Cascade radical cyclisations involving enamide double bonds. A synthetic approach to azasteroids

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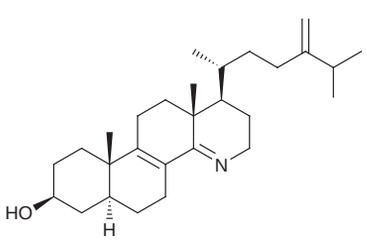
1 PERKIN COMMUNICATION

Treatment of the enamide selenoesters 8 and 14 with Bu_3SnH–AIBN is shown to lead to the nitrogen tricycle 9 (63%) and the D-homo-12-azasteroid 16 (45%) respectively, by way of serial stereoselective 6-*endo-trig* radical cyclisations.

Although azasteroids are not abundant in Nature, a wide variety have been synthesised and several of their members display interesting biological properties. Thus, the azasteroid **1** produced by the mold *Geotrichum flavobrunneum*[1] exhibits broad spectrum antifungal activity, and several synthetic 4- and 6-azasteroids are 5α-dehydrogenase inhibitors.[2] Chandonium iodide **2** acts as a neuromuscular blocking agent,[3] whereas other



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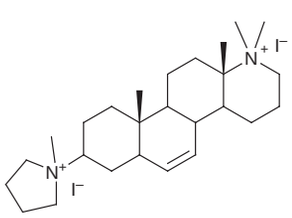

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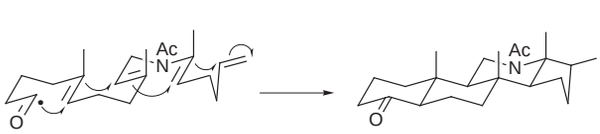
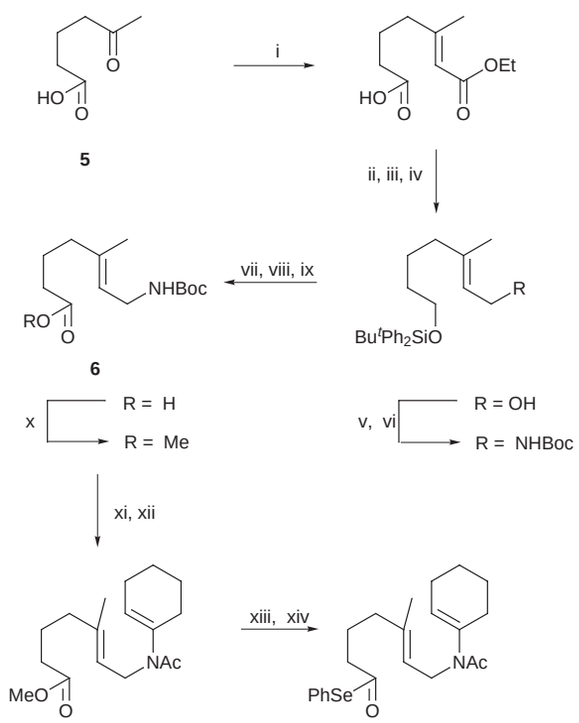
azasteroids show useful antibacterial and hypotensive activities.[4] Hitherto, synthetic work directed towards azasteroids has relied largely on the degradation of conveniently available steroids followed by reconstitution with simultaneous introduction of nitrogen functionality.[5] By building on our expertise in the area of cascade polycyclisations from polyene acyl radical precursors[6] we now demonstrate a facile approach to the synthesis of azasteroids from polyene enamide selenoesters based on the serial 6-*endo-trig* radical cyclisations highlighted below, *viz*. **3**→**4**.[7,8]



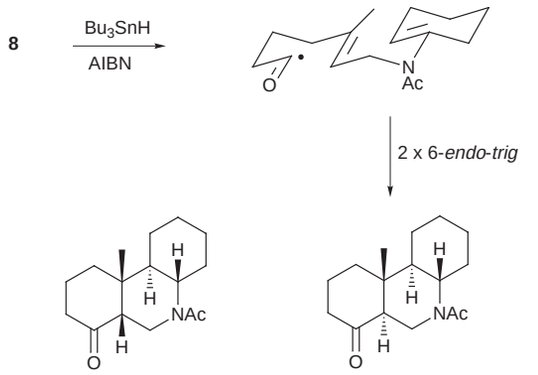
3 **4**

We first examined the sequential 6-*endo*, 6-*endo-trig* cyclisation of the enamide selenoester **8** with a view to synthesis of the reduced phenanthridine derivative **9**. The selenoester **8** was prepared as a 2:1 mixture of *Z*- and *E*-isomers from the keto acid **5**, *via* the allylamine derivative **6** and the enamide **7** as key intermediates (Scheme 1).[9] Treatment of a solution of **8** in benzene at reflux with Bu_3SnH–AIBN, followed by work-up and purification by chromatography gave a single tricyclic product[10] in 63% yield. Detailed analysis of the NMR spectroscopic data obtained for this major product and comparison with similar data for related molecules[6b] established that it had the *trans*, *anti*,*trans*-phenanthridine structure **9**. On re-chromatography after storage for one year the corresponding *cis* A/B ring fused epimer **10** was separated as crystals, whose structure and stereochemistry were established by X-ray crystallography.[11] When a solution of the *cis* A/B ring fused epimer was heated in methanol in the presence of sodium methoxide for 60 h it underwent epimerisation at C-5 to regenerate the *trans*,*anti*, *trans*-tricycle **9**.



Scheme 1 *Reagents and conditions*: i, $(EtO)_2P(O)CH_2CO_2Et$, NaH, 96%; ii, Bu^iOCOCl, NEt_3, then $NaBH_4$, MeOH, 84%; iii, Bu^tPh_2SiCl, imidazole, 99%; iv, DIBAL-H, CH_2Cl_2, −78 °C, 92%; v, TsNHBoc, DEAD, PPh_3, 99%; vi, Na/Hg, Na_2HPO_4, 85%; vii, TBAF, PTSA, 99%; viii, Dess–Martin periodinane, 70%; ix, KH_2PO_4, $NaClO_2$, Bu^tOH, H_2O, 2-methylbut-2-ene, 97%; x, $TMSCHN_2$, MeOH, 95%; xi, TFA, 99%; xii, NEt_3 then cyclohexanone, molecular sieves (4 Å) then acetyl chloride, NEt_3, DMAP, 56%; xiii, LiOH, H_2O, 85%; xiv, Ph_2Se_2, PBu_3, 73%

To explore further the scope of radical-based polyene cyclisations with enamides, we next synthesised the selenoester **14**



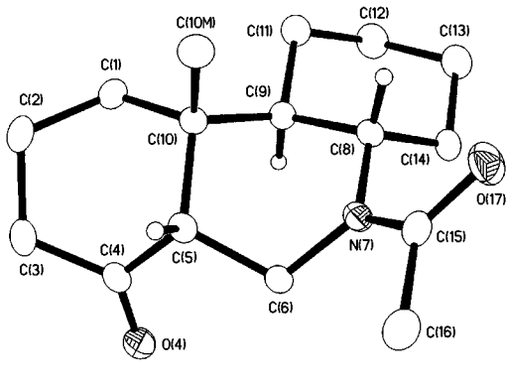
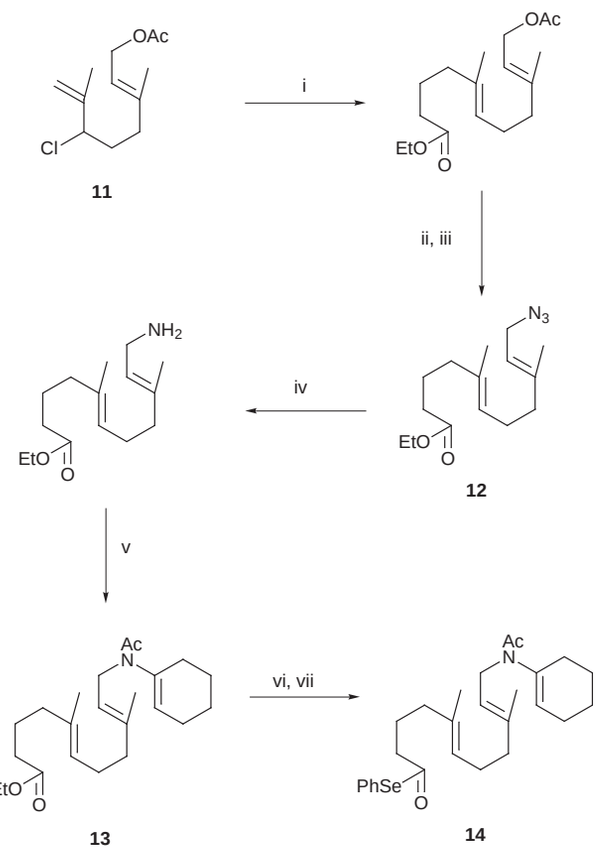
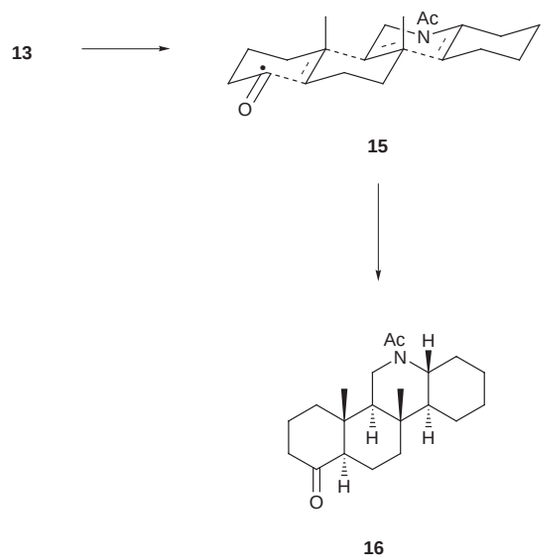


Fig. 1 ORTEP diagram of compound **10**





Scheme 2 *Reagents and conditions*: i, [(1-ethoxycyclopropyl)oxy]-trimethylsilane, $ZnCl_2$, Me_3SiCl, CuBr·DMS, 89%; ii, KCN, EtOH, reflux, 83%; iii, $Zn(N_3)_2$·2py, DIAD, PPh_3, 38–62%; iv, PPh_3 then H_2O, 74%; v, cyclohexanone, molecular sieves (4 Å) then acetyl chloride, lutidine, 43%; vi, LiOH, H_2O, 99%; vii, *N*-(phenylseleno)phthalimide, PBu_3, CH_2Cl_2, −30 °C, 80%

containing additional alkene unsaturation. The ester **14** was produced from the known *E*-alkenyl acetate **11**[12] as a 2:1 mixture of *E*- and *Z*-isomers at C-5, and proceeding *via* the azide **12** and the enamide **13** as key intermediates (Scheme 2).[9] When a solution of the selenoester **14** in benzene was treated with Bu_3SnH–AIBN, under the same conditions used to synthesise **9** and **8**, it was converted into the corresponding D-homo-12-azasteroid **16** which was produced as a 4:1 mixture of diastereoisomers in 45% yield. Separation by chromatography and analysis of NMR data, together with comparison of these data with those of **9** and other model compounds,[6b] demonstrated that the major product resulting from the cyclisation of **14** had the *trans*,*anti*,*trans*,*anti*,*trans* geometry shown in formula **16**.[9] These investigations then, similar to the outcome of our complementary studies leading to steroids and related 6-membered ring-fused carbocycles, suggest that the polyene chains in these radical cyclisations must assume a highly organised transition state conformation, *e.g.* **15**, to account for the high regio- and stereo-selectivities observed in the cascade polycyclisations.

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9 All new compounds showed satisfactory spectroscopic data, together with microanalytical and/or mass spectrometry data. Data for **9**: δ_H(500 MHz, $CDCl_3$; *J*/Hz) 3.73 (1H, dd, *J* 13.9 and 8.3, C*H*HN), 3.43 (1H, dd, *J* 13.9 and 7.1, CH*H*N), 3.37 (1H, app. td, *J* 10.7 and 2.8, C*H*N), 2.51 (1H, app. t, *J* 7.7, COC*H*), 2.48–2.30 (2H, m, CH_2CO), 2.14 (3H, s, $NCOCH_3$), 2.10 (1H, m), 1.97 (1H, m), 1.91–1.73 (4H, m), 1.56–1.38 (5H, m), 1.32 (1H, m), 1.12 (1H, m), 0.71 (3H, s, CCH_3); δ_C(125.8 MHz, $CDCl_3$) 209.8 (s), 171.9 (s), 57.4 (d), 57.1 (d), 52.0 (d), 40.7 (s), 40.4 (t), 40.1 (t), 36.0 (t), 31.7 (t), 26.4 (t), 26.1 (t), 25.6 (t), 23.6 (q), 22.3 (t), 13.0 (q); ν_{max}(liquid film)/cm^{-1} 2934 (s), 2359 (s), 1714 (s), 1634 (s), 1454 (s), 1200 (s), 1049 (m), 668 (s); *m*/*z* (EI) 263.1883 (M^+; $C_{16}H_{25}NO_2$ requires *M*, 263.1885). Data for **16**: δ_H(360 MHz, $CDCl_3$) 3.55 (2H, m, $CHCH_2N$), 3.32 (1H, dd, *J* 10.6 and 2.6, $NCHCH_2$), 2.32 (3H, m), 2.11 (3H, s, $NCOCH_3$), 2.15–0.97 (18H, m), 0.85 (3H, s, CCH_3), 0.83 (3H, s, CCH_3); δ_C(90.6 MHz, $CDCl_3$) 212.2 (s), 171.8 (s), 59.4 (d), 57.9 (d, br), 55.8 (d), 55.0 (d), 43.0 (s), 41.7 (t, br), 40.8 (t), 37.6 (t), 36.3 (t), 33.9 (s), 33.6 (t), 26.6 (t), 25.4 (t), 25.3 (t), 23.0 (q), 22.1 (t), 17.1 (t), 14.7 (q), 13.4 (q); *m*/*z* (EI) 331.2500 (M^+; $C_{21}H_{33}NO_2$ requires *M*, 331.2511).

10 In a typical procedure, a solution of Bu_3SnH (60 mg, 0.21 mmol) and AIBN (7 mg) in degassed benzene (2 cm^3) was added dropwise over 2 h to a refluxing solution of **8** (70 mg, 0.17 mmol) and AIBN (8 mg) in degassed benzene (38 cm^3) under argon, and the solution was then heated under reflux for a further 2 h. The solution was evaporated to dryness *in vacuo*, and the residue was then purified by chromatography on silica using EtOAc–light petroleum (bp 40–60 °C) (1:3) as eluent to give the tricycle **9** (30 mg, 65%) as a colourless oil.

11 $C_{16}H_{25}NO_2$, $M = 263.37$. Triclinic, $a = 5.884(2)$, $b = 9.265(3)$, $c = 13.687(6)$ Å, $\alpha = 77.23(3)$, $\beta = 83.17(4)$, $\gamma = 76.63(3)°$, $V = 706.2(5)$ $Å^3$, $T = 150(2)$ K, space group $P\bar{1}$ (No. 2), $Z = 2$, $D_x = 1.239$ g cm^{-3}, μ(Mo-Kα) = 0.080 mm^{-1}. Structure solution and refinement employed all 2464 unique reflections. Final R_1 [2071 $F \geqslant 4\sigma(F)$] = 0.0438, wR_2 [F^2, all data] = 0.106, $S[F^2] = 1.15$ for 174 refined parameters. 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 page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/223.

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