Synthesis based on cyclohexadienes. Part 22.[1] Formal syntheses of patchouli alcohol and norpatchoulenol

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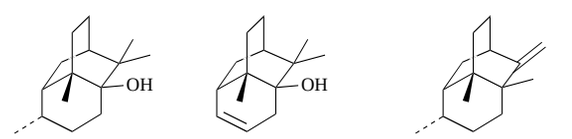
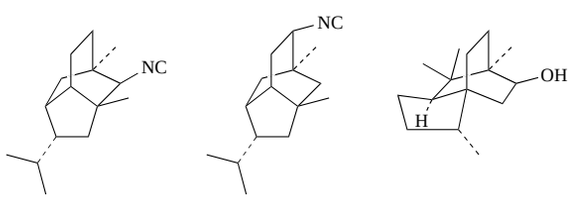
The preparation of 6-*endo*-formyl-1,3,3-trimethylbicyclo[2.2.2]octan-2-one 7 and 6-*endo*-acetyl-1,3,3-trimethylbicyclo[2.2.2]octan-2-one 8, the two key intermediates for the synthesis of patchouli alcohol 1 and norpatchoulenol 2, is reported by a simple and short method from 2-methylbenzoic acid.

Introduction

A number of natural products contain the bicyclo[2.2.2]octane framework with a bridgehead methyl group as their structural subunit. These are exemplified by the complex tricyclic sesquiterpenes patchouli alcohol **1**, norpatchoulenol **2**, seychellene **3**, 2-isocyanopupukeanane **4**, 9-isocyanopupukeanane **5** and *allo*-cedrol **6**. The presence of a unique tricyclic ring system in



1 **2** **3**



4 **5** **6**

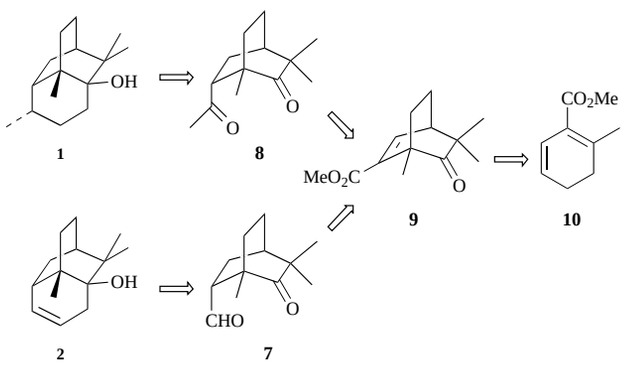
conjunction with a bridgehead methyl group in these molecules makes them synthetically challenging targets.

The sesquiterpenes patchouli alcohol **1** and norpatchoulenol **2** have been known for over 100 years.[2,3] Patchouli alcohol and norpatchoulenol, the major and minor constituents of patchouli oil isolated from the East Indian shrub *Pogestemon patchouli*, have been widely used in the perfumery industry. Compounds **1** and **2** possess the unique tricyclo[5.3.1.0^{3,8}]undecane carbon skeleton with three contiguous quaternary centres. Hence their synthesis is challenging, but has been successfully accomplished by several groups.[4,5] In continuation of our interest in the synthesis of sesquiterpenes using dihydrobenzenes,[6] we report herein a formal synthesis of compounds **1** and **2** which involves a Diels–Alder reaction and catalytic hydrogenation as the key steps.

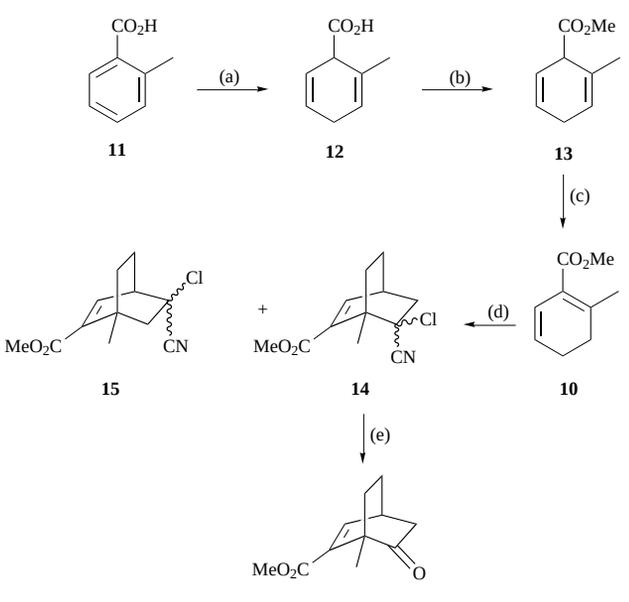
Results and discussion

A retrosynthetic analysis for target molecules **1** and **2** (Scheme 1) suggests that the keto aldehyde **7** and the dione **8** would be the key intermediates for norpatchoulenol and patchouli alcohol, respectively, as they have been converted into their respective targets earlier.[4e]

Reduction of 2-methylbenzoic acid **11** with sodium in liquid ammonia and quenching with ammonium chloride afforded the 2-methylcyclohexa-2,5-dienecarboxylic acid **12** in 96% yield (Scheme 2). Esterification of acid **12** with either methanol–



Scheme 1

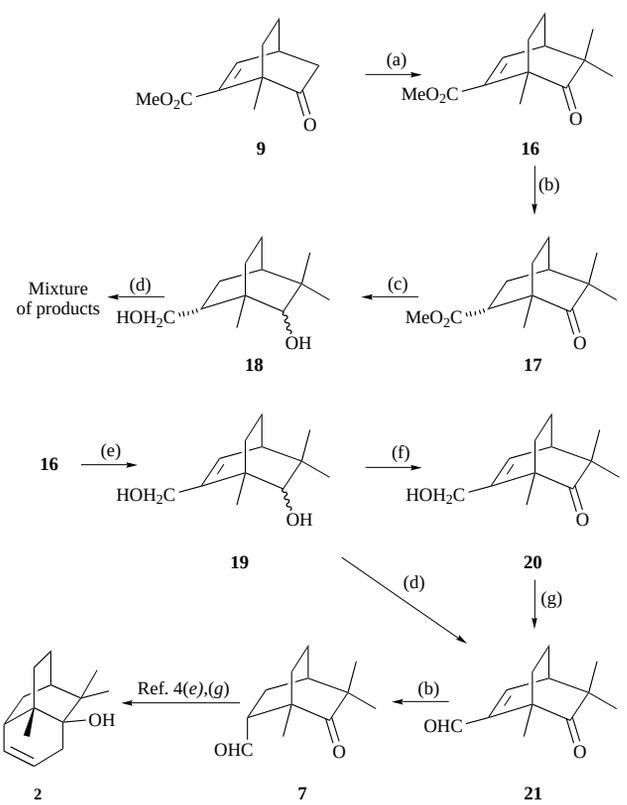


Scheme 2 *Reagents and conditions:* (a) Na, liq. NH_3, THF; (b) MeOH–conc. H_2SO_4; or CH_2N_2, Et_2O, 0 °C; (c) DBU (cat.), benzene, reflux, 5 h; (d) CH_2=C(Cl)CN, benzene, 90 °C, 48 h; (e) (i) aq. KOH, DMSO, 55 °C, 48 h; (ii) CH_2N_2, Et_2O, 0 °C

sulfuric acid or diazomethane afforded the diene ester **13** in 86% yield. Isomerization of the diene ester **13** with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene afforded the conjugated diene ester **10**, whose structure was deduced from its spectral data, in particular the ^{1}H NMR spectrum. The ^{1}H NMR spectrum showed a singlet at δ 2.2 for the olefinic methyl group, a doublet at δ 6.32 and a doublet of triplets at δ 5.74 for the olefinic protons. The IR spectrum of compound **10** showed a strong absorption at 1722 cm^{-1}. The diene ester **10** underwent cycloaddition

smoothly with α-chloroacrylonitrile to afford a separable mixture of regioisomeric bicyclo[2.2.2]octene adducts **14** and **15** in the ratio 4:1, respectively. The ^{1}H NMR spectrum of compound **14** showed two doublets at δ 7.42 and 7.46 for the olefinic proton and that of compound **15** showed one doublet at δ 7.1 for the same proton. The IR spectrum of these adducts showed a medium absorption at 2240 cm^{-1} for the cyano group. The mass spectrum showed the base peak at *m*/*z* 152 corresponding to the retro-Diels–Alder fragmentation product. Hydrolysis of the adduct **14** with aq. KOH in dimethyl sulfoxide (DMSO)[7] at 55 °C for 48 h, followed by esterification with diazomethane, furnished the keto ester **9** in 62% yield whose structure was deduced from its spectral data. The IR spectrum showed the absence of a band at 2240 cm^{-1} due to the cyano group. The mass spectrum showed its base peak at *m*/*z* 152, corresponding to the diene obtained by the loss of a ketene, due to retro-Diels–Alder fragmentation.

Attempted methylation of the keto ester **9** with sodium hydride and methyl iodide in solvents like dimethylformamide (DMF) and tetrahydrofuran (THF), afforded a mixture of methylated products besides the starting material. Dimethylation of the keto ester **9** was successfully achieved with NaH in 1,2-dimethoxyethane (DME) and methyl iodide (Scheme 3).

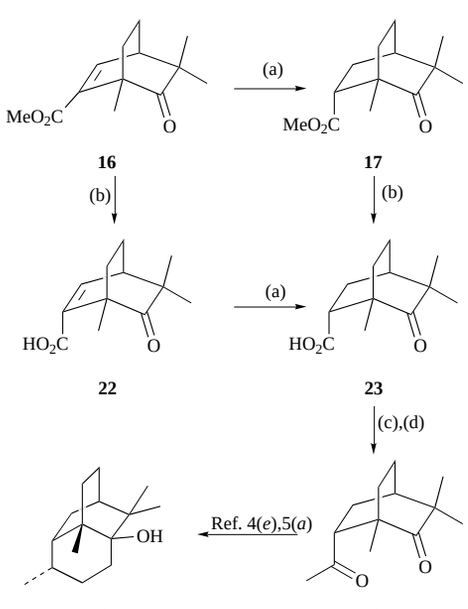


Scheme 3 *Reagents and conditions:* (a) NaH, MeI, DME, 0 to 60 °C; (b) H_2, 10% Pd–C, EtOH; (c) LAH, Et_2O, 0 °C, 5 h; (d) PCC, CH_2Cl_2 or PDC, CH_2Cl_2, room temp., 3 h; (e) DIBALH, THF, −78 °C, 2 h; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 30 min; (g) MnO_2, CH_2Cl_2, 8 h

Having obtained the bicyclic keto ester **16** in good yield, the next step would be to utilize the ester group of compound **16** as the latent functionality for the aldehyde and the acetyl groups. Catalytic hydrogenation of compound **16** afforded the saturated keto ester **17** stereoselectively, the product having the methoxycarbonyl group occupying the *endo* position, as evidenced from its spectral data. Thus, the ^{1}H NMR spectrum of compound **17** showed the absence of olefinic protons and three singlets at δ 0.87, 1.11 and 1.19 for the three methyl groups. The IR spectrum of compound **17** showed the presence of two strong absorption bands at 1737 and 1710 cm^{-1}. Exclusive formation of the *endo* isomer could be attributed to the approach of the hydrogen and the catalyst from the *exo* face to avoid the steric hindrance posed by the *endo* methyl group.

Lithium aluminium hydride (LAH) reduction of the keto ester **17** afforded the diol **18** in good yield. Since the oxidation of diol **18** gave a mixture of products which could not be separated, the unsaturated ester **16** was reduced with diisobutylaluminium hydride (DIBALH) to afford the diol **19** whose structure was deduced from the spectral data. The ^{1}H NMR spectrum of diol **19** showed the absence of a singlet at δ 3.7 due to a methoxycarbonyl group. The appearance of the olefinic proton in the upfield region (δ 6.32 as a doublet) confirms the proposed structure. Furthermore, the IR spectrum of diol **19** indicated the absence of a carbonyl absorption. Oxidation of the diol **19** under Swern oxidation conditions afforded the keto alcohol **20** wherein only the secondary alcohol was oxidized and the primary allylic alcohol group was unperturbed. The diol **19** was oxidized to the keto aldehyde **21** with pyridinium dichromate (PDC) or pyridinium chlorochromate (PCC) in dichloromethane. Similarly the keto alcohol **20** also furnished keto aldehyde **21** when oxidized with manganese dioxide. The keto aldehyde **21** had IR absorptions at 1720 and 1700 cm^{-1} for the ketone and the unsaturated aldehyde, respectively. The aldehyde hydrogen appeared as a singlet at δ 9.57 in its ^{1}H NMR spectrum. The mass spectrum showed its base peak at *m*/*z* 122, corresponding to the diene obtained by the loss of a dimethylketene due to retro-Diels–Alder fragmentation. Hydrogenation of the keto aldehyde **21** afforded the keto aldehyde **7**. The spectral data of product **7** agreed with those reported,[4e,4g] which were kindly provided by Professor Hsi-Liu of the University of Alberta, Canada.

Hydrolysis of the keto ester **16** with LiOH/MeOH afforded the unsaturated keto acid **22**, which was hydrogenated to the saturated keto acid **23** (Scheme 4). Hydrolysis of the keto ester



Scheme 4 *Reagents and conditions:* (a) H_2, 10% Pd–C, EtOH; (b) LiOH, MeOH, room temp., 15 h; (c) $(COCl)_2$, benzene, DMF (1 drop), CH_2Cl_2, 5 h; (d) Me_2CuLi, Et_2O, −78 to 0 °C

17 with LiOH/MeOH also afforded the keto acid **23**. The keto acid displayed a broad absorption at 1690 cm^{-1} in its IR spectrum and its ^{1}H NMR spectrum showed the absence of any olefinic proton. The carboxy group was found to be in the *endo* position, as evidenced by spectral data. The keto acid **23** was converted into the diketone **8** *via* its acid chloride on treatment with oxalyl dichloride followed by reaction with lithium dimethylcuprate. The spectral data of the diketone **8** were found to be identical with those reported.[4e]

In conclusion, a short and simple method for the preparation of 6-*endo*-formyl-1,3,3-trimethylbicyclo[2.2.2]octan-2-one **7** and 6-*endo*-acetyl-1,3,3-trimethylbicyclo[2.2.2]octan-2-one **8** is reported from readily available 2-methylbenzoic acid involving Birch reduction, Diels–Alder reaction and catalytic hydrogenation as the key steps.

Experimental

Mps are uncorrected and were recorded on a Mettler FP1 instrument. IR Spectra were recorded for either neat samples or solutions in $CHCl_3$ on either an Hitachi 270-50 or a Perkin-Elmer 781 spectrophotometer. ^{1}H NMR (60, 90, 200, 270 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on a Varian T-60, JEOL FX-90Q, Bruker ACF-200 or a Bruker WH-270 spectrophotometer. All NMR spectra were recorded for solutions in $CDCl_3$ with $SiMe_4$ as internal standard for ^{1}H NMR and the central line of $CDCl_3$ (δ_C 77.1) for ^{13}C NMR spectra. Chemical shifts are reported in δ units and J values are in Hz. High-resolution mass measurements were carried out with a JEOL JMS-DX 303 GC–MS instrument using a direct inlet mode. Elemental analyses were carried out using a Carlo Erba 1106 analyser. Unless otherwise stated, all materials were obtained from commercial suppliers and were used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under a N_2 atmosphere whenever necessary. Benzene was distilled over LAH prior to use. CH_2Cl_2 was distilled over CaH_2 and stored over 4 Å molecular sieves. Absolute ethanol was obtained by distillation over magnesium ethoxide and was stored over 4 Å molecular sieves. Liquid ammonia was distilled over sodamide prior to use. MeLi was prepared from MeI and lithium and was standardized before use. Column chromatography was performed on silica gel (60–120 mesh) by elution with a light petroleum (distillation range 60–80 °C)–ethyl acetate mixture. Sodium hydride was 60% in oil, and was used after being washed with light petroleum.

2-Methylcyclohexa-2,5-dienecarboxylic acid 12

To a stirred solution of 2-methylbenzoic acid **11** (13.69 g, 100 mmol) in dry THF (100 cm^3) was added liq. ammonia (600 cm^3) by distillation and then sodium (350 mmol) in small pieces until the blue colour persisted. After 30 min, excess sodium was destroyed by addition of solid ammonium chloride, and the ammonia was allowed to evaporate off. The reaction product was dissolved in water and washed with diethyl ether to remove impurities. The aqueous solution was cooled, acidified with 5% HCl, extracted with diethyl ether, and the combined extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product **12**, which was recrystallized from light petroleum (13 g, 96%), mp 77 °C (lit.,[8] 77–78 °C); ν_{max}(Nujol)/cm^{-1} 3300–2300, 1695 and 1650; δ_H(90 MHz; $CDCl_3$) 1.8 (3 H, s, $=CMe_3$), 2.6–2.9 (2 H, m), 3.6 (1 H, m, $-CH\,CO_2H$), 5.6–6.1 (3 H, m, olefinic) and 11.6 (1 H, s, CO_2H); δ_C(22.5 MHz; $CDCl_3$) 21.92 (q), 26.78 (t), 47.0 (d), 121.75 (d), 122.42 (d), 127.172 (d), 128.05 (s) and 179.24 (s); *m*/*z* 138 (M$^+$, 20%), 93 (100), 91 (50) and 77 (60) (Found: M$^+$, 138.0680; C, 69.6; H, 7.3%. Calc. for $C_8H_{10}O_2$: *M*, 138.0681; C, 69.5; H, 7.3%).

Methyl 2-methylcyclohexa-2,5-dienecarboxylate 13

The acid **12** (11 g, 80 mmol), MeOH (150 cm^3) and conc. H_2SO_4 (1 cm^3) were refluxed together for 6 h. After removal of methanol under reduced pressure, saturated aq. sodium hydrogen carbonate was added and the mixture was extracted with diethyl ether (3 × 100 cm^3). The combined ether extract was washed successively with water and brine, and dried over Na_2SO_4. Removal of the solvent followed by distillation (bp 62 °C/10 mmHg) gave liquid ester **13** (10.5 g, 86%); ν_{max}(neat)/cm^{-1} 2914 and 1737; δ_H(90 MHz; $CDCl_3$) 1.72 (3 H, s, =CMe), 2.6–2.7 (2 H, m), 3.6 (1 H, m, $CHCO_2Me$), 3.73 (3 H, s, CO_2Me) and 5.5–6.0 (3 H, m, olefinic); *m*/*z* 152 (M$^+$, 100%), 137 (35), 120 (50) and 93 (80).

Methyl 2-methylcyclohexa-1,5-dienecarboxylate 10

The ester **13** (10 g, 65.7 mmol) was refluxed with DBU (0.5 cm^3, cat.) in benzene (70 cm^3) for 5 h. The benzene layer was washed successively with 2% HCl, water and brine, and was dried over Na_2SO_4. Removal of the solvent followed by short-path distillation gave liquid ester **10** (60 °C/10 mmHg) (9 g, 90%); ν_{max}(neat)/cm^{-1} 2926 and 1722; δ_H(200 MHz; $CDCl_3$) 2.05–2.37 (4 H, m, CH_2CH_2), 2.19 (3 H, s, =CMe), 3.75 (3 H, s, CO_2Me), 5.74 (1 H, dt, J 9.5 and 8, $=CHCH_2$) and 6.32 (1 H, d, J 9.5, CH=$CHCH_2$.

Methyl 6-chloro-6-cyano-1-methylbicyclo[2.2.2]oct-2-ene-2-carboxylate 14 and methyl 5-chloro-5-cyano-1-methylbicyclo-[2.2.2]oct-2-ene-2-carboxylate 15

A benzene solution of compound **10** (8 g, 52 mmol), 2-chloroacrylonitrile (10 cm^3) and hydroquinone (20 mg) was refluxed under nitrogen for 48 h. The solvent was removed and the residue was loaded on a column packed with silica gel. Elution with ethyl acetate–hexane (1:30) initially gave the adduct **15** (500 mg). Further elution with ethyl acetate–hexane (1:15) gave a mixture of adducts **14** and **15** (5 g). Elution with the same solvent gave isomer **14** (5 g) (overall yield, 84%). Repeated column chromatography of the mixture of adducts afforded more of compound **14**.

For compound **14**: ν_{max}(neat)/cm^{-1} 2920, 2240 and 1722; δ_H(270 MHz; $CDCl_3$) 1.2–2.7 (6 H, m), 1.69 and 1.75 (3 H, s, Me), 2.83 (1 H, m, bridgehead proton), 3.75 and 3.77 (3 H, s, CO_2Me) and 7.42 and 7.46 (1 H, d, J 7, olefinic); *m*/*z* 239 (M$^+$, 20%), 208 (35), 152 (100) and 93 (100) (Found: M$^+$, 239.0732. $C_{12}H_{14}ClNO_2$ requires *M*, 239.0713).

For compound **15**: ν_{max}(neat)/cm^{-1} 2918, 2235 and 1720; δ_H(60 MHz; $CDCl_3$) 1.4–3.1 (6 H, m), 1.41 (3 H, s, Me), 3.32 (1 H, m, bridgehead proton), 3.76 (3 H, s, CO_2Me) and 7.1 (1 H, d, J 6.8, olefinic) (Found: C, 60.35; H, 5.98; N, 5.92. $C_{12}H_{14}ClNO_2$ requires C, 60.13; H, 5.88; N, 5.84%).

Methyl 1-methyl-6-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate 9

A solution of the adduct **14** (4.5 g, 18.8 mmol) in DMSO (35 cm^3) and 20% aq. KOH (25 cm^3) was stirred at 55 °C for 48 h. The reaction mixture was then acidified with dil. HCl and extracted with diethyl ether (5 × 50 cm^3). The extract was washed successively with water and brine, and dried over Na_2SO_4. After removal of the solvent, the crude acid was esterified with ethereal diazomethane and the ester was purified by chromatography over silica gel [ethyl acetate–hexane (1:9) as eluent] to yield the keto ester **9** (2.3 g, 62%); ν_{max}(neat)/cm^{-1} 2944 and 1725; δ_H(200 MHz; $CDCl_3$) 1.46 (3 H, s, Me), 1.5–2.24 (6 H, m), 3.1 (1 H, m, bridgehead proton), 3.72 (3 H, s, CO_2Me) and 7.4 (1 H, d, J 6.8, olefinic); δ_C(22.5 MHz; $CDCl_3$) 15.73 (q), 24.46 (t), 30.98 (t), 31.65 (d), 38.17 (t), 49.34 (s), 50.77 (q), 134.02 (s), 146.52 (d), 164.32 (s) and 210.09 (s); *m*/*z* 194 (M$^+$, 10%), 152 (100), 120 (40) and 93 (60) (Found: M$^+$, 194.0960. $C_{11}H_{14}O_3$ requires *M*, 194.0943).

Methyl 1,5,5-trimethyl-6-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate 16

A solution of keto ester **9** (1 g, 5.15 mmol) in dry DME (15 cm^3) was added to a suspension of sodium hydride (700 mg, 16 mmol) in dry DME and the mixture was stirred at 0 °C. After 15 min a solution of methyl iodide (1.7 cm^3, 26 mmol) in dry DME was added and the mixture was stirred at 60 °C for 3 h, poured onto a large excess of water and extracted with diethyl ether (3 × 30 cm^3). The extract was washed successively with water and brine and dried over $NaSO_4$. Evaporation of the mixture followed by purification of the product by column chromatography using ethyl acetate–hexane (1:19) as eluent furnished the dialkylated keto ester **16** (980 mg, 86%);

ν_{max}(neat)/cm^{-1} 2938 and 1728; δ_H(200 MHz; $CDCl_3$) 1.04 (3 H, s, Me), 1.12 (3 H, s, Me), 1.43 (3 H, s, Me), 1.3–1.7 (2 H, m), 2.06 (2 H, m), 2.73 (1 H, m, bridgehead proton), 3.72 (3 H, s, CO_2Me) and 7.47 (1 H, d, *J* 6.8, olefinic); δ_C(22.5 MHz, $CDCl_3$) 16.58 (q), 21.33 (t), 24.43 (q), 27.52 (q), 30.84 (t), 42.78 (s), 43.78 (d), 49.96 (s), 51.18 (q), 132.45 (s), 148.59 (d), 164.73 (s) and 214.8 (s); *m*/*z* 222 (M^+, 30%), 191 (35), 152 (100), 93 (65) and 43 (95) (Found: M^+, 222.1260. $C_{13}H_{18}O_3$ requires *M*, 222.1256).

Methyl *endo*-1,5,5-trimethyl-6-oxobicyclo[2.2.2]octane-2-carboxylate 17

A solution of the unsaturated ester **16** (500 mg, 2.25 mmol) in ethanol (15 cm^3) was stirred under hydrogen in the presence of 10% Pd–C catalyst (50 mg) for 8 h. The catalyst was filtered off and the solvent was evaporated to obtain the *above compound* **17** (500 mg, ≈100%); ν_{max}(neat)/cm^{-1} 2926, 1737 and 1710; δ_H(200 MHz; $CDCl_3$) 0.87 (3 H, s, Me), 1.11 (3 H, s, Me), 1.19 (3 H, s, Me), 1.5–2.2 (7 H, m), 2.71 (1 H, dd, *J* 6.6 and 4.6, C*H*CO_2Me) and 3.59 (3 H, s, CO_2Me); δ_C(22.5 MHz; $CDCl_3$) 17.5 (q), 21.15 (t), 22.37 (t), 24.47 (q), 26.57 (q), 30.44 (t), 36.76 (d), 43.27 (s), 44.59 (s), 47.15 (d), 50.34 (q), 174 (s) and 216.8 (s); *m*/*z* 224 (60%), 136 (100) and 93 (95) (Found: M^+, 224.1420. $C_{13}H_{20}O_3$ requires *M*, 224.1412).

6-*endo*-Hydroxymethyl-1,3,3-trimethylbicyclo[2.2.2]octan-2-ol 18

To a magnetically stirred, ice-cold suspension of LAH (200 mg) in dry diethyl ether (10 cm^3) was added dropwise an ethereal solution (5 cm^3) of the keto ester **17** (112 mg, 0.5 mmol). The reaction mixture was stirred at 0 °C for 5 h and quenched by successive addition of EtOAc (1 cm^3), water (1 cm^3) and 15% aq. sodium hydroxide (1 cm^3). The aluminium salts were filtered off and washed with diethyl ether. The combined ether layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the mixture and purification of the residue by silica gel column chromatography using ethyl acetate–hexane (1:3) as eluent furnished the *diol* **18** (89 mg, 90%); ν_{max}(neat)/cm^{-1} 3300br, 2940 and 1060; δ_H(90 MHz; $CDCl_3$) 0.85 (3 H, s, Me), 0.93 (6 H, s, 2 × Me), 1.1–1.98 (7 H, m), 2.9 (1 H, s, C*H*OH), 3.25 (1 H, m), 3.5 (2 H, ABq, *J* 12, CH_2OH) and 4.75 (1 H, br s, OH) (Found: C, 72.88; H, 11.33. $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.18%).

6-Hydroxymethyl-1,3,3-trimethylbicyclo[2.2.2]oct-5-en-2-ol 19

To a magnetically stirred solution of keto ester **16** (500 mg, 2.25 mmol) at −78 °C (EtOAc, liq. N_2) in dry THF (20 cm^3) was slowly added a hexane solution of DIBALH (8 cm^3; 1 M solution) and the mixture was stirred for a further 2 h. Excess DIBALH was destroyed by addition of MeOH and the aluminium complex was hydrolysed by the addition of 10 cm^3 of saturated aq. sodium potassium tartrate. After separation of the layers, the aqueous layer was extracted with diethyl ether (3 × 25 cm^3). The combined organic layer was washed successively with water and brine, and dried over Na_2SO_4. Evaporation of the mixture followed by column chromatography using ethyl acetate–hexane (3:1) as eluent yielded the *diol* **19** (420 mg, 95%) (inseparable mixture of *endo* and *exo* alcohols); ν_{max}(neat)/cm^{-1} 3300, 2920, 1440 and 1040; δ_H(200 MHz; $CDCl_3$) 0.78 and 0.83 (3 H, 2 s, Me), 0.9 and 1.0 (3 H, 2 s, Me), 1.1 and 1.2 (3 H, 2 s, Me), 0.8–2.1 (5 H, m), 2.9 and 3.12 (1 H, 2 s, C*H*OH), 4.1 and 4.2 (2 H, s and AB_q, *J* 11.5, CH_2OH) and 6.16 and 6.32 (1 H, 2 d, *J* 6.4, olefinic); *m*/*z* 196 (M^+, 2%), 124 (100), 106 (100) and 93 (100) (Found: M^+, 196.1451. $C_{12}H_{20}O_2$ requires *M*, 196.1463).

6-Hydroxymethyl-1,3,3-trimethylbicyclo[2.2.2]oct-5-en-2-one 20

To a solution of oxalyl dichloride (400 mg, 2.4 mmol) in dry dichloromethane (6 cm^3) was added dry DMSO (0.4 cm^3, 4.8 mmol) in dichloromethane (1 cm^3) in drops at −78 °C. After stirring the mixture for 10 min, a solution of the diol **19** (200 mg, 1 mmol) in dichloromethane (1 cm^3) was added slowly and the mixture was stirred for a further 30 min. Triethylamine (1 cm^3) was added and the cooling bath was removed. Water (5 cm^3) was added to the reaction mixture at room temperature and the mixture was stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined layer was washed successively with water, dil. HCl, water and saturated aq. sodium hydrogen carbonate, and dried. Evaporation of the mixture at room temperature afforded the *keto alcohol* **20** (162 mg, 85%); ν_{max}(neat)/cm^{-1} 3300, 2929 and 1720; δ_H(200 MHz; $CDCl_3$) 0.95 (3 H, s, Me), 1.02 (3 H, s, Me), 1.27 (3 H, s, Me), 1.3–2.1 (4 H, m), 2.53 (1 H, m, bridgehead proton), 4.01 (2 H, s, CH_2OH) and 6.55 (1 H, d, *J* 6.7, olefinic) (Found: C, 74.69; H, 9.57. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34%).

1,5,5-Trimethyl-6-oxobicyclo[2.2.2]oct-2-ene-2-carbaldehyde 21

(i) To a stirred mixture of PCC (1.07 g, 5 mmol) and silica gel (1.5 g) in dry dichloromethane (10 cm^3) was added a solution of the diol **19** (200 mg, 1 mmol) in dichloromethane (2 cm^3) and the reaction mixture was stirred at 25 °C for a period of 3 h. Diethyl ether (50 cm^3) was added and the reaction mixture was filtered through a pad of Celite and washed with diethyl ether (2 × 15 cm^3). The combined filtrate was evaporated to yield a crude product, which was purified by column chromatography over silica gel [ethyl acetate–light petroleum (1:9)] to furnish the keto aldehyde **21** (165 mg, 80%).

(ii) To stirred solution of the keto alcohol **20** (150 mg, 0.75 mmol) in dichloromethane was added freshly prepared, active manganese dioxide (500 mg) and the reaction mixture was stirred for 8 h. Diethyl ether (30 cm^3) was added and the reaction mixture was filtered through a pad of Celite and washed with diethyl ether (2 × 15 cm^3). The combined filtrate was evaporated to afford the crude *product* **21**, which was purified by column chromatography; ν_{max}(neat)/cm^{-1} 2930, 2820, 2720, 1720 and 1700; δ_H(200 MHz; $CDCl_3$) 0.9–2.2 (4 H, m), 1.03 (3 H, s, Me), 1.17 (3 H, s, Me), 1.52 (3 H, s, Me), 2.82 (1 H, m, bridgehead proton), 7.55 (1 H, d, *J* 7.2, olefinic), 9.57 (1 H, s, CHO); *m*/*z* (M^+, 20%), 138 (20), 122 (100) and 93 (80) (Found: M^+, 192.1166. $C_{12}H_{16}O_2$ requires *M*, 192.1150).

1,5,5-Trimethyl-6-oxobicyclo[2.2.2]octane-2-*endo*-carbaldehyde

The keto aldehyde **21** (300 mg, 1.5 mmol) was hydrogenated in ethanol (15 cm^3) in the presence of 10% Pd–C catalyst (20 mg) until the hydrogen absorption ceased. The catalyst was filtered off and the solvent was evaporated to afford the pure *keto aldehyde* **7** (260 mg, 90%); ν_{max}(neat)/cm^{-1} 2920, 2820, 2720 and 1720; δ_H(200 MHz; $CDCl_3$) 0.9–2.6 (7 H, m), 1.05 (3 H, s, Me), 1.11 (3 H, s, Me), 1.16 (3 H, s, Me), 2.62 (1 H, m) and 9.43 (1 H, d, *J* 4.5, CHO) (Found: C, 74.6; H, 9.7. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.33%).

1,5,5-Trimethyl-6-oxobicyclo[2.2.2]oct-2-ene-2-carboxylic acid 22

A solution of the keto ester **16** (200 mg, 1.1 mmol) and LiOH (38 mg, 2.25 mmol) in MeOH (5 cm^3) was stirred for 15 h. The reaction mixture was concentrated *in vacuo*, acidified with dil. HCl and extracted with diethyl ether (3 × 25 cm^3). The combined extract was washed successively with water and brine, and dried over Na_2SO_4. Removal of the solvent gave oily acid **22** (170 mg, 90%); ν_{max}(neat)/cm^{-1} 3400–2800br and 1710–1680s; δ_H(90 MHz; $CDCl_3$) 1.05 (3 H, s, Me), 1.11 (3 H, s, Me), 1.2–3.2 (5 H, m), 1.45 (3 H, s, Me) and 7.52 (1 H, d, *J* 6.8, olefinic).

1,5,5-Trimethyl-6-oxobicyclo[2.2.2]octane-2-*endo*-carboxylic acid 23

(i) A solution of the keto ester **17** (100 mg, 0.6 mmol) and LiOH (20 mg, 1.25 mmol) in MeOH (2 cm^3) was stirred for 17 h. The reaction mixture was concentrated *in vacuo*, acidified with dil.

HCl and extracted with diethyl ether (3 × 10 cm^3). The combined extract was washed successively with water and brine, and dried over Na_2SO_4. Removal of the solvent afforded oily acid **23** (80 mg, 90).

(ii) The keto acid **22** (120 mg, 0.6 mmol) was hydrogenated in ethanol (5 cm^3) in the presence of 10% Pd–C catalyst (10 mg) until the hydrogen absorption ceased. The catalyst was filtered off and the solvent was evaporated to afford the *keto acid* **23** (110 mg, 95%); ν_{max}(neat)/cm^{-1} 3200–2800 and 1700–1670; δ_H(90 MHz; $CDCl_3$) 0.99 (3 H, s, Me), 1.12 (3 H, s, Me), 1.2 (3 H, s, Me), 0.9–2.2 (7 H, m), 2.75 (1 H, dd, *J* 7.6 and 4.5, C*H*CO_2H) and 8.7 (1 H, br s, CO_2H) (Found: C, 68.94; H, 8.8. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.62%).

6-*endo*-Acetyl-1,3,3-trimethylbicyclo[2.2.2]octan-2-one 8

The keto acid **23** (120 mg, 0.6 mmol) was dissolved in 2 cm^3 of benzene and excess of oxalyl dichloride (1 cm^3) and 1 drop of dry DMF was added at 0 °C. After the mixture had been stirred for 5 h at room temperature, benzene and excess of oxalyl dichloride were removed *in vacuo* to give the crude acid chloride.

To a suspension of copper(I) iodide (342 mg, 1.8 mmol) in dry diethyl ether (10 cm^3) was added a 1 M solution of MeLi (3.6 cm^3, 3.6 mmol) at 0 °C. After 5 min, the reaction mixture was cooled to −78 °C and a solution of the crude acid chloride obtained above in diethyl ether was slowly added. After 15 min at −78 °C the reaction mixture was treated with absolute methanol (2 cm^3) and was then brought to room temperature before being poured into an equal volume of saturated aq. ammonium chloride and extracted with diethyl ether (3 × 20 cm^3). The combined extract was washed successively with water and brine, and dried over Na_2SO_4. Removal of the solvent at reduced pressure afforded the *dione* **8** as a low melting solid; ν_{max}(neat)/cm^{-1} 1720; δ_H(90 MHz; $CDCl_3$) 0.92 (3 H, s, Me), 1.14 (3 H, s, Me), 1.16 (3 H, s, Me), 1.3–2.1 (7 H, m), 2.13 (3 H, s, $COCH_3$) and 2.96 (1 H, m); δ_C(22.5 MHz; $CDCl_3$) 18.2, 21.9, 23.2, 25.0, 26.9, 30.9, 31.3, 37.7, 43.8, 45.3, 54.1, 210.3 and 218.7 (Found: C, 75.16; H, 9.67. $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.67%).

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