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Complementary Approaches To The Stereoselective Preparations of Cis and Trans Aminohydrins

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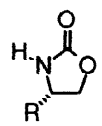
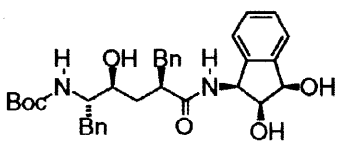
Abstract: Approaches to the stereoselective synthesis of 1,2-aminohydrins from an epoxide are described. Various trans aminols are prepared via amination of 7,8-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene employing trimethylaluminum as a catalyst. Cis aminols are generated via conversion of the epoxide to the acetyl protected trans chlorohydrin followed by direct amine substitution and deprotection.

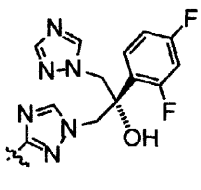
Vicinal aminoalcohols are important structural motifs in natural products, therapeutic agents, chiral directing groups, and carcinogen-DNA adducts. Examples illustrated below include the Evan's type asymmetric auxiliary[1] and fragments of both the HIV protease inhibitor[2] and antimicrobial agent D0870,[3] the latter two incorporating two aminol units each. Furthermore, there is a strong interest in polycyclic aromatic hydrocarbon (PAH)-DNA adducts (such as that of benzo[*a*]pyrene diol epoxide (BPDE)) containing both cis and trans aminol linkages for carcinogenesis studies.[4] These aminohydrins could be obtained via epoxide amination[5] with targeted amino groups; however, the couplings of epoxides with weak nucleophiles are often inaccessible or inefficient. In addition, while cyclic trans products are often generated via direct epoxide amination, cis isomers are not. Here we report the development of general approaches for the synthesis of cis or trans aminohydrins from a common benzylic epoxide.



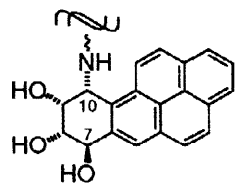
chiral auxiliary



HIV protease inhibitor fragment



D0870 fragment



BPDE-DNA adduct

Efforts to promote epoxide amination routes to PAH-DNA adducts and other biologically important aminols have been frustrated by the poor nucleophilicity of the targeted amines. Additionally, the stereoselective generation of *cis*-BPDE-DNA adducts are unlikely via this route. Thus our goal is the development of mild, complementary avenues for the preparation of a diverse array of cis or trans aminohydrins that are compatible with base-sensitive functionalities, as well as sterically or electronically deactivated amines. Our approach to the preparation of cis aminoalcohols parallels the proposed mechanism of halide-catalyzed BPDE-DNA cis adduct formation via conversion to the trans chlorohydrin followed by substitution with DNA (Scheme 1).[6] Trans aminol adducts will be prepared by epoxide amination employing Lewis acid-assisted couplings.[7] We initially investigated the conversion of a model benzylic epoxide, 7,8-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (EBP), to the trans and cis anilinohydrins. Various other amines were subsequently examined to assess the generality of this approach.

Cis Aminoalcohols via Chlorohydrins. EBP was converted to the corresponding mixture of cis and trans chlorohydrins (CHBP; see trans CHBP in Scheme 2) in good yield by treatment with lithium chloride (16 equiv, rt for 2 h, 97% crude yield) under acidic conditions (20:1 THF/AcOH).[8] The approximate 5:1 mixture (trans *vs* cis) of isomers generated by this procedure was isolated by semi-preparative HPLC (Rainin 21x100;

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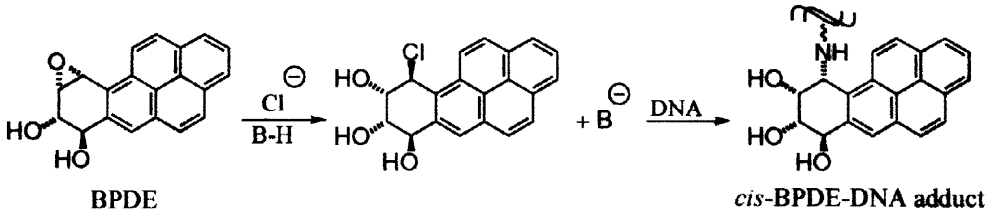
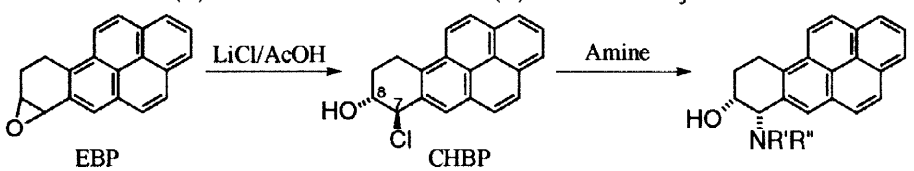
Scheme 1: Halide-Catalyzed Formation of BPDE-DNA Cis Adducts.



mm silica gel 20% EtOAc in hexanes at 12 mL/min) to afford the faster eluting trans isomer as the major product (60%) and a small amount of the minor cis product (13%). Substitution at the C7 for each isomer was confirmed by ^1H and ^{13}C NMR chemical shift values for the H7 (major: δ (in ppm) = 5.47; minor: 5.79) and C7 (major: δ = 72.2; minor: 69.0). No occurrence of C8 substitution was detected. The major product was identified as the trans isomer on the basis of its larger $J_{7,8}$ value (6.3 Hz *vs* 2.7 Hz)[9] and its complete transformation to the epoxide upon exposure to base ($NaN(TMS)_2$, THF, 0 °C). Under identical conditions, the minor isomer did not transform.

Scheme 2: (±)-EBP Conversion to the (±)-Cis Aminohydrin Derivative.

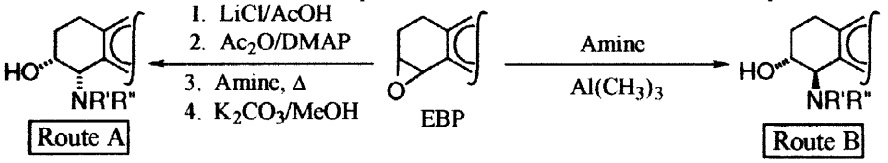


The conversion of *trans*-CHBP to *cis*-7-anilino-7,8,9,10-tetrahydrobenzo[*a*]pyren-8-ol (*cis*-anilinohydrin) occurred upon exposure to neat aniline (rt overnight) to give an approximate 3.8:1 (cis *vs* trans) mixture of adducts in a crude yield of 90% as measured by HPLC (silica gel, 50% EtOAc in hexanes at 1 mL/min) and ^1H NMR spectroscopy. Lower temperatures and/or fewer equivalents of aniline (reactions diluted in THF) slowed reaction rates as well as decreased diastereoselectivies. The isomers were identified as benzylic amines accordingly based on ^1H NMR chemical shift values (H7). The more mobile major diastereomer was assigned as the cis isomer based on the pattern of $J_{7,8}$ measurements (1.8 Hz *vs* the slower eluting diastereomer: 7.2 Hz).[10] In addition, the trans products for the chloro- and aminohydrins each exhibited H7 signals upfield (~0.3 ppm) of the respective cis isomers.

Exposure of *trans*-CHBP to morpholine also gave a mixture of isomers (approximately 1:3.3 cis *vs* trans). The increased proportion of trans product obtained with morpholine relative to aniline is consistent with EBP regeneration by the more sterically hindered amine followed by epoxide amination. To circumvent this problem, we investigated the effect of hydroxyl protection on the selectivity in *trans*-CHBP aminations. Initial attempts at direct formation of trans acetylated CHBP from EBP with acetyl chloride led surprisingly to protected *cis*-CHBP, as did TBDMSCl (DMF/imidazole). Verification of the C7, C8 cis relationship was confirmed by the eventual conversion to *trans*-anilinohydrin. Subsequently, it was found that reacting *trans*-CHBP with acetic anhydride and DMAP led to near quantitative yields of acetylated *trans*-CHBP. Trans acetylated CHBP was converted to the corresponding protected cis aminoalcohol upon exposure to neat amine (see Table, route A) under optimal conditions. Some deacetylation was encountered in the amination step as indicated by the isolated mixture of cis and trans aminols and, in the case of *n*-butylamine only, EBP. Deprotection (K_2CO_3, MeOH) of the acetylated aminols proceeded quantitatively.

Trans Aminoalcohol Preparations. Our preliminary efforts to enforce the uncatalyzed addition of aniline to EBP (THF, rt) resulted in slow transformations and poor yields. Heating the mixtures accelerated EBP consumption but lead to product decomposition. Several reported catalysts (Al_2O_3, $ZnBr_2$, $LiClO_4$,

Table: Stereoselective Preparations of Cis and Trans Aminohydrins.



entry	amine	route	Temp (°C)	cis / trans		yield (%)*
1	aniline	A	35	79	21	62
2	aniline	B	rt	0	100	98
3	*n*-butylamine	A	40	100	0	24
4	*n*-butylamine	B	rt	0	100	55
5	morpholine	A	65	86	14	39
6	morpholine	B	rt	0	100	86

* Overall isolated yields of the aminohydrin reported from the common epoxide, EBP.

$(NH_4)_2Ce(NO_3)_6$, $Pd(PPh_3)_3$ and $Ti(O\text{-}iPr)_4$)[11] gave no evidence of product formation. Our previous success with trimethylaluminum-catalyzed epoxide openings by carboxylic acids[12] and its reported assistance in an intramolecular epoxide amination[13] prompted its application to the amination of EBP.

Trimethylaluminum induced a complete coupling of EBP and aniline in less than 1 h (THF, 0 °C) in nearly quantitative yield (see Table, route B).[14] A single product was formed which was identical (NMR and HPLC) to the previously prepared *trans*-anilinohydrin. Several experiments elucidated the role of the catalyst, temperature and solvent. The epoxide opening proceeded with 0.1 equiv in 4 h, though the preparation of *trans*-anilinohydrin was complete within 20 min with 0.5 equiv of catalyst (rt). Aminations progressed faster at rt without decreasing selectivity, and the highest rates and yields were obtained with THF and toluene. In addition to aniline, *n*-butylamine, *tert*-butylamine, morpholine, benzylamine and 1-naphthylamine each gave their respective trans product upon exposure to trimethylaluminum. This procedure also induced adduct formation with other epoxides (1,2-epoxyhexane and cyclohexene oxide) as well.[15] Thus, trimethylaluminum serves as an excellent catalyst for the trans amination of epoxides.

In summary, we have demonstrated the stereoselective formation of both cis and trans aminohydrin adducts from the common benzylic epoxide, EBP. Cis aminoalcohols are obtained via epoxide hydrochlorination followed by halide displacement with a variety of amines. The stereoselectivity of these preparations are enhanced upon protection of the halohydrin hydroxl group as the acetate. Exclusively, trans epoxide aminations occur upon exposure of a mixture of epoxide and amine to the catalyst trimethylaluminum. We are continuing to examine the generality of these methods with other amines and epoxides, including the preparation of cis and trans PAH-deoxynucleoside adducts.

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9. (±)-*trans*-CHBP; ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.17 (m, 1H, *H9*), 2.61 (m, 1H, *H9*), 3.5-3.8 (m, 2H, *H10*), 4.38 (m, 1H, *H8*), 5.47 (d, J = 6.6 Hz, 1H, *H7*), 7.9-8.4 (m, 8H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.4, 27.1, 64.8, 72.2, 122.7, 124.4, 125.2, 125.2, 125.8, 127.1, 127.6, 127.9, 128.4, 129.5, 130.0, 130.8, 131.4, 131.6. (±)-*cis*-CHBP; ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.2-2.6 (m, 2H, *H9*), 3.44 (m, 1H, *H10*), 3.80 (m, 1H, *H10*), 4.37 (m, 1H, *H8*), 5.79 (d, J = 2.7 Hz, 1H, *H7*), 7.9-8.3 (m, 8H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.5, 26.5, 66.5, 69.0, 122.8, 124.9, 125.3, 126.3, 126.9, 127.2, 127.3, 128.0, 128.8, 129.1, 130.1, 131.0, 131.4, 132.4.

10. (±)-*cis*-Anilinohydrin; ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.29 (m, 2H, *H9*), 3.43 (dt, J = 17.0, 6.5 Hz, 1H, *H10*), 3.73 (dt, J = 17.0, 6.5 Hz, 1H, *H10*), 4.41 (m, 1H, *H8*), 5.09 (d, J = 3.5 Hz, 1H, *H7*), 6.87 (t, J = 7.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 7.30 (m, 2H), 7.88 (d, J = 9.0 Hz, 1H), 7.96 (m, 2H), 8.14 (m, 4H), 8.26 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 24.1, 28.4, 58.7, 68.2, 114.7, 119.3, 123.4, 124.7, 125.0, 125.6, 125.9, 126.5, 127.5, 127.8, 128.3, 129.2, 130.1, 130.3, 130.6, 131.3, 131.8, 135.1, 148.9. (±)-*trans*-Anilinohydrin; ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.25 (m, 1H, *H9*), 2.50 (m, 1H, *H9*), 3.5-3.83 (m, 2H, *H10*), 4.24 (m, 1H, *H8*), 4.95 (d, J = 7.1 Hz, 1H, *H7*), 6.90 (m, 3H), 7.26 (m, 2H), 7.95 (m, 3H), 8.2 (m, 5H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 24.5, 28.4, 60.8, 70.7, 113.8, 118.7, 123.4, 124.5, 125.0, 125.3, 125.5, 126.4, 127.4, 127.9, 128.2, 129.1, 130.2, 130.5, 131.3, 131.8, 135.2, 148.6.

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14. To a mixture of EBP (1 equiv) and amine (2 equiv) in 0.06M THF was added 0.5 equiv of trimethylaluminum (2M in heptane) at rt under a nitrogen atmosphere. The reaction was stirred until monitored complete by TLC. Note, trimethylaluminum supplied by Albermale, Inc. worked consistently better than that supplied by other vendors.

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