Synthesis based on cyclohexadienes. Part 23. 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[4.3.1.0^2,6]decane carbon framework (isotwistane) 1, the first example of which, 9-isocyanopupukeanane 2, was reported by Scheuer et al., 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 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 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.

A total synthesis of these sesquiterpenes is challenging since they possess (i) a new rearranged isoprenoid skeleton with a unique tricyclo[4.3.1.0^2,6]decane 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. In continuation of our interest 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 11 by a Diels-Alder 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 and often results in isomeric diene mixtures. This has been overcome 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 in the total synthesis of (±)-seychellene 12 and extended to the preparation of the keto ester 13 as a synthon for the total synthesis of eremolactone 14.

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 17 can be obtained from 3-methylbenzoic acid 18 employing the methodology developed earlier.

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
chloride afforded quantitatively 3-methylcyclohexa-2,5-diene-1,4-cyclohexanedione 19 (Scheme 2), the structure of which was confirmed from its analytical and spectral data. 3-Methylcyclohexa-2,5-diene-1,4-cyclohexanedione 19 was esterified by treatment with either MeOH or conc. H₂SO₄ 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 ¹H 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 ¹H NMR signals at δ 6.88 (d, lone olefinic H), 3.7 (s, CO₂Me), 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 data. The ¹H NMR spectrum of 22 showed signals at δ 1.05 (d, endo Me), 1.33 (s, bridgehead Me), 3.82 (s, CO₂Me) 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: ¹H NMR signals at δ 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-chloroperbenzoic acid (MCPBA) afforded the epoxy keto ester 23 (Scheme 4) in the ¹H
NMR spectrum of which there was no signal at $\delta$ 5.1 (t) but instead one at $\delta$ 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') 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 as ideal for generation of the radical which will undergo an intramolecular 5-exo-trig cyclisation to pupukean-2-one 6.

With this in mind, we hydrolysed the $\alpha,\beta$-unsaturated keto ester 15 with LiOH in MeOH to afford the keto acid 26 (Scheme 5), whose IR spectrum showed broad absorption at 3200–2800 and 1700 cm$^{-1}$ and in the $^1$H NMR spectrum of which there was no signal at $\delta$ 3.8 (s, CO$_2$Me). 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 $\delta$ 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 3320–2800 and 1700 cm$^{-1}$. The $^1$H NMR spectrum of 27 showed signals at $\delta$ 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 thiohydroxamate ester 25 via its acid chloride followed by treatment of this with the sodium salt of 1-hydroxypropidine-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 thio- pyryl compound 32. The spectral data of 33 were identical with those reported.$^7$ The $^1$H NMR spectrum of 33 showed signals at $\delta$ 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 cycladdition to give a regioselective 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$_2$Cl$_2$ 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$_3$Et$_2$O 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 Me and lithium and standardised before use. BuLi was prepared from BuCl and lithium and standardised before use. BuH in THF was prepared from BF₃·Et₂O and NaBH₄ 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 (Na₂SO₄) 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 solutions in KBr or in thin films. For NMR spectra, see Experimental. Other physical data are uncorrected and were recorded on a JEOL FX-90Q, FT-80 and Bruker AMX-400 spectrophotometers. All the NMR spectra were recorded on solutions in CDCl₃ with TMS as an internal standard for 1H NMR and the central line of CDCl₃ (77.1 ppm) for 13C 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-diene-carboxylic acid 19

Sodium metal (348 mg, 14.6 mmol) was added to the mixture of the n-toluic acid 18 (13.6 g, 100 mmol) in dry THF (150 cm³) 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 (Na₂SO₄) and evaporated to yield the acid 19 (11 g, 80%), mp 78 °C (hexane) (lit. 78.5–82.5 °C; vmax/cm⁻¹ 3300–2300 and 1695; δH 1.74 (3H, s, Me), 2.62 (2H, d, J 9, 5.2 Hz, 1H, CH₃COOH), 5.5 (1H, m, olefinic) and 5.9 (2H, m, olefinic); δC 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. C₉H₆O₂ requires C, 69.54; H, 7.29%).

Methyl 3-methylcyclohexa-2,5-diene-carboxylate 20

A mixture of the acid 19 (10 g, 72 mmol) and conc. H₂SO₄ (20 ml) was refluxed for 12 h. The excess methanesulphonic acid was removed under reduced pressure and the residue was taken up in ether and the solution washed with aqueous NH₄Cl and extracted with ether (3 × 50 ml). The ether extract was washed with water and brine, dried (Na₂SO₄) and evaporated. Distillation of the residue gave the ester 20 (9.9 g, 90%) (bp 52 °C/2 mmHg); vmax/cm⁻¹ 3010, 2930 and 1722; δH 1.04 (3H, J 7, 1.1 Hz, CH₃), 1.3 (3H, s, Me), 1.4–1.8 (4H, m), 2.1 (1H, CH₂CH₃), 3.36 (1H, m, bridgehead H), 5.39 (1H, s, CO₂HMe), 6.89 (1H, d, J 6.1 Hz, bridgehead H), 7.02 (1H, s, olefinic) (Found: C, 60.53; H, 5.99; N, 5.44. C₈H₁₄O₂ requires C, 60.13; H, 5.88; N, 5.84%).

Methyl 3-aryl-5-endo-(3-methylbut-2-enyl)-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 disopropylamine (2.1 ml, 16.1 mmol) in THF (30 ml) at −78 °C under argon. The resultant solution of lithium disopropylamide was stirred for 1 h at −78 °C for 45 min after which a solution of the ketone 16 (2.8 g, 75%); vmax/cm⁻¹ 3010, 2930 and 1722; δH 1.27 (3H, s, Me), 1.4–1.9 (4H, m), 2.07 (2H, d, J 2, CH₃CO), 3.53 (1H, m, bridgehead H), 3.75 (1H, s, CO₂Me) and 6.88 (1H, d, J 2, olefinic); δC 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; C₉H₁₄O₂ requires M⁺, 194.0943).

Methyl 1-5-dimethyl-6-oxobicyclo[2.2.2]oct-2-ene-3-carboxylate 23

To a freshly prepared LDA solution prepared from a 1 m solution of BuLi (10.5 ml, 10.5 mmol) and disopropylamine (1.5 ml, 11.53 mmol) in THF (20 ml) at −78 °C under argon, was added dropwise a solution of the ketone 22 (2.9, 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-
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 CH₂Cl₂ (5 ml) was added the keto ester 15 (280 mg, 1.1 mmol) in CH₂Cl₂ (5 ml). The resultant mixture was stirred for 1.5 h at the same temperature after which it was diluted with CH₂Cl₂ (25 ml) and washed with 10% aq. Na₂SO₃ saturated aq. NaHCO₃, water and brine and then dried (Na₂SO₄) and evaporated to afford the ester 23 (260 mg, 90%); νmax/cm⁻¹ 3290 and 1722; δ (s, Me), 0.93 (3H, 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, CO₂Me) 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 CH₂Cl₂ (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%); νmax/cm⁻¹ 2920, 2939 and 1715; δ (s, Me), 0.98 (6H, t, 2 × Me), 1.2–2.4 (10H, m), 1.53 (3H, s, Me), 1.68 (3H, s, Me), 3.67 (3H, s, CO₂Me) 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. C₁₉H₂₀O₂ requires M⁺, 278.1882).

1,3-Dimethyl-3-endo-(3-methylbut-2-ene)-2-oxobicyclo[2.2.2]oct-5-ene-5-carboxylic acid 27

A solution of the keto ester 30 (250 mg, 0.93 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 (Na₂SO₄) and evaporated to afford a colourless oil 28 (800 mg, 90%); νmax/cm⁻¹ 3300–2800 and 1700; δ (s, Me), 0.92 (3H, Me), 1.1 (3H, 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-(3-methylbut-2-ene)-5-[(2-pyridylthio)bicyclo[2.2.2]oct-1-ene-2-one 32 and 5-[(2-pyridin-2-yl)thieno-2-yl)bicyclo[2.2.2]oct-1-ene-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 DMAP (0.5 mmol) and of DMAP (10 mg) in benzene (35 ml) at reflux. 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-hydroxy-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 ABN (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 (Na₂SO₄) and evaporated. Column chromatography of the residue (ethyl acetate–hexane as eluent) afforded initially 5-[(2-pyridin-2-yl)thieno-2-yl)bicyclo[2.2.2]oct-1-ene-2-one 33 (15 mg, 35%). Further elution with the same solvent afforded the ketone 32 (3 mg, 5%). For 32: νmax/cm⁻¹ 1710; δ (s, Me), 0.82 and 0.89 (9H, d, J 7, 2 × Me), 0.92 (3H, s, Me), 1.12 (3H, s, Me), 1.01–2.01 (11H, m) and 1.24 (1H, m); m/z 220 (M⁺, 30%), 140 (49) and 93 (100) (Found: M⁺, 220.1831. C₁₉H₂₁O₂ requires M⁺, 220.1828). For 32: νmax/cm⁻¹ 1715; δ (s, Me), 1.01 (3H, s, Me), 1.2–2.5 (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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References

1 For Part 22 of the series, see ref. 8.


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