Pergamon

Tetrahedron Letters, Vol. 36, No. 16, pp. 2737-2740, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00385-1

Enantioselective Synthesis of the Tumorigenic *Anti*-Diol Epoxide Metabolites of Benzo[a]pyrene

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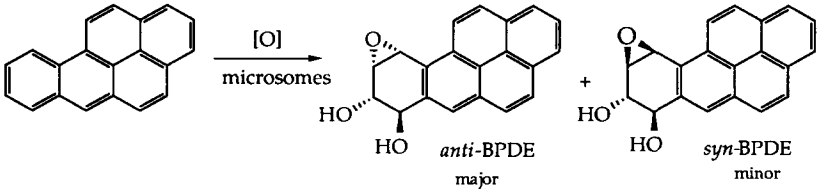
Abstract: Efficient, highly enantioselective syntheses of (+) and (-)-*anti*-benzo[a]pyrene diol epoxide (BPDE) from 9,10-dihydrobenzo[a]pyrene are described. Initial epoxidation catalyzed by (salen) Mn(III) complex gives 7,8-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (>90% ee). Acid-catalyzed hydration occurs regio- and stereoselectively to furnish the *trans*-tetrahydrodiols which are converted into the optically active *anti*-BPDEs.

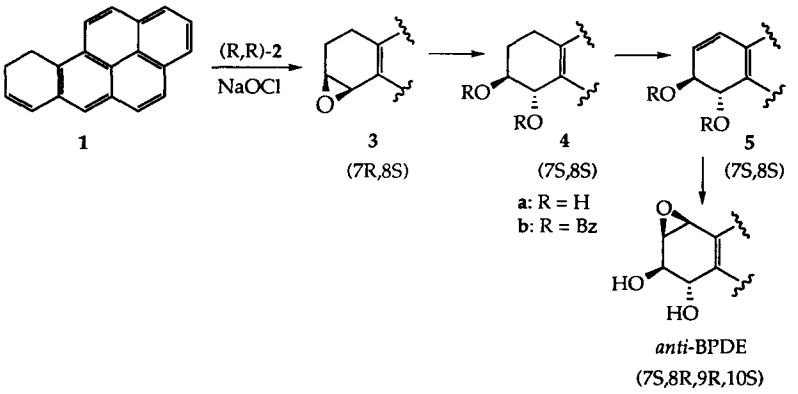
Benzo[a]pyrene, a widespread environmetal contaminant, is activated by microsomal enzymes to highly tumorigenic *anti*- and *syn*-benzo[a]pyrene diol epoxide (BPDE) metabolites.[1,2] Covalent binding of *anti*- and *syn*-BPDE takes place predominantly at the exocyclic amino groups of deoxyguanosine and deoxyadenosine in DNA to form adducts that are believed to initiate molecular events that lead to cancer. However, the specific DNA lesions that result in tumor induction are not established,[3] and the mechanism of carcinogenesis of benzo-[a]pyrene and other polycyclic aromatic hydrocarbons (PAHs) at the molecular-genetic level remains obscure.



Investigations of the molecular structures and biological properties of the nucleic acid adducts have been seriously hampered by the relatively poor accessibility of the optically pure enantiomers of *anti*-BPDE and other PAH diol epoxides.[4] These compounds are currently obtainable only via conversion of the racemic dihydrodiol precursors to diastereomeric esters that must be resolved by HPLC methods[5] or by the direct separation of the racemic diol epoxides or their precursors on chiral HPLC columns.[6] Neither of these methods is suitable for preparation on sufficiently large scale. We report herein the enantioselective synthesis of both (+)- and (-)-*anti*-BPDE with excellent enantioselectivity based on asymmetric epoxidation of 9,10-dihydrobenzo[a]pyrene (**1**) catalyzed by the (salen)Mn(III) complexes developed by Jacobsen.[7]

The synthetic approach entails a four step sequence based on **1** (Scheme 1). Epoxidation of **1** was effected with bleach as the stoichiometric oxidant in the presence of commercially available (R,R)-N,N'-bis(3,5-di-*tert*-butylsalicyclidene)-1,2-cyclohexanediaminomanganese(III) chloride (**2**) as the catalyst (4 mol%) to afford stereoselectively the (7R,8S)-enantiomer of the corresponding epoxide (**3**) with >90% ee.[8] Addition of catalytic levels (0.25 equiv) of 4-phenylpyridine N-oxide (4-PPNO) greatly improved the product yield, but had only a slight, though consistently beneficial, effect on enantioselectivity and reaction rate (Table 1).[9] In the absence of this additive, epoxidation of **1** gave complicated mixtures of products with low yields of (7R,8S)-7,8-epoxy-

Scheme 1



7,8,9,10-tetrahydrobenzo[a]pyrene (**3**) and complete conversion of the starting olefin. Under these conditions, the epoxide product **3** decomposed rapidly, although neither the (salen) Mn(III) complex nor NaOCl alone appeared to promote its decomposition. When **3** was prepared from **1** in the presence of 0.25 equiv of 4-PPNO in methylene chloride, reaction proceeded rapidly without significant epoxide loss. Prior observations with other compounds[9] suggest that the donor ligand 4-PPNO serves to enhance the rate of oxidation relative to the rate of product decomposition. Coordination of the N-oxide to the mildly Lewis acid acidic Mn(III) and/or to Mn(V)oxo intermediates appears to effectively retard epoxide decomposition and also to inhibit secondary reaction pathways involving complexation of epoxide to the manganese center.

Table 1. Enantioselective epoxidation of 9,10-dihydrobenzo[a]pyrene.[a]

Entry	NaOCl	4-PPNO	time (h)	yield (%)[b]	ee (%)[c]
1	1.5	0	6	25	91
2	3	0	2	36	nd[e]
3	2	0	0.5	12[d]	nd
4	3	0.25	0.75	72	93
5	3	1.0	0.75	70	94

[a]All reactions were carried out in CH_2Cl_2 at 7 °C in the presence of **2** (4 mol%) except as other wise indicated. [b]Isolated yield. [c]Determined by measurement of the optical purity of **5b**. [d]50 mol% of **2** employed. [e]nd = not determined.

Although purification of **3** could be effected by flash chromatography, this epoxide was sufficiently pure to use directly in the subsequent hydrolysis step. The stereoselectivity of acid-catalyzed hydrolysis of **3** was found to be solvent dependent. Treatment of **3** with catalytic amounts (0.05-0.1 equiv) of 10-camphor-sulfonic acid (CSA) in acetone/H_2O (4:1) generated *trans*-(7S,8S)-7,8-dihydroxy-7,8,9,10-tetrahydrobenzo-[a]pyrene (**4a**) in a highly regio- and stereoselective ring-opening process in which the stereochemistry of the benzylic carbon atom of the epoxide ring was inverted.[10] Equally high stereoselectivity was observed for

similar reactions in acetone/H_2O in the presence of TsOH or CF_3CO_2H. However, similar reactions in either THF/H_2O (4:1) or *p*-dioxane /H_2O (4:1), gave variable amounts of the *cis*-dihydrodiol.

Protection of the diol function of **4a** prior to dehydrogenation was effected by dibenzoylation with benzoyl chloride/pyridine and 4-(N,N-dimethylamino)-pyridine (DMAP). Treatment of the dibenzoate ester **4b** with DDQ by the established procedure[11] furnished the dihydrodiol dibenzoate ester **5b** which was converted to the free dihydrodiol **5a** by cleavage with NaOMe in MeOH.[11b] The overall yield of the enantiomerically pure (-) (7S, 8S)-dihydrodiol **5a** by this sequence was 65% from 9,10-dihydrobenzo[a]pyrene. The enantiomeric integrity of the epoxide was maintained through the reaction sequence, as evidenced by the isolation of **4a** and **5a** with optical purities > 90% ee.

A similar reaction sequence employing the (S,S)-(salen)Mn(III) catalyst was employed to synthesize the corresponding enantiomeric (+) (7R, 8R)-dihydrodiol which was obtained with comparable optical purity. Conversion of the individual optically pure dihydrodiol isomers to the corresponding *anti*-diol epoxides by epoxidation with *m*-chloroperbenzoic acid has previously been described.[5a,12] Consequently, the method described herein provides convenient synthetic access to these important compounds. The *syn*-diol epoxide isomers are expected to equally accessible via conversion of the individual dihydrodiol enantiomers to the bromohydrin derivatives followed by base-catalyzed cyclization by established procedures.[4,11b] This enantioselective synthetic strategy may be expected to be applicable to the preparative scale synthesis of many other PAH diol epoxides.

Acknowledgement. This research was supported by grants from the American Cancer Society (CN-22) and the National Institute of Environmental Health Sciences (ES 04732).

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2. The *anti* diol epoxide is defined as the isomer in which the epoxide function is on the opposite face as the benzylic hydroxyl group; the *syn* isomer has these groups on the same face.

3. The principal DNA-bound adduct formed by metabolism of benzo[a]pyrene in mammalian tissues arises from covalent binding of (R,S,S,R) (+)-*anti*-BPDE to deoxyguanine. However, it cannot be assumed that this isomer is more important biologically, since metabolism of more potent PAH carcinogens, such as 7,12-dimethylbenz[a]anthracene and benzo[g]chrysene, shows less clearcut preference: Cheng, S. C.; Prakash, A. S.; Pigott, M. A.; Hilton, B. D.; Lee, H.; Harvey, R. G.; Dipple, A. Carcinogenesis **1988**, 9, 1721; Szeliga, J.; Lee, H.; Harvey, R. G.; Page, J. E.; Ross, H. L.; Routledge, M. N.; Hilton, B. D.; Dipple, A. Chem. Res. Toxicol. **1994**, 7, 420.

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8. Typical epoxidation experiment: To a solution of **1** (254 mg, 1.0 mmol) and 4-PPNO (44 mg, 0.25 mmol) in CH_2Cl_2 (20 mL) was added the salen Mn(III) complex (R,R)-**2** (26 mg, 4% mol). The brown solution was cooled to 0 °C and then combined with 4.0 mL of precooled phosphate-buffered bleach solution (pH =11.3, ~0.8 M). The two phase mixture was stirred at 7 °C and reaction progress was monitored by TLC. After 45 min, the solution was filtered through a short column of silica gel and quickly eluted with CH_2Cl_2. Solvent was evaporated rapidly using a Dry Ice condenser to give a yellow solid which could be further purified by fast chromatography on a short column of silica gel eluted with CH_2Cl_2 to give (7R,8S)-**3** (194 mg, 72%): ^{1}H NMR (500 MHz) ($CDCl_3$) δ 1.92 (m, 1H), 2.66 (m, 1H), 3.03 (m, 1H), 3.60 (m, 1H), 3.90 (m, 1H), 4.22 (m, 1H), 7.92 (t, 1H, J = 7.7 Hz), 7.96, (broad s, 2H), 8.01 (d, 1H, J = 9.3 Hz), 8.08 (d, 1H, J = 7.4 Hz), 8.09 (d, 1H, J = 7.5 Hz), 8.13, (s, 1H), 8.18 (d, 1H, J = 9.3 Hz). Enantiomeric excess was determined by measurement of the optical purity of the corresponding tetrahydrodiols by HPLC separation on a Regis reversible covalent leucine chiral column (25x4.6 cm), 5 μ particle diam., mobile phase hexane-isopropanol.

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10. Hydrolysis and dibenzoylation of epoxide, representative procedure: The (7R,8S)-epoxide was dissolved in acetone/H_2O (4:1 by vol, 20 mL), CSA (12 mg) was added, and the mixture was stirred for 2 h. EtOAc was added and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave the crude diol as a pale yellow solid. To this was added benzoyl choride (0.30 mL), pyridine, (2.0 mL), and DMAP (10 mg) in CH_2Cl_2 (15 mL) and the mixture was stirred overnight. Ether was added and the organic layer was washed with $NaHCO_3$ solution, brine, dried over Na_2SO_4, and evaporated to dryness. Chromatography of the residue on a column of silica gel eluted with 1:1 hexane-CH_2Cl_2 to give *trans*-(7S, 8S)-7,8-dibenzoyloxy-7,8,9,10-tetrahydrobenzo[a]pyrene as a white solid (322 mg, 65% from **1**): $[\alpha]_D$: +78.0 (0.52, $CHCl_3$); ^{1}H NMR (500 MHz) ($CDCl_3$) δ 2.52 (m, 1H), 2.72 (m, 1H), 3.70 (m, 2H), 5.75 (m, 1H), 6.93 (d, 1H, J = 6.0 Hz), 7.29 (t, 2H, J = 7.7 Hz), 7.36 (t, 2H, J = 7.7 Hz), 7.42 (m, 1H), 7.48 (m, 1H), 7.89-7.96 (m, 5H), 8.04 (d, 1H, J = 1.2 Hz), 8.06 (s, 1H), 8.09-8.15 (m, 4H), 8.24 (d, 1H, J = 9.3 Hz).

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12. Epoxidation of the (-)-dihydrodiol **5a** gives the (7S, 8R, 9R, 10S) (+)-*anti*-diol epoxide.

(*Received in USA* 27 *January* 1995; *accepted* 28 *February* 1995)