Synthesis based on cyclohexadienes. Part 23.[1] Total synthesis of 5-*epi*-pupukean-2-one

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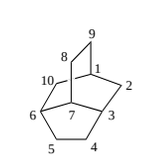
A new strategy for the construction of the isotwistane skeleton is reported from easily available cyclohexadienes which involves stereoselective alkylation of a bicyclooctenone derivative and a decarboxylative 5-*exo-trig* radical cyclisation as the key steps in the total synthesis of 5-*epi*-pupukean-2-one.

A few naturally occurring sesquiterpenes have the unique tricyclo[4.3.1.0^{3,7}]decane carbon framework (isotwistane) **1**, the first example of which, 9-isocyanopupukeanane **2**, was reported by Scheuer *et al*.,[2] who isolated it from the nudibranch *Phyllidia varicosa* and also from its prey, a sponge *Hymeniacidon* sp. An isomeric substance, 2-isocyanopupukeanane **3** was subsequently isolated[3] from the same source by this group. The pupukeananes are named after the place where the mollusk and sponge were collected.

Structures of **2** and **3** were established by chemical degradation through the corresponding ketones **5** and **6** and confirmed



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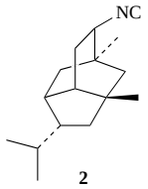

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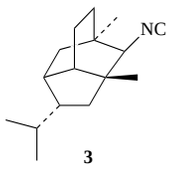

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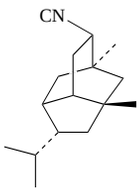
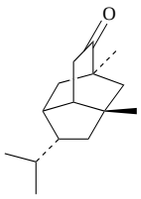


9-*epi*-isocyano-pupukeanane **4**



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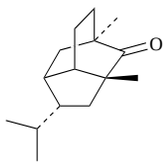

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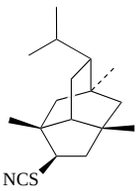
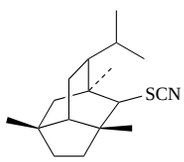
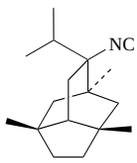


4-Thiocyanato-neopupukeanane **7**



2-Thiocyanato-neopupukeanane **8**

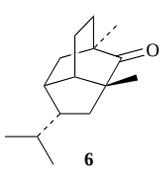


9-Isocyano-neopupukeanane **9**

by a single crystal X-ray analysis; the absolute configuration of the two compounds was also established in the latter study. Since then, several other pupukeananes have been isolated.[4,5]

A total synthesis of these sesquiterpenes is challenging since they possess (i) a new rearranged isoprenoid skeleton with a unique tricyclo[4.3.1.0^{3,7}]undecane framework having a bicyclo[2.2.2]octane subunit with a methyl group at the bridgehead position and (ii) an isopropyl group in a thermodynamically unfavourable position. Owing to their unique molecular architecture, several syntheses of these tricyclic sesquiterpenes have been reported.[6,7] In continuation of our interest[8] in the total synthesis of sesquiterpenes having a bicyclo[2.2.2]octane structural subunit with a bridgehead methyl group, herein we report the total synthesis of 5-*epi*-pupukean-2-one, an epimer of the degradation product of 2-isocyanopupukeanane.

A closer examination of pupukean-2-one **6** reveals that it contains a bicyclo[2.2.2]octane subunit **10** with a bridgehead methyl group. Although, this structural subunit can be readily made from 1-methylcyclohexa-1,3-diene[9] **11** by a Diels–Alder



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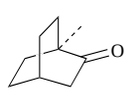

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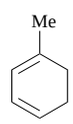

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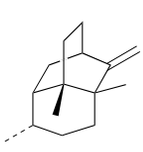
reaction with a ketene equivalent, this method suffers from two disadvantages: (i) the cycloaddition will not be regiospecific and (ii) preparation of the 1-methylcyclohexa-1,3-diene involves cumbersome procedures[9] and often results in isomeric diene mixtures. This has been overcome[10] in our laboratory by utilising dihydrotoluic acids as the equivalent of 1-methylcyclohexa-1,3-dienes which resulted in the regiospecific construction of the functionalised bicyclo[2.2.2]octene carboxylates having a bridgehead methyl group.

This new methodology has been both utilised[11] in the total synthesis of (±)-seychellene **12** and extended[12] to the preparation of the keto ester **13** as a synthon for the total synthesis of eremolactone **14**.



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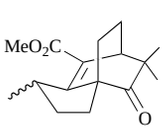

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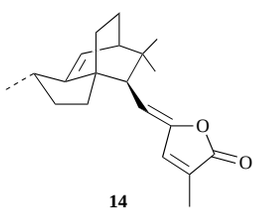

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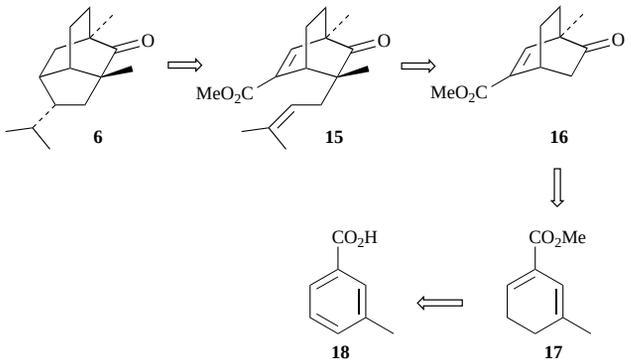
With this background, we initiated a new strategy for the total synthesis of pupukean-2-one **6**. The retrosynthesis of **6** (see Scheme 1) suggests that **15** would be the ideal choice for an intramolecular cyclisation to afford the tricyclic skeleton. The keto ester **15** can be prepared from the bicyclic keto ester **16** which, in turn, can be made by cycloaddition of the diene **17** with a ketene equivalent. The conjugated diene ester **17** can be obtained from 3-methylbenzoic acid **18** employing the methodology developed earlier.[10]

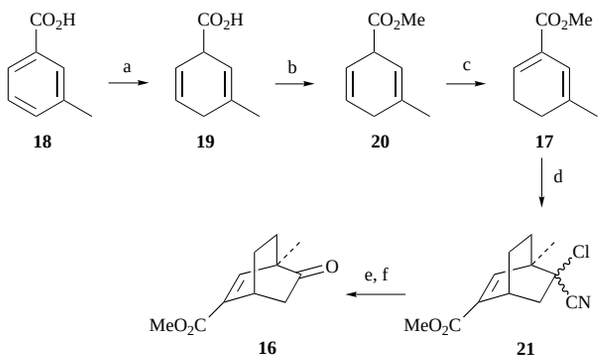
Results and discussion

Synthesis of the bicyclic intermediate 16

Reduction of 3-methylbenzoic acid **18** with sodium in liquid ammonia and quenching of the reaction with ammonium



Scheme 1



Scheme 2 *Reagents and conditions*: a, Na/liq. NH_3, THF, reflux; b, MeOH/H^+ (or) CH_2N_2; c, DBU (cat), benzene, heat; d, CH_2=C(Cl)CN, benzene, heat; e, aq. KOH/DMSO; f, CH_2N_2

chloride afforded quantitatively 3-methylcyclohexa-2,5-dienecarboxylic acid **19** (Scheme 2), the structure of which was confirmed from its analytical and spectral data. 3-Methylcyclohexa-2,5-dienecarboxylic acid **19** was esterified by treatment with either MeOH/conc. H_2SO_4 or diazomethane to afford the methyl ester **20** which showed IR absorption at 1730 cm^{-1} (saturated ester). This on treatment with a catalytic amount of DBU in refluxing benzene afforded the conjugated diene ester **17**, whose structure was deduced from spectral evidence; IR absorption at 1720 and 1600 cm^{-1} (α,β-unsaturated carbonyl and olefinic stretching frequencies, respectively) and ^{1}H NMR signals at δ 6.76 and 6.12 (both t, olefinic H) and 1.85 (s, Me); disappearance of the methine proton multiplet adjacent to the ester group was also discovered.

Diels–Alder reaction of the diene ester **17** with α-chloroacrylonitrile afforded the bicyclic adduct **21** which showed IR absorption at 2240 and 1723 cm^{-1} (nitrile and unsaturated ester) and ^{1}H NMR signals at δ 6.88 (d, lone olefinic H), 3.7 (s, CO_2Me), 3.3 (br, bridgehead H) and 1.5 (s, Me); the mass spectrum showed its base peak at 152 due to the diene obtained by the loss of a ketene formed by the retro-Diels–Alder fragmentation. This spectral evidence supported the assignment of structure **21** to the cycloaddition product. This structure was further confirmed by converting the compound into the keto ester **16** by a hydrolysis with 20% aqueous potassium hydroxide in dimethyl sulfoxide followed by esterification with diazomethane. The IR spectrum of the keto ester **16** showed no CN absorption at 2240 cm^{-1} although there was absorption at 1722 cm^{-1} (unsaturated ester and the keto group).

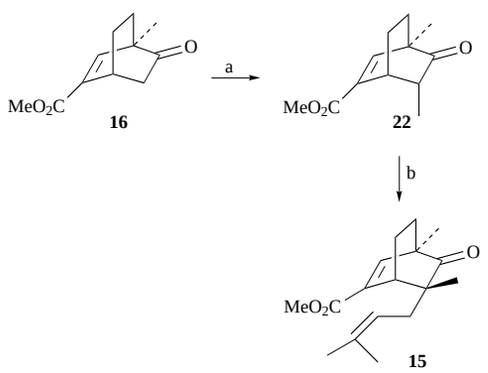
Synthesis of 5-*epi*-pupukean-2-one 33

The bicyclic keto ester **16** having been prepared in good yield, its conversion into pupukean-2-one **6** required (i) introduction of a methyl group α to the carbonyl group; (ii) introduction of a five-carbon unit α to the carbonyl group in the *endo* position; (iii) intramolecular cyclisation to form the tricyclic system; and (iv) removal of the methoxycarbonyl group.

Although introduction of a methyl group and a five-carbon unit α to the carbonyl group could be achieved through successive alkylations, the question remained as to the stereochemistry of the alkylating groups. The order in which the alkylation is carried out depends on whether the alkyl group is *endo* or *exo*.

The alkylation of lithium enolates generated from bicyclic ketones at low temperature has been reported to yield exclusively the *endo* alkylated products.[13] Thus, further efforts were directed towards the synthesis of pupukean-2-one **6**, from the bicyclic keto ester **16** with the order of alkylation: first, methylation followed by alkylation with the five-carbon unit.

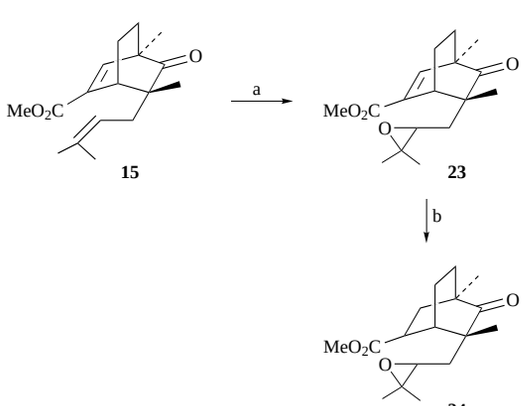
Since the five-carbon unit forms the latent functionality of the five-membered ring and an isopropyl group, the prenyl group was chosen as the five-carbon unit. Thus, alkylation of the lithium enolate, generated from the bicyclic keto ester **16** with MeI afforded the monomethylated product **22** having an *endo* methyl group (Scheme 3) as evidenced from its spectral



Scheme 3 *Reagents and conditions*: a, LDA, MeI, THF, −78 °C; b, LDA, Me_2C=$CHCH_2Br$, THF, HMPA, −78 °C

data. The ^{1}H NMR spectrum of **22** showed signals at δ 1.05 (d, *endo* Me), 1.33 (s, bridgehead Me), 3.82 (s, CO_2Me) and 6.86 (d, olefinic H). The mass spectrum showed a base peak at 152, corresponding to loss of methyl ketene in a retro Diels–Alder fragmentation. Further, alkylation of the keto ester **22** with LDA and quenching with 3,3-dimethylallyl bromide gave the product **15** as a single isomer with an *endo* prenyl group as evidenced by its spectral data: ^{1}H NMR signals at δ_H 1.05, 1.25, 1.5 and 1.68 (Me), 3.26 (m, bridgehead H) and 5.05 and 6.8 (both s, olefinic H).

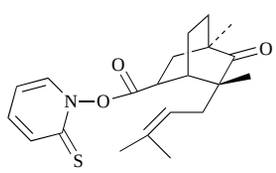
The bicyclic keto ester **15** with all the functional groups having been prepared, the next task was its cyclisation to the tricyclic system. Initially, a base-catalysed cyclisation was attempted, which is briefly discussed below. Selective epoxidation of the keto ester **15** with *m*-chloroperoxybenzoic acid (MCPBA) afforded the epoxy keto ester **23** (Scheme 4) in the ^{1}H



Scheme 4 *Reagents and conditions*: a, MCPBA, CH_2Cl_2; b, H_2, Pd–C, EtOAc

NMR spectrum of which there was no signal at δ 5.1 (t) but instead one at δ 2.92 (t, epoxide-bearing CH). Hydrogenation of the epoxy keto ester **23** afforded the saturated keto ester **24** whose IR spectrum showed strong absorption at 1737 and 1720 cm^{-1} (ester and the keto). Attempted intramolecular cyclisation of the epoxy keto ester **24** with various bases (LDA and KOBu^t) gave only recovery of starting material.

Since the base-catalysed intramolecular cyclisation of the epoxy keto ester **24** failed to produce the tricyclic skeleton present in pupukean-2-one **6**, intramolecular radical mediated cyclisation was then attempted. The thiohydroxamate ester **25** was considered[14] as ideal for generation of the radical



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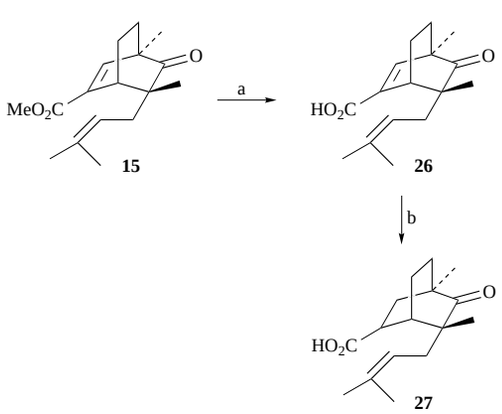
which will undergo an intramolecular 5-*exo*-*trig* cyclisation to pupukean-2-one **6**.

With this in mind, we hydrolysed the α,β-unsaturated keto ester **15** with LiOH in MeOH to afford the keto acid **26** (Scheme 5), whose IR spectrum showed broad absorption at

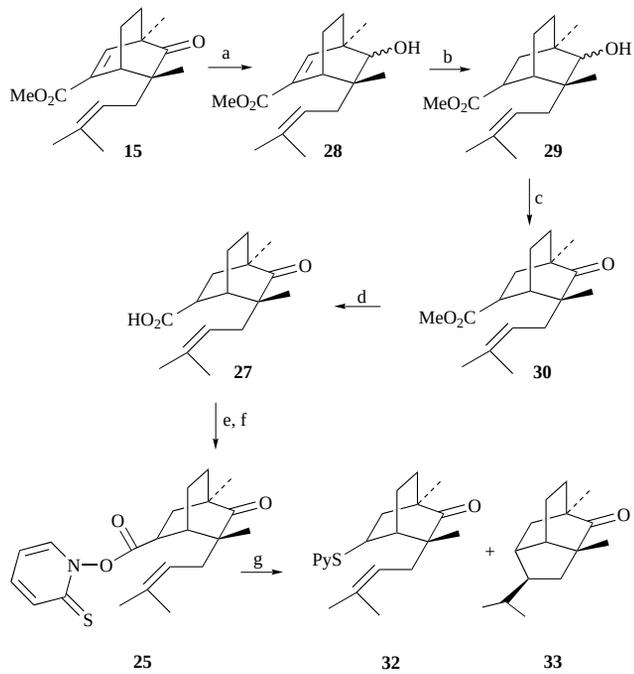


15 **26** **27**

Scheme 5 *Reagents and conditions*: a, LiOH, MeOH; b, Li/liq. NH_3

3200–2800 and 1690 cm^{-1} and in the ^{1}H NMR spectrum of which there was no signal at δ 3.8 (s, CO_2Me). Since metal–ammonia reduction of the keto acid **26** under a variety of conditions followed by oxidation of the resulting product afforded the keto acid **27** in only poor yield (<10%), an alternative strategy was adopted to obtain the thiohydroxamate ester **25** (see Scheme 6).

Reduction of the keto ester **15** with sodium borohydride afforded the hydroxy ester **28**, whose IR spectrum showed strong absorption at 3300 and 1720 cm^{-1} (OH and ester, respectively). Selective reduction of the hydroxy ester **28** with Mg in MeOH[15] gave the bicyclic hydroxy ester **29**, whose IR spectrum showed strong absorption at 3320 and 1735 cm^{-1} (OH and ester, respectively) and in the ^{1}H NMR spectrum of which there was no signal at δ 6.9 (olefinic H). PCC oxidation of the hydroxy ester **29** afforded the keto ester **30** whose structure was deduced from the spectral data: IR spectrum of **30** showed strong absorption at 1735 and 1720 cm^{-1} (ester and keto) but none at 3320 cm^{-1}. Whilst hydrolysis of **30** with KOH in MeOH failed to give the keto acid **27**, LiOH in THF gave a mixture of the keto ester **30** and the keto acid **27**. Finally, **30** was successfully hydrolysed with LiOH/MeOH to the keto acid **27**, whose IR spectrum showed absorption at 3300–2800 and 1700 cm^{-1}. The ^{1}H NMR spectrum of **27** showed signals at δ 0.96 and 1.14 (both s, bridgehead Me), 1.67 and 1.72 (both s, allylic Me) and 5.12 (s, olefinic H). The keto acid **27** was converted into the



15 **28** **29** **30** **27** **25** **32** **33**

Scheme 6 *Reagents and conditions*: a, $NaBH_4$, EtOH; b, Mg, MeOH; c, PCC, CH_2Cl_2; d, LiOH, MeOH; e, $(COCl)_2$; f, 1-hydroxypyridine-2-thione sodium salt **31**; g, TBTH, AIBN, heat

thiohydroxamate ester **25** *via* its acid chloride followed by treatment of this with the sodium salt of 1-hydroxypyridine-2-thione **31**. The resultant crude thiohydroxamate ester **25** underwent smooth Barton's decarboxylation[14] followed by an intramolecular 5-*exo*-*trig* radical cyclisation to afford the 5-*epi*-pupukean-2-one **33** along with a little of the uncyclised thiopyridyl compound **32**. The spectral data of **33** were identical with those reported.[7] The ^{1}H NMR spectrum of **33** showed signals at δ 0.83 and 0.9 (both d), 0.92 and 1.13 (both s, bridgehead Me) and 2.16 (m, 10-*exo* H). It is interesting to note that, as expected, the carboxy group of *m*-toluic acid played three significant roles: (i) helped in the formation of the required diene during the base-catalysed isomerisation; (ii) controlled the cycloaddition to give a regiospecific adduct; and (iii) finally turned into a latent functionality for the generation of a radical for the formation of the isotwistane skeleton.

In conclusion, an efficient method for the construction of the isotwistane skeleton is reported from easily available cyclohexadienes involving, as the key steps, stereoselective alkylations of a bicyclo[2.2.2]octenone and a decarboxylative radical cyclisation which culminated in the total synthesis of 5-*epi*-pupukean-2-one. Some of the salient features of this strategy are: preparation of the required diene from the readily available *m*-toluic acid; the construction of the bicyclo[2.2.2]-octane moiety with a bridgehead methyl group; successive highly stereoselective alkylation of the bicyclo[2.2.2]octenone with electrophiles: and a decarboxylative 5-*exo*-*trig* radical cyclisation route to the isotwistane skeleton.

Experimental

General

Unless otherwise stated, all materials were obtained from commercial suppliers and were used without further purification. THF and ether were distilled from sodium benzophenone ketyl under a N_2 atmosphere whenever necessary. Benzene and toluene were distilled over CaH_2 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 stored over 4 Å molecular sieves. Liquid ammonia was distilled over sodamide prior to use. $BF_3{\cdot}Et_2O$ was distilled

over LAH just before use. Wherever NaH is mentioned, it is a 60% dispersion in mineral oil and was used after being twice washed with dry light petroleum. MeLi was prepared from MeI and lithium and standardised before use. BuLi was prepared from BuCl and lithium and standardised before use. BH_3 in THF was prepared from $BF_3{\cdot}Et_2O$ and $NaBH_4$ in THF and standardised prior to use.

All reactions involving air- and moisture-sensitive reagents were performed under a blanket of argon. Glassware used for these reactions were dried in an oven at 150 °C and cooled under an atmosphere of nitrogen. Wherever it is mentioned, 'work-up' means that the reaction mixture was poured into water and extracted with ether; the combined ether extracts were then washed with water and brine, dried (Na_2SO_4) and concentrated on a rotary evaporator at aspirator pressure to give the product mixture. Column chromatography was performed on silica gel (60–120 mesh). TLC was performed with Acme's silica gel. Hexane refers to light petroleum boiling in the range 60–80 °C.

Mp and bp are uncorrected and were recorded on a Mettler FP1 instrument. IR spectra were recorded as either neat samples or solution in $CHCl_3$ on either Hitachi 270-50 or Perkin-Elmer 781 spectrophotometer. ^{1}H NMR (90) and ^{13}C NMR (22.5, 100 MHz) spectra were recorded on JEOL FX-90Q, Bruker ACF-200 and Bruker AMX-400 spectrophotometers. All the NMR spectra were recorded on solutions in $CDCl_3$ with TMS as internal standard for ^{1}H NMR and the central line of $CDCl_3$ (77.1 ppm) for ^{13}C NMR spectra. Chemical shifts are reported in δ units and J values are given 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.

3-Methylcyclohexa-2,5-dienecarboxylic acid 19

Sodium metal (348 mmol) was added to the mixture of the *m*-toluic acid **18** (13.6 g, 100 mmol) in dry THF (150 cm^3) and anhydrous liquid ammonia (700 ml) until the blue colour persisted. After the mixture had been stirred for 30 min, excess of sodium was destroyed by addition of solid ammonium chloride until it became colourless. After the ammonia had been allowed to evaporate, the residue was dissolved in water and the solution washed with ether to remove impurities. It was then acidified with 5% aq. HCl and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4) and evaporated to yield the acid **19** (11 g, 80%), mp 79 °C (hexane) (lit.,[19] 78.5–82.5 °C); ν_{max}/cm^{-1} 3300–2300 and 1695; δ_H 1.74 (3H, s, Me), 2.62 (2H, d, *J* 9), 3.72 (1H, m, C*H*CO$_2$H), 5.5 (1H, m, olefinic) and 5.9 (2H, m, olefinic); δ_C 23.1 (q), 30.6 (t), 42.7 (d), 115.9 (d), 121.3 (d), 126.7 (d), 134.2 (s) and 179.6 (s) (Found: C, 69.38; H, 7.2. $C_8H_{10}O_2$ requires C, 69.54; H, 7.29%).

Methyl 3-methylcyclohexa-2,5-dienecarboxylate 20

A mixture of the acid **19** (10 g, 72 mmol) and conc. H_2SO_4 (0.5 ml) in MeOH (100 ml) was refluxed for 12 h. The excess methanol was removed under reduced pressure and the residue was taken up in ether and the solution washed with aq. $NaHCO_3$ water and brine, dried (Na_2SO_4) and evaporated. Distillation of the residue gave the ester **20** (9.1 g, 90%) (bp 52 °C/2 mm); ν_{max}/cm^{-1} 3010, 2920 and 1735; δ_H 1.72 (3H, s, Me), 2.58 (2H, d, *J* 9.1), 3.68 (1H, m, C*H*CO$_2$Me), 3.75 (3H, s, CO$_2$Me), 5.5 (1H, br s, olefinic) and 5.81 (2H, br s, olefinic).

Methyl 5-methylcyclohexa-1,5-dienecarboxylate 17

The above ester **20** (8 g, 52 mmol) was refluxed with DBU (0.5 ml) in benzene (60 ml) for 5 h, after which the mixture was washed successively with 2% aq. HCl, water and brine, dried (Na_2SO_4) and evaporated. Distillation of the residue (60 °C, 3 mmHg) gave a **17** as a colourless liquid (7.2 g, 90%); ν_{max}/cm^{-1} 3010, 2930 and 1722; δ_H 1.82 (3H, s, Me), 1.6–2.4 (4H, m), 3.75 (3H, s, CO$_2$Me), 6.12 (1H, t, *J* 1.2, olefinic), 6.78 (1H, t, *J* 4.2, olefinic).

Methyl 6-chloro-6-cyano-1-methylbicyclo[2.2.2]oct-2-ene-3-carboxylate 21

A mixture of the diene **17** (7 g, 46 mmol), α-chloroacrylonitrile (10 ml) and hydroquinone (20 mg) in benzene (10 ml) was refluxed for 36 h and then evaporated. The residue was loaded on a column of silica gel. Elution with ethyl acetate–hexane (1:19) gave an epimeric mixture of the adducts **21** as a viscous liquid (9.2 g, 86%); ν_{max}/cm^{-1} 3030, 2920, 2240 and 1723; δ_H 1.3–2.3 (5H, m), 1.57 (3H, s, Me), 2.67 (1H, d, $\frac{1}{2}$AB$_q$, *J* 14.4 and 1.8), 3.31 (1H, m, bridgehead H), 3.77 (3H, s, CO$_2$Me) and 6.88 and 7.02 (1H, s, olefinic) (Found: C, 60.53; H, 5.99; N, 5.44. $C_{12}H_{14}ClNO_2$ requires C, 60.13; H, 5.88; N, 5.84%).

Methyl 1-methyl-6-oxobicyclo[2.2.2]oct-2-ene-3-carboxylate 16

A solution of the adduct **21** (4.5 g, 18.8 mmol) in DMSO (35 ml) and 20% aqueous KOH (25 ml) was stirred at 55 °C for 48 h, after which the reaction mixture was acidified with dilute HCl and extracted with ether. The ether extract was washed with water and brine, dried (Na_2SO_4) and evaporated. The resulting crude acid was esterified with ethereal diazomethane and purified by chromatography over silica gel (ethyl acetate–hexane, 1:9, as eluent) to yield the keto ester **16** (2.8 g, 75%); ν_{max}/cm^{-1} 3010, 2930 and 1722; δ_H 1.27 (3H, s, Me), 1.4–1.9 (4H, m), 2.07 (2H, d, *J* 2, COCH$_2$), 3.53 (1H, m, bridgehead H), 3.75 (3H, s, CO$_2$Me) and 6.88 (1H, d, *J* 2, olefinic); δ_C 17.0 (q), 25.5 (t), 30.1 (t), 31.5 (d), 39.2 (t), 50.4 (s), 51.4 (q), 139.1 (s), 143.3 (d), 164.1 (s) and 210.7 (s); *m*/*z* 194 (M$^+$, 60%), 152 (100), 93 (50) and 31 (20) (Found: M$^+$, 194.0939 $C_{11}H_{14}O$ requires *M*, 194.0943).

Methyl 1,5-dimethyl-6-oxobicyclo[2.2.2]oct-2-ene-3-carboxylate 22

A 1 M solution of BuLi in hexane (14.7 ml, 14.7 mmol) was added to diisopropylamine (2.1 ml, 16.1 mmol) in THF (30 ml) at −78 °C under argon. The resultant solution of lithium diisopropylamide was stirred for 1 h at −78 °C for 45 min after which a solution of the ketone **16** (2.6 g, 13.4 mmol) in dry THF (40 ml) was added dropwise to it. The resultant lithium enolate was stirred at −78 °C for 1 h after which a solution of MeI (2.5 ml, 40 mmol) in THF was added at once. After being stirred for 1 h, the reaction mixture was poured onto saturated aqueous NH_4Cl and extracted with ether (3 × 50 ml). The combined ether extracts were washed successively with water, aqueous sodium thiosulfate, water and brine and then dried (Na_2SO_4) and evaporated. Purification of the product by column chromatography (ethyl acetate–light petroleum, 1:9) afforded the product **22** (2.5 g, 90%); ν_{max}/cm^{-1} 3010, 2930 and 1722; δ_H 1.04 (3H, d, *J* 7.1, CH$_3$CH), 1.3 (3H, s, Me), 1.4–1.8 (4H, m), 2.1 (1H, m, CHCH$_3$), 3.36 (1H, m, bridgehead H), 3.79 (3H, s, CO$_2$Me) and 6.9 (1H, d, *J* 1.9, olefinic); δ_C 16.1 (q), 16.9 (q), 25.4 (t), 29.1 (t), 37.8 (d), 42.5 (d), 49.6 (s), 50.9 (q), 137.8 (s), 141.7 (d), 164.1 (s) and 211 (s); *m*/*z* 208 (M$^+$, 20%), 152 (100) and 93 (50) (Found: M$^+$, 208.1101. $C_{12}H_{16}O_3$ requires *M*, 208.1099).

Methyl 1,5-dimethyl-5-*endo*-(3-methylbut-2-enyl)-6-oxobicyclo-[2.2.2]oct-2-ene-3-carboxylate 15

To a freshly prepared LDA solution [prepared from a 1 M solution of BuLi (10.5 ml, 10.5 mmol) and diisopropylamine (1.5 ml, 11.53 mmol) in THF (20 ml)] at −78 °C under argon, was added dropwise a solution of the ketone **22** (2 g, 9.61 mmol) in THF (30 ml). The resultant enolate was stirred for 1 h at the same temperature and then quenched with a solution of prenyl bromide (2.5 ml, 20 mmol) in THF; HMPA (3.8 ml, 20 mmol) was then added to the mixture. After being stirred overnight the reaction mixture was poured onto 2 M aqueous HCl (100 ml). Work-up followed by column chromatography (ethyl acetate–light petroleum, 1:9) then afforded compound **15** as a colour-

less oil (2.1 g, 80%); ν_{max}/cm^{-1} 3010, 2920 and 1725; δ_H 1.06 (3H, s, Me), 1.26 (3H, s, Me), 1.4–2.1 (6H, m), 1.49 (3H, s, Me), 1.67 (3H, s, Me), 3.26 (1H, m, bridgehead H), 3.74 (3H, s, CO_2Me), 5.06 (1H, t, *J* 6.8, olefinic) and 6.78 (1H, s, olefinic); δ_C 17.2 (2 × q), 21.0 (q), 21.9 (t), 25.4 (q), 30.0 (t), 36.5 (t), 40.0 (d), 45.9 (s), 50.1 (s), 51.0 (q), 119.1 (d), 133.5 (s), 139.9 (s), 140.8 (d), 163.9 (s) and 213.9 (s); *m*/*z* 276 (M^+, 85%), 152 (100), 124 (25) and 96 (45) (Found: M^+, 276.1718. $C_{17}H_{24}O_3$ requires *M*, 276.1725).

Methyl 1,5-dimethyl-5-*endo*-(3-methyl-2,3-epoxybutyl)-6-oxobicyclo[2.2.2]oct-2-ene-3-carboxylate 23

To an ice-cold solution of MCPBA (600 mg), in CH_2Cl_2 (5 ml) was added the keto ester **15** (280 mg, 1 mmol) in CH_2Cl_2 (5 ml). The resultant mixture was stirred for 1.5 h at the same temperature after which it was diluted with CH_2Cl_2 (25 ml) and washed with 10% aq. Na_2SO_3, saturated aq. $NaHCO_3$, water and brine and then dried (Na_2SO_4) and evaporated to afford the epoxy ester **23** (260 mg, 90%); ν_{max}/cm^{-1} 2920 and 1720; δ_H 0.9–2.0 (6H, m), 1.16 (3H, s, Me), 1.17 (3H, s, Me), 1.21 (6H, s, 2 × Me), 2.9 (1H, t, *J* 6.8, OCH), 3.38 (3H, m, bridgehead H), 3.73 (3H, s, CO_2Me) and 6.84 (1H, br s, olefinic).

Methyl 1,3-dimethyl-3-*endo*-(3-methyl-2,3-epoxybutyl)-2-oxobicyclo[2.2.2]octane-5-carboxylate 24

A suspension of the epoxy keto ester **23** (200 mg, 0.62 mmol) and 10% Pd–C (20 mg) in dry EtOAc (10 ml) was magnetically stirred under an H_2 atmosphere for 12 h. After this, the reaction mixture was filtered through a Celite pad and evaporated under reduced pressure to furnish the saturated epoxy keto ester **24** (190 mg, 95%); ν_{max}/cm^{-1} 1735; δ_H 1.1 (3H, s, Me), 1.12 (3H, s, Me), 1.17 (3H, s, Me), 1.18 (3H, s, Me), 1.2–2.1 (10H, m), 2.92 (1H, t, *J* 6.7, OCH) and 3.74 (3H, s, CO_2Me).

1,5-Dimethyl-5-*endo*-(3-methylbut-2-enyl)-6-oxobicyclo[2.2.2]-oct-2-ene-3-carboxylic acid 26

A mixture of the keto ester **15** (1 g, 3.62 mmol), LiOH (116 mg, 7.25 mmol) and MeOH (5 ml) was stirred for 15 h and then concentrated *in vacuo*, acidified with dil. aq. HCl and extracted with ether (3 × 25 ml). The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated to give a colourless oil **26** (800 mg, 90%); ν_{max}/cm^{-1} 3300–2800 and 1690; δ_H 1.12 (3H, s, Me), 1.31 (3H, s, Me), 1.2–2.4 (6H, m), 1.53 (3H, s, Me), 1.66 (3H, s, Me), 3.28 (1H, m, bridgehead H), 5.07 (1H, t, *J* 8.7, olefinic) and 6.98 (1H, d, *J* 1.9, olefinic) (Found: C, 73.65; H, 8.76. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

Methyl 1,5-dimethyl-6-hydroxy-5-*endo*-(3-methylbut-2-enyl)-bicyclo[2.2.2]oct-2-ene-3-carboxylate 28

To a solution of the keto ester **15** (800 mg, 2.9 mmol) in MeOH (10 ml) was added sodium borohydride (200 mg) at 0 °C. The mixture was stirred at room temperature for 1 h, after which it was evaporated under reduced pressure, treated with saturated aqueous ammonium chloride and extracted with ether. The ether extract was washed with water and brine, dried (Na_2SO_4) and evaporated. Chromatography of the crude product over silica gel using ethyl acetate–hexane (1 : 9) as eluent provided the alcohol **28** (750 mg, 96%) as a colourless oil; ν_{max}/cm^{-1} 3300, 2930 and 1722; δ_H 0.94 (3H, s, Me), 1.16 (3H, s, Me), 1.2–1.9 (6H, m), 1.49 (3H, s, Me), 1.66 (3H, s, Me), 2.78 (1H, m, bridgehead H), 3.0 and 3.07 (1H, m, CHOH), 3.73 (3H, s, CO_2Me), 5.17 (1H, t, *J* 8.2, olefinic) and 6.86 (1H, d, *J* 1.9, olefinic); *m*/*z* 278 (M^+, 20%), 152 (100), 126 (80) and 93 (100) (Found: M^+, 278.1872 $C_{17}H_{26}O_3$ requires *M*, 278.1882).

Methyl 1,3-dimethyl-3-*endo*-(3-methylbut-2-enyl)-2-oxobicyclo-[2.2.2]octane-5-carboxylate 30

A mixture of the hydroxy ester **28** (650 mg, 2.33 mmol), Mg turnings (600 mg, 250 mmol) and MeOH (10 ml) was stirred at room temperature for 12 h after which it was evaporated under reduced pressure. The residue was acidified with dil. aq. HCl (20 ml) and extracted with ether (3 × 25 ml). The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. Purification by column chromatography using ethyl acetate–hexane (1 : 9) as eluent afforded **29** as a colourless oil (650 mg, 90%); ν_{max}/cm^{-1} 3300, 2930 and 1735; δ_H 0.89 (3H, s, Me), 0.93 (3H, s, Me), 1.1–2.6 (10H, m), 1.54 (3H, s, Me), 1.69 (3H, s, Me), 3.13 (1H, m, CHOH), 3.67 (3H, s, CO_2Me) and 5.16 (1H, t, *J* 8.4).

A slurry of the hydroxy ester **29** (500 mg, 1.78 mmol), PCC (600 mg, 2.67 mmol) and NaOAc (2 g) in dry CH_2Cl_2 (10 ml) was stirred for 3 h, after which it was evaporated, diluted with ether filtered through a pad of Celite and evaporated. The residue was chromatographed over silica gel (ethyl acetate–hexane, 1 : 9) to afford the keto ester **30** (380 mg, 80%); ν_{max}/cm^{-1} 2920, 1735 and 1715; δ_H 0.98 (6H, s, 2 × Me), 1.1–2.4 (10H, m), 1.53 (3H, s, Me), 1.68 (3H, s, Me), 3.67 (3H, s, CO_2Me) and 5.05 (1H, m, olefinic); *m*/*z* 278 (M^+, 18%), 210 (24), 124 (50), 93 (25), 69 (33) and 41 (3) (Found: M^+, 278.1884. $C_{17}H_{26}O_3$ requires *M*, 278.1882).

1,3-Dimethyl-3-*endo*-(3-methylbut-2-enyl)-2-oxobicyclo[2.2.2]-octane-5-carboxylic acid 27

A solution of the keto ester **30** (250 mg, 0.9 mmol), LiOH (30 mg, 1.75 mmol) and MeOH (5 ml) was stirred for 15 h, after which it was concentrated *in vacuo*, acidified with dil. aq. HCl and extracted with ether (3 × 15 ml). The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated to give a colourless oil **27** (180 mg, 80%); ν_{max}/cm^{-1} 3200–2800 and 1700; δ_H 0.92 (3H, s, Me), 1.1 (3H, s, Me), 1.2–2.4 (9H, m), 1.64 (3H, s, Me), 1.73 (3H, s, Me), 2.98 (1H, m) and 5.16 (1H, t, *J* 8.1, olefinic).

1,3-Dimethyl-3-*endo*-(2-methylbut-2-enyl)-5-(2-pyridylthio)-bicyclo[2.2.2]octan-2-one 32 and 5-*epi*-pupukean-2-one 33

To a solution of the acid **27** (50 mg, 0.15 mmol), in benzene (1 ml) at 25 °C was added oxalyl chloride (0.5 ml) and DMF (1 drop). After 5 h, solvent and excess of oxalyl chloride were removed on a rotary evaporator to give the crude acid chloride. The crude acid chloride in benzene (5 ml) was added to a suspension of 1-hydroxypyridine-2-thione sodium salt (30 mg, 0.2 mmol) and of DMAP (10 mg) in benzene (35 ml) at reflux. After 15 min, tributyltin hydride (0.2 ml) and AIBN (5 mg) in benzene (5 ml) were added dropwise over 30 min to the mixture. After 3 h, the mixture was evaporated under reduced pressure and the residue was vigorously stirred for 10 h in a two-phase system comprising a saturated solution of iodine in dichloromethane (10 ml) and saturated aqueous KF (10 ml). The resultant residue was filtered through a pad of Celite and washed with dichloromethane. The combined dichloromethane extracts were washed with aqueous sodium thiosulfate solution, water and brine, dried (Na_2SO_4) and evaporated. Column chromatography of the residue (ethyl acetate–hexane as eluent) afforded initially 5-*epi*-pupukean-2-one **33** (15 mg, 35%). Further elution with the same solvent afforded the ketone **32** (3 mg, 5%). For **33**: ν_{max}/cm^{-1} 1710; δ_H 0.82 and 0.89 (6H, d, *J* 7, 2 × Me), 0.92 (3H, s, Me), 1.12 (3H, s, Me), 1.01–2.01 (11H, m) and 2.14 (1H, m); *m*/*z* 220 (M^+, 30%), 149 (40) and 93 (100) (Found: M^+, 220.1831. $C_{15}H_{24}O$ requires *M*, 220.1828). For **32**; ν_{max}/cm^{-1} 1715; δ_H 1.01 (3H, s, Me), 1–2.5 (9H, m), 1.17 (3H, s, Me), 1.65 (3H, s, Me), 1.74 (3H, s, Me), 2.9 (1H, m), 5.15 (1H, m, olefinic), 7.3 (1H, m), 7.6 (2H, m) and 8.4 (1H, t, *J* 7).

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