Notes

Unprecedented Selectivity in the Reaction of 1,2:5,6-Dianhydro-3,4-*O*-Isopropylidenehexitols with Benzylamine: A Practical Synthesis of 3,4,5,6-Tetrahydroxyazepanes†,‡

Braj B. Lohray,* Yaruva Jayamma,‡ and Manashi Chatterjee

Basic Research & Drug Discovery, Dr. Reddy's Research Foundation, Bollaram Road, Miyapur, Hyderabad 500 138, India

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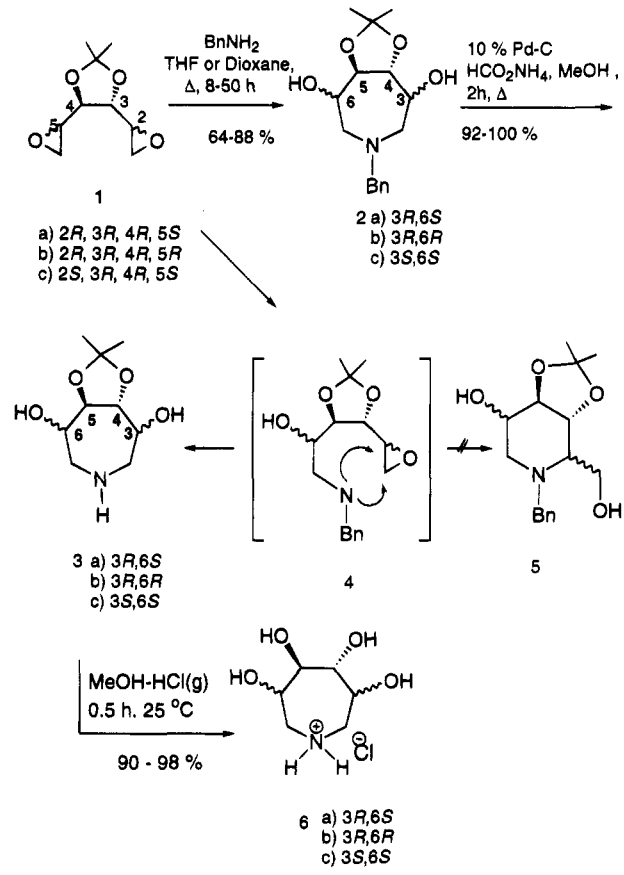
In recent years, there has been renewed interest in the synthesis of sugar-like alkaloids such as deoxynojirimycin, deoxymannojirimycin, castanospermine, and their epimers due to their anti-HIV activities such as inhibition of the maturation of glycoprotein gp120 of HIV-1.[1] These aza sugars are known to inhibit a number of glycosidase enzymes[2] and have been found to have antidiabetic[3] and anticancer activity.[4] Paulsen,[5] Ganem,[6] and more recently Depezay[7] have reported the reaction of epoxides with amine to furnish a mixture of six-membered and seven-membered cyclic aza sugars in nearly a 1:1 ratio. We wish to report unprecedented selectivity in the reaction of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene hexitols **1a-c** with benzylamine to furnish azepane **2a-c** as the only isolable products in good yield (Scheme 1).

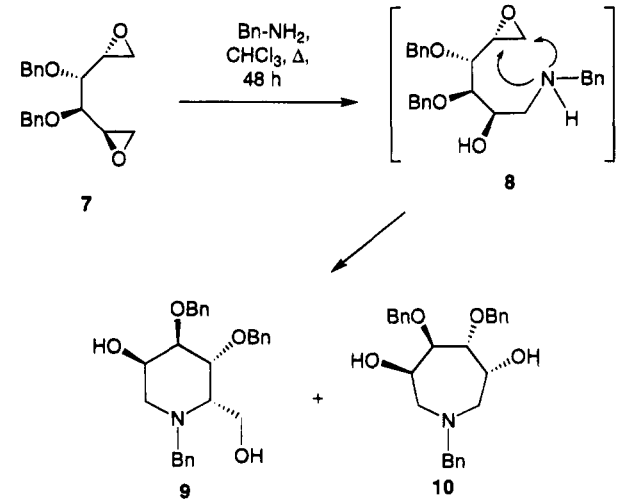
During the course of our investigations into the synthesis of compounds having anti-HIV activity, we needed to develop a practical method for the synthesis of polyhydroxy aza sugar derivatives. The reaction of 1,2:5,6-dianhydro-3,4-*O*-dibenzyl-D-mannitol (**7**) with benzylamine[5-7] is known to furnish nearly a 1:1 mixture of six-membered (**9**) and seven-membered (**10**) aza sugar derivatives (Scheme 2). Examination of a model of **7** indicates free rotation around the C_3-C_4 bond. Initial nucleophilic attack of benzylamine at the terminal carbon of the epoxide would furnish intermediate **8**. The amine moiety of the intermediate **8** can subsequently attack intramolecularly with equal ease at the C_5 or C_6 carbon atom of the epoxide, furnishing six-membered (**9**) and seven-membered (**10**) aza sugar derivatives. Interestingly, we found that the reaction of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-sorbitol (**1a**) with benzylamine gave only the seven-membered aza sugar **2a**.

In fact, we were unable to detect the formation of the six-membered aza sugar derivative **5a**. This result led us to carefully examine a model of bisepoxide **1**, which lacks free rotation around the C_3-C_4 bond due to the

Scheme 1



Scheme 2



† Dedicated to Prof. S. Chandrasekran on his 50th birthday.

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(1) (a) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229; *FEBS Lett.* **1988**, *237*, 128 and references cited therein. (b) Fleet, G. W. J. *Chem. Brit.* **1989**, 287. (c) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497. (d) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (e) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199.

(2) (a) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; Cenci de Bello, I.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365. (b) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. (c) Look, G. C.; Fotsch, C. H.; Wong, C. H. *Acc. Chem. Res.* **1993**, *26*, 182 and references cited therein.

(3) (a) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C. H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539. (b) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (c) See ref 1c.

(4) (a) Spearman, M. A.; Jamieson, J. C.; Wright, J. A. *Expt. Cell. Res.* **1987**, *168*, 116. (b) Tsukamoto, K.; Uno, A.; Shimada, S.; Imokaw, G. *Clin. Res.* **1989**, *37A*, 722.

(5) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 512.

(6) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165.

(7) Poitout, L.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293.

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presence of a *trans*- acetonide group. Interestingly, in the intermediate **4**, the amine group is slightly farther situated from the C_5 center than C_6, and it appears that this might be the reason for the exclusive selectivity for the formation of seven-membered ring heterocycles. However, it is difficult to point out the actual reason for this high selectivity with the present understanding. Similar reactions were performed with 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol (**1b**) and 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-L-iditol (**1c**) with benzylamine. In all the cases, only seven-membered azepane derivatives **2a-c** were isolated in 64−88% yield after purification by chromatography. Careful monitoring of the reaction showed the formation of an intermediate, presumably **4**, which cyclizes exclusively to azepane derivatives **2a-c**. Attempts to isolate this intermediate **4** were not successful. This is remarkable, especially, when one compares the reaction of 1,2:5,6-dianhydro-3,4-*O*-dibenzyl-D-mannitol (**7**) with benzylamine, which gave nearly a 1:1 mixture of six-membered (**9**) and seven-membered (**10**) products (Scheme 2).[5-7]

Although such a high selectivity due to the introduction of the *trans*-acetonide group may not be unique, it is nonetheless rare. Examination of a model of the bisepoxides **1a-c** and their reaction with benzylamine suggests that the reaction proceeds *via* a preferential 7-*endo-tet*-cyclization process which is allowed by Baldwin's rules.[8]

The bisepoxides **1a,b** were prepared from 3,4-*O*-isopropylidene-D-hexitols in 85−87% yield by a one-pot procedure.[9] The other bisepoxide **1c** was prepared from 3,4-*O*-isopropylidene-D-mannitol in an improved yield by modification of a reported process.[10] The bisepoxides **1a-c** were separately treated with benzylamine in refluxing THF or dioxane for 8−50 h to furnish a 64−88% isolated yield of *N*-benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepanes **2a-c**. Transfer hydrogenation of **2a-c** proceeded smoothly to furnish 92−100% yields of 3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepanes **3a-c**. Removal of the acetonide protecting group by the treatment of **3a-c** with methanolic HCl afforded tetrahydroxyazepanes as hydrochloride salts **6a-c**, respectively, in 90−98% yields.

To summarize, the presence of a *trans*-acetonide group in 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D/L-hexitol exerted a dramatic influence on the selectivity of the reaction leading exclusively to a 7-*endo-tet*-type cyclization process.

Experimental Section

1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-D-sorbitol (**1a**) and 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol (**1b**) were prepared from the corresponding hexitol by a one-pot procedure,[9] and 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-L-iditol (**1c**) was prepared by the reported procedure in excellent yield (85−87%).[10] Benzylamine was distilled before use. THF, methanol, and dioxane were dried and distilled before use. Ammonium formate and Pd−C (10%) were obtained from LOBA fine chemicals. Flash chromatography was performed using silica gel, EM Science (230−400 mesh). Gas chromatography was carried out on a Shimadzu 17 AFW using a DB-1 (0.25 mm × 30 M) column. Melting points are uncorrected. Stereochemical assignments are based on the stereochemistry of the starting sugar derivatives.

Reaction of 1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-D-sorbitol (1a) with Benzylamine. To a solution of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-sorbitol (**1a**) (2.2 g, 11.8 mmol) in dry THF (20 mL) was added freshly distilled benzylamine (1.54 mL, 14.16 mmol) under argon atmosphere, and the reaction mixture was refluxed for 50 h during which time all the bisepoxide **1a** reacted (GC monitored). The solvent was removed under reduced pressure, and the product was chromatographed on silica gel to afford pure (3*R*,4*R*,5*R*,6*S*)-1-*N*-benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (**2a**) (2.2 g, 64%) as a colorless syrupy liquid: $[\alpha]^{25}_D = -15.4°$ (*c* 1.53, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.5 (s, 6H), 2.5 (bs, 2H) 2.67 (dt, J = 9.41, 5.88 Hz, 2H), 3.0 (dt, J = 13.5, 5.88 Hz, 2H), 3.72 (m, 3H), 3.95 (dd, J = 8.2, 3.5 Hz, 1H), 4.07 (m, 1H), 4.20 (dd, J = 8.23, 8.23 Hz, 1H), 7.3 (s, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.9, 27.5, 61.0, 62.1, 64.1, 65.7, 72.6, 78.3, 78.8, 109.6, 127.5, 128.6, 128.7, 139.3; MS *m*/*z* (relative intensity) 294 (M^+ + 1) (11).

Reaction of 1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-D-mannitol (1b) with Benzylamine. The reaction of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol (**1b**) (1.86 g, 10 mmol) with benzylamine (1.06 g, 1.08 mL, 9.9 mmol) for 8 h under the above experimental conditions furnished (3*R*,4*R*,5*R*,6*R*)-1-*N*-benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (**2b**) (2.58 g, 88%) as a colorless crystalline solid: mp 80−82 °C; $[\alpha]^{25}_D$ = +78.2° (*c* 1.91, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 6H), 2.75 (m, 4H), 3.8 (m, 7H), 5.25 (bs, 1H), 7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.9, 58.0, 60.6, 70.5, 82.4, 109.2, 127.2, 128.4, 128.8, 129.2.

Reaction of 1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-L-iditol (1c) with Benzylamine. The reaction of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-L-iditol (**1c**) (0.82 g, 4.43 mmol) with benzylamine (0.95 g, 0.97 mL, 8.86 mmol) for 30 h under the above experimental conditions afforded (3*S*,4*R*,5*R*,6*S*)-1-*N*-benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (**2c**) (0.83 g, 64%) as a white crystalline solid: mp 144−145 °C; $[\alpha]^{25}_D$ = +30.3° (*c* 1.85, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 6H), 2.3 (bs, 2H), 2.65 (dd, J = 14.6, 4.8 Hz, 2H), 3.0 (dd, J = 14.6, 4.9 Hz, 2H) 3.8 (m, 6H), 7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.2, 61.8, 64.1, 72.2, 81.1, 109.8, 127.4, 128.5, 128.8, 139.1. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.30; H, 7.81; N, 4.76. Found: C 65.42; H, 7.90; N, 4.94.

Hydrogenolysis of (3*R*,4*R*,5*R*,6*S*)-1-*N*-Benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (2a). A mixture of **2a** (0.5 g, 1.7 mmol), methanol (6 mL), ammonium formate (0.43 g, 6.8 mmol), and Pd−C (10%, 0.14 g) was heated at reflux under argon for 2 h (TLC monitored). The reaction mixture was filtered through a pad of Celite to remove the catalyst, and the filtrate was evaporated under reduced pressure to furnish (3*R*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (**3a**) (0.34 g, *ca.* 100%) as a syrupy oil: $[\alpha]^{25}_D = -21.5°$ (*c* 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.4 (s, 3H), 1.45 (s, 3H), 2.95 (m, 4H), 3.15 (bs, 3H), 3.7 (m, 2H), 4.2 (m, 1H), 4.3 (dd, J = 9.52, 9.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.7, 27.1, 54.4, 55.7, 66.6, 72.2, 78.3, 78.6, 109.2; MS *m*/*z* (relative intensity) 204 (M^+ + 1) (49).

Hydrogenolysis of (3*R*,4*R*,5*R*,6*R*)-1-*N*-Benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (2b). Hydrogenolysis was carried out by the above method using **2b** (0.59 g, 2 mmol), methanol (8 mL), ammonium formate (0.5 g, 8 mmol), and Pd−C (10%, 0.15 g) for 2 h to furnish (3*R*,4*R*,5*R*,6*R*)-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (**3b**) as a colorless crystalline solid (0.37 g, 92%): mp 98−100 °C; $[\alpha]^{25}_D$ = +51.5° (*c* 2.21, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 6H), 2.82 (m, 4H), 4.0 (m, 7H); ^{13}C NMR (50 MHz, D_2O) δ 27.2, 51.6, 71.0, 81.2, 111.3.

Hydrogenolysis of (3*S*,4*R*,5*R*,6*S*)-1-*N*-Benzyl-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (2c). Hydrogenolysis was carried out by the above method using **2c** (0.59 g, 2 mmol), methanol (8 mL), ammonium formate (0.5 g, 8 mmol), and Pd−C (10%, 0.15 g) for 2 h to furnish (3*S*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxy-4,5-*O*-isopropylideneazepane (**3c**) as a colorless crystalline solid (0.38 g, 94%): mp 74−75 °C; $[\alpha]^{25}_D$ = +36.0° (*c* 1.92, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 6H), 2.75 (bs, 3H), 2.85 (dd, J = 14.6, 4.9 Hz, 2H); 3.12 (dd, J = 14.6, 4.9 Hz, 2H), 3.8 (m, 4H); ^{13}C NMR (50 MHz, D_2O) δ 26.9, 53.1, 72.1, 80.9, 110.9. Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 53.44; H, 8.12; N, 6.84.

Removal of the Acetonide Group of (3*R*,4*R*,5*R*,6*S*)-

(8) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(9) Lohray, B. B.; Chatterjee, M.; Jayamma, Y. Manuscript in preparation.
(10) Le Merrer, Y.; Dureault, A.; Greck, C.; Micas-Languin, D.; Graiver, C.; Depezay, J.-C. *Heterocycles* **1987**, *25*, 541.

3,4,5,6-Tetrahydroxy-4,5-*O*-isopropylideneazepane (3a). The syrupy liquid **3a** (0.3 g, 1.47 mmol) was dissolved in dry methanol (1 mL), and methanolic HCl(g) (2 mL) was added. The reaction mixture was stirred for 0.5 h at *ca.* 25 °C during which time a white solid precipitated. The solvent was removed under reduced pressure, and the residue was washed with anhydrous ether (4 × 2 mL) to furnish (3*R*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxyazepane hydrochloride (**6a**) (0.26 g, 90%) as a crystalline solid: mp 190–191 °C; $[\alpha]^{25}_D = -23.3°$ (*c* 1.16, D_2O); ^1H NMR (200 MHz, D_2O) δ 3.35 (m, 4H), 3.75 (m, 2H); 3.95 (m, 1H); 4.25 (m, 1H); ^{13}C NMR (50 MHz, D_2O) δ 47.1, 47.3, 68.0, 68.9, 75.4 and 75.9; MS *m*/*z* (relative intensity) 164 ($M^+ - Cl$) (70). Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.09; H, 7.02; N, 7.02. Found: C, 36.00; H, 7.50; N, 7.34.

Removal of the Acetonide Group of (3*R*,4*R*,5*R*,6*R*)-3,4,5,6-Tetrahydroxy-4,5-*O*-isopropylideneazepane (3b). The compound **3b** (0.4 g, 2 mmol) under the above experimental conditions furnished (3*R*,4*R*,5*R*,6*R*)-3,4,5,6-tetrahydroxyazepane hydrochloride (**6b**) (0.39 g, 97%) as a white crystalline solid: mp > 300 °C dec; $[\alpha]^{25}_D = +26.6°$ (*c* 2.1, H_2O); ^1H NMR (200 MHz, D_2O) δ 3.4 (m, 4H), 3.85 (m, 2H); 4.5 (m, 2H); ^{13}C NMR (50 MHz, D_2O) δ 50.7, 51.5, 66.8, 67.0, 71.6, 72.3; MS *m*/*z* (relative intensity) 164 ($M^+ - Cl$) (40). Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.09; H, 7.02; N, 7.02. Found: C, 36.42; H, 7.31; N, 7.04.

Removal of the Acetonide Group of (3*S*,4*R*,5*R*,6*S*)-3,4,5,6-Tetrahydroxy-4,5-*O*-isopropylideneazepane (3c). The compound **3c** (0.2 g, 1 mmol) under the above experimental conditions furnished (3*S*,4*R*,5*R*,6*S*)-3,4,5,6-tetrahydroxyazepane hydrochloride (**6c**) (0.2 g, 98%) as a white crystalline solid: mp 146–148 °C; $[\alpha]^{25}_D = +13.0°$ (*c* 0.8, D_2O); ^1H NMR (200 MHz, D_2O) δ 3.2 (dd, J = 14.1, 7.6 Hz, 2H) 3.4 (dd, J = 13.2, 2.6 Hz, 2H); 3.7 (m, 2H); 4.1 (m, 2H); ^{13}C NMR (50 MHz, D_2O) δ 47.6, 68.4, 77.4; MS *m*/*z* (relative intensity) 164 ($M^+ - Cl$) (42). Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.09; H, 7.02; N, 7.02. Found: C, 35.90; H, 7.00; N, 6.96.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **2a-c**, **3a-c**, and **6a-c** and mass spectra of **6a-c** are available (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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