shown that $Te(CH_3)_4$ completely decomposed after 4 h at 120 °C. Since, as shown above, the $Te(CH_3)_6$ sample in $C_6D_6$ survived for 4.5 h at 140 °C unchanged, $Te(CH_3)_6$ is clearly much more thermally stable than $Te(CH_3)_4$.
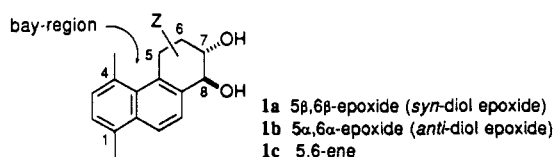
# A Novel Regio- and Stereocontrolled Synthesis of Diol Epoxide and *trans*-Dihydrodiol Metabolites of Polycyclic Aromatic Hydrocarbons. An Application to the Synthesis of the Bay-Region *syn*- and *anti*-Diol Epoxides of the Carcinogen 1,4-Dimethylphenanthrene[†]

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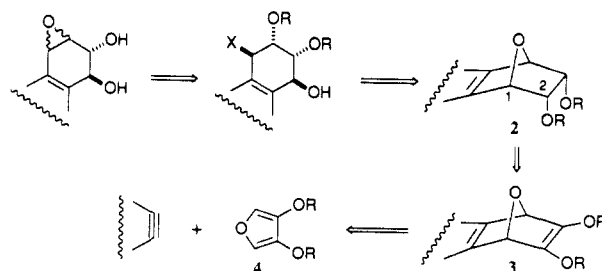Ann Arbor, Michigan 48109

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Carcinogenic polycyclic aromatic hydrocarbons (PAHs) require metabolic activation in order to exert their tumorigenic activity, typically to the diol epoxides[1] as predicted by the bay-region concept.[2] While a number of synthetic methods toward these



1a 5β,6β-epoxide (*syn*-diol epoxide)
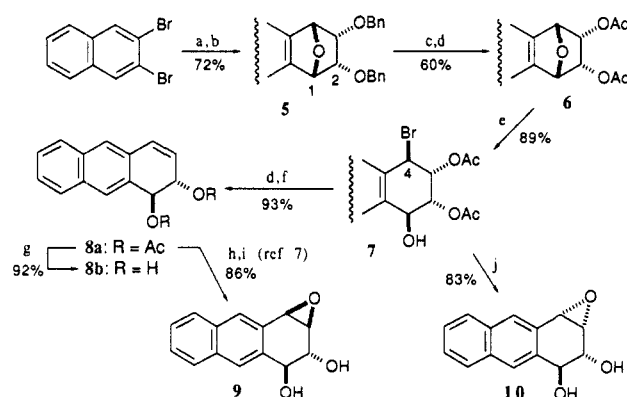1b 5α,6α-epoxide (*anti*-diol epoxide)
1c 5,6-ene

diol epoxides are described in the literature,[3] it was felt that a new, entirely different approach may be needed that achieves regio- and stereochemically controlled synthesis of these metabolites, particularly the bay-region analogues. In the following we delineate a generally applicable, efficient synthesis of PAH diol epoxides and *trans*-dihydrodiols and its application to the first synthesis of the putative active metabolites, the bay-region diol epoxides of the carcinogen 1,4-dimethylphenanthrene (1,4-DMPh).[4]

Our strategy is illustrated in Scheme I in the form of retrosynthetic analysis. This approach entails (1) the initial cycloaddition between an aryne and a 3,4-dialkoxyfuran, (2) the stereoselective hydrogenation of the cycloadduct **3** from the exo side, and (3) the regioselective ether-bridge opening of **2** with a ster-

[†] Dedicated to Professor Koji Nakanishi on the occasion of his receipt of the 1990 Cope Award from the American Chemical Society and the 1990 Imperial Prize of Japan Academy.

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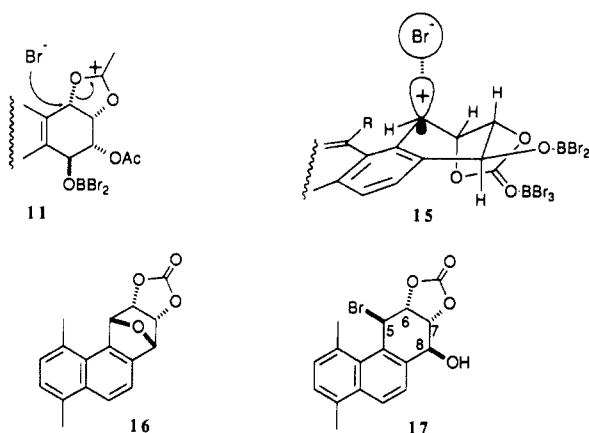
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**Scheme I**



**Scheme II**[a]



[a] Conditions: (a) **4** [R = Bn (ref 5); 2.5 equiv], *n*-BuLi (1.1 equiv)/THF, -78 °C → room temperature, 12 h; (b) $H_2/PtO_2$, benzene/EtOH, room temperature, 4 h; (c) $BF_3 \cdot Et_2O$ (4.2 equiv), EtSH (70 equiv)/$CH_2Cl_2$, 0 °C, 6 h; (d) $Ac_2O$/pyridine, room temperature, overnight; (e) $BBr_3$ (1.5 equiv)/$CH_2Cl_2$, 0 °C, 30 min; (f) $Cr(ClO_4)_2$, ethylenediamine/DMF, 0 °C, 20 min (ref 6); (g) $NH_3$/MeOH, 0 °C → 10 °C, 3 h; (h) *N*-bromoacetamide (NBA)/20% aqueous THF, 0 °C, 4 h; (i) NaOMe (1.2 equiv)/THF, MeOH, room temperature, 2 h; (j) same as (i), 1 h.

**Scheme III**[a]



12a/b            13a/b            14a/b
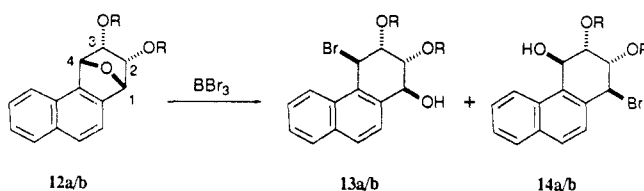
[a] a series, R = Ac; b series, R = O(C=O)O.

eocontrolled incorporation of an appropriate nucleophile. It should be noted that the trans relationship between the two oxygen groups at C-1 and -2 in **2** forms the basis of our synthetic strategy toward these PAH metabolites.

In an effort to assess the feasibility of this approach, the synthesis of the diol epoxides and *trans*-dihydrodiols of the linear PAHs naphthalene and anthracene was probed. Interestingly, the synthesis of the diol epoxides of anthracene has not been reported in the literature, presumably due to the lack of tumorigenic activity of anthracene. These derivatives of both naphthalene and anthracene can be efficiently synthesized, as summarized in Scheme II for the anthracene series, under complete stereochemical control based on the aryne 3,4-bis(benzyloxy)furan cycloaddition approach. Thus, the synthesis of *syn*-9 and *anti*-diol epoxides **10** and 1,2-*trans*-dihydrodiol **8b** of anthracene has been efficiently achieved from 2,3-dibromonaphthalene in 31, 32, and 33% overall yields, respectively.[8]

Unlike the examples described above, the physiologically more potent PAH diol epoxides have the epoxide group in the bay region. Therefore, the application of the present methodology in the

(8) Both naphthalene *syn*- and *anti*-diol epoxide derivatives have also been synthesized in a similar manner from 1-(tosyloxy)-2-bromobenzene in comparable yields.

synthesis of these derivatives often necessitates the regiochemically controlled boron tribromide mediated opening of the nonsymmetric 1,4-ether. The selective ether-bond cleavage at the benzylic carbon in the bay region followed by the stereocontrolled introduction of the bromine atom at the carbon would give a bromo alcohol (e.g., 13) ideally suited for the synthesis of the bay-region diol epoxides. In order to address this regioselectivity issue, the BBr₃-mediated ether opening of the readily available nonsymmetric phenanthrene derivatives 12 was first examined. Contrary to the anticipated contribution of the more stable bay-region benzylic carbocation character[2] to the transition state in the ether ring-opening reaction, treatment of diacetate 12a[9] with BBr₃ at 0 °C resulted in the exclusive formation of bromo alcohol 14a (95%) with virtually no formation of the desired regioisomer 13a. Notably, the bromine atom in 14a was introduced with overall retention of the configuration in the reaction (see 11). In an attempt to reverse this regiochemical selectivity for the ether-ring opening with BBr₃, cyclic carbonate 12b, prepared from 12 (R = H) with *N,N'*-carbonyldiimidazole in 98% yield, was subjected to the above BBr₃ conditions at −20 °C. This gave preferentially the desired bay-region bromide 13b (75%) with overall retention of stereochemistry along with regioisomer 14b (16%). While a mechanistic rationale for this observed reversal in regioselectivity of the ether-ring opening remains ambiguous, it may be reasonable to assume that 12b, unable to provide a direct anchimeric assistance by the carbonate group, may be opened preferentially to the more stable bay-region benzylic carbocation intermediate. This intermediate is likely to adopt a half-chair conformation in the transition state, as indicated in 15 (R = H), with a bromine anion



*t*-Bu/THF, 0 °C, for 1 h afforded *syn*-diol epoxide 1a (mp 145–146 °C) in 75% overall yield from 1c. The formation of the anti isomer 1b from 17 proved to be problematic. The use of the aqueous basic conditions that were effective in similar cases resulted in the clean formation of the hydrolysis product of the epoxide, i.e., (±)-5β,6α,7α,8β-tetraol. This problem of hydrolysis was circumvented by the use of the two-phase, aqueous base/THF system for the reaction. Thus, treatment of bromo alcohol 17 with 4.0 M NaOH/THF (1/20) at room temperature for 20 min produced the desired *anti*-diol epoxide 1b (mp 151–152 °C) in 93% yield. Preliminary biological studies indicate that these two diol epoxides 1a and 1b are potent mutagens.[11]

In conclusion, the novel methodology described above should have general applicability for the synthesis of biologically important bay-region diol epoxide and *trans*-dihydrodiol metabolites of various carcinogenic PAHs. In particular, the unique two-phase, aqueous NaOH/THF conditions may offer a valuable solution to the synthesis of bay-region *anti*-diol epoxides.

**Supplementary Material Available:** Experimental details for the synthesis of 1a, 1b, and 1c and spectroscopic and microanalytical data for these and their synthetic intermediates (11 pages). Ordering information is given on any current masthead page.

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approaching from the axial direction due to the steric congestion imposed by the bay-region aromatic hydrogen, thus providing bromo alcohol 13b with overall retention of stereochemistry at the bay-region benzylic carbon. Bromo alcohol 13b was subsequently converted into syn and anti bay-region diol epoxides, 1,2-*trans*-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydrophenanthrenes, in three [(i) Cr(II);[6] (ii) NBA/20% aqueous THF; (iii) KO-*t*-Bu/THF; 66% overall yield] and one (0.5 M NaOH/50% aqueous dioxane; 83% yield) steps, respectively.

The methodology established above was next applied to the synthesis of the putative metabolites 1a, 1b, and 1c of the carcinogen 1,4-dimethylphenanthrene. The requisite cyclic carbonate 16 was obtained in overall 50% yield from 1-(tosyloxy)-2-bromo-5,8-dimethylnaphthalene[10] through its initial 1-naphthyne reaction with 4 (R = Bn) followed by catalytic hydrogenation of the cycloadduct, removal of the benzyl group, and cyclic carbonate formation. Treatment of 16 with BBr₃ (3.0 equiv) at −40 °C resulted in the smooth, exclusive formation of the desired bromo alcohol 17 in 83% yield. Reductive elimination of the bromo carbonate unit in 17 with Cr(ClO₄)₂ produced 7,8-*trans*-dihydrodiol 1c in 81% yield. Treatment of the bromo hydrin produced from 1c (NBA/20% aqueous THF, 0 °C, 3 h) with KO-

(9) Obtained in four steps from 1-bromo-2-(tosyloxy)naphthalene in 53% overall yield following the identical sequence used for the synthesis of 6.
(10) Jung, K.-Y.; Koreeda, M. *J. Org. Chem.* **1989,** *54,* 5667.

# Urethane-Protected Amino Acid *N*-Carboxy Anhydrides and Their Use in Peptide Synthesis

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We report the general synthesis of novel urethane-protected amino acid *N*-carboxy anhydrides (UNCAs, I) and their use in peptide synthesis. We have prepared many of the [(9-fluorenylmethyl)oxy]carbonyl (Fmoc), benzyloxycarbonyl (Z), and *tert*-butyloxycarbonyl (Boc) protected amino acid NCAs. These compounds are stable (in the absence of water), crystalline solids. They are highly reactive toward nucleophiles and form peptide bonds quickly and cleanly with carbon dioxide as the only coproduct.
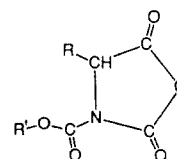


Several researchers have attempted to use amino acid *N*-carboxy anhydrides (NCAs) in stepwise polypeptide synthesis.[1] However,