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New Radical Mediated Polyolefin Cyclisations Directed Towards Steroid Ring Synthesis

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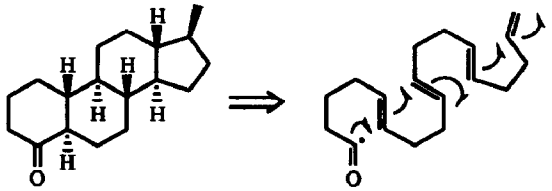
Abstract: Treatment of appropriately substituted 5,9-diene, 5,9,13-triene and 5,9,13,17-tetraene phenoselenyl esters, *e.g.* **1a**, **9** and **14**, with Bu_3SnH-AIBN is shown to lead to linear and angular six-ring fused polycycles, *viz* **2**, **11** and **15** respectively, *via* consecutive 6-*endo*-trig modes of cyclisations starting from the corresponding polyolefin acyl radical intermediates.

Studies of the sequential cyclisations of polyolefinic substrates in the presence of electrophilic reagents leading to polycycle constructions, pioneered by W S Johnson, have provided organic chemistry with one of its major and enduring methods for steroid ring synthesis.[1] Although these novel electrophilic polyolefin cyclisations mimic closely the biogenetic pathway to steroids from squalene oxide, it is now over thirty years since Breslow[2] first entertained the possibility of an alternative, free radical, mechanism for the oxidative cyclisation of squalene. Breslow's hypothesis, which was demonstrated for the case of cyclisation of farnesyl acetate to decalin derivatives in the presence of benzoyl peroxide,[3] and later by Julia[4] for the cyclisation of substituted 2,6,10-tridecatrienes, has more recently been revisited by Snider[5] and by Zoretic[6] in their independent studies of the oxidative free radical cyclisations of polyolefinic β-keto esters with Mn(III) and Cu(II) reagents. In contemporaneous studies we have investigated the scope for polyolefin precursors in the elaboration of steroid ring systems by consecutive free radical six-ring forming reactions under *reductive* conditions. In this *Letter* we show that free radical cyclisations of polyolefin selenyl esters, under clean conditions in the presence of Bu_3SnH-AIBN, provide stereospecifically linear and angular six-ring fused polycycles *via* consecutive 6-*endo*-trig modes of cyclisation.

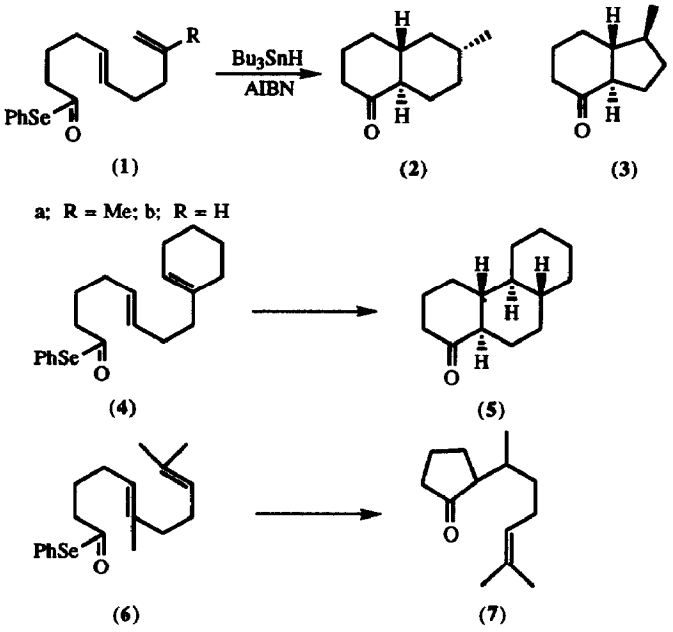


Scheme 1

The construction of linear, angular and spiro-fused polycycles by way of sequential radical mediated cyclisation reactions from alkyl radical centres is well documented.[7] Furthermore, with very few exceptions 5-*exo*-trig cyclisations are generally preferred over 6-*endo*-trig closures from hex-5-en-1-yl radical intermediates.[8,9] The unusual tendency of hex-5-en-1-oyl (*i.e. acyl*) radicals to cyclise *via* the 6-*endo*-trig mode, leading to six-ring carbocycles,[10,11,12] prompted us to evaluate the consecutive cyclisations of a range of (5,9,13-) polyolefinic acyl radical intermediates produced from the corresponding phenylselenyl esters, with a

view to steroid ring constructions (Scheme 1).

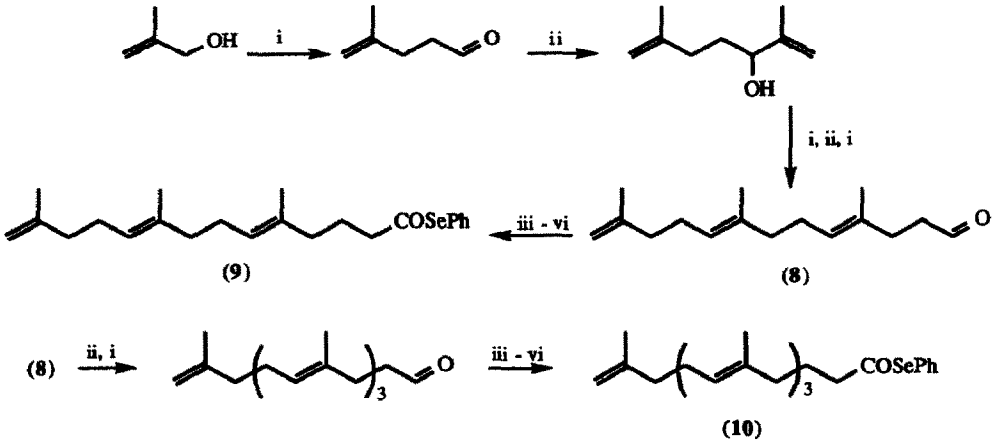
We first examined the cyclisation of the acyl radical intermediate produced from the diene selenyl ester **1a**.[13] The ester **1a** was obtained from the corresponding carboxylic acid simply by treatment with diphenyl diselenide and tributylphosphine in benzene at 25°C for 3h. When a solution of the phenyl selenyl ester **1a** in benzene was treated with Bu_3SnH-AIBN (reflux, 8h) it was found to undergo two consecutive 6-*endo*-trig cyclisations leading to the *trans*-decalone **2** in 77% yield.[14] In addition, treatment of the cyclohexene substituted phenyl selenyl ester **4**, under identical conditions, led to the crystalline *trans,anti,trans*-tricyclic ketone **5**, m.p. 71.5-73°C, in 72% yield. The structure and stereochemistry of **5** followed from comparison of data with those of an authentic sample synthesised independently.[15] The consecutive 6-*endo*-trig modes of cyclisation observed for the selenyl esters **1a** and **4** can be contrasted with the corresponding cyclisations of the differentially methyl-substituted olefin substrates **1b** and **6**, which instead produced the cyclopentanes (**3**; 75%) and (**7**; 85%) respectively.



We next investigated the tandem radical cyclisation of the *E,E*-triene phenyl selenyl ester **9**. The ester **9** was smoothly produced from 2-methylpropenol, *via* the central trienal intermediate **8**, using a series of Claisen rearrangements (Scheme 1). When **9** was treated with Bu_3SnH-AIBN (C_6H_6 reflux, 24h) it underwent three consecutive 6-*endo*-trig cyclisations giving rise to a 3:1 mixture of 13-methyl epimers of the tricyclic ketone **11** in 63% yield;[16] a small amount of the substituted indanone **12** was also produced in the cyclisation of **9**.

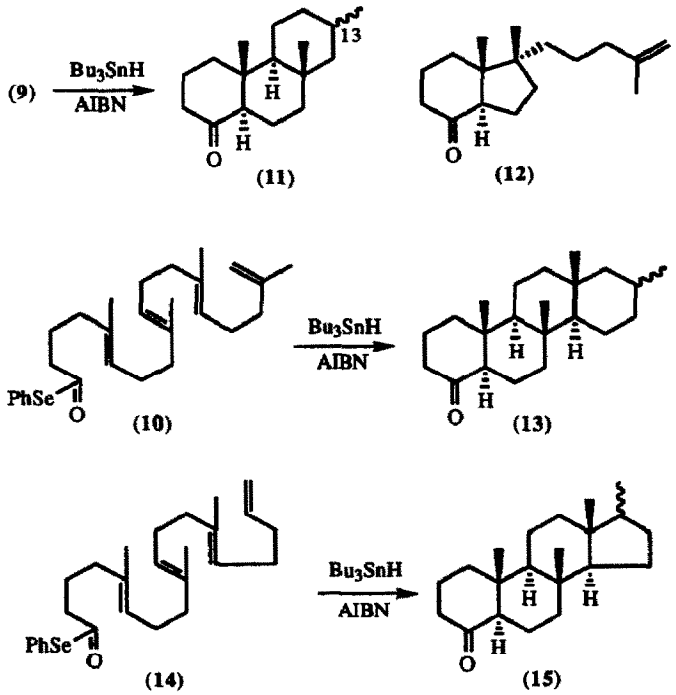
The trienal intermediate **8** used in the synthesis of the triene **9** was also employed to synthesise the all-*E*-tetraene phenyl selenyl ester **10** (Scheme 2).[14] Free radical mediated cyclisation of **10** with Bu_3SnH-AIBN in benzene at reflux for 24h gave stereospecifically the *trans* ring-fused tetracyclic ketone **13** as a 1:1 mixture of ring D methyl epimers in a satisfying 53% yield.[16] In a similar manner the tetraene ester **14** lacking methyl substitution at the terminal double bond, underwent three consecutive 6-*endo*-trig radical cyclisations followed by a 5-*exo*-trig closure leading to the steroid tetracyclic ketone **15** in a similar 51% yield.[16]

The stereospecific tandem 6-*endo*-trig cyclisations of the polyolefin substituted acyl radical intermediates produced from the phenyl selenyl esters **1a**, **4**, **9** **10** and **14** are quite remarkable, and they offer immense scope for the rapid construction of a range of substituted linear and angular-fused cyclohexanes, including steroid systems. It is tempting to rationalise the stereospecificities observed in the cyclisations of the triene **9**



Reagents: i, $EtOCH{:}CH_2$, $Hg(OAc)_2$, reflux, 6h., sealed tube, 120°C, 24h. (40–50%); ii, 2-bromomagnesium propene (45–66%); iii, $MeOCH_2PPh_3Cl$, LHMDS, THF, 0°C–25°C (70%); iv, PCC, CH_2Cl_2 (73%); v, K_2CO_3-MeOH, reflux, 24 h. (76%); vi, Ph_2Se_2, Bu_3P, PhH, 25°C, 18h. (70%).

Scheme 2



and the tetraenes **10** and **14** on the basis of fully concerted mechanisms *via* chair conformations of their all-*E* polyolefin acyl radical intermediates. Other factors, not least substitution and stereochemistry of the olefin units, are also important however, and these factors together with synthetic applications of the new polyolefin cyclisations, are now under active investigation in our laboratory.

Acknowledgements

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References

1. For recent reviews see: (a) Sutherland, J.K. "Polyene Cyclisations", in *Contemporary Organic Synthesis*, Vol 3, 341, Ed. Trost, B.W. Pergamon Press, **1991**; (b) Taylor, S.K. *Org. Prep. Proc. Int.*, **1992**, *24*, 247. For recent reference and bibliography see: Fish, P.V.; Sudhakar, A.R.; Johnson, W.S., *Tetrahedron Lett.*, **1993**, *34*, 7849.
2. Breslow, R.; Barrett, E.; Mohacsi, E. *Tetrahedron Lett.*, **1962**, 1207.
3. Breslow, R.; Olin, S.S.; Groves, J.T. *Tetrahedron Lett.*, **1968**, 1837.
4. Julia, M. *Tetrahedron Lett.*, **1973**, 4464.
5. Dombroski, M.A.; Kates, S.A.; Snider, B.B. *J. Am. Chem. Soc.*, **1990**, *112*, 2759.
6. Zoretic, P.A.; Wang, X.; Caspar, M.L. *Tetrahedron Lett.*, **1991**, *32*, 4819.
7. For an overview see: Curran, D.P. *Advances in Free Radical Chemistry*, Tanner, D., Ed.; JAI: Greenwich, **1990**, p.157. See also: Schwartz, C.E.; Curran, D.P. *J. Am. Chem. Soc.*, **1990**, *112*, 9272.
8. a) Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.*, **1987**, *52*, 959; b) Beckwith, A.L.J.; *Tetrahedron*, **1981**, *37*, 3073; c) Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron*, **1985**, *41*, 3925; d) Curran, D.P. *Synthesis*, **1988**, 417; e) Curran, D.P. *Synthesis*, **1988**, 489; Julia, M. *Acc. Chem. Res.*, **1971**, *4*, 386.
9. Lee, E.R.; Lakomy, I.; Bigler, P.; Scheffold, R. *Helv. Chim. Acta*, **1991**, *74*, 146.
10. a) Cekovic, Z. *Tetrahedron Lett.*, **1972**, 749; b) Walsh, E.J. Jr.; Messinger II, J.M.; Grudoski, D.A.; Allchin, C.A. *Tetrahedron Lett.*, **1980**, *21*, 4409.
11. a) Boger, D.L.; Mathvink, R.J. *J. Org. Chem.*, **1988**, *53*, 3377; b) Boger, D.L.; Mathvink, R.J. *J. Org. Chem.*, **1989**, *54*, 1779; c) Boger, D.L. Mathvink, R.J. *J. Am. Chem. Soc.*, **1990**, *112*, 4003; d) Boger, D.L. Mathvink, R.J. *J. Am. Chem. Soc.*, **1990**, *112*, 4008; e) Boger, D.L. Mathvink, R.J. *J. Org. Chem.*, **1990**, *55*, 5442; f) Boger, D.L. Mathvink, R.J. *J. Org. Chem.*, **1992**, *57*, 1429.
12. a) Crich, D.; Fortt, S.M. *Tetrahedron Lett.*, **1987**, *28*, 2895; b) Crich, D.; Fortt, S.M. *Tetrahedron Lett.*, **1988**, *29*, 2585; c) Crich, D.; Fortt, S.M. *Tetrahedron*, **1989**, *45*, 6581; d) Crich, D.; Eustace, K.A.; Ritchie, T.J. *Heterocycles*, **1989**, *28*, 67; e) Batty, D.; Crich, D.; Fortt, S.M. *J. Chem. Soc., Chem. Commun.*, **1989**, 1366; f) Batty, D.; Crich, D.; Fortt, S.M. *J. Chem. Soc., Perkin Trans., 1* **1990**, 2875; g) Crich, D.; Eustace, K.A.; Fortt, S.M. Ritchie, T.J. *Tetrahedron*, **1990**, *46*, 2135; h) Batty, D.; Crich, D. *Tetrahedron Lett.*, **1992**, *33*, 875.
13. Both Boger and Crich and their respective colleagues have also examined aspects of tandem cyclisations of acyl radicals produced from unsaturated selenyl esters. See under references 11 and 12.
14. Satisfactory spectroscopic data together with mass spectrometry and microanalytical data were obtained for all new compounds.
15. Alcaide, B.; Luengo, J.; Fernandez, F. *An. Quim. Ser. C*, **1981**, *77*, 200; Alcaide, B.; Fernandez, F. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1665.
16. The stereochemistries assigned to **11**, **13** and **15** are somewhat tentative at this time, and followed from detailed inspection of their ^{1}H and ^{13}C n.m.r. data (including 2D spectra) and comparison of these data with those of model compounds such as **2**, **5** and literature models. Calculation of ^{13}C shifts helped to confirm the assignments. Details will be discussed in the full paper. Attempts to obtain suitable crystals of derivatives from **11**, **13**, and **15** for X-ray crystal structure determinations have not so far been successful.

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