Novel cascade of seven radical-mediated 6-*endo-trig* cyclisations leading to a unique all-*trans*, *anti* heptacycle

Sandeep Handa and Gerald Pattenden *

School of Chemistry, Nottingham University, Nottingham, UK NG7 2RD

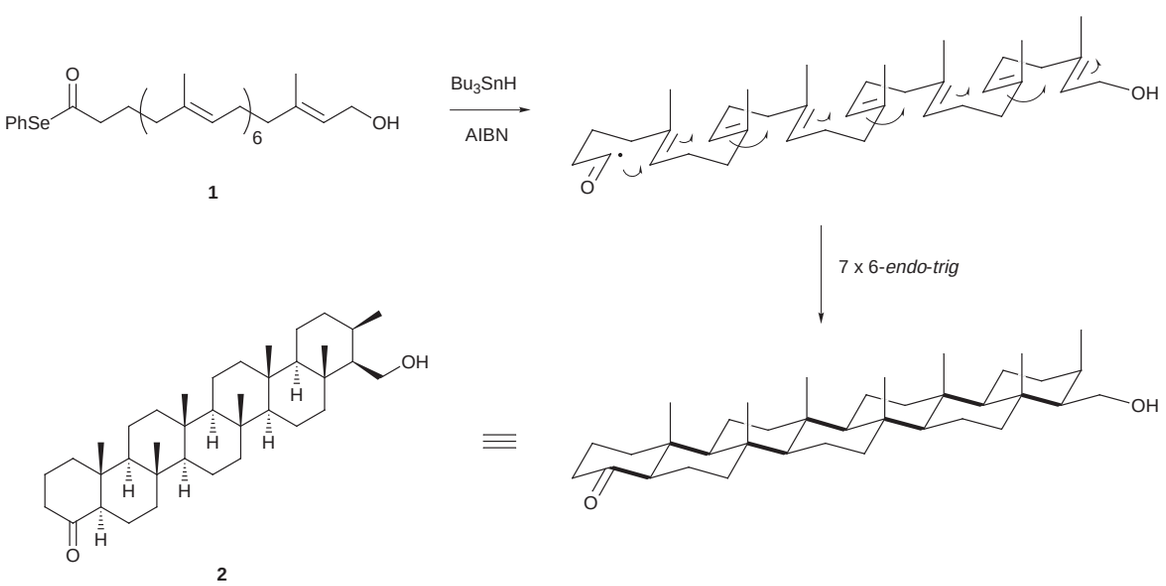
Received (in Cambridge) 8th February 1999, Accepted 2nd March 1999

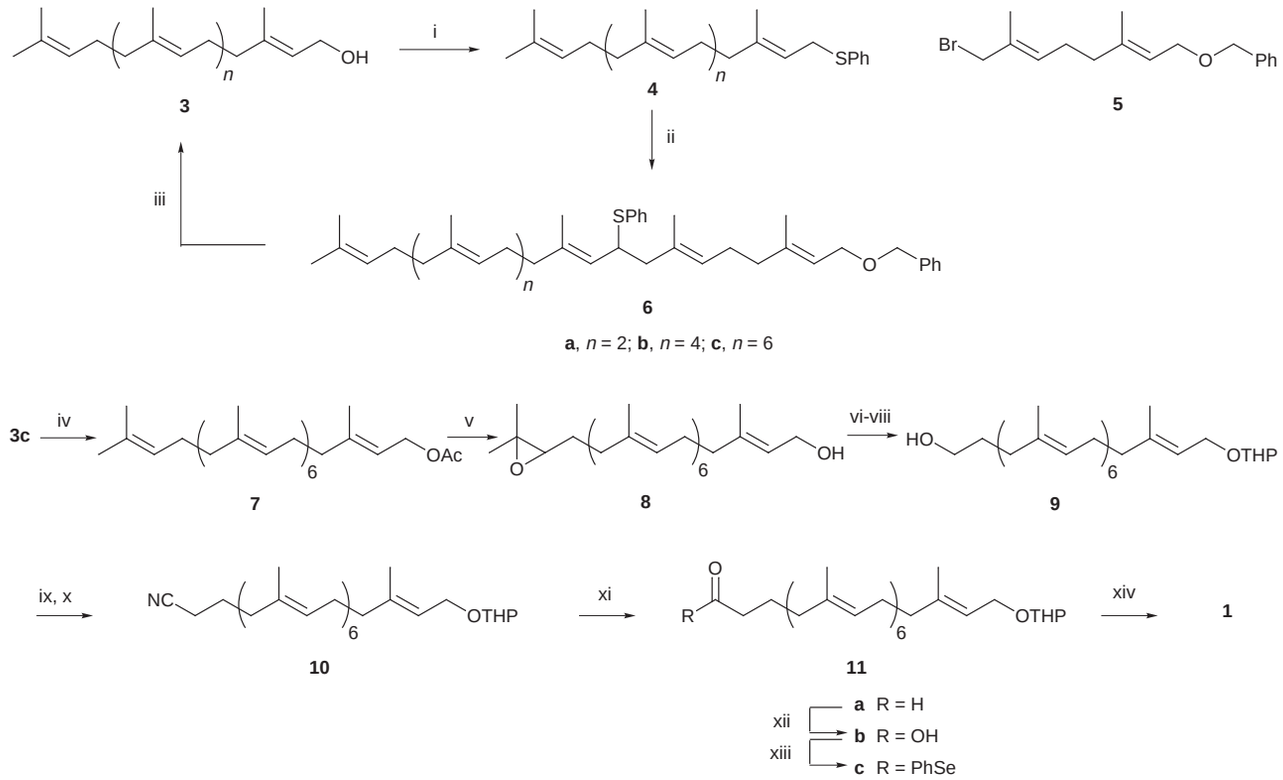
A cascade of seven radical-mediated 6-*endo-trig* cyclisations from the all-*E*-heptaene selenoate ester 1 results in the production of the all-*trans*, *anti* heptacycle 2 together with the isolation of the all-*trans*, *anti* tetracycle 15.

In recent years, we have examined the scope for an extensive range of complementary radical-mediated cascade processes from polyene precursors in the synthesis of a variety of polycyclic ring systems, including taxoids and steroids.[1] These radical cascades have included those based on serial 6-*endo-trig* cyclisations from polyene acyl precursors,[1a] radical-mediated macrocyclisations from alkyl radicals in tandem with radical transannulations,[1b] consecutive oxy (and aminyl) radical fragmentation–transannulation–cyclisation sequences,[1c] and several combinations of these processes.[1d] In many of these investigations, we have generated sufficient circumstantial evidence to suggest that there is a significant degree of "pre-organisation" in the polyene precursor molecules, and in the reaction intermediates, favouring the pathways followed in the polycycle constructions. In order to evaluate some of the limits of the extent to which radical intermediates can be utilised in the synthesis of polycycles, we have now attempted an unprecedented cascade of *seven* sequential radical-mediated 6-*endo-trig* cyclisations with a view to the synthesis of the novel (steroidal-type) heptacycle **2** from the linear heptenoyl radical precursor **1**.

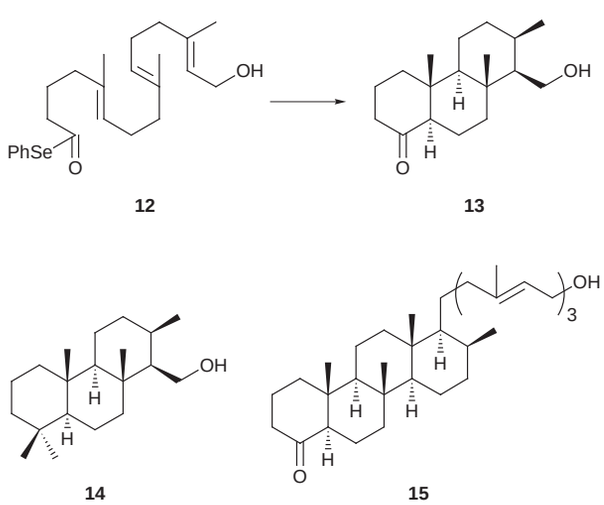
The selenoate cyclisation precursor **1** was synthesised from all-*E*-geranylgeraniol **3a** involving two successive C_{10} homologations, *viz.* **3a**→**3b**→**3c**, as outlined in Scheme 1.[2] Thus, phenylthioetherification of **3a**, followed by alkylation of the resulting sulfide **4a** with the allyl bromide **5** first gave the C_{30}-compound **6a** which on reduction with lithium in ethylamine at −78 °C led to the corresponding hexenyl alcohol **3b**. Repetition of this sequence, *i.e.* thioetherification, alkylation and reduction, then converted the alcohol **3b** into the known octaprenyl alcohol **3c**[2] which was secured in the all-*E* configuration by purification of the corresponding acetate using chromatography on silver nitrate impregnated silica gel.[3] Selective epoxidation of the terminal double bond in the acetate **7** using NBS in THF–H_2O followed by saponification next produced the all-*E*-epoxyalcohol **8**. Treatment of the epoxide **8** with aqueous periodic acid resulted in hydrolysis and simultaneous 1,2-diol cleavage producing the corresponding aldehyde which was then converted into the primary alcohol **9** using two steps. Mesylation of **9** followed by a displacement reaction with cyanide next led to the nitrile **10** which was converted into the corresponding carboxylic acid **11b** *via* a series of functional group transformations. Finally, treatment of the acid **11b** with *N*-(phenylseleno)phthalimide–PBu_3 followed by deprotection of the resulting selenoate ester **11c**, gave the hydroxyheptenoate precursor **1**[3] for the aforementioned attempted cascade radical cyclisation.

Treatment of a solution of the selenoate **1** in dry degassed benzene (3 mM), at reflux, with Bu_3SnH (syringe pump addition over 8 h) in the presence of AIBN, followed by chromatography resulted in the isolation of two products. Analysis of the spectroscopic data for the more polar of these two products (*ca.* 20% isolated yield)[4] indicated that the acyl radical intermediate had indeed successfully undergone a series of seven sequential 6-*endo-trig* cyclisations generating the heptacyclic ketone **2**. Assignment of the all *trans*, *anti*-stereochemistry to **2** followed from comparison of the chemical shifts of the signals in its ^{13}C NMR spectrum with those observed for the tricyclic ketone **13** which had been prepared in an analogous fashion to **2** by radical cyclisation of the corresponding triene selenoate **12**. Thus, in the first instance we were able to assign the tricyclic ketone **13** as having complete *trans*, *anti*-stereochemistry. This was achieved by comparison of its ^{13}C NMR resonances with those of the known alcohol **14**[5] and using the model proposed by Beierbeck *et al.*[6] to take into account their differing substitution at the C-4 position (steroidal numbering). Using this semi-empirical approach, the agreement between the ^{13}C chemical





Scheme 1 *Reagents and conditions*: i, Bu^{n}Li, THF–DMPU, −78 °C; TsCl, 0 °C; LiSPh (89–93%); ii, Bu^{n}Li, THF, −78 °C; **5**, −78 °C (78–86%); iii, Li, $EtNH_2$, THF, −78 °C (86–94%); iv, $(CH_3CO)_2O$, Et_3N, DMAP, CH_2Cl_2 (99%); v, NBS, THF, H_2O; K_2CO_3, MeOH (53%); vi, HIO_4, THF, H_2O; vii, DHP, PPTS, CH_2Cl_2; viii, $NaBH_4$, Et_2O, MeOH (56%—over 3 steps); ix, CH_3SO_2Cl, Et_3N, CH_2Cl, 0 °C; x, NaCN, DMSO, 70 °C (87%—over 2 steps); xi, DIBAL-H, $C_6H_5CH_3$, −78 °C (89%); xii, KH_2PO_4, Bu^{t}OH, H_2O, $NaClO_2$, 2-methylbut-2-ene (95%); xiii, *N*-(phenylseleno)phthalimide, PBu_3, CH_2Cl_2, −30 °C (76%); xiv, PTSA, MeOH (93%).



shifts observed for **13** and those predicted based on **14** was excellent, with the majority of values lying in the range $\Delta\delta \pm 0.7$ ppm (largest difference +2.6 ppm; average $\Delta\delta = +0.1$ ppm). Such a close correlation between these two systems can be taken as firm evidence for the tricyclic ketone **13** having complete *trans*, *anti*-stereochemistry.[7] From this starting point, we were able to apply a similar analysis for the heptacycle **2**, directly comparing the ^{13}C chemical shifts for those carbon atoms 'common' to both **13** and **2** (*i.e.* rings A, F and G) and using the model of Beierbeck *et al.*[6] to calculate ^{13}C chemical shifts for those structural features particular to **2** (*i.e.* rings B, C, D and E) based upon a complete *trans*, *anti*-stereochemistry. An excellent correlation was obtained with the majority of the differences between observed shifts and those predicted lying in the range of $\Delta\delta \pm 0.6$ ppm (largest difference + 5.4 ppm; average $\Delta\delta = +1.0$ ppm). Once again this excellent agreement can be taken as firm evidence for the complete *trans*, *anti*-stereochemistry assigned to the heptacycle **2**.

In addition to the heptacycle **2** a further component was recovered from the reaction mixture (*ca.* 25%) after treatment of **1** with Bu_3SnH–AIBN. This molecule was assigned the tetracyclic structure **15** on the basis of analysis of its ^1H and ^{13}C NMR spectroscopic data and comparison with corresponding data obtained for **2**, **13** and **14**. The aforementioned study has indeed demonstrated that the scope for radical cascade processes in the synthesis of serial linear/angular fused decalin/perhydrophenanthrene ring systems of the type displayed in conventional steroids is enormous. Further aspects, exploring other limitations, of cascade radical reactions in alternative polycycle constructs, are now in progress in our laboratories.[8]

Acknowledgements

We thank the EPSRC for support of this work *via* a Postdoctoral Fellowship to Dr S. Handa, who was also the proud recipient of the "Raphael Prize" in Chemistry at Cambridge in 1990. G. P. owes a great debt to Ralph Raphael for the inspiration and encouragement he provided during his early career in academe.

Notes and references

1 See for example, (*a*) L. Chen, G. B. Gill, G. Pattenden and H. Simonian, *J. Chem. Soc., Perkin Trans. 1*, 1996, 31; Reference 7 below; and extensive bibliography contained in these publications; (*b*) S. A. Hitchcock, S. J. Houldsworth, G. Pattenden, D. C. Pryde, N. M. Thomson and A. J. Blake, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3181; (*c*) G. J. Hollingworth, G. Pattenden and D. J. Schulz, *Aust. J. Chem.*, 1995, **48**, 381; (*d*) S. Handa and G. Pattenden, *Chem. Commun.*, 1998, 311; S. Handa and G. Pattenden, *Contemp. Org. Synth.*, 1997, **4**, 196.

2 For a similar strategy for the synthesis of the octaprenol **3c** see: (*a*) K. Sato, S. Inoue, A. Onishi, N. Uchida and N. Minowa, *J. Chem. Soc., Perkin Trans. 1*, 1981, 761; (*b*) E. E. van Tamelen and S. A. Marson, *Bioorg. Chem.*, 1982, **11**, 219.

3 All new compounds displayed satisfactory spectroscopic data together with microanalytical and/or mass spectrometric data.

4 Typical procedure: A solution of tributyltin hydride (8 μl, 8.7 mg, 29.8 μmol) and AIBN (1 mg) in benzene (2 ml) was added dropwise over 8 h to a refluxing solution of the phenyl selenoate **1** (16.9 mg, 23.9 μmol) and AIBN (0.5 mg) in dry degassed benzene (6 ml). The mixture was heated under reflux for a further 3 h, then cooled and evaporated to dryness *in vacuo.* The residue was purified by chromatography on silica gel using diethyl ether–light petroleum (bp 40–60 °C) as eluent and gave the heptacycle **2** (2.3 mg, 17%) as colourless crystals, mp 269–271 °C (ethyl acetate–pentane); $\nu_{max}(CHCl_3)/cm^{-1}$ 3626, 2928, 2853, 1700, 1465, 1387, 1260, 1110 and 1010; δ_H(500 MHz; $CDCl_3$) 3.85 (1H, dd, *J* 4.3 and 10.4 Hz, C*H*HOH), 3.59 (1H, app. t, *J* 10.4 Hz, CH*H*OCH), 2.31–2.27 (2H, m), 2.14–0.74 (complex series of multiplets), 0.95 (3H, d, *J* 7.6 Hz, CHCH_3), 0.85 (3H, s, CH_3), 0.84 (3H, s, CH_3), 0.81 (6H, s, 2 × CH_3), 0.79 (3H, s, CH_3) and 0.71 (3H, s, CH_3); δ_C(125.8 MHz; $CDCl_3$) 213.8 (s), 61.6 (d), 61.5 (d), 61.4 (2 × d), 60.9 (t), 59.7 (d), 59.1 (d), 56.1 (d), 43.4 (s), 42.0 (t), 41.9 (t), 41.8 (t), 41.7 (t), 40.8 (t), 38.7 (t), 38.1 (t), 37.8 (2 × s), 37.7 (s), 37.6 (s), 37.5 (s), 34.5 (t), 28.3 (d), 22.3 (t), 18.2 (t), 18.2 (q), 17.4 (q), 17.3 (q), 17.2 (q), 17.11 (t), 17.07 (2 × t), 17.0 (q), 16.9 (t), 16.2 (t), 15.4 (q) and 13.8 (q); *m*/*z* (CI) 533.4704 ((M + H^+) − H_2O, $C_{38}H_{61}O$ requires 533.4722): and the tetracycle **15** (~25%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 2938, 2875, 2852, 1698, 1663, 1451, 1386, 1265 and 1228; δ_H(500 MHz; $CDCl_3$) 5.43 (1H, t, *J* 6.7 Hz, C=C*H*CH_2OH), 5.13–5.10 (2H, m, 2 × C=CH), 4.16 (2H, d, *J* 6.7 Hz, CH_2OH), 2.27–0.80 (complex series of multiplets), 1.68 (3H, s, C=C(CH_3)), 1.60 (6H, s, 2 × C=C(CH_3)), 0.91 (3H, d, *J* 7.1 Hz, CHCH_3), 0.86 (3H, s, CH_3), 0.85 (3H, s, CH_3), 0.84 (3H, s, CH_3); δ_C(125.8 MHz; $CDCl_3$) 213.8 (s), 139.8 (s), 135.4 (s), 135.0 (s), 124.2 (d), 123.7 (d), 123.3 (d), 65.8 (t), 61.4 (d), 61.1 (d), 59.7 (d), 51.9 (d), 43.4 (s), 42.0 (t), 41.8 (t), 40.8 (t), 39.7 (t), 39.5 (t), 38.1 (t), 38.0 (t), 37.7 (t), 37.5 (s), 37.4 (s), 30.3 (d), 26.6 (t), 26.3 (t), 22.3 (t), 21.4 (t), 17.3 (2 × q), 17.1 (3 × t), 16.3 (q), 16.0 (q), 15.9 (q), 15.3 (q) and 13.8 (q); *m*/*z* (EI) 532.4669 (M^+ − H_2O, $C_{38}H_{60}O$ requires 532.4644).

5 D. S. de Miranda, G. Brendolan, P. M. Imamura, M. González Sierra, A. J. Marsaioli and E. A. Rúveda, *J. Org. Chem.*, 1981, **46**, 4851.

6 H. Beierbeck, J. K. Saunders and J. W. Apsimon, *Can. J. Chem.*, 1977, **55**, 2813; H. Beierbeck and J. K. Saunders, *Can. J. Chem.*, 1975, **53**, 1307.

7 For a similar ^{13}C NMR based analysis of the stereochemistry of fused cyclohexane systems see: A. Batsanov, L. Chen, G. B. Gill and G. Pattenden, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 45.

8 For some novel polycyclisations using the Heck reaction leading to penta- and heptacycles see: T. Sighihara, C. Coperet, Z. Owczarczyk, L. S. Harding and E. Negishi, *J. Am. Chem. Soc.*, 1994, **116**, 7923; B. M. Trost and Y. Shi, *J. Am. Chem. Soc.*, 1993, **115**, 9421.

Communication 9/01079C