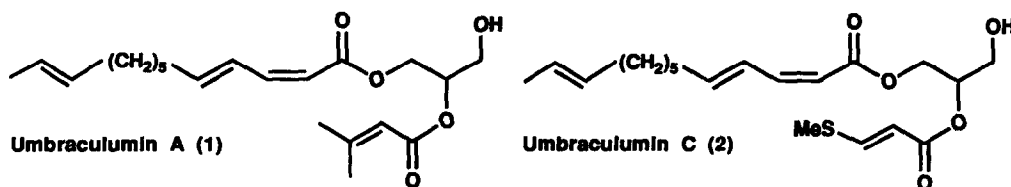


THE SYNTHESIS AND ABSOLUTE CONFIGURATION OF THE NOVEL ICHTHYOTOXIC DIACYLGLYCEROL, UMBRACULUMIN A

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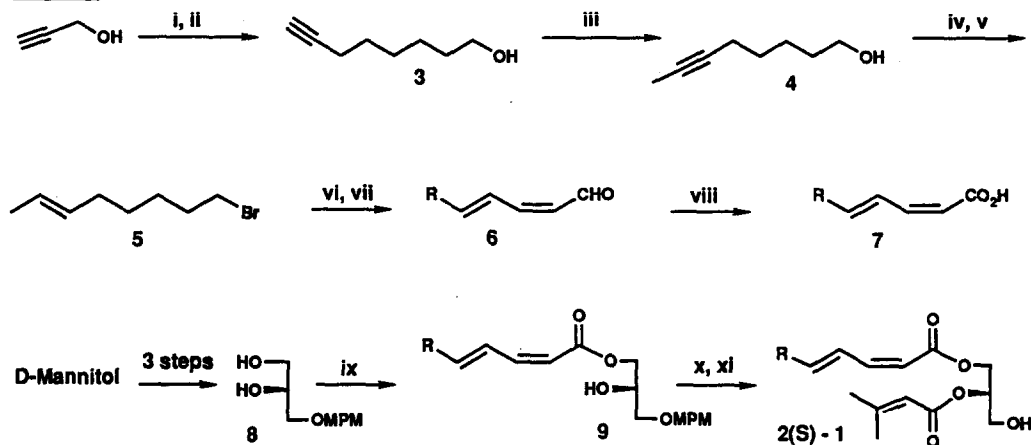
Abstract: A total synthesis of umbraculumin A (1) in homochiral form is described.

Skin extracts of the opisthobranch mollusc *Umbraculum mediterraneum* were recently shown to contain the novel diacylglycerols umbraculumin A (1) and umbraculumin C (2), their structures being determined by spectroscopic means.¹ These compounds were shown to be very toxic to the mosquito fish *Gambusia affinis* at 10 µg/ml and 0.1 µg/ml, respectively.¹ Given the current interest in marine defense allomones¹⁻³ and our own involvement with the development of stereospecific routes to conjugated polyenes^{3,4} and the synthesis and biological screening of novel diacylglycerols,⁵ we embarked upon the synthesis of umbraculumin A. The successful synthesis, which is shown in the Scheme, also serves to establish the absolute configuration of umbraculumin A.



The key carboxylic acid **7**⁶ was prepared by oxidation of aldehyde **6**, readily available by organolithium addition to pyrylium perchlorate using our recently published methodology.^{3,4} Homologation of propargyl alcohol followed by "zipper" isomerisation⁷ gave the 1-alkyne **3** which was efficiently converted into the isomeric 2-alkyne **4** using Brandsma's procedure.^{8,9} Alkyne reduction followed by bromination gave the *E*-alkenyl bromide **5**. Lithiation of **5** followed by addition of pyrylium perchlorate and rearrangement of the resulting 2*H*-pyran produced the requisite *Z,E*-dienal **6**.^{3,4}

With acid **7** in hand, we prepared the 4-methoxybenzylated glycerol derivative **8**¹⁰ in chiral form from D-mannitol. Acylation of **8** with acid **7** gave the 1-acyl derivative **9** in 50% yield accompanied by smaller amounts of the 2-acyl isomer and diacylated material. Acylation of **9** with seneciolic acid followed by removal of the protecting group using DDQ gave umbraculumin A as an oil, $[\alpha]_D -27.7$ (c 0.7, CHCl₃), lit.¹ $[\alpha]_D -24.3$ (c 0.8, CHCl₃), with ¹H- and ¹³C-NMR spectral data entirely consistent with the literature¹ values. The use of D-mannitol as starting material establishes that umbraculumin A has the 2(*S*)-configuration i.e. it is an *sn*-1,2-diacylglycerol. We are currently optimising the synthetic procedures described above and will then apply them to the synthesis of umbraculumin C. This work will be described in a full paper.

SCHEME

Reagents [MPM = 4-MeOC₆H₄CH₂-; R = *E*-CH₃CH=CH(CH₂)₅-]

(i) LINH₂, NH₃ (liq.), C₅H₁₁Br (85%) (ii) H₂N(CH₂)₃NH₂, Li, ^tBuOK (85%)

(iii) ^tBuOK, DMSO, 80°C, 5 min (93%) (iv) Li, NH₃ (liq.) (98%)

(v) Ph₂PCH₂CH₂PPh₂, 2Br₂ (94%) (vi) Li, ether (vii) Pyrylium perchlorate (57% over 2 steps)

(viii) NaClO₂, aq. ^tBuOH, 2-methylbut-2-ene (92%) (ix) 7, DCC, DMAP (50%)

(x) Me₂C=CHCO₂H, DCC, DMAP, 10d (xi) DDQ, aq. CH₂Cl₂ (29% over 2 steps)

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References

- G. Cimino, A. Crispino, A. Spinella and G. Sodano, *Tetrahedron Lett.*, 1988, **29**, 3613.
- G. Cimino, S. De Rosa, S. De Stefano, R. Morrone and G. Sodano, *Tetrahedron*, 1985, **41**, 1093 and references therein.
- B. C. Borner and R. J. K. Taylor, *J. Chem. Res.(S)*, 1990, 162.
- M. Furber, J. M. Herbert and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1989, 683 and references therein.
- J. C. Briggs, A. H. Haines and R. J. K. Taylor, unpublished results.
- All new compounds gave consistent spectral and analytical/mass spectrometric data.
- S. R. Macaulay, *J. Org. Chem.*, 1980, **45**, 734.
- Preparative Acetylenic Chemistry, 2nd Ed., L. Brandsma, Elsevier, 1988 (p. 231-234).
- An alternative procedure involving methylation of the dianion derived from hept-5-yn-1-ol was also employed but was less convenient and gave variable yields of 4.
- S. F. Martin and J. A. Josey, *Tetrahedron Lett.*, 1988, **29**, 3631;
P.W. Manley, D. P. Tuffin, N. M. Allanson, P. E. Buckle, N. Lad, S. M. F. Lai, D. O. Lunt, R. A. Porter and P. J. Wade, *J. Med. Chem.*, 1987, **30**, 1812.