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 $Te(CH_3)_4$.

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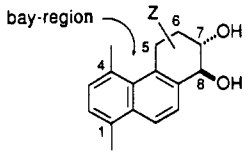
Carcinogenic polycyclic aromatic hydrocarbons (PAHs) require metabolic activation in order to exert their tumorigenic activity, typically to the diol epoxides[1] as predicted by the bay-region concept.[2] While a number of synthetic methods toward these

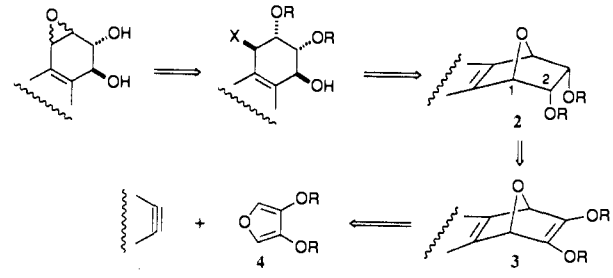


1a 5β,6β-epoxide (*syn*-diol epoxide)
1b 5α,6α-epoxide (*anti*-diol epoxide)
1c 5,6-ene

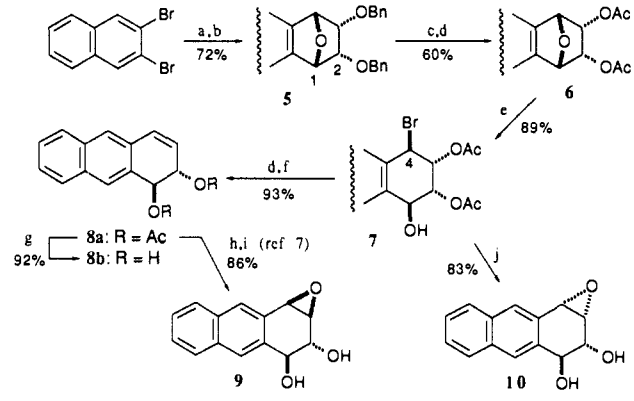
diol epoxides are described in the literature,[3] it was felt that a new, entirely different approach may be needed that achieves regio- and stereochemically controlled synthesis of these metabolites, particularly the bay-region analogues. In the following we delineate a generally applicable, efficient 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 stereocontrolled 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.

Scheme I

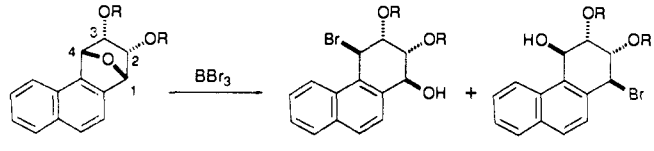


Scheme II[a]



[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.

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

† 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.

(1) *Polycyclic Hydrocarbons and Carcinogenesis*; ACS Monograph 283; Harvey, R. G., Ed.; American Chemical Society, Washington, DC, 1985.

(2) Lehr, R. E.; Kumar, S.; Levin, W.; Wood, A. W.; Chang, R. L.; Conney, A. H.; Yagi, H.; Sayer, J. M.; Jerina, D. M. In: Reference 1, pp 63-84.

(3) (a) Harvey, R. G. In: Reference 1, pp 35-62. (b) Harvey, R. G. *Synthesis* **1986**, 605.

(4) (a) LaVoie, E. J.; Tulley-Freiler, L.; Hoffmann, D. *Cancer Res.* **1981**, *41*, 3441. (b) LaVoie, E. J.; Bedenko, V.; Tulley-Freiler, L.; Hoffmann, D. *Ibid.* **1982**, *42*, 4045. (c) LaVoie, J. E.; Tulley-Freiler, L.; Bedenko, V.; Hoffmann, D. *Mutat. Res.* **1983**, *116*, 91. (d) Hecht, S. S.; Amin, S.; Melikian, A. A.; LaVoie, E. J.; Hoffmann, D. In: Reference 1, pp 85-105.

(5) (a) Iten, P. X.; Hofmann, A. A.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 430. (b) Koreeda, M.; Jung, K.-Y.; Ichita, J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2129, and references cited therein.

(6) Singleton, D. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1967**, *89*, 6547; **1968**, *90*, 1582.

(7) (a) Yagi, H.; Hernandez, O.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6881. (b) Yagi, H.; Thakker, D. R.; Hernandez, O.; Koreeda, M.; Jerina, D. M. *Ibid.* **1977**, *99*, 1604.

(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.

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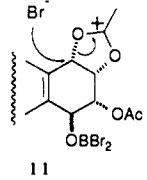
synthesis of these derivatives often necessitates the regiochemically controlled boron tribromide mediated opening of the nonsymmetric 1,4-ether. The selective ether-bond cleavage at the benzylic carbon in the bay region followed by the stereocontrolled introduction of the bromine atom at the carbon 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 BBr_3-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 BBr_3 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 BBr_3, cyclic carbonate **12b**, prepared from **12** (R = H) with *N,N'*-carbonyldiimidazole in 98% yield, was subjected to the above BBr_3 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



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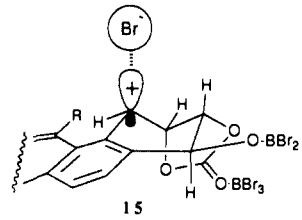

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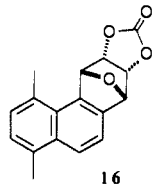
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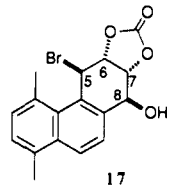

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approaching from the axial direction due to the steric congestion imposed by the bay-region aromatic hydrogen, thus providing bromo alcohol **13b** with overall retention of stereochemistry at the bay-region benzylic carbon. Bromo alcohol **13b** was 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 BBr_3 (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 $Cr(ClO_4)_2$ 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-*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.

Acknowledgment. We thank the National Institutes of Health (CA 28158) for generous financial support of this work.

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.

(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.
(11) Sinsheimer, J. E.; Giri, A. K.; Messerly, E. A.; Jung, K.-Y.; Koreeda, M. *Carcinogenesis* **1989**, *10*, 1123.

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

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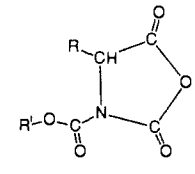
We report the general synthesis of novel urethane-protected amino acid *N*-carboxy anhydrides (UNCAs, I) and their use in peptide synthesis. We have prepared many of the [(9-fluorenylmethyl)oxy]carbonyl (Fmoc), benzyloxycarbonyl (Z), and *tert*-butyloxycarbonyl (Boc) protected amino acid NCAs. These 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,

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