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Photoaddition reactions of 3-nitro-2-enopyranoside derivatives in 1,3-dioxolane

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ABSTRACT

Irradiation of 3-nitro-2-enopyranoside derivatives having α-D-*erythro*, β-D-*threo*, and α-D-*threo* configurations in 1,3-dioxolane afforded adducts in moderate yields. Structural assignment of the adducts, including conformational analyses of the 1,3-dioxolanyl moiety, were performed.

INTRODUCTION

Detailed studies of the stereochemistry of nucleophilic addition-reactions to 2-enopyranoside derivatives having an electron-withdrawing group at C-2 or C-3 revealed that the direction of approach of a nucleophile is mainly controlled by three factors, including electrostatic repulsion[1].

Evaluation of each of the factors is required to improve the reliability of stereochemical prediction. In this context, free-radical reactions are attractive, because they seem to be almost free from electrostatic repulsion as compared with nucleophilic addition-reactions. We have already performed photoaddition reactions of the methyl 2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside **1** in oxolane and 1,3-dioxolane[2], in which the adducts having the *manno* (**2** and **3**) and *gluco* (**4**, **5**, and **6**) configurations were isolated. Although the total yield of photoadducts in the reaction with oxolane was ~ 10% higher than that with 1,3-dioxolane, the former reaction was much more complicated than the latter, because of generation of the additional chiral center at the oxolanyl moiety.

Therefore, we have now performed photoaddition reactions of 2,3-dideoxy-3-nitro-hex-2-enopyranoside derivatives having the α-D-*erythro* (**7**), β-D-*threo* (**12**), and α-D-*threo* (**17**) configurations in 1,3-dioxolane.

RESULTS AND DISCUSSION

A solution of the methyl α-D-*erythro*-hex-2-enopyranoside **7** in 1,3-dioxolane was irradiated under nitrogen with a high-pressure mercury lamp for 40 h at ~ 8°. By column chromatography, the α-D-*manno* (**8**), α-D-*gluco* (**9**), and α-D-*allo* (**10**) isomers,

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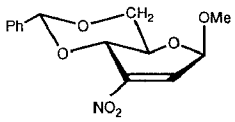

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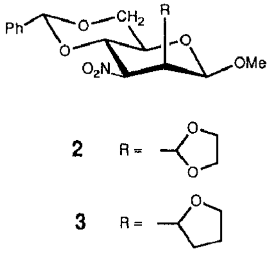

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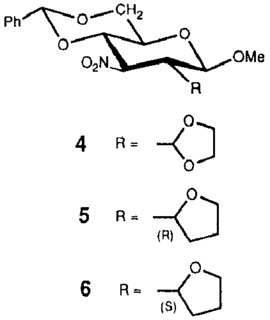

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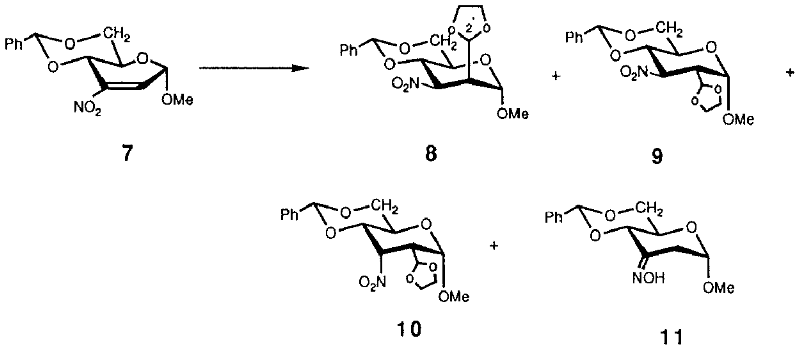
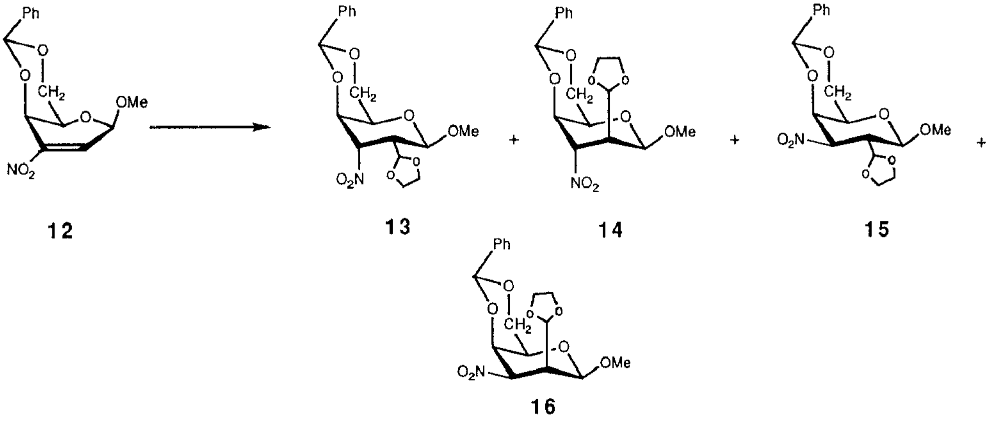
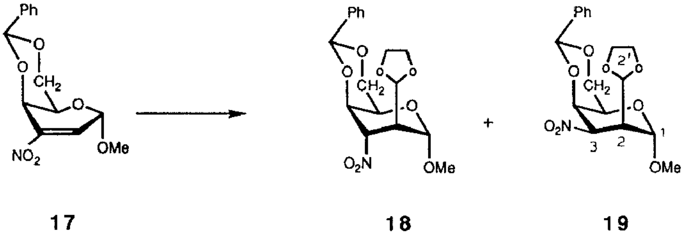


7 → **8** + **9** + **10** + **11**



12 → **13** + **14** + **15** + **16**



17 → **18** + **19**

and the 3-oxime **11** were isolated successively in 43, 7, 5, and 10% yields, respectively. The physical data for the last compound were in good agreement with those reported in the literature[3]. Differentiation of H-1 and H-2′ (the H-2 signal of 1,3-dioxolanyl moiety) is often difficult from the coupling constants and chemical shifts only, because both signals are caused by acetal methine protons coupled only with the H-2 proton. Signals for H-1 of **8**, **9**, and **10** could be unambiguously assigned by n.O.e. difference spectra irradiated at the anomeric methoxyl signals. The α-D-*manno*, α-D-*gluco*, and α-D-*allo* configurations were assigned to **8**, **9**, and **10**, respectively, on the basis of coupling constants. The α-D-*allo* structure of **10** was confirmed by its partial epimerization to the α-D-*gluco* isomer **9** by treatment with sodium deuteroxide.

Similar photoreaction of the β-D-*threo* isomer **12** provided all possible four adducts, the β-D-*gulo* (**13**), β-D-*ido* (**14**), β-D-*galacto* (**15**), and β-D-*talo* (**16**) isomers, in 10, 5, 19, and 4% yields, respectively. Assignments of H-1 signals were achieved by n.O.e. difference spectra irradiated at the signals of the OMe and/or the H-1 signals. The equatorial orientation of the 1,3-dioxolanyl moiety in **13** and **15** was deduced by the large $J_{1,2}$ values. Small and large $J_{2,3}$ values, 4.6 Hz for **13** and 11.5 Hz for **15**, indicated axial and equatorial orientation, respectively, of the nitro group. This was in good agreement with the fact that the H-1 and H-5 signals of **13** appeared at lower field than the corresponding signals of **15**, because of anisotropy of the nitro group[4]. The β-D-*ido* and β-D-*talo* configurations were assigned to **14** and **16** by comparison with the chemical shifts of H-1 and H-5; these signals appeared in the former at lower field than in the latter. The β-D-*gulo* structure of **13** was confirmed by its epimerization into the β-D-*galacto* isomer **15**.

Similar photoreaction of the α-D-*threo* isomer **17** afforded two adducts having the α-D-*ido* (**18**, 17%) and α-D-*talo* (**19**, 46%) configurations. These two products were revealed to be 3-epimers, because treatment of both with 0.2M sodium deuteroxide in acetone-d_6 gave the 3-deutero derivative of **19**. Small $J_{2,3}$ values (2.4 Hz for **18** and 4.6 Hz for **19**) exclude the possibility of the α-D-*galacto* configuration for these products. The H-5 signal for **18** (δ 4.00) appeared at lower field than that for **19** (δ 3.63), revealing that the nitro group occupies the axial position in **18** and the equatorial one in **19**. This assignment is in harmony with the expected thermodynamic stabilities, as the equatorial orientation of the nitro group in 3-nitro pyranosides is generally favored[5].

Conformational analyses of the 1,3-dioxolanyl moieties. — Three gauche conformers (I–III) were taken into consideration for the α-D-*gluco* isomer **9**. Apparently interaction between the anomeric methoxyl group and O-3′ (one of the ring oxygen atoms of the 1,3-dioxolanyl moiety, see II in Fig. 1) [written as (OMe, O-3′)] is repulsive and if this repulsion is more serious than that between the nitro group and O-1′ (I in Fig. 1) (NO_2, O-1′), conformer I should be more stable than conformer II. If **9** occupied essentially conformation II, the fairly large $J_{2,2'}$ value (6.9 Hz) would suggest a small deformation that moves H-2′ close to H-2. On the n.O.e. difference spectrum irradiated at the H-2′ resonance, the H-2 signal was negligible, but H-1 and H-3 signals were observed (~ 2 and 6%, respectively), indicating that compound **9** exists mainly in a deformed conformer I, in which H-2′ seems to move slightly toward H-1. Thus it is likely that the

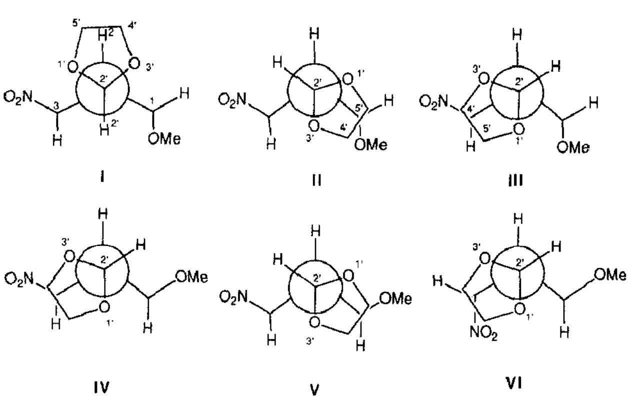


Fig. 1. Newman projections of the conformations, viewed from C-2′ to C-2, for the α-D-*gluco* (**9**), β-D-*gluco* (**4**), β-D-*galacto* (**15**), and β-D-*gulo* isomers (**13**).

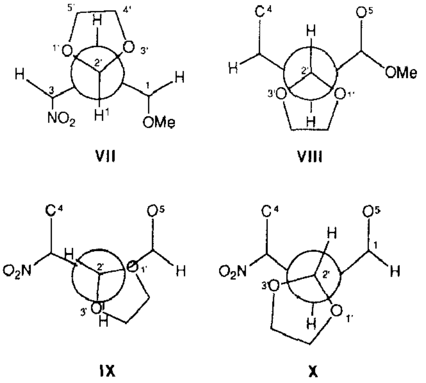


Fig. 2. Newman projections of the conformations, viewed from C-2′ to C-2, for the α-D-*allo* (**10**), β-D-*ido* (**14**), and α-D-*manno* isomers (**8**).

repulsion due to (OMe, O-3′) is larger than that due to (NO_2, O-1′). Small $J_{2,2'}$ coupling constants for the β-D-*gluco* **4** (1.6 Hz) and β-D-*galacto* isomers **15** (2.3 Hz) suggest that these should exist mainly in conformations IV or V. As judged from n.O.e. difference spectra of **4** and **15** irradiated at the H-2′ resonance, in which H-3 was not observed but H-2 (10% for **4** and 9% for **15**) and H-1 (2% for **4** and 3% for **15**) were observed, both isomers probably prefer conformation IV. A repulsive effect of (OMe, O-1′) is again indicated in the β-D-*gulo* isomer **13**; a small $J_{2,2'}$ value (3.3 Hz) and n.O.e. difference spectra [H-2 signals (9%) were observed by the irradiation at H-2′, but not H-3] suggested that **13** exists in conformation VI. The α-D-*allo* isomer **10** should assume conformation VII (see Fig. 2), because other conformers are destabilized by (OMe, O-1′) or (OMe, O-3′); this is supported by the large $J_{2,2'}$ value (>7.9 Hz). In the cases of the β-D-*ido* **14**, β-D-*talo* **16**, α-D-*ido* **18**, and α-D-*talo* isomers **19**, large $J_{2,2'}$ values (>6.9 Hz) indicate that H-2′ is directed towards the pyranose ring, thus implying conformation VIII as illustrated by **14**; in these compounds O-4 has the axial disposition. In the α-D-*manno* isomer **8**, the n.O.e. difference spectrum with irradiation at H-2′ was not conclusive because of partial overlap of H-3 with H-2′ signals, both in chloroform-*d* and benzene-d_6. Irradiation at H-1 did not enhance the H-2′ signal, but did enhance the methoxyl (5%) and H-2 (6%) signals. Similar irradiation at H-4 enhanced the benzylidene methine (20%), H-6a (5%), and signals overlapped by H-3 and H-2′ signals (20%), and irradiation at H-2 enhanced H-1 (8%) as well as H-3 and H-2′ (20%) signals. In addition to these data a fairly large $J_{2,2'}$ value (5.9 Hz) suggested that **8** adopts conformation IX rather than X.

TABLE I

Chemical shifts from ^{1}H-n.m.r. spectra[a]

Compd.	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6′*	*H-2′*	*PhCH*	*OMe*
8	5.02 (br.s)	2.92 (t)	5.02 (dd)	4.63 (m)		3.8–4.0 (m)		5.05 (d)	5.71 (s)	3.40 (s)
9	4.93 (d)	2.66 (ddd)	5.01 (dd)	4.11 (t)	3.91 (dt)	3.81 (t)	4.32 (dd)	5.11 (d)	5.54 (s)	3.41 (s)
10	4.81 (d)	2.24 (ddd)	5.19 (t)	3.78 (dd)	4.89 (dt)	3.70 (t)	4.39 (dd)	4.50 (d)	5.57 (s)	3.41 (s)
13	5.29 (d)	2.65 (ddd)	5.21 (dd)	4.20 (br.s)	4.15 (br.s)	4.40 (dd)	4.14 (dd)	5.18 (d)	5.59 (s)	3.59 (s)
14	4.97 (d)	2.81 (dt)	5.15 (dd)	4.43 (t)	3.87 (t)	4.35 (dd)	4.11 (dd)	5.29 (d)	5.57 (s)	3.52 (s)
15	4.49 (d)	3.26 (dt)	4.92 (dd)	4.46 (d)	3.46 (d)	4.39 (dd)	4.13 (dd)	5.09 (d)	5.55 (s)	3.54 (s)
16	4.54 (d)	3.24 (m)	4.30 (dd)	4.79 (dd)	3.37 (br.d)	4.43 (dd)	4.21 (dd)	5.69 (d)	5.71 (s)	3.60 (s)
18	4.94 (d)	3.27 (dd)	4.83 (t)	4.79 (br.s)	4.00 (br.d)	4.32 (dd)	4.21 (dd)	5.40 (d)	5.61 (s)	3.34 (s)
19	5.10 (br.s)	2.97 (dd)	4.79 (br.s)	4.83 (br.s)	3.63 (br.d)	4.36 (dd)	4.19 (dd)	5.62 (d)	5.70 (S)	3.43 (s)

[a] All spectra recorded at 270 MHz in $CDCl_3$; chemical shifts are in δ values relative to internal Me_4Si.

TABLE II

First-order coupling constants (Hz)[a]

Compd.	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{2,2'}$
8	≤1.0	5.9	10.9	8.9				5.9
9	3.6	11.2	9.9	9.9	9.9	4.6	9.9	6.9
10	3.6	4.6	4.6	9.9	10.4	5.0	10.4	7.9
13	9.2	4.6	2.0	1.2	1.2	2.0	12.5	3.3
14	2.6	6.9	1.4	1.4	1.4	1.8	12.7	6.9
15	8.6	11.5	4.3	≤1.0	1.7	1.7	12.5	2.3
16	2.3	4.4	2.4	1.2	1.2	1.9	12.2	7.9
18	1.6	2.4	2.4	≤1.0	1.5	1.8	12.6	7.9
19	≤1.0	4.6	2.6	1.3	1.8	1.8	12.5	8.2

[a] All spectra measured at 270 MHz in $CDCl_3$.

From these conformational analyses it may be concluded that the repulsion of (OMe, O-1′) is more serious than that of (NO_2, O-1′). However, the present data allow no definitive conclusion as to whether (NO_2, O-1′) is attractive or repulsive. If (NO_2, O-1′) were attractive, the α-D-*manno* isomer **8** should adopt conformation X, but since it appears more likely to prefer conformation IX, (NO_2, O-1′) may be repulsive. However, this is not conclusive, because the conformation of the nitro group was not taken into consideration.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were determined with a Horiba High Sensitivity Polarimeter (SEPA-200). ^{1}H-N.m.r. spectra were recorded at 270 MHz with a JNM-EX270 spectrometer in $CDCl_3$ with Me_4Si as internal standard. The integration values in n.O.e. difference spectra are estimated only roughly, because measurement conditions were not completely optimized. I.r. spectra were recorded from KBr pellets. Solutions were dried over $MgSO_4$ and evaporated under diminished pressure. Column chromatography was conducted on silica gel (Wakogel C-300) with 20:1 (v/v) toluene–EtOAc. Analytical samples were prepared by recrystallization from 2-propanol, unless otherwise stated.

Irradiation of **7** *in 1,3-dioxolane.* — To a solution of **7** (ref. 6, 500 mg, 1.7 mmol) in 1,3-dioxolane (50 mL, freshly distilled from $LiAlH_4$ before use) was cooled to 8° and irradiated in a Riko photoreactor with high-pressure mercury lamp in a H_2O–ethylene glycol Pyrex immersion-well for 40 h under N_2. After evaporation of the solvent, the remaining syrup was chromatographed to give successively the α-D-*manno* **8** (270 mg, 43%), α-D-*gluco* **9** (43 mg, 7%), α-D-*allo* **10** (30 mg, 5%), and 3-oxime **11** (47 mg, 10%). The oxime **11** had spectral data (i.r. and ^{1}H-n.m.r.) identical with those in the literature[3].

Physical data for **8**: m.p. 103–105°, $[\alpha]_D^{25}$ +25° (*c* 1, $CHCl_3$); ν_{max} 1560 cm^{-1} (NO_2); ^{1}H-n.m.r. (C_6D_6): δ 4.94 (br. s, 1 H, H-1), 2.94 (t, 1 H, $J_{2,2'} = J_{2,3}$ 6.0 Hz, H-2), 5.04 (dd, 1 H, $J_{3,4}$ 10.9 Hz, H-3), 4.61 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.77 (dt, 1 H, $J_{5,6a}$ 10.1, $J_{5,6e}$ 4.5 Hz, H-5), 3.57 (t, 1 H, $J_{6a,6e}$ 10.1 Hz, H-6*a*), 4.67 (dd, 1 H, H-6*e*), 5.02 (d, 1 H, H-2′), 5.42 (s, 1 H, PhCH), and 2.84 (s, 3 H, OMe).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.80; H, 5.88; N, 3.73.

Physical data for **9**: m.p. 123–124.5°, $[\alpha]_D^{25}$ +31° (*c* 0.4, $CHCl_3$); ν_{max} 1560 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.68; H, 5.90; N, 3.62.

Physical data for **10**: m.p. 158–160°, $[\alpha]_D^{25}$ +36° (*c* 1, $CHCl_3$); ν_{max} 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.80; H, 5.91; N, 3.86.

Epimerization of **10** (10 mg) with 0.2M NaOD (3 drops) in acetone-d_6 (0.4 mL) was monitored by ^{1}H-n.m.r. spectroscopy. Even after 4 days, most of **10** was unchanged. In fact, a ^{1}H-n.m.r. spectrum in $CDCl_3$ of a crude mixture, obtained by deionization with cation-exchange resin (Amberlite IR-120, H^+) after 4 days, revealed it to be mainly **10** (not deuterated at C-3), together with small amounts (<20%) of the 3-deutero derivative of **9**.

Irradiation of **12** *in 1,3-dioxolane.* — Similar photoreaction of **12** (ref. 7, 500 mg, 1.7 mmol) except for shortening the irradiation time to 28 h, followed by column chromatography with 15:1 (v/v) toluene–EtOAc, gave successively the β-D-*gulo* **13** (61 mg, 10%), β-D-*ido* **14** (31 mg, 5%), β-D-*galacto* **15** (118 mg, 19%), and β-D-*talo* isomers **16** (25 mg, 4%).

Physical data for **13**: syrup, $[\alpha]_D^{25}$ −46° (*c* 1, $CHCl_3$); ν_{max} 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.78; H, 5.52; N, 4.00.

Physical data for **14**: m.p. 138–139°, $[\alpha]_D^{25}$ −25° (*c* 1, $CHCl_3$); ν_{max} 1555 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.32; H, 5.36; N, 3.98.

Physical data for **15**: m.p. 207.5–208°, $[\alpha]_D^{25}$ +77° (*c* 1, $CHCl_3$); ν_{max} 1555 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.82; H, 5.66; N, 4.01.

Physical data for **16**: m.p. 182–184°, $[\alpha]_D^{25}$ −4° (*c* 1, $CHCl_3$); ν_{max} 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.61; H, 5,60; N, 3.68.

Almost the same results were obtained when the photoreaction was performed at −10°.

A solution of **13** (10 mg) with 0.2M NaOD (3 drops) in acetone-d_6 (4 mL) was stirred for 10 min and then deionized with cation-exchange resin (Amberlite IR-120, H^+). The ^{1}H-n.m.r. spectrum of the resulting residue showed that it was the 3-deutero derivative of **15**. The same product was obtained by similar treatment of **15** for 3 h.

Irradiation of **17** *in 1,3-dioxolane.* — The nitro alkene **17** (ref. 7, 500 mg, 1.7 mmol) was similarly irradiated for 40 h. Evaporation of the solvent gave a crystalline residue, recrystallization of which from 2-propanol gave **19**. After evaporation of the mother liquor, the resulting syrup was chromatographed to give the α-D-*ido* **18** (108 mg, 17%) and α-D-*talo* isomers **19** (total 285 mg, 46%).

Physical data for **18**: m.p. 131–133°, $[\alpha]_D^{25}$ +39° (*c* 1, $CHCl_3$); ν_{max} 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.73; H, 5.64; N, 4.00.

Physical data for **19**: m.p. 119–122°, $[\alpha]_D^{25}$ +79° (*c* 1, $CHCl_3$); ν_{max} 1550 cm^{-1} (NO_2).

Anal. Calc. for $C_{17}H_{21}NO_8$: C, 55.58; H, 5.76; N, 3.81. Found: C, 55.81; H, 5.68; N, 4.05.

To a solution of **18** (15 mg) in acetone-d_6 (0.5 mL) was added 0.2M NaOD (0.1 mL). After 13.5 h, the mixture was poured into acetone containing cation-exchange resin (Amberlite IR-120, H^+). After removal of the resin, the filtrate was concentrated to yield the 3-deutero derivative of **19** in almost quantitative yield.

Similar treatment of **19** gave the 3-deutero derivative of **19**.

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