Chemoenzymatic synthesis of arene oxides and *trans*-dihydrodiols from *cis*-dihydrodiols of monosubstituted benzenes

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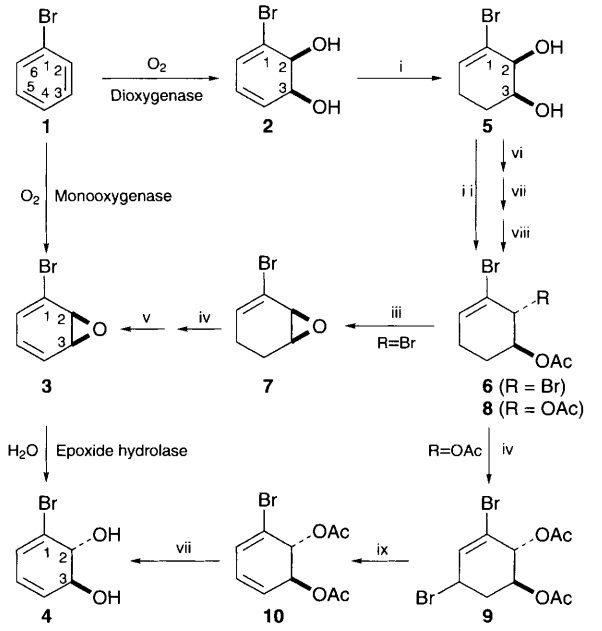
cis-Dihydrodiol bacterial metabolites of monosubstituted benzenes are used in the chemoenzymatic synthesis of the corresponding arene oxide and _trans_-dihydrodiol mammalian metabolites.

Monocyclic arene metabolism is of current interest in view of studies into the mechanism of chemically induced carcinogenesis, *e.g.* from benzene,[1,2] the cytotoxic nature of some mammalian metabolites, *e.g.* from bromobenzene,[3,4] and the value of bacterial *cis*-diol metabolites in chiral synthesis, *e.g.* from iodobenzene.[5–7] In animal[1–4] and fungal[8] systems monooxygenase-catalysed oxidation of arenes proceeds *via* arene oxide and *trans*-dihydrodiol intermediates which are generally difficult to detect (due to very low yields) or to synthesise chemically in enantiopure form (due to the lack of chiral precursors). Recent reports from these and other laboratories have shown that bacterial dioxygenase-catalysed oxidation of arenes, using mutant strains of *Pseudomonas putida*, generally give excellent yields of the enantiopure *cis*-dihydrodiol arene metabolites which are finding increasing use in the synthesis of chiral target molecules.[9–11]

This report indicates how the elusive arene oxide and *trans*-dihydrodiol metabolites, resulting from monooxygenase-catalysed oxidation in animals and fungi, can be obtained by chemoenzymatic routes based on the *cis*-dihydrodiols which are readily available from the bacterial biotransformation of arenes. The approach appears to be generally applicable to a range of 2,3-arene oxide and *trans*-dihydrodiol metabolites of the corresponding 1-substituted arenes where the halogen atom can be readily replaced.† The initial studies have been carried out on the [2*S*,3*S*]-*cis*-dihydrodiol metabolite **2** derived from bromobenzene **1**. The synthesis is based on a remarkably selective hydrogenation of the less substituted double bond of the dienylhalide and was achieved in *ca.* 85% yield using a rhodium (5%) on alumina catalyst. This novel method has also been applied to a wide range of *cis*-dihydrodiol metabolites from monosubstituted arenes (> 8 examples to date) and is found to give a new series of stable *cis*-tetrahydrodiols in good yield with considerable potential as chiral synthons. Thus, reaction of the *cis*-tetrahydrodiol **5** with 2-acetoxyisobutyryl bromide (modelled on earlier studies[12]) occurred in a regio- and stereoselective manner to give the *trans*-bromoacetate **6** (*ca.* 90% yield). Treatment of the latter compound with NaOMe gave the dihydroarene oxide **7** of bromobenzene (*ca.* 95% yield) which in turn was converted to the corresponding arene oxide **3** using an allylic bromination–dehydrobromination sequence (*ca.* 80%).

The arene oxide **3** was obtained in an overall yield of *ca.* 58%, from the corresponding *cis*-dihydrodiol precursor **2**, in a highly pure form. This route compares very favourably in terms of yield and purity with the previously reported synthesis of halobenzene arene oxides from racemic precursors.[13] Arene oxide **3** gave no optical rotation or CD spectrum although derived from enantiopure precursors. This appears to be the first demonstration of spontaneous racemisation of an arene oxide derivative of a monocyclic arene (racemisation has previously been demonstrated for some arene oxide metabolites of polycyclic arenes[14]) and is consistent with equilibration *via* an undetectable proportion of the corresponding oxepine. The ^{1}H NMR spectrum was however typical of 2,3-arene oxides[13,14] and showed no evidence of the minor oxepine tautomer. *cis*-Dihydrodiol metabolites of naphthalene and quinoline have earlier been utilized in the chemoenzymatic synthesis of enantiopure arene oxides[15,16] which showed no evidence of racemisation and from these optically pure *trans*-dihydrodiols were obtained.[15]

The more hindered allylic chiral centre in the unprotected *cis*-tetrahydrodiol **5** was exclusively found to undergo inversion of configuration yielding a 4-nitrobenzoate (*ca.* 70% yield) using the standard Mitsunobu inversion procedure. Hydrolysis of the ester and diesterification of the resultant *trans*-tetrahydrodiol yielded the tetrahydro *trans*-diacetate **8** (*ca.* 95% yield) which was, in turn, converted to the [2*R*,3*S*]-*trans*-dihydrodiol **4** (*ca.* 85%) *via* intermediates **9** and **10** using a similar bromination–dehydrobromination sequence to that employed for arene oxide **3**. Thus, the *trans*-dihydrodiol **4** was obtained, from the corresponding *cis*-dihydrodiol **2**, in an overall yield of *ca.* 45%. The general applicability of this method is demonstrated by the synthesis of the *trans*-dihydrodiols (**11**, **12**) from the *cis*-dihydrodiols of chloro- and iodo-benzene (*via* the corresponding *cis*-tetrahydrodiols **14** and **15**) and substitution of the iodine atom in *trans* dihydrodiol **12** by a vinyl group to give a *trans*-dihydrodiol of styrene **13** (*ca.* 50% yield). Using identical conditions, replacement of the iodine atom in the *cis*-tetra-



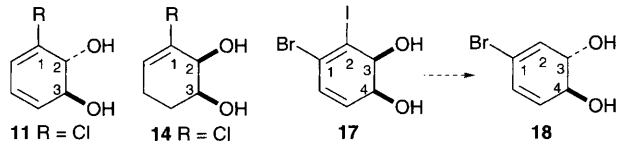
Scheme 1 *Reagents*: i, Rh/Al_2O_3–H_2; ii, $AcOCMe_2COBr$; iii, NaOMe; iv, *N*-bromosuccinimide; v, DBU; vi, diethyl azodicarboxylate, Ph_3P, $4\text{-}NO_2C_6H_4CO_2H$; vii, K_2CO_3; viii, Ac_2O; ix, Li_2CO_3/LiCl

hydrodiol **15** with a vinyl group gave compound **16** ($[\alpha]_D$ − 122°, $CHCl_3$). *cis*-Tetrahydrodiol **16** was isolated as a metabolite of styrene using the MME strain of *Pseudomonas putida* ($[\alpha]_D$ − 79°, $CHCl_3$).[17]

The *cis*-tetrahydrodiols, *e.g.* **5**, **14**, **15** and **16**, were found to be readily converted to the corresponding di-MTPA esters thus providing a new method for the separation, and determination of ee/absolute configuration. This procedure complements the previously reported routes based upon direct chiral stationary phase HPLC separation and analysis,[18] and indirect separation and analysis involving formation of the di-MTPA esters of 4-phenyl-1,2,4-triazoline-3,5-dione adducts[19] or of chiral phenylboronate derivatives.[20]

The synthetic approach to the previously unavailable 2,3-arene oxide **3** and enantiopure *trans*-2,3-dihydrodiol **4** derivatives of bromobenzene **1**, shown in Scheme 1, has now also been applied to the *cis*-dihydrodiol derivatives of disubstituted arenes *e.g.* *cis*-diol **17**. By a simple modification of the method reported above (*e.g.* catalytic hydrogenolysis to remove the iodine atom) *cis*-dihydrodiol **17** has been successfully converted to *trans*-3,4-dihydrodiol **18** of the [3*S*,4*S*]-configuration. The latter compound was reported in racemic form by multistep chemical synthesis.[21] The optical rotations and absolute configurations of the enzymatically produced enantiopure *cis*-dihydrodiols (**2** and **17**), and the chemoenzymatically synthesised *cis*-tetrahydrodiols (**5**, **14**, **15** and **16**), and *trans*-dihydrodiols (**4**, **11**, **12**, **13** and **18**) are given in Table 1.

The results contained in this report demonstrate that it is now possible to convert readily available monocyclic arene *cis*-dihydrodiols into arene oxides and enantiopure *trans*-dihydrodiols which are normally obtained only as transient benzenoid metabolites in animals and fungi. During preparation of this communication an alternative approach to the synthesis of *trans*-2,3-dihydrodiol derivatives from *cis*-2,3-dihydrodiol precursors has appeared.[22] Our synthetic route has a number of advantages over previously reported methods including (i) wide applicability to both 2,3- and 3,4-*trans*-diol derivatives of known configuration using readily replaceable substituents, (ii) high overall yield and purity of products (iii) mild reaction conditions, and (iv) production of configurationally unstable arene oxides. The availability of a new range of stable *cis*-tetrahydrodiols resulting from this study, which can readily be stereochemically assigned from the corresponding di-MTPA esters, provides a useful new addition to the chiral pool.



11 R = Cl
12 R = I
13 R = Vinyl

14 R = Cl
15 R = I
16 R = Vinyl

17

18

Table 1 Optical rotations and absolute configurations of *cis*- and *trans*-diols

Compound	$[\alpha]_D°$ (MeOH)	Configuration (*cis*)	Compound	$[\alpha]_D°$ (MeOH)	Configuration (*trans*)
2	+20	2*S*,3*S*	**4**	+458	2*R*,3*S*
17	+75	3*S*,4*S*	**11**	+505	2*R*,3*S*
5	−114	2*S*,3*S*	**12**	+256	2*R*,3*S*
14	−158	2*S*,3*S*	**13**	+626	2*S*,3*S*
15	−84	2*S*,3*S*	**18**	+220	3*S*,4*S*
16	−122[a]	2*R*,3*S*			

[a] In $CHCl_3$ solution.

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Footnote

† The numbering system used for both arene oxide and dihydrodiol metabolites relates to that of the parent arene bearing a substituent at C-1.

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