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Stereocontrolled Synthesis of *syn*- and *anti*-Diol Epoxide Metabolites of Triphenylene

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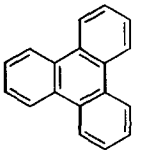
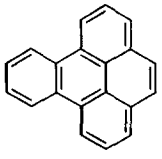
Abstract: The synthesis of both *syn*- and *anti*-diol epoxide metabolites of triphenylene has been achieved under complete stereochemical control commencing with commercially available 9-phenanthrol in 18% (9 steps) and 37% (8 steps) overall yields, respectively. The exceptionally high stereoselectivity of the dimethyldioxirane oxidation of *trans*-dihydrodiol having the quasi-diaxially disposed hydroxyl groups is particularly noteworthy. Copyright © 1996 Elsevier Science Ltd

Triphenylene (**1**) and benzo[*e*]pyrene (B[*e*]P) (**2**) have been implicated as being able to influence the carcinogenicity of more active polycyclic aromatic hydrocarbons (PAHs) in spite of the weakly active carcinogenic potency of these two PAHs.[1] The mildly active PAHs with such effects are termed cocarcinogens.[2] Thus, the extremely weak carcinogen B[*e*]P, which is often found in the environment along with its more potent isomer B[*a*]P, has been suggested to be such a cocarcinogen. It is known that while B[*e*]P inhibits the carcinogenic activity of highly potent 7,12-dimethylbenz[*a*]anthracene and dibenz[*a,b*]anthracene, it enhances the activity of B[*a*]P. Interestingly, the activity of other common PAHs tested did not seem to be affected by the presence of B[*e*]P.[3] While no such behavior of triphenylene has been reported, in view of its structural similarity with B[*e*]P, it is quite conceivable that these two PHAs may exhibit similar cocarcinogenicity.

Although both *syn*- and *anti*-diol epoxide metabolites of triphenylene, **3** and **4**, respectively, have been prepared,[4] the reported syntheses suffer from low stereoselectivity. In the following, we wish to delineate a highly stereocontrolled synthesis of both *syn*- and *anti*-diol epoxide metabolites of triphenylene through the use of the aryne-3,4-bis(benzyloxy)furan cycloaddition approach.[5]



1



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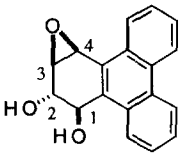

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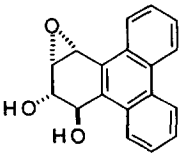

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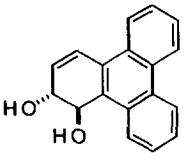
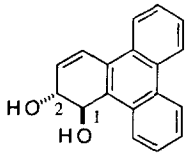


5

The *trans*-dihydrodiol and diol epoxide metabolites of both triphenylene (**5** and **3/4**, respectively) and B[*e*]P adopt conformations distinct from those of the corresponding metabolites of most of other bay-region-containing PAHs. The two hydroxyl groups of the triphenylene and B[*e*]P metabolites are disposed preferentially in a quasi-diaxial orientation, clearly manifesting the severe interactions between the quasi-diequatorial hydroxyls and the bay-region aromatic hydrogen. In contrast, the two hydroxyl groups of the biologically significant metabolites of most of the other bay-region-containing PAHs are located in the non-bay-region, thereby occupying the quasi-diequatorial orientation. This unique propensity for adopting the diaxial-like orientation of the two hydroxyl in the *trans*-dihydrodiol and diol epoxide metabolites of triphenylene may be closely related to the lack of significant mutagenic activity of the latter.[6] The quasi-diaxial nature of the two hydroxyl groups of *trans*-dihydrodiol evidently causes problems in the synthesis of its epoxide derivative since the two trans quasi-axial hydroxyl groups often direct the entry of certain reagents from the opposite faces (see eq 1).[4] Moreover, treatment of **5** with NBS/aq DMSO resulted in the formation



5

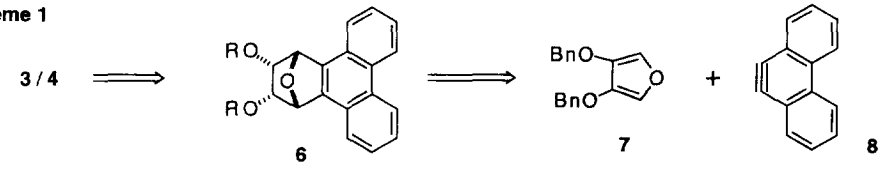
MCPBA → *syn*-diol epoxide (**3**) + *anti*-diol epoxide (**4**) (1)

1 : 1

of the all axial (±)-3β-bromo-1β,2α,4α-triol product as the major product (71%). Therefore, the *syn*-diol epoxide (**3**) was accessible only from the minor 3α-bromo-1β,2α,4β-triol (29%) by base treatment.[4b]

It was envisaged that the use of the aryne-3,4-bis(benzyloxy)furan cycloaddition approach[5] developed in these laboratories should result in the stereocontrolled synthesis of triphenylene *anti*-diol epoxide (**3**), and possibly the *syn*-isomer (**4**) as well, on the basis of the retrosynthetic analysis shown in Scheme 1. The

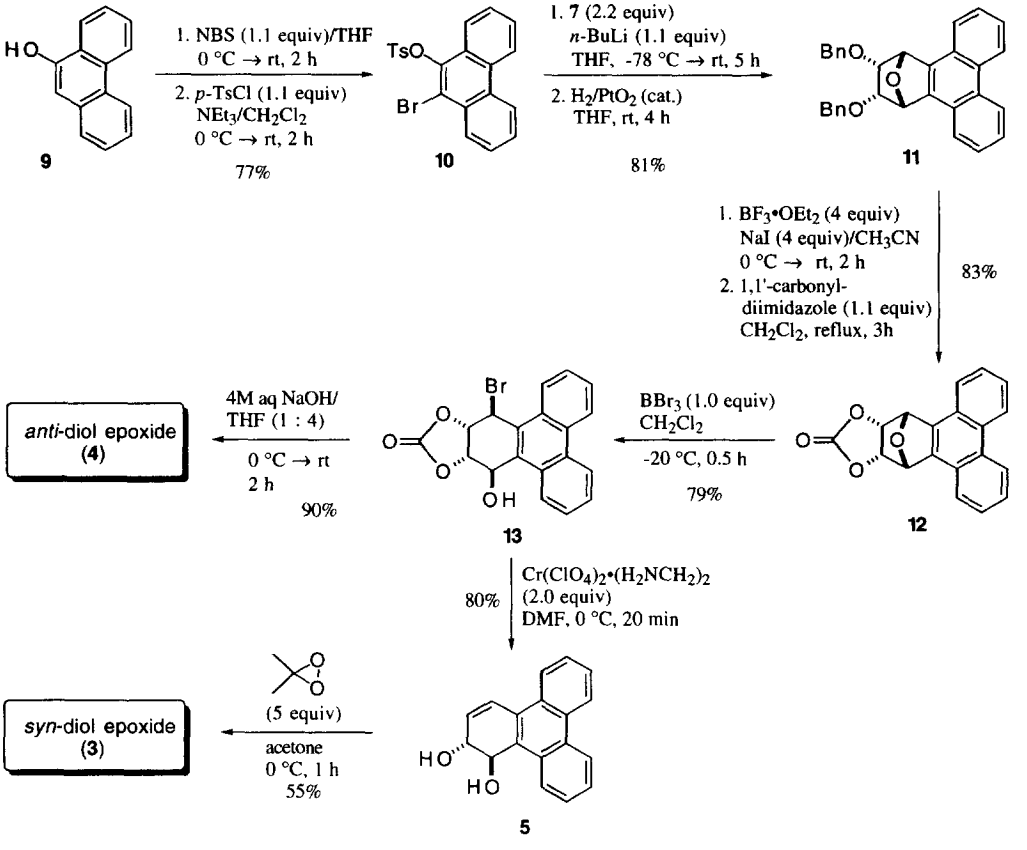
Scheme 1



6 **7** **8**

completed synthesis of **3** and **4** is summarized in Scheme 2. The aryne precursor **10** was readily accessible from commercially available 9-phenanthrol (**9**). The crucial reaction of the aryne generated *in situ* from **10** and 3,4-bis(benzyloxy)furan (**6**) proceeded smoothly, giving rise to the cycloadduct which was immediately reduced to **11**. The ether-ring opening of cyclic carbonate ether **12**[7,8] with BBr_3 cleanly provided bromide **13** with overall retention of the configuration at C-4 as expected. Treatment of bromo-alcohol **13** under the two-phase aq NaOH/THF conditions afforded the *anti*-diol epoxide **4** in excellent yield as a single stereoisomer. The synthesis of the syn isomer was achieved in two steps from bromo-alcohol **13**.[9] Thus, reductive elimination of the vicinal *trans*-bromo alcohol carbonate unit in **13** with the use of the Cr^{II} reagent[10] resulted in the formation of *trans*-1,2-dihydrodiol **14**,[4b,11] which was immediately treated with dimethyldioxirane[12] to

Scheme 2



provide *syn*-diol epoxide **3** in 44% overall yield from **13** with complete stereoselectivity. The preferential formation of the *syn*-diol epoxide derivative from a *trans*-dihydrodiol in which two hydroxyl groups are disposed quasi-diaxially has been reported.[13,14] This facial selectivity has been rationalized in terms of the anti-periplanar effect caused by the preferential axial orientation of the allylic hydroxyl group.[13] Nevertheless, it is of considerable interest to note that the epoxidation is directed by the quasi-axially oriented homoallylic, benzylic alcohol to provide exclusively the *syn*-diol epoxide.

In summary, the synthesis of both *syn*- and *anti*-diol epoxide metabolites of triphenylene has been achieved under complete stereochemical control commencing with commercially available 9-phenanthrol in 18% (9 steps) and 37% (8 steps) overall yields, respectively. The complete stereoselectivity of the 1,2-dimethyldioxirane oxidation of *trans*-dihydrodiol having the quasi-diaxially disposed hydroxyl groups is particularly noteworthy.

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7. Unlike those unsymmetrical PAH systems, a symmetrical system such as the present one does not involve the regioselectivity issue for the ether-bridge opening. Therefore, the diol unit could be protected as the diacetate. However, the bromo-alcohol product obtained by the BBr_3 treatment of the diacetate derivative (i.e., the diacetate derivative instead of the cyclic carbonate in **12**) was found to be relatively unstable, presumably due to the favorable *trans*-diaxial orientation between the vicinal bromo-acetate groups.
8. Data for **12**: mp 210-211 °C (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dd, 2H, J = 2.9, 1.7 Hz), 6.47 (dd, 2H, J = 2.9, 1.7 Hz), 7.72-7.78 (m, 4H), 8.15-8.17 (m, 2H), 8.90-8.92 (m, 2H); ^{13}C NMR (90 MHz, 1: 9 DMSO-d_6/acetone-d_6) δ 76.28 (d), 80.66 (d), 124.50 (d), 125.80 (d), 127.55 (s), 128.01 (d), 128.17 (d), 131.18 (s), 137.88 (s), 154.54 (s); IR (KBr) 3075, 1799 (s), 1790 (s), 1361, 1151, 1088 (s), 1076, 755, 725 cm^{-1}. Anal. Calc for $C_{19}H_{12}O_4$: C, 74.99; H, 3.98. Found: C, 74.63; H, 3.78.
9. Data for **13**: ^{1}H NMR (360 MHz, acetone-d_6) δ 5.04 (br d, 1H, J = 4.6 Hz, OH), 5.74 and 6.02 (ABq, 2H, J_{AB} = 8.2 Hz; the 5.74 and 6.02 peaks each are further split into doublets with J = 1.8 and 1.6 Hz, respectively), 6.03 (dd, 1H, J = 4.6, 1.8 Hz), 6.44 (d, 1H, J = 1.6 Hz), 7.76-7.86 (m, 4H), 8.42-8.48 (m, 2H), 8.93-8.97 (m, 2H); ^{13}C NMR (90 MHz, acetone-d_6) δ 38.13 (d), 63.86 (d), 78.40 (d), 78.96 (d), 124.20 (d), 124.27 (d), 124.61 (d), 125.20 (d), 128.61 (d), 128.75 (s), 128.85 (d), 129.03 (d), 129.52 (s), 130.99 (s), 131.93 (s), 132.17 (s), 153.64 (s); IR (KBr) 3450 (br s), 1814 (s), 1793 (s), 1448, 1368, 1355, 1188, 1062, 765, 723 cm^{-1}. Anal. Calc for $C_{19}H_{13}O_4Br$: C, 59.24; H, 3.40. Found: C, 59.20; H, 3.35.
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11. ^{1}H NMR data for **5** (360 MHz, acetone-d_6) δ 4.43 (br dd, 1H, J = 5.6, 1.8 Hz), 5.42 (br s, 1H), 6.48 (ddd, 1H, J = 9.9, 5.6, 1.1 Hz), 7.56 (d, 1H, J = 9.9 Hz), 7.65-7.73 (m, 2H), 8.42-8.47 (m, 2H), 8.83-8.89 (m, 2H).
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