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FREE RADICAL REACTIONS IN SYNTHESIS. TOTAL SYNTHESIS OF ISOAMIJIOL.

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Summary: The dolastane carbon framework present in isoamijiol(1) is elaborated from the enamine(5) using seven carbon-carbon bond forming reactions, four of which involve free radical intermediates.

Illustrations of the use of free radical intermediates in the synthesis of both natural and non-natural organic compounds have burgeoned in recent years.[1] In this *Letter* we highlight further scope for the use of free radicals by describing a total synthesis of the marine metabolite isoamijiol (1), starting from cyclopentanone, which uses seven carbon-carbon bond forming reactions, four of which involve free radical intermediates.

Isoamijiol(1) is the principal secondary metabolite in the brown seaweed *Dictyota linearis*, where it co-occurs with amijiol(2*a*) and amijidictyol(2*b*);[2] extracts of *D.linearis* are reported to show pronounced antimicrobial activity. A novel and unusual feature of isoamijiol is the presence of an *bis*-allylic alcohol unit associated with ring C; this feature is also found in capnellenediol(3)[3] and the artolide lactone(4).[4]

Our overall strategy for the synthesis of the ('dolastane') carbon skeleton present in isoamijiol involved first elaboration of the 5,7-ring fused (A/B) portion(11) by an intramolecular [2+2] photocycloaddition (*viz* 7→ 8)-intermolecular reductive coupling (*viz* 8→10)- cyclobutane fragmentation (*viz* 10→11) sequence, followed by annulation of ring C using intramolecular reductive coupling of the terminal acetylenic ketone intermediate (14*b*)(to 15).

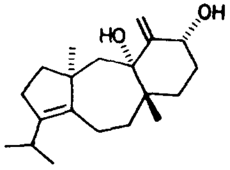
Thus, acylation of the enamine(5) derived from cyclopentanone, with 4-methyl-4-pentanoyl chloride,[5] followed by hydrolysis, first gave the 1,3-dione(6) as a pale yellow liquid, b.p. 77-9°C at 0.1mm Hg. Treatment of the dione with *tert*-butyldimethylsilyl chloride in the presence of triethylamine then led to the silyl enol ether(7), present as a 3:2 mixture of *exo*- and *endo*-isomers.[6] Irradiation of (7) in hexane, through Pyrex filtered light from a 450 watt medium pressure lamp (8h), produced a single photoadduct, m.p. 39-41°C, in 68% yield.[7] The structure of this adduct was established as (8), following fragmentation and aldolisation (aqueous HF, then aqueous NaOH) to the highly crystalline tricyclic alcohol (9), m.p. 152-4°C whose constitution was proven by single crystal X-ray analysis.

Addition of a dilute solution of the photoadduct (8) in acetone to a slurry of Ti°(from $TiCl_3$ and Li wire)[9] under dimethoxyethane, over 4h (motor-syringe) resulted in smooth intermolecular reductive coupling producing (76%) the alkene(10) as a colourless oil, δ_H 1.56-2.4(m, 12H), 1.69(d, *J*1.6,:CMe), 1.64(d, *J*1.5, :CMe), 0.93(Me), 0.86($SiBu^t$), 0.04(SiMe), 0.02(SiMe) p.p.m. Fragmentation of the cyclobutane ring in (10), was easily accomplished by brief treatment with aqueous HF,[10] leading to the central azulenone intermediate (11; 62%),[11] colourless oil, ν_{max}1695cm.$^{-1}$,δ_H2.65 (m, :CCHMe$_2$), 2.54(2H, 4-H), 2.41(m, 2H, 6-H), 1.86-2.02(m, :CCH_2), 1.52-1.85(m, 6H), 1.01(Me), 0.97(d, *J*6.8, CHMe), 0.94(d, *J*6.8, CHMe)p.p.m.

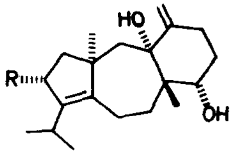
Alkylation of the enolate derived from (11)(LiHMDS, HMPA in THF at -15°C) with the iodo-alkyne(12) was both regio- and stereo- selective, producing the α-epimer(13) of the substituted azulenone. Treatment of (13) with sodium hydride in dimethoxyethane, followed by addition of methyl iodide and stirring at 25°C for 24h then led to the *bis*-alkylated azulenone (14*a*; 60%)[12] present as a 4:1 mixture of α- and β- epimers, *i.e*. (14*a*) predominating. Deprotection of the tri-isopropylsilylacetylenic ketone(14*a*) ($Bu_4\overset{+}{N}\overset{-}{F}$, THF, 25°C, 2min) revealed the terminal acetylenic ketone intermediate (14*b*) which, in the presence of sodium naphthalene radical anion (THF, 25°C, 3min) gave the deoxyisoamijiol(15; 41%) as a colourless oil.[13] The *trans*-geometry about the B/C ring junction in (15) followed conclusively from inspection and comparison of n.m.r. spectral data with those of model systems and natural isoamijiol (e.g. δ1.35 and 0.78 p.p.m. for angular Me groups in (15) and δ1.34 and 0.77p.p.m. for the Me groups in natural isoamijiol).[14]

The synthesis of (±)-isoamijiol(1) was then completed by treatment of (15) with selenium dioxide in the presence of *t*-butylhydroperoxide, which produced the *syn*-orientated *bis*-allylic alcohol(1).[15] The synthetic isoamijiol did not separate from naturally derived material in mixed chromatography, and their p.m.r. spectral data were superimposable. A small amount (10-15%) of the triene-diol (16) was also produced during the oxidation of (15), and all attempts to separate the compound from the synthetic isoamijiol proved unsuccessful.

We thank Professor Ochi (Kochi University) for a sample of natural isoamijiol and the SERC for a studentship (to G.M.R.). We also thank May and Baker Ltd. for financial support (CASE award to G.M.R.) and Dr. D. Warburton for his interest.



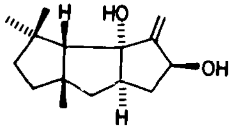
(1)



(2)

a R = H

b R = OAc



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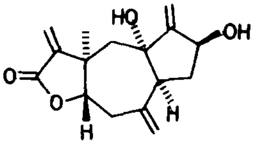

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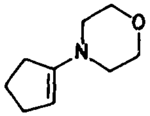

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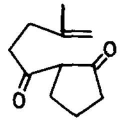

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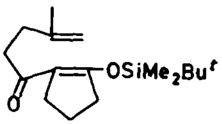

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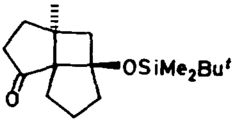

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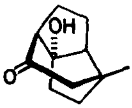

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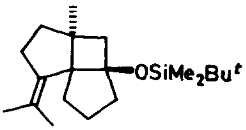

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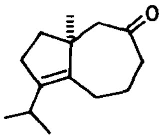
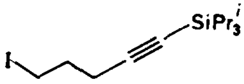
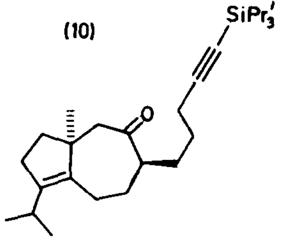


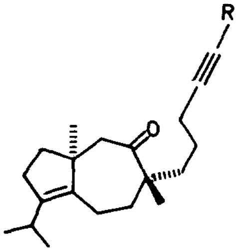
(11)



(12)



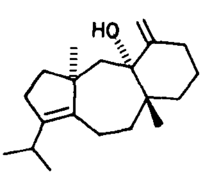
(13)



(14)

a, R = $SiPr_3^i$

b, R = H



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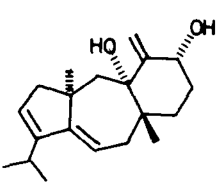

(16)

References

1. For recent review and leading references see: D.J. Hart, *Science*, 1984, **223**, 883; see also 'Selectivity and Synthetic Applications of Radical Reactions', Tetrahedron Symposia (in print), *Tetrahedron*, 1985, **41**, 3887-4302.
2. M. Ochi, M., Watanabe, I. Miura, M. Taniguchi, and T. Tokoroyama, *Chemistry Lett*., 1980, 1229, N. Harada, Y. Yokota, J. Iwabuchi, H. Uda and M. Ochi, *J.Chem.Soc*., *Chem.Commun*., 1984, 1220: see also: H.H. Sun, O.J. McConnell, W. Fenical, K. Hirotsu and J. Clardy, *Tetrahedron*, 1980, **37**, 1237.
3. Y.M. Sheikh, G. Singy, M. Kaisin, H. Eggert, C. Djerassi, B. Tursch, D. Daloze and J.C. Braekman, *Tetrahedron*, 1976, **32**, 1171. For synthesis see: G. Pattenden and S.J. Teague, *Tetrahedron Lett*., 1982, **23**, 5471.
4. A.F. Halim, A.M. Zaghloul, C. Zdero and F. Bohlmann, *Phytochemistry*, 1983, **22**, 1510 and refs. therein.
5. C.A. Grob and A. Waldner, *Helv.Chim.Acta*, 1979, **62**, 1854.
6. Satisfactory spectral data and microanalytical or mass spectroscopic data were obtained for all new compounds.
7. *cf*. M.J. Begley, M. Mellor and G. Pattenden, *J.Chem.Soc*., *Perkin Trans.I*, 1983, 1905; H. Seto, S. Hirokawa, Y. Fujimoto and T. Tatsuno, *Chemistry Lett*., 1983, 989.
8. We thank Dr. M.J. Begley of this Department for this analysis.
9. J.E. McMurry, M.P. Fleming, K.L. Kees and L.R. Krepski, *J.Org.Chem*., 1978, **43**, 3255.
10. *cf*. G. Pattenden and S.J. Teague, *Tetrahedron Lett*., 1984, **25**, 3021.
11. For a non specific synthesis of (11) see: H. Wolf, M. Kolleck and W. Rascher, *Chem.Ber*., 1976, **109**, 2805.
12. Use of the tri-isopropylsilyl protected acetylenic intermediate (13) was essential for the success of this reaction.
13. Deoxyisoamijiol(15) showed: ν_{max}3450, 1640cm^{-1}, δ_H4.8(t,*J*1.5,:CHH), 4.8(m, :CHH),2.6(qq,*J*6.9 and 6.8,CHMe$_2$),2.57-2.44(6-H,9-H,10-βH),2.34-2.1(2-H, 8-H,10-αH),2.11(d,*J*14.5,4-βH), 2.1-1.4(m,8H),1.48(d,*J*14.6,4-αH),1.35(Me), 0.94(d,J6.8,CHMe),0.92(d,J6.8,CHMe),0.78(Me)p.p.m. δ_C154.0,138.9(2xs), 108.3(t),78.9,50.9,47.7(t), 43.0(t), 41.8, 38.2(t), 32.1(t), 31.8(t), 27.4(t), 26.8(dq), 22.8(t), 22.5(t), 21.3(q), 20.4(q), 17.7(q)p.p.m.
14. For model work etc., see: G. Pattenden and G.M. Robertson, *Tetrahedron*, 1985, **41**,4001; models clearly demonstrate that cyclisation to a *cis*-fused B/C ring junction is strongly disfavoured due to the development of steric interactions between the incoming pentynyl chain and the bicylic ring system in (14*b*).
15. For model study, see refs. 3 and 14.
16. For related structures see: P. Crews, T.E. Klein, E.R. Hogue and B.L. Myers, *J.Org.Chem*., 1982, **47**, 811.

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