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Synthesis of Bromoxone

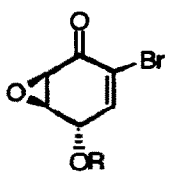
Elisabeth C. L. Gautier,[a] Norman J. Lewis,[b] Alexander McKillop,[a*] and Richard J. K. Taylor[a,#,*]

[a]School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, U. K.

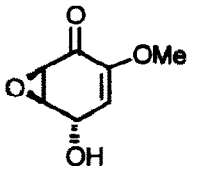
[b]SmithKline Beecham Pharmaceuticals, Old Powder Mills, Leigh, Tonbridge TN11 9AN, U. K.

Abstract **A short synthetic route to the natural product bromoxone is reported (5 steps, 15% overall yield), involving regioselective monoepoxidation of an electrolytically-derived quinone monoketal followed by stereoselective ketone reduction.**

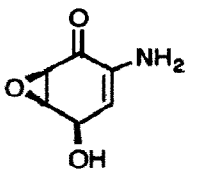
Bromoxone (**1**), and its acetylated derivative (**2**), were isolated in 1987 from a newly discovered species of acorn worm belonging to the genus *Ptychodera* found in deep underwater caves on the island of Maui.[1] The structure of (**2**) was confirmed by X-ray crystallography and (**1**) was converted into (**2**) by acetylation. Compound (**2**) was shown to possess antitumour properties.[1] Compounds (**1**) and (**2**) belong to a rapidly increasing group of bioactive epoxyquinol natural products which includes chaloxone (**3**),[2] the antibiotic MM14201 (**4**)[3] and the antibiotic LL-C10037α (**5**),[4] which was shown to be the *N*-acetylated enantiomer of (**4**) during biosynthetic studies.[5] 2-Alkyl-substituted analogues such as epoxydon[6] are also known and there is a large family of complex 4-substituted epoxyquinols which includes the colabomycin/manumycin families of antibiotics[7] and the diepoxycyclohexanone aranorosin.[8]



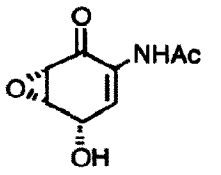
(**1**), R = H
(**2**), R = Ac



(**3**)



(**4**)



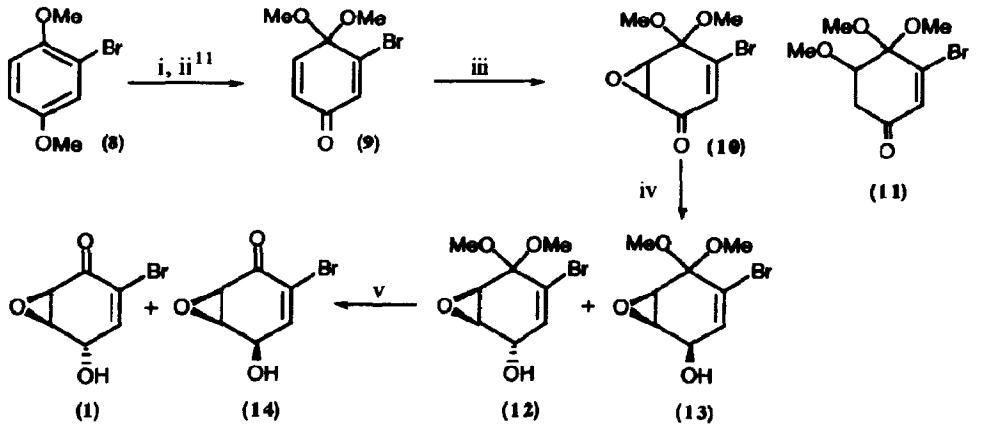
(**5**)

In an ongoing programme in this area we have recently completed the synthesis of (-)-aranorosin[9] and are now investigating synthetic routes to colabomycin, manumycin and related compounds. In this *Letter* we report the viability of one of these synthetic approaches by carrying out the first synthesis of bromoxone (**1**) in racemic form (Scheme).[10] Thus bromoquinone monoketal (**9**) was readily prepared from (**8**) by anodic oxidation followed by selective ketal monohydrolysis.[11] Efficient monoepoxidation of (**9**) proved to be extremely difficult. The best yield of (**10**) from alkaline hydrogen peroxide systems was 21% using NaOH/MeOH, with the methanol adduct (**11**) being formed as a by-product in 33% yield. The use of tert-butyl hydroperoxide/base in THF at low temperature gave better yields, the best being 43-46% with KOBu^t or KH as base (see Scheme). With BuLi as base[12] the reaction was much slower and the best yield obtained was 33%. Hydride reduction of

Present address: Department of Chemistry, University of York, York YO1 5DD

(**10**) showed a remarkable stereochemical dependency on the choice of base and solvent (Scheme). The *syn*-hydroxyepoxide (**13**) predominated using $NaBH_4$ (methanol), L-selectride (THF) and DibalH (dichloromethane) but the stereoselectivity was low. Remarkably, the use of DibalH in THF gave a 9:1 predominance of the required *anti*-isomer (**12**). Compounds (**12**) and (**13**) could be separated by repeated recrystallisation but the mixture was usually employed in the deprotection step. This proved difficult, but success was achieved with montmorillonite K10 clay. Bromoxone (**1**) was separated from its epimer (**14**) by florosil chromatography in 53% yield over the final two steps (decomposition occurred on silica or alumina). Epibromoxone (**14**) was obtained in up to 36% yield in a similar manner using in the deprotection step the 33:67 mixture of (**12**) and (**13**) obtained from L-selectride reduction of (**10**). We are currently extending this methodology to more complex members of this natural product family.

Scheme



Reagents:

(i) Anodic oxidation, KOH/MeOH (87%)[11]
(ii) AcOH, acetone (71%)[11]
(iii) ^tBuOOH, KH, THF, -50°C (46%)
(iv) DibalH, THF, -78°C to rt
(v) K-10, CH_2Cl_2 [(**1**), 53% over 2 steps]

Reduction of (**10**)	(**12**):(**13**)
$NaBH_4$, MeOH, 0°C	40:60
$NaBH_4$, $CeCl_3$, MeOH, 0°C	50:50
L-Selectride, THF, -78°C	33:67
DibalH, CH_2Cl_2, -50°C	33:67
DibalH, THF, -78°C to rt	90:10

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