

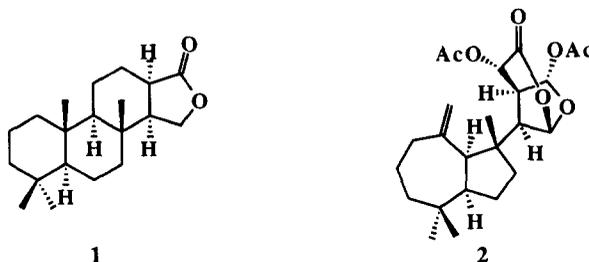
Cascade Radical Processes Leading to Polycycle Constructions. The Total Synthesis of Spongian-16-one

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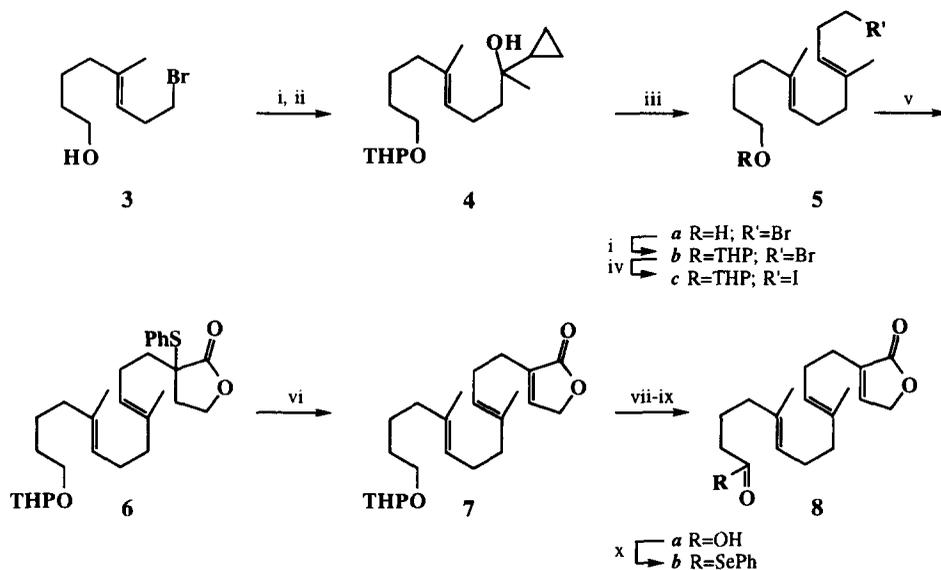
Abstract: A concise total synthesis of the marine sponge metabolite spongian-16-one **1**, which features a novel cascade of three consecutive 6-*endo-trig* radical cyclisations from a polyene acyl radical intermediate as a key step, viz **9** → **10**, is described. Copyright © 1996 Elsevier Science Ltd

Spongian-16-one **1** is a tetracyclic diterpene which was isolated recently from the marine sponges *Dictyodendrilla cavernosa*¹ and *Chelonaplysilla violacea*² found off the coasts of Australia and New Zealand. The molecule is implicated in the biogenesis of the hydrazulene-based diterpene aplyviolacene **2**^{2,3} (also known as macfarlandin E⁴) found in *C. violacea*, and also in the nudibranch *Chromodoris macfarlandi*,⁴ and from a *Dysidea* sp. of sponge.⁵ Several members of the spongian family of diterpenes isolated from the Canary Island sponge *Spongia officinalis*⁶ have been found to have modest antimicrobial activity, and their synthesis has attracted attention.⁷ In previous synthetic studies we have demonstrated how acyl/alkyl radical cyclisations of polyene selenoates, in the presence of Bu₃SnH-AIBN, can lead to linear and angular six-membered fused polycycles via regio- and stereo-selective consecutive 6-*endo-trig* modes of cyclisation.⁸ We now illustrate how this novel approach to complex polycycle construction can be applied in a concise synthesis of spongian-16-one **1**.



The strategy we followed for the total synthesis of spongian-16-one **1** was based on elaboration of the dienebutenolide selenoate **8b**, followed by serial 6-*endo-trig* radical cyclisation initiated from the acyl radical intermediate **9** derived from **8b**, and manipulation of the ketone functionality in the product **10**, to the corresponding *gem*-dimethyl group, viz **8b** → **9** → **1**. The selenoate **8b** was prepared as shown in Scheme 1. Thus, protection of the known bromo alcohol **3**⁹ as its tetrahydropyranyl ether followed by lithiation and reaction with cyclopropyl methyl ketone¹⁰ first led to the substituted cyclopropylmethanol **4**. Ring-opening of **4** using

48% HBr at -20°C^{11} next led to the homoallylic bromide **5a**, which was then reprotected as its tetrahydropyranyl ether **5b** and converted to the corresponding iodide **5c** under Finkelstein conditions. Addition of the iodide **5c** to the lithium enolate derived from 2-phenylthiobutyrolactone¹² next gave the substituted butyrolactone **6**, which on oxidation and elimination of the elements of phenylsulphonic acid¹³ was converted into the corresponding butenolide **7**. A series of functional group interconversions then converted the tetrahydropyranyl ether group in **7** into the carboxylic acid **8a**, which on treatment with N-phenylselenophthalimide-Bu₃P¹⁴ finally gave rise to the central diene butenolide selenoate intermediate **8b**.



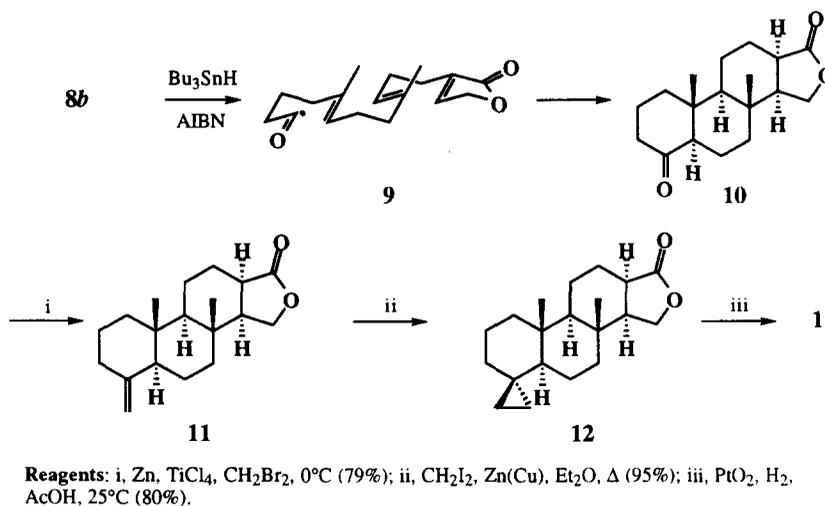
Reagents: i, DHP, PPTS, 25°C (95%); ii, Li, THF, 0°C , methylcyclopropylketone (80%); iii, 48% HBr, -20°C (86%); iv, NaI, Me₂CO, 25°C (89%); v, 2-phenylthiobutyrolactone, LDA, HMPA, -78°C (71%); vi, mCPBA, -78°C to 0°C , then Δ , C₆H₅Me, CaCO₃ ($\sim 80\%$); vii, PPTS, EtOH, 55°C (94%); viii, Dess-Martin periodinane (89%); ix, NaH₂PO₄, *t*BuOH, H₂O, NaClO₂, 2-methylbut-2-ene (82%); x, N-phenylselenophthalimide, Bu₃P, -30°C (86%).

Scheme 1

Treatment of a solution the Se-phenylselenoate **8b** in dry degassed benzene at reflux with Bu₃SnH (syringe pump addition over 8h)⁸ in the presence of AIBN, resulted in a smooth cascade of three consecutive 6-*endo-trig* radical cyclisations from the acyl radical intermediate **9**, leading to the tetracyclic keto-lactone **10** (>90% one diastereoisomer) in 65% yield (Scheme 2). The *trans, anti, trans, anti, cis*-stereochemistry **10** assigned to the crystalline tetracyclic product (mp $178\text{--}180^{\circ}\text{C}$) followed from analysis of its ¹³C nmr spectroscopic data and comparison of these data with those of previously analysed polycycles produced in earlier work.⁸ The geometry shown in structure **10** was also confirmed by X-ray crystallographic analysis.¹⁵

The synthesis of (\pm) spongian-16-one **1** from the keto-lactone **10** was completed following conversion to the cyclopropane intermediate **12** via the product **11** of methylenation¹⁶ of **10**, and finally hydrogenolysis.¹⁷ The synthetic spongian-16-one was obtained as colourless crystals, mp $137\text{--}139^{\circ}\text{C}$, and had pmr and cmr spectroscopic data which were superimposable on those recorded for the natural product.^{1,2,18} This novel approach to the construction of the polycyclic framework in spongian-16-one, based on a cascade of three

consecutive 6-*endo-trig* radical cyclisations, has several merits over alternative methods for polycycle constructions. Applications of the approach to other polycycles, including aza-steroids, are now in progress.



Scheme 2

ACKNOWLEDGEMENTS

We thank Professors R C Cambie and W C Taylor for supplying copies of the pmr and cmr spectra they recorded for natural spongian-16-one from *D. cavernosa* and *C. violacea* respectively. We also thank Glaxo Group Research for a Research Fellowship (to LR) and Dr D Tapoczay (Glaxo-Wellcome) for his interest in this study.

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18. All new compounds showed satisfactory spectroscopic data, together with appropriate mass spectrometry and/or elemental microanalytical data. **10**: ¹H NMR (500 MHz CDCl₃) 4.22 (1H, d, *J* 9.9 Hz), 4.12 (1H, dd, *J* 9.9 and 5.4 Hz), 2.58 (1H, dd, *J* 7.9 and 7.9 Hz), 2.35 (1H, m), 2.29 (1H, dd, *J* 4.6 and 4.6 Hz), 2.17 (1H, dd, *J* 11.6 and 3.5 Hz), 2.12 (1H, dd, *J* 7.9 and 5.4 Hz), 2.00-1.92 (2H, m), 1.91-1.86 (1H, m), 1.83 (1H, ddd, *J* 13.1, 3.2 and 3.2 Hz), 1.73-1.50 (4H, m), 1.39-1.28 (2H, m), 1.04 (1H, dd, *J* 12.2 and 1.9 Hz), 0.98-0.88 (2H, m), 0.88 (3H, s), 0.72 (3H, s); ¹³C NMR (125 MHz, CDCl₃) 212.6 (s), 178.7 (s), 67.4 (t), 59.6 (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), 14.2 (q); HRMS (EI+) calcd for C₁₈H₂₆O₃ M⁺ 290.1882, found 290.1885. **1**: ¹H NMR (500 MHz CDCl₃) 4.22 (1H, d, *J* 9.8 Hz), 4.11 (1H, dd, *J* 9.8 and 5.4 Hz), 2.54 (1H, dd, *J* 7.8 and 7.8 Hz), 2.31 (1H, dd, *J* 14.1 and 5.0 Hz), 2.09 (1H, dd, *J* 7.8 and 5.4 Hz), 1.84 (1H, ddd, *J* 12.7, 3.2 and 3.2 Hz), 1.74 (1H, brd, *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 and 4.1 Hz), 1.04 (1H, ddd, *J* 12.9, 12.9 and 3.8 Hz), 0.87 (3H, s), 0.86 (3H, s), 0.83 (3H, s), 0.82 (3H, s), 0.89-0.79 (1H, m), 0.76 (1H, dd, *J* 12.0 and 2.4 Hz); ¹³C NMR (125 MHz CDCl₃) 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), 16.3 (q), 15.5 (q); HRMS (EI+) calcd for C₂₀H₃₂O₂ M⁺ 304.2402, found 304.2345.

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