172.0 s; EIMS, m/z (relative intensity) 307 (M^+, 18), 278 (14), 264 (18), 248 (31), 152 (67), 139 (28), 138 (30), 83 (46), 81 (38), 80 (40), 69 (40), 68 (36), 67 (46), 57 (42), 55 (100).

Hydrogenolysis of Dysidazirine (1): Methyl (*R*)-2-Aminooctadecanoate (5) and β-Enamino Ester 3. A solution of 1 (32.7 mg) in CH_2Cl_2 (2.0 mL) was added to a stirred slurry of prehydrogenated platinum oxide (21 mg) in CH_2Cl_2 (2.0 mL) under 1 atm of hydrogen. The mixture was stirred for 5.5 h and then eluted through a short column of silica (0.6 × 4 cm) with 1:1 ethyl acetate/hexanes to provide three fractions.

(i) A UV-active, nonpolar fraction (15.8 mg). Purification of this by HPLC (Partisil M9/50, 1:3 ethyl acetate/hexanes) gave pure β-enamino ester **3** (3.5 mg).

β-Enamino ester 3: low melting solid, FTIR (neat) 3440, 3330, 1741, 1672, 1651, 1620, 1578 cm^{-1}; UV (MeOH) 275 nm (ε 17 300); ^1H NMR δ 0.89 (t, 3 H, J = 6.4 Hz), 1.26 (br s, 28 H), 1.50 (m, 2 H), 2.13 (t, 2 H, J = 7.6 Hz), 3.66 (s, 3 H), 4.55 (s, 1 H); EIMS, m/z (relative intensity) 311 (M^+, 69), 280 (66), 129 (79), 128 (100), 116 (97), 115 (100), 83 (92), 74 (54), 69 (53), 57 (100), 55 (97); HRMS, m/z 311.2813, $C_{19}H_{37}NO_2$ requires 311.2824.

(ii) Further elution (ethyl acetate) gave a ninhydrin-positive fraction (8 mg) which was purified by HPLC (Partisil M9/50, 5:95 2-propanol/ethyl acetate) to afford ester **5** (2.8 mg).

Methyl (*R*)-2-aminooctadecanoate (5): oil, FTIR (neat) 3394, 1723 cm^{-1}; ^1H NMR δ 0.89 (t, 3 H, J = 6.5 Hz), 1.26 (br s, 30 H), 3.45 (br t, 1 H, J = 6.1 Hz), 3.72 (s, 3 H); EIMS, m/z (relative intensity) 313 (M^+, 20), 257 (23), 255 (86), 255 (86), 254 (98), 102 (49), 88 (63), 57 (67), 55 (78), 56 (100), 55 (78). Amino ester **5** was identical (by ^1H NMR, IR, MS) with racemic methyl 2-aminooctadecanoate prepared by ammonolysis of 2-bromostearic acid.[10]

The hydrochloride salt of **5** was prepared by evaporation of a solution of **5** (0.5 mg) in MeOH (1 mL) containing concentrated hydrochloric acid (2 drops). Crystallization from ethyl acetate gave colorless needles, mp 114–115 °C (cf. lit.[10] for racemic compound, mp 112 °C).

(iii) Finally, elution with 10% 2-propanol/ethyl acetate gave a second, polar ninhydrin-positive fraction (3.1 mg), containing the β-amino ester **4**: ^1H NMR δ 2.28 (dd, 1 H, J = 15.7, 8.9 Hz), 2.48 (dd, 1 H, J = 15.7, 4.0 Hz), 3.18 (m, 1 H), 3.70 (s, 3 H). Irradiation of the H-3 signal (δ 3.18) collapsed the diastereotopic methylene proton signals (δ 2.28, 2.48) to an AB quartet.

Hydrolysis of Ester 5: (*R*)-2-Aminooctadecanoic Acid (7). Hydrochloric acid (6 M, 1.0 mL) and water (1.0 mL) were added to a solution of **5** in THF (2.0 mL), and the mixture was heated at reflux under nitrogen (12 h). After cooling, the volatiles were removed under reduced pressure and the residue was crystallized from glacial acetic acid to afford the sparingly soluble α-amino acid **7**: mp 224–226 °C (cf. lit.[10] mp 221–222 °C for racemic compound); FABMS, m/z 300 (MH^+).

***p*-Bromobenzamides of Amino Acid Methyl Esters.** A solution of ester **5** (2.8 mg, 9.0 μmol) in dry CH_2Cl_2 (0.5 mL) was treated with pyridine (0.10 mL), (dimethylamino)pyridine (DMAP), and a solution of *p*-bromobenzoyl chloride (5.9 mg, 27 μmol) in CH_2Cl_2 (0.6 mL). The mixture was allowed to warm to room temperature over 30 min and then treated with ice-cold saturated sodium bicarbonate solution (0.5 mL). After 15 min the mixture was partitioned against CH_2Cl_2 (2 × 3 mL) and the combined organic layers were washed with water (1 mL), dried over sodium sulfate, and evaporated to afford crude benzamide (6.3 mg). This was purified by HPLC (silica gel, 4:25 ethyl acetate/hexanes) to give pure methyl (*R*)-2-(*p*-bromobenzamido)octadecanoate (**8**, 2.5 mg).

Benzamide 8: mp 76–77 °C (ethyl acetate/hexanes); $[\alpha]_D$ +9° (*c* 0.2, MeOH); UV (MeOH) 241 nm (ε 19 500); CD (MeOH) 223 nm (Δε +1.4), 242 (−1.7); IR 3303, 2917, 2850, 1744, 1643, 1592 cm^{-1}; ^1H NMR δ 0.89 (t, 3 H, J = 6.7 Hz), 1.25 (br s, 28 H), 1.7–2.1 (m, 2 H), 3.80 (s, 3 H), 4.80 (ddd, 1 H, J = 7.7, 6.8, 5.5 Hz), 6.60 (br d, 1 H, J = 7.7 Hz), 7.60 (d, 2 H, J = 8.8 Hz), 7.68 (d, 2 H, J = 8.8 Hz); EIMS m/z (relative intensity) 497 (M^+, 34), 495 (38), 439 (73), 437 (74), 313 (96), 273 (83), 271 (87), 185 (100), 183 (100), 57 (44), 56 (36), 55 (45).

A suspension of (+)-(*S*)-norleucine (Aldrich, 100 mg) in dry MeOH (10 mL) was cooled to 0 °C and saturated with HCl. The resulting clear solution was heated under reflux (3 h), cooled, and evaporated. A portion (50 mg) of the resulting crude methyl ester hydrochloride was *p*-bromobenzoylated as for **5** except for the addition of triethylamine (3 equiv) to neutralize the HCl. Crystallization from ethyl acetate/hexanes gave pure methyl (*S*)-2-(*p*-bromobenzamido)hexanoate (**9**, 66 mg, 77%) as colorless needles.

Benzamide 9: mp 94–95 °C; UV (MeOH) 241 nm (ε 12 200); CD (MeOH) 222 nm (Δε −1.59), 240 (+1.88); FTIR 3350, 2956, 1744, 1655 cm^{-1}; ^1H NMR δ 0.91 (t, 3 H, J = 7.0 Hz), 1.35 (m, 4 H), 1.70–2.10 (m, 2 H), 3.80 (s, 3 H), 4.81 (ddd, 1 H, J = 7.6, 6.9, 5.5 Hz), 6.64 (br d, 1 H, J = 7.6 Hz), 7.61 (d, 2 H, J = 8.7 Hz), 7.67 (d, 2 H, J = 8.7 Hz); EIMS, m/z (relative intensity) 329 (M^+, 19), 327 (18), 273 (47), 271 (60), 270 (64), 268 (67), 185 (100), 183 (100), 157 (22), 155 (23).

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Registry No. 1, 113507-74-7; 3, 113507-75-8; 5, 113532-98-2; 7, 100680-17-9; 8, 113507-76-9; 9, 113507-77-0; *p*-BrC_6H_4COCl, 586-75-4; (±)-(*S*)-norleucine, 327-57-1.

On the Mechanism of Sodium Cyanoborohydride Reduction of Tosylhydrazones

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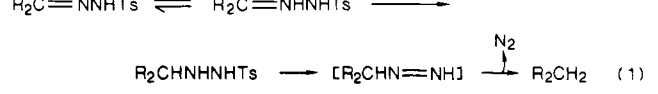
Reduction of tosylhydrazone derivatives of saturated ketones and aldehydes with sodium cyanoborohydride in acidic media is a synthetically useful method for the conversion of carbonyl compounds to the corresponding alkanes.[1] With α,β-unsaturated tosylhydrazones, this reduction produces alkenes[2] with double bond migration to the site originally occupied by the carbonyl group.[1c,3] The reaction course for the reduction of α,β-unsaturated tosylhydrazones has been shown[2,4] to proceed with initial protonation of the tosylhydrazone to form an imminium cation followed by hydride reduction of the C=N double bond.[1,2,5] Subsequent *p*-toluenesulfinate elimination and then loss of N_2 afford the corresponding reduced hydrocarbon (eq 1).[6] Similar results have also been found in



(1)

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(2) However, exceptions are known for the reduction of α,β-unsaturated tosylhydrazones in which alkanes or alkenes or both may be formed depending on the nature of the carbonyl precursors, see: Taylor, E. J.; Djerassi, C. *J. Am. Chem. Soc.* **1976**, *98*, 2275.

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Table I. Products of the Reduction of Compound 2 with Various Combinations of Deuteriated and/or Undeuteriated Reagents in THF/MeOH(D)

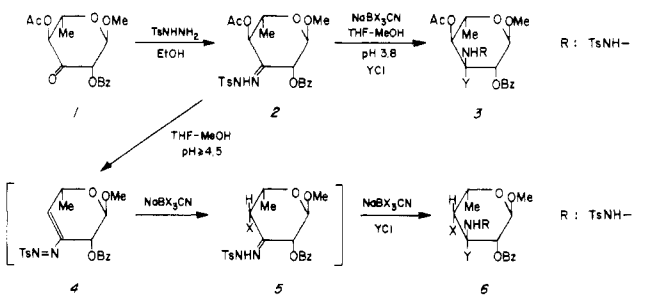
reducing agent	acid	compd 3	compd 6
$NaBH_3CN$	HCl	Y = H	X = H, Y = H
$NaBD_3CN$	HCl	Y = H	X = D, Y = H
$NaBH_3CN$	DCl	Y = D	X = H, Y = D
$NaBD_3CN$	DCl	Y = D	X = D, Y = D

the reduction of saturated tosylhydrazones with $NaBH_3CN$[7] and other borane/boron hydride reagents.[5c,8] Since the hydride incorporation should occur exclusively at the original carbonyl carbon based on the above mechanism (eq 1), reduction of tosylhydrazones holds promise for the preparation of molecules with regiospecific isotopic labeling.[9] As a part of our efforts to study deoxy sugar biosynthesis, we have employed this reduction procedure with labeled cyanohydridoborate to prepare stereospecifically deuteriated 3,6-dideoxyhexoses for detailed enzymatic analysis. Summarized here are the results found in these labeling studies, which are difficult to reconcile with the aforementioned mechanism, and our comments on the mechanistic insights deduced from these observations.

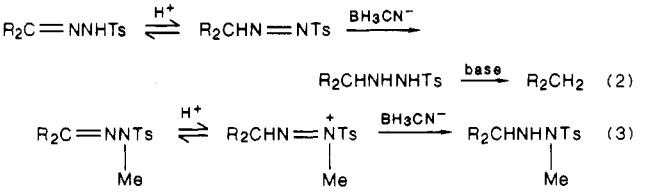
The reduction was conducted at 0 °C with excess of $NaBH_3CN$ and a trace amount of methyl orange in THF/MeOH (1:1 by volume) according to a procedure developed by Nair and Sinhababu.[10] The acidity of the reaction mixture was adjusted by dropwise addition of methanolic HCl solution to keep the color of the solution at the red-yellow transition point (pH ~3.8).[10] This mild condition offers significant advantages over the traditional method (DMF–sulfolane, 105–110 °C),[1,2] since the amount of unsaturated sugar products (Bamford–Stevens products)[11] is minimized and the tosylhydrazine intermediate can be isolated. Characterization of the resulting tosylhydrazine would allow us to define the stereochemical outcome of this reduction step unambiguously. The tosylhydrazine can then be converted to the deoxy sugar by the treatment with sodium acetate in ethanol under reflux.[8b,10,12]

The keto sugar **1** serves as the source of our starting compound **2**. This keto sugar can be readily prepared from methyl L-rhamnoside.[13] A series of experiments were carried out in which compound **2** was reduced to the corresponding tosylhydrazine **3**[14] by utilizing various combinations of deuteriated and undeuteriated reagents (Scheme I). The results are summarized in Table I. *In contrast to earlier reports, these results surprisingly revealed that the hydrogen atom being delivered to the*

Scheme I



imino carbon is not derived from the boron reducing agent, but from the most acidic source (HCl or DCl). Although it is conceivable that the solvent-mediated hydrogen exchange of cyanohydridoborate occurs prior to imine reduction, this possibility has been excluded by a parallel study in which the exchange of BH_3CN^- with solvent hydrogen under identical conditions was found to be insignificant.[15] This coincides with Kreevoy's findings that BH_3CN^- is stable in acid down to pH 3.[16] The observed deuterium incorporation patterns implicate that the reaction sequence may start with an acid-catalyzed hydrazone–azohydrazine tautomerization step[17] with solvent hydrogen incorporation at the original carbonyl carbon (C-3 in compound **2**). This is followed by reduction of the more reactive azo intermediate to furnish the end product **3** (eq 2). Identical results were found in the reduction of the *N,N*-methyltosylhydrazone derivative of **2** (compound **7**). In this case, isomerization leading to protonation at C-3 (compound **8**) may be assisted by the lone pair electrons on the disubstituted nitrogen atom (eq 3).



When compound **2** was reduced with $NaBH_3CN$ in THF–MeOH at slightly more basic conditions (pH ≥4.5) at room temperature overnight, deoxygenation at C-4 was found, and compound **6** was obtained in 75% yield. The C-4 acetyl group was replaced with inversion by a hydrogen donated by the boron reducing agent, but the hydrogen derived from HCl was again placed exclusively at the original carbonyl carbon in compound **6** (Table I).[18] Thus,

(7) Klein, H.; Midgley, I.; Djerassi, C., unpublished results cited in ref 2. Since the hydrazine intermediate was not isolable under their reduction conditions, it is actually very difficult to ascertain whether deuterium incorporated at the original carbonyl carbon was derived directly from the deuteride reducing agent.

(8) (a) Kabalka, G. W.; Yang, D. T. C; Chandler, J. H.; Baker, J. D., *Jr. Synthesis* **1977**, 124. (b) Kabalka, G. W.; Baker, J. D., Jr.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512.

(9) Schenk, G.; Albrecht, H. P.; Lietz, H. *Arzneim.-Forsch* **1978**, *28* (I), 518. (b) Renaud, R. N.; Bovenkamp., J. W. *Can. J. Chem.* **1978**, *55*, 650. (c) See ref 2, 4, and 8a for other examples.

(10) Nair, V.; Sinhababu, A. K. *J. Org. Chem.* **1978**, *26*, 5013.

(11) (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735. (b) Shapiro, R. H. *Org. React. (N.Y.)* **1976**, *23*, 405 and references cited therein. (c) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

(12) Brown, D. M.; Jones, G. H. *J. Chem. Soc. C* **1967**, 252.

(13) Han, O.; Liu, H. W. *Tetrahedron Lett.* **1987**, 1073.

(14) Difference NOE experiments reveal the proximity between 2-H/5-H and 3-H/4-H in compound **3**. These results plus the 2D COSY analysis allow one to assign the conformation of the pyranose ring as $_4B^1$ and configuration at C-3 as *S* in compound **3**.

(15) Exchange of hydrogens in cyanohydridoborate was attempted by mixing $NaBH_3CN$ in the absence of tosylhydrazone with DCl in THF–MeOD solution under the identical reaction conditions as described in the text. The boron reducing agent was then recovered and purified by recrystallization of its monodioxanate complex (see: Wittig, G.; Raff, P. *Ann.* **1951**, *573*, 202). The hydrogen content of BH_3CN^- in this complex was then analyzed by ^1H NMR using dioxane signal as an internal standard.

(16) Kreevoy, M. M.; Hutchins, J. E. C. *J. Am. Chem. Soc.* **1969**, *91*, 4329.

(17) Tautomerization between aryl hydrazone and the corresponding azo species is well-precedented; however, acid or base is generally required to initiate the interconversion (Buckingham, J. *Q. Rev.* **1969**, *23*, 37 and references cited therein). For example, Robinson has reported that the polyphosphoric acid catalyzed cyclization of certain (*p*-nitrophenyl)-hydrazones to indazoles may proceed through their azo tautomers (Robinson, B. *Tetrahedron Lett.* **1967**, 5085). Such hydrazone–azohydrazine tautomerization is expected to be an equilibrium process and in the present case is acid catalyzed. Even if the tautomerization is intramolecular in nature, the rapid equilibrium with facile exchange of the labile N-H with solvent hydrogen under acidic condition would eventually lead to exclusive solvent hydrogen incorporation at C-3 of compound **2**.

the chemical nature of the reduction products (chemoselectivity) seems to be pH dependent, but the labeling outcome and the resulting stereochemistry at C-3 are identical in the two cases. Since the generation of azoaryl alkene from arylhydrazone in dilute alkaline as well as in diluted acidic solutions is known,[19] the formation of **6** under the prescribed conditions can be rationalized as proceeding via intermediates **4** and **5** and may be triggered by proton abstraction of the acidic hydrazone hydrogen.[20] A similar mechanism has been proposed to account for the intermediacy of a benzeneazo ene derivative in acid-catalyzed C_β nucleophilic substitution of tosylhydrazone having a leaving group adjacent to the imino carbon.[19a,21] The stereoselectivity of deuterium incorporation at C-4 of **4** may be ascribed to the steric hindrance excerted by the quasi-axial 1-methoxy group in a ${}_0H^1$ conformation that would prevent the attack of deuteride from above the ring.[22] Since the hydrogens incorporated at C-4 and C-3 are derived exclusively from the reducing agent and the acid, respectively, these results further confirm that hydrogen exchange between $NaBH_3CN$ and acidic medium is insignificant.

The experiments summarized herein in conjunction with the earlier work performed by Djerassi and his co-workers[7] strongly suggest that sodium cyanoborohydride reduction of saturated tosylhydrazone proceeds via two different mechanisms depending on the reaction conditions. The enhancement of the hydride delivery ability of $NaBH_3CN$ by polar, aprotic solvents (DMF–sulfolane) at high temperature (105–110 °C) may allow the reduction of the iminium system (eq 1) to take place directly. In contrast, the reduction step occurs only after a prior tautomerization to generate a more reactive azo intermediate when the reaction is conducted in more acidic, protic solvents (THF–MeOH) at low temperature (0 °C) (eq 2). These unexpected findings clearly demonstrate that one can never underestimate the complexity of the mechanism of even a well-documented reaction. Furthermore, the labeling patterns found in this cases indicate that reduction and hydrogen incorporation of tosylhydrazones having a rigid conformation under the aforementioned conditions are stereospecific. It can be a useful method for the preparation of stereospecifically labeled molecules.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Mass spectra were obtained with a VG 7070E-HF spectrometer. ^1H and ^{13}C NMR spectra were recorded on an IBM NR/200 or NR/300 spectrometer. Chemical shifts were reported in ppm on the δ scale relative to internal standard (tetramethylsilane) with coupling constants given in hertz. NMR assignments labeled with * or † may be interchangable. Flash chromatography was performed in columns of various diameters with Baker (230–400 mesh) silica gel by elution with the solvents reported. Analytical thin-layer chromatography (TLC) were carried out on Merck silica gel 60 G-254 plates (25 mm) and developed with the solvents mentioned. TLC spots were visualized either with UV light or by dipping into the staining solutions of vanilin/ethanol/H_2SO_4 (1:98:1) or phosphomolybdic acid (7% EtOH solution) and then heating. Methanolic DCl solution was prepared by mixing acetyl chloride with methanol-d_1 and then trapping the vapor (DCl) generated from this exothermic reaction in chilled deuteriated methanol.[23] The exact amount of acid (DCl) in this methanol solution was determined by the standard titration method. Solvents, unless otherwise specified, were reagent grade and distilled once prior to use.

Methyl 4-*O*-Acetyl-2-*O*-benzoyl-6-deoxy-α-L-*arabino*-hexopyranosid-3-ulose (1). To a chilled (−78 °C) orange suspension of pyridinium chlorochromate (11.6 g, 54 mmol) and 3-Å molecular sieves (11 g, activated at 250 °C for 24 h) in 150 mL of dry methylene chloride was added methyl 4-*O*-acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside[13] (6.6 g, 21 mmol) in one portion. The reaction mixture was allowed to warm up gradually to room temperature and stirred under nitrogen for 2 h. After completion, the reaction mixture was treated with a solution of methylene chloride–ether (1:1 by volume). The black precipitate was filtered off via a pad of silica gel and washed with methylene chloride–ether (1:1) solution. The combined filtrates were evaporated to give the desired product **1** as a colorless syrup in 92% yield. ^1H NMR ($CDCl_3$): 8.06 (2 H, d, J = 7.2; ortho H's), 7.61 (1 H; t, J = 7.4; para H), 7.35 (2 H; dd, J = 7.4, 7.2; meta H's), 5.34 (1 H; d, J = 9.8; 4-H), 5.24 (1 H; br s; 2-H), 5.10 (1 H; br s; 1-H), 4.14 (1 H; m; 5-H), 3.43 (3 H; s; OMe), 2.18 (3 H; s; CH_3C=O), 1.42 (3 H; d, J = 6.2; 5-Me). ^{13}C NMR ($CDCl_3$): 194.9 (C-3), 169.4 (CH_3C=O), 164.9 (PhC=O), 133.9–128.6 (Ar C's), 100.3 (C-1), 77.2 (C-4)*, 76.6 (C-2)*, 68.8 (C-5), 55.5 (OMe), 20.5 (CH_3C=O), 18.6 (C-6). Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.62. Found: C, 59.86; H, 5.64.

Methyl 4-*O*-Acetyl-2-*O*-benzoyl-6-deoxy-α-L-*arabino*-hexopyranosid-3-ulose (*p*-Tolylsulfonyl)hydrazone (2). To a well agitated solution of **1** (204 mg, 0.67 mmol) in 1.5 mL of absolute ethanol was added *p*-toluenesulfonohydrazide (136 mg, 0.73 mmol) in portions. The reaction mixture was stirred for 30 min at room temperature, during which time the resulting hydrazone precipitated as white crystals. Ether (2 mL) was added at the end of the reaction. The crystalline product was collected by filtration and washed thoroughly with cold ether. The yield was quantitative. MP 172–173 °C. ^1H NMR ($CDCl_3$): 9.59 (1 H; s; NH), 7.96, 7.21 (2 H's each; d, J = 7.2; AB q of tosyl ring H's), 7.72 (2 H; d, J = 8.1; ortho H's), 7.61 (1 H; t, J = 7.4; para H), 7.44 (2 H; dd, J = 8.1, 7.4; meta H's), 5.33 (1 H; br s; 2-H), 4.95 (1 H; d, J = 9.9; 4-H), 4.91 (1 H; s; 1-H), 4.11 (1 H; m; 5-H), 3.39 (3 H; s; OMe), 2.34 (3 H; s; Ts Me), 2.04 (3 H; s; CH_3C=O), 1.29 (3 H; d, J = 6.2; 5-Me). ^{13}C NMR ($CDCl_3$): 169.1 (CH_3C=O), 166.5 (PhC=O), 143.9 (C-3), 144.8–127.8 (Ar C's), 98.9 (C-1), 71.0 (C-4), 67.4 (C-2)*, 66.4 (C-5)*, 55.0 (OMe), 21.6 (TsMe), 20.6 (CH_3C=O), 18.1 (C-6). Anal. Calcd for $C_{23}H_{26}N_2O_8S$: C, 56.31; H, 5.34; N, 5.71; S, 6.54. Found: C, 56.16; H, 5.07; N, 5.80; S, 6.52.

Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3,6-dideoxy-3-[2-(*p*-tolylsulfonyl)hydrazino]-α-L-*altro*-hexopyranoside (3). To a stirred mixture of tosylhydrazone **2** (200 mg, 0.42 mmol) and trace amount of methyl orange in a solution of 1:1 THF–MeOH (6 mL) under nitrogen was added two drops of HCl (6 N in dry MeOH) at 0 °C. After the mixture was stirred for 10 min, sodium cyanoborohydride (1 M in dry THF) was added dropwise until the color of the solution was about to change to yellow. Additional amounts of HCl (0.5 mL, 6 N in MeOH) and $NaBH_3CN$ (~1 mL, 1 M in THF) were added to this milky (NaCl percipitate) orange solution keeping the color of the solution at the red-yellow transition point (orange, pH ~3.8). The mixture was stirred at 0 °C at this pH, and the progress of the reaction was monitored by TLC. The addition of HCl and $NaBH_3CN$ was repeated every 2 h until the reaction was complete (two more times, total reaction time was 6 h). The mixture was then neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with aqueous HCl (6 N), aqueous $NaHCO_3$, and brine, respectively, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude product was purified by flash chromatography

(18) The stereochemistry at C-3 and C-4 of compound **6** was determined by 2D COSY and NOE difference experiments. The long-range (W-type) couplings observed between H-1/H-3 and H-2/H-4 clearly indicates that the pyranose ring of **6** adopts a ${}_4C^1$ conformation.

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(20) Although the pK_a of the NH proton of tosylhydrazone **2** is not known, the pK_a of acetone mesylhydrazone is about 8.5: Powell, J. W.; Whiting, M. C. *Tetrahedron* **1959**, *7*, 305.

(21) (a) Simon, H.; Moldenhauer, W. *Chem. Ber.* **1968**, *101*, 2124. (b) Kraus, A.; Simon, H. *Chem. Ber.* **1972**, *105*, 954.

(22) Attempts to isolate and characterize intermediate **4** by adjusting the pH with lithium diisopropylamide (THF solution) failed. Thus, the possibility of a S_N2 displacement of the C-4 acetyl group by the hydride reducing agent cannot be excluded.

(23) Brown, H. C.; Groot, C. *J. Am. Chem. Soc.* **1942**, *64*, 2223.

(benzene/EtOAc/EtOH 27:2:1). Compound **3** was isolated as a light yellow syrup in 75% yield. ^{1}H NMR ($CDCl_3$): 8.02, 7.11 (2 H's each; d, J = 7.0; AB q of tosyl ring H's), 7.64 (2 H; d, J = 8.3; ortho H's), 7.60 (1 H; t, J = 7.5; para H), 7.46 (2 H; dd, J = 8.3, 7.5; meta H's), 6.45 (1 H; br s; NHTs), 5.08 (1 H; dd, J = 5.7, 3.0; 2-H), 4.98 (1 H; dd, J = 7.6, 4.0; 4-H), 4.70 (1 H; d, J = 3.0; 1-H), 4.20 (1 H; br d, J = 8.5; NHN), 4.04 (1 H; m; 5-H), 3.48 (1 H; m; 3-H), 3.36 (3 H; s; OMe), 2.27 (3 H; s; Ts Me), 2.10 (3 H; s; CH_3C=O), 1.25 (3 H; d, J = 6.5; 5-Me). ^{13}C NMR ($CDCl_3$): 170.4 (CH_3C=O), 165.5 (PhC=O), 144.0–128.1 (Ar C's), 98.6 (C-1), 71.6 (C-4), 69.8 (C-2), 64.7 (C-5), 58.8 (C-3), 55.9 (OMe), 21.5 (TsMe), 21.1 (CH_3C=O), 17.3 (C-6). Cl-MS (NH_3): m/z 510 ($M^+ + 1 + NH_3$), 493 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{28}N_2O_8S$: C, 56.09; H, 5.69; N, 5.69; S, 6.50. Found: C, 56.17; H, 5.91; N, 5.67; S, 6.29.

Methyl 2-*O*-Benzoyl-3,4,6-trideoxy-3-[2-(*p*-tolylsulfonyl)hydrazino]-α-L-*arabino*-hexopyranoside (6). To a stirred solution of tosylhydrazone **2** (176 mg, 0.37 mmol) in a mixture of 1:1 THF–MeOH (5 mL) under nitrogen were added sodium cyanoborohydride (1.5 mL, 1 M THF solution) and a trace amount of methyl orange. Hydrogen chloride (2.3 N in dry MeOH) was then added dropwise (~1.6 mL) at room temperature, keeping the color of the solution yellow (pH ~4.5, slightly over its transiton point). The addition of $NaBH_3CN$ (1.5 mL, 1 M THF solution) and HCl (2.3 N MeOH solution) was repeated every 2 h for three times. The reaction was then stirred overnight. The resulting milky mixture was neutralized with aqueous $NaHCO_3$ and extracted with methylene chloride. The combined organic extracts were washed with 6 N HCl solution and brine, respectively, dried (anhydrous Na_2SO_4), and then evaporated in vacuo. Compound **6** was purified from this yellow oily residue by flash chromatography (EtOAc/benzene, 1:4). The yield was 75%. ^{1}H NMR ($CDCl_3$): 7.99, 7.27 (2 H's each; d, J = 7.8; AB q of tosyl ring H's), 7.82 (2 H; d, J = 8.2; ortho H's), 7.56 (1 H; t, J = 7.3; para H), 7.43 (2 H; dd, J = 8.2, 7.3; meta H's), 6.43 (1 H; br s; NHTs), 4.92 (1 H; br d, J = 1.8; 2-H), 4.72 (1 H; br s; 1-H), 4.36 (1 H; br d, J = 8.7; NHN), 3.93 (1 H; m; 5-H), 3.34 (3 H; s; OMe), 3.08 (1 H; br s; 3-H), 2.30 (3 H; s; Ts Me), 1.73 (2 H; br s; 4-H's), 1.18 (3 H; d, J = 6.2; 5-Me). ^{13}C NMR ($CDCl_3$): 165.5 (PhC=O), 143.9–128.1 (Ar C's), 99.0 (C-1), 66.8 (C-2), 60.1 (C-5), 55.8 (C-3), 55.4 (OMe), 31.8 (C-4), 21.6 (TsMe)*, 21.2 (C-6)*. CI-MS (NH_3): m/z 449 ($M^+ + 1 + NH_3$), 435 ($M^+ + 1$). Anal. Calcd for $C_{21}H_{26}N_2O_8S$: C, 58.06; H, 5.99; N, 6.45; S, 7.37. Found: C, 58.36; H, 6.18; N, 6.28; S, 7.10.

***N*-Methyl-*N*-tosylhydrazine.** Tosyl chloride (6.08 g, 31.9 mmol) dissolved in a minimal amount of benzene (30 mL) was added dropwise to a solution of methylhydrazine (5 mL, 94.1 mmol) in 25 mL of water. The resulting solution was stirred at 25 °C for 30 min. The excess of methylhydrazine and benzene was evaporated, leaving a white precipitate dispersed in water. The precipitate was collected, washed with a minimum amount of water, redissolved in warm methylene chloride, and filtered through a short column of magnesium sulfate. The combined filtrate was concentrated to a smaller volume (ca 5 mL), to which an equal volume of hexane was added. The resulting solution was left undisturbed at 4 °C. The desired product was isolated as white crystals in 77% yield, mp 81–83 °C (lit.[24] mp 80–82 °C). ^{1}H NMR ($CDCl_3$): 7.45 (4 H; m; Ar H's), 3.45 (2 H; s; NH's), 2.75 (3 H; s; NMe), 2.40 (3 H; s; Ts Me).

Methyl 4-*O*-Acetyl-2-*O*-benzoyl-6-deoxy-α-L-*arabino*-hexopyranosid-3-ulose *N*-Methyl-*N*-(*p*-tolylsulfonyl)hydrazone (7). *N*-Methyl-*N*-tosylhydrazine (157 mg, 0.78 mmol) was added in one portion to a solution of keto sugar **2** (200 mg, 0.62 mmol) in 2 mL of freshly distilled methanol. The crystalline hydrazine dissolved within 30 min, and the resulting colorless solution was stirred at room temperature for 1.5 h. The reaction mixture was then poured into a solution of saturated NH_4Cl and extracted several times with ether. The combined ether extracts were washed with brine, dried (anhydrous $MgSO_4$), and evaporated to give an oily residue (335 mg). This crude mixture was loaded onto a silica column (10 g) and eluted gradiently with EtOAc/hexane (2–15%). The less polar fraction which gave two heavily overlapped spots on TLC (EtOAc/hexane, 1:1; R_f 0.59) was a mixture of unreacted starting keto sugar **2** and its C-2 epimer (i.e., the C-2 epimerized keto sugar, methyl 4-*O*-acetyl-2-*O*-benzoyl-6-deoxy-α-L-*ribo*-hexopyranosid-3-ulose. ^{1}H NMR ($CDCl_3$): 8.10 (2 H; d, J = 7.1; ortho H's), 7.58 (1 H; t, J = 7.4; para H), 7.44 (2 H; dd, J = 7.4, 7.1; meta H's), 5.63 (1 H; d, J = 4.2; H-2), 5.26 (1 H; d, J = 4.2; 1-H), 5.06 (1 H; d, J = 9.9; 4-H), 4.15 (1 H; m; 5-H), 3.46 (3 H; s; OMe), 2.17 (3 H; s; CH_3C=O), 1.42 (3 H; d, J = 6.2; 5-Me). ^{13}C NMR ($CDCl_3$): 191.2 (C-3), 169.3 (CH_3C=O), 164.5 (PhC=O), 134.0–128.5 (Ar C's), 98.2 (C-1), 74.8 (C-4)*, 73.2 (C-2)*, 65.8 (C-5), 55.3 (OMe), 20.6 (CH_3C=O), 15.8 (C-6)). The desired hydrazone **7** was found in the more polar fractions (EtOAc/hexane, 1:1; R_f = 0.55) and isolated in two isomeric forms. Isomer b was the major product. However, Isomer a became the predominant one when the reaction was allowed to proceed for 10 h. Isomer a. ^{1}H NMR ($CDCl_3$): 8.15–6.80 (9 H; m; Ar H's), 6.43 (1 H; d, J = 1.6; H-2), 5.51 (1 H; d, J = 9.8; H-4), 4.95 (1 H; d, J = 1.6; 1-H), 4.04 (1 H; m; 5-H), 3.38 (3 H; s; OMe), 2.74 (3 H; s; NMe), 2.36 (3 H; s; Ts Me), 2.07 (3 H; s; CH_3C=O), 1.36 (3 H; d, J = 6.2; 5-Me). Isomer b. ^{1}H NMR ($CDCl_3$): 8.15–6.80 (9 H; m; Ar H's), 5.72 (1 H; d, J = 4.8; 2-H), 5.71 (1 H; d, J = 6.4; 4-H), 4.99 (1 H; d, J = 4.8; 1-H), 4.45 (1 H; m; 5-H), 3.52 (3 H, s; OMe), 2.60 (3 H; s; NMe), 2.27 (3 H; s; Ts Me), 2.15 (3 H; s; CH_3C=O), 1.40 (3 H; d, J = 6.5; 5-Me). ^{13}C NMR ($CDCl_3$): 170.1 (CH_3C=O), 167.7 (PhC=O), 144.1 (C-3), 133.4–128.5 (Ar C's), 99.8 (C-1), 74.0 (C-4), 71.4 (C-2), 69.6 (C-5), 56.0 (OMe), 40.0 (NMe), 21.5 (Ts Me), 20.9 (CH_3C=O), 17.0 (C-6). Anal. Calcd for $C_{24}H_{28}N_2O_8S$: C, 57.14; H, 5.56; N, 5.56; S, 6.35. Found: C, 57.62; H, 5.82; N, 5.58; S, 6.30.

Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3,6-dideoxy-3-[*N*-methyl-*N*-(tolylsulfonyl)hydrazino]-α-L-*altro*-hexopyranoside (8). Reduction of the *N*-methyl-*N*-tosyl sugar hydrazone **7** under the identical conditions used for the preparation of **3** led to the formation of the titled compound **8** together with a destosylated hydrazine compound as the major product. ^{1}H NMR ($CDCl_3$) of the titled compound: 8.15–7.20 (9 H; m; Ar H's), 5.22 (1 H; dd, J = 5.1, 2.5; 2-H), 5.02 (1 H; dd, J = 8.2, 4.0; 4-H), 4.73 (1 H; d, J = 2.5; 1-H), 4.02 (1 H; m; 5-H), 3.84 (1 H; dd, J = 5.1, 4.0; 3-H), 3.56 (1 H; d, J = 6.7; NHN), 3.36 (3 H; s; OMe), 2.85 (3 H; s; NMe), 2.38 (3 H; s; Ts Me), 2.16 (3 H; s; CH_3C=O), 1.28 (3 H; d, J = 6.7; 5-Me). ^{13}C NMR ($CDCl_3$): 170.0 (CH_3C=O), 165.9 (PhC=O), 144.1–128.5 (Ar C's), 98.7 (C-1), 71.3 (C-2)*, 70.2 (C-4)*, 64.4 (C-5), 59.2 (C-3), 55.8 (OMe), 40.7 (NMe), 21.6 (Ts Me), 21.1 (CH_3C=O), 17.3 (C-6). High-resolution FAB-MS: calcd for $C_{24}H_{30}N_2O_8S$ 507.1801, found 507.1791. ^{1}H NMR ($CDCl_3$) of the destosylated hydrazine, methyl 4-*O*-acetyl-2-*O*-benzoyl-3,6-dideoxy-3-(*N*-methylhydrazino)-α-L-*altro*-hexopyranoside: 8.05 (2 H; d, J = 8.0; ortho H's), 7.62–7.41 (3 H; m; para H, meta H's), 5.27–5.20 (2 H; m; 2-H, 4-H), 4.78 (1 H; d, J = 1.9; 1-H), 4.61 (1 H; dq, J = 8.6, 6.5; 5-H), 4.02 (1 H; t, J = 4.2; 3-H), 3.85 (3 H; s; OMe), 3.42 (3 H; s; NMe), 2.04 (3 H; s; CH_3C=O), 1.36 (3 H; d, J = 6.5; 5-Me). ^{13}C NMR ($CDCl_3$): 169.9 (CH_3C=O), 165.2 (PhC=O), 133.4-128.5 (Ar C's), 98.8 (C-1), 72.2 (C-4)*, 71.9 (C-2)*, 64.5 (C-5), 57.4 (C-3), 55.5 (OMe), 29.7 (NMe), 20.9 (CH_3C=O), 17.4 (C-6). Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.95; H, 6.82; N, 7.95. Found: C, 58.20; H, 6.85; N, 7.99.

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Registry No. **1**, 111476-69-8; **2**, 113668-65-8; **3**, 113668-66-9; **6** (X = H, Y = H), 113668-67-0; **6** (X = D, Y = H), 113668-71-6; **6** (X = H, Y = D), 113668-72-7; **6** (X = D, Y = D), 113668-73-8; **7** (isomer 1), 113668-68-1; **7** (isomer 2), 113685-63-5; **8**, 113668-69-2; $NaBD_3CN$, 25895-62-9; methyl 4-*O*-acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside, 79681-50-8; *p*-toluenesulfonohydrazide, 1576-35-8; sodium cyanoborohydride, 25895-60-7; methylhydrazine, 60-34-4; *N*-methyl-*N*-tosylhydrazine, 22547-51-9; methyl 4-*O*-acetyl-2-*O*-benzoyl-3,6-dideoxy-3-(*N*-methylhydrazino)-α-L-*altro*-hexopyranoside, 113668-70-5.

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