1}H n.m.r.) with an authentic specimen already prepared.

Methylation of the Cyano Ketone (**6**).—To a stirred solution of di-isopropylamine (1 ml) in dry THF (8 ml) cooled to 0 °C was added butyl-lithium (1.6M; 3 ml). To the mixture cooled to 0 °C was added HMPA (1 ml) and, after the mixture had been stirred for another 30 min, a solution of the cyano ketone (**6**) (250 mg) in THF (5 ml) was added. To the reaction mixture, previously stirred for an additional 20 min, was added methyl iodide (0.5 ml). The alkylated product mixture was stirred for another 1 h at between −60 and −70 °C and was then allowed to attain room temperature. The reaction mixture was diluted with saturated aqueous ammonium chloride and extracted with ether; the extract was washed and dried. Removal of the solvent yielded an oily material, which was chromatographed over silica gel. Elution with hexane–ether (90:10) afforded compound (**11**) (18 mg, 25%), m.p. 120—122 °C (from ether); *m/z* 245 (M^+), and 230 (M^+ − Me); $\nu_{max.}$(KBr) 2 220 (CN) and 1 660 cm^{-1} (CO); δ 1.46—1.19 (4 s, 15 H, together 5 × Me) and 6.06 (s, 1 H).

The same eluate yielded compound (**12**), 1,5,5,8a-tetramethyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalene-1-carbonitrile, an oily material (17 mg, 16%), *m/z* 231 (M^+) and 204 (M^+ − HCN); $\nu_{max.}$(KBr) 2 225 (CN) and 1 660 cm^{-1} (CO); δ 1.15 (s, 3 H), 1.21 (s, 3 H), 1.45 (s, 3 H), and 1.60 (s, 3 H) (together 4 × Me), and 6.01 (s, 1 H, 4-H).

Hexane–ether (85:15) eluted 4,4a,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (**16**) (11 mg, 12%), m.p. 90—93 °C; *m/z* 204 (M^+); $\nu_{max.}$(KBr) 1 625 cm^{-1} (CO); δ 1.30 (s, 3 H), 1.40 (s, 6 H) (4a-, 8-, and 8-Me), 1.65 (s, 3 H, 4-Me), and 6.46 and 6.81 (2 H, 1- and 3-H).

It is worthwhile to mention that owing to insufficient quantity of material, the purity of products (**11**), (**12**), and (**16**) was insufficient for accurate elemental analysis results to be obtained.

Methylation of the Dienone (**15**).—To an ice-cold suspension of copper(I) iodide (350 mg) in dry dioxane (8 ml) was added ethereal methyl-lithium (2 ml; 1.6M). After the mixture had been stirred at 0 °C for 10 min, it was treated with a solution of dienone (**15**) (250 mg) in dry dioxane (5 ml), then stirred at 20 °C for 6 h, poured into saturated aqueous ammonium chloride (12 ml), and treated with conc. ammonium hydroxide to ensure the complete decomposition of residual lithium. The alkaline solution was extracted with ether, and the extract was washed and dried. Evaporation of the solvent followed by chromatographic purification over alumina (eluant ether–hexane 35:65) yielded the methylation product, a mixture of epimers (**13**) and (**14**) (121 mg, 45%). Purification of the resulting mixture over preparative alumina plates (150 F_{254} Type T) (Merck) developed ether–hexane 40:60) yielded one *methylated product* (54 mg, 20%), *m/z* 206 (M^+); $\nu_{max.}$ 1 665 cm^{-1} (CO); δ 0.86 (d, 3 H, *J* 6 Hz, 4-Me), 1.16 (s, 3 H), 1.20 (s, 3 H), 1.43 (s, 3 H) (8-, 8-, and 4a-Me), and 5.81 (s, 1 H, 1-H) (Found: C, 81.45; H, 10.7. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%).

Another *methylated product* was also obtained on further elution (67 mg, 23%), *m/z* 206 (M^+); $\nu_{max.}$ 1 658 cm^{-1} (CO); δ 0.95 (d, 3 H, *J* 6 Hz, 4-Me), 1.13 (s, 3 H), 1.15 (s, 3 H), 1.42 (s, 3 H) (8-, 8-, and 4a-Me), and 5.75 (1 H, 1-H) (Found: C, 81.5; H, 10.7%).

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