Chemoenzymatic total syntheses of the sesquiterpene (−)-patchoulenone†

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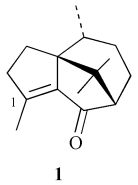
The bicyclo[5.3.1]undec-7(8)-en-3-one **6**, which is prepared from the monochiral *cis*-1,2-dihydrocatechol **4**, affords a mixture of products **7**, **8** and **9** on exposure to protic acid. Each of compounds **8** and **9** rearranges to congener **7** on treatment with $SnCl_2$ or upon sustained reaction with protic acid. Reaction of the last compound with hydrogen in the presence of palladium on carbon affords a mixture of the saturated diols **10** and **11** with the latter capable of elaboration to (−)-patchoulenone (**1**) in four simple steps. An alternate and more efficient route to compound **11** involved a radical cyclisation route wherein enone **6** was treated with SmI_2 and thiophenol, the latter reagent being employed to ensure efficient reduction. The major product, **12**, thus formed was then debenzylated to give the patchoulenone precursor **11**. In an even more efficient route to the title sesquiterpene, the bicyclo[2.2.2]octenone **21** was reacted with isopropenyllithium to give the dienol **22**, which engaged in an anionic oxy-Cope rearrangement to afford the bicyclo[5.3.1]undec-7(8)-enone **23** and for which an X-ray crystal structure determination has been carried out. Reductive cyclisation of the last compound using SmI_2 in the presence of thiophenol then gave, in a stereoselective manner, diol monoether **24**, which after subjection to debenzylation, oxidation and dehydration steps afforded (−)-patchoulenone (**1**).

(−)-Patchoulenone (**1**) is a prominent member of the cyperene class of sesquiterpenes and was first isolated in 1964 from *Cyperus rotundus* Linné (*Cyperaceae*), a plant common in Sudan, India, China, Thailand and Japan.[1,2] The compound has also been identified as a constituent of, *inter alia*, the root bark of *Uvaria narum* Wall. (*Annonaceae*)[3] and *Piptostigma fugax*.[4] Despite a number of the source plants being used in traditional medicines, only a modest amount is known about the biological properties of (−)-patchoulenone. Thus, compound **1** shows[2] *in vitro* activity (EC_{50} 1.08×10^{-4} M) against the malarial parasite *Plasmodium falciparum*, strong anti-fungal activity against *Rhizoctonia solani* and *Saprolegnia asterophora*,[4] and significant toxicity in a brine shrimp bioassay.[4] The isomeric sesquiterpene cyperotundone (**2**)[5] and its deoxygenated counterpart cyperene (**3**)[6] have been isolated from the same or related plant sources. Once again, there is little information available regarding the biological properties of these congeners.



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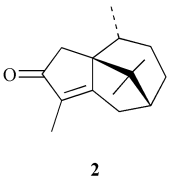

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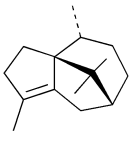

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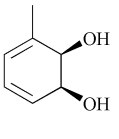

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† Aspects of this work have been reported in preliminary form: M. Banwell and M. McLeod, *Chem. Commun.*, 1998, 1851.

The 1,4,9,9-tetramethyl-2,4,5,6,7,8-hexahydro-3*H*-3a,7-methanoazulene framework associated with the cyperene-type sesquiterpenes has been the subject of a number of synthetic studies[7] and the title compound has itself been synthesised by Hikino *et al.*,[8] who used (+)-camphor as the starting material. The racemic modification of patchoulenone has also been prepared *via* the Lewis acid catalysed addition of a diazo ketone to a tethered olefin.[9] We now report two distinct and chemoenzymatic total syntheses of (−)-patchoulenone that employ the monochiral *cis*-1,2-dihydrocatechol **4**, obtained by microbial oxidation of toluene, as starting material.[10]

Results and discussion

Mechanistic and synthetic studies concerning a key transannular cyclisation reaction – construction of the patchoulenone framework

In connection with the development of synthetic approaches to taxoids, we have described[11] the conversion of the dihydrocatechol **4** into the diene **5** and shown that the latter readily engages in an oxy-anionic Cope reaction to give the bicyclo[5.3.1]undec-7(8)-en-3-one **6** (Scheme 1). As has been observed in a closely related system,[12] the carbon-carbon double bond and carbonyl group within enone **6** are in sufficiently close proximity that the compound exhibits a significant absorption (ε 2475) at λ_{max} 245 nm. As a consequence of the proximity of these moieties, compound **6** engages in a rapid, acid-catalysed intramolecular Prins reaction[13] to give isomer **7**, which embodies the tricyclic framework associated with cyperene-type natural products such as **1**–**3**. These observations prompted a detailed investigation of the conversion **6** → **7** with a view to optimising the yield of this process so that it could be exploited in the synthesis of (−)-patchoulenone (**1**). In this connection, a deuterochloroform solution of compound

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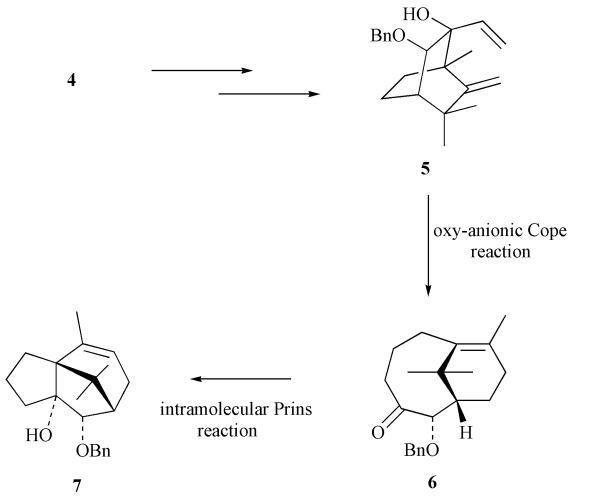
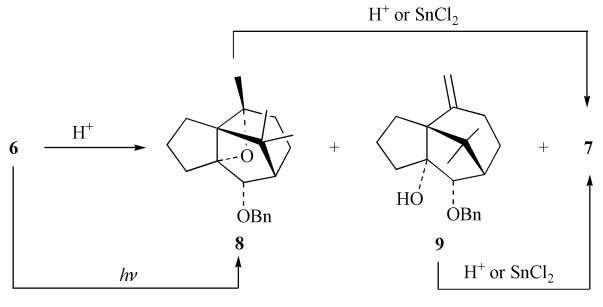


Scheme 1

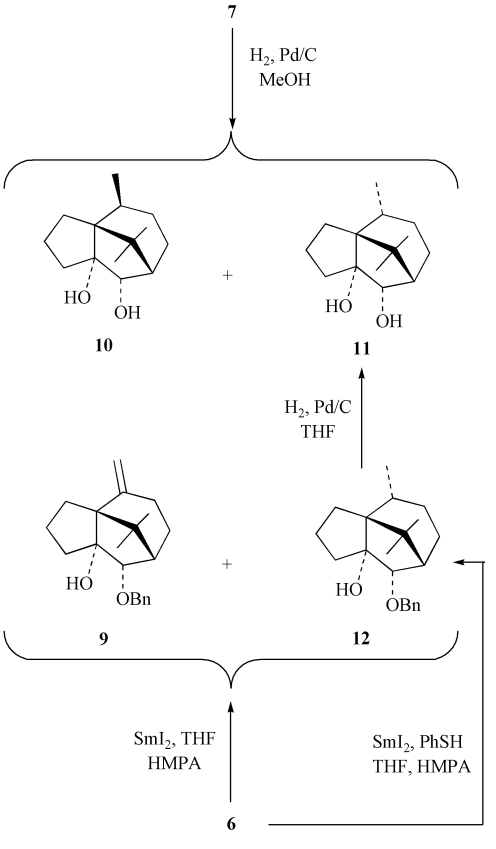
6 containing traces of acid was observed, by ^{1}H NMR techniques, to be consumed within 15 min at room temperature. Under these conditions a mixture of three products was obtained with the major ones being identified as the tricyclic alkene **7** and the oxetane **8** (Scheme 2).[14] A trace of the isomeric system **9** was also detected. After 24 h compounds **8** and **9** had both been cleanly converted into isomer **7**. That these conversions are acid-catalysed follows from the observation that a solution of compound **6** in base-washed deuterochloroform is completely stable and even after 24 h none of the above-mentioned rearrangement products could be detected. Furthermore, when a crystal of camphorsulfonic acid is added to the NMR sample the isomerisation process commences immediately, although the process is slower than that observed when HCl is the catalyst. These observations are consistent with the operation of an intramolecular Prins reaction and confirmation of the structure of oxetane **8** generated in these processes follows from the fact that this compound can be formed in high yield by subjecting precursor **6** to an intramolecular Paterno–Büchi reaction.[15] Furthermore, when a pure sample of compound **8** produced in this way was treated with acidic deuterochloroform it was readily converted into alkene **7**.

The close mechanistic relationship between the Prins reaction and the carbonyl-ene reaction, which can be catalysed by Lewis acids, prompted treatment of a solution of substrate **6** with tin(II) chloride ($SnCl_2$)[16] in deuterochloroform solution. Under such conditions the rapid formation of the ene product **7** occurs and small amounts of the oxetane **8**, but not the isomeric alkene **9**, can be detected by ^{1}H NMR techniques (interestingly, independent subjection of compounds **8** and **9** to treatment with $SnCl_2$ results in their rather slow – although still high yielding – conversion into isomer **7**). These results suggest that compounds **8** and **9** are not intermediates in the Lewis acid catalysed carbonyl-ene reaction. Such results also suggest that the mechanisms associated with the Brønsted acid and Lewis acid catalysed conversions **6** → **7** are different. Thus, the former process is most likely a stepwise one while the latter is a concerted event. In a preparative sense the most effective method for acquiring useful quantities of compound **7** involved treating precursor **6** with catalytic amounts of $SnCl_2$ in chloroform at 18 °C for 1 h and under these conditions a 97% yield of product was obtained.

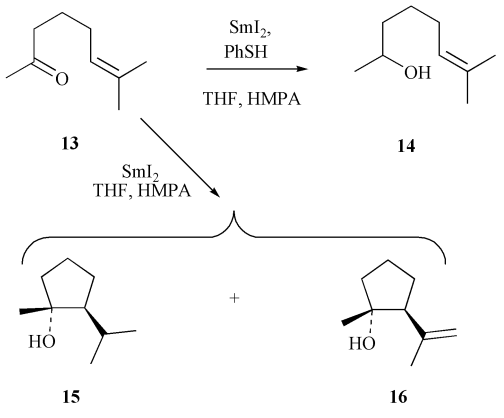
The synthesis of patchoulenone from compound **7** requires, *inter alia*, the diastereofacially selective hydrogenation of the double bond within the latter. In the event (Scheme 3), reaction of alkene **7** with dihydrogen in the presence of palladium on carbon afforded, as a consequence of hydrogenation of the alkene double bond and hydrogenolytic cleavage of the benzyl ether moiety, a *ca.* 1:3 mixture of product **10** and the required epimer **11** (80% combined yield). These products could be separated from one another by flash chromatography and the structure of the major one follows from its conversion into patchoulenone. While the selectivity of this hydrogenation process is not especially high it compares rather favourably with related examples reported by Büchi,[7] Hikino,[8] and Erman.[9] Nevertheless, we considered alternate means for producing compound **11** so as to achieve a more efficient process. In this connection the one-electron reduction of the carbonyl group within compound **6** would give a radical anion that might be expected to undergo a 5-*exo*-*trig* cyclisation onto the nearby double bond and the resulting tertiary radical might be further reduced and then protonated to give compound **12**, the monobenzyl ether of the target compound **11**. Since such reductive cyclisations have been effected with samarium(II) iodide,[17] substrate **6** was reacted with this reagent (Scheme 3) in a mixture of THF and HMPA at 0 °C. After 15 min all of the starting material had been consumed and a mixture of the target product **12** (39%) and the previously observed alkene **9** (54%) was obtained. On the basis that this mixture of products might derive, at least in part, from disproportionation



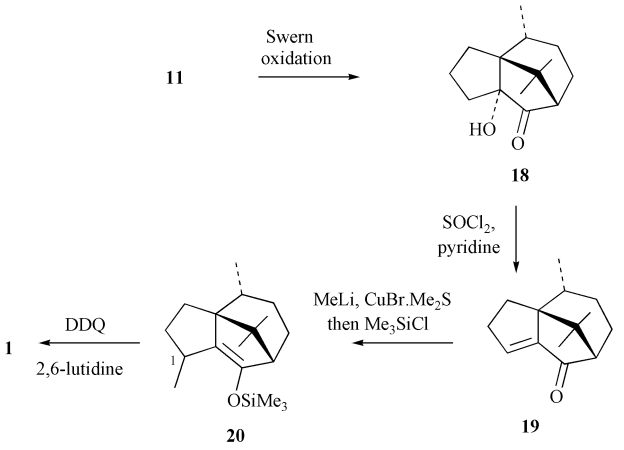
Scheme 2



Scheme 3



Scheme 4



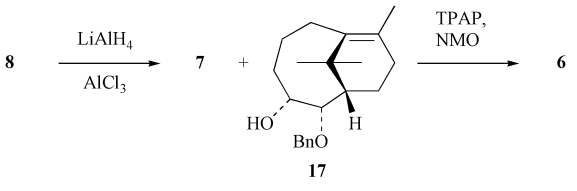
Scheme 6

of the above-mentioned tertiary radical,[18–20] it was considered that the inclusion of a hydrogen donor source in the reducing medium might afford higher yields of the reductive cyclisation product **12**. In the event, treatment of compound **6** with samarium(II) iodide under the same conditions as used before, save for the addition (or inclusion) of thiophenol (1 M),[21,22] afforded the tricyclic alcohol **12** (71% yield), the structure of which follows from its hydrogenolytic cleavage to diol **11** (95%). There was no sign of any product resulting from direct reduction (no cyclisation) of the carbonyl group within the starting ketone **6**.[23] This outcome is taken as testimony to the rapid rate at which the derived radical anion cyclises onto the proximate double bond since reaction of the model unsaturated ketone **13**[24] (Scheme 4) under the same conditions (*i.e.* SmI_2 with thiophenol present) only gives the direct reduction product **14** (87%). Interestingly, reaction of the same model ketone with SmI_2 alone gives equimolar quantities of the reductive cyclisation product **15** and its unsaturated counterpart **16** (63% combined yield). It is presumed that this mixture of products derives from disproportionation of the tertiary radical resulting from 5-*exo*-*trig* cyclisation of the initially formed radical anion.

The reductive cleavage of photochemically generated oxetane **8** was also examined as an alternate means for preparing compound **12** (Scheme 5).[15a,b] However, when substrate **8** was treated with a mixture of lithium aluminium hydride (LAH) and aluminium trichloride, the product **17** (65%), which is isomeric with the hoped-for alcohol **12**, was obtained along with small quantities (6%) of compound **7**. Treatment of the major product of this reaction with the Ley–Griffith oxidant[25] gave ketone **6** (85%) and this sequence of events is taken to imply that in the first step the oxetane **8** is isomerised to ketone **6** by the aluminium trichloride, which is, in turn, reduced to the observed alcohol by the LAH.

Completion of the first synthesis of (−)-patchoulenone

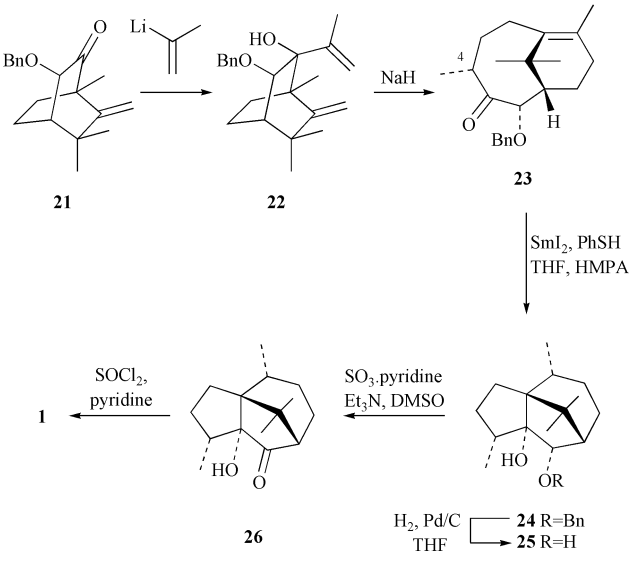
The exploitation of compound **11** in the completion of our first synthesis of (−)-patchoulenone (**1**) is shown in Scheme 6. Thus, the diol was treated with the Swern reagent and the resulting acyloin **18** (91%) subjected to dehydration with thionyl chloride in pyridine. The ensuing enone **19** (68%) was reacted with the Gilman reagent derived from methyllithium and the commercially available copper(I) bromide/dimethyl sulfide complex.[26] The enolate anion thus formed was trapped with trimethylsilyl chloride to give the silylenol ether **20**. This compound was obtained as a single diastereoisomer (at C–1) but its instability prevented determination of the configuration at the newly created stereogenic centre. Dehydrogenation of compound **20** was most conveniently effected with DDQ and 2,6-lutidine[27] and in this manner the title compound (**1**) was obtained (77% from **19**) as a white crystalline solid. The physical and spectroscopic data obtained on this material match those reported[1] for the natural product.



Scheme 5

A second and more efficient synthesis of (−)-patchoulenone

The synthesis of (−)-patchoulenone outlined above is capable of improvement to the extent that the latter steps used for installing the C–1 methyl group could be avoided by incorporating this substituent at an earlier stage in the synthesis. To these ends, the previously reported[11] ketone **21** (Scheme 7) was reacted with isopropenyllithium (generated *in situ* from 2-bromopropene and *tert*-butyllithium) and the nucleophilic addition product **22** thereby obtained in 89% yield. The illustrated stereochemistry associated with this product, which is expected on the basis of the blocking effect of the benzyloxy group within precursor **21**, follows from its ready participation in a sodium hydride promoted anionic oxy-Cope



Scheme 7

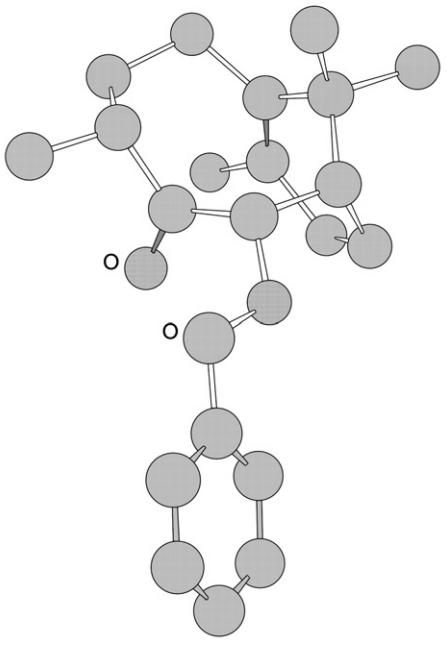


Fig. 1 CS Chem3D Pro™ drawing of compound **23** generated using data derived from an X-ray crystallographic study (hydrogen atoms omitted for clarity).

rearrangement process to give, after protic work-up, the bicyclo[5.3.1]undec-7(8)-en-3-one **23** (76% from **21**) as a white crystalline solid. The structure of the last compound was established by single-crystal X-ray analysis (Fig. 1 and Table 1), which reveals that the methyl group at C–4 is in the α-configuration and that the ketone and carbon-carbon double bond moieties are in a close spatial relationship to one another. As a consequence, and in keeping with the behaviour of its nor-analogue **6**, compound **23** readily participated in a reductive cyclisation reaction when subjected to reaction with SmI_2 in the presence of thiophenol. The product of this reaction, compound **24** (74%), was readily debenzylated with dihydrogen in the presence of palladium on carbon, to give diol **25** (97%), which was oxidised to acyloin **26** (66% at 79% conversion) with the Parikh–von Doering reagent. Dehydration of the last compound with thionyl chloride/pyridine then afforded (−)-patchoulenone (**1**) (72%), which was identical, in all respects, with the material obtained by the route described above.

Table 1 Crystallographic data for compound **23**

Formula	$C_{22}H_{30}O_2$
FW	326.48
Crystal system	monoclinic
Space group	$P2_1$ (#4)
a/Å	10.017(1)
b/Å	9.245(2)
c/Å	11.062(1)
β/°	112.073(7)
Z	2
T/°C	23
λ/Å	1.54178
μ/cm^{-1}	5.18
No. of reflections	1621
Unique reflections [$I > 3\sigma(I)$]	864
S	1.79
R	0.042
wR	0.033

Experimental

Unless otherwise specified, ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer using $CDCl_3$ as solvent. Infrared spectra were recorded on either a Perkin–Elmer 683 or 1800 FTIR instrument while mass spectral analyses were conducted on a VG Micromass 7070F double-focussing spectrometer. Melting points were recorded on a Reichert hot-stage microscope and are uncorrected. Thin layer chromatographic analyses were carried out on aluminium-backed 0.2 mm thick silica gel 60 GF_{254} plates supplied by Merck while flash chromatographic purifications were conducted according to the method of Still *et al.*[28] and using Merck silica gel 60 (230–400 mesh) as adsorbent. All solvents and common reagents were purified by established procedures.[29]

Unless otherwise specified, all reactions were carried out under an atmosphere of dry nitrogen.

Synthetic studies

(1*S*,2*S*)-8,11,11-Trimethyl-2-(phenylmethoxy)bicyclo[5.3.1]-undec-7(8)-en-3-one (6). Dienol **5**[11] (218 mg, 0.70 mmol) was added to a flask containing sodium hydride (41.8 mg, 1.74 mmol) in THF (7 mL) and the resulting mixture heated at reflux for 3 h. Upon cooling the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash chromatography (15% ethyl acetate–petroleum ether) afforded **6** as colourless oil (196 mg, 90%); $[\alpha]_D$ −96.0 (*c* 1.3, $CHCl_3$); R_f 0.37 (15% ethyl acetate–petroleum ether); λ_{max} (ε) (EtOH) 245 (2475), 205 (13 460), 201 (14 230); (CH_3CN) 237 (3125), 204 (sh, 15 620) nm; ν_{max} 1692 (s), 1639 (w), 1606 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34–7.27 (5H, m), 4.49 (1H, d, *J* 12.0 Hz), 4.26 (1H, d, *J* 12.0 Hz), 4.24 (1H, d, *J* 4.3 Hz), 2.40–2.00 (8H, m), 1.82–1.72 (3H, m), 1.44 (3H, s), 1.37 (3H, s), 1.07 (3H, s); δ_C (75 MHz, $CDCl_3$) 210.8, 138.1, 137.9, 134.5, 128.3, 127.8, 127.6, 81.2, 71.0, 56.0, 42.8, 36.3, 29.0, 27.2, 26.6, 26.5, 25.9, 20.4, 15.9; *m*/*z* 312 (M^+, 7%), 294 (24), 221 (17), 204 (34), 188 (15), 175 (22), 165 (21), 152 (29), 135 (35), 121 (23), 109 (25), 91 (100). Found (HRMS): M^+, 312.2084; $C_{21}H_{28}O_2$ requires 312.2089.

(3a*R*,7*S*,8*S*,8a*R*)-2,3,7,8-Tetrahydro-4,9,9-trimethyl-8-(phenylmethoxy)-1*H*-3a,7-methanoazulene-8a(6*H*)-ol (7). Tin(II) chloride (11.3 mg, 0.00596 mmol) was added to a magnetically stirred solution of **6** (75 mg, 0.240 mmol) in chloroform (1 mL) and the resulting mixture stirred at 18 °C for 1 h, then quenched with sodium bicarbonate solution (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried over magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Purification by flash chromatography (10% ethyl acetate–petroleum ether) afforded **7** as colourless oil (73 mg, 97%), $[\alpha]_D$ −32.0 (*c* 2.0, $CHCl_3$); Anal. found: C, 80.82; H, 8.84; $C_{21}H_{28}O_2$ requires C, 80.73; H, 9.03%; R_f 0.45 (10% ethyl acetate–petroleum ether); ν_{max} 3547 (m), 1606 (w), 1500 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.28 (5H, m), 5.41 (1H, s), 4.73 (1H, d, *J* 11.8 Hz), 4.42 (1H, d, *J* 11.8 Hz), 3.92 (1H, d, *J* 6.5 Hz), 2.99 (1H, br s), 2.46 (1H, d, *J* 15.8 Hz), 2.12–1.73 (7H, m), 1.69 (3H, s), 1.58 (1H, m), 1.01 (3H, s), 1.00 (3H, s); δ_C (75 MHz, $CDCl_3$) 140.5, 138.7, 128.2, 127.5, 127.4, 121.1, 91.5, 83.8, 72.3, 65.2, 50.4, 42.1, 39.2, 27.5, 26.7, 25.6, 25.1, 23.3, 21.7; *m*/*z* 312 (M^+, 17%), 294 (34), 221 (22), 204 (59), 189 (19), 175 (30), 147 (33), 135 (65), 121 (34), 101 (31), 91 (100). Found (HRMS): M^+ 312.2086; $C_{21}H_{28}O_2$ requires 312.2089.

Acid-catalysed formation of compounds 7, 8 and 9. A solution of **6** (7.5 mg, 0.0240 mmol) in deuterochloroform (1 mL, Cambridge Isotopes, Ag stabilised) was monitored by ^{1}H NMR spectroscopy at 0.08, 0.25, 1.5, 4.5, 8.5 and 24 h intervals. After 0.25 h ^{1}H NMR spectroscopic analysis revealed the near complete consumption of starting material and the formation of three new products, which had chemical shifts corresponding to **7**, **8** and **9** (*ca.* 5:5:1 ratio). These products were converted over 24 h into **7**. In a control experiment, a solution of **6** (7.5 mg, 0.0240 mmol) in deuterochloroform (1 mL, Cambridge Isotopes, Ag stabilised) that had been filtered through basic alumina was monitored by ^{1}H NMR spectroscopic methods and showed no change after 24 h.

Photochemical synthesis of (3a*S*,4*R*,7*S*,8*S*,8a*R*)-hexahydro-4,9,9-trimethyl-8-(phenylmethoxy)-1*H*-3a,7-methanoazulene-4,8a-oxide (8). A solution of **6** (21 mg, 0.0672 mmol) in deuteroacetonitrile (1 mL) was placed in a Rayonet reactor and irradiated at 254 nm for 0.5 h after which time no starting material was observable by ^{1}H NMR techniques. The mixture was concentrated under reduced pressure and subject to flash chromatography (8% ethyl acetate–petroleum ether) to afford **8** (10.9 mg, 52%) as a colourless oil, $[\alpha]_D$ −36.3 (*c* 0.5, $CHCl_3$); R_f 0.36 (15% ethyl acetate–petroleum ether); ν_{max} 1456, 1370, 1125 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.25 (5H, m), 4.60 (1H, d, *J* 12.2 Hz), 4.48 (1H, d, *J* 12.2 Hz), 3.93 (1H, d, *J* 5.6 Hz), 2.47–2.39 (2H, m), 2.26 (1H, m), 2.17 (1H, m), 1.96–1.52 (6H, m), 1.29 (1H, m), 1.23 (3H, s), 0.96 (3H, s), 0.82 (3H, s); δ_C (75 MHz, $CDCl_3$) 139.0, 128.2, 127.5, 127.3, 94.5, 85.4, 81.0, 71.1, 62.9, 53.6, 37.8, 36.5, 33.3, 31.9, 27.9, 23.8, 23.2, 20.9, 17.4; *m*/*z* 312 (M^+, 4%), 221 (39), 204 (50), 188 (30), 175 (17), 163 (36), 145 (46), 135 (43), 119 (24), 109 (39), 91 (100). Found (HRMS): M^+ 312.2094; $C_{21}H_{28}O_2$ requires 312.2089.

Tin(II) chloride catalysed transformation of 8 into 7. A solution of **8** (2.1 mg, 0.0067 mmol) in chloroform was treated with tin(II) chloride (cat.) and the resulting mixture stirred for 3 h at 18 °C, at which point thin layer chromatography revealed the complete conversion of **8** into **7**. Accordingly, the reaction mixture was quenched with sodium bicarbonate (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried over magnesium sulfate and concentrated under reduced pressure to give **7** as a colourless oil.

Tin(II) chloride catalysed transformation of 9 into 7. A solution of **9** (8.0 mg, 0.0256 mmol) in chloroform (1 mL) was treated with tin(II) chloride (1.2 mg, 0.0064 mmol) and the resulting mixture stirred for 48 h at 18 °C. The reaction mixture was quenched with sodium bicarbonate solution (10 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried over magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Subjection of this material to flash chromatography (10% ethyl acetate–petroleum ether) afforded **7** (7.2 mg, 90%) as a colourless oil.

(3a*R*,4*S*,7*S*,8*S*,8a*R*)-Hexahydro-4,9,9-trimethyl-1*H*-3a,7-methanoazulene-8,8a(4*H*)-diol (10) and (3a*R*,4*R*,7*S*,8*S*,8a*R*)-hexahydro-4,9,9-trimethyl-1*H*-3a,7-methanoazulene-8,8a(4*H*)-diol (11). Compound **7** (83.8 mg, 0.263 mmol) was dissolved in methanol (3.0 mL) containing 10% palladium on carbon (28.0 mg) and the resulting mixture placed in a Parr hydrogenator under a hydrogen atmosphere (60 psi) and rocked for 48 h at 18 °C. The mixture was then filtered to remove the catalyst and concentrated under reduced pressure. Subjection of the residue to column chromatography (25% ethyl acetate–petroleum ether, 2 elutions) gave **10** (12.6 mg, 21%) as a colourless oil; $[\alpha]_D$ +37.2 (*c* 0.7, $CHCl_3$); R_f 0.22 (25% ethyl acetate–petroleum ether); ν_{max} 3331 (br, s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.24 (1H, app t, *J* 5.9 Hz), 2.97 (1H, d, *J* 6.0 Hz), 2.89 (1H, s), 2.21 (1H, m), 2.10–1.60 (9H, m), 1.50 (1H, m), 1.26–1.18 (1H, m), 1.08 (3H, d, *J* 7.8 Hz), 1.08 (3H, s), 0.91 (3H, s); δ_C (75 MHz, $CDCl_3$) 88.4, 76.6, 61.6, 51.6, 46.0, 40.1, 33.8, 31.2, 28.1, 25.6, 25.2, 24.4, 21.7, 19.4; *m*/*z* 224 (M^+, 13%), 206 (46), 194 (50), 191 (40), 179 (24), 173 (27), 163 (42), 150 (45), 137 (49), 135 (43), 125 (73), 122 (61), 111 (100). Found (HRMS): M^+ 224.1772; $C_{14}H_{24}O_2$ requires 224.1776.

A second fraction afforded **11** (35.5 mg, 59%) as a colourless oil; $[\alpha]_D$ −21.4 (*c* 0.6, $CHCl_3$); R_f 0.27 (25% ethyl acetate–petroleum ether); ν_{max} 3312 (br s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.19 (1H, app t, *J* 6.4 Hz), 3.01 (1H, d, *J* 6.8 Hz), 2.44 (1H, s), 2.09–1.40 (12H, m), 1.11 (3H, d, *J* 6.8 Hz), 0.92 (6H, s); δ_C (75 MHz, $CDCl_3$) 90.0, 75.4, 61.0, 52.0, 45.6, 40.5, 34.4, 28.1, 27.9, 27.2, 26.9, 22.8, 20.8, 18.5; *m*/*z* 224 (M^+, 6%), 206 (27), 194 (20), 191 (16), 163 (14), 150 (19), 137 (18), 135 (22), 125 (100), 122 (40), 111 (80). Found (HRMS): M^+ 224.1777; $C_{14}H_{24}O_2$ requires 224.1776.

Samarium(II) iodide mediated formation of (3a*R*,7*S*,8*S*,8a*R*)-hexahydro-9,9-dimethyl-4-methylene-8-(phenyl-methoxy)-1*H*-3a,7-methanoazulene-8a(4*H*)-ol (9) and (3a*R*,4*R*,7*S*,8*S*,8a*R*)-hexahydro-4,9,9-trimethyl-8-(phenylmethoxy)-1*H*-3a,7-methanoazulene-8a(4*H*)-ol (12). A magnetically stirred solution of ketone **6** (20.0 mg, 0.0640 mmol) and hexamethylphosphoramide (0.8 mL) in THF (2.4 mL) maintained at 0 °C was treated dropwise with samarium(II) iodide (1.00 mL of a 0.1 M solution in THF, 0.100 mmol). The completion of the reaction was indicated by the appearance of a moderately persistent purple colour. The reaction mixture was then poured into water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried over magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Subjection of this material to flash chromatography (12% ether–petroleum ether, 2 elutions) gave **9** (10.8 mg, 54%) as a colourless oil; $[\alpha]_D$ +65 (*c* 0.4, $CHCl_3$); R_f 0.35 (10% ethyl acetate–petroleum ether); ν_{max} 3530 (m), 3331 (m), 1635 (s), 1606 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.31 (5H, m), 4.78 (1H, s), 4.68 (1H, m), 4.64 (2H, m), 4.05 (1H, d, *J* 6.1 Hz), 3.26 (1H, s), 2.57 (1H, m), 2.24–1.53 (10H, m), 0.96 (3H, s), 0.83 (3H, s); δ_C (75 MHz, $CDCl_3$) 151.4, 138.1, 128.4, 127.7, 127.4, 107.5, 87.4, 84.3, 72.7, 67.4, 50.3, 46.0, 40.4, 29.7, 26.8, 26.7, 24.8, 23.3, 21.6; *m*/*z* 312 (M^+, 3%), 294 (39), 221 (24), 204 (71), 203 (68), 185 (37), 175 (41), 161 (39), 147 (23), 135 (37), 133 (40), 119 (32), 105 (36), 91 (100). Found (HRMS): M^+ 312.2096; $C_{21}H_{28}O_2$ requires 312.2089.

The second fraction afforded **12** (7.8 mg, 39%), mp 53–54 °C; $[\alpha]_D$ +17.9 (*c* 0.9, $CHCl_3$); R_f 0.48 (10% ethyl acetate–petroleum ether); ν_{max} 3549 (s), 1605 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.29 (5H, m), 4.60 (2H, m), 3.95 (1H, d, *J* 5.9 Hz), 3.32 (1H, s), 2.08–1.33 (12H, m), 1.14 (3H, d, *J* 6.8 Hz), 0.93 (3H, s), 0.91 (3H, s); δ_C (75 MHz, $CDCl_3$) 138.2, 128.4, 127.7, 127.4, 89.4, 83.1, 72.6, 60.9, 50.5, 45.7, 40.6, 34.7, 28.2, 28.1, 27.1, 27.0, 22.8, 21.5, 18.4; *m*/*z* 223 ($M^+ - C_7H_7$, 100%), 205 (22) 149 (13), 135 (35), 125 (15), 121 (12), 111 (18), 109 (16), 91 (71). Found (HRMS): $M^+ - C_7H_7$ 223.1699; $C_{14}H_{23}O_2$ requires 223.1698.

Samarium(II) iodide–thiophenol mediated synthesis of (12). A magnetically stirred solution of ketone **6** (10.0 mg, 0.0320 mmol) and hexamethylphosphoramide (0.32 mL) in THF (0.96 mL) maintained at 0 °C was treated dropwise with thiophenol (0.131 mL, 1.28 mmol), followed by samarium(II) iodide (0.96 mL of a 0.1 M solution in THF, 0.096 mmol). The completion of the reaction was indicated by the appearance of a persistent purple colour. The reaction mixture

was then poured into potassium hydroxide (10 mL of a 0.5 M solution) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with potassium hydroxide (10 mL of a 0.5 M solution), then brine (1 × 10 mL), before being dried over magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Subjection of this material to flash chromatography (10% ethyl acetate–petroleum ether) gave **12** (7.1 mg, 71%) as a colourless oil. This material was identical, in all respects, with a sample of **12** obtained as described immediately above.

Hydrogenation of 12 to give 11. Ten percent palladium on carbon (2 mg) was added to a magnetically stirred solution of **12** (7.8 mg, 0.0248 mmol) in THF (1.0 mL) and the atmosphere exchanged for hydrogen. After 0.75 h the reaction mixture was filtered to remove the catalyst, concentrated under reduced pressure, then filtered through a short plug of silica (25% ethyl acetate–petroleum ether) to afford the diol **11** (5.3 mg, 95%) as a crystalline solid, identical, in all respects, with authentic material.

7-Methyloct-6-en-2-one (13). A magnetically stirred solution of 3,4-dihydro-2*H*-pyran (10 mL, 0.110 mol) in THF (100 mL) was cooled to 0 °C (ice bath) and hydrochloric acid (20 mL of a 1 M aqueous solution) was added in one portion. Stirring was continued for 4 h after which sodium hydroxide (15 mL of a 1 M aqueous solution) was added, giving pH 7 (indicator paper). The mixture was extracted with diethyl ether (3 × 50 mL), the combined organic extract washed with brine (2 × 25 mL), dried over magnesium sulfate, concentrated under reduced pressure, then filtered through a short pad of silica (25% ethyl acetate–petroleum ether) to give tetrahydro-2-hydroxy-2*H*-pyran[30] (5.77 g, 52%), bp 70 °C (10 mmHg, Kugelrohr), as a colourless oil; R_f 0.21 (25% ethyl acetate–petroleum ether); ν_{max} 3377 (br s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.89 (1H, m), 4.25 (1H, d, *J* 4.9 Hz), 4.02 (1H, m), 3.54 (1H, m), 1.86–1.77 (2H, m), 1.54–1.49 (4H, m); δ_C (75 MHz, $CDCl_3$) 94.5, 63.9, 31.9, 25.2, 20.3; *m*/*z* 102 (M^+, 35%), 101 (M^+–H, 36), 85 (62), 84 (56), 83 (39), 74 (20), 69 (14), 56 (100).

THF (86 mL) was added to a mixture of isopropyltriphenylphosphonium bromide (8.15 g, 0.0212 mol) and potassium hydride (656 mg, 0.0164 mol) and the resulting suspension was stirred at 18 °C. A solution of tetrahydro-2-hydroxy-2*H*-pyran (2.11 g, 0.0207 mol) in THF (5 mL + 5 mL washing) was added by cannula, resulting in the evolution of gas. The ensuing mixture was heated at reflux for 2 h after which time a pale pink colour developed. The cooled reaction mixture was diluted with water (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extract was washed with brine (2 × 25 mL), dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow oil. Purification by flash chromatography (25% ethyl acetate–petroleum ether) afforded 6-methylhept-5-en-1-ol[31] (2.12 g, 80%) as a colourless oil; R_f 0.36 (25% ethyl acetate–petroleum ether); ν_{max} 3330 (br s), 1673 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.12 (1H, m), 3.63 (2H, app q, *J* 6.1 Hz), 2.00 (2H, m), 1.84 (1H, t, *J* 5.2 Hz), 1.69 (3H, s), 1.60 (3H, s), 1.56 (2H, m), 1.40 (2H, m); δ_C (75 MHz, $CDCl_3$) 131.7, 124.4, 62.9, 32.4, 27.8, 26.0, 25.7, 17.7; *m*/*z* 128 (M^+, 47%), 110 (14), 95 (54), 85 (12), 82 (100), 69 (87). Found (HRMS): M^+ 128.1205; $C_8H_{16}O$ requires 128.1201.

A magnetically stirred solution of 6-methylhept-5-en-1-ol (0.379 g, 2.96 mmol) in dichloromethane (6 mL) was treated with 4-methylmorpholine *N*-oxide (1.04 g, 8.86 mmol), powdered 4 Å molecular sieves (1.50 g) and tetrapropylammonium perruthenate (52 mg, 0.148 mmol). The reaction mixture was stirred for 1 h at 18 °C, then filtered through silica (dichloromethane) and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography (10% ethyl acetate–petroleum ether) afforded 6-methylhept-5-enal[31] (0.370 g, 99%) as a colourless oil; R_f 0.44 (10% ethyl acetate–petroleum ether); ν_{max} 1727 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.76 (1H, t, *J* 1.8 Hz), 5.08 (1H, m), 2.42 (2H, td, *J* 7.3, 1.8 Hz), 2.03 (2H, q, *J* 7.3 Hz), 1.69 (3H, s), 1.67 [2H, m, (obscured)], 1.60 (3H, s); δ_C (75 MHz, $CDCl_3$) 202.9, 132.8, 123.3, 43.4, 27.3, 25.7, 22.3, 17.7; *m*/*z* (GCMS) 126 (M^+, 7%), 108 ($M^+ - H_2O$, 5), 93 ($M^+ - H_2O - CH_3$, 3), 82 (100), 69 (30), 67 (80), 55 (28).

Methylmagnesium chloride (1.81 mL of a 3 M solution in THF, 5.43 mmol) was added, dropwise, to a magnetically stirred solution of 6-methylhept-5-enal (0.229 g, 1.81 mmol) in diethyl ether (9 mL) maintained at 0 °C (ice bath) under a nitrogen atmosphere. The resulting mixture was then carefully quenched with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with brine (1 × 20 mL), dried over sodium sulfate and concentrated under reduced pressure to give a pale yellow oil. Purification by flash chromatography (25% ethyl acetate–petroleum ether) afforded 7-methyloct-6-en-2-ol[32] (**14**; 188 mg, 73%) as a colourless oil; R_f 0.38 (25% ethyl acetate–petroleum ether); ν_{max} 3355 (br s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.11 (1H, m), 3.79 (1H, m), 1.99 (2H, m), 1.69 (3H, s), 1.61 [1H, m (partially obscured)], 1.60 (3H, s), 1.50–1.32 (4H, m), 1.18 (3H, d, *J* 6.2 Hz); δ_C (75 MHz, $CDCl_3$) 131.7, 124.5, 68.1, 39.0, 28.0, 26.1, 25.8, 23.5, 17.7; *m*/*z* 142 (M^+, 27%), 109 (21), 95 (31), 82 (100), 71 (38), 69 (42), 67 (47), 55 (31). Found (HRMS): M^+ 142.1358; $C_9H_{18}O$ requires 142.1358.

A magnetically stirred solution of 7-methyloct-6-en-2-ol (153 mg, 1.07 mmol) in dichloromethane (4.3 mL) was treated with 4-methylmorpholine *N*-oxide (379 mg, 3.23 mmol), powdered 4 Åmolecular sieves (0.500 g) and tetrapropylammonium perruthenate (19 mg, 0.0541 mmol). The ensuing mixture was stirred for 4 h at 18 °C, then filtered through silica (dichloromethane) and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography (10% ethyl acetate–petroleum ether) afforded 7-methyloct-6-en-2-one (**13**;[33] 144 mg, 95%) as a colourless oil; R_f 0.63 (25% ethyl acetate–petroleum ether); ν_{max} 1717 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.08 (1H, m), 2.44 (2H, t, *J* 7.45), 2.14 (3H, s), 1.99 (2H, m), 1.69 (3H, s), 1.66–1.56 [2H, m (obscured)], 1.59 (3H, s); δ_C (75 MHz, $CDCl_3$) 209.4, 132.4, 123.7, 43.2, 29.9, 27.3, 25.7, 24.0, 17.7; *m*/*z* 140 (M^+, 13%), 82 (100), 67 (54).

Samarium(II) iodide–thiophenol mediated synthesis of (14). A magnetically stirred solution of 7-methyloct-6-en-2-one (**13**; 20 mg, 0.143 mmol) and hexamethylphosphoramide (0.32 mL) in THF (0.96 mL), maintained at 0 °C (ice bath), was treated with thiophenol (0.146 mL, 1.43 mmol), followed by the dropwise addition of samarium(II) iodide (3.8 mL of a 0.1 M solution in THF, 0.380 mmol). The completion of the reaction was indicated by the persistence of a purple colour. The reaction mixture was then poured into potassium hydroxide (10 mL of a 0.5 M aqueous solution) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), then dried with magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Purification by flash chromatography (20% ethyl acetate–petroleum ether) gave 7-methyloct-6-en-2-ol (**14**; 18 mg, 87%) as a colourless oil and identical, in all respects, with the material obtained by the method described immediately above.

(1*R,2*S**)-1-Methyl-2-isopropylcyclopentanol (15) and (1*R**,2*S**)-1-Methyl-2-(2′-propenyl)cyclopentanol (16).** Samarium(II) iodide solution (2.30 mL of a 0.1 M solution in THF, 0.230 mmol) was added, dropwise, to a magnetically stirred solution of 7-methyloct-6-en-2-one (**13**; 20.0 mg, 0.143 mmol) and hexamethylphosphoramide (0.32 mL) in THF (0.96 mL), maintained at 0 °C (ice bath) under a nitrogen atmosphere. The completion of the reaction was indicated by the persistence of a purple colour. The reaction mixture was then poured

into water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL) and concentrated under reduced pressure to give a colourless oil. Separation of the crude mixture by column chromatography (12% ethyl acetate–petroleum ether, 2 elutions) gave compound **15**[34] (6.2 mg, 31%); R_f 0.39 (20% ethyl acetate–petroleum ether); ν_{max} 3375 (br m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.93 (1H, m), 1.75–1.13 (8H, m), 1.19 (3H, s), 1.03 (3H, d, *J* 6.4 Hz), 0.89 (3H, d, *J* 6.5 Hz); δ_C (75 MHz, $CDCl_3$) 80.7, 56.4, 43.2, 29.4, 28.7, 22.4, 22.3, 22.0, 19.6; *m*/*z* (GCMS) 142 (M^+, 3%), 127 ($M^+ - Me$, 7), 124 ($M^+ - H_2O$, 10), 109 ($M^+ - H_2O - CH_3$, 42), 95 (10), 82 (100), 71 (95), 67 (29), 58 (42).

A second fraction afforded compound **16** (6.3 mg, 32%); R_f 0.36 (20% ethyl acetate–petroleum ether); ν_{max} 3374 (br s), 3082 (m), 1644 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.87 (1H, s), 4.74 (1H, s), 2.44 (1H, app t, *J* 8.9 Hz), 1.88 (1H, m), 1.81 (3H, s), 1.77–1.60 (6H, m), 1.14 (3H, s); δ_C (75 MHz, $CDCl_3$) 145.6, 111.5, 80.9, 57.3, 41.3, 28.1, 24.2, 23.0, 20.7; *m*/*z* (GCMS) 140 (M^+, 1%), 122 ($M^+ - H_2O - CH_3$, 8), 107 (5), 82 (100), 71 (25), 67 (41), 55 (23). Found (HRMS): M^+ 140.1197; $C_9H_{16}O$ requires 140.1201.

(1*S*,2*S*,3*R*)-8,11,11-Trimethyl-2-(phenylmethoxy)bicyclo-[5.3.1]undec-7-en-3-ol (17). Lithium aluminium hydride (174 μL of a 1 M solution in THF, 0.174 mmol) was added to aluminium trichloride (84 mg, 0.0630 mmol) and the ensuing mixture stirred for 15 min at 18 °C. The resulting mixture was treated with a solution of **8** (10.9 mg, 0.0349 mmol) in THF (0.25 mL + 0.25 mL washing), then heated at 70 °C for 8 h. After this time the reaction mixture was cooled to 0 °C and quenched by the dropwise addition of ethyl acetate (0.5 mL), then tartaric acid (10 mL of a 1 M aqueous solution). Stirring was continued until clear layers resulted. The mixture was then extracted with diethyl ether (3 × 10 mL), the combined organic extract washed with brine (1 × 10 mL), dried over magnesium sulfate, then concentrated under reduced pressure. Purification by flash chromatography (15% ethyl acetate–petroleum ether) afforded **17** (7.1 mg, 65%) as a colourless oil, $[\alpha]_D$ −91 (*c* 0.2 $CHCl_3$); R_f 0.43 (15% ethyl acetate–petroleum ether); ν_{max} 3538 (m), 3461 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.24 (5H, m), 4.54 (2H, m), 4.19 (1H, app t, *J* 10.4 Hz), 3.42 (1H, dd, *J* 5.0, 1.8 Hz), 2.41–2.28 (3H, m), 2.19–1.98 (4H, m), 1.89–1.80 (2H, m), 1.76 (3H, s), 1.63 (1H, m), 1.51 (1H, m), 1.43 (1H, d, exch), 1.16 (3H, s), 1.08 (3H, s); δ_C (75 MHz, $CDCl_3$) 142.0, 139.0, 128.2, 128.1, 128.0, 127.6, 127.4, 84.3, 72.0, 70.9, 49.0, 36.5, 31.2, 28.5, 28.0, 25.4, 22.7, 20.7, 17.1; *m*/*z* 314 (M^+, 8%), 223 (13), 205 (20), 188 (16), 173 (25), 163 (19), 145 (47), 133 (23), 123 (25), 107 (36), 91 (100). Found (HRMS): M^+ 314.2246; $C_{21}H_{30}O_2$ requires 314.2246.

Oxidation of alcohol 17 to ketone 6. A magnetically stirred solution of **17** (7.0 mg, 0.0223 mmol) in dichloromethane (0.5 mL) was treated with 4-methylmorpholine *N*-oxide (7.9 mg, 0.0674 mmol) and powdered 4 Å molecular sieves (20 mg), followed by tetrapropylammonium perruthenate (0.8 mg, 0.0020 mmol). The resulting mixture was stirred for 4 h at 18 °C and then filtered through silica (dichloromethane washing) and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography (10% ethyl acetate–petroleum ether) afforded **6** (5.9 mg, 85%) as a colourless oil that was identical, in all respects, with authentic material.

(3a*R*,4*R*,7*S*,8a*R*)-Hexahydro-8a-hydroxy-4,9,9-trimethyl-1*H*-3a,7-methanoazulene-8(4*H*)-one (18). A magnetically stirred solution of dimethyl sulfoxide (66 μL, 0.932 mmol) in dichloromethane (1 mL) maintained at −78 °C was treated with oxalyl chloride (49 μL, 0.559 mmol) and the resulting mixture stirred at −78 °C for 0.5 h. A solution of diol **11** (41.8 mg, 0.186 mmol) in dichloromethane (0.5 mL + 0.5 mL washing) was then added by cannula and the resulting mixture stirred at −78 °C for 0.5 h. Triethylamine (156 μL, 1.12 mmol) was added and the mixture stirred at −78 °C for 10 min, then allowed to warm to 18 °C over 20 min. The reaction mixture was then poured into water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried with magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Subjection of this material to flash chromatography (10% ethyl acetate–petroleum ether) gave **18** (37.9 mg, 91%) as a colourless oil; $[\alpha]_D$ −0.19 (*c* 1.0, $CHCl_3$); R_f 0.23 (10% ethyl acetate–petroleum ether); ν_{max} 3456 (br s), 1736 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.25 (1H, m), 2.26–1.55 (12H, m), 1.14 (3H, d, *J* 7.0 Hz), 1.04 (3H, s), 0.95 (3H, s); δ_C (75 MHz, $CDCl_3$) 225.0, 91.5, 60.8, 59.2, 42.2, 38.7, 33.4, 28.7, 27.5, 27.2, 26.3, 25.3, 20.6, 18.1; *m*/*z* 222 (M^+, 0.5%), 194 (48), 179 (24), 161 (11), 151 (15), 137 (31), 125 (53), 124 (51), 111 (100). Found (HRMS): M^+ 222.1619; $C_{14}H_{22}O_2$ requires 222.1620.

(3a*R*,4*R*,7*S*)-2,3,5,6,7,8-Hexahydro-4,9,9-trimethyl-4*H*-3a,7-methanoazulene-8-one (19). Thionyl chloride (337 μL, 4.61 mmol) was added to a magnetically stirred solution of **18** (20.7 mg, 0.0931 mmol) in pyridine (920 μL). The resulting mixture was heated to 40 °C for 1 h, then poured onto ice (10 g) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried with magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Subjection of this material to flash chromatography (10% ethyl acetate–petroleum ether) gave **19** (13.0 mg, 68%) as a colourless oil; $[\alpha]_D$ −150 (*c* 0.5, $CHCl_3$); R_f 0.37 (10% ethyl acetate–petroleum ether); ν_{max} 1705 (s), 1639 (m) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.49 (1H, dd, *J* 3.6, 2.1 Hz), 2.78–2.55 (2H, m), 2.22 (1H, m), 2.11 (1H, app t, *J* 3.5 Hz), 2.04–1.88 (2H, m), 1.79–1.72 (2H, m), 1.59 (1H, m), 1.14 (1H, m), 1.05 (3H, s), 0.89 (3H, s), 0.86 (3H, d, *J* 6.5 Hz); δ_C (75 MHz, $CDCl_3$) 206.8, 148.4, 132.7, 63.1, 62.8, 40.9, 37.8, 34.8, 28.0, 27.3, 26.5, 26.2, 18.9, 17.7; *m*/*z* 204 (M^+, 100%), 189 (17), 161 (48), 149 (38), 133 (49), 122 (30), 105 (30), 91 (52). Found (HRMS): M^+ 204.1512; $C_{14}H_{20}O$ requires 204.1514.

(−)-Patchoulenone (1). A magnetically stirred suspension of copper(I) bromide/dimethyl sulfide complex (0.0503 mg, 0.245 mmol) in THF (1 mL) was cooled to −78 °C then treated with methyllithium (445 μL of a 1.10 M solution in diethyl ether, 0.489 mmol). The initially yellow solution faded to colourless within 5 min, after which it was warmed to −40 °C for 0.5 h. The solution was then re-cooled to −78 °C and hexamethylphosphoramide (85 μL, 0.489 mmol) was added, followed by **19** (10 mg, 0.0489 mmol) in THF (0.5 mL + 0.5 mL washing), giving a bright yellow solution that was immediately treated with trimethylsilyl chloride (62 μL, 0.489 mmol), resulting in rapid decolourisation. The reaction mixture was stirred for 0.5 h at −78 °C, then quenched at this temperature with pH 7.4 buffer (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried with magnesium sulfate and concentrated under reduced pressure to give enol ether **20** as a clear, colourless oil. This material was dissolved in dichloromethane (2 mL) and 2,6-lutidine (37 μL, 0.318 mmol) was added, followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (44.4 mg, 0.196 mmol). After 5 min the reaction mixture was poured into sodium bicarbonate (10 mL of a saturated aqueous solution) and extracted with dichloromethane (2 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried with magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Purification by flash chromatography (10% ethyl acetate–petroleum ether) afforded

(−)-patchoulenone (**1**) as colourless crystals (8.2 mg, 77%), mp 50–51 °C (lit.[1] 52.5 °C); $[\alpha]_D$ −101 (*c* 0.4, $CHCl_3$) [lit.[1] −97.1 (*c* 8.0)]; R_f 0.36 (10% ethyl acetate–petroleum ether); ν_{max} 1710 (s), 1660 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.83 (1H, m), 2.49 (1H, dd, *J* 18.2, 10.2 Hz), 2.23 (1H, m), 2.12 (3H, s), 2.11 (1H, m, partially obscured), 2.05–1.88 (2H, m), 1.82–1.57 (3H, m), 1.21 (1H, m), 1.67 (3H, s), 0.94 (3H, s), 0.89 (3H, d, *J* 6.5 Hz); δ_C (75 MHz, $CDCl_3$) 207.4, 148.6, 139.6, 63.6, 63.0, 43.4, 41.4, 34.6, 28.0, 26.4, 26.2, 25.9, 19.0, 17.9, 15.2; *m*/*z* 218 (M^+, 100), 203 (43), 189 (14), 175 (78), 161 (40), 147 (50), 133 (29), 105 (30), 91 (31). Found (HRMS): M^+ 218.1670; $C_{15}H_{22}O$ requires 218.1671.

(1*S*,2*S*,4*R*)-4,8,11,11-Tetramethyl-2-(phenylmethoxy)-bicyclo[5.3.1]undec-7(8)-en-3-one (23). A flask containing 2-bromopropene (0.458 mL, 5.16 mmol) in diethyl ether (10 mL), maintained at −78 °C under a nitrogen atmosphere, was charged with *tert*-butyllithium (6.07 mL of a 1.7 M solution in pentane, 0.0103 mol) and the resulting mixture stirred at −78 °C for 15 min. Ketone **21** (294 mg, 1.03 mmol) in diethyl ether (1.0 mL + 1.0 mL washing) was then added by cannula and the reaction mixture was stirred for 5 min at −78 °C before being warmed to 18 °C, then quenched with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with brine (1 × 20 mL), dried with magnesium sulfate and concentrated under reduced pressure. Subjection of the residue to flash chromatography (10% ethyl acetate–petroleum ether) afforded **22** (0.299 g, 89%) as a colourless oil. This material was immediately dissolved in THF (5.0 mL + 4.0 mL washing) and the resulting solution was added to a flask containing sodium hydride (41.8 mg, 1.74 mmol). The ensuing mixture was heated at reflux for 3 h, then cooled, quenched with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extract was washed with brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure. Subjection of the residue to flash chromatography (10% ethyl acetate–petroleum ether) afforded **23** [257 mg, 86% (76% from **21**)] as a colourless oil, mp 100–102 °C; $[\alpha]_D$ −60 (*c* 1.0, $CHCl_3$); R_f 0.36 (10% ethyl acetate–petroleum ether); λ_{max} (ε) (EtOH) 252 (2108), 207 (11 468); (CH_3CN) 248 (2650), 204 (sh, 16 151); (hexane) 244 (2748), 196 (18 655) nm; ν_{max} 1691 (s), 1609 (w), 1585 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33–7.24 (5H, m), 4.48 (1H, d, *J* 12.0 Hz), 4.26 (1H, d, *J* 5.4 Hz), 4.18 (1H, d, *J* 12.0 Hz), 2.70 (1H, m), 2.40–2.27 (3H, m), 2.21–1.95 (3H, m), 1.91–1.70 (2H, m), 1.54 (1H, m), 1.44 (3H, s), 1.42 (3H, s), 1.07 (3H, s), 0.92 (3H, d, *J* 6.7 Hz); δ_C (75 MHz, $CDCl_3$) 216.2, 138.3, 136.1, 135.0, 128.3, 127.5, 84.5, 71.0, 55.9, 45.0, 36.3, 36.2, 29.9, 28.3, 27.3, 25.4, 20.5, 18.2, 15.7 (one signal overlapping or obscured); *m*/*z* 326 (M^+, 11%), 308 (15), 235 (18), 218 (76), 189 (18), 165 (30), 149 (48), 137 (43), 123 (17), 109 (31), 91 (100). Found (HRMS): M^+ 326.2246; $C_{22}H_{30}O_2$ requires 326.2246.

(1*R*,3a*R*,4*R*,7*S*,8*S*,8a*R*)-Hexahydro-1,4,9,9-tetramethyl-8-(phenylmethoxy)-1*H*-3a,7-methanoazulene-8a(4*H*)-ol (24). A magnetically stirred solution of **23** (50 mg, 0.153 mmol) and hexamethylphosphoramide (0.68 mL) in THF (2.06 mL), maintained at 0 °C, was treated with thiophenol (0.314 mL, 3.06 mmol) and then, dropwise, samarium(II) iodide (3.8 mL of a 0.1 M solution in THF, 0.380 mmol). The completion of the reaction was indicated by the persistence of a purple colour. The reaction mixture was then poured into potassium hydroxide (1 × 10 mL of a 0.5 M solution) and extracted with diethyl ether (3 × 10 mL). The combined organic extract was washed with potassium hydroxide (10 mL of a 0.5 M solution) and brine (1 × 10 mL), then dried with magnesium sulfate and concentrated under reduced pressure to give a colourless oil. Subjection of this material to flash chromatography (10% diethyl ether–petroleum ether) gave **24** (37 mg, 74%) as a colourless oil; $[\alpha]_D$ +21.2 (*c* 2.1, $CHCl_3$); R_f 0.47 (5% diethyl ether–petroleum ether); ν_{max} 3530 (s), 1606 (w) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.29 (5H, m), 4.63–4.54 (2H, m), 3.85 (1H, d, *J* 5.9 Hz), 2.96 (1H, s), 2.09–2.06 (2H, m), 1.87–1.48 (8H, m), 1.33 (1H, m), 1.13 (3H, d, *J* 6.6 Hz), 0.94 (3H, s), 0.93 (3H, s), 0.89 (3H, d, *J* 6.4 Hz); δ_C (75 MHz, $CDCl_3$) 138.2, 128.4, 127.7, 127.5, 88.9, 81.7, 72.3, 60.9, 50.3, 46.2, 40.6, 35.5, 35.4, 28.5, 28.1, 25.8, 23.3, 21.6, 18.5, 12.6; *m*/*z* 328 (M^+, 0.4%), 237 (94), 219 (31), 207 (20), 201 (11), 177 (10), 163 (25), 149 (52), 139 (29), 125 (31), 123 (25), 121 (25), 109 (31), 91 (100). Found (HRMS): M^+ 328.2401; $C_{22}H_{32}O_2$ requires 328.2402.

(1*R*,3a*R*,4*R*,7*S*,8*S*,8a*R*)-Hexahydro-1,4,9,9-tetramethyl-1*H*-3a,7-methanoazulene-8,8a(4*H*)-diol (25). A magnetically stirred solution of **24** (35.2 mg, 0.107 mmol) in THF (2.0 mL) was treated with 10% palladium on carbon (11 mg) and the atmosphere was exchanged for hydrogen. After 3 h at 18 °C the reaction mixture was filtered to remove the catalyst, concentrated under reduced pressure and the residue filtered through a short plug of silica (15% ethyl acetate–petroleum ether) to afford **25** (24.8 mg, 97%) as a crystalline solid, mp 168–169 °C (sealed tube); $[\alpha]_D$ −17.8 (*c* 0.5, $CHCl_3$); R_f 0.38 (15% ethyl acetate–petroleum ether); ν_{max} 3349 (br s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.13 (1H, dd, *J* 7.3, 6.0 Hz), 2.43 (1H, d, *J* 7.4 Hz), 2.18 (1H, s), 2.07–1.39 (11H, m), 1.11 (3H, d, *J* 6.8 Hz), 0.97 (3H, s), 0.92 (3H, s), 0.92 (3H, d, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 89.1, 74.4, 60.9, 52.3, 46.0, 40.5, 35.4, 35.2, 28.3, 28.0, 25.8, 23.2, 20.7, 18.6, 12.3; *m*/*z* 238 (M^+, 25%), 220 (27), 208 (19), 180 (15), 152 (39), 139 (100), 125 (55), 122 (30), 107 (18). Found (HRMS): M^+ 238.1937; $C_{15}H_{26}O_2$ requires 238.1933.

(1*R*,3a*R*,4*R*,7*S*,8a*R*)-Hexahydro-8a-hydroxy-1,4,9,9-tetramethyl-1*H*-3a,7-methanoazulene-8(4*H*)-one (26). A flask containing sulfur trioxide/pyridine complex (63.7 mg, 0.0667 mmol) was charged with dichloromethane (0.75 mL), then dimethyl sulfoxide (0.25 mL) and triethylamine (0.130 mL, 0.933 mmol). The resulting solution was added, by cannula, to a flask containing **25** (15.9 mg, 0.0667 mmol) and the ensuing mixture stirred at 18 °C for 24 h, then at 35 °C for 24 h and then diluted with water (10 mL) and extracted with hexane (3 × 10 mL). The combined organic extract was washed with brine (1 × 10 mL), dried with magnesium sulfate and concentrated under reduced pressure to afford a light yellow oil. Subjection of this material to flash chromatography (10% ethyl acetate–petroleum ether) afforded **25** (3.4 mg, 21% recovery) and ketone **26** (8.3 mg, 66% at 79% conversion) as colourless crystals, mp 107–108 °C (sealed tube); $[\alpha]_D$ +11.2 (*c* 0.6, $CHCl_3$); R_f 0.53 (15% ethyl acetate–petroleum ether); ν_{max} 3522 (s), 3434 (s), 1728 (s) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.29–2.17 (3H, m), 1.99–1.55 (9H, m), 1.12 (3H, d, *J* 6.7 Hz), 1.03–1.01 (9H, m); δ_C (75 MHz, $CDCl_3$) 224.9, 89.9, 60.9, 59.8, 43.2, 38.9, 35.1, 34.2, 29.7, 27.6, 26.3, 25.3, 21.1, 18.0, 13.1; *m*/*z* 236 (M^+, 0.7%), 208 (78), 193 (22), 165 (11), 151 (37), 139 (63), 138 (60), 125 (100), 110 (48). Found (HRMS): M^+ 236.1773; $C_{15}H_{24}O_2$ requires 236.1776.

(−)-Patchoulenone (1). A magnetically stirred solution of **26** (8.3 mg, 0.0351 mmol) in pyridine (0.426 mL) was treated with thionyl chloride (0.128 mL, 1.75 mmol). The resulting solution warmed to 40 °C and stirred at this temperature for 22 h. The ensuing mixture was cooled to 18 °C, diluted with diethyl ether (10 mL), then poured into water (10 mL). The aqueous phase was separated and re-extracted with ether (2 × 10 mL). The combined organic extract was washed with brine (1 × 10

mL), dried with magnesium sulfate and concentrated under reduced pressure to afford a light yellow oil. Subjection of this material to flash chromatography (8% ethyl acetate–petroleum ether) afforded (−)-patchoulenone (**1**; 5.5 mg, 72%) as colourless crystals. This material was identical, in all respects, with the sample obtained as described earlier.

Crystal data and refinement details for compound 23

Crystallographic data for the title compound are given in Table 1. Intensity data were collected on a Rigaku AFC6R diffractometer using the $\omega - 2\theta$ scan technique to a maximum 2θ value of 120°. Scans of $(1.20 + 0.30\ \tan\theta)°$ were made at a speed of 16° min^{-1} (in omega). The weak reflections [$I < 10.0\sigma(I)$] were rescanned (maximum of four scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1.

Three representative reflections were measured after every 150 reflections, which revealed that no decay correction was required. An empirical absorption correction based on azimuthal scans was applied, which resulted in transmission factors ranging from 0.94 to 1.00. The data were corrected for Lorentz and polarisation effects.

The structure was solved by direct methods[35] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at geometrically determined positions, which were periodically recalculated but were not refined. The final cycle of full-matrix least-squares refinement was based on 864 observed reflections [$I > 3.00\sigma(I)$] and 217 variable parameters. The maximum and minimum peaks on the final difference Fourier map correspond to 0.13 and −0.11 *e* $Å^{-3}$, respectively. All calculations were performed using the teXsan[36] crystallographic software package of Molecular Structure Corporation.

CCDC reference number 188927. See http://www.rsc.org/suppdata/nj/b2/b206372g/ for crystallographic files in CIF or other electronic format.

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