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Nucleophilic addition reactions of 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-D-*erythro*-hex-2-enitol and its 5a-carba derivative

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Abstract

Reactions of the title compounds with several nucelophiles suggested that the ring oxygen atom (O-5) accelerated the reactivity of the nitro alkene moiety, but scarcely affected the stereoselectivity of the nucleophilic attack.

Keywords: Nucleophilic addition; 1,5-Anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-D-*erythro*-hex-2-enitol; 5a-Carba derivative

1. Introduction

The solvent used influences both the reactivity and also the direction of approach of hydrazoic acid to 1,5-anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-D-*erythro*-hex-2-enitol (**1**). In polar solvents, hydrazoic acid attacks smoothly from the upper side (axial attack), whereas in nonpolar solvents attack occurs slowly from the lower side (equatorial attack) [1]. One possible explanation involves through-space interaction of the ring oxygen atom (O-5). Dreiding models suggest that the pyranose ring atoms (except C-5) occupy the almost same plane [1] and that the upper part of the p-orbital on O-5 is closer to the π-orbital on C-2 than its lower part. If the p-orbital electrons on O-5 are delocalized into the electron-deficient carbon atom (C-2), axial attack of a nucleophile should

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[1] Such a distortion is supported by molecular-orbital calculations on a 4,6-*O*-methylene derivative instead of a 4,6-*O*-benzylidene derivative **1** [2]. The dihedral angles of O-5–C-1–C-2–C-3 and C-2–C-3–C-4–C-5 were 7.5 and 26.3° in AM1 [3], 13.6 and 20.6° in STO-3G [4], and 8.5 and 21.7° in 3-21G [4].

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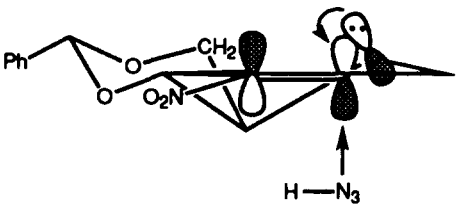


Fig. 1.

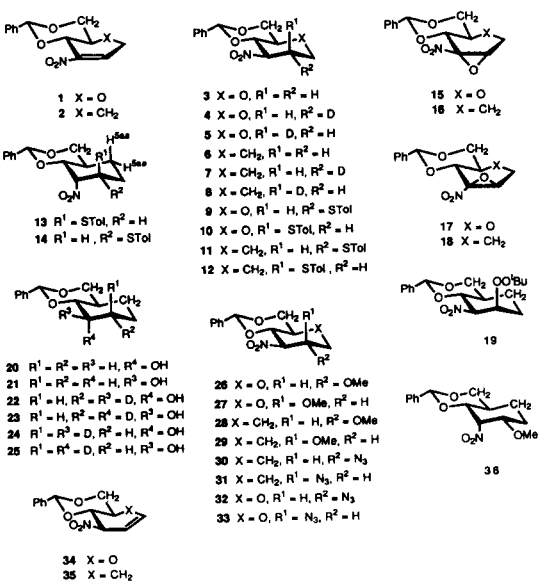
be retarded (Fig. 1). Such a delocalization should be more extensive in nonpolar solvents than in polar ones. This assumption gives a rationale for the solvent effects just described. If so, the reactivity of **1** should be lower than that of the corresponding 5a-carba sugar **2**.

In order to clarify whether or not the ring oxygen atom affects the stereoselectivity and/or reactivity in nucleophilic additions, we have studied the reactions of **1** and **2** with several nucleophiles.

2. Results and discussion

As already reported [1], reduction of nitro sugar **1** with sodium borodeuteride gave a 2:1 mixture of equatorially and axially monodeuterated derivatives **4** and **5**. Similar reduction of 5a-carba sugar **2** afforded a 2:1 mixture of monodeuterated derivatives **7** and **8** in 75% yield, thus in good agreement with the results for **1**.

Treatment of **1** with *p*-toluenethiol in the presence of a catalytic amount of triethylamine provided a 1:2 mixture of the *gluco* and *manno* adducts (**9** and **10**) in high yield. Under the same conditions neither adduct epimerized. Similar reaction of **2** afforded a 7:16:1:1 mixture of the *gluco* (**11**), *manno* (**12**), *altro* (**13**), and *allo* (**14**) products. Under the same conditions, the *manno* isomer **12** was recovered in almost quantitative yield, suggesting that the nucleophilic attack is controlled kinetically. However, treatment of a mixture of **12**, **13**, and **14** with a small amount of DBU caused epimerization and gave the *gluco* isomer **11**.



We have earlier found that treatment of **1** with *tert*-butyl hydroperoxide in the presence of sodium hydroxide yielded epoxides having the *allo* and *manno* configurations (**15** and **17**) in the ratio of 1.8:1, as judged from the ^{1}H NMR spectrum [5]. Similar epoxidation of **2** afforded a 13:2:9 mixture of the epoxides **16** and **18** and the 2-*O*-*tert*-butoxy derivative **19**. Several attempts at isolation of **16** failed because it was partially decomposed during column chromatography on silica gel and preparative TLC. The *allo* structure for **16** was tentatively assigned, because the doublet signal of H-4 appeared at lower field than the corresponding signal of **18** by ~ 0.9 ppm, because of the anisotropy of the nitro group [5]. The *manno* configuration for **18** was suggested by the coupling constants, $J_{1a,2}$ 2.0, $J_{1e,2}$ 1.7 Hz, and chemically confirmed. Reduction of **18** with lithium aluminum hydride afforded the 2-deoxy derivatives **20** and **21** in the ratio of 5:1, and compound **20** was isolated. The dideuterio derivative **22** was isolated from a mixture generated by reduction of **18** with lithium aluminum deuteride. The equatorial positions at C-2 and C-3 of **22** were deuterated, indicating that **18** has the *manno* configuration, because rearside attack of a deuteride ion to an epoxy ring is known [6]. The dioxy structure of **19** was determined by elemental analysis, IR, and mass spectroscopy. The *manno* configuration was assigned to **19** on the basis of coupling constants, $J_{1a,2} = J_{1e,2} = J_{2,3} = 3.3$ and $J_{3,4}$ 10.2 Hz.

Treatment of **1** (0.19 mmol) with 0.01 M sodium methoxide (1 mL) in methanol (10 mL) for 1.5 h at room temperature afforded the adducts having the *gluco* (**26**, 71%) and *manno* (**27**, 18%) configurations, along with the 1-enitol (**34**, 6%). The last compound was identical with an authentic sample [1]. No epimerization of **27** was observed under the conditions employed. Under the same conditions, however, the double bond of **2** migrated to give the 1-enitol **35**, instead of adducts. These results suggested that the electrophilicity of **1** was higher than that of **2**, because we had already found that the double-bond migration from C-2 to C-1 occurred more readily in **1** than in **2** upon treatment with triethylamine [7]. When **2** was treated with an equimolar amount of 0.01 M methanolic sodium methoxide at room temperature for 20 min, three adducts having the *gluco*, *manno*, and *allo* configurations (**28**, **29**, and **36**) were obtained in the ratio of 11:4:1. Under the conditions used for the preparation of these adducts, the *manno* adduct **29** was recovered in almost quantitative yield.

Although compound **1** reacted with hydrazoic acid in chloroform, the 5a-carba sugar **2** was recovered intact under the same conditions. These results again indicated that the electrophilicity of **2** was lower than that of **1**. However, when **2** was treated with sodium azide in the presence of acetic acid, a 1:6 mixture of the *gluco* and *manno* adducts (**30** and **31**) was obtained in 76% yield. Under the same conditions, compound **1** afforded a 1:1 mixture of the *gluco* and *manno* adducts (**32** and **33**) in almost quantitative yield. The adducts **31**, **32**, and **33** were recovered under the conditions employed.

From these experimental results it may be concluded that delocalization of the lone-pair electrons on O-5 into the C-2 position is not important, at least for the reactivity and stereoselectivity. The higher reactivity of **1** toward the nucleophiles is attributable to the inductive effect of O-5. In six-membered rings, axial attack generally predominates over the alternative attacks, because the former gives a thermodynamically favorable chair intermediate, whereas the latter leads to an unfavorable boat one due to stereoelectronic control [8]. In the present cases, however, axial attack is retarded owing to $A^{(1,3)}$ strain

[9] between O-4 and one of the oxygen atoms of an intermediary nitronate. Therefore, low stereoselectivities observed in the nucleophilic addition-reactions of **1** and **2** suggested that these two factors are comparable. Besides these two factors, axial attack should be suppressed by electrostatic repulsion because of the lone pair on O-5 in the case of **1** and by steric hindrance due to the axial hydrogen atom (H-5a*a*) in the case of **2**. These two factors should be again comparable, because stereoselectivities with **1** were almost the same as those with **2**, except the case of hydrazoic acid. This exception is acceptable, since hydrazoic acid is linear, and therefore, steric hindrance becomes small compared with the other nucleophiles, and leads predominantly to the *manno* adduct **31** in the case of **2**.

3. Experimental

General methods.—Melting points are uncorrected. Optical rotations were determined with a Horiba High Sensitivity Polarimeter (SEPA-200). The ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively, with a spectrometer (JNM-EX270) in $CDCl_3$ with Me_4Si as the internal standard. Fast-atom bombardment (FAB) mass spectra were recorded with a JMS-AX505 HA for high-resolution, or a low-resolution instrument (SIMS). IR spectra were recorded for KBr pellets. Reaction mixtures were dried over $MgSO_4$ and evaporated under diminished pressure. Column chromatography was conducted on silica gel (Wakogel C-300 or Merck Silica gel 60, 70–230 mesh; the latter is cited therein).

*1,5-Anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-*D*-arabino-hexitol* (**3**).—A solution of **1** [1,10] (20 mg, 0.08 mmol) in oxolane (2 mL, distilled over $LiAlH_4$) was cooled to −30°C and $NaBH_4$ (6 mg, 0.16 mmol) was added. After 2 h at −30°C, the reaction was quenched with aq M HCl and extracted with CH_2Cl_2. The extracts were washed with aq satd NaCl (twice), dried, and evaporated. The residue was chromatographed with Merck silica gel eluting with toluene to give 15 mg (75%) of **3**, identical with an authentic sample [1]; ^{1}H NMR data (C_6D_6): δ 2.68 (dt, 1 H, $J_{1a,1e} = J_{1a,2a} = 12.2$, $J_{1a,2e}$ 2.2 Hz, H-1*a*), 3.35 (ddd, 1 H, $J_{1e,2a}$ 5.4, $J_{1e,2e}$ 1.4 Hz, H-1*e*), 1.86 (qd, 1 H, $J_{2a,2e} = J_{2a,3} = 12.2$ Hz, H-2*a*), 1.41 (m, 1 H, $J_{2e,3}$ 4.9 Hz, H-2*e*), 4.35 (ddd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 4.00 (t, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 2.99 (td, 1 H, $J_{5,6a}$ 10.2, $J_{5,6e}$ 4.9 Hz, H-5), 3.45 (t, 1 H, $J_{6a,6e}$ 10.2 Hz, H-6*a*), 4.13 (dd, 1 H, H-6*e*), and 5.20 (s, 1 H, PhCH).

A similar reduction of **1** (10 mg, 0.04 mmol) with sodium borodeuteride (2 mg, 0.05 mmol) gave the 2-deuterio derivatives **4** and **5** in the ratio of 2:1.

*1,5-Anhydro-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-5a-carba-DL-arabino-hexitol* (**6**).—A solution of **2** [7] (20 mg, 0.08 mmol) in oxolane (2 mL, distilled over $LiAlH_4$) was cooled to −30°C and $NaBH_4$ (6 mg, 0.16 mmol) was added. After 2 h at −30°C, the reaction was quenched with aq M HCl and extracted with CH_2Cl_2. The extracts were washed with aq satd NaCl (twice), dried, and evaporated. The residue was chromatographed with Merck silica gel eluting with toluene to give 15 mg (75%) of **6**; mp 107–109°C (isopropyl ether); ν_{max} 1550 cm^{-1} (NO_2); ^{1}H NMR (C_6D_6): δ 0.58 (qt, 1 H, $J_{1a,1e} = J_{1a,2a} = J_{1a,5aa} = 13.6$, $J_{1a,2e} = J_{1a,5ae} = 3.6$, H-1*a*), 1.07 (m, 1 H, H-1*e*), 1.47 (qd, 1 H, $J_{1e,2a}$ 4.0, $J_{2a,2e} = J_{2a,3} = 13.6$, H-2*a*), 1.66 (m, 1 H, H-2*e*), 4.29 (ddd,

1 H, $J_{2e,3}$ 4.6, $J_{3,4}$ 9,9 Hz, H-3), 3.73 (t, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 1.30 (m, 1 H, H-5), 0.26 (qd, 1 H, $J_{5,5aa} = J_{5aa,5ae} = 13.6$, $J_{1e,5aa} = 3.6$ Hz, H-5a*a*), 0.69 (m, 1 H, H-5a*e*), 3.04 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 11.2$ Hz, H-6*a*), 3.71 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), and 5.38 (s, 1 H, PhCH). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.11; H, 6.79; N, 5.09.

A similar reduction of **2** (12 mg, 0.05 mmol) with $NaBD_4$ (4 mg, 0.10 mmol) afforded a 2:1 mixture of **7** and **8** (as judged from ^{1}H NMR spectroscopy) in 50% yield (6 mg).

Reaction of **1** *with* p-*toluenethiol.*—To a solution of **1** (100 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) was added TolSH (47 mg, 0.38 mmol). The mixture was cooled to −30°C and a drop of Et_3N was added. After stirring for 20 min at −30°C, the mixture was partitioned between aq M HCl and CH_2Cl_2 and the organic layer was washed with aq satd NaCl, dried, and evaporated. The residue was chromatographed with toluene to 100:1 toluene–EtOAc, to give successively **9** (28 mg, 19%), a 1:2.7 mixture (70 mg, 48%) of **9** and **10**, and **10** (42 mg, 29%)

Physical data for **9**: mp 213–214°C (*i*-PrOH); $[\alpha]_D^{25}$ +69° (*c* 1.0, CH_2Cl_2); ν_{max} 1555 cm^{-1} (NO_2); ^{1}H NMR: δ 3.40 (t, 1 H, $J_{1a,1e}$ 11.2, $J_{1a,2}$ 11.6 Hz, H-1*a*), 4.20 (dd, 1 H, $J_{1e,2}$ 4.6 Hz, H-1*e*), 3.50 (td, 1 H, $J_{2,3}$ 11.2 Hz, H-2), 4.63 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 4.09 (t, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 3.28 (td, 1 H, $J_{5,6a}$ 9.9, $J_{5,6e}$ 5.0 Hz, H-5), 3.71 (t, 1 H, $J_{6a,6e}$ 10.6 Hz, H-6*a*), 4.29 (dd, 1 H, H-6*e*), 4.84 (s, 1 H, PhCH), and 1.55 (s, 3 H, C_6H_4Me). Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62; S, 8.28. Found: C, 61.75; H, 5.25; N, 3.41; S, 8.00.

Physical data for **10**: mp 212–214°C (*i*-PrOH); $[\alpha]_D^{25}$ +73° (*c* 1.0, CH_2Cl_2); ν_{max} 1550 cm^{-1} (NO_2); ^{1}H NMR (C_6D_6): δ 2.97 (dd, 1 H, $J_{1a,1e}$ 12.2, $J_{1a,2}$ 2.0 Hz, H-1*a*), 3.87 (dd, 1 H, $J_{1e,2}$ 1.7 Hz, H-1*e*), 3.37 (dt, 1 H, $J_{2,3}$ 4.6 Hz, H-2), 4.34 (dd, 1 H, $J_{3,4}$ 10.6 Hz, H-3), 4.51 (dd, 1 H, $J_{4,5}$ 9.2 Hz, H-4), 2.97 (ddd, 1 H, H-5), 3.52 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.2$ Hz, H-6*a*), 4.11 (dd, 1 H, $J_{5,6e}$ 4.6 Hz, H-6*e*), 5.30 (s, 1 H, PhCH), and 2.00 (s, 3 H, C_6H_4Me). Anal. Calcd for $C_{20}H_{21}NO_5S$: C, 62.00; H, 5.46; N, 3.62; S, 8.28. Found: C, 61.84; H, 5.41; N, 3.47; S, 8.03.

A similar treatment of **9** (8 mg, 0.02 mmol) or **10** (5.2 mg, 0.01 mmol) with a drop of Et_3N for 20 min at −30°C resulted in the recovery of **9** or **10**, respectively, in almost quantitative yield, as judged from TLC and ^{1}H NMR spectroscopy.

When a 1:2 mixture (15 mg) of **9** and **10** in CH_2Cl_2 (5 mL) in the presence of two drops of DBU was stirred for 30 min at room temperature, a 1:1 mixture of the *gluco* isomer **9** and 1-enitol **34** was obtained in almost quantitative yield as judged from TLC and ^{1}H NMR spectroscopy.

Reaction of **2** *with* p-*toluenethiol.*—A solution of **2** (20 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was cooled to −30°C and TolSH (11 mg, 0.09 mmol) was added. To the solution was added dropwise a solution of Et_3N (3.8 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) with stirring. After stirring for 5 min at −30°C, the reaction was quenched with aq M HCl and the mixture was washed with aq satd NaCl (twice), dried, and evaporated. The residue, the ^{1}H NMR spectrum of which showed it to be a 7:16:1:1 mixture of **11**, **12**, **13**, and **14**, was chromatographed with Merck silica gel eluting with 20:1 to 10:1 hexane–EtOAc to give successively 1.8 mg (6%) of **13**, a mixture (25.4 mg, 86%) of **11** and **12**, and 1.4 mg (5%) of **14**. Compound **12** was isolated by fractional recrystallization

(three times) from EtOAc–hexane. Compound **11** was isolated after epimerization of a mixture (100 mg) of **12**, **13**, and **14** in CH_2Cl_2 (2 mL) with a drop of DBU at −10°C for 5 min. However, epimerization of the *manno* isomer **12** was not observed upon treatment with Et_3N under the same conditions as for the preparation of the mixture containing **12** as the major product.

Physical data for **11**: mp 160–161°C (EtOAc–hexane); ν_{max} 1555 cm^{-1} (NO_2); ^1H NMR: δ 1.45 (qd, 1 H, $J_{1a,1e} = J_{1a,2} = J_{1a,5aa} = 12.9$, $J_{1a,5ae}$ 3.3 Hz, H-1*a*), 2.22 (br d and q, 1 H, $J_{1e,2} = J_{1e,5aa} = J_{1e,5ae} = 3.3$ Hz, H-1*e*), 3.26 (ddd, 1 H, $J_{2,3}$ 11.2 Hz, H-2), 4.52 (dd, 1 H, $J_{3,4}$ 9.9 Hz, H-3), 4.01 (t, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 1.71 (m, 1 H, H-5), 1.15 (dq, 1 H, $J_{5,5aa} = J_{5aa,5ae} = 12.9$ Hz, H-5a*a*), 1.61 (dq, 1 H, $J_{5,5ae}$ 3.3 Hz, H-5a*e*), 3.60 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.9$ Hz, H-6*a*), 4.19 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), 5.51 (s, 1 H, PhCH), and 2.36 (s, 3 H, STol). ^{13}C NMR: δ 24.3 (C-1), 47.5 (C-2), 90.9 (C-3), 81.5 (C-4), 37.8 (C-5), 30.9 (C-5a), 70.7 (C-6), 101.2 (PhCH), and 21.2 (STol). Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63; S, 8.32. Found: C, 65.51; H, 5.89; N, 3.56; S, 8.28.

Physical data for **12**: mp 159–160.5°C (EtOAc–hexane); ν_{max} 1550 cm^{-1} (NO_2); ^1H NMR: δ 1.79–1.98 (m, 2 H, H-1*a*,5), 2.13 (dq, 1 H, $J_{1a,1e}$ 13.5, $J_{1e,2} = J_{1e,5aa} = J_{1e,5ae} = 3.0$ Hz, H-1*e*), 3.96 (br d and t, 1 H, $J_{1a,2}$ 3.0, $J_{2,3}$ 5.0 Hz, H-2), 4.79 (dd, 1 H, $J_{3,4}$ 10.6 Hz, H-3), 4.43 (t, 1 H, $J_{4,5}$ 10.6 Hz, H-4), 1.63 (dq, 1 H, $J_{1a,5aa} = J_{5,5aa} = J_{5aa,5ae} = 12.9$ Hz, H-5a*a*), 1.46 (m, 1 H, H-5a*e*), 3.78 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 11.2$ Hz, H-6*a*), 4.20 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), 5.72 (s, 1 H, PhCH), and 2.33 (s, 3 H, STol). Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63; S, 8.32. Found: C, 65.71; H, 6.14; N, 3.90; S, 8.57.

Physical data for **13**: syrup; ν_{max} 1550 cm^{-1} (NO_2); ^1H NMR: δ 2.51–2.78 (m, 2 H, H-1*a*,5), 1.99 (br d, 1 H, $J_{1a,1e}$ 14.9, H-1*e*), 3.90 (br d and t, 1 H, $J_{1a,2}$ 4.6, $J_{1e,2} = J_{2,3} = 1.3$ Hz, H-2), 4.95 (dd, 1 H, $J_{3,4}$ 5.0 Hz, H-3), 4.39 (dd, 1 H, $J_{4,5}$ 10.9 Hz, H-4), 1.42 (dq, 1 H, $J_{1a,5aa} = J_{5,5aa} = J_{5aa,5ae} = 13.5$ Hz, $J_{1e,5aa}$ 4.0 Hz, H-5a*a*), 1.62 (m, 1 H, H-5a*e*), 3.65 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.9$ Hz, H-6*a*), 4.20 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), 5.63 (s, 1 H, PhCH), and 2.34 (s, 3 H, STol). Mass spectrum: calcd for $C_{14}H_{12}NO_4S$: *m*/*z* 384.127 (M − H) and 386.143 (M + H); found: *m*/*z* 384.126 (M − H) and 386.141 (M + H).

Physical data for **14**: syrup; ν_{max} 1550 cm^{-1} (NO_2); ^1H NMR: δ 2.24–2.41 (m, 4 H, H-1*a* and STol), 2.04 (m, 1 H, H-1*e*), 3.19 (dt, 1 H, $J_{1a,2}$ 13.2, $J_{1e,2} = J_{2,3} = 4.3$ Hz, H-2), 5.01 (t, 1 H, $J_{3,4}$ 4.3 Hz, H-3), 3.64 (dd, 1 H, $J_{4,5}$ 10.9 Hz, H-4), 2.72 (m, 1 H, H-5), 1.10 (qd, 1 H, $J_{1a,5aa} = J_{5,5aa} = J_{5aa,5ae} = 13.2$, $J_{1e,5aa}$ 4.3 Hz, H-5a*a*), 1.84 (br d and q, 1 H, $J_{1a,5ae} = J_{5,5ae} = J_{1e,5ae} = 3.6$ Hz, H-5a*e*), 3.51 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.9$ Hz, H-6*a*), 4.20 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), and 5.49 (s, 1 H, PhCH). Mass spectrum: calcd for $C_{14}H_{12}NO_4S$: *m*/*z*408.125 (M + Na); found: *m*/*z*408.128.

Oxidation of **2** *with* tert-*butyl hydroperoxide*.—Compound **2** (30 mg, 0.11 mmol) was dissolved in 1,4-dioxane (1.7 mL) and stirred vigorously. To the solution was added Bu^tOOH (purity ~ 80%, 0.6 mL) and then aq M NaOH (3 drops). After 1 min, the mixture was diluted with EtOAc and washed with aq $Na_2S_2O_3$, NaCl (twice), dried, and evaporated to give 35 mg (~ 100%) of residue, the ^1H NMR spectrum of which showed it to be a 13:2:9 mixture of **16**:**18**:**19**. Two-dimensional TLC revealed that **16** was decomposed on TLC. The residue was chromatographed with 10:1 hexane–EtOAc to give

successively 2 mg (6%) of **18** and 15 mg (38%) of **19**. Compound **19** was pure enough for elemental analysis without recrystallization.

Physical data for **18**: mp 123.5–124°C (Et_2O); ν_{max} 1560 cm^{-1} (NO_2); ^1H NMR: δ 2.04 (dddd, 1 H, $J_{1a,1e}$ 15.8, $J_{1a,2}$ 2.0, $J_{1a,5aa}$ 11.2, $J_{1a,5ae}$ 6.3 Hz, H-1*a*), 2.27 (tdd, 1 H, $J_{1e,2} = J_{1e,5ae} = 1.7$, $J_{1e,5aa}$ 4.9 Hz, H-1*e*), 3.88 (br s, 1 H, H-2), 4.04 (d, 1 H, $J_{4,5}$ 11.2 Hz, H-4), 1.99 (m, 1 H, H-5), 1.06 (qd, 1 H, $J_{5,5aa} = J_{5aa,5ae} = 11.2$ Hz, H-5a*a*), 1.43 (tdd, 1 H, $J_{5,5ae}$ 1.7 Hz, H-5a*e*), 3.68 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 11.2$ Hz, H-6*a*), 4.21 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), and 5.62 (s, 1 H, PhCH). ^{13}C NMR: δ 23.5 (C-1), 60.1 (C-2), 86.8 (C-3), 76.6 (C-4), 37.5 (C-5), 17.2 (C-5a), 71.0 (C-6), and 102.2 (PhCH). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.89; H, 5.17; N, 4.75.

Physical data for **19**: mp 88–90°C; ν_{max} 1560 cm^{-1} (NO_2); ^1H NMR: δ 1.38–1.62 (m, 3 H, H-1*a*,5a*a*,5a*e*), 2.46 (dq, 1 H, $J_{1a,1e}$ 13.9, $J_{1e,2} = J_{1e,5aa} = J_{1e,5ae} = 3.3$ Hz, H-1*e*), 4.87 (q, 1 H, $J_{1a,2} = J_{2,3} = 3.3$ Hz, H-2), 4.59 (dd, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 4.47 (t, 1 H, $J_{4,5}$ 10.2 Hz, H-4), 1.88 (m, 1 H, H-5), 3.76 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.9$ Hz, H-6*a*), 4.20 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), 5.70 (s, 1 H, PhCH), and 1.19 (s, 9 H, Bu^t). ^{13}C NMR: δ 27.4 (C-1), 79.7 (C-2), 86.8 (C-3), 75.9 (C-4), 39.0 (C-5), 19.2 (C-5a), 70.8 (C-6), 81.6 (Bu^t), 26.1 (Me of Bu^t), and 101.3 (PhCH). Mass spectrum: *m/z* 352 (M + H), 89 (Bu^tOO^+), 73 (Bu^tO^+), and 57 (Bu^{t+}). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.49; H, 6.96; N, 3.72.

Reduction of **18** *with lithium aluminum hydride.*—To a solution of **18** (10 mg, 0.04 mmol) in oxolane (1 mL, distilled over Na) was added $LiAlH_4$ (5 mg, 0.13 mmol). After stirring for 2 h, the reaction was quenched by the addition of diethyl ether containing H_2O. The mixture was extracted with EtOAc and the extracts were washed successively with aq M HCl, aq satd NaCl, aq $NaHCO_3$, and aq satd NaCl (twice), dried, and evaporated. The residue was purified by preparative TLC with 20:1 and 10:1 $CHCl_3$–MeOH to give 7 mg (88%) of a 5:1 mixture of **20** and **21**. Compound **20** was isolated by crystallization, but **21** was not fully purified; but its structure was suggested by ^1H NMR: δ 3.59 (ddd, 1 H, $J_{2a,3}$ 10.6, $J_{2e,3}$ 4.6, $J_{3,4}$ 10.2 Hz, H-3), 3.09 (t, 1 H, $J_{4,5}$ 10.2 Hz, H-4), 1.50 (m, 1 H, H-5), 3.18 (t, 1 H, $J_{5,6a}$ 10.6, $J_{6a,6e}$ 10.9 Hz, H-6*a*), and 3.85 (dd, 1 H, $J_{5,6e}$ 4,3 Hz, H-6*e*).

Physical data for **20**: mp 94.5–96°C (isopropyl ether), ν_{max} 3465 cm^{-1} (OH); ^1H NMR (C_6D_6): δ 1.79 (qt, 1 H, $J_{1a,1e} = J_{1a,2a} = J_{1a,5aa} = 12.5$, $J_{1a,2e} = J_{1a,5ae} = 4.0$ Hz, H-1*a*), 1.23 (m, 1 H, H-1*e*), 1.21 (m, 1 H, H-2*a*), 1.92 (m, 1 H, H-2*e*), 3.97 (q, 1 H, $J_{2a,3} = J_{2e,3} = J_{3,4} = 2.6$ Hz, H-3), 3.02 (dd, 1 H, $J_{4,5}$ 10.2 Hz, H-4), 2.28 (m, 1 H, H-5), 1.20 (m, 1 H, H-5a*e*), 0.49 (qd, 1 H, $J_{1e,5a}$ 4.0, $J_{5,5aa} = J_{5aa,5ae} = 12.5$ Hz, H-5a*a*), 3.20 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.7$ Hz, H-6*a*), 3.92 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), 5.51 (s, 1 H, PhCH), and 2.02 (br s, 1 H, OH). ^{13}C NMR: δ 25.7 (C-1), 30.4 (C-2), 67.4 (C-3), 83.4 (C-4), 33.4 (C-5), 19.2 (C-5a), 72.0 (C-6), and 101.9 (PhCH). Mass spectrum: calcd for $C_{14}H_{18}O_3$: *m/z* 235.134 (M + H); found: *m/z* 235.132 (M + H).

A similar reduction of **18** with $LiAlD_4$ gave a 5:1 mixture (7 mg, 82%) of **22** and **23**.

Isolation of **16** has not been accomplished, because it partially decomposed on silica gel or during crystallization, but its structure was tentatively assigned by the appearance of H-4 signals at lower field than those of the *manno* isomer **18** because of the anisotropy of the nitro group; ^1H NMR data for **16**: δ 4.95 (d, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 3.71 (t, 1 H,

$J_{5,6a} = J_{6,6a} = 11.1$ Hz, H-6*a*), 4.17 (dd, $J_{5,6e}$ 4.3 Hz, H-6*e*), and 5.71 (s, 1 H, PhCH). The following experiment also supported the assignment.

Compound **2** (50 mg, 0.19 mmol) was similarly treated with Bu^{t}OOH. The crude product was dissolved in oxolane (5 mL), to which was added $LiAlD_4$ (24 mg, 0.57 mmol). After stirring overnight, similar workup as just described and separation by the use of preparative TLC eluting with toluene, 10:1 and 20:1 $CHCl_3$–MeOH gave a 17:3 mixture of **22** + **24**:**23** + **25**. The former mixture was isolated in 56% yield (25 mg, based on **2**) and the ratio of **22** to **24** proved to be ~ 1:5, but the isolation of **24** was not accomplished.

Reaction of **1** *with methanol.*—To a solution of **1** (50 mg, 0.19 mmol) in MeOH (10 mL) was added 0.01 M NaOMe (1 mL) at room temperature. After 1.5 h, to the mixture were added aq M HCl and CH_2Cl_2 and the organic layer was washed with aq satd NaCl, dried, and evaporated. The residue was chromatographed with 20:1 to 5:1 hexane–EtOAc to give successively **34** (2.9 mg, 6%), **26** (33.5 mg, 63%), a 9:1 mixture (4.7 mg, 9%) of **26** and **27**, and **27** (9.2 mg, 17%). Compound **34** was identical with an authentic sample by ^{1}H NMR and IR spectroscopy. Compounds **26** and **27** were pure enough for elemental analysis without recrystallization.

Physical data for **26**: mp 142–144°C; $[\alpha]_D^{25}$ −43° (*c* 1.0, CH_2Cl_2); ν_{max} 1555 cm^{-1} (NO_2); ^{1}H NMR: δ 3.32 (dd, 1 H, $J_{1a,1e}$ 11.6, $J_{1a,2}$ 10.6 Hz, H-1*a*), 4.25 (dd, 1 H, $J_{1e,2}$ 5.6 Hz, H-1*e*), 3.99 (td, 1 H, $J_{2,3}$ 9.9 Hz, H-2), 4.66 (t, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 4.03 (dd, 1 H, $J_{4,5}$ 9.2 Hz, H-4), 3.40 (broad td, 1 H, $J_{5,6a}$ 10.2, $J_{5,6e}$ 5.0 Hz, H-5), 3.74 (t, 1 H, $J_{6a,6e}$ 10.6 Hz, H-6*a*), 4.38 (dd, 1 H, H-6*e*), 5.52 (s, 1 H, PhCH), and 3.41 (s, 3 H, OMe). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 56.95; H, 6.01; N, 4.95.

Physical data for **27**: syrup; $[\alpha]_D^{25}$ −86° (*c* 0.8, CH_2Cl_2); ν_{max} 1560 cm^{-1} (NO_2); ^{1}H NMR: δ 3.56 (dd, 1 H, $J_{1a,1e}$ 13.2, $J_{1a,2}$ 1.0 Hz, H-1*a*), 4.26 (dd, 1 H, $J_{1e,2}$ 1.7 Hz, H-1*e*), 4.10 (td, 1 H, $J_{2,3}$ 3.6 Hz, H-2), 4.68 (dd, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 4.56 (dd, 1 H, $J_{4,5}$ 8.9 Hz, H-4), 3.41 (ddd, 1 H, $J_{5,6a}$ 10.2, $J_{5,6e}$ 5.0 Hz, H-5), 3.89 (t, 1 H, $J_{6a,6e}$ 10.2 Hz, H-6*a*), 4.34 (dd, 1 H, H-6*e*), 5.61 (s, 1 H, PhCH), and 3.39 (s, 3 H, OMe). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 57.25; H, 5.70; N, 4.70.

Similar treatment of **26** (8 mg) and **27** (12 mg) with methanolic NaOMe resulted in the recovery of **26** (7 mg) and **27** (8.5 mg), respectively.

Reaction of **2** *with methanolic sodium methoxide.*—To a cooled solution (−10°C) of **2** (20 mg, 0.08 mmol) in MeOH (1 mL, distilled over Mg) was added methanolic NaOMe (0.01 M, 8 mL) with stirring. The mixture was allowed to warm to room temperature and then stirred for an additional 20 min at ambient temperature. The mixture was poured into ice-cooled aq M HCl and extracted with CH_2Cl_2, the extracts were washed with aq satd NaCl (twice), dried, and evaporated. The ^{1}H NMR spectrum of the residue (20.5 mg, 91%) showed it to be a 11:4:1 mixture of **28**, **29**, and **36**. These compounds were separated by preparative TLC with 3:1 hexane–EtOAc.

Under the same conditions the *manno* adduct **29** (2 mg) was recovered in almost quantitative yield.

Physical data for **28**: mp 115–116°C (*i*-PrOH); ν_{max} 1560 and 1550 cm^{-1} (NO_2); ^{1}H NMR: δ 1.40 (tdd, 1 H, $J_{1a,1e} = J_{1a,5aa} = 13.2$, $J_{1a,2}$ 11.2, $J_{1a,5ae}$ 3.6 Hz, H-1*a*), 2.34 (ddt, 1 H, $J_{1e,2}$ 4.6, $J_{1e,5aa} = J_{1e,5ae} = 3.6$ Hz, H-1*e*), 3.78 (ddd, 1 H, $J_{2,3}$ 10.2 Hz, H-2),

4.58 (t, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 3.98 (t, 1 H, $J_{4,5}$ 10.2 Hz, H-4), 1.90 (m, 1 H, H-5), 1.09 (qd, 1 H, $J_{5,5aa} = J_{5aa,5ae} = 13.2$ Hz, H-5a*a*), 1.69 (dq, 1 H, $J_{5,5ae}$ 3.6 Hz, H-5a*e*), 3.64 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 11.2$ Hz, H-6*a*), 4.24 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), 5.52 (s, 1 H, PhCH), and 3.36 (s, 3 H, OMe). ^{13}C NMR: δ 28.1 (C-1), 79.5 (C-2), 92.1 (C-3), 79.8 (C-4), 38.1 (C-5), 21.5 (C-5a), 70.8 (C-6), 101.2 (PhCH), and 57.4 (OMe). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.14; H, 6.42; N, 4.55.

Physical data for **29**: mp 164–165.5°C (*i*-PrOH); ν_{max} 1550 cm^{-1} (NO_2); ^{1}H NMR: δ 0.51–0.66 (m, 2 H, H-1*a*,5a*e*), 1.27–1.48 (m, 2 H, H-1*e*,5), 3.66 (td, 1 H, $J_{1a,2}$ 3.0, $J_{1e,2} = J_{2,3} = 3.6$ Hz, H-2), 4.14 (dd, 1 H, $J_{3,4}$ 10.6 Hz, H-3), 4.47 (t, 1 H, $J_{4,5}$ 10.6 Hz, H-4), 0.88 (m, 1 H, H-5a*a*), 3.19 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.9$ Hz, H-6*a*), 3.78 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), 5.51 (s, 1 H, PhCH), and 2.81 (s, 3 H, OMe). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.13; H, 6.30; N, 4.50.

Physical data for **36**: mp 135–136°C (*i*-PrOH); ν_{max} 1550 cm^{-1} (NO_2) (NaCl); ^{1}H NMR: δ 2.17 (m, 1 H, H-1*a*), 2.01 (m, 1 H, H-1*e*), 3.53 (dt, 1 H, $J_{1a,2}$ 11.9, $J_{1e,2} = J_{2,3} = 4.6$ Hz, H-2), 5.44 (t, 1 H, $J_{3,4}$ 4.6 Hz, H-3), 3.66 (dd, 1 H, $J_{4,5}$ 10.9 Hz, H-4), 2.83 (m, 1 H, H-5), 0.96 (qd, 1 H, $J_{1a,5aa} = J_{5,5aa} = J_{5aa,5ae} = 13.5$, $J_{1e,5aa}$ 4.3 Hz, H-5a*a*), 1.79 (dq, 1 H, $J_{1a,5ae} = J_{1e,5ae} = J_{5,5aa} = 4.0$ Hz, H-5a*e*), 3.52 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 11.2$ Hz, H-6*a*), 4.25 (dd, 1 H, $J_{5,6e}$ 4.6 Hz, H-6*e*), 5.55 (s, 1 H, PhCH), and 3.46 (s, 3 H, OMe). Mass spectrum: calcd for $C_{15}H_{19}NO_5$: *m*/*z* 292.119 (M − 1) and 294.134 (M + 1); found: *m*/*z* 292.118 (M − 1) and 294.134 (M + 1).

To an ice-cooled solution of **2** (10 mg, 0.04 mmol) in MeOH (1 mL) was added 0.01 M NaOMe (0.2 mL). After stirring for 1 h, no reaction occurred (TLC). The mixture was then allowed to warm to room temperature and to stand for an additional 1 h. Although under the same conditions compound **1** gave the adducts, a similar reaction of **2** gave the 1-enitol **35** as the major product.

Reaction of **2** *with hydrazoic acid.*—To a cooled solution (−20°C) of **2** (15 mg, 0.06 mmol) in MeCN (0.75 mL) were added NaN_3 (9 mg, 0.12 mmol) and a drop of AcOH with stirring. The mixture was allowed to warm to room temperature. After 1.5 h, the mixture was diluted with EtOAc and washed with H_2O, aq $NaHCO_3$, aq satd NaCl, dried, and evaporated. The ^{1}H NMR spectrum of the residue showed it to be a 1:6 mixture of **30** and **31**. The residue was chromatographed on silica gel eluting with 9:1 hexane–EtOAc to give a mixture (13 mg, 76%) of **30** and **31**. Compound **31** was isolated by fractional crystallization from EtOAc (three times).

Under the same conditions the *manno* adduct **31** (3 mg) was recovered quantitatively as judged by ^{1}H NMR spectroscopy.

To a cooled solution (−20°C) of **2** (30 mg, 0.11 mmol) in DMF (1 mL) were added NaN_3 (9 mg, 0.12 mmol) and three drops of AcOH with stirring. The mixture was allowed to warm to room temperature. After 7 h, the mixture was diluted with EtOAc and washed with H_2O, aq $NaHCO_3$, aq satd NaCl, dried, and evaporated. The ^{1}H NMR spectrum of the residue showed it to be a 7:3 mixture of **30** and **31**, along with small amounts of glycal derivative **35**. After preparative TLC, a mixture (25 mg, 71%) of **30** and **31** was obtained, from which **30** (7 mg, 20%) was isolated by fractional crystallization from EtOAc (twice).

Physical data for **30**: mp 138–139°C (EtOAc–hexane); 2110 cm^{-1} (N_3) and ν_{max} 1560, 1548 cm^{-1} (NO_2); ^{1}H NMR: δ 1.63 (qd, 1 H, $J_{1a,1e} = J_{1a,2} = J_{1a,5aa} = 12.9$,

$J_{1a,5ae}$ 4.0 Hz, H-1*a*), 2.31 (m, 1 H, H-1*e*), 3.94–4.04 (m, 2 H, H-2,4), 4.84 (t, 1 H, $J_{2,3} = J_{3,4} = 10.2$ Hz, H-3), 1.91 (m, 1 H, H-5), 1.20 (qd, 1 H, $J_{1e,5aa}$ 4.0, $J_{5,5aa} = J_{5aa,5ae} = 12.9$ Hz, H-5a*a*), 1.75 (dq, 1 H, $J_{1e,5ae} = J_{5,5ae} = 4.0$ Hz, H-5a*e*), 3.66 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 11.2$ Hz, H-6*a*), 4.25 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), and 5.53 (s, 1 H, PhCH). Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 54.99; H, 5.43; N, 18.15.

Physical data for **31**: mp 169–170°C (EtOAc); ν_{max} 2140 and 2090 (N_3) and 1550 cm^{-1} (NO_2); ^1H NMR (C_6D_6): δ 0.44–0.79 (m, 3 H, H-1*a*,5a*a*,5a*e*), 1.12–1.27 (m, 2 H, H-1*e*,5), 3.60 (q, 1 H, $J_{1a,2} = J_{1e,2} = J_{2,3} = 3.6$ Hz, H-2), 3.95 (dd, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 4.18 (t, 1 H, $J_{4,5}$ 10.2 Hz, H-4), 3.08 (t, 1 H, $J_{5,6a} = J_{6a,6e} = 10.9$ Hz, H-6*a*), 3.68 (dd, 1 H, $J_{5,6e}$ 4.3 Hz, H-6*e*), and 5.41 (s, 1 H, PhCH). Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.52; H, 5.10; N, 18.48.

Reaction of 1,5-anhydro sugar **1** *with hydrazoic acid.*—To a cooled solution (−20°C) of **1** (20 mg, 0.08 mmol) in MeCN (1 mL) were added NaN_3 (15 mg, 0.23 mmol) and two drops of AcOH with stirring. After 30 min at −20°C, the mixture was diluted with EtOAc and washed with H_2O, aq $NaHCO_3$, aq satd NaCl, dried, and evaporated. The ^1H NMR spectrum of the residue showed it to be a 1:1 mixture of **32** and **33**. The residue was chromatographed with toluene to give a mixture (23 mg, ~100%) of **32** and **33**. Fractional recrystallization from isopropyl ether gave **33**. After evaporation of the filtrate, the residue was treated with Et_3N for 5 h to give a 6:1 mixture of **32** and **33**, from which crystals of **32** were obtained by recrystallization from isopropyl ether. Compound **32** and **33** were identical with respective authentic samples [1].

Compounds **32** and **33** (4 mg) were equilibrated to give a ~6:1 mixture in the presence of Et_3N (0.4 equimolar) for ~5 h, but under the conditions employed for the preparation of these adducts the epimerization was not observed, as judged by ^1H NMR spectroscopy.

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