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Enantioselective Synthesis of the K-region *trans*-9,10-Dihydrodiol of Benzo[*g*]chrysene

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Abstract: Efficient enantioselective syntheses of both enantiomers of the title compound are achieved (>99% ee) via asymmetric dihydroxylation of a stilbene-type precursor using Sharpless catalysts followed by intramolecular biaryl coupling with $Pd(PPh_3)_2Cl_2$. This is the first example of direct enantioselective synthesis of a K-region dihydrodiol.

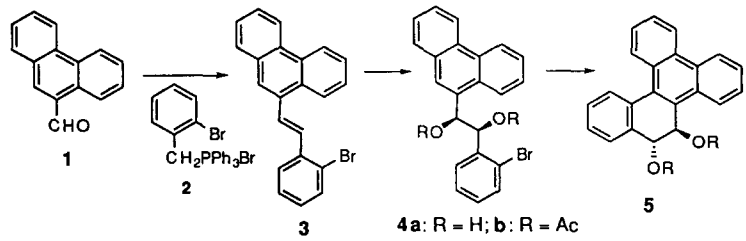
Dihydrodiols are important secondary metabolites of carcinogenic polycyclic aromatic hydrocarbons (PAHs) produced by the hydration, enzymatic or nonenzymatic, of the primary arene oxides.[1] Despite their biological importance, methods for the direct enantioselective synthesis of the dihydrodiols have not been available. While resolution of the corresponding racemic dihydrodiols can sometimes be accomplished by chromatography on chiral HPLC columns,[2] this method has limited applicability and is unsuitable for preparative scale separations. Consequently, the optically pure enantiomers of dihydrodiols are usually obtained by resolution of the corresponding racemic dihydrodiols through chromatographic separation of diastereomeric ester derivatives.[1,3] We recently reported a method for the efficient enantioselective synthesis of PAH non-K-region dihydrodiols.[4] We report herein an efficient stereoselective synthesis of a K-region dihydrodiol, specifically the 9,10-dihydrodiol of benzo[*g*]chrysene (**5**), with excellent enantioselectivity (>99% ee).

As outlined in Scheme 1, synthesis of (-)- and (+)-**5** was accomplished by a five step sequence based on Wittig reaction of phenanthrene-9-carboxaldehyde (**1**) with (2-bromobenzy)triphenylphosphonium bromide (**2**). This reaction took place smoothly in refluxing dichloromethane in the presence of K_2CO_3 and a catalytic amount of 18-crown-6 to furnish 1-(2-bromobenzy)-2-(9-phenanthryl)ethene (**3**) in 95% yield. The mixture of the E and Z isomers of **3** isomerized to the pure E-isomer on irradiation with a tungsten filament lamp in the presence of a crystal of iodine in refluxing heptane.[5] The *trans* stereochemistry of this isomer was confirmed by its ^1H NMR spectrum which revealed a coupling constant of J =16 Hz for the olefinic protons. Osmium tetraoxide-catalyzed asymmetric dihydroxylation of the olefin **3** by the method of Sharpless[6a] in the presence of the $(DHQD)_2PHAL$ catalyst and methanesulfonamide afforded the dihydroxylation product (**4a**) in > 99% ee. Similar reaction of **3** with the isomeric Sharpless catalyst $(DHQ)_2PHAL$ furnished the enantiomeric product also in > 99% ee. The ee values were determined by HPLC using a chiral column (Pirkle covalent leucine eluted with hexane/isopropanol 9:1, 1.0 ml/min). The absolute structures were assigned on the basis of the Sharpless model.[6]

With the chiral information incorporated into the carbon bridge, the dihydrodiol **4a** was converted into the diacetate (**4b**) by stirring overnight with Ac_2O in pyridine in the presence of a catalytic amount of *p*-(*N*,*N*-dimethylamino)pyridine (DMAP). Intramolecular cyclodehydrobromination[7] of **4b** catalyzed by $Pd(PPh_3)_2Cl_2$ in dimethylacetamide provided benzo[*g*]chrysene 9,10-dihydrodiol diacetate (**5b**) in an isolated yield of 72%. Control experiments established that the asymmetry of the two chiral centers in **5b** were preserved during cyclization. In order to more firmly establish its absolute structure, the optically pure diacetate **5b** was converted to

the free dihydrodiol (**5a**) by treatment with NaOMe in THF/methanol. The physical and spectral data for **5a** ($[\alpha]_D$: -805 (c, 0.17, THF) were essentially identical with those reported for authentic (-)-*trans*-(9R,10R)-9,10-dihydroxy-9,10-dihydrobenzo[*g*]chrysene ($[\alpha]_D$: -795 (c, 0.12, THF).[8] The optically pure (+)-*trans*-(9S,10S)-enantiomer was obtained by a similar synthetic sequence from the other enantiomer of **4a**.

Scheme 1



The foregoing synthesis is the first instance of asymmetric synthesis of a PAH K-region dihydrodiol. It is relatively efficient, providing both enantiomers in 54% overall yield in five steps from available precursors. In principle, the strategy is adapable to the enantioselective synthesis of a wide range of PAH K-region *trans*-dihydrodiols.

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