A New Synthetic Route to Non-K and Bay Region Arene Oxide Metabolites From *cis*-Diols

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Arene oxides of naphthalene, quinoline, triphenylene, benzo[*e*]pyrene, and dibenz[*a,c*]anthracene have been synthesised in enantiopure (**1a–c**) or racemic form (**1d–f**), free from oxepine isomers (**3d–f**) from *cis*-diol precursors (**7a–f**) *via* chloroacetate (**9a–f**) or dimesylate (**13a**) intermediates.

Arene oxides have been established as the initially formed metabolites during biodegradation of both aza-polycyclic (APAH) and polycyclic aromatic hydrocarbons (PAH) in mammals.[1] The arene oxides **1** of naphthalene **1a**,[2] quinoline **1b** and **1c**,[3,4] triphenylene, **1d**,[5] benzo[*e*]pyrene, **1e**[6] and dibenz[*a,c*]anthracene **1f**[7] have thus previously been synthesised and implicated as mammalian metabolites by direct detection, **1a** and **2a**,[8,9] or by isolation of the derived phenolic or *trans*-dihydrodiol metabolites. It has been predicted, on the basis of perturbation molecular orbital calculations,[10] that some arene oxides will exist as separable enantiomers (*e.g.* **1a**) while others (*e.g.* **1d–f**) will spontaneously racemize *via* the corresponding unstable oxepine isomer **2** (Scheme 1).

When arene oxides, particularly of the larger members of the PAH series (*e.g.* **1d–f**), were synthesised *via* the dibromoester derivatives (**5d–f**), in order to confirm their predicted racemization (Schemes 1 and 2), they were consistently found to be accompanied by the corresponding oxepine tautomers **3d–f**.[5–7] Removal of these more stable oxepines is often very difficult due to the similar chromatographic properties and greater instability of the isomeric arene oxides **1**.

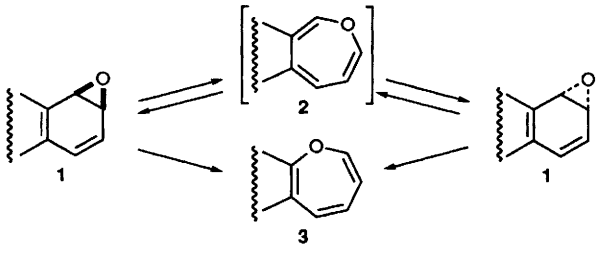
This communication describes an alternative synthetic strategy to (i) the enantiopure arene oxides **1a–c** of either configuration starting from the corresponding enantiopure *cis*-dihydrodiol metabolites **4a–c**, obtained by bacterial oxidation of the parent arenes, and (ii) racemic samples of the arene oxides **1d–f** without the concomitant formation of the corresponding oxepine **3**.

Our first synthetic approach was based upon the conversion of K-region *cis*-diols to K-region[1] arene oxides *via* a dioxolane intermediate.[11–13] This approach, in the past, appeared to be unsuccessful for the synthesis of the non-K-region[1] arene oxide **1a** and was thus assumed to be limited to K-region arene oxides.[12]

Samples of (1*R*,2*S*)-*cis*-1,2-dihydroxy-1,2-dihydronaphthalene **4a**, ($[\alpha]_D$ + 246), (5*R*,6*S*)-*cis*-5,6-dihydroxy-5,6-dihydroquinoline **4b** ($[\alpha]_D$ + 220) and (8*R*,7*S*)-*cis*-7,8-dihydroxy-7,8-dihydroquinoline **4c** ($[\alpha]_D$ + 45) were available from biotransformation studies[14,15] using the soil bacterium *Pseudomonas putida* UV4 and from related synthetic studies.[16,17] Catalytic hydrogenation (Pd/C) of the *cis*-dihydrodiols **4a–c** yielded the corresponding *cis*-tetrahydrodiols **7a–c** (*ca.* 80–95% yield).[15] (Table 1). The dioxolane derivatives **8a–c**, obtained by treatment of the *cis*-diols **7a–c** with trimethylorthoacetate, proved to be mixtures of stereoisomers (*ca.* 80–95% yield) and were converted, without separation, to the corresponding chloroacetates **9a–c** by treatment with trimethylsilyl chloride (*ca.* 90–95% yield) as shown in Scheme 3. The tetrahydroepoxides **10a–c** were subsequently formed by base treatment of the corresponding chloroacetates **9a–c** (*ca.* 60–90% yield).

The arene oxides **1a–c** were obtained, from either the corresponding tetrahydroepoxides **10a–c** or the chloroacetates **9a–c**, by a two step reaction sequence involving benzylic bromination, to yield the bromoepoxides **11a–c** or the bromochloroacetates **12a–c**, followed by dehydrobromination. The method utilizes the available bacterial metabolites of bicyclic PAH or APAH **4a–c**,[15] for synthesis of the 'elusive' arene oxide metabolites **1a–c** formed in mammalian systems, in sufficient quantities for chemical and biological studies. Although this is the first reported synthesis of arene oxide **1c** in enantiomerically pure form, it has also been obtained in either enantiomeric form using the appropriate bromo MTPA diastereoisomer.[17]

One major drawback of the bacterial metabolism route to *cis*-dihydrodiols of naphthalene **4a** and quinoline **4b** and **4c**, is the availability of only one enantiomer[14,15] (Table 1). The conversion of *cis*-tetrahydrodiol **7a** to tetrahydroepoxide **10a** of either (1*S*,2*R*) configuration (*ca.* 30% overall yield) *via* the



Scheme 1

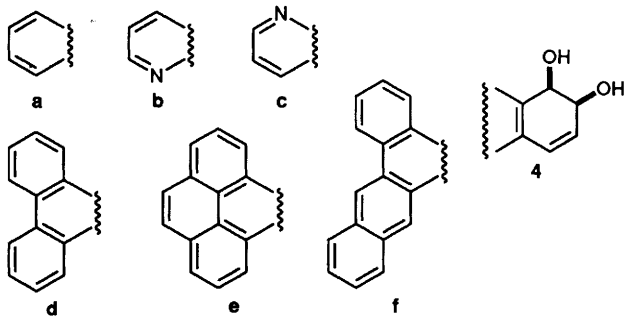
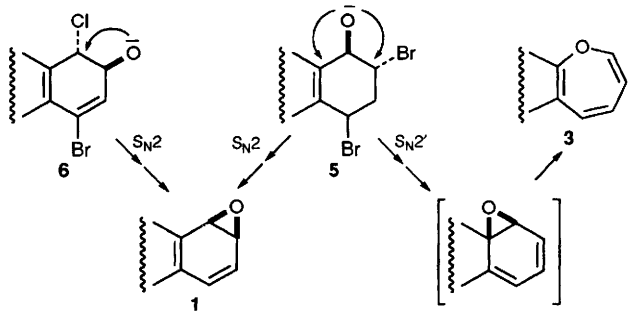


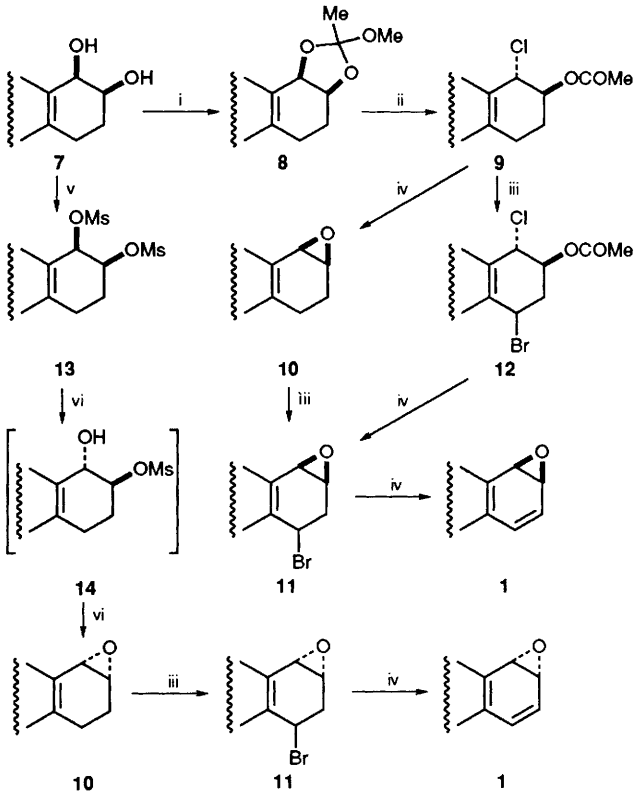
Table 1 Optical rotations and absolute configurations (Ab. con.) of the *cis*-tetrahydrodiols **7**, the derived tetrahydroepoxides **10** and the arene oxides **1** obtained *via* the chloroacetates **9**

Compound	$[\alpha]_D$[a]	Ab. con.
7a	−39	1*R*,2*S*
7b	−7[b]	5*R*,6*S*
7c	−72[b]	8*R*,7*S*
10a	+133	1*R*,2*S*
10a[c]	−138	1*S*,2*R*
10b	+96	5*R*,6*S*
10c	+157	8*R*,7*S*
1a	+127	1*R*,2*S*
1a[c]	−125	1*S*,2*R*
1b	−23	5*R*,6*S*
1c	+55	8*R*,7*S*

[a] In $CHCl_3$ solvent. [b] In MeOH solvent. [c] Obtained *via* the dimesylate **13**



Scheme 2



Scheme 3 *Reagents* i, $MeC(OMe)_3$, toluene; ii, Me_3SiCl, Et_3N; iii, NBS iv, NaOMe; v, $MeSO_2Cl$, Et_3N; vi, KOH, H_2O, TBAB, toluene

dimesylate **13a** or (1*R*,2*S*) configuration through the chloroacetate **9a** demonstrates how a single *cis*-dihydrodiol enantiomer can be manipulated to yield either enantiomer of tetrahydroepoxide **10a** or arene oxide **1a**. Although the monomesylate intermediate **14a** was not isolated, it was assumed that nucleophilic displacement of the benzylic mesylate group in compound **13a** by a hydroxide anion, proceeded exclusively by an S_N2 mechanism *i.e.* inversion of configuration occurred (Scheme 3). The dimesylate method has not yet been used in the synthesis of the azaarene oxides **1b** and **1c**, but its general applicability has recently been established by epoxide formation in other bicyclic ring systems.[17]

The tetracyclic **7d** and pentacyclic **7e** and **7f** *cis*-tetrahydrodiols were obtained in racemic form by osmium tetroxide dihydroxylation of the corresponding dihydroarenes (*ca.* 60–80% yield) whose syntheses were reported earlier.[5–7] Following a synthetic sequence, similar to that outlined for the arene oxides **1a–c** (Scheme 3), the *cis*-tetrahydrodiols **7d–f** were also converted *via* the chlorobromoacetates **12d–f** to the corresponding arene oxides **1d–f** in overall yields of *ca.* 30–50%. The arene oxides **1d–f** were found to be totally free from the stable oxepine isomers **3d–f**. This observation strongly supports the view expressed in earlier reports,[5–7] that the concomitant formation of both arene oxide **1d–f** and oxepine **3d–f** from the dibromoester derivative **5** is due to two competing pathways involving cyclization through an S_N2 mechanism (to yield arene oxide **1**) or an S_N2' mechanism (to yield oxepine **3**). The use of the bromochloroacetate derivative **6** ensured that only an S_N2 cyclization mechanism was possible (to yield arene oxide **1**) (Scheme 2).

Using the approach outlined in Scheme 3 the synthesis of bay-region[1] arene oxides, from the larger members of the PAH or APAH series (*e.g.* **1d–f**), can now be readily achieved without the co-formation of an oxepine tautomer (*e.g.* **3d–f**). Moreover, by making use of optically active *cis*-diol precursors (*e.g.* **7a–c**) it is also possible, in principle to obtain the corresponding enantiopure tetrahydroepoxides **10a–c** and non-K-region[1] arene oxides **1a–c** of either configuration in significant quantities.

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