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Enantiopure arene dioxides: chemoenzymatic synthesis and application in the production of *trans*-3,4-dihydrodiols

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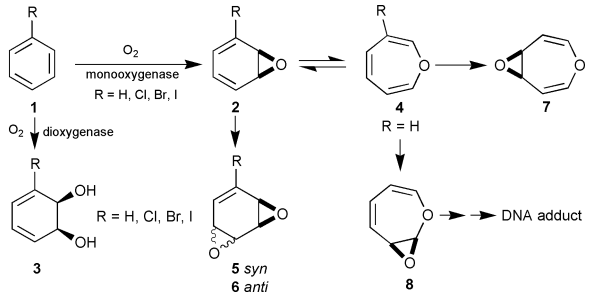
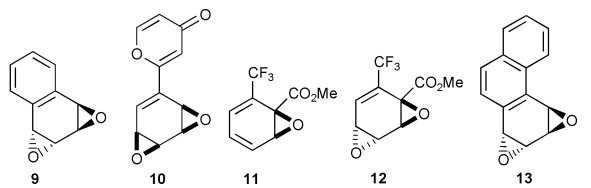
Enantiopure *syn*- and *anti*-arene dioxides are synthesised from *cis*-dihydrodiol metabolites; *anti*-benzene dioxides are reduced to enantiopure *trans*-3,4-dihydrodiols while *syn*-benzene dioxides racemise thermally *via* 1,4-dioxocins.

The metabolism of monocyclic arenes by bacteria (procaryotes) occurs *via* dioxygenase-catalysed dihydroxylation to yield *cis*-dihydrodiols (*e.g.* metabolite **3** from benzene **1**, R = H).[1] In fungi or animals (eucaryotes) however, benzene ring metabolism proceeds *via* monooxygenase-catalysed epoxidation to yield a rapidly equilibrating arene oxide–oxepine tautomeric mixture (*e.g.* metabolites **2** ⇌ **4** from benzene **1,** R = H, Scheme 1).[2]



Scheme 1

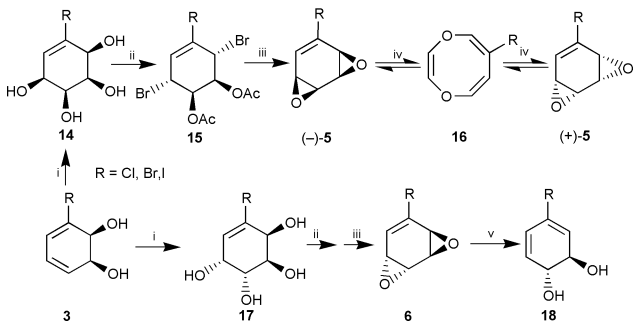
When further oxidation of benzene oxide–oxepine, **2** ⇌ **4** (R = H), was carried out using dimethyl dioxirane (DMD) as oxidant epoxidation occurred exclusively on the oxepine valence tautomer **4**. The minor symmetrical oxepine epoxide **7** was isolated but the major oxepine epoxide **8** rearranged spontaneously to *Z*,*Z*-muconaldehyde.[3] Oxepine epoxide **8** and *Z*,*Z*-muconaldehyde have been implicated in DNA adduct formation and possibly the carcinogenicity of benzene (Scheme 1).[4] Evidence that arene dioxides can be formed in eucaryotic systems is provided by the isolation of the *anti*-naphthalene dioxide **9** as a liver metabolite of naphthalene,[5] and the *syn*-benzene dioxide **10** as a fungal metabolite.[6]



Following earlier studies of remote site epoxidation of arene oxide derivatives of polycyclic arenes using DMD,[7] we have extended this method to the synthesis of *anti*-arene dioxides in mono- and polycyclic arenes. Thus the stable benzene oxide metabolite **11**[8] was found to yield only *anti*-benzene dioxide **12** upon treatment with DMD. The formation of **12** from a benzene oxide tautomer, and of oxirane **7** from an oxepine tautomer,[3] indicates that epoxidation can occur on either form. The DMD epoxidation of configurationally stable (+)-1*R*,2*S*-naphthalene oxide ([α]$_D$ +145, $CHCl_3$) gave only (+)-1*R*,2*R*,3*R*,4*R*-*anti*-naphthalene dioxide **9** ([α]$_D$ +1, $CHCl_3$).† Conversely phenanthrene 3,4-oxide was found to spontaneously racemise *via* an undetected oxepine intermediate and only the racemic form of *anti*-dioxides **13** could be obtained by DMD oxidation. The spontaneous racemization of benzene oxides[9] similarly precludes the synthesis of enantiopure *anti*-benzene dioxides by the chemical oxidation route.

Racemic samples of *syn*-**5**[10] (R = Br, CO_2H, CHO) and *anti*-benzene dioxides **6**[11–13] (R = H) were synthesised earlier by multistep routes; only compound **6** (R = H) was obtained in enantiopure form.[12,13] The availability of *cis*-dihydrodiol enantiomers **3** (R = Cl, Br, I) from bacterial metabolism,[1,2] prompted the following new approach to the synthesis of enantiopure *syn*-**5** and *anti*-benzene dioxides **6**, (Scheme 2). A mixture of *syn*- (**14**, 85%) and *anti*-tetraol (**17,** 15%) derivatives of *cis*-dihydrodiols **3** (R = Cl, Br, I), obtained (80% yield) using the osmylation procedure reported by Donohoe *et al.*,[14] was separated (charcoal–Celite chromatography, EtOH–H_2O as eluent). Reaction of *syn*-tetraols **14** (R = Cl, Br, I) with 2-acetoxyisobutyryl bromide afforded *bis*-bromoacetates **15** (R = Cl, Br, I) in *ca*. 86% yield. Cyclization using NaOMe yielded the 3*S*,4*S*,5*S*,6*S*-*syn*-benzene dioxides **5** (R = Cl, Br, I, in *ca*. 75% yield) with [α]$_D$ values of −59, −56, and −56 in $CHCl_3$ respectively. Reaction of the *bis*-acetonide derivative of *syn*-tetraol **14** (R = I) with PhMgBr, and deprotection of the acetonide groups, yielded *syn*-tetraol **14** (R = Ph), which was similarly converted to 3*S*,4*S*,5*R*,6*R*-*syn*-benzene dioxide **5** (R = Ph, [α]$_D$ −42, $CHCl_3$). Application of this method to *anti*-tetraols **17** (R = Cl, Br, I) gave 3*R*,4*R*,5*S*,6*S*-*anti*-benzene dioxides **6** (R = Cl, Br, I, 78 % yield) with [α]$_D$ values of −115, −54, and −6 in $CHCl_3$ respectively (Scheme 2). Hydrogenolysis (H_2, Pd/C, NaOAc, MeOH) of the 3,4-acetonide derivative of *anti*-tetraol **17** (R = I), and deprotection, yielded the parent compound conduritol E, **17** (R = H), [α]$_D$ − 320, H_2O; it was converted to 1*R*,2*R*,3*R*,4*R*-*anti*-benzene dioxide **6** (R = H, [α]$_D$ −319, $CHCl_3$) using the method shown in Scheme 2.

The method of conversion of *cis*-dihydrodiols to *anti*-arene dioxides (Scheme 2) was also applied to polycyclic arenes. Thus, 1*R*,2*R*,3*R*,4*R*-*anti*-naphthalene dioxide **9** ([α]$_D$ + 1, $CHCl_3$; +14, MeOH)† was synthesised from the available *cis*-1*R*,2*S*-dihydrodiol metabolite of naphthalene ([α]$_D$ + 247, $CHCl_3$). Similarly the *cis*-3*S*, 4*R*-dihydrodiol metabolite of



Scheme 2 *Reagents*: i, OsO_4, CH_2Cl_2, TMNO; ii, $AcOCMe_2COBr$, MeCN; iii, NaOMe, Et_2O; iv, toluene, 85 °C; v, CO, $Pd(OAc)_2$, K_2CO_3, THF–H_2O.

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phenanthrene ($[\alpha]_D$ + 35, MeOH) was converted to an enantiopure sample of 1*R*,2*R*,3*R*,4*R*-*anti*-phenanthrene dioxide **13** ($[\alpha]_D$ + 47, MeOH).

Attempts to form the carbomethoxy-substituted *anti*-benzene dioxide **6** (R = CO_2Me) from the corresponding vinyl iodide **6** (R = I), using a reported[15] palladium-catalysed carbonylation procedure for aryl iodides (CO, $Pd(OAc)_2$, K_2CO_3, THF–H_2O, rt) formed *trans*-3,4-dihydrodiol **18** (R = I, $[\alpha]_D$ −145, MeOH) in excellent yield (>85%) after 0.75 h. The *anti*-benzene dioxides **6** (R = Cl, Br) also yielded 1*R*,2*R*-*trans*-3,4-dihydrodiols **18** (R = Cl, $[\alpha]_D$ −176, MeOH) and **18** (R = Br, $[\alpha]_D$ −253, MeOH) in high yields; a complex mixture of products was obtained from the corresponding *syn*-benzene dioxides **5** (R = Cl, Br, I). The mechanism of conversion of *anti*-benzene dioxides **6** to the corresponding *trans*-3,4-dihydrodiols **18** may involve opening of one epoxide ring followed by formation of a π-allyl palladium complex and rearrangement, *via* an oxetane intermediate, with CO acting as a reducing agent.

The *trans*-dihydrodiols **18** (R = H, Cl, Br) have been detected as minor metabolites of the parent benzene substrates in animal liver systems and have been converted to diol epoxides which are implicated in DNA adduct formation and mutagenicity.[16,17] Palladium-catalysed reaction of *trans*-dihydrodiol **18** (R = I) under similar conditions (CO, $Pd(OAc)_2$, NaOAc, MeOH, rt), but for an extended period (18 h) resulted in the substitution of the iodine atom with a carbomethoxy group to give the 3*R*,4*R*-*trans*-dihydrodiol **18** (R = CO_2Me, $[\alpha]_D$ −94, MeOH) in 80% yield. The *trans*-3,4-dihydroxy-3,4-dihydrobenzoic acid **18** (R = CO_2H), a hydrolysis product of chorismic acid, appears to be a growth promoter.[17] The four step approach to the synthesis of single enantiomer *trans*-3,4-dihydrodiols **18** (R = Cl, Br, I) from *cis*-2,3-dihydrodiols (Scheme 2) represents a significant improvement over earlier routes requiring eight[9] or more[16] steps. The *syn*-benzene dioxides **5** (R = Cl, Br, I, Ph), in common with other *syn*-benzene dioxides **5** (R = H, CO_2H, CHO),[8] were found to undergo a retro-Diels–Alder cycloaddition reaction to yield the corresponding 1,4-dioxocins **16** at relatively low (~85 °C) temperature. Since an enantiopure sample of a *syn*-benzene dioxide was available, a thermal racemization study on the (−)-*syn*-dioxide of iodobenzene **5** (R = I) was carried out (toluene, 85 °C). Total racemization occurred over 2 h (HPLC by Chiralcel OB, α 1.32, iPrOH:hexane, 1:5). NMR analysis showed that the equilibrium mixture contained both the residual *syn*-benzene dioxide **5** (R = I), as a minor component (12%), and the corresponding 1,4-dioxocin isomer **16** (R = I) as a major component (88%). Chromatographic separation of compounds **16** and **5** (R = I) followed by heating either component as before yielded the same equilibrium mixture. This unusual example of a concerted racemisation of four chiral centres in one enantiomer was not observed for the *anti*-benzene dioxide **6** (R = I).

In conclusion we have shown that: (i) arene oxides yield isolable *anti*-arene dioxides by DMD oxidation, (ii) enantiopure samples of *syn*-**5** and *anti*-arene dioxides **6**, **9**, **13** are obtained in high yields from the corresponding *cis*-dihydrodiol metabolites, (iii) *anti*-benzene dioxides **6** are precursors for a new route to *trans*-3,4-dihydrodiols **18**, (iv) racemisation of a *syn*-benzene dioxide enantiomer containing four chiral centres occurs thermally.

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Notes and references

† The $[\alpha]_D$ values observed for the enantiopure *anti*-arene dioxides **6** (R = H) and **9** are significantly different from those reported,[12] furthermore, the stereochemistry of (+) *anti*-dioxide **9** was incorrectly assigned.[12]

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