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

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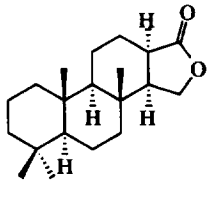
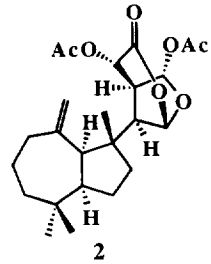
Abstract: A concise total synthesis of the marine sponge metabolite spongian-16-one **1**, which features a novel cascade of three consecutive 6-*endo-trig* radical cyclisations from a polyene acyl radical intermediate as a key step, *viz* **9** → **10**, is described. Copyright © 1996 Elsevier Science 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 E[4]) 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 Bu_3SnH-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**.



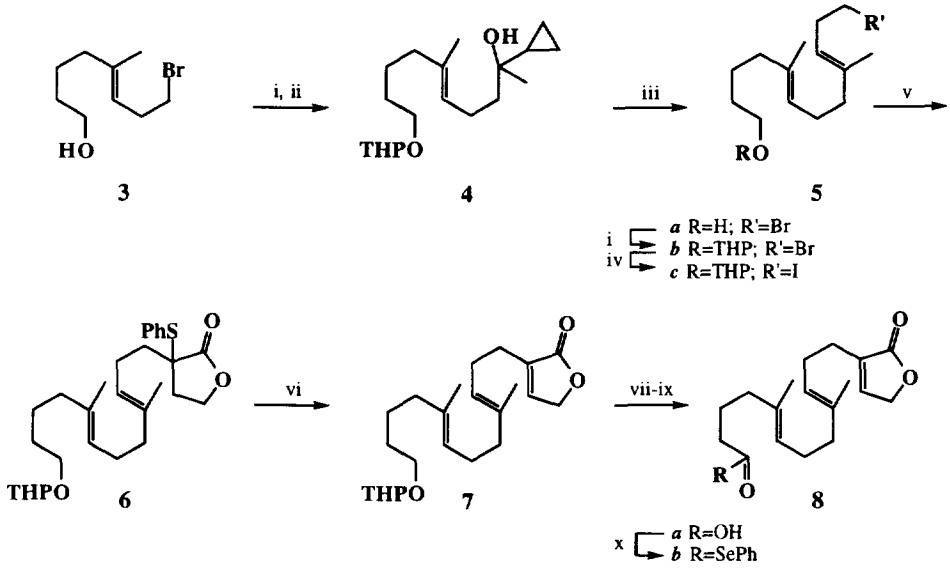
1



2

The strategy we followed for the total synthesis of spongian-16-one **1** was based on elaboration of the dienebutenolide selenoate **8*b***, followed by serial 6-*endo-trig* radical cyclisation initiated from the acyl radical intermediate **9** derived from **8*b***, and manipulation of the ketone functionality in the product **10**, to the corresponding *gem*-dimethyl group, *viz* **8*b*** → **9** → **1**. The selenoate **8*b*** 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 ketone[10] first led to the substituted cyclopropylmethanol **4**. Ring-opening of **4** using

48% HBr at -20°C[11] next led to the homoallylic bromide **5*a***, which was then reprotected as its tetrahydropyranyl ether **5*b*** and converted to the corresponding iodide **5*c*** under Finkelstein conditions. Addition of the iodide **5*c*** to the lithium enolate derived from 2-phenylthiobutyrolactone[12] next gave the substituted butyrolactone **6**, which on oxidation and elimination of the elements of phenylsulphinic acid[13] 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 **8*a***, which on treatment with N-phenylselenophthalimide-Bu_3P[14] finally gave rise to the central diene butenolide selenoate intermediate **8*b***.



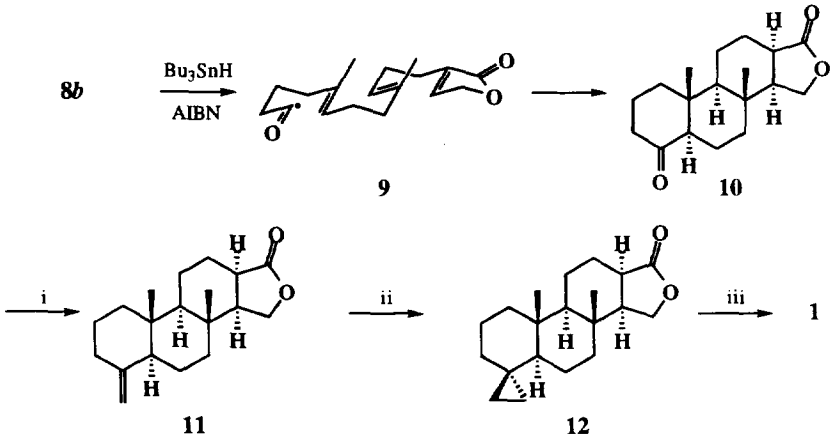
Reagents: i, DHP, PPTS, 25°C (95%); ii, Li, THF, 0°C, methylcyclopropylketone (80%); iii, 48% HBr, -20°C (86%); iv, NaI, Me_2CO, 25°C (89%); v, 2-phenylthiobutyrolactone, LDA, HMPA, -78°C (71%); vi, *m*CPBA, -78°C to 0°C, then Δ, C_6H_5Me, $CaCO_3$ (~80%); vii, PPTS, EtOH, 55°C (94%);viii, Dess-Martin periodinane (89%); ix, NaH_2PO_4, *t*BuOH, H_2O, $NaClO_2$, 2-methylbut-2-ene (82%); x, N-phenylselenophthalimide, Bu_3P, -30°C (86%).

Scheme 1

Treatment of a solution the Se-phenylselenoate **8*b*** in dry degassed benzene at reflux with Bu_3SnH (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 178-180°C) followed from analysis of its ^{13}C 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 (±) spongian-16-one **1** from the keto-lactone **10** was completed following conversion to the cyclopropane intermediate **12** *via* the product **11** of methylenation[16] of **10**, and finally hydrogenolysis.[17] The synthetic spongian-16-one was obtained as colourless crystals, mp 137-139°C, and had pmr and cmr spectroscopic data which were superimpossible 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.



Reagents: i, Zn, $TiCl_4$, CH_2Br_2, 0°C (79%); ii, CH_2I_2, Zn(Cu), Et_2O, Δ (95%); iii, PtO_2, H_2, AcOH, 25°C (80%).

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 Tapolczay (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**: ^{1}H NMR (500 MHz $CDCl_3$) 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), 1.73-150 (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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{18}H_{26}O_3$ M^+ 290.1882, found 290.1885. **1**: ^{1}H NMR (500 MHz $CDCl_3$) 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); ^{13}C NMR (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), 16.3 (q), 15.5 (q); HRMS (EI+) calcd for $C_{20}H_{32}O_2$ M^+ 304.2402, found 304.2345.

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