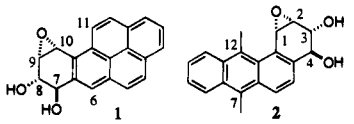
Regio- and Stereocontrolled Synthesis of the Bay-Region *anti*-Diol Epoxide Metabolites of the Potent Carcinogens Benzo[*a*]pyrene and 7,12-Dimethylbenz[*a*]anthracene

Masato Koreeda* and Ramesh Gopalaswamy

Department of Chemistry, The University of Michigan Ann Arbor, Michigan 48109-1055

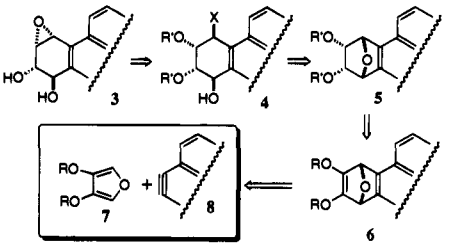
Received May 9, 1995

Benzo[*a*]pyrene (BP) and 7,12-dimethylbenz[*a*]anthracene (7,12-DMBA) are two of the most potent carcinogens known,[1] and a substantial volume of research accomplished thus far points to the notion that their bay-region *anti*-diol epoxide metabolites **1** and **2**, respectively, are the crucial ultimate carcinogenic forms of these polycyclic aromatic hydrocarbons (PAHs).[1−3] The synthesis of these extremely labile compounds

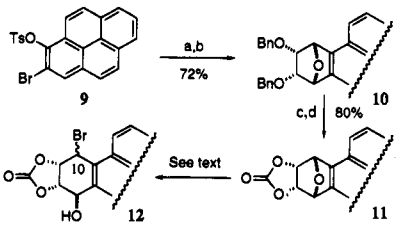


presents a formidable challenge for synthetic chemists; while the synthesis of **1** has been amply documented,[4] the bay-region *anti*-diol epoxide metabolite of 7,12-DMBA, **2**, reportedly has been synthesized but has not been characterized in any respect.[5,6] We had earlier established a novel, generally applicable synthesis of PAH bay-region diol epoxides featuring the use of an arene−3,4-bis(benzyloxy)furan cycloaddition reaction followed by a stereo- and regioselective opening of the ether bridge (see Scheme 1).[7] While the thrust of this approach should be applicable for the synthesis of diol epoxides **1** and **2**, the extreme propensity toward generating the highly delocalized bay-region benzylic carbocation has necessitated extensive reevaluation on the choice of the reagent and fine-tuning of the reaction conditions. In the following, we describe a convenient synthesis of the bay-region *anti*-diol epoxide metabolites of the carcinogens BP and 7,12-DMBA, **1** and **2**, respectively. This represents the first isolation and spectroscopic characterization of the highly biologically important diol epoxide **2**.

Scheme 1

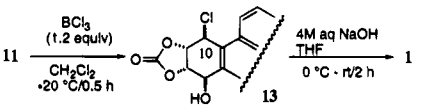


Scheme 2[a]



[a] Reagents and conditions: (a) **7** [R = benzyl (Bn)] (2.5 equiv), *n*-BuLi (2.5 equiv)/THF, −78 °C to room temperature, 5 h; (b) H_2 (1 atm), PtO_2 (cat.)/THF, room temperature, 4 h; (c) $BF_3{\cdot}OEt_2$ (1.1 equiv), NaI (1.1 equiv)/CH_3CN, 0 °C to room temperature, 2 h; (d) 1,1′-carbonyldiimidazole (1.5 equiv)/CH_2Cl_2, reflux, 3 h.

Scheme 3



The synthesis of the known BP metabolite **1**[4] was undertaken first as a test case for these highly labile *anti*-diol epoxide metabolites. The requisite cyclic carbonate **11** was readily accessible from bromo tosylate **9**[8] in four steps in 56% overall yield (Scheme 2). Thus, the aryne generated from bromo tosylate **9** reacted smoothly with 3,4-bis(benzyloxy)furan (**7**; R = Bn) to provide, following catalytic hydrogenation of the crude cycloadduct, the ether-bridged product **10** as a single stereoisomer in 72% overall yield from **9**. On the basis of our previous synthetic work,[7] this benzyl ether-protected **10** needed to be converted into the cyclic carbonate derivative **11** for the regioselective opening of the five-membered ether bridge at the bay-region benzylic carbon C-10. Installation of the 10β-halide required for the formation of 9α,10α-epoxide by opening of the ether bridge in **11** proved problematic. The virtually complete regioselective ether-bridge opening by boron tribromide (1 equiv, −20 °C, CH_2Cl_2) was realized as predicted on the premise that the formation of the more stable bay-region benzylic carbocation would be favored.[9] However, the stereochemical integrity of the resulting 10β-bromide (**12**; X = β-Br)[10]

(1) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge University Press: Cambridge, U.K., 1991. Lehr, R. L.; Kumar, S.; Levin, W.; Wood, A. W.; Chang, R. L.; Conney, A. H.; Yagi, H.; Sayer, J. M.; Jerina, D. M. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 63−84.

(2) Osborne, M. R.; Crosby, N. T. *Benzopyrenes*; Cambridge University Press: Cambridge, U.K., 1987. Newman, M. S.; Tierney, B.; Veeraraghavan, S. *The Chemistry and Biology of benz[a]anthracenes*; Cambridge University Press: Cambridge, U.K., 1988.

(3) It should also be noted that in the case of 7,12-DMBA current attention has been focused more on the *syn*-diol epoxide isomer of **2** due primarily to the extensive binding of this *syn*-diol epoxide to deoxyadenosine residues in DNA of mammalian cells; see: Cheng, S. C.; Prakash, A. S.; Pigott, M. A.; Hilton, B. D.; Roman, J. M.; Lee, H.; Harvey, R. G.; Dipple, A. *Chem. Res. Toxicol.* **1988**, *1*, 216−221.

(4) (a) McCaustland, D. J.; Engel, J. F. *Tetrahedron Lett.* **1975**, 2549−2552. (b) Yagi, H.; Hernandez, O.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6881−6883. (c) Beland, F. A.; Harvey, R. G. *J. Chem. Soc., Chem. Commun.* **1976**, 84−85. (d) Yagi, H.; Thakker, D. R.; Hernandez, O.; Koreeda, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 1604−1611. (e) See also: Harvey, R. G. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 35−62.

(5) Diol epoxide **2** was produced by treatment of 7,12-DMBA *trans*-3,4-dihydrodiol with *m*CPBA in THF, but the product could not be isolated due to its instability. Therefore, the diol epoxide was converted into the *tert*-butyl mercaptan adduct, presumably at C-1, which was obtained in 15% overall yield from the dihydrodiol. See: Lee, H.; Harvey, R. G. *J. Org. Chem.* **1986**, *51*, 3502−3507.

(6) In a recent communication, P. K. Sharma, Department of Chemistry, The Ohio State University, Columbus, Ohio, reported the synthesis of **2** (see: Sharma, P. K. *Synth. Commun.* **1993**, *23*, 389−394). However, no pertinent information on this compound such as melting point, ^1H and ^{13}C NMR, and IR spectroscopic data is provided in the report. Instead, the author described the compound as if it had been previously isolated and characterized by citing a reference (ref 18). Unfortunately, no reference corresponding to the one given by the author could be located. Our request to Dr. Sharma for the information on the physical and spectroscopic properties of the reported diol epoxide for the purpose of direct comparison has not been answered.

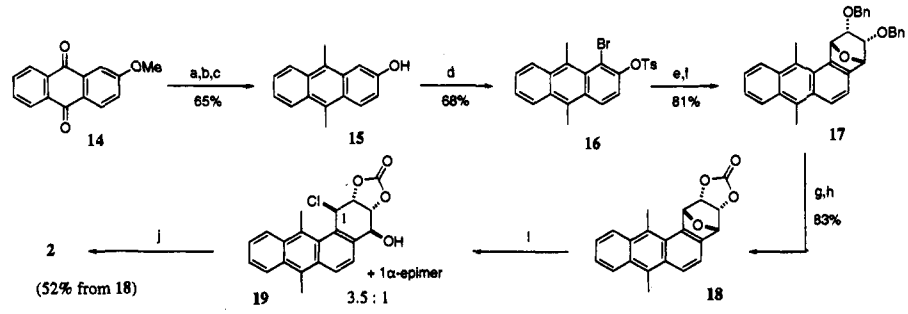
(7) Koreeda, M.; Jung, K.-Y.; Hirota, M. *J. Am. Chem. Soc.* **1990**, *112*, 7413−7414.

(8) Prepared from commercially available 1-bromopyrene (Aldrich Chemical Co., Milwaukee, WI) in four steps in 64% overall yield: (1) *n*-BuLi (2.2 equiv)/THF, −78 °C, 15 min, then $B(OMe)_3$ (1.1 equiv), −78 °C to room temperature, 1 h; (2) 30% aqueous H_2O_2 (excess), 0 °C to room temperature, 1 h (87% yield for steps 1 and 2); (3) Br_2 (1.5 equiv), *t*-BuNH, (1.1 equiv)/toluene, −78 °C to room temperature, 6 h (78%); (4) *p*-TsCl (1.1 equiv), Et_3N (2 equiv)/CH_2Cl_2, 0 °C to room temperature, 2 h (95%).

(9) A variety of bay-region benzylic carbocations are shown to be more stable than their corresponding non-bay-region counterparts by AM1 calculations, and the degree of regioselective ether-ring opening seems to be correlated with the extent of the difference in relative heats of formation of the two benzylic cations: Gopalaswamy, R.; Koreeda, M. Submitted for publication.

0002-7863/95/1517-10595$09.00/0

Scheme 4[a]



[a] Reagents and conditions: (a) MeLi (4 equiv)/benzene, room temperature, 3 h; (b) TMSCl (3 equiv), NaI (3 equiv)/CH_3CN, room temperature, 0.5 h (83% for a and b); (c) BBr_3 (1 equiv)/CH_2Cl_2, −78 °C to room temperature (78%); (d) NBS (1.1 equiv)/THF, −35 to −30 °C, 15 min; DBU (2.2 equiv), −35 °C, 10 min; *p*-TsCl (1.5 equiv), room temperature, 2 h; (e) **7** (R = Bn) (2.5 equiv), *n*-BuLi (1.1 equiv)/THF, −78 °C to room temperature, 5 h; (f) H_2 (1 atm)/PtO_2/THF, room temperature, 5 h; (g) $BF_3{\cdot}OEt_2$ (5.0 equiv), NaI (5.0 equiv)/CH_3CN, room temperature, 6 h (87%); (h) 1,1′-carbonyldiimidazole (1.1 equiv)/CH_2Cl_2, reflux, 2.5 h (95%); (i) BCl_3 (1.0 equiv)/CH_2Cl_2, −20 °C, 0.5 h; (j) 4 M NaOH/THF (1:10), 0 °C, 15 min.

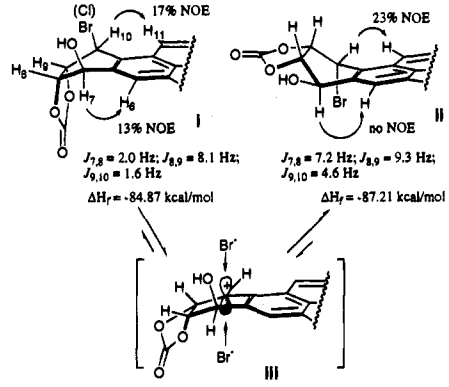


Figure 1. Conformations of the 10β- (**i**) and 10α- (**ii**) bromides **12** deduced from $^1H-^1H$ NMR decoupling experiments and NOE measurements (360 MHz; $CDCl_3$) and AM1 calculations.

could not be maintained as it was found to gradually epimerize into, via the highly stabilized bay-region benzylic cation intermediate **iii** (Figure 1), the 10α-bromide upon standing at room temperature over a period of a few hours. This problem of epimerization was subsequently circumvented by the use of boron trichloride for the ether-bridge opening of **11** (Scheme 3). The resulting 10β-chloride **13** was found to be stable at room temperature at least for a day. The assignments of the stereochemistry at C-10 as well as the conformation of the benzocyclohexyl rings of these epimeric bromides were validated through $^1H-^1H$ decoupling experiments and NOE measurement between pertinent protons (Figure 1). Note, however, that the 10β-chloro product **13** (*vide ante*) was used for the NOE measurements in lieu of the 10β-bromo product since the two 10β-halo products exhibit virtually superimposable proton spectral patterns except for the chemical shifts of the peaks assignable to 10α-H and the 10β-chloro product **13** was much more stable. The results of semiempirical MO calculations with the use of an AM1 Hamiltonian revealed that the two boat forms **i** and **ii** shown in Figure 1 are the most stable conformations for the 10β- and 10α-bromo products (**12**), respectively. Furthermore, comparison of the heats of formation of **i** and **ii** estimated from the AM1 calculations indicates that the latter is more stable by 2.34 kcal/mol. Subjection of chloride **13** to two-phase alkaline/THF conditions[7] resulted in the clean formation of crystalline *anti*-diol epoxide **1**,[4] thus constituting a convenient, highly effective synthesis (six steps, 38% overall yield) of **1** from readily available bromo tosylate **9**.

A similar aryne−bis(benzyloxy)furan cycloaddition approach was explored for the synthesis of the bay-region *anti*-diol epoxide metabolite of 7,12-DMBA, **2**. The precursor to the requisite aryne, **16**, was prepared from commercially available 2-methoxy-9,10-anthraquinone (**14**)[11,12] (Scheme 4). The cycloaddition product **17**, obtained after hydrogenation of the cycloadduct in 81% overall yield from **16**, was converted into the cyclic carbonate derivative **18**. The ether bridge of **18** was then to be treated with boron trichloride to provide the 1β-chloro derivative. However, as 7,12-DMBA is generally considered substantially more potent in its carcinogenicity than BP, it was quite conceivable that this biological potency may be a manifestation of the extremely facile formation of the bay-region benzylic carbocation. Therefore, uncertainty persisted as to the bay-region 1β-chloride being still too labile to be utilized as the penultimate intermediate in the synthesis of the diol epoxide **2**. Treatment of **18** with 1.0 equiv of boron trichloride at −20 °C gave rise to the desired 1β-chloro product **19** together with the epimerized 1α-chloro isomer in a 3.5:1 ratio in a combined yield of 77%. This result seems to indicate that, even under extremely mild conditions with chloride as a substituent at C-1, some stereochemical leakage to the more stable 1α-chloride is unavoidable in the present case. Fortunately, subsequent treatment of this mixture of 1-chlorides with two-phase 4 M aqueous NaOH/THF[7] followed by flash column chromatography using Et_3N−deactivated silica gel resulted in the isolation of crystalline *anti*-diol epoxide **2** (mp 133−135 °C) in 52% overall yield from **18**. The bay-region *anti*-diol epoxide was thus obtained in satisfactory purity based on various spectroscopic analyses.

The synthesis of the bay-region *anti*-diol epoxide metabolites **1** and **2** described above attests the versatility of the aryne−bis(benzyloxy)furan cycloaddition approach as a generally applicable means for the synthesis of diol epoxide derivatives of a variety of polycyclic aromatic hydrocarbons. Current efforts in these laboratories include studies on the reactions of diol epoxide **2** with a number of nucleophiles including DNAs and a series of oligonucleotides.

Acknowledgment. We thank the National Institutes of Health for generous financial support of this research (Grant #CA28158).

Supporting Information Available: Experimental details for the reactions and spectroscopic and analytical data of the compounds described in this communication (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA951508I

(10) The initial formation of the 10β-bromide **12** or chloride **13** may be best rationalized by postulating the intramolecular delivery of the halide anion onto the carbocation at C-10 from the C-7 trihaloborate group generated by ring-opening of the ether-bridge/boron trihalide complex.

(11) (a) Graebe, C.; Bernhard, H. *Justus Leibigs Ann. Chem.* **1906**, *349*, 222−231. (b) Perkin, A. G.; Whattam, T. W. *J. Chem. Soc.* **1922**, *121*, 289−300. (c) Haddon, R. C. *Aust. J. Chem.* **1982**, *35*, 1733−1738.

(12) Interestingly, bromination of **15** with NBS resulted in the monobromide having the 1-bromo-1(*H*)-2-keto form, which was shown by AM1 calculations to be more stable by >3 kcal/mol than its aromatized tautomer, 1-bromo-2-hydroxy-9,10-anthracene, presumably due to the severe peri interaction between the 1-bromo and 10-methyl groups in the aromatized form (details to be published as part of a full account).