A Tandem Radical Cyclisation Approach to the Hexahydrobenzofuran Skeleton for Avermectin Synthesis

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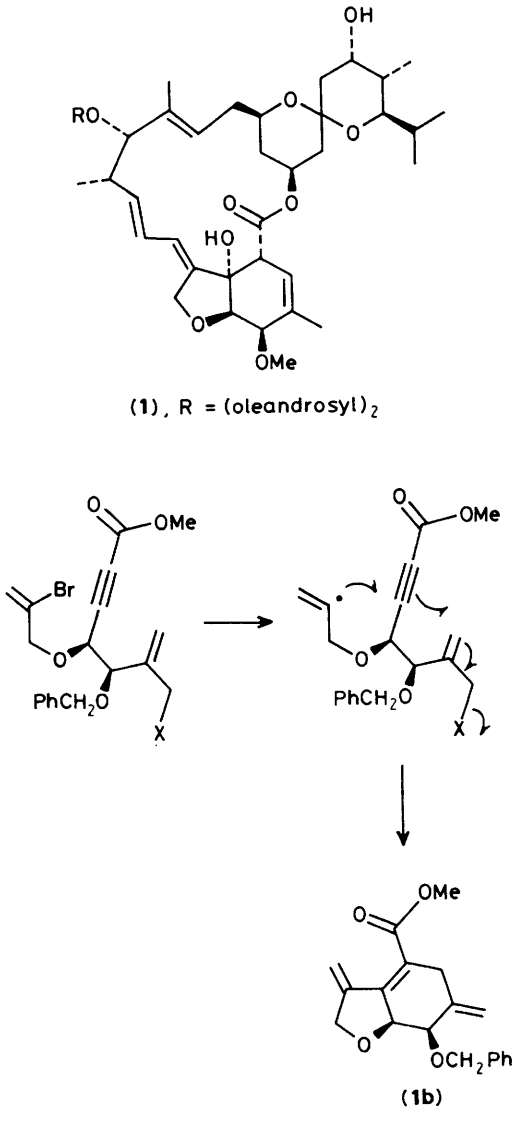
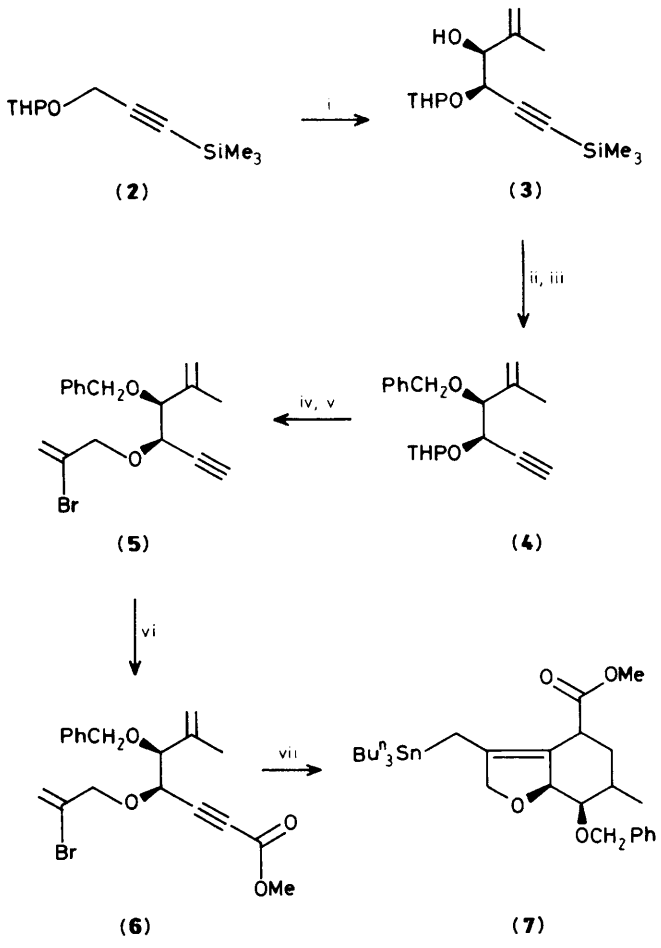
A rapid entry into the hexahydrobenzofuran skeleton is described which uses a tandem radical cyclisation on a simple *erythro* ether as the key step.

The avermectins are a group of eight structurally related compounds possessing broad spectrum insecticidal activity of unprecedented magnitude.[1] Avermectin A_{2b}(**1**) for example has exceedingly high antiparasitic activity but low mammalian toxicity,[2] which highlights the commercial importance of these compounds. Their important biological activity has resulted in extensive research both to synthesise the avermectins, and to arrive at suitably related structures for biological evaluation. Here we present our preliminary contribution for the synthesis of the hexahydrobenzofuran portion of the avermectins. The method is short compared with existing routes[3] and has a measure of flexibility to allow the facile construction of



Scheme 1. X = $SnBu^n_3$ or SPh.



Scheme 2. *Reagents and conditions:* i, Bu^tLi, $Ti(OPr^i)_4$, CH_2=C(Me)CHO, −96 °C, tetrahydrofuran (THF), 80%; ii, NaOH–MeOH, 97%; iii, NaH, $PhCH_2Br$, dimethoxyethane, 86%; iv, HCl–MeOH, 93%; v, CH_2=C(Br)CH_2Br, 50% NaOH(aq.), CH_2Cl_2, cetyltrimethylammonium bromide (20 mol %), 79%; vi, Bu^nLi, MeOCOCl, −78 °C, 67%; vii, Bu^n_3SnH (2 equiv.), azoisobutyronitrile (AIBN) (10 mol %), C_6H_6, 80 °C, 43%. THP = tetrahydropyran-2-yl.

analogues. Our initial idea for hexahydrobenzofuran construction involved use of the tandem radical cyclisation shown in Scheme 1.

In order to investigate the sequence outlined in Scheme 1, we treated the silylated acetylene (**2**) with t-butyl-lithium, and the resulting anion was treated sequentially with titanium tetraisopropoxide[4] and methacrolein to give the *erythro* alcohol† derivate (**3**) as the exclusive product (80%) (Scheme 2). Protodesilation with NaOH–MeOH (93%) followed by benzylation of (**3**) with sodium hydride and benzyl bromide gave (**4**) in 86% yield. Removal of the tetrahydropyranyl group in (**4**) with dil. HCl, followed by etherification with 2,3-dibromopropene under phase transfer conditions[5] gave the benzyl ether (**5**).

Treatment of (**5**) with n-butyl-lithium in ether followed by workup with methyl chloroformate gave the ester (**6**) (67%). With the ester (**6**) prepared we were able to try to form the 6,5-ring system required for avermectin synthesis. It was found that the quality of Bu^n_3SnH used was critical for the success of the reaction. When freshly prepared Bu^n_3SnH (2 equiv.) was added slowly to a solution of (**6**) in boiling benzene containing AIBN,[6] the allyl stannane (**7**) was obtained as one isomer in 43% yield as shown by ^{13}C n.m.r. analysis.‡ This result proved the viability of the approach; the allyl stannane is presumably formed by the 1,6-addition of tributyltin radicals to the initially formed α,β,γ,δ-unsaturated ester (**1b**). We are now working towards the total synthesis of the avermectins, using X = SPh (Scheme 1) which will avoid the problems associated with double bond deconjugation in the six membered ring.[7]

† All new compounds were characterised by ^1H and ^{13}C n.m.r., i.r., mass spectral and/or microanalytical data.

‡ ^{13}C n.m.r. (67.9 MHz, C_6D_6) δ 174.0 (s), 139.8 (s), 130.7 (s), 118.8 (s), 92.2 (d), 80.6 (t), 80.5 (t), 75.1 (d), 51.0 (q), 43.2 (d), 33.6 (d), 32.4 (t), 30.2 (t), 29.5 (t), 27.8 (t), 18.2 (q), 13.9 (q), 10.3 (t). [Spectrum with $CDCl_3$ as solvent also shows 116.4, 116.2, 116.09 (d).] ^1H n.m.r. (270 MHz, $CDCl_3$, Me_4Si) δ 7.2 (5H, m, ArH), 4.86 (1H, d, *J* 12 Hz, $-OCH_2Ph$), 4.67 (1H, m, C-6), 4.59 (1H, d, *J* 12 Hz, OCH_2Ph), 4.48 (2H, m, C-8′), 3.72 (1H, s, $-OCH_3$), 3.57 (1H, m, C-2), 3.05 (1H, m, C-5), 1.9—0.8 [35H, m (including 0.95, d, *J* 6.6 Hz, CH_3-4)]. (Avermectin numbering).

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References

1 J. R. Egerton, D. A. Ostlind, L. S. Blair, C. H. Eary, D. Suhayda, S. Cifelli, R. F. Riek, and W. C. Campbell, *Antimicrob. Agents Chemother.*, 1979, **15**, 372.
2 A. G. M. Barrett, R. A. Carr, S. V. Attwood, M. A. W. Finch, and G. Richardson, 'Recent Advances in the Chemistry of Insect Control,' ed. N. F. James, The Royal Society of Chemistry, Special Publication No. 53, London, 1985, p. 257.
3 M. T. Crimmins, W. G. Hollis, Jr., and J. G. Lever, *Tetrahedron Lett.*, 1987, **28**, 3647; M. E. Jung and L. J. Street, *J. Am. Chem. Soc.*, 1984, **106**, 8327, and references cited therein.
4 H. Hiraoka, K. Furuta, N. Ikeda, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2777.
5 A. D. Kaye and G. Pattenden, *Tetrahedron Lett.*, 1986, **27**, 2033.
6 D. P. Curran and D. M. Rakiewicz, *Tetrahedron*, 1985, **41**, 3943; G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, 1983, **105**, 3720.
7 S. Hanessian, D. Dybé, and P. J. Hodges, *J. Am. Chem. Soc.*, 1987, **109**, 7063.