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Note

Michael reactions on conformationally flexible methyl 3-*C*-nitro-hex-2-enopyranoside derivatives

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Abstract

Dimethyl malonate and dibenzoylmethane attacked the C-2 position of the title 3-nitro-2-enopyranosides from the side opposite the anomeric methoxyl group to afford the 3-enopyranosides (S_N2' products). In the case of 2,4-pentanedione and ethyl acetoacetate, further intramolecular cyclization occurred to yield dihydropyran derivatives.

Keywords: Nitro sugar; The Michael reaction; Intramolecular cyclization; S_N2' reaction

1. Introduction

If a Michael acceptor is conformationally flexible, the direction of approach by nucleophiles should be determined by the conformer from which the reaction proceeds. For a 2-enopyranoside derivative, two half-chair conformations, ^5H_O and $^OH_5$, may be involved. However, only the $^OH_5$ conformation is allowed in the case of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-nitro-β- (**1**) and -α-D-hex-2-enopyranoside (**2**), because ring inversion is prevented by the 4,6-*O*-benzylidene group. After studies of nucleophilic addition reactions of these conformationally rigid 2-enopyranoside derivatives [1], we have studied similar reactions of conformationally flexible 2-enopyranosides. We have previously reported sodium borodeuteride reductions of methyl 4,6-di-*O*-acetyl-2,3-dideoxy-3-*C*-nitro-β-D-*erythro*-hex-2-enopyranoside (**3**), its α-D anomer **4**, and their 4-epimers [2], as well as their oxidation of **4** with peroxides [3]. In these reactions, all nucleophiles added at C-2 from the side opposite the anomeric methoxyl group, as observed in similar reactions of the 4,6-*O*-benzylidene derivatives **1** and **2** [4]. It is noteworthy that the β-D anomer **3** adopts the ^5H_O conformation, while the α-D anomer **4** has the $^OH_5$ conformation [2].

Active methylene compounds also attacked the 2-position of 4,6-*O*-benzylidene derivatives **1** [5] and **2** [6] with high stereoselectivity trans manner to the anomeric methoxyl group.

For comparison with these results we have now performed reactions of 4,6-diacetates **3** and **4** with active methylene compounds.

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2. Results and discussion

Although the reactions of 4,6-*O*-benzylidene derivatives **1** and **2** with diethyl malonate proceeded smoothly to give adducts in good yields, similar reaction of the 4,6-di-*O*-acetyl-β-D anomer **3** with dimethyl malonate afforded many products, partially because of deacetylation. After attempts to improve the yield by varying the solvents, bases, and reaction temperature, we obtained the S_N2' product **5** when the reaction was performed at −20 °C in oxolane in the presence of sodium hydride. Although the reaction proceeded cleanly, the isolated yield of **5** was moderate (44%) because of partial decomposition of **5** during chromatographic separation. The structure of **5** as deduced by IR and ^{1}H NMR spectra was confirmed by comparison with an authentic sample prepared from methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-nitro-β-D-glucopyranoside (**9**) via debenzylidenation, regioselective acetylation at C-6, and subsequent dehydration. The ^1H_o conformation for **5** could be assigned by the $J_{1,2}$ coupling (0 Hz) and confirmed by the $^1J_{C\text{-}1,H\text{-}1}$ value (173 Hz) [7].

Similar reaction with dibenzoylmethane also gave the S_N2' product **6**, having the ^1H_o conformation, in 77% yield. Several attempts to introduce another dibenzoylmethane group into the nitroalkene moiety of **6** were unsuccessful (Scheme 1).

Treatment of the β-D anomer **3** with 2,4-pentanedione gave a complex mixture, because of intramolecular cyclization of a initially formed S_N2' product. Such a cyclization should involve attack of an enolate, generated from the acetyl group, on the nitroalkene moiety, giving the dihydropyran derivative. Attempts at suppressing the cyclization or isolating the S_N2' product corresponding to **5** were not successful. We therefore tried to find suitable conditions for the cyclization and isolated the bicyclic product **7** in 77% yield. In the ^{13}C NMR spectrum the C-2 signal appeared at a much higher field than that of C-4, indicating that the oxygen atom was attached to C-4. The *allo* configuration having the $^1C_4$ conformation was assigned to **7** by the NOE difference spectrum and the $^1J_{C\text{-}1,H\text{-}1}$ value (171 Hz). This structure is reasonable because an intermediary S_N2' product corresponding to **5** has a structure suitable for intramolecular cyclization. It is noteworthy that the structure assigned as the most favorable heat of formation, as calculated by the semiempirical molecular orbital method (AM1 [8]): −243.3 (*allo*, $^1C_4$), −240.4 (*allo*, $^{o,3}B$), −239.1 (*gluco*, $^1C_4$), −239.5 (*gluco*, $^{o,3}B$), −236.7 (*ido*, $^4C_1$), −237.6 (*ido*, $B_{o,3}$), −236.6 (*talo*, $^4C_1$), and −237.5 kcal/mol (*talo*, $B_{o,3}$) (Fig. 1).

Treatment of **3** with ethyl acetoacetate afforded the bicyclic compound **8** in 91% yield. The *allo* configuration having the $^1C_4$ conformation for **8** was again deduced from the NMR data.

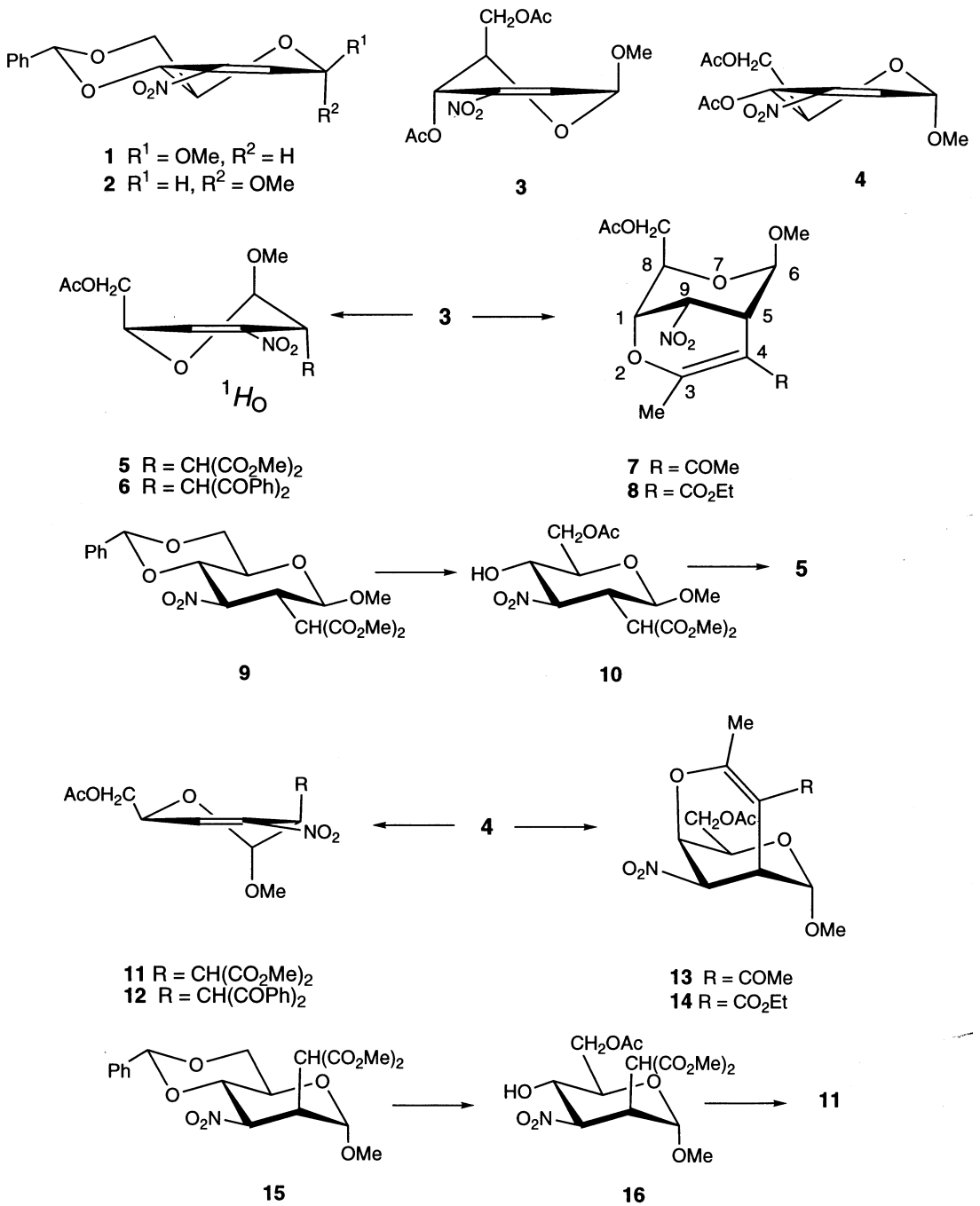
Similar reactions of the α-D anomer **4** with dimethyl malonate and dibenzoylmethane afforded the S_N2' products **11** and **12** in 29 and 89% yields, respectively. The *threo* structure for **11** was confirmed by comparison with an authentic sample prepared from the known 4,6-*O*-benzylidene-α-D-mannopyranoside derivative **15** [9]. The $^OH_1$ conformation for **11** and **12** was deduced by $J_{1,2}$ (0 Hz), the allylic long-range coupling, $J_{2,4}$ (0 Hz) [10], and $^1J_{C\text{-}1,H\text{-}1}$ values. Cyclization again occurred in the reactions with 2,4-pentanedione and ethyl acetoacetate to give **13** and **14** in 97 and 98% yields, respectively. The *talo* configuration having the $^4C_1$ conformation was assigned to these bicyclic compounds by the NOE difference spectra and the $^1J_{C\text{-}1,H\text{-}1}$ values. The structure assigned to **13** is the most favorable one calculated by the AM1 method in the following, possible eight derivatives: −237.3 (*allo*, $^1C_4$), −239.1 (*allo*, $^{o,3}B$), −236.3 (*gluco*, $^1C_4$), −239.7 (*gluco*, $^{o,3}B$), −241.1 (*ido*, $^4C_1$), −236.5 (*ido*, $B_{o,3}$), −242.9 (*talo*, $^4C_1$), and −239.4 kcal/mol (*talo*, $B_{o,3}$) (Fig. 1).

Active methylene compounds thus attacked the 2-position of 3-nitro-2-enopyranosides **3** and **4** exclusively from the side opposite the anomeric methoxyl group, as observed in similar reactions of the 4,6-*O*-benzylidene derivatives **1** and **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 JNM-EX270 spectrometer for solutions in $CDCl_3$ with Me_4Si as the internal standard. The integration values in the NOE difference spectra are estimated only approximately, because measurement conditions were not completely optimized. 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).

Methyl 6-O-acetyl-2,3,4-trideoxy-2-C-bis-(methoxycarbonyl)methyl-3-C-nitro-β-D-erythro-hex-3-enopyranoside (**5**).—(a) From **3**. A



Scheme 1.

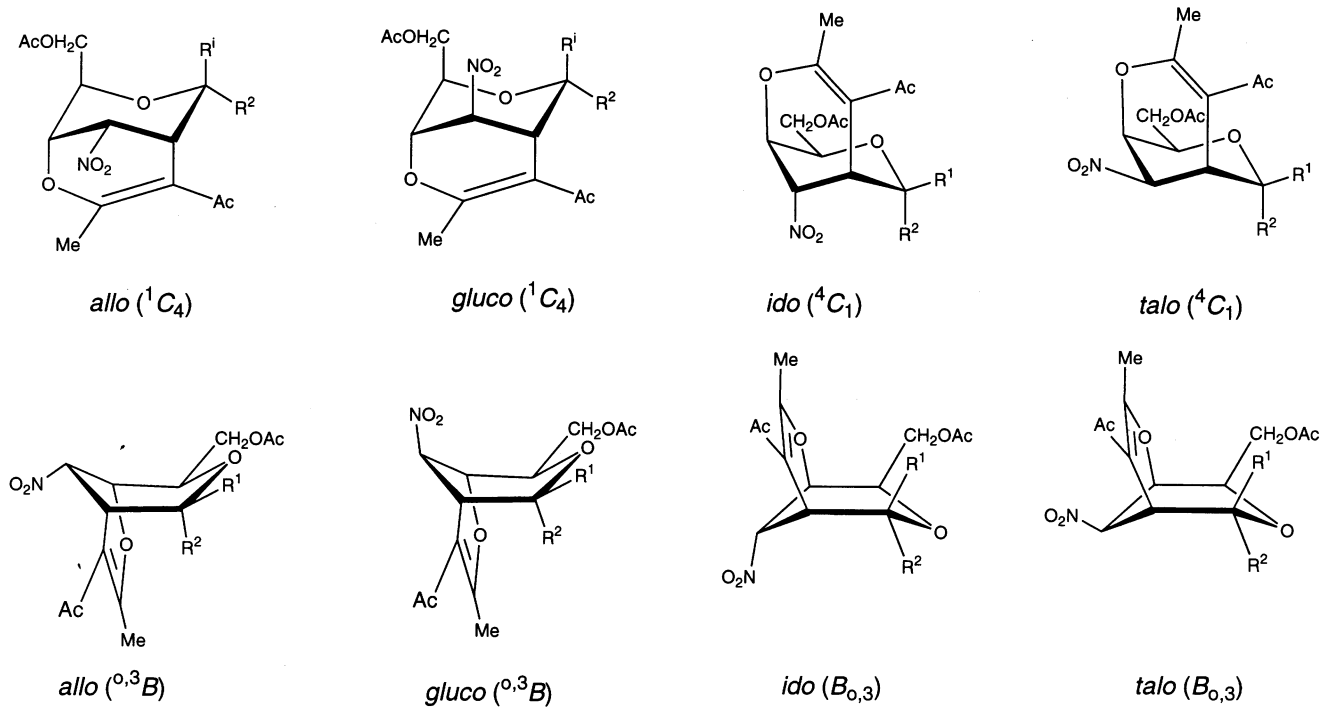


Fig. 1. Possible eight structures for **7** and **13** calculated by the AM1 method. R = OMe and R^2 = H or R^1 = H and R^2 = OMe.

suspension of NaH (10 mg, 0.23 mmol) in oxolane (5 mL) was stirred under N_2 and cooled to −20 °C. To the solution were added successively dimethyl malonate (70 mg, 0.53 mmol) in oxolane (1 mL) and **3** [2] (50 mg, 0.17 mmol) in oxolane (1 mL). After confirming the disappearance of **3** on thin-layer chromatography (TLC) (within 5 min), aq NH_4Cl was added and the mixture was diluted with EtOAc. The organic layer was washed with aq satd NaCl, dried, and evaporated to a syrup that was chromatographed with 50:1 toluene–EtOAc to give 27.5 mg (44%) of **5** as a syrup; $[\alpha]_D^{25}$ −93° (*c* 1.0, CH_2Cl_2); ν_{max} broad 1730 (OAc and CO_2Me), and 1530 cm^{-1} (NO_2); ^1H NMR: δ 5.13 (s, 1 H, H-1), 3.77 (dd, 1 H, $J_{2,2'}$ 5.6, $J_{2,4}$ 0, $J_{2,5}$ 1.0 Hz, H-2), 7.44 (d, 1 H, $J_{4,5}$ 2.6 Hz, H-4), 4.67 (br t, 1 H, $J_{5,6}$ 7.3, $J_{5,6'}$ 6.6 Hz, H-5), 4.30 (dd, 1 H, $J_{6,6'}$ 10.9 Hz, H-6), 4.14 (dd, 1 H, H-6′), 3.44 (s, 3 H, OMe), 2.12 (s, 3 H, OAc), 3.73 (s, 3 H, CO_2Me), 3.76 (s, 3 H, CO_2Me), and 3.61 (d, 1 H, H-2′); ^{13}C NMR: δ 98.82 (C-1), 38.30 (C-2), 131.70 (C-4), 69.11 (C-5), 64.98 (C-6), 56.26 (OMe), 20.72 (OAc), 52.89 (Me), 53.03 (COMe), and 50.80 (C-2′); $^1J_{C\text{-}1,H\text{-}1}$ 173 Hz. Anal. Calcd for $C_{14}H_{19}NO_{10}$: C, 46.54; H, 5.30; N, 3.88. Found: C, 46.84; H, 5.46; N, 3.82.

(b) From **10**. A stirred solution of **10** (160 mg, 0.42 mmol) and MsCl (53 mg, 0.46 mmol) in oxolane (5 mL) was cooled to −20 °C and Et_3N (100 mg, 1.0 mmol) in 2 mL of oxolane was added. After stirring for 30 min at −20 °C, the mixture was diluted with EtOAc (30 mL) and the organic layer was washed with aq M HCl (10 mL) and aq satd NaCl (3 × 10 mL), and then dried and evaporated. The residue was purified by column chromatography to give 91 mg (60%) of **5**, identical with an authentic sample by IR and ^1H NMR spectra.

*Methyl 6-*O*-acetyl-2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-nitro-β-*D*-glucopyranoside* (**10**).—A suspension of **9** (1.0 g, 2.35 mmol) in 70% aq AcOH (50 mL) was stirred for 2 h at 80 °C. The mixture was evaporated below 50 °C and the resulting syrup was chromatographed with 9:1 toluene–MeOH to give the debenzylidenated product (650 mg, 82%). Without further purification, the crude product (1.93 mmol) was dissolved in pyridine (5 mL), and AcCl (200 mg, 2.55 mmol) was added at 0 °C and the mixture was stirred for 4 h at 0 °C. To the mixture was added MeOH (1 mL) at a rate so that the temperature did

not exceed 5 °C. After stirring for an additional 30 min at ambient temperature, the mixture was diluted with EtOAc (30 mL) and the organic layer was washed with aq $NaHCO_3$ (20 mL), aq satd NaCl (20 mL), aq M HCl, and aq satd NaCl (2 × 20 mL), and then dried and evaporated. The resulting syrup was purified on a column of silica gel with 10:1 toluene–EtOAc to give 530 mg (72%) of **10** as a syrup; $[\alpha]_D^{25}$ −64° (*c* 0.8, CH_2Cl_2); ν_{max} 3450 (OH), 1740 (OAc), and 1555 cm^{-1} (NO_2); ^1H NMR: δ 5.01 (d, 1 H, $J_{1,2}$ 8.6 Hz, H-1), 2.85 (ddd, 1 H, $J_{2,2'}$ 3.6, $J_{2,3}$ 11.9 Hz, H-2), 4.84 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 4.02 (dt, 1 H, $J_{4,5}$ 9.9, $J_{4,OH}$ 5.0 Hz, H-4), 3.55 (ddd, 1 H, $J_{5,6}$ 3.3, $J_{5,6'}$ 2.3 Hz, H-5), 4.62 (dd, 1 H, $J_{6,6'}$ 12.2 Hz, H-6), 4.25 (dd, 1 H, H-6′), 3.46 (d, 1 H, H-2′), 3.45 (s, 3 H, OMe), 2.17 (s, 3 H, OAc), 3.79 (s, 3 H, CO_2Me), and 3.71 (s, 3 H, CO_2Me); ^{13}C NMR: δ 101.33 (C-1), 44.76 (C-2), 89.07 (C-3), 68.18 (C-4), 73.91 (C-5), 62.73 (C-6), 57.72, 52.76, 52.67, and 20.8. Anal. Calcd for $C_{14}H_{21}NO_{11}$: C, 44.33; H, 5.58; N, 3.69. Found: C, 44.52; H, 5.85; N, 3.58.

*Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-nitro-β-*D*-glucopyranoside* (**9**).—To a cooled (−20 °C) suspension of **1** [11] (250 mg, 0.85 mmol) and NaH (37 mg, 0.9 mmol) in oxolane (10 mL) was added dropwise dimethyl malonate (169 mg, 1.28 mmol) in oxolane (5 mL) and then stirring was continued for an additional 15 min at −20 °C. After addition of aq HCl, the mixture was extracted with EtOAc. The combined extracts were washed with aq satd NaCl (twice), dried, and evaporated. The residue was chromatographed with 40:1 and 30:1 hexane–EtOAc and 50:1 toluene–EtOAc to give 330 mg (91%) of **9**; mp 141–141.5 °C (*i*-PrOH), $[\alpha]_D^{25}$ −69° (*c* 1.0, CH_2Cl_2); ν_{max} 1770, 1740 (OAc), and 1560 cm^{-1} (NO_2); ^1H NMR (C_6D_6): δ 5.13 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1), 2.93 (ddd, 1 H, $J_{2,2'}$ 3.6, $J_{2,3}$ 11.9 Hz, H-2), 5.04 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 4.19 (t, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 3.61 (ddd, 1 H, $J_{5,6a}$ 9.6, $J_{5,6e}$ 5.0 Hz, H-5), 3.85 (t, 1 H, $J_{6a,6e}$ 10.6 Hz, H-6*a*), 4.41 (dd, 1 H, H-6*e*), 3.51 (d, 1 H, H-2′), 3.47 (s, 3 H, OMe), 3.80 (s, 3 H, CO_2Me), and 3.73 (s, 3 H, CO_2Me). Anal. Calcd for $C_{19}H_{23}NO_{10}$: C, 53.65; H, 5.45; N, 3.29. Found: C, 53.80; H, 5.51; N, 3.09.

*Methyl 6-*O*-acetyl-2-*C*-dibenzoylmethyl-2,3,4-trideoxy-3-*C*-nitro-β-*D*-erythro-hex-3-enopyranoside* (**6**).—A stirred suspension of NaH (10 mg, 0.23 mmol) in oxolane (5 mL) was cooled to −20 °C under N_2, and dibenzoylmethane (116 mg, 0.52 mmol) in oxolane (1 mL) and **3** (50 mg, 0.17 mmol) in oxolane (1 mL) were successively added. The mixture was stirred for 5 min at −20 °C and treated with aq NH_4Cl and then diluted with EtOAc. The organic layer was washed with aq satd NaCl, dried, and evaporated. The syrup obtained was chromatographed with 100:1 toluene–EtOAc to give 60 mg (77%) of **6** as a syrup; $[\alpha]_D^{25}$ −49° (*c* 1.0, CH_2Cl_2); ν_{max} 1740 (OAc), 1690, 1670 (COPh), and 1525 cm^{-1} (C=C–NO_2); ^1H NMR (C_6D_6): δ 5.57 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 4.43 (td, 1 H, $J_{2,2'}$ 3.3, $J_{2,5}$ 1.7 Hz, H-2), ~7.18 (overlapped with C_6H_5, H-4), 3.92 (br tt, 1 H, $J_{4,5}$ 2.0, $J_{5,6}$ 6.6, $J_{5,6'}$ 5.1 Hz, H-5), 3.99 (dd, 1 H, $J_{6,6'}$ 9.5 Hz, H-6), 3.77 (dd, 1 H, H-6′), 5.80 (d, 1 H, H-2′), 3.13 (s, 3 H, OMe), 1.54 (s, 3 H, OAc), 6.9–7.2 (m, 6 H, C_6H_5), 7.76 (br d, 2 H, C_6H_5), and 7.94 (br d, 2 H, C_6H_5); ^{13}C NMR: δ 99.81 (C-1), 39.89 (C-2), 128.97 (C-4), 69.56 (C-5), 65.37 (C-6), 57.07 (OMe), 21.39 (OAc), and 54.50 (C-2'); $^1J_{C\text{-}1,H\text{-}1}$ 173 Hz. Anal. Calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.56; H, 5.14; N, 3.12.

*(1*S*,5*R*,6*R*,8*R*,9*S*)-8-Acetoxymethyl-4-acetyl-6-methoxy-3-methyl-9-nitro-2,7-dioxabicyclo[3.3.1]non-3-ene* (**7**).—A stirred suspension of NaH (20 mg, 0.5 mmol) in oxolane (4 mL) was cooled to −20 °C and 2,4-pentanedione (100 mg, 1.0 mmol) in oxolane (2 mL) and **3** (50 mg, 0.17 mmol) in oxolane (2 mL) were successively added. The starting material **3** disappeared (TLC) within 1 min. The mixture was allowed to rise to 0 °C over a period of ~30 min and kept for an additional hour at 0 °C. After addition of aq NH_4Cl, the mixture was diluted with EtOAc and the organic layer was washed with aq satd NaCl (twice), dried, and evaporated. The resulting syrup was chromatographed with 50:1 toluene–EtOAc to give 44 mg (77%) of **7** as a syrup; $[\alpha]_D^{25}$ −39° (*c* 0.5, CH_2Cl_2); ν_{max} 1750

(OAc), 1680 and 1620 (C=C–Ac), and 1560 cm^{-1} (NO_2); ^1H NMR (C_6D_6) (carbohydrate numbering is used in NMR data through this article): δ 4.65 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 4.14 (td, 1 H, $J_{2,3}$ 3.0, $J_{2,4}$ 2.0 Hz, H-2), 4.62 (dd, 1 H, $J_{3,4}$ 2.0 Hz, H-3), 4.98 (q, 1 H, $J_{4,5}$ 2.0 Hz, H-4), 4.23 (ddd, 1 H, $J_{5,6}$ 8.9, $J_{5,6'}$ 5.9 Hz, H-5), 3.89 (dd, 1 H, $J_{6,6'}$ 11.6 Hz, H-6), 3.98 (dd, 1 H, H-6′), 2.96 (s, 3 H, OMe), 1.58 (s, 3 H, OAc), 1.87 (s, 3 H, CAc), and 1.84 (s, 3 H, C=C–Me); NOE difference spectrum: H-2 (9%), H-4 (6%), and H-6 and H-6′ (7%) irradiated at H-3; ^{13}C NMR: δ 102.18 (C-1), 35.70 (C-2), 70.96 (C-3), 69.68 (C-4), 77.49 (C-5), 62.38 (C-6), 56.36 (OMe), 20.59 (OAc), 20.92 (Me), and 30.30 (COMe); $^1J_{C\text{-}1,H\text{-}1}$ 171 Hz. Anal. Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 51.04; H, 5.79; N, 4.25.

By shortening the reaction time by 5 min and quenching the reaction at −20 °C a mixture of **7** and the S_N2' product corresponding to **5** was obtained, as judged by ^1H NMR spectroscopy {4.93 (1 H, d, $J_{1,2}$ 2.3 Hz, H-1), 3.76 (1 H, dt, $J_{2,2'}$ 5.9, $J_{2,5}$ 2.3 Hz, H-2), 7.40 (1 H, d, $J_{4,5}$ 2.6 Hz, H-4), 4.72 (1 H, m, H-5), 4.16 (1 H, dd, $J_{5,6}$ 6.6, $J_{6,6'}$ 10.9 Hz, H-6), 4.28 (1 H, dd, $J_{5,6'}$ 6.9 Hz, H-6′), 3.91 (1 H, d, H-2′), 3.41 (3 H, s, OMe), 2.22, 2.20, and 2.12 (3 H, all s, 2 × COMe, OAc)}.

*(1*S*,5*R*,6*R*,8*R*,9*S*) - 8 - Acetoxymethyl - 4-ethoxycarbonyl-6-methoxy-3-methyl-9-nitro-2,7-dioxabicyclo[3.3.1]non-3-ene* (**8**).—Similar treatment of **3** (30 mg, 0.10 mmol) with ethyl acetoacetate (68 mg, 0.52 mmol) in the presence of NaH (12 mg, 0.3 mmol) afforded 34 mg (91%) of **8** as a syrup; $[\alpha]_D^{25}$ −37° (*c* 1.0, CH_2Cl_2); ν_{max} 1740 (OAc), 1710, 1680, and 1625 (C=C–CO_2Et), and 1550 cm^{-1} (NO_2); ^1H NMR (C_6D_6): δ 4.82 (d, 1 H, $J_{1,2}$ 2.3 Hz, H-1), 4.22 (td, 1 H, $J_{2,3}$ 3.0, $J_{2,4}$ 2.0 Hz, H-2), 4.65 (dd, 1 H, $J_{3,4}$ 2.0 Hz, H-3), 5.01 (q, 1 H, $J_{4,5}$ 1.7 Hz, H-4), 4.25 (ddd, 1 H, $J_{5,6}$ 8.9, $J_{5,6'}$ 5.9 Hz, H-5), 3.89 (dd, 1 H, $J_{6,6'}$ 11.5 Hz, H-6), 4.01 (dd, 1 H, H-6′), 2.99 (s, 3 H, OMe), 1.59 (s, 3 H, OAc), 0.91 (s, 3 H, OCH_2CH_3), 3.96 (q, 2 H, OCH_2CH_3), and 2.25 (s, 3 H, C=C–Me); NOE difference spectrum: H-2 and H-5 (12%), H-4 (7.5%) and H-6 (major) and H-6′ (minor) (7%) irradiated at H-3; $^1J_{C\text{-}1,H\text{-}1}$ 173 Hz. Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90. Found: C, 50.40; H, 6.03; N, 4.05.

*Methyl 6-*O*-acetyl-2,3,4-trideoxy-2-*C*-bis-(methoxycarbonyl)methyl-3-*C*-nitro-α-*D*-threo-hex-3-enopyranoside* (**11**).—(a) From **4**. A suspension of NaH (40 mg, 0.92 mmol) in oxolane (5 mL) was cooled to −20 °C under N_2. To the solution dimethyl malonate (180 mg, 1.36 mmol) in oxolane (1 mL) and **4** [2] (200 mg, 0.69 mmol) in oxolane (1 mL) were successively added. The mixture was stirred for 5 min and then partitioned between aq NH_4Cl and EtOAc (70 mL). The organic layer was washed with aq satd NaCl, dried, and evaporated to a syrup, which was chromatographed with 50:1 and 30:1 toluene–EtOAc to give 72 mg (29%) of **11** as a syrup. Compound **11** partially decomposed during chromatographic separation; $[\alpha]_D^{25}$ +38° (*c* 1.0, CH_2Cl_2); ν_{max} 1730 (ester), and 1530 cm^{-1} (NO_2); ^1H NMR: δ 5.10 (s, 1 H, H-1), 3.72 (dd, 1 H, $J_{2,2'}$ 6.3, $J_{2,5}$ 2.6 Hz, H-2), 7.36 (d, 1 H, $J_{4,5}$ 2.3 Hz, H-4), 4.55 (br tt, 1 H, $J_{5,6}$ 5.3, $J_{5,6'}$ 5.0 Hz, H-5), 4.39 (dd, 1 H, $J_{6,6'}$ 11.2 Hz, H-6), 4.20 (dd, 1 H, H-6′), 3.64 (d, 1 H, H-2′), 3.46 (s, 3 H, OMe), 2.12 (s, 3 H, OAc), 3.72 (s, 3 H, COMe), and 3.75 (s, 3 H, COMe); ^{13}C NMR: δ 98.74 (C-1), 38.37 (C-2), 132.22 (C-4), 66.67 (C-5), 63.30 (C-6), 55.98 (OMe), 20.60 ($OCOCH_3$), 52.78 ($COMe$), and 51.79 (C-2′); $^1J_{C\text{-}1,H\text{-}1}$ 177 Hz. Anal. Calcd for $C_{14}H_{19}NO_{10}$: C, 46.54; H, 5.30; N, 3.88. Found: C, 46.64; H, 5.45; N, 4.08.

(b) From **16**. A stirred solution of **16** (70 mg, 0.18 mmol) and MsCl (60 mg, 0.52 mmol) in oxolane (5 mL) was cooled to −20 °C and Et_3N (140 mg, 1.4 mmol) in oxolane (2 mL) was added. After stirring for 2 h at −20 °C and an additional 2 h at 0 °C, the mixture was diluted with EtOAc (30 mL) and the organic layer was washed with aq M HCl (10 mL) and aq satd NaCl (3 × 10 mL), dried, and evaporated. The residue was purified by column chromatography to give 15 mg (22%) of **11**, identical with an authentic sample obtained from IR and ^1H NMR spectra.

*Methyl6-*O*-acetyl-2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-nitro-α-*D*-manno-pyranoside* (**16**).—A suspension of **15** [9] (1.0 g, 2.35 mmol) in 90% aq AcOH (30 mL) was stirred for 4 h at 70 °C. The mixture was

evaporated to a syrup below 50 °C and then chromatographed with 9:1 toluene–MeOH to give the debenzylidenated product (550 mg, 69%). Without further purification, to the crude product (1.63 mmol) dissolved in pyridine (2 mL) was added AcCl (140 mg, 1.78 mmol) at −20 °C and the mixture was stirred for 2 h at ambient temperature. To the mixture was added MeOH (1 mL) at such a rate that the temperature did not exceed 5 °C. After stirring for 30 min, the mixture was diluted with EtOAc and the organic layer was washed with aq $NaHCO_3$ (20 mL), aq satd NaCl (2 × 20 mL), aq M HCl (20 mL), and aq satd NaCl (2 × 20 mL), and then dried and evaporated. The residue was purified by chromatography with 10:1 toluene–EtOAc to give 280 mg (45%) of **16**; mp 86–90 °C, $[\alpha]_D^{25}$ −3° (*c* 1.0, MeOH); ν_{max} 3480 (OH), 1740 (OAc), and 1560 cm^{-1} (NO_2); ^1H NMR: δ 4.93 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 3.50 (ddd, 1 H, $J_{2,2'}$ 6.6, $J_{2,3}$ 5.0 Hz, H-2), 5.10 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 4.02 (dt, 1 H, $J_{4,5}$ 9.9, $J_{4,OH}$ 5.0 Hz, H-4), ~3.8 (H-5), 4.45 (dd, 1 H, $J_{5,6}$ 4.6, $J_{6,6'}$ 12.2 Hz, H-6), 4.38 (dd, 1 H, $J_{5,6'}$ 2.6 Hz, H-6′), 3.65 (d, 1 H, H-2′), 3.46 (s, 3 H, OMe), 2.20 (s, 3 H, OAc), 3.76 (s, 3 H, CO_2Me), and 3.81 (s, 3 H, CO_2Me). Anal. Calcd for $C_{14}H_{21}NO_{11}$: C, 44.33; H, 5.58; N, 3.69. Found: C, 44.53; H, 5.48; N, 3.66.

Methyl 6-O-acetyl-2-C-dibenzoylmethyl-2,3,4-trideoxy-3-C-nitro-α-D-threo-hex-3-enopyranoside (**12**).—A stirred suspension of NaH (20 mg, 0.5 mmol) in oxolane (5 mL) was cooled to −20 °C under N_2. To the solution dibenzoylmethane (195 mg, 0.87 mmol) in oxolane (1 mL) and **4** (50 mg, 0.17 mmol) in oxolane (1 mL) were successively added. After stirring for 30 min at −20 °C, the mixture was diluted with EtOAc and the organic layer was washed with aq satd NaCl (twice), dried, and evaporated. The resulting syrup was chromatographed with 100:1 toluene–EtOAc to give 70 mg (89%) of **12** as a syrup; $[\alpha]_D^{25}$ −22° (*c* 0.9, CH_2Cl_2); ν_{max} 1740 (OAc), 1690, 1670 (COPh) and 1530 cm^{-1} (C=C–NO_2); ^1H NMR: δ 5.30 (s, 1 H, H-1), 4.02 (t, 1 H, $J_{2,2'} = J_{2,5}$ 3.0 Hz, H-2), 7.14 (d, 1 H, $J_{4,5}$ 1.3 Hz, H-4), 4.36 (br td, 1 H, $J_{5,6} = J_{5,6'}$ 6.6 Hz, H-5), 3.59 (dd, 1 H, $J_{6,6'}$ 11.2 Hz, H-6), 3.23 (dd, 1 H, H-6′), 5.64 (d, 1 H, H-2′), 3.49 (s, 3 H, OMe), and 2.02 (s, 3 H, OAc); NOE difference spectrum: H-4 (12%) irradiated at H-5 and H-2 (8%) and OMe (6%) irradiation at H-1; ^{13}C NMR: δ 98.44 (C-1), 39.05 (C-2), 146.54 (C-3), 127.69 (overlap with C_6H_5, tentative C-4), 65.34 (C-5), 63.22 (C-6), 56.05 (OMe), and 54.11 (C-2′); $^1J_{C\text{-}1,H\text{-}1}$ 172 Hz. Anal. Calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.56; H, 5.38; N, 3.08.

(1R,5S,6S,8R,9R)-8-Acetoxymethyl-4-acetyl-6-methoxy-3-methyl-9-nitro-2,7-dioxabicyclo[3.3.1]non-3-ene (**13**).—A stirred suspension of NaH (20 mg, 0.5 mmol) in oxolane (4 mL) was cooled to −20 °C under N_2. To the solution 2,4-pentanedione (100 mg, 1.0 mmol) in oxolane (2 mL) and **4** (50 mg, 0.17 mmol) in oxolane (2 mL) were successively added. The starting material **4** disappeared (TLC) within 1 min. The mixture was allowed to rise to 0 °C over a period of 30 min and kept for an additional hour, and then diluted with EtOAc (60 mL). The organic layer was washed with aq satd NaCl, dried, and evaporated. The residue was chromatographed with 50:1 toluene–EtOAc to give 55 mg (97%) of **13**; mp 91.5–92.5 °C (toluene–hexane), $[\alpha]_D^{25}$ −1° (*c* 0.9, CH_2Cl_2); ν_{max} 1750 (OAc), 1680 and 1620 (C=C–Ac), and 1560 cm^{-1} (NO_2); ^1H NMR: δ 4.71 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 3.96 (dt, 1 H, $J_{2,3}$ 3.3, $J_{2,4}$ 2.0 Hz, H-2), 4.99 (dd, 1 H, $J_{3,4}$ 1.7 Hz, H-3), 5.06 (br s, 1 H, H-4), 4.05 (t, 1 H, $J_{5,6}$ 6.6, $J_{5,6'}$ 6.3 Hz, H-5), 4.28 (dd, 1 H, $J_{6,6'}$ 11.3 Hz, H-6), 4.23 (dd, 1 H, H-6′), 3.42 (s, 3 H, OMe), 2.12, 2.28, 2.33 (all s, 3 H, OMe, OAc, C=C–Me); NOE difference spectrum: H-3 (13%), H-4 (10%) and H-6 and H-6′ (4%) irradiated at H-5, and H-2 (10%), H-4 (4.5%), H-5 (11%) irradiated at H-3; ^{13}C NMR: δ 100.85 (C-1), 35.67 (C-2), 73.89 (C-3), 69.27 (C-4), 71.05 (C-5), 62.21 (C-6), 55.55 (OMe), 20.74, 20.86, 30.35 ($OCOCH_3$, $COCH_3$, Me), 170.58 ($OCOCH_3$), and 195.76 ($COCH_3$); $^1J_{C\text{-}1,H\text{-}1}$ 175 Hz. Anal. Calcd for $C_{14}H_{19}NO_8$: C, 51.06; H, 5.82; N, 4.25. Found: C, 51.05; H, 5.80; N, 4.28.

By shortening the reaction time by 5 min and quenching the reaction at −20 °C a mix-

ture of **13** and the S_N2' product corresponding to **11** was obtained, as judged from ^1H NMR spectroscopy {4.68 (1 H, d, $J_{1,2}$ 2.0 Hz, H-1), ~3.97 (overlapped with H-2 of **13**, H-2), and 7.39 (1 H, d, $J_{4,5}$ 2.4 Hz, H-4)}.

*(1*R,*5*S,*6*S,*8*R,*9*R*)-8-Acetoxymethyl-4-ethoxycarbonyl-6-methoxy-3-methyl-9-nitro-2,7-dioxabicyclo[3.3.1]non-3-ene* (**14**).—Similar treatment of **4** (50 mg, 0.17 mmol) with ethyl acetoacetate (115 mg, 0.88 mmol) in the presence of NaH (20 mg, 0.5 mmol) gave 61 mg (98%) of **14**; mp 130.5–132 °C (toluene–hexane), $[\alpha]_D^{25}$ −0° (*c* 1.4, CH_2Cl_2); ν_{max} 1740 (OAc), 1710 and 1620 (C=C–COOEt), and 1550 cm^{-1} (NO_2); ^1H NMR: δ 4.78 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 3.91 (dt, 1 H, $J_{2,3}$ 3.3, $J_{2,4}$ 2.0 Hz, H-2), 4.97 (dd, 1 H, $J_{3,4}$ 2.0 Hz, H-3), 5.04 (br s, 1 H, H-4), 4.05 (t, 1 H, $J_{5,6}$ 6.6, $J_{5,6'}$ 6.3 Hz, H-5), 4.28 (dd, 1 H, $J_{6,6'}$ 11.6 Hz, H-6), 4.22 (dd, 1 H, H-6′), 3.43 (s, 3 H, OMe), 2.12 (s, 3 H, OAc), 1.30 (s, 3 H, OCH_2CH_3), 4.20 (q, 2 H, OCH_2CH_3), and 2.29 (s, 3 H, C=C–Me); NOE difference spectrum: H-4 (12%), H-3 (12%), and H-6 and H-6′ (7%) irradiated at H-5; ^{13}C NMR: δ 101.19 (C-1) 36.00 (C-2), 74.11 (C-3), 69.53 (C-4), 71.52 (C-5), 62.36 (C-6), 55.81 (OMe), 60.65 (OCH_2CH_3), 20.97 (OAc or Me), 19.98 (Me or OAc), and 14.58 (OCH_2CH_3); $^1J_{C\text{-}1,H\text{-}1}$ 172 Hz. Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90. Found: C, 50.16; H, 5.91; N, 3.93.

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