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NEIGHBORING GROUP EFFECTS IN THE REGIOSELECTIVE CYCLIZATION OF VICINAL *trans*-1,2-BROMOHYDRINS TO EPOXIDES

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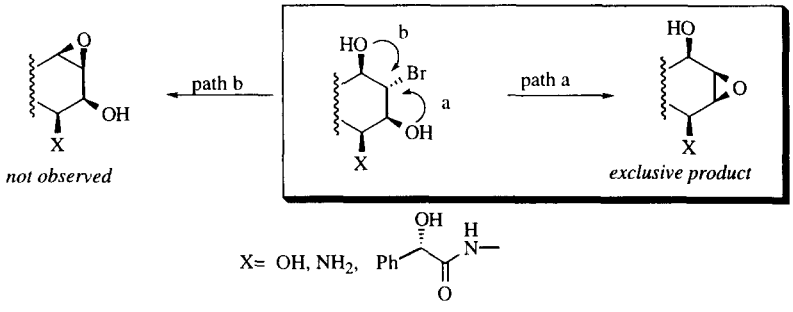
Abstract: Bromocyclopentitols and amino (or amido) bromocyclopentitols having a C-Br bond *trans* to two different vicinal hydroxyl groups show selectivity in base-promoted epoxide formation. The role of adjacent polar substituents in directing bromohydrin cyclization is discussed.

Epoxides are versatile functional groups in synthesis, and can generally be prepared from alkenes either directly, using peracids, or indirectly, by HOBr addition and cyclization of the corresponding bromohydrin.[1] The two methods are stereochemically complementary, with the bromohydrin route providing access in cyclic systems to the sterically more hindered epoxide.[2] Adjacent polar groups, especially allylic alcohol and amide NH groups can direct peracid-mediated alkene epoxidations.[3] Proximal hydroxy and acetoxy groups can also affect the course of epoxide ring opening.[4] However, the effect of nearby polar substituents on the cyclization of *trans*-1,2-bromohydrins to epoxides has not been investigated.

In connection with synthetic studies on trehazolin,[5,6] we had occasion to prepare a number of bromocyclitols having a C-Br bond *trans* to two different vicinal hydroxyl groups. With their overlapping 1,2-bromohydrins, such systems are capable of forming regioisomeric epoxides. However, in each instance we observed high levels of selectivity favoring nucleophilic attack by the hydroxyl group vicinal to the X-group shown.



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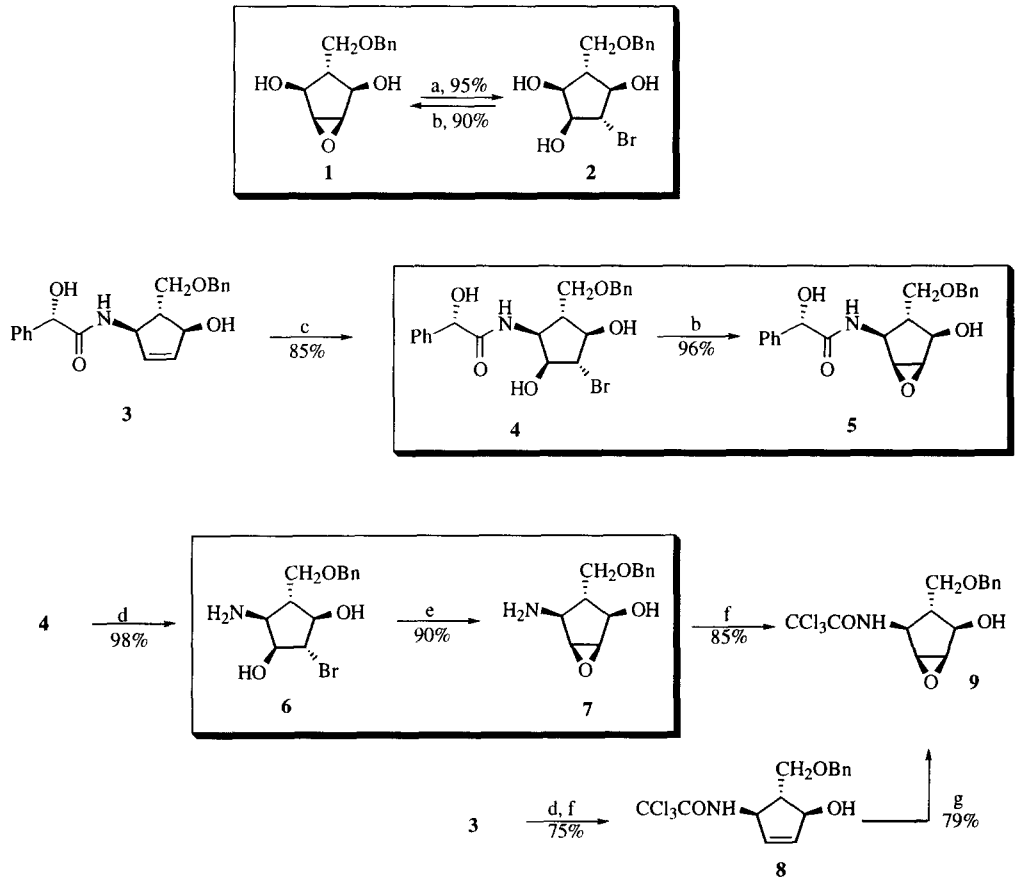
The regiochemistry of bromohydrin cyclization was examined in a series of bromocyclopentitols embodying the requisite (1,3/2)-dihydroxybromocycloalkane unit. Bromocyclopentitols **2**, **4**, and **6** having an additional hydroxy, amido, or amino substituent *cis* to one of the bromohydrin OH groups were prepared as shown in Scheme 1. Reaction of the known[7] epoxide **1** with 48% HBr in Et_2O afforded **2** in 95% yield. Amidoalcohol **3**, prepared by the reaction of (benzyloxymethyl)cyclopentadiene[8] with R-mandelohydroxamic acid and Bu_4NIO_4 following a published protocol,[9] afforded **4**[6] upon treatment with N-bromosuccinimide in wet 1,4-dioxane. Hydrolysis of **4** (0.5 *N* HCl) generated **6** in 98% yield.

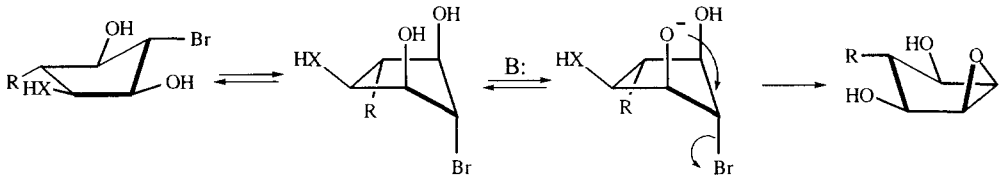


(a) 48% HBr, Et_2O, (b) Na_2CO_3-CH_3OH, (c) NBS, 20:1 dioxane-H_2O; (d) 0.5 *N* HCl, CH_3OH, reflux; (e) 0.5 *N* NH_3-H_2O, (f) $(CCl_3CO)_2O$, pyr-CH_2Cl_2; (g) Oxone™, H_2O-acetone.

Scheme 1

Cyclization of **2** and **4** to the corresponding epoxide was achieved by stirring a methanol solution of each bromohydrin with powdered Na_2CO_3 for 16-24 h. Cyclization of **6** was performed using 0.5 *N* NH_3-H_2O for 2 h. Under these kinetically-controlled conditions, each bromohydrin efficiently formed a single epoxide (**1**, **5**, **7**) whose identity was conclusively established by comparison with a reference sample. Authentic **5**[10] was obtained by *syn*-epoxidation of **3** with *m*-chloroperoxybenzoic acid (MCPBA, CH_2Cl_2, rt). The structure of epoxide **7** was confirmed by comparing its trichloroacetylated derivative **9**[11] with an authentic sample prepared by *syn*-epoxidation of **8** (Scheme 1).

Earlier studies indicate the complex nature of polar substituent effects on epoxide opening and rearrangement reactions.[12] The related bromohydrin cyclizations reported here might involve ring conformational change, alkoxide formation, or nucleophilic attack as the rate-determining step (see Scheme 2), with each of those processes potentially affected by a vicinal alcohol, amine, or amide group. While intramolecular hydrogen bonding[13] has been shown to increase the acidity of hydrogen-bond-accepting OH groups,[14] cyclization of **2** in either 9:1 or 1:1 methanol:water also gave **1** as the exclusive product, indicating that internal H-bonding is not a factor in selectivity.



Scheme 2

Additional studies are needed to elucidate the role of structural, conformational, and inductive effects on bromohydrin closure. The methodology described here may find utility in the synthesis of bioactive cyclic polyols and aminocyclitols, which are components of a variety of potent antibiotics (e.g. kanamycins, streptomycins, neomycins) and glycosidase inhibitors (trehazolin, allosamidin, mannostatin).

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10. For **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.24 (m, 10 H), 5.07 (d, 1 H, J = 8 Hz), 4.45 (s, 2 H), 4.31 (br t, 1 H), 4.11 (m, 1 H), 3.65-3.45 (m, 4 H), 1.65, (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 139.2, 137.7, 128.8, 128.6, 128.4, 127.8, 127.6, 126.7, 74.3, 73.8, 73.4, 68.6, 57.3, 56.2, 50.6, 45.3.

11. For **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.32 (m, 5 H), 5.32 (br d, 1 H), 4.64-4.48 (m, 3 H), 3.89, 3.78 (br m, each 1 H), 3.55 (m, 2 H), 2.09 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6, 137.8, 137.0, 131.4, 128.5, 127.8, 127.7, 78.3, 73.5, 70.3, 58.3, 56.3.

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