Enantioselective Synthesis of the (+)-*anti*-7,8-Dihydrodiol-9,10-epoxide of the Potent Carcinogen Benzo[*a*]pyrene

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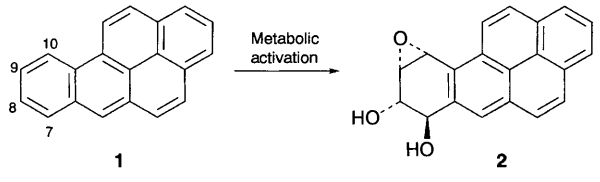
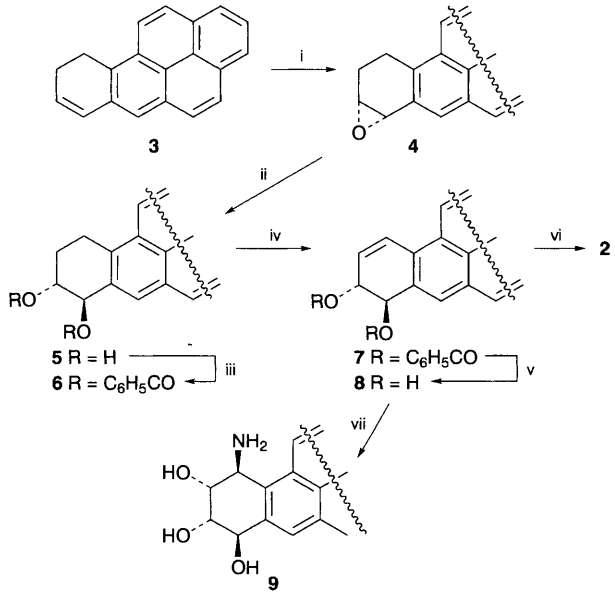
The title compound, the most important genotoxic metabolite of benzo[*a*]pyrene, has been prepared efficiently in a synthesis which capitalized on Jacobsen-type enantioselective epoxidation of 9,10-dihydrobenzo[*a*]pyrene, cleavage of the epoxide by KOH–Me_2SO to give the tetrahydro-*trans*-7,8-diol, and formation of the dibenzoate from which the contaminating antipode was removed by crystallization.

Polycyclic aromatic hydrocarbons (PAHs) are omnipresent carcinogenic pollutants in the environment as products of incomplete combustion. The formation of PAH metabolites and the interactions of these metabolites with DNA have been studied very extensively.[1] Benzo[*a*]pyrene **1** has been studied in greatest detail; its key metabolite is the *anti*-7,8-dihydrodiol-9,10-epoxide **2** having configurations *R,S,S,R* at functionalized positions 7–10, respectively (Scheme 1). Two general approaches for synthesis of pure enantiomers of BPDE and other PAH diol epoxides have been reported: (*a*) conversion of racemic intermediates to diastereoisomeric esters (by reaction of chiral acids) which could be separated chromatographically[2] and (*b*) separation of enantiomers of the diol epoxides or of their precursors using chiral HPLC columns.[3] However, chemical and biological studies of the interactions of **2** with DNA and other biomolecules have been hindered by the high cost and poor availability of the enantiomerically pure diol epoxides prepared by these methods. Herein we describe an asymmetric synthesis of **2**, the directness and simplicity of which should improve the availability of this important compound.



Scheme 1



Scheme 2 *Reagents and conditions*: i, (*S,S*) Jacobsen catalyst, NaOCl, tetralin, CH_2Cl_2, 0 °C, 2.5 h; ii, 0.5 mol dm^{-3} aq. KOH–Me_2SO (2 : 3, *v* : *v*), 80 °C, 24 h; iii, $(C_6H_5CO)_2O$, DMAP, Et_3N, CH_2Cl_2, room temp., 2 h; iv, DDQ, dioxane (purified), reflux, 14 h; v, NaOMe, MeOH–THF (1 : 1, *v* : *v*), reflux, 10 min; vi, MCPBA (> 95%), THF, 2 h, room temp.; vii, liq. NH_3, THF, 75–80 °C (Parr bomb), 48 h

Jacobsen has recently reported the use of chiral Mn catalysts for epoxidations.[4,5] These catalysts afford a high degree of asymmetric induction in the epoxidation of unfunctionalized *Z* alkenes. We have used the (*S,S*) form of *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride to catalyse epoxidation of 7,8-dihydrobenzo[*a*]pyrene **3** by aq. NaOCl to give epoxide **4** (Scheme 2).d Model studies carried out by Jacobsen predict the (*S,S*) catalyst should give mainly the 7*S*,8*R* enantiomer of **4**. The reaction was carried out in CH_2Cl_2 at 0 °C for 2.5 h. Chromatography (EtOAc–hexane) gave **4** in 21% yield. Hydrocarbon **1** was also formed as a byproduct of the oxidation; the extent of formation of **1** was minimized by addition of tetralin to the reaction mixture. The epoxide ring of **4** was opened with KOH to give tetrahydrodiol **5** in 64% yield after chromatography. The diol was benzoylated to give tetrahydrodibenzoate **6** in 92% yield. The NMR spectra ($CDCl_3$) of **6** in the presence of Eu(hfc)$_3$ indicated a 93 : 7 mixture of enantiomers. Enantiomeric enrichment was achieved by dissolving **6** in a minimum amount of THF followed by precipitation with hexane; the enriched material was recovered from the supernatant solution. No evidence of antipodal contamination could be detected in NMR spectra recorded in the presence of Eu(hfc)$_3$; the method would detect 3% contamination by the minor enantiomer.

The synthesis of **2** was completed following literature procedures. **6** was dehydrogenated using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to give **7** (59%).[6] Methanolysis of **7** gave dihydrodiol **8** (90%) which was epoxidized with MCPBA to give **2** (52%).[7] The material was dextrorotatory, confirming that the configuration was, in fact, 7*R*,8*S*,9*S*,10*R*. This result proved that the initial epoxidation had, as predicted, given predominantly the 7*S*,8*R* form of **4** and that ring opening had occurred by selective S_N2 attack at the 7 position of **4** to give the 7*R*,8*R* form of **5**. Attack at the 8 position would have given the enantiomer of **5**.

The optical purity of **2** was established by treatment with anhydrous ammonia to give aminotriol **9**[8] which was treated with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate to form the glucosylthiourea derivative.[9] The diastereoisomeric thioureas derived from (±)-**9** were well resolved on C18 reverse-phase HPLC; similar analysis of the chiral sample showed it to be free of stereoisomeric contamination (> 99% e.e.).

We anticipate the synthetic methodology will have general applicability for preparation of individual enantiomers of other stereo- and regio-isomers of **2** and of diol epoxides of other PAHs.[10]

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