Novel Intramolecular Cyclisations Involving Ketene Radical Intermediates as an Approach to the Synthesis of Polyquinanes

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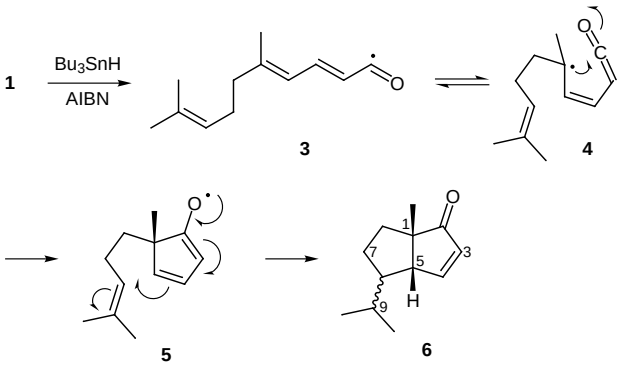
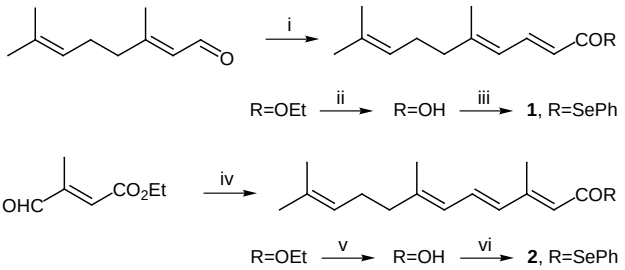
Abstract: Treatment of the polyene selenyl ester **1** with Bu_3SnH-AIBN leads to a concise synthesis of the diquinane **6** via a novel cyclisation involving a ketenyl radical intermediate. By contrast under the same radical initiating conditions the selenyl esters **2** and **10** produced cyclopentenone products, *viz* **9** and **11**, and the allene substituted selenyl ester **16** led to the unusual cyclooctadienone **18**.

Key words: cyclisations, tandem radical reactions

A wide range of ingenious methods based on tandem radical-mediated cyclisation processes are now available for the synthesis of ring-fused cyclopentanes, including naturally occurring linear, angular and propellane triquinanoids.[1] In recent studies we have identified the scope for α,β-unsaturated acyl radical intermediates, reacting as their α-ketenyl radical counterparts, *viz* R-CH=CH-•CO↔R-•CH-CH=C=O, in the synthesis of ring fused cyclopentanones;[2] we have also applied this chemistry in a formal synthesis of the natural 3,3,3-propellane, (±)-modhephene.[3] In pursuance of further novel chemistry associated with acyl radical intermediates[4] we have now synthesised a range of new α,β-unsaturated selenyl esters containing additional alkene bonds and examined their modes of radical cyclisation.



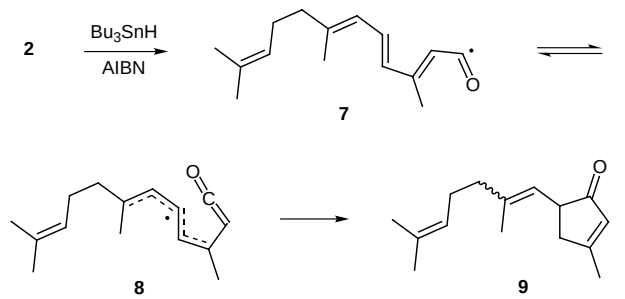
Thus, we first examined the radical cyclisation chemistry associated with the polyene acyl radical intermediates produced from the polyunsaturated selenyl esters **1** and **2**. The phenyl selenyl esters **1** and **2** were smoothly synthesised from citral and geranyltriphenylphosphonium bromide respectively as highlighted in Scheme 1.[5] When a solution of the α,β,γ,δ-unsaturated selenyl ester **1** in benzene was treated with Bu_3SnH-AIBN at reflux over 4.5h,



Reagents and conditions: i, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°-r.t., 82%; ii, KOH, MeOH/H_2O (1.2:1), Δ, 99%; iii, *N*-(phenylseleno)phthalimide (NPSP), Bu_3P, CH_2Cl_2, -30°, 74%; iv, geranyltriphenylphosphonium bromide, n-BuLi, THF, r.t., 90%; v, KOH, MeOH/H_2O (1.2:1), Δ, 73%; vi, NPSP, Bu_3P, CH_2Cl_2, -30°, 97%.

Scheme 1

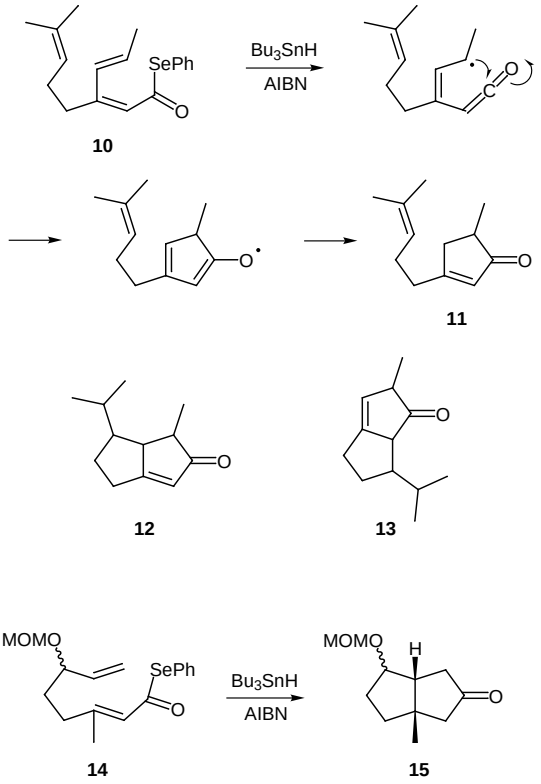
it underwent tandem cyclisation to produce a 1:1 mixture of diastereomers of the bicyclo[3.3.0]octenone **6** in 69% yield.[6] The bicyclooctenone **6** is produced from the selenyl ester **1** by way of a 5-*exo*-dig cyclisation of the unsaturated α-ketenyl radical counterpart **4** of the diene acyl radical intermediate **3**, leading to the dienolate radical **5**, followed by a 5-*exo*-trig cyclisation onto the adjacent butenyl double bond. The diastereomers of **6** could be separated by chromatography and their structures followed conclusively from examination of their n.m.r. spectroscopic properties and comparison with corresponding data for similar compounds in the literature.[7] By contrast when a solution of the conjugated triene selenyl ester **2** was treated with Bu_3SnH-AIBN the only product produced was a mixture of *E* and *Z* isomers of the simple cyclopentanone **9** (75%) resulting from mono-cyclisation of the radical intermediate **7** via **8**. In a similar manner the radical cyclisation of the α,β,γ,δ-unsaturated selenyl ester

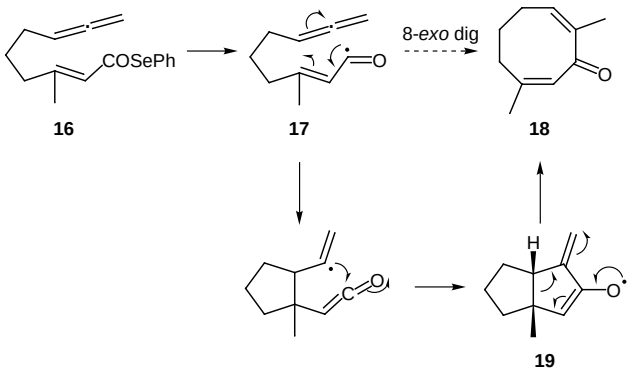


10 gave rise to only the cyclopentenone **11** (56%); neither of the anticipated bicyclooctenones **12** and **13** were detected amongst the products.

In earlier studies we have shown that the 2,7-diene selenyl ester **14** undergoes bi-cyclisation leading to a concise synthesis of the diquinane **15**.[2] Interestingly, when the non-conjugated double bond in the selenyl ester **14** was replaced by an allene electrophore, as in the allene ester **16**, treatment with Bu_3SnH-AIBN led to the novel cyclooctadienone **18** in an unoptimised 25% yield. We surmise that the cyclooctadienone **18** is produced from the selenyl ester **16** by way of ring opening of the bicyclooctene radical intermediate **19** rather than by a direct acyl radical 8-*endo*/*exo* dig cyclisation involving the intermediate **17.**

The studies described here considerably extend our knowledge base for the use of acyl radical-mediated cyclisations in the synthesis of polyquinanes. Extensions to these fundamental studies and their applications in target synthesis, particularly within the pentalenene family of triquinanoids, are in progress in our laboratories.





Acknowledgement

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References and Notes

(1) See for example: C. P. Jasperse, D. P. Curran and T. L. Fevig, *Chem. Rev.* **1991**, *91*, 1237; S. Kim, J. H. Cheong and J. Yoo, *Synlett* **1998**, 981; P. Devin, L. Fensterbank and M. Malacria, *J. Org. Chem.* **1998**, *63*, 6764 and references cited therein.

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(5) Satisfactory spectroscopic data were obtained for all new compounds. Experimental procedures for the preparation of the precursors to **1** were based on those of W. Boland, A. Gaebler, U. Preiss and H. Simon, *Helv. Chim. Acta* **1991**, *74*, 1773, and for the conversion of the acids into the selenyl esters on that of K. C. Nicolaou, N. A. Petasis and D. A. Claremon, *Tetrahedron* **1985**, *41*, 4835.

(6) Typical procedure: A solution of tributyltin hydride (245μL, 0.91mmol) and AIBN (6mg, 37μmol) in dry benzene (5mL), was added dropwise over 4.5h (*via* syringe pump) to a stirred, refluxing solution of **1** (253mg, 0.76mmol) and AIBN (6mg, 37μmol) in dry, degassed benzene (210mL), under an atmosphere of argon. The resulting mixture was heated for a further 6h, then allowed to cool to room temperature. The solvent was evaporated under reduced pressure to leave an oil, which was purified by column chromatography on silica gel (eluent:0-5% diethyl ether - 40-60 petroleum ether) to give a 1:1 mixture of the diastereomeric bicycles **6** (93mg, 0.52mmol, 69%), as a pale yellow oil. Repeated chromatography afforded clean samples of each compound: λ_{max}/nm (EtOH) 224 (6825) and 290 (603); ν_{max}/cm^{-1} (film) 1710, 1586; δ_H (diastereomer 1) 0.90 (d, *J* 6.5, CH_3-C_9), 0.90-0.96 (m, H_a-C_7), 1.08 (d, *J* 6.5, CH_3-C_9), 1.17 (s, CH_3-C_1), 1.32 (dd, *J* 6.0 and 13.0, H_a-C_8), 1.35-1.45 (m, H-C_9), 1.60-1.70 (m, H-C_6 and H_b-C_7), 1.92 (dd, *J* 6.4 and 13.0, H_b-C_8), 2.93 (dm, *J* 6.7, H-C_5), 6.22 (dd, *J* 1.7 and 5.8, H-C_3) and 7.61 (dd, *J* 2.6 and 5.8, H-C_4); δ_H (diastereomer 2) 0.92 (d, *J* 6.6, CH_3-C_9), 1.02 (d, *J* 6.6, CH_3-C_9), 1.19 (s, CH_3-C_1), 1.35-1.45 (m, H-C_6,), 1.5-1.8 (m, 2H-C_7, 2H-C_8 and H-C_9), 2.65 (dm, *J* 5.7, H-C_5), 5.96 (dd, *J* 1.7 and 5.7, H-C_3) and 7.52 (dd, *J* 2.8 and 5.7, H-C_4); δ_C (diastereomer 1) 22.0, 22.2 and 22.5 (CH_3 x 3), 28.8 (CH_2), 30.2 (CH), 37.0 (CH_2), 50.5 (CH), 54.1 (quat. C), 56.4 (CH), 134.9 and 163.9 (= CHx2), and 215.7 (C = O); δ_C (diastereomer 2) 21.3, 21.6 and 22.6 (CH_3 x 3), 31.3 (CH_2), 32.4 (CH), 34.9 (CH_2), 51.6 (CH), 54.6 (quat. C), 60.0 (CH), 130.5 and 166.4 (= CHx2), and 215.1 (C = O); m/z 178.1360 (M^+. $C_{12}H_{18}O$ requires M^+, 178.1358).

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