Total Synthesis of (±)-4-Epi-helminthosporal

Brian D. Gray and J. Allen Miller*†

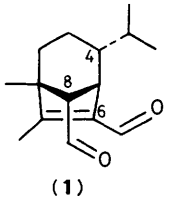
Department of Chemistry, The University, Dundee DD1 4HN, Scotland

(±)-4-Epi-helminthosporal, (**2**), is synthesised from geranyl chloride and 3-methoxy-1-phenylthiopropyne, by a five stage sequence in which the key step, leading to the bicyclo[3.2.1]oct-6-ene skeleton, is a zinc chloride catalysed [3 + 2]cycloaddition of an allyl cation to an alkyne.

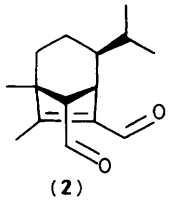
The helminthosporanes are a group of sesquiterpene derivatives which came into prominence in the 1960's as a consequence of the effect of certain fungi upon plant growth.[1–3] Although there is some uncertainty[3,4] about the specific family members responsible for large scale and commercially very significant crop damage, the dialdehyde helminthosporal, (**1**), has been the target for synthetic study by a number of organic chemists.[5–7] Several analogues have also attracted synthetic attention.[8,9] This communication describes a new and very direct route to helminthosporanes, as illustrated by the preparation of (±)-4-epi-helminthosporal (**2**).

We have recently reported the regio- and stereo-selective Lewis acid catalysed [3 + 2]cycloaddition of monoterpene chlorides with alkynes to give bicyclo[3.2.1]oct-6-enes.[10] This cycloaddition appeared to be ideally suited for application to the synthesis of helminthosporal derivatives, provided that suitable functionality could be placed at the C-6 and C-8 (bridge) positions of the bicyclic skeleton. Our strategy therefore required an alkyne component (for the [3 + 2]-cycloaddition) which has a functionalised one carbon side-chain, and which has, as the other ligand, a readily replaceable group, capable of controlling the cycloaddition regiochemistry. 3-Methoxy-1-phenylthiopropyne (**4**) appeared to fulfill these criteria.‡

Zinc chloride catalysed reaction of geranyl chloride (**3**) and 3-methoxy-1-phenylthiopropyne (**4**) proceeded at room temperature to give bicyclic chloride (**5**), as a single diastereoisomer, in 85% yield (Scheme 1). The stereochemistry of (**5**) at the bridge (C-8), and at the carbon (C-4) bearing the isopropyl group was assigned as reported previously.[10] Heating of a toluene solution of (**5**) with alumina (deactivated to between 2 and 3 on the Brockmann scale)[12] resulted in hydrolysis of the bridge chlorine to afford the bicyclic alcohol (**6**) (86% yield). Analysis of the n.m.r. spectrum of (**6**) indicated that hydrolysis had taken place with retention of the bridge stereochemistry, *i.e.* $J(H^5–H^8)$ 5 Hz. The structure of (**6**) was confirmed by single crystal *X*-ray analysis.[13]



(**1**)



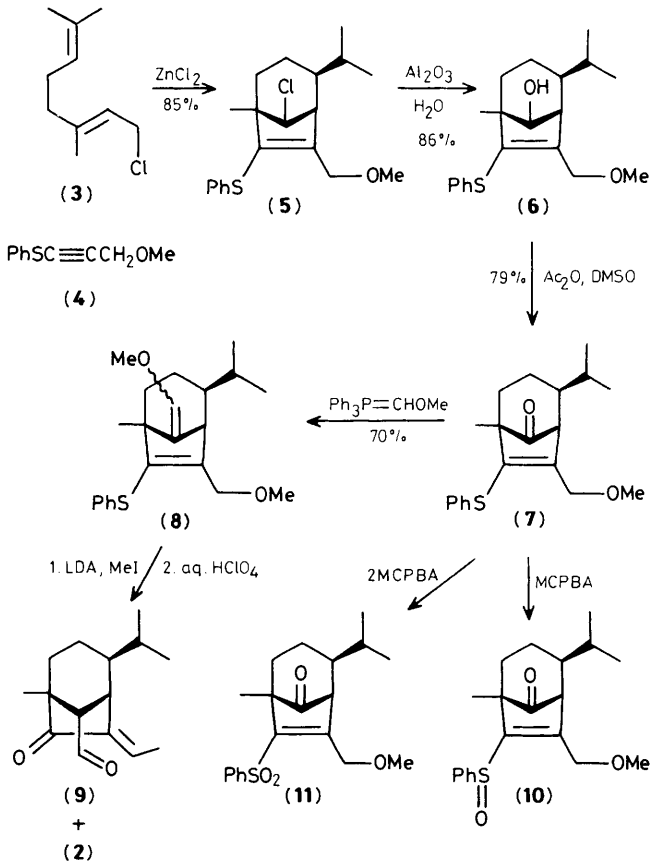
(**2**)

† *Present address:* Department of Medicinal Chemistry, The Wellcome Research Laboratories, Beckenham, Kent BR3 3BS, U.K.

‡ Unfortunately, simple but-2-ynyl derivatives, such as $MeC{\equiv}CCH_2OMe$, do not undergo [3 + 2]cycloaddition. The regiochemical basis for selection of a sulphur ligand as a control element is described in ref. 11.

Moffatt oxidation of (**6**), then Wittig olefination with methoxymethylenetriphenylphosphorane, gave the enol ethers (**8**), as a mixture of geometric isomers, which were purified by chromatography. Treatment of (**8**) with lithium di-isopropylamide at −78 °C, followed by quenching of the resulting allylic lithio derivative with methyl iodide, gave a mixture of methylated products, which were hydrolysed with 35% perchloric acid. Chromatography gave 4-epi-helminthosporal (**2**)§ together with the ketoaldehyde (**9**), in a ratio of 1 : 2.5 respectively.

Under these conditions, methylation of the lithio derivative of vinyl sulphide (**8**) was expected to favour attack α- to the sulphur, but this was clearly not the case. In an effort to



Scheme 1. DMSO = dimethyl sulphoxide, LDA = Lithium di-isopropylamide, MCPBA-*m*-chloroperbenzoic acid. All structures are shown as one enantiomer only.

§ *Spectral data*: $\nu_{max.}$, 2710, 1710, 1650 cm^{-1}; δ_H 0.93 (d, *J* 6 Hz, 3H), 1.05 (d, *J* 6 Hz, 3H), 1.19 (s, 3H), 2.05 (s, 3H), 2.32 (d, *J* 4 Hz, 1H), 3.21 (m, 1H), 9.48 (d, *J* 4 Hz, 1H), 9.97 (s, 1H). Satisfactory analytical and spectroscopic data were obtained on intermediates.

improve the α-selectivity of the allylic methylation, ketone (**7**) was converted into the corresponding sulphoxide and sulphone, (**10**) and (**11**) respectively, with appropriate equivalents of *m*-chloroperbenzoic acid. However Wittig olefination of (**10**) and (**11**) did not proceed smoothly.

Despite the lack of selectivity in the methylation step, this sequence offers a relatively short entry into the helminthosporane family, and, moreover, is clearly suitable for modification in order to prepare analogues with potential biological activity.

We thank the Carnegie Trust for financial support (scholarship to B. D. G.).

Received, 23rd February 1987; Com. 237

References

1 R. A. Ludwig, *Can. J. Botany*, 1957, **35**, 291.
2 P. De Mayo, E. Y. Spencer, and R. W. White, *Can J. Chem.*, 1961, **39**, 1608.
3 P. de Mayo, R. E. Williams, and E. Y. Spencer, *Can. J. Chem.*, 1965, **43**, 1357.
4 H. G. Cutler, F. G. Cromley, R. H. Cox, E. E. Davis, J. L. Harper, R. J. Cole, and D. R. Sumner, *J. Agric. Food Chem.*, 1982, **30**, 658.
5 E. J. Corey and S. Nozoe, *J. Am. Chem. Soc.*, 1965, **87**, 5728.
6 M. Yanagiya, K. Kameko, T. Kayi, and T. Matsumoto, *Tetrahedron Lett.*, 1979, **20**, 1761.
7 Y. Shizuri, K. Suyama, and S. Yamamura, *J. Chem. Soc., Chem. Commun.*, 1986, 63.
8 L. N. Mander, J. V. Turner, and B. G. Coombe, *Aust. J. Chem.*, 1974, **27**, 1985.
9 J. Mann and H. J. Overton, *Tetrahedron Lett.*, 1985, **26**, 6133.
10 B. D. Gray and J. A. Miller, *J. Chem. Res. (S)*, in the press.
11 B. D. Gray, C. M. McMillan, J. A. Miller, and G. M. Ullah, *Tetrahedron Lett.*, 1987, **28**, 689.
12 H. Brockmann and H. Schodder, *Chem. Ber.*, 1941, **74B**, 73.
13 B. D. Gray, J. A. Miller, and T. J. R. Weakley, *Acta Crystallogr., Sect. C*, 1987, in the press.