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Concise Synthesis of Enantiomers of 4-Aminobutane-1,2,3-triol

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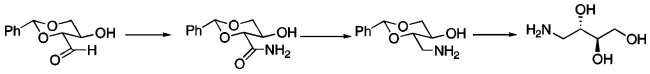
Received December 12, 2007

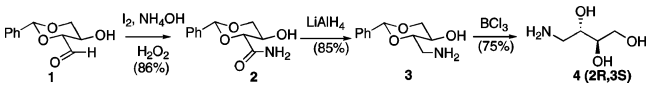


A very efficient synthesis of (2*R*,3*S*) and (2*S*,3*R*)-4-aminobutane-1,2,3-triol has been developed using either D- or L-glucose as the starting material. A key step is the one-pot conversion of an aldehyde to an amide, the scope of which has been extended to include other carbohydrate-derived aldehydes.

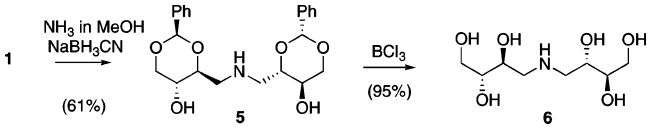
A common mechanism of environmental toxins is alkylation of DNA by oxidized metabolites.[1] Investigation of the details of the DNA adducts formed requires isomerically pure aminopolyols, which can be coupled to halopurines by a post-oligomerization strategy.[2] In order to synthesize adducts of the oxidized metabolites of the toxin butadiene, an efficient synthesis of the 2*R*,3*S* and 2*S*,3*R* isomers of 4-aminobutane-1,2,3-triol was required. It was envisioned that the isomers would be prepared from either D- or L-glucose. Synthesis of the aminotriol (Scheme 1) began with the known D-glucose-derived aldehyde **1**, which was prepared by oxidative cleavage of the 4,6-*O*-benzylidene of D-glucopyranose.[3,4] The aldehyde was converted directly to the novel amide **2** using iodine, aqueous ammonia, and peroxide.

There are only two reports of this direct conversion in the literature, neither of which has been applied to carbohydrate-derived aldehydes.[5,6] Reduction to the primary amine proceeded smoothly to afford **3**. Attempts to hydrolyze the benzylidene with aqueous acid resulted in decomposition; however, Lewis acid-catalyzed cleavage afforded the (2*R*,3*S*)-4-aminobutane-1,2,3-triol **4**. Following the same procedure, L-glucose afforded the enantiomer of **4**.

SCHEME 1. Synthesis of (2*R*,3*S*)-4-Aminobutane-1,2,3-triol



SCHEME 2. Synthesis of Dimeric Aminohexols



Initial attempts to convert the aldehyde **1** to the corresponding primary amine **3** via reductive amination were unsuccessful on several fronts. Although reductive amination with benzylamine afforded the corresponding benzyl-protected amine, all attempts to cleave the benzyl group by reductive removal failed.[7] Also, reductive amination with hydroxylamine led only to decomposition. Finally, direct reductive amination of aldehyde **1** with ammonia gas/sodium cyanoborohydride afforded only the novel dimer **5** and none of the desired primary amine, as shown in Scheme 2.

Lewis acid catalyzed cleavage of the benzylidene afforded the dimeric secondary amine **6**. Dimers such as **5** are generally considered as unavoidable products of direct reductive amination with ammonia; however, the chiral aminoalcohols **5** and **6** are potentially useful for several applications, including utility as chiral synthons and potential chiral ligands for organometallic catalysis.[8,9]

Further investigation of the scope of Shie and Fang's procedure shows that the process works well for several other carbohydrate and amino acid-derived aldehydes. Table 1 shows a few examples of the synthesis of synthetically useful amides.

Optical rotations of the amides in Table 1 are consistent with those reported in the literature and indicate that no racemization occurred.[10] Amides **8** and **10** have been used both in the synthesis of natural products and as peptide precursors.[11,12] Also,

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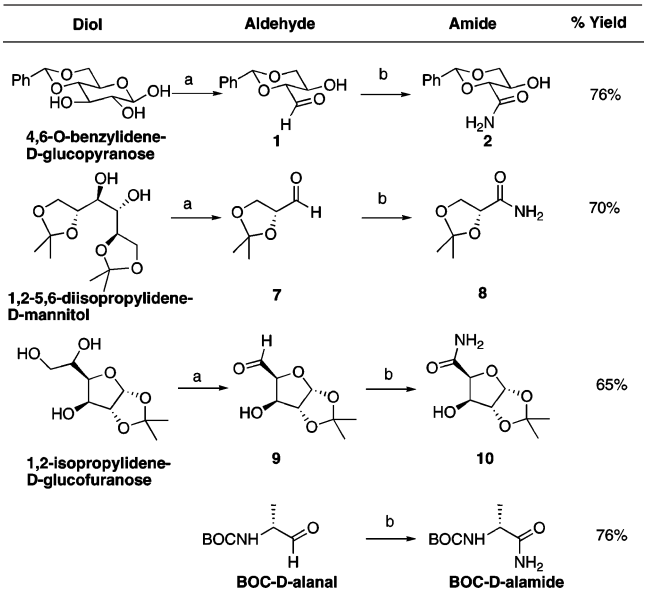
10.1021/jo702647n CCC: $40.75
Published on Web 03/01/2008

TABLE 1. Application of One-Step Aldehyde to Amide Conversion to Carbohydrate and Amino Acid Derived Aldehydes



[a] $NaIO_4$ on silica gel. [b] I_2, NH_4OH followed by H_2O_2.

amide **2** is a potential synthon in the synthesis of natural products such as swainsonine and castanospermine.[13]

In conclusion, a very efficient synthesis of several novel chiral aminoalcohols has been developed from inexpensive, readily available starting materials. Both the (2*S*,3*R*) and (2*R*,3*S*) enantiomers of 4-aminobutane-1,2,3-triol have been prepared, as well as two novel dimeric amino alcohols. In addition, the scope of a direct aldehyde to amide conversion has been extended to carbohydrate-derived aldehydes.

Experimental Section

(2*R*,4*R*,5*R*)-5-Hydroxy-2-phenyl-1,3-dioxane-4-carbaldehyde (1). To a suspension of 4,6-*O*-benzylidene-D-glucopyranose (600 mg, 2.2mmol) in 16 mL of dichloromethane was added freshly prepared sodium periodate on silica gel: sodium periodate (700 mg, 1.3 mmol of $NaIO_4$) was dissolved in 1.5 mL of hot H_2O and then mixed with 2.6 g of silica gel. The resulting suspension was stirred at 25 °C for 2 h, filtered, and washed with ethyl acetate, and the solvent was removed to afford 425 mg (91%) of aldehyde **1**, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 9.68 (d, J = 1.7 Hz, 1H, aldehyde), 8.05−7.41 (m, 5H, aryl), 5.30 (s, 1H, acetal), 5.27 (m, 1H, C5H), 4.48 (dd, J = 5.7 and 10.9 Hz), 1H, C-6βH), 4.27 (dd, J = 1.7 and 9.7 Hz, 1H, C4H), 3.79 (apparent t, J = 10.9 Hz, 1H, C-6αH), 1.66 (broad s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 196.6 (C=O), 159.4, 129.7, 128.5, 126.3 (aryl), 101.3 (acetal), 80.9 (C6), 67.6 (C5), 61.5 (C4).

(2*R*,4*R*,5*R*)-5-Hydroxy-2-phenyl-1,3-dioxane-4-carboxamide (2). The aldehyde (441 mg, 12.1mmol) was dissolved in 1.0 mL of tetrahydrofuran. Aqueous ammonium hydroxide (13.0 mL of 28% solution) was added, followed by iodine (591 mg, 2.3mmol). The mixture was stirred at room temperature for 2 h, during which time the brown mixture turned colorless. After 2 h, hydrogen peroxide (1.3 mL of 35% solution) was added. Stirring was continued for 2 h. The solution was extracted twice with dichloromethane, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and filtered. Evaporation afforded 408 mg (86%) of a white solid which was used in the next step without further purification: mp 148 °C dec; $[\alpha]_D$ = +8.1 (*c* 0.014 g/mL, acetone); IR ($CHCl_3$) 3657 (NH), 3392 (OH), 1643 (C=O) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 7.51 (m, 2H, aryl), 7.35 (m, 3H, aryl), 5.67 (s, 1H, acetal), 4.61 (1H, OH), 4.20 (dd, 1H, J = 10.3, 5.1 Hz, C6H$_B$,), 4.10 (d, 1H, J = 9.16 Hz, C4H), 3.78 (m, 1H, C5H), 3.63 (app t, J = 10.31 Hz, C6$_A$); ^{13}C NMR (acetone-d_6) δ 173.6 (C=O), 128.89 (aryl), 128.0 (aryl), 126.5-(aryl), 101.0 (acetal), 78.8 (C4), 70.5 (C6), 64.4 (C5); HRMS (FAB) calcd for $C_{11}H_{14}NO_4$ (M + H) 224.0923, found 224.0912.

(2*S*,4*S*,5*S*)-5-Hydroxy-2-phenyl-1,3-dioxane-4-carboxamide: $[\alpha]_D$ = −8.3 (*c* 0.02 g/mL, acetone); all other data were identical to those for the 2*R*,4*R*,5*R* isomer.

(2*R*,4*S*,5*R*)-4-(Aminomethyl)-2-phenyl-1,3-dioxan-5-ol (3). The amide (254 mg, 1.2 mmol) was dissolved in 4 mL of anhydrous tetrahydrofuran and added to a suspension of lithium aluminum hydride (0.22 g, 5.8mmol) in 12 mL of anhydrous tetrahydrofuran under an argon atmosphere at 0 °C. The mixture was stirred at room temperature for 1 h and then at reflux for 5 h. The mixture was cooled to 0 °C, and 0.5 mL of water was added dropwise to destroy excess lithium aluminum hydride. The resulting mixture was filtered through Celite and washed with ether. The ether solution was dried with anhydrous magnesium sulfate, filtered, and evaporated. The crude product was purified by flash column chromatography on silica gel, eluting with 85:8:7 acetonitrile/water/NH_4OH to afford 186 mg (77%) of the amine: $[\alpha]_D$ = −9.0 (*c* 0.0032 g/mL, acetone); IR ($CHCl_3$) 3379, 3300 cm^{-1}; ^{1}H NMR (CD_3OD) δ 7.48 (m, 2H, aryl), 7.32 (m, 3H, aryl), 5.51 (s, 1H, acetal H), 4.17 (dd, 1H, J = 5.1, 10.3 Hz, C6H), 3.55 (m, 3H, C6H, C5H, C4H), 3.08 (dd, 1H, J = 2.3, 13.2 Hz, CHN), 2.79 (dd, 1H, J = 6.9, 13.4 Hz, CHN); ^{13}C NMR (CD_3OD) δ 138.2 (aryl), 128.5 (aryl), 128.0 (aryl), 126.0 (aryl), 101.0 (acetal), 82.8 (C4), 70.6 (C6), 63.1 (C5), 47.4 (CH_2N); HRMS (FAB) calcd for $C_{11}H_{16}NO_3$ (M + H) 210.1130, found 210.1146.

(2*R*,3*S*)-4-Aminobutane-1,2,3-triol (4). The benzylidene **3** (186 mg, 0.9mmol) was dissolved in 6.0 mL of anhydrous dichloromethane and cooled to −78 °C under an argon atmosphere. A solution of boron trichloride in dichloromethane was added (1.1 mmol of a 1 M solution). The resulting mixture was stirred at −78 °C for 1.5 h, poured into water, and extracted with dichloromethane. The organic layer was washed once with water, and the aqueous phase was lyophilized to afford a tan solid. The crude product was purified by flash column chromatography on C18 reverse-phase silica gel, eluting with water and then 86:9:5 acetonitrile/water/NH_4OH. Lyophilization afforded 105 mg (75%) of the aminotriol: $[\alpha]_D$ = −5.9 (*c* 0.023 g/mL, H_2O); ^{1}H NMR (D_2O) δ 3.61 (m, 4H, C2H, C3H, C1H), 3.16 (m, 1H, C4H), 2.90 (m, 1H, C4H); ^{13}C NMR (D_2O) δ 73.0 (C3), 67.6 (C2), 62.2 (C1), 41.8 (C4); HRMS (FAB) calcd for $C_4H_{12}NO_3$ (M + H) 122.0817, found 122.0816.

(2*S*,3*R*)-4-Aminobutane-1,2,3-triol (4): $[\alpha]_D$ = +6.6 (*c* 0.025 g/mL, H_2O); all other data were identical to those for the 2*R*,3*S* isomer.

(2*R*,2′*R*,4*S*,4′*S*,5*R*,5′*R*)-4,4′-Azanediylbis(methylene)bis(2-phenyl-1,3-dioxan-5-ol). The aldehyde (374 mg, 1.8 mmol) was dissolved in 50 mL of methanol and cooled to 0 °C. Ammonia gas was bubbled into the solution for 5 min and stirring continued at 25 °C for 1 h. Sodium cyanoborohydride (453 mg, 7.2mmol) was added, and the resulting mixture was stirred at 25 °C for 18 h. The methanol was evaporated, and the residue was diluted with 10 mL of water and extracted twice with chloroform. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent evaporated to afford 220 mg (61%) of the amine: $[\alpha]_D$ = −18.0 (*c* 0.017 g/mL, $CHCl_3$); IR ($CHCl_3$) 3657 (NH), 3392 (OH), 1092 (C−O stretch) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55−7.25 (m, 5H, aryl H), 5.49 (s, 1H, acetal), 4.27 (m, 2H, C6,6′H), 3.68 (m, 3H, C4,4′H, C5,5′H, CHN), 3.07 (m, 1H, CHN); ^{13}C NMR ($CDCl_3$) δ137.5, 129.2, 128.4, 126.2 (aryl), 101.2 (acetal), 79.2 (C5,5′), 71.1

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(C6,6′), 69.7 (C4,4′), 52.0 (CH_2N); HRMS (FAB) calcd for $C_{22}H_{28}NO_6$ (M + H) 402.1917, found 402.1917.

(2*R*,2′*R*,3*S*,3′*S*)-4,4′-Azanediyldibutane-1,2,3-triol) (6). To a solution of benzylidene **5** (140 mg, 0.35 mmol) in 3 mL of dichloromethane at −78 °C under an argon atmosphere was added a solution of boron trichloride in dichloromethane (1.0 mL, 1.0mmol). The solution was stirred at −78 °C for 1.5 h, diluted with dichloromethane, and extracted twice with water. Lyophilization of the aqueous phase afforded 90 mg (100%) of the HCl salt of **6**: $[\alpha]_D = -8.3$ (*c* 0.015 g/mL, H_2O); ^{1}H NMR (D_2O) δ 3.81-(m, 1H, *C*2,2′H), 3.62−3.48 (m, 4H, C3,3′H, C1,1′H), 3.25 (dd, 1H, J = 3.0, 12.9 Hz, C4,4′H), 3.04 (dd, 1H, J = 9.6, 12.9 Hz, C4,4′H); ^{13}C NMR (D_2O) δ73.1 (C3,3′), 66.6 (*C*2,2′), 62.1 (C1,1′), 49.9 (C4,4′); HRMS (FAB) calcd for $C_8H_{20}NO_6$ (M + H) 226.1291, found 226.1301.

Acknowledgment. NMR spectra were recorded on a spectrometer purchased with a grant from the National Science Foundation through the NSF-RUI program (no. 0321211).

Supporting Information Available: ^{1}H and^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702647N