Cascade radical cyclisations leading to polycyclic diterpenes. Total synthesis of (±)-spongian-16-one

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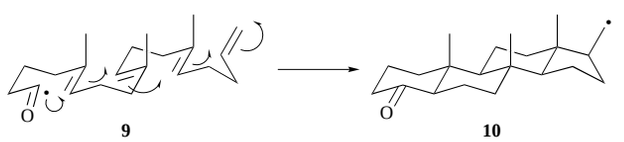
A cascade of three consecutive 6-*endo*-*trig* radical cyclisations from the polyene acyl radical intermediate 12 derived from the selenoate 11 is used to construct the *trans*,*anti*,*trans*,*anti*,*cis*-tetracyclic keto lactone 20 in one step. Manipulation of the ketone function in 20 to the corresponding *gem*-dimethyl substituted carbon then completed a concise synthesis of the marine metabolite spongian-16-one 1.

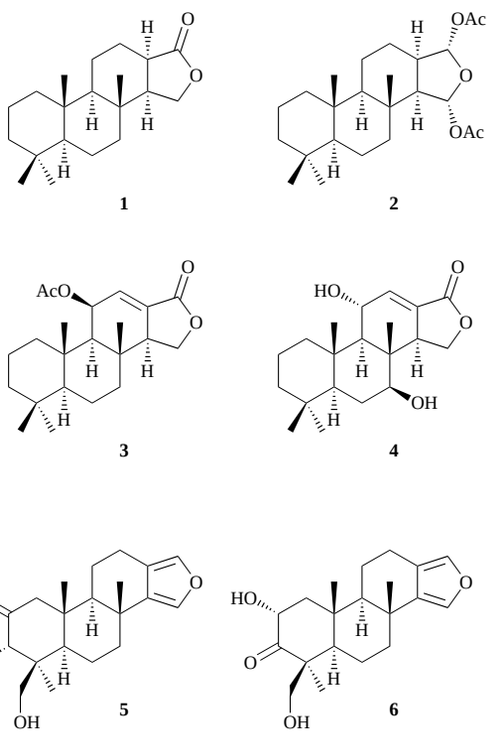
A wide variety of oxygenated tetracyclic diterpenes have been isolated from the marine sponge order Dictyoceratida, and several of these metabolites show antimicrobial activity, whilst others have been found to exhibit activity against *Herpes simplex* virus, type 1, and P388 murine leukemia cells. Representative members of this family of diterpenes include: spongian-16-one **1** and spongiandiyl acetate **2**[1] isolated from *Dictyodendrilla cavernosa*[2] and *Chelonaplysilla violacea*[3] found off the coasts of Australia and New Zealand; the spongianenones **3** and **4** produced by the Canary Island sponge *Spongia officinalis*;[4] and the furanoditerpenes spongiadiol **5** and isospongiadiol **6** isolated from the deep water Caribbean sponge *Spongia linnaeus*.[5]

In spite of their interesting biological properties, until quite recently very few synthetic studies amongst this class of compound had been described.[6,7] In a similar manner to the way nature elaborates the steroid ring system, *via* enzyme-mediated electrophilic cyclisation of squalene oxide, the carbocyclic backbones in the metabolites **1**–**6** are produced in nature *via* electrophilic cyclisation of a preorganised geranylgeraniol substrate, as indicated in **7**→**8** (Scheme 1). In several earlier publications[8] we have developed the idea of elaborating linear and angular six-membered fused carbocycles from polyene acyl *radical* precursors *via* consecutive 6-*endo*-*trig* modes of cyclisation, *viz* **9**→**10** (Scheme 2).[7] We have also applied this strategy in the synthesis of several steroidal ring systems, including azasteroids,[9] and applied it in a concise total synthesis of (±)-spongian-16-one **1**.[10] This paper describes the full details of this total synthesis.



9 **10**

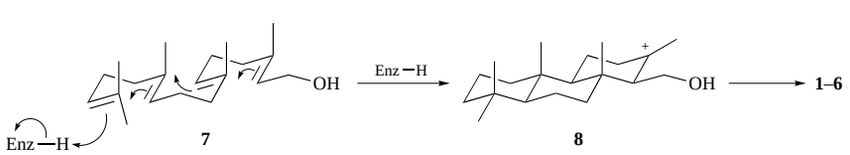
Scheme 2



1 **2** **3** **4** **5** **6**

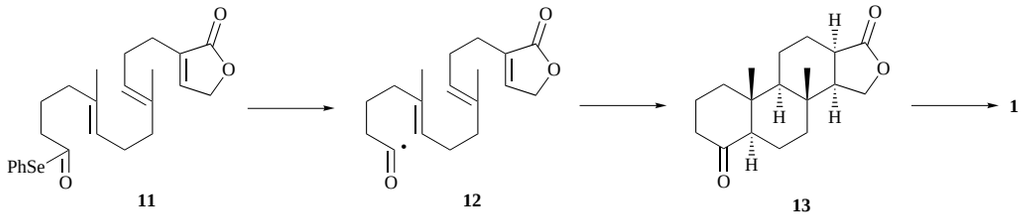
The overall strategy we followed for the total synthesis of spongian-16-one **1** is shown in Scheme 3 and was based on elaboration of the butenolide substituted polyene selenoate **11**, followed by serial 6-*endo*-*trig* radical cyclisation from the intermediate acyl radical **12** and manipulation of the ketone functionality in the product **13**. At the outset of our synthetic work, although we were confident that the cascade cyclisation **12**→**13** would produce the required *trans*,*anti*,*trans*,*anti*-stereochemistry for the A,B,C-ring system in the tetracyclic ketone **13**, we were less sure of the outcome of the ring C/D stereochemistry in this product; we argued however that this particular cyclisation would most likely lead ultimately to the thermodynamically more stable (natural) *cis*-C/D ring junction stereochemistry.

The butenolide substituted polyene selenoate **11** was prepared from the known (*E*)-bromo alcohol[11] **14a** as shown in Scheme 4. Thus, protection of the bromo alcohol as its tetrahydropyranyl ether **14b** followed by lithiation and reaction with cyclopropyl methyl ketone,[12] first led to the substituted cyclopropylmethanol **15** in 80% yield. Treatment of **15** with 48% HBr at −20 °C, according to the procedure of Julia *et al.*,[13] resulted in ring-opening of the cyclopropane and formation of

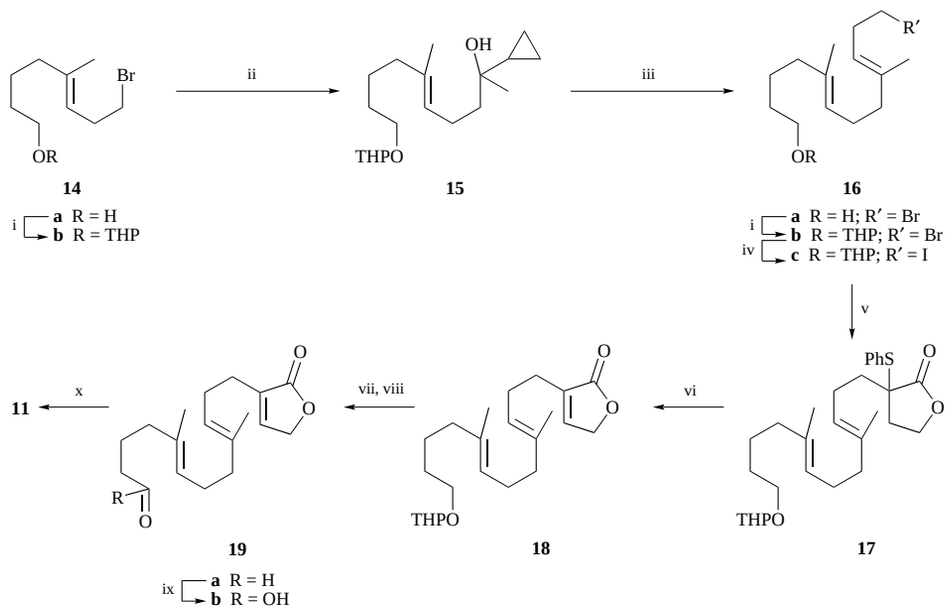


7 **8**

Scheme 1



Scheme 3



Scheme 4 *Reagents*: i, DHP, PPTS, 25 °C (95%); ii, Li, THF, 0 °C, methyl cyclopropyl ketone (80%); iii, 48% HBr, −20 °C (86%); iv, NaI, Me_2CO, 25 °C (89%); v, 2-phenylthiobutyrolactone, LDA, HMPA, −78 °C (71%); vi, MCPBA, −78 °C to 0 °C, then Δ, C_6H_5Me, $CaCO_3$ (~80%); vii, PPTS, EtOH, 55 °C (94%); viii, Dess–Martin periodinane (89%); ix, NaH_2PO_4, Bu′OH, H_2O, $NaClO_2$, 2-methylbut-2-ene (82%); x, *N*-phenylselenophthalimide, Bu_3P, −30 °C (86%)

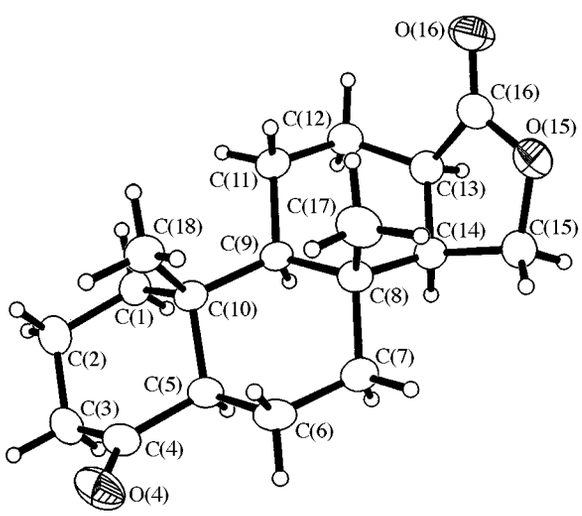


Fig. 1 X-Ray structure of tetracyclic keto lactone **20**

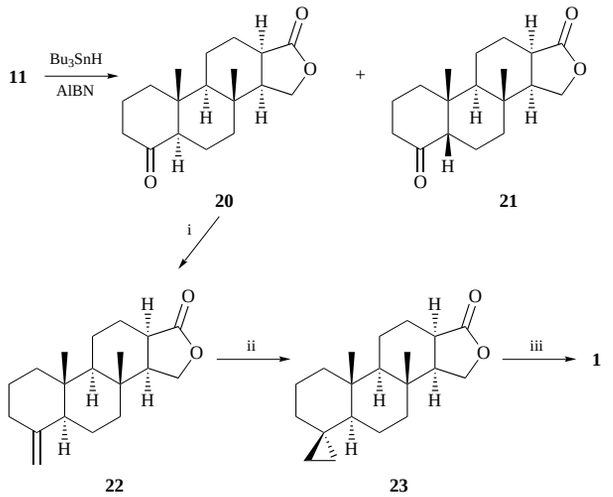
the (*E*)-homoallylic bromide **16b** accompanied by smaller amounts of the deprotected bromide **16a**, which could be reprotected leading to **16b** in an overall 80% yield. The (*E*)-homoallylic bromide **16b** was next converted into the corresponding iodide **16c**, under Finkelstein conditions, which was then used to alkylate the lithium enolate derived from 2-phenylthiobutyrolactone[14] leading to the substituted butyrolactone **17**. Oxidation of **17** with *m*-chloroperbenzoic acid led to the corresponding sulfoxide which readily eliminated the elements of phenylsulfinic acid on heating in toluene for 3 h,[15] producing the butenolide **18** in 61% yield. Deprotection of **18**, followed by sequential oxidation of the resulting alcohol using Dess–Martin periodinane and sodium chlorite next led to the carboxylic acid **19b**, which was finally converted into the selenoate **11** in 86% yield using *N*-phenylselenophthalimide–tributylphosphine.[16]

When a solution of the selenoate **11** in dry degassed benzene was heated to reflux and treated dropwise over 8 h with a solution of Bu_3SnH and AIBN in benzene,[8] work-up and chromatography gave the tetracyclic keto lactone **20** as colourless needles, mp 178–180 °C, in 53% yield. The *trans*,*anti*,*trans*,*anti*,*cis*-stereochemistry assigned to this tetracycle resulting from the cascade of three consecutive 6-*endo*-*trig* radical cyclisations from the acyl radical intermediate **12** followed from analysis of its ^{13}C NMR spectroscopic data and comparison of these data with those of previously produced polycycles from our earlier work.[8] The geometry was also confirmed by X-ray crystallographic analysis (Fig. 1). A small amount of a minor diastereoisomer of the structure **20** was separated by chromatography and the spectroscopic data for this compound support the *cis*,*anti*,*trans*,*anti*,*cis*-stereochemistry shown in **21**;† it is possible that this isomer is produced as a result of specific epimerisation of the C5 centre in **20**, either during the reaction or during chromatographic purification rather than during the cascade radical cyclisation.

With the complete tetracyclic core **20** of spongian-16-one now available, with the correct *trans*,*anti*,*trans*,*anti*,*cis*-stereochemistry, all that was needed to complete the total synthesis of

† This stereochemistry follows from inspection and comparison of NMR data with model compounds prepared during these studies and in earlier work.[8]

(±)-**1** was to manipulate the ring A ketone function in **20** to the corresponding *gem*-dimethyl substituted carbon. This conversion was readily accomplished following methylenation of **20** using Lombardo's conditions,[17] leading to **22**, then Simmons–Smith cyclopropanation of **22** to the corresponding cyclopropane **23**, and finally hydrogenolysis[18] of **23** (Scheme 5). The



Scheme 5 *Reagents*: i, Zn, $TiCl_4$, CH_2Br_2, 0 °C (79%); ii, CH_2I_2, Zn(Cu), Et_2O (95%); iii, PtO_2, H_2, HOAc, 25 °C (80%)

synthetic (±)-spongianone was obtained as colourless crystals, and had ^{1}H and ^{13}C NMR spectroscopic data which were superimposable on those recorded for the natural product isolated from *D. cavernosa*.[2,19]

Experimental

For general experimental details, see ref. 8.

(*E*)-2-[(8-Bromo-5-methyloct-5-enyl)oxy]tetrahydro-2*H*-pyran 14b

A solution of 8-bromo-5-methyloct-5-en-1-ol[11] (2.60 g, 11.8 mmol), dihydropyran (1.61 cm^3, 1.48 g, 17.6 mmol) and pyridinium toluene-*p*-sulfonate (297 mg, 1.18 mmol) in dichloromethane (35 cm^3) was stirred at room temperature for 4 h. The solution was diluted with diethyl ether (150 cm^3) and then washed with 1:1 saturated brine–water (50 cm^3). The organic phase was dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (1:19) as eluent gave the *tetrahydropyran* (3.4 g, 95%) as a colourless oil; ν_{max}(film)/cm^{-1} 1654; δ_H(270 MHz, $CDCl_3$) 5.16–5.10 (1H, m, −CH=), 4.57 (1H, br s, CH_2CHO_2), 3.89–3.82 (1H, m), 3.77–3.69 (1H, m), 3.51–3.29 (4H, m), 2.60–2.52 (2H, m), 2.08–1.99 (2H, m), 1.84–1.53 (10H, m) and 1.70 (3H, s, Me); δ_C(67.8 MHz, $CDCl_3$) 138.5 (s), 120.9 (d), 98.8 (d), 67.4 (t), 62.3 (t), 39.3 (t), 32.8 (t), 31.6 (t), 30.7 (t), 29.2 (t), 25.4 (t), 24.3 (t), 19.6 (t) and 16.0 (q); *m*/*z* (EI) 202.0354 (M^+ − THPOH, $C_9H_{15}Br$ requires 202.0357).

(*E*)-2-[(9-Cyclopropyl-9-hydroxy-5-methyldec-5-enyl)oxy]tetrahydro-2*H*-pyran 15

One third of a solution of the bromide **14b** (3.38 g, 11.1 mmol) and methyl cyclopropyl ketone[12] (3.30 cm^3, 2.79 g, 33.2 mmol) in THF (13 cm^3) was added to lithium wire (1 mm) (461 mg, 66.4 mmol) under THF (57 cm^3) in an atmosphere of argon at 0 °C. The remainder of the solution was added over 25 min and the mixture was then stirred at 0 °C for 4 h. Excess lithium was removed with tweezers and the reaction was then diluted with diethyl ether (150 cm^3). The mixture was washed with saturated aqueous ammonium chloride (75 cm^3) and saturated aqueous sodium hydrogen carbonate (75 cm^3), and then each of the separated aqueous phases was extracted with diethyl ether (100 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:4) as eluent gave the alcohol (2.8 g, 80%) as a colourless oil; ν_{max}(film)/cm^{-1} 3454 and 1654; δ_H(250 MHz, $CDCl_3$) 5.16 (1H, br t, *J* ~6.7 Hz, −CH=), 4.57 (1H, br s, CH_2CHO_2), 3.91–3.83 (1H, m), 3.76–3.72 (1H, m), 3.53–3.43 (1H, m), 3.41–3.35 (1H, m), 2.16–1.98 (4H, m), 1.73–1.48 (12H, m), 1.59 (3H, s, Me), 1.12 (3H, s, Me), 0.91 (1H, d, *J* 6.4 Hz) and 0.39–0.32 (4H, m, 2 × $-CH_2$); δ_C(67.8 MHz, $CDCl_3$) 135.1 (s), 124.6 (d), 98.7 (d), 71.0 (s), 67.5, 62.2, 42.9, 39.3, 30.7, 29.2, 25.8, 25.4, 24.4, 22.6, 20.9, 19.6, 15.8, 0.5 (t) and 0.4 (t); *m*/*z* (EI) 208.1822 (M^+ − THPOH, $C_{14}H_{24}O$ requires 208.1827).

(*E*,*E*)-2-[(12-Bromo-5,9-dimethyldodeca-5,9-dienyl)oxy]tetrahydro-2*H*-pyran 16b

The alcohol **15** (2.75 g, 8.86 mmol) was added dropwise over 5 min to vigorously stirred 48% HBr (5 cm^3) at −20 °C.[13] The mixture was stirred for a further 1 h at this temperature and then diluted with diethyl ether (100 cm^3) and water (50 cm^3). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (50 cm^3) and brine (50 cm^3), and then both of the separated aqueous phases were extracted with diethyl ether (2 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (1:9 to 1:4) as eluent gave (i) the tetrahydropyran homoallylic *bromide* (eluted first) (2.0 g, 59%) as a colourless oil (Found: C, 61.4; H, 9.1. $C_{19}H_{33}BrO_2$ requires C, 61.1; H, 8.9%); ν_{max}(film)/cm^{-1} 1661; δ_H(250 MHz, $CDCl_3$) 5.15–5.10 (2H, m, 2 × −CH=), 4.57 (1H, br s, CH_2CHO_2), 3.87–3.82 (1H, m), 3.75–3.71 (1H, m), 3.51–3.46 (1H, m), 3.40–3.29 (3H, m), 2.61–2.55 (2H, m), 2.10–1.97 (4H, m), 1.84–1.45 (12H, m), 1.62 (3H, s, Me) and 1.58 (3H, s, Me); δ_C(67.8 MHz, $CDCl_3$) 138.5 (s), 135.1 (s), 124.0 (d), 120.8 (d), 98.8 (d), 67.5 (t), 62.3 (t), 39.6 (t), 39.4 (t), 32.8 (t), 31.7 (t), 30.7 (t), 29.2 (t), 26.3 (t), 25.5 (t), 24.5 (t), 19.7 (t), 16.2 (q) and 15.8 (q); and (ii) the *alcohol* **16a** (eluted second) (688 mg, 27%) as a colourless oil; ν_{max}(film)/cm^{-1} 3356 and 1653; δ_H(250 MHz, $CDCl_3$) 5.16–5.10 (2H, m, 2 × −CH=), 3.89–3.82 (2H, m, CH_2OH), 3.37–3.30 (2H, m, CH_2Br), 2.61–2.53 (2H, m), 2.11–2.00 (6H, m), 1.71–1.41 (4H, m), 1.63 (3H, s, Me) and 1.59 (3H, s, Me); δ_C(67.8 MHz, $CDCl_3$) 138.5 (s), 135.0 (s), 124.1 (d), 120.9 (d), 62.9 (t), 39.6 (t), 39.3 (t), 32.9 (t), 32.3 (t), 31.6 (t), 26.3 (t), 24.0 (t), 16.2 (q) and 15.8 (q); *m*/*z* (EI) 208.1835 (M^+ − HBr, $C_{14}H_{24}O$ requires 208.1827). The alcohol **16a** was reprotected using the following procedure: a solution of the alcohol (688 mg, 2.38 mmol), dihydropyran (326 μl, 300 mg, 3.57 mmol) and pyridinium toluene-*p*-sulfonate (60 mg, 0.238 mmol) in dichloromethane (10 cm^3) was stirred at room temperature for 18 h. The reaction was diluted with diethyl ether (100 cm^3) and then washed with 1:1 saturated brine–water (50 cm^3). The separated aqueous layer was extracted with diethyl ether (75 cm^3) and the combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (1:9) as eluent gave the *tetrahydropyran* **16b** (751 mg, 85%) as a colourless oil.

(*E*,*E*)-2-[(5,9-Dimethyl-12-iodododeca-5,9-dienyl)oxy]tetrahydro-2*H*-pyran 16c

A mixture of the bromide **16b** (2.84 g, 7.61 mmol) and sodium iodide (2.85 g, 19.0 mmol) in acetone (25 cm^3) was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the residue was then partitioned between diethyl ether (100 cm^3) and water (50 cm^3). The separated diethyl ether layer was washed with saturated aqueous sodium thiosulfate (25 cm^3) and brine (25 cm^3) and then each of the aqueous layers was extracted with diethyl ether (75 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–

light petroleum (bp 40–60 °C) (1:9) as eluent gave the *iodide* (2.8 g, 89%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 1654; δ_H(400 MHz, $CDCl_3$) 5.11 (2H, m, 2 × −CH=), 4.59 (1H, br s, CH_2CHO_2), 3.90–3.85 (1H, m), 3.75–3.71 (1H, m), 3.52–3.50 (1H, m), 3.40–3.38 (1H, m), 3.14–3.08 (2H, m), 2.62–2.58 (2H, m), 2.10–1.96 (8H, m), 1.85–1.46 (8H, m), 1.61 (3H, s, Me) and 1.60 (3H, s, Me); δ_C(67.8 MHz, $CDCl_3$) 138.0 (s), 135.0 (s), 124.0 (d), 122.9 (d), 98.7 (d), 67.4 (t), 62.2 (t), 39.5 (t), 39.3 (t), 30.7 (t), 29.2 (t), 26.2 (t), 25.4 (t), 24.2 (t), 22.3 (t), 19.6 (t), 16.2 (q), 15.8 (q) and 6.0 (t); *m*/*z* (EI) 420.1522 (M^+, $C_{19}H_{33}IO_2$ requires 420.1525).

(*E*,*E*)-4,5-Dihydro-3-[4,8-dimethyl-12-[(tetrahydro-2*H*-pyran-2-yl)oxy]dodeca-3,7-dienyl]-3-phenylthiofuran-2(3*H*)-one 17

n-Butyllithium (8.94 cm^3, 14.3 mmol, 1.6 M in hexanes) was added to a solution of diisopropylamine (2.51 cm^3, 1.81 g, 17.9 mmol) in THF (25 cm^3) cooled to 0 °C. After 15 min the solution was cooled to −78 °C, where it was stirred for a further 15 min and then 2-phenylthiobutyrolactone[14] (2.31 g, 11.9 mmol) in THF (10 cm^3) was added dropwise over 30 min. The mixture was allowed to warm to −50 °C over 2 h. The reaction was recooled to −78 °C and then a solution of the iodide **16c** (2.51 g, 5.98 mmol) and HMPA (2.08 cm^3, 2.14 g, 11.9 mmol) in THF (10 cm^3) was added dropwise over 5 min. The mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature overnight when it was diluted with diethyl ether (150 cm^3) and water (50 cm^3). The separated ethereal layer was washed with brine (50 cm^3) and both aqueous phases were then extracted with diethyl ether (100 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) as eluent (1:4) gave the *dihydrofuranone* (2.1 g, 71%) as a colourless oil; ν_{max}(film)/cm^{-1} 1769 and 1669; δ_H(250 MHz, $CDCl_3$) 7.56–7.54 (2H, m, 2 × aryl-H), 7.44–7.33 (3H, m, 3 × aryl-H), 5.09 (2H, m, 2 × −CH=), 4.58 (1H, br s, CH_2CHO_2), 4.26–4.22 (2H, m, CH_2O), 3.92–3.86 (1H, m), 3.75–3.74 (1H, m), 3.51–3.48 (1H, m), 3.40–3.38 (1H, m), 2.50–2.20 (6H, m), 2.06–1.40 (16H, m) and 1.61 (6H, s, 2 × Me); δ_C(67.8 MHz, $CDCl_3$) 176.1, 137.0, 136.4, 135.0, 129.4, 128.9, 127.5, 124.1, 122.5, 98.8, 67.5, 64.9, 62.3, 53.9, 39.6, 39.4, 34.6, 34.3, 30.7, 29.2, 26.4, 25.4, 24.5, 23.1, 19.7, 16.1 and 15.8; *m*/*z* (ES) 509.2667 (M^+ + Na, $C_{29}H_{42}O_4SNa$ requires 509.2701).

(*E*,*E*)-3-[4,8-Dimethyl-12-[(tetrahydro-2*H*-pyran-2-yl)oxy]-dodeca-3,7-dienyl]furan-2(5*H*)-one 18

m-Chloroperoxybenzoic acid (962 mg, 4.74 mmol, 85%) was added in one portion to a solution of the thioether **17** (1.92 g, 3.95 mmol) in dichloromethane (20 cm^3) at −78 °C. The stirred mixture was allowed to warm to 0 °C over 3 h and then diethyl ether (125 cm^3) was added. The resulting solution was washed with a mixture of saturated aqueous sodium thiosulfate (50 cm^3) and saturated aqueous sodium hydrogen carbonate (150 cm^3), and the separated organic layer was then dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was dissolved in toluene (20 cm^3) and solid calcium carbonate (1.0 g) was then added. The reaction was heated under reflux for 3 h, then cooled, filtered through Florisil, and evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (1:4) as eluent gave (i) recovered starting material (eluted first) (410 mg, 23%), and (ii) the *furanone* (eluted second) (912 mg, 61%) as a colourless oil; ν_{max}(film)/cm^{-1} 1755; δ_H(250 MHz, $CDCl_3$) 7.11 (1H, m, −CH=), 5.12–5.08 (2H, m, 2 × −CH=), 4.76–4.74 (2H, m, CH_2O), 4.55 (1H, br s, CH_2CHO_2), 3.89–3.82 (1H, m), 3.77–3.68 (1H, m), 3.53–3.46 (1H, m), 3.43–3.31 (1H, m), 2.30–2.25 (4H, m), 2.04–1.95 (6H, m), 1.89–1.40 (10H, m), 1.59 (3H, s, Me) and 1.58 (3H, s, Me); δ_C(67.8 MHz, $CDCl_3$) 174.4 (s), 144.7 (d), 137.0 (s), 135.3 (s), 134.2 (s), 124.5 (d), 122.9 (d), 99.2 (d), 70.4 (t), 67.8 (t), 62.7 (t), 39.9 (t), 39.7 (t), 31.1 (t), 29.6 (t), 26.8 (t), 26.0 (t), 25.8 (t), 25.7 (t), 24.8 (t), 20.0 (t), 16.4 (q) and 16.1 (q); *m*/*z* (EI) 274.1939 (M^+ − THPOH, $C_{18}H_{26}O_2$ requires 274.1933).

(*E*,*E*)-3-(4,8-Dimethyl-12-oxododeca-3,7-dienyl)furan-2(5*H*)-one 19a

(*a*) Pyridinium toluene-*p*-sulfonate (60 mg, 0.238 mmol) was added to a solution of the furanone **18** (896 mg, 2.38 mmol) in ethanol (19 cm^3), and the mixture was then warmed to 55 °C for 4 h. The mixture was cooled and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (1:1) as eluent gave (*E*,*E*)-3-(4,8-dimethyl-12-hydroxydodeca-3,7-dienyl)furan-2(5*H*)-one (610 mg, 88%) as a colourless oil; ν_{max}(film)/cm^{-1} 3426, 1748 and 1650; δ_H(250 MHz, $CDCl_3$) 7.12 (1H, t, *J* 1.8 Hz, −CH=), 5.12 (2H, m, 2 × −CH=), 4.78 (2H, d, *J* 1.8 Hz, CH_2O), 3.86 (2H, t, *J* 6.5 Hz, CH_2OH), 2.33–2.26 (4H, m), 2.09–1.95 (6H, m), 1.69–1.39 (4H, m) and 1.61 (6H, s, 2 × Me); δ_C(67.8 MHz, $CDCl_3$) 174.7 (s), 144.3 (d), 136.5 (s), 135.1 (s), 134.0 (s), 124.2 (d), 122.7 (d), 70.1 (t), 62.9 (t), 39.6 (t), 39.3 (t), 32.3 (t), 26.4 (t), 25.6 (t), 25.4 (t), 24.0 (t), 16.0 (q) and 15.8 (q); *m*/*z* (EI) 292.2060 (M^+, $C_{18}H_{28}O_3$ requires 292.2039).

(*b*) Dess–Martin periodinane (1.09 g, 2.56 mmol) was added portionwise over 5 min to a stirred solution of the alcohol from (*a*) (500 mg, 1.71 mmol) in dichloromethane (15 cm^3) at room temperature. The mixture was stirred at room temperature for 1 h, then diluted with diethyl ether (40 cm^3) and stirred with a solution of sodium hydrogen carbonate (1 g) and sodium thiosulfate (3.25 g) in water (50 cm^3) for 30 min until two layers had formed. The separated ethereal layer was washed with brine (50 cm^3), and both aqueous layers were then extracted with diethyl ether (2 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (1:2) as eluent gave the *aldehyde* (436 mg, 89%) as a colourless oil; ν_{max}(film)/cm^{-1} 1754, 1722 and 1652; δ_H(250 MHz, $CDCl_3$) 9.76 (1H, t, *J* 1.7 Hz, CHO), 7.11 (1H, br s, −CH=), 5.13–5.09 (2H, m, 2 × −CH=), 4.77 (2H, m, CH_2O), 2.42–2.25 (6H, m), 2.08–1.97 (6H, m), 1.76–1.67 (2H, m), 1.60 (3H, s, Me) and 1.58 (3H, s, Me); δ_C(67.8 MHz, $CDCl_3$) 203.1 (s), 174.5 (s), 144.7 (d), 136.8 (s), 134.3 (s), 134.2 (s), 125.6 (d), 123.1 (d), 70.4 (t), 43.5 (t), 39.8 (t), 39.1 (t), 26.8 (t), 26.0 (t), 25.8 (t), 20.5 (t), 16.4 (q) and 16.0 (q); *m*/*z* (EI) 290.1883 (M^+, $C_{18}H_{26}O_3$ requires 290.1882).

(*E*,*E*)-5,9-Dimethyl-12-(2-oxo-5*H*-furan-3-yl)dodeca-5,9-dienoic acid 19b

A solution of sodium chlorite (1.75 g, 15.4 mmol, 80% tech) in water (7.4 cm^3) was added to a vigorously stirred mixture of the aldehyde **19a** (430 mg, 1.48 mmol) and sodium dihydrogen phosphate (1.75 g, 11.2 mmol) in *tert*-butyl alcohol (36 cm^3), 2-methylbut-2-ene (7.4 cm^3) and water (7.4 cm^3) at room temperature. The mixture was stirred at room temperature for 5 h, and then evaporated *in vacuo*. The residue was partitioned between ethyl acetate (50 cm^3) and water (10 cm^3), and then the aqueous layer was extracted with ethyl acetate (2 × 50 cm^3). The combined organic extracts were washed with brine (35 cm^3) then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *acid* (370 mg, 82%) as a colourless oil; ν_{max}(film)/cm^{-1} 3676–2377, 1747, 1709 and 1651; δ_H(400 MHz, $CDCl_3$) 7.11 (1H, br s, −CH=), 5.16–5.05 (2H, m, 2 × −CH=), 4.76 (2H, br s, CH_2O), 2.33–2.28 (6H, m), 2.06–1.99 (6H, m), 1.75–1.53 (2H, m), 1.60 (3H, s, Me) and 1.59 (3H, s, Me); δ_C(67.8 MHz, $CDCl_3$) 179.0 (s), 174.8 (s), 144.5 (d), 136.4 (s), 134.1 (s), 133.9 (s), 125.1 (d), 122.8 (d), 70.1 (t), 39.5 (t), 38.7 (t), 33.2 (t), 26.3 (t), 25.6 (t), 25.4 (t), 22.6 (t), 16.0 (q) and 15.7 (q).

***Se*-Phenyl (*E*,*E*)-5,9-dimethyl-12-(2-oxo-5*H*-furan-3-yl)dodeca-5,9-dieneselenoate 11**

Tributylphosphine (164 μl, 133 mg, 0.653 mmol) was added dropwise over 5 min to a stirred solution of the acid **19b** (100

mg, 0.326 mmol) in dichloromethane (6.0 cm^3) at −30 °C. After 5 min *N*-phenylselenophthalimide (197 mg, 0.653 mmol) was added in one portion, and the mixture was then stirred at −30 °C for 3 h. The mixture was diluted with dichloromethane (20 cm^3) and then washed with water (20 cm^3) and brine (20 cm^3). The separated aqueous layers were extracted with dichloromethane (20 cm^3), and the combined organic extracts dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (1:4) as eluent gave the *selenyl ester* (116 mg, 80%) as a colourless oil; ν_{max}(film)/cm^{-1} 1754 and 1722; δ_H(250 MHz, $CDCl_3$) 7.53–7.49 (2H, m, 2 × aryl-H), 7.40–7.38 (3H, m, 3 × aryl-H), 7.10 (1H, br s, −CH=), 5.15–5.07 (2H, m, 2 × −CH=), 4.75 (2H, br s, CH_2O), 2.67 (2H, t, *J* 7.3 Hz), 2.32–2.26 (4H, m), 2.06–1.98 (6H, m), 1.85–1.67 (2H, m) and 1.58 (6H, s, 2 × Me); δ_C(67.8 MHz, $CDCl_3$) 201.0 (s), 174.5 (s), 144.3 (d), 136.1 (s), 135.7 (d), 133.9 (s), 133.6 (s), 129.2 (d), 128.8 (d), 125.5 (d), 125.4 (s), 122.8 (d), 70.1 (t), 46.8 (t), 39.5 (t), 38.5 (t), 26.5 (t), 25.7 (t), 25.4 (t), 23.4 (t), 16.0 (q) and 15.7 (q); *m*/*z* (EI) 289.1811 (M^+ − PhSe, $C_{18}H_{25}O_3$ requires 289.1804).

(5β,13α)- and (5α,13α)-8-Methyl-18-nor-16-oxaandrostan-4,17-dione 20

A solution of the phenylselenyl ester **11** (111 mg, 0.249 mmol) and AIBN (15 mg) in dry degassed benzene (25 cm^3) was warmed to reflux under argon and then treated dropwise over 8 h with a solution of tributyltin hydride (101 μl, 109 mg, 0.3742 mmol) and AIBN (15 mg) in benzene (6 cm^3). The mixture was heated under reflux for a further 12 h, then cooled and the solvent removed *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (3:7) as eluent gave (i) the *cis*,*anti*,*trans*,*anti*,*cis*-diastereoisomer of the *tetracycle* (eluted first) (9 mg, 12%) as a white amorphous solid; ν_{max}(CH_2Cl_2) 1764 and 1708; δ_H(360 MHz, $CDCl_3$) 4.20 (1H, d, *J* 9.9 Hz, H-15), 4.10 (1H, dd, *J* 9.9, 5.3 Hz, H-15), 2.54 (1H, dd, *J* 7.9, 7.9 Hz, H-13), 2.39–2.22 (4H, m), 2.18 (1H, br s), 2.09 (1H, dd, *J* 7.9, 5.3 Hz, H-14), 2.06–2.03 (1H, m), 1.96–1.25 (8H, m), 1.11 (3H, s, Me), 1.08–1.04 (1H, m), 0.91 (3H, s, Me) and 0.88–0.80 (1H, m); δ_C(90.6 MHz, $CDCl_3$) 212.7 (s), 178.8 (s), 67.6 (t), 55.5 (d), 50.1 (d), 45.1 (d), 41.4 (t), 40.1 (s), 38.6 (t), 37.3 (d), 35.4 (s), 35.4 (t), 25.5 (q), 22.1 (t), 20.1 (t), 17.6 (t), 16.5 (t) and 15.3 (q); *m*/*z* (EI) 290.1884 (M^+, $C_{18}H_{26}O_3$ requires 290.1882); and (ii) the *trans*,*anti*,*trans*,*anti*,*cis*-diastereoisomer of the *tetracycle* (eluted second) (38 mg, 53%) as white needles, mp 178–180 °C (from ethyl acetate–light petroleum); ν_{max}(CH_2Cl_2)/cm^{-1} 1764 and 1708; δ_H(500 MHz, $CDCl_3$) 4.22 (1H, d, *J* 9.9 Hz, H-15), 4.12 (1H, dd, *J* 9.9, 5.4 Hz, H-15), 2.58 (1H, dd, *J* 7.9, 7.9 Hz, H-13), 2.35 (1H, m), 2.29 (1H, dd, *J* 4.6, 4.6 Hz), 2.17 (1H, dd, *J* 11.6, 3.5 Hz), 2.12 (1H, dd, *J* 7.9, 5.4 Hz, H-14), 2.00–1.92 (2H, m), 1.91–1.86 (1H, m), 1.83 (1H, app. dt, *J* 13.1, 13.2 Hz), 1.73–1.50 (4H, m), 1.39–1.28 (2H, m), 1.04 (1H, dd, *J* 12.2, 1.9 Hz), 0.98–0.88 (2H, m), 0.88 (3H, s, Me) and 0.72 (3H, s, Me); δ_C(125 MHz, $CDCl_3$) 212.6 (s), 178.7 (s), 67.4 (t), 59.6 (d), 53.8 (d), 50.3 (d), 42.6 (s), 40.5 (t), 39.0 (t), 38.4 (t), 37.2 (d), 35.4 (s), 22.1 (t), 21.9 (t), 18.1 (t), 16.6 (t), 15.1 (q) and 14.2 (q); *m*/*z* (EI) 290.1885 (M^+, $C_{18}H_{26}O_3$ requires 290.1882).

X-Ray crystal structure determination of 20

A colourless block was mounted on a glass fibre and transferred to the diffractometer.

Crystal data. $C_{18}H_{26}O_3$, $M = 290.39$, monoclinic, $a = 7.561(2)$, $b = 17.779(2)$, $c = 11.949(2)$ Å, $\beta = 106.99(2)°$, $V = 1536.1(5)$ Å^3 [from 2θ values of 48 reflections measured at ±ω ($28 \leqslant 2\theta \leqslant 34°$, $\lambda = 0.710\,73$ Å, $T = 298$ K)], space group $P2_1/c$ (No. 14), $Z = 4$, $D_x = 1.256$ g cm^{-3}, colourless block 0.42 × 0.35 × 0.27 mm, μ(Mo-Kα) = 0.084 mm^{-1}.

Data collection and processing. Stoe Stadi-4 four-circle diffractometer, ω/θ scans with ω scan width (0.90 + 0.35 tan θ)°, graphite-monochromated Mo-Kα X-radiation; 2689 unique reflections measured to $2\theta_{max} = 50°$, giving 1830 with $F \geqslant 4\sigma(F)$ and 2679 which were retained in all calculations. Slight crystal decay (4%) was observed and corrected for during data processing; no corrections were applied for absorption.

Structure solution and refinement. Automatic direct methods[20] (all non-H atoms). Full-matrix least squares refinement[21] with all non-H atoms anisotropic; hydrogen atoms were included at geometrically calculated positions and refined freely with $U_{iso}(H) = xU_{eq}(C)$ [$x = 1.5$ for methyl hydrogens and 1.2 for others]. The weighting scheme $w^{-1} = [\sigma^2(F_c) + (0.039P)^2 + 0.35P]$, $P = 1/3[MAX(F_o^2,0) + 2F_c^2]$, gave satisfactory agreement analyses. Final R_1 [$F \geqslant 4\sigma(F)$] = 0.0426, wR_2 [all data] = 0.1039, $S[F^2] = 1.05$ for 269 refined parameters. An extinction correction[21] refined to 0.0051(9) and the final ΔF synthesis showed no peaks above ±0.14 e Å^{-3}. Fig. 1 was produced using SHELXTL/PC.[22]

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web pages (http://chemistry.rsc.org/rsc/p1pifa.htm). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/183.

(5α,13α)-8-Methyl-4-methylene-18-nor-16-oxaandrostan-17-one 22

A solution of titanium tetrachloride (10 cm^3, 10.0 mmol, 1.0 M in CH_2Cl_2) was added dropwise over 10 min to a vigorously stirred suspension of activated zinc dust (2.87 g, 44.0 mmol) and dibromomethane (1.01 cm^3, 2.43 g, 14.0 mmol) in THF (25 cm^3) at −40 °C. The mixture was warmed to 0 °C, and then stirred in a cold room at 0 °C for 18 h. A portion (0.5 cm^3) of this Lombardo reagent was added dropwise over 5 min to a solution of the ketone **20** (10 mg, 0.0344 mmol) in dichloromethane (1 cm^3) at 0 °C, and the reaction was then stirred at 0 °C for 30 min. The mixture was poured into saturated aqueous sodium hydrogen carbonate (15 cm^3) and then extracted with diethyl ether (20 cm^3). The separated organic phase was washed with water (20 cm^3), and both separated aqueous layers were then extracted with diethyl ether (20 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (3:17) as eluent gave the *alkene* (7.8 mg, 79%) as white needles, mp 130–135 °C (from diethyl ether–light petroleum); ν_{max}(CH_2Cl_2)/cm^{-1} 1771 and 1645; δ_H(500 MHz, $CDCl_3$) 4.72 (1H, s, =C*H*H), 4.47 (1H, s, =C*H*H), 4.23 (1H, d, *J* 9.8 Hz, H-15), 4.12 (1H, d, *J* 9.8, 5.4 Hz, H-15), 2.57 (1H, dd, *J* 8.0, 8.0 Hz, H-13), 2.34 (1H, dd, *J* 14.0, 4.4 Hz), 2.28 (1H, dd, *J* 13.0, 4.4 Hz), 2.13 (1H, dd, *J* 8.0, 5.4 Hz, H-14), 1.98 (1H, ddd, *J* 13.0, 13.0, 5.9 Hz), 1.86–1.79 (2H, m), 1.72–1.41 (5H, m), 1.39–1.17 (2H, m), 1.08 (1H, ddd, *J* 12.9, 12.9, 4.0 Hz), 1.01 (1H, ddd, *J* 13.0, 13.0, 4.8 Hz), 0.97–0.83 (2H, m), 0.89 (3H, s, Me) and 0.65 (3H, s, Me); δ_C(125 MHz, $CDCl_3$) 179.0 (s), 150.5 (s), 105.4 (t), 67.5 (t), 54.0 (d), 52.5 (d), 50.4 (d), 40.3 (t), 39.7 (t), 39.1 (s), 37.4 (d), 36.3 (t), 35.7 (s), 23.0 (t), 22.4 (t), 20.4 (t), 18.0 (t), 15.2 (q) and 13.8 (q); *m*/*z* (EI) 288.2099 (M^+, $C_{19}H_{28}O_2$ requires 288.2089).

(5α,13α)-8′-Methylspiro[cyclopropane-1,4′-[18]nor[16]oxaandrostan[17]one] 23

A solution of diiodomethane (6.5 μl, 21.7 mg, 0.081 mmol) in diethyl ether (0.2 cm^3) was added dropwise over 2 h to a refluxing mixture of zinc–copper couple (9 mg, 0.135 mmol) and the alkene **22** (3.9 mg, 0.0135 mmol) in diethyl ether (0.5 cm^3). The mixture was heated under reflux for a further 60 h, then cooled and diluted with diethyl ether (20 cm^3) and water (20 cm^3). The separated aqueous layer was extracted with diethyl ether (20 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on

silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (3:17) as eluent gave the *cyclopropane* (4.1 mg, 95%) as white needles, mp 144–148 °C (from diethyl ether–light petroleum); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2929, 2850 and 1770; δ_H(500 MHz, $CDCl_3$) 4.20 (1H, d, *J* 9.8 Hz, H-15), 4.11 (1H, dd, *J* 9.8, 5.4 Hz, H-15), 2.55 (1H, dd, *J* 8.0, 7.8 Hz, H-13), 2.32 (1H, dd, *J* 14.0, 5.2 Hz), 2.10 (1H, dd, *J* 7.8, 5.4 Hz, H-14), 1.84 (1H, br d, *J* 12.5 Hz), 1.78–1.74 (2H, m), 1.72–1.55 (4H, m), 1.48–1.41 (2H, m), 1.31 (1H, ddd, *J* 12.8, 12.8, 4.9 Hz), 1.09–0.81 (4H, m), 0.85 (6H, s, 2 × Me), 0.79 (1H, dd, *J* 12.4, 2.0 Hz), 0.46–0.41 (2H, m, 2 × cyclopropyl), 0.25–0.22 (H, m, cyclopropyl) and −0.16 to −0.19 (1H, m, cyclopropyl); δ_C(125 MHz, $CDCl_3$) 179.2 (s), 67.6 (t), 54.5 (d), 50.6 (d), 48.9 (d), 40.8 (t), 40.1 (t), 38.8 (t), 38.4 (s), 37.5 (d), 35.6 (s), 22.5 (t), 20.7 (t), 19.0 (s), 17.6 (2 × t), 15.5 (q), 14.7 (q), 9.3 (t) and 6.1 (t); *m/z* (EI) 302.2242 (M^+, $C_{20}H_{30}O_2$ requires 302.2246).

(5α,13α)-4,4,8-Trimethyl-18-nor-16-oxaandrostan-17-one (spongian-16-one) 1

Platinum(IV) oxide (1.5 mg, 0.0066 mmol, 50 mol%) was added to a solution of the cyclopropane **23** (4 mg, 0.0132 mmol) in distilled glacial acetic acid (0.2 cm^3), and the mixture was then stirred under an atmosphere of hydrogen for 40 h. The mixture was diluted with diethyl ether (20 cm^3) and then washed with saturated aqueous sodium hydrogen carbonate (2 × 15 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated *in vacuo*. Chromatography of the residue on silica gel using ethyl acetate–light petroleum (bp 40–60 °C) (3:17) as eluent gave (±)-*spongian*-16-*one* (3.2 mg, 80%) as white needles, mp 137–139 °C (from diethyl ether–light petroleum) (Found: C, 78.2; H, 10.6. $C_{20}H_{32}O_2$ requires C, 78.1; H, 10.7%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2977, 2928, 2869, 1768, 1444, 1386 and 1111; δ_H(500 MHz, $CDCl_3$) 4.22 (1H, d, *J* 9.8 Hz, H-15), 4.11 (1H, dd, *J* 9.8, 5.4 Hz, H-15), 2.54 (1H, dd, *J* 7.8, 7.8 Hz, H-13), 2.31 (1H, dd, *J* 14.1, 5.0 Hz), 2.09 (1H, dd, *J* 7.8, 5.4 Hz, H-14), 1.84 (1H, ddd, *J* 12.7, 3.2, 3.2 Hz), 1.74 (1H, br d, *J* 12.7 Hz), 1.69–1.50 (4H, m), 1.44–1.24 (5H, m), 1.14 (1H, ddd, *J* 13.2, 13.2, 4.1 Hz), 1.04 (1H, ddd, *J* 12.9, 12.9, 3.8 Hz), 0.87 (3H, s, Me), 0.86 (3H, s, Me), 0.83 (3H, s, Me), 0.82 (3H, s, Me), 0.89–0.79 (1H, m) and 0.76 (1H, dd, *J* 12.0, 2.4 Hz); δ_C(125 MHz, $CDCl_3$) 179.0 (s), 67.6 (t), 56.7 (d), 56.4 (d), 50.6 (d), 42.2 (t), 42.0 (t), 40.0 (t), 37.4 (d), 37.4 (s), 35.7 (s), 33.4 (q), 33.4 (s), 22.4 (t), 21.5 (q), 18.5 (t), 17.9 (t), 17.3 (t), 16.3 (q) and 15.5 (q); *m/z* (EI) 304.2345 (M^+, $C_{20}H_{32}O_2$ requires 304.2402).

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