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A STEREOSPECIFIC SYNTHESIS OF CHALOXONE

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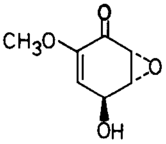
Abstract - Chaloxone, 5-hydroxy-3-methoxy-7-oxabicyclo[4.1.0.]hept-3-en-2-one, has been synthesised from benzoquinone via a diepoxide.

Chaloxone (1), together with the methyl ester of (+)-3,4-anhydroshikimic acid (2), was isolated from the fungus Chalara microspora (Corda) Hughes.[1,2]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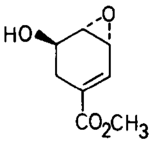
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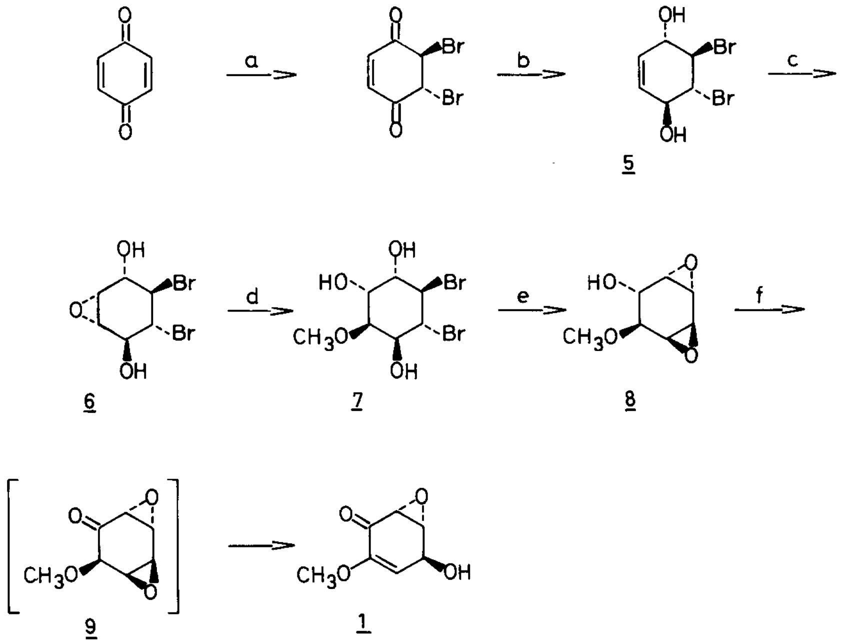
The synthesis of chaloxone (1) involves the introduction of many different functional groups, with the epoxide trans to the hydroxyl group. A synthetic strategy was chosen, whereby this configuration should be obtained by an epoxide elimination (e.g. 3 → 4) in the final stage of the reaction sequence. A synthesis of 6 described in a publication by Altenbach et al.[3] made it possible to test the idea. Furthermore, the symmetry of 5 is highly favourable for the scheme.


3 4

The epoxide 6 (1.0g) was refluxed for 24h in MeOH (20ml) with a catalytic amount of $BF_3 \cdot Et_2O$ (0.1ml) to yield 7 (1.0g, 90%) mp. 190-192°C (EtOAc, MeOH); ^1H NMR (acetone-d_6): [δ4.4-3.9 (3H,m), 3.9-3.0 (6H,m), 3.5 (3H,s)]. The epoxide opens to give a trans diaxial relation between the MeO- and the new HO- group.[4] 7 (0.50g) in dry dioxane (10ml) was added to potassium t-butoxide (0.36g) in t-butanol (10ml) at RT. After stirring for 1h, the solvents were evaporated and the residue triturated with dry acetone. Filtration of the solution through a short column of alumina (grade III) and evaporation yielded almost pure diepoxide 8 (0.22g, 89%) [^1H NMR ($CDCl_3$): δ 4.1 (1H, CHOH, d, J=8Hz), 3.9-3.4 (6H,m), 3.65 (3H,s)].



a: Br_2, CCl_4. b: $NaBH_4$, ether/H_2O. c: m-CPBA, $CHCl_3$. d: MeOH, cat. $BF_3 \cdot Et_2O$.
e: t-BuOK, t-BuOH/dioxane. f: $CrO_3 \cdot Py_2$, CH_2Cl_2.

Diepoxide 8 (100mg) in dry CH_2Cl_2 (3ml) was added at RT to $CrO_3 \cdot Py_2$ (6 equiv.) in dry CH_2Cl_2 (20ml).[5] The mixture was stirred for 20 min, diluted with ether and filtered through alumina (grade III). The solvents were removed at a low temperature, and from the residue chaloxone (1) (40mg, 40%) [mp. 150-152°C] was obtained by crystallization from EtOAC/ether. The oxidized diepoxide 9 was never detected, and presumably underwent spontaneous elimination to chaloxone (1) under the reaction conditions. Spectroscopic data for synthetic chaloxone (1) were identical with those of the material isolated from Chalara microspora.

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