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α-Ketene Alkyl and α,β-Unsaturated Acyl Radical Intermediates in Ring Constructions

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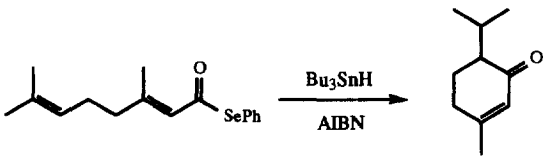
Abstract: Treatment of the *E*-α,β-unsaturated selenyl esters **1** and **3a** with Bu_3SnH-AIBN produces the corresponding cyclohexenones **2** and **7/8** respectively *via* presumed α-ketene alkyl radical intermediates. In a similar manner the cyclopropyl ester **9** leads to a mixture of **12** and **13**, and the 2,7-diene selenyl ester **15** undergoes a novel bi-cyclisation producing the diquinane **17** in 76% yield.

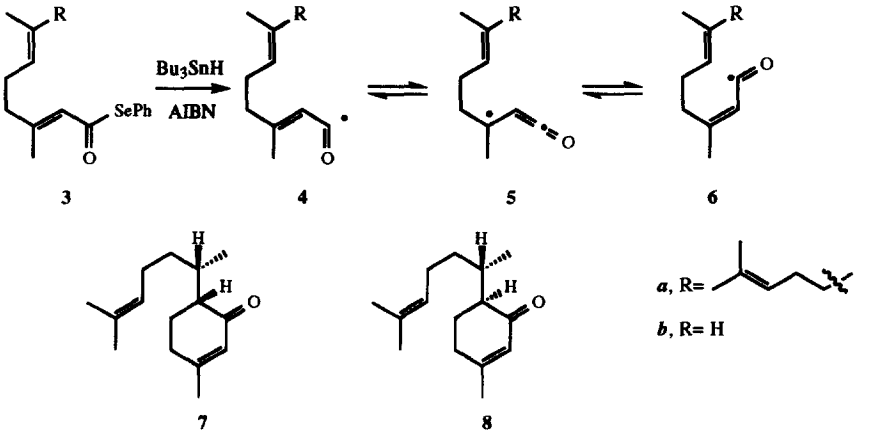
Acyl radicals derived from saturated carboxylic acid derivatives, *e.g.* acid chlorides,[1] selenides,[2] cobalt salophens,[3] S-acyl xanthates,[4] and tellurides,[5] are powerful synthetic intermediates which have been used widely in a range of carbo- and hetero-cyclic ring constructions.[1-6] In earlier studies we have evaluated the consecutive cyclisations of a range of (5-, 9-, 13-) polyolefinic acyl radical intermediates, and demonstrated their scope in the synthesis of linear and angular fused 6-ring systems, including steroid ring structures.[7] Our contemporaneous, complementary interests in the total syntheses of the neurotoxin lophotoxin[8] and the PAF antagonist phomactin A,[9] employing the macrocyclisation of an α,β-unsaturated acyl radical intermediate onto an alkene electrophore as a key strategem, have led us to evaluate some of the fundamental chemistry of α,β-unsaturated acyl radicals in some detail.[10] In this communication we describe the synthesis of a range of geometrically pure *E*-α,β-unsaturated acyl selenides incorporating additional alkene unsaturation, and their radical-mediated cyclisations to 2-cyclohexenones and diquinanes implicating novel α-ketene alkyl radicals as key intermediates.



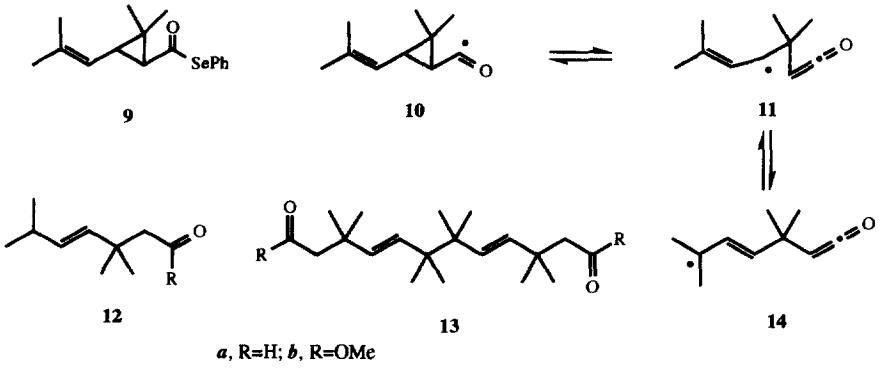
1 **2**

Thus, we first examined the chemistry of the *E*-unsaturated selenyl ester **1** derived from straightforward treatment of geranoic acid with *N*-phenylselenophthalimide and Bu_3P.[11] When a solution of **1** in dry benzene was heated under reflux in the presence of Bu_3SnH and catalytic AIBN for 1.5h, work-up and chromatography led to a single product in 86% whose spectroscopic data were identical with the known odoriferous cyclohexenone monoterpene piperitone **2** found in oil of eucalyptus.[12] In a similar manner, treatment of the *E*-

2, *E*-6 selenyl ester **3a**, produced from farnesoic acid, with Bu_3SnH-AIBN under identical reaction conditions led to a 1:1 mixture of the sesquiterpene (±)-bisabolone **7** and its epimer **8**,[13] in a combined yield of 71%.[14]

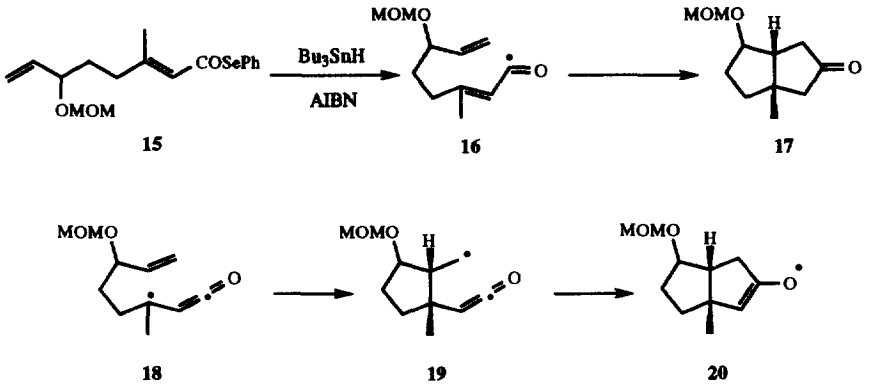


The formation of the cyclohexenones **2** and **7**, from the *E*-2 unsaturated acyclic selenyl esters **1** and **3a** respectively, in the presence of Bu_3SnH-AIBN, is interesting. We believe the cyclohexenones are produced as a result of 6-*exo-trig* cyclisations of *Z*-2 unsaturated acyl radical intermediates, *viz* **6**, produced from the corresponding *E*-2 acyl radicals **4** by way of the novel and unusual α-ketene radical species **5**.[15] To give credence to this suggestion we examined the chemistry of the cyclopropyl acyl radical intermediate **10** produced from the selenyl ester **9** derived from chrysanthemic acid.[16] To our pleasure we found that when **9** was treated with Bu_3SnH-AIBN in hot benzene the major products were the γ,δ-unsaturated aldehyde **12a** and the corresponding dimer **13a**. Furthermore, when the same reaction was conducted in hot benzene containing 10% methanol, the product was the methyl ester **13b**.[17] We believe that these data lend support to the intermediacy of the β- **11** and δ-ketene radicals **14** between the cyclopropyl acyl radical **10** and the observed products **12** and **13**. Thus reduction of the ketene unit in **14**[18] (in benzene), preceeded by or followed by hydrogen abstraction or dimerisation, leads to **12a** and **13a**, whereas a similar sequence in MeOH involving ionic alcohol addition to the ketene moiety in **14** would lead to **13b**.



As a corollary to the aforementioned studies, and as a prelude to further exploitations of the scope for α,β-unsaturated acyl radical intermediates in synthesis, we designed the 2,7-diene selenyl ester **15**,[19] with a view to effecting a tandem cyclisation involving the α-ketene alkyl radical **18** and the ketene electrophore in

concert. Thus, to our satisfaction we found that when the 2,7-diene selenyl ester **15** was treated with Bu_3SnH-AIBN in hot benzene, it underwent a remarkably efficient bicyclisation producing a 2:1 mixture of MOM-ether epimers of the diquinane **17** in 76% yield. We suggest that the diquinane is produced *via* sequential formation of the α,β-unsaturated acyl **16**, the α-ketene alkyl **18** and the alkyl radical **19** intermediates, involving successive 5-*exo-trig* and 5-*exo-dig* cyclisations, the latter involving cyclisation onto a ketene carbonyl electrophore leading to the enolate radical intermediate **20**, *ie* **16**→**18**→**19**→**20**. Further work is now in progress to complement these studies and extend the scope of these novel radical cyclisations to alternative carbo- and hetero-cyclic ring constructions.



15 **16** **17**

18 **19** **20**

Acknowledgements

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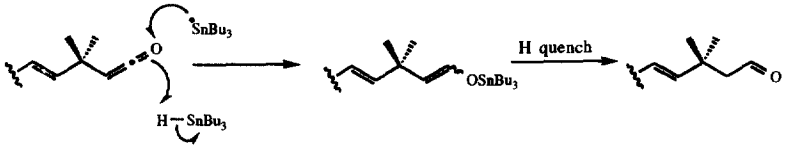
References and Notes

1. a) Cekovic, Z., *Tetrahehdron Lett.*, **1972**, 749; b) Walsh, Jr., E.J.; Messinger II, J.M.; Grudoski, D.A.; Allchin, C.A., *Tetrahedron Lett.*, **1980**, *21*, 4409.
2. a) Pfenninger, J.; Heuberger, C.; Graf, W., *Helv. Chim. Acta*, **1980**, *63*, 2328; b) Crich, D.; Fortt, S.M.,*Tetrahedron Lett.*, **1987**, *28*, 2895; c) Boger, D.L.; Mathvink, R.J., *J. Org. Chem.*, **1988**, *53*, 3377; d) Crich, D.; Fortt, S.M., *Tetrahedron Lett.*, **1988**, *29*, 2585; e) Crich, D.; Fortt, S.M., *Tetrahedron*, **1989**, *45*, 6581; f)Boger, D.L.; Mathvink, R.J., *J. Am. Chem. Soc.*, **1990**, *112* , 4003; g) Boger, D.L.; Mathvink, R.J., *J. Am. Chem. Soc.*, **1990**, *112* , 4008; h) Boger, D.L.; Mathvink, R.J., *J. Org. Chem.*, **1990**, *55*, 5442; i) Boger, D.L.; Mathvink, R.J. *J. Org. Chem.*, **1992**, *57*, 1429.
3. a) Coveney, D.J.; Patel, V.F.; Pattenden, G., *Tetrahedron Lett.*, **1987**, *28*, 5949; b) Coveney, D.J.; Patel, V.F.; Pattenden, G.; Thompson, D.M., *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2721.
4. Delduc, P.; Tailhan, C.; Zard, S.Z., *J. Chem. Soc.. Chem. Comm.*, **1988**, 308.
5. a) Chen, C.; Crich, D., *Tetrahedron Lett.*, **1993**, *34*, 1545; b) Crich, D.; Chen, C.; Hwang, J-T.; Yuan, H.; Papadatos, A.; Walter, R.I., *J. Am. Chem. Soc.*, **1994**, *116*, 8937.
6. a) Crich, D.; Eustace, K.A.; Ritchie, T.J., *Heterocycles*, **1989**, *28*, 67;b) Evans, P.A.; Roseman, J.D., *Tetrahedron Lett.*, **1995**, **36**, 31.
7. a) Chen, L.; Gill, G.B.; Pattenden, G., *Tetrahedron Lett.*, **1994**, *35*, 2593; b) Batsanov, A.; Chen, L.;

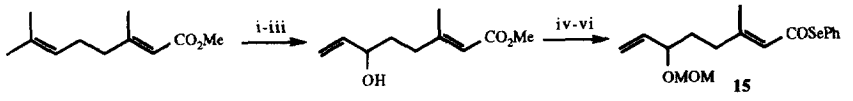
Gill, G.B.; Pattenden, G., *J. Chem. Soc., Perkin Trans. 1*, **1995**, in press.

8. a) Astley, M.P.; Pattenden, G. *Synlett.*; **1991**, 335; b) Astley, M.P.; Pattenden, G., *Synthesis*, **1992**, 101.
9. Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Harumitsu, K.; Hata, T.; Hanzawa, H., *J. Am. Chem. Soc.*, **1991**, *113*, 5463.
10. a) Penn, J.H.; liu, F., *J. Org. Chem.*, **1994**, *59*, 2608; b) Boger, D.L.; Mathvink, R.J., *J. Org. Chem.*, **1992**, *57*, 1429; c) Montheard, J-P.; Delepine, M., *C. R. Acad. Sc. Paris*, **1965**, *260*, 577.
11. a) Nicolaou, K.C.; Petasis, N.A.; Claremon, D.A., *Tetrahedron*, **1985**, *41*, 4835; b) Grieco, P.A.; Jaw, J.Y.; Claremon, D.A.; Nicolaou, K.C., *J. Org. Chem.*, **1981**, *46*, 1215.
12. Melikyan, M.O.; Tatevosyan, G.T., *J. Gen. Chem. USSR (Engl. Tran.)*, **1951**, *21*, 767.
13. Ghisalberti, E.L.; Jefferies, P.R.; Stuart, A.D., *Aust. J. Chem.*, **1979**, *32*, 1627.
14. All new compounds showed satisfactory spectroscopic, mass spectrometry and/or elemental analysis data.
15. Erman, W.F.; Gibson, T.W., *Tetrahedron*, **1969**, *25*, 2493.
16. Arlt, D.; Jautelat, M.; Lantzsch, R., *Angew. Chem. Int. Ed. Engl.*, **1981**, *20*, 703.
17. The authors would like to thank Nicola Herbert of this department for performing this experiment.
18. The reduction of the ketene in **14** under the reaction conditions may be explained as follows:



For other examples of tributylstannyl enolate generation *via* tributylstannyl radical additions to carbonyl compounds, see: a) Enholm, E.J.; Xie, Y.; Abboud, K.A., *J. Org. Chem.*, **1995**, *60*, 1112; b) Enholm, E.J.; Jia, Z.J., *Tetrahedron Lett.*, **1995**, *36*, 6819.

19. The cyclisation precursor **15** was synthesised from methyl geranoate as shown below:



15

Reagents: i, MCPBA, CH_2Cl_2, 90%; ii, $HClO_4$, THF/H_2O then KIO_4, 92%; iii, CH_2:CHMgCl, THF, 64%; iv, MOM-Cl, Hünigs base, CH_2Cl_2, 60%; v, LiOH, THF/H_2O, 93%; vi, NPSP, Bu_3P, CH_2Cl_2, -20°C, 62%.

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