Notes

Reactions of Nitro Sugars. 37.[1] Preparation of Nitro Olefins via Methanesulfonates

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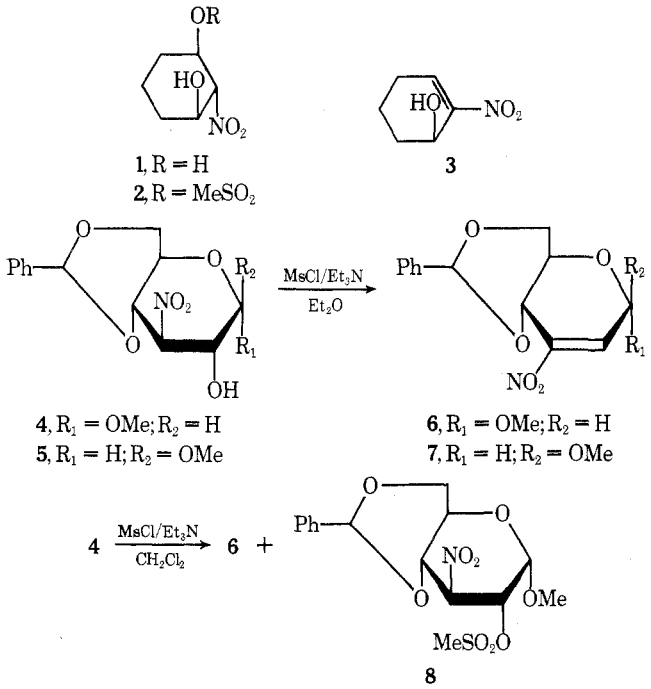
In continuation of our studies on the reactivity of nitro carbohydrates[1] we became interested in the preparation and the chemical behavior of *O*-methylsulfonyl derivatives. Such esters have not yet been described in the field of nitro sugars, and we were unable to find pertinent references in reviews[2-4] covering aliphatic nitro alcohols in general. Obviously, one should expect such mesylates to be useful intermediates for a variety of synthetic interconversions. The recent appearance of a brief note[5] reporting the dehydration of several simple nitro alcohols by the action of methanesulfonyl chloride and triethylamine (without isolation of intermediary mesylates) prompts us to disclose some results of our own work on this subject.

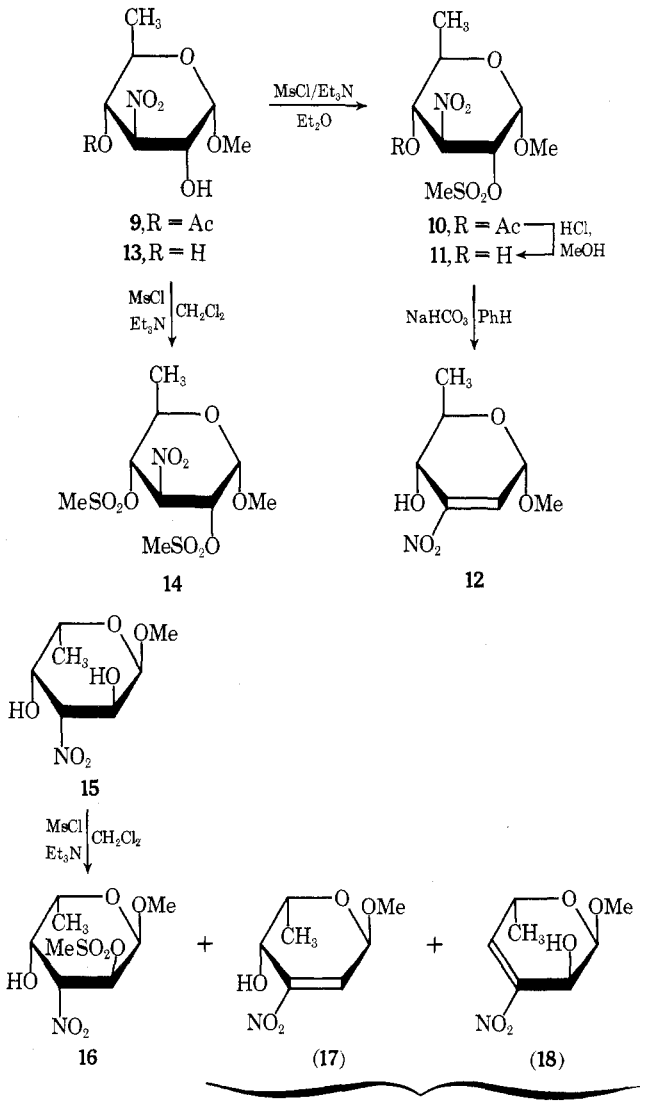
2-Nitro-1,3-cyclohexanediol (**1**), which served as a model compound, reacted with 1 molar equiv of mesyl chloride in dichloromethane, in the presence of triethylamine, to give its crystalline monomesylate (**2**) in approximately 60% yield. In addition, there seemed to arise some dimesylate (faster moving on TLC) and a small amount of olefin (**3**). Treatment of **2** with sodium bicarbonate in refluxing benzene for 3 h gave 2-nitrocyclohex-2-en-1-ol (**3**) which was readily isolated in 97% yield in this way whereas it had previously been obtained[6] by alkaline dehydration of **1** in lesser yield and only after column chromatographic purification.



Methyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-α-D-glucopyranoside (**4**) and its β anomer (**5**) were converted by mesyl chloride and triethylamine in ether (30 min at 25 °C) into the 2,3-unsaturated derivatives **6** and **7**, respectively, in yields of 80–90%. Although preparation of these nitro olefins from the alcohols by acetylation followed by dehydroacetoxylation can be done routinely,[7-9] the present procedure offers the advantage of greater simplicity and a much shorter reaction time.

In the case of the reaction of **4** we have been able to isolate intermediate 2-mesylate (**8**) in 20% yield when the reaction was carried out in dichloromethane, even though elimination giving **6** was predominant then too.

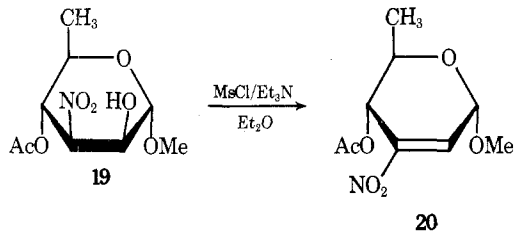
By contrast, mesylation of methyl 4-*O*-acetyl-3,6-dideoxy-3-nitro-α-D-glucopyranoside (**9**) gave in 80% yield the crystalline 2-mesylate (**10**). This product was first de-O-acetylated by acid-catalyzed methanolysis giving almost quantitatively methyl 3,6-dideoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (**11**), which was then converted into the olefin, methyl 2,3,6-trideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**12**), by means of sodium bicarbonate in refluxing benzene (3 h; yield 92%). Elimination of methanesulfonic acid could also be effected with triethylamine but this required a longer reaction time and was accompanied by browning of the reaction solution.



Mesylation of **13** (the parent glycoside of **9** lacking the 4-*O*-acetyl group) likewise proceeded without a significant de-

gree of elimination; it gave the crystalline 2,4-dimesylate **14** in 75% yield. However **14**, similar to the monomesylate **11**, did suffer elimination on treatment with sodium bicarbonate in benzene at reflux for 12 h. Although investigation of this reaction has not yet been completed,[10] it is evident and noteworthy that the mesyl esters **10**, **11**, and **14** related to the 3,6-dideoxy-3-nitro-D-glucoside **13** are more stable than those derived from the 4,6-O-benzylidenated 3-deoxy-3-nitro-D-glucosides **4** and **5**. It was therefore interesting to study the behavior of stereoisomeric 3,6-dideoxy glycosides from the galacto and manno series.

Methyl 3,6-dideoxy-3-nitro-α-L-galactopyranoside (**15**) was mesylated by use of excess reagent. The reaction was relatively sluggish and no dimesylation was observed, but the 2-mesylate **16** was obtained crystalline in 48% yield. The remainder of the product was a syrupy mixture of what appeared to be mainly two compounds that failed to separate in column chromatography. The NMR spectrum of the mixture revealed that it contained nonmesylated nitro olefins, showing signals in the olefinic proton region (δ 7.0–7.3) but not in the mesyl group region (δ 3.0); OCH_3 and C–CH_3 signals occurred in their proper places. Evidently the galactoside **15**, unlike the glucoside **13**, underwent dehydration[11] to a considerable extent during the process of mesylation, which might suggest a lesser stability of its sulfonic esters. We were therefore surprised to find that the isolated monomesylate **16** was quite resistant to elimination as it remained unchanged for 6 h in refluxing benzene or toluene in the presence of sodium bicarbonate. One is thus led to conclude that **16** was not an intermediate in the formation of the olefins. Although the structures of the latter have not been established, formulas **17** and **18** suggest themselves at first glance and if they are correct it may be assumed that elimination involving the axial functionality at C-4 proceeds quite readily to give **18**, and that **17** owes its origin to allylic rearrangement of **18** which could possibly have occurred during the chromatographic processing. This idea is supported by the behavior of methyl 4-O-acetyl-3,6-dideoxy-3-nitro-α-D-mannopyranoside (**19**) in mesylation. In strong contrast to its α-D-gluco isomer (**9**), the mannoside **19** (whose free hydroxyl group is axial) was smoothly converted into the nitro olefin **20** (yield 65%) and no intermediary mesylate could be isolated.



19 **20**

In summary, we have shown that treatment of nitro sugars with mesyl chloride and triethylamine offers an attractive route to nitro olefinic derivatives which is potentially superior to the customary acetylation–dehydroacetoxylation sequence. However, the efficacy of the method varies and appears to depend on structural and configurational features in the substrate which influence the ease of formation and stability of intermediary methanesulfonate esters.

Experimental Section

Thin layer chromatography was performed on silica gel G (E. Merck) using, unless otherwise specified, 1:2 ethyl acetate–petroleum ether (solvent A) or 5% methanol in chloroform (solvent B) as the developing phase. All column chromatographic separations were routinely monitored by TLC. The NMR data refer to 100-MHz spectra of solutions in $CDCl_3$, internally standardized with tetramethylsilane. Infrared spectra were taken from Nujol mulls unless otherwise indicated. Optical rotations were recorded at room temperature in a Perkin-Elmer 141 automatic polarimeter.

***t*-2-Nitrocyclohexane-*r*-1,*c*-3-diol Monomethanesulfonate (2).** The diol[6,12] **1** (500 mg) was dissolved in dichloromethane (7 ml), and methanesulfonyl chloride (MsCl, 0.25 ml) was added with stirring at room temperature. After 5 min triethylamine (0.5 ml) was added under cooling of the reaction vessel with cold water. After 30 min, some remnant **1** and a strong, slightly faster moving spot due to **2** were seen by TLC with ethyl acetate–carbon tetrachloride (1:1). There were two additional, faint, fast-moving spots that were not identified. Anhydrous ether (10 ml) was added, an insoluble precipitate was removed, and the clear filtrate was evaporated with addition of several portions of 1-propanol. The resulting syrup was chromatographed on a column of silica gel (10 g) by means of the above TLC eluent. The fractions containing fast-moving by-products were discarded. Subsequent fractions that contained **2** only yielded a syrup from which two portions of added propanol were evaporated. The material then crystallized on standing overnight at 25 °C, yield 445 mg (60%) of crystalline **2**: mp 81–83 °C; ν_{max} (neat syrup) 3200–3600 (OH), 1550 (NO_2), and 1165 cm^{-1} (OMs); NMR δ 4.95 (1 H, sextet, J = 10 and 5 Hz, H-1), 4.47 (1 H, t, J = 10 Hz, H-2), 4.1 (1 H, m, sextet after D_2O exchange, H-3).

Anal. Calcd for $C_7H_{13}NO_6S$ (239.2): C, 35.14; H, 5.47; S, 13.40. Found: C, 35.19; H, 5.41; S, 13.18.

2-Nitrocyclohex-2-en-1-ol (3). A solution of **2** (300 mg) in dry benzene (3 ml) was heated for 3 h at reflux in the presence of dry sodium hydrogen carbonate (0.5 g). TLC with solvent A revealed total conversion of **2** into one faster migrating product. The cooled reaction mixture was filtered and the filtrate evaporated to give **3** as a colorless oil (175 mg, 97%). Its NMR spectrum ($CDCl_3$) agreed in every respect with that of **3** obtained previously by a different method.[6]

An attempt was made to prepare **3** directly from **1**, without the isolation of **2**, by carrying out the mesylation in *ether* solution (partial suspension) using double the amounts of mesyl chloride and triethylamine. Although **1** reacted completely according to TLC, the olefin **3** produced was accompanied by a product of very similar mobility (its mesyl derivative?), and **3** could only in part be separated by chromatography (yield 40%).

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (6). Nitro glycoside[13,14] **4** (100 mg) in andydrous ether (5 ml) was treated with methanesulfonyl chloride (0.05 ml) for 15 min at 20 °C, then triethylamine (0.06 ml) was added under cooling with water, and the mixture was stirred at room temperature for 45 min. At this time TLC (solvent A) indicated conversion of most of **4**, and the reaction was allowed to proceed for another 30 min. The supernatant solution was then decanted from a sticky, brown precipitate, washed with saturated, aqueous sodium bicarbonate solution followed by water, and dried over Na_2SO_4. Evaporation gave crystalline **6** (84 mg, 90%), mp 183–184 °C, undepressed upon admixture af authentic[7] **6**. The NMR spectrum was superimposable on that of authentic **6**.

Methyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (8). To nitro glycoside **4** (200 mg) in dichloromethane (3 ml) was added MsCl (0.06 ml) and, after 5 min, triethylamine (0.08 ml) was added with stirring and external cooling by cold water. After 5 min, TLC (solvent A) showed a spot of **8** together with a stronger spot of faster moving **6**. Anhydrous ether (10 ml) was added to the reaction mixture which was stirred at 0 °C for 15 min; the precipitate was then removed by filtration and the filtrate evaporated to give a partially crystalline residue from which two portions of propanol were evaporated. The mixture was chromatographed on silica gel (7 g) with solvent A. This gave first **6** (123 mg, 65%), mp 183 °C, and secondly, **8** (50 mg, 20%): mp 215–216 °C; $[\alpha]_D$ +73.1° (*c* 0.6, chloroform); NMR δ 7.40 (5 H, Ph), 5.55 (1 H, s, PhCH), 5.1 region (3 H, unresolved, H-1, -2, -3), 4.37 (1 H, q, H-6, $J_{5,6}$ = 3, $J_{6,6'}$ = 9 Hz), 4.15 (m, 1 H, H-5), 3.7–4.0 (2 H, H-4 and -6′), 3.54 (3 H, s, OCH_3), 3.03 (3 H, s, OMs).

Anal. Calcd for $C_{15}H_{19}NO_9S$ (389.4): C, 46.26; H, 4.91; S, 8.23. Found: C, 46.10; H, 4.77; S, 8.15.

Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (7). From the nitro glycoside[8,9,14] **5** (200 mg), the olefin **7** (74 mg, 78.5%) was obtained by exactly the same procedure as described above for **6**; the product was identified with an authentic sample[8,9] by an undepressed mixture melting point, 142–144 °C.

Methyl 4-*O*-Acetyl-3,6-dideoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (10). To a stirred solution of the 4-acetate[15] **9** (1.0 g) in anhydrous ether (15 ml) was added MsCl (0.5 ml) and, after 5 min, triethylamine (1.0 ml). The mixture was stirred for 10 min, after which **9** proved completely converted into **10** (TLC with solvent A). The solution was decanted from a sticky precipitate and evaporated to dryness with several additions of 1-propanol. The re-

maining syrup crystallized upon trituration with hexane. Recrystallized from ethyl acetate–petroleum ether, compound **10** (1.05 g, 80%) showed mp 161 °C; $[\alpha]_D$ +154° (*c* 1, chloroform), ν_{max} 1740 (OAc), 1560 (NO_2), and 1175 cm^{-1} (OMs); NMR δ 5 region (4 H, ring protons, unresolved), 3.88 (1 H, m, H-5), 3.50 (3 H, s, OCH_3), 3.01 (3 H, s, OMs), 2.10 (3 H, s, OAc), 1.24 (3 H, d, J = 6.5 Hz, C–CH_3).

Anal. Calcd for $C_{10}H_{17}NO_9S$ (327.3): C, 36.69; H, 5.23; S, 9.79. Found: C, 36.82; H, 5.25; S, 9.81.

Methyl 3,6-Dideoxy-2-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (11). A solution of the 4-acetate **10** (900 mg) in acetone (1 ml) and 3% methanolic hydrogen chloride (9 ml of a solution that had been made by adding 1 ml of acetyl chloride to 20 ml of dry methanol) was kept at 40–50 °C for a few hours until TLC (solvent B) showed absence of starting material and sole presence of one new spot. The reaction mixture was then evaporated to give a brownish syrup which was passed through a 10-g silica gel column with ether to remove colored impurities. Evaporation of the effluent gave 772 mg of **11** which was recrystallized from ethyl acetate–petroleum ether to give pure **11** (768 mg, 98%): mp 106–107 °C; $[\alpha]_D$ +148° (*c* 1, chloroform); ν_{max} 3500 (OH), 1560 (NO_2), and 1170 cm^{-1} (OMs); NMR δ 3.49 (3 H, s, OMe), 3.03 (3 H, s, OMs), 1.36 (3 H, d, J = 6 Hz, C-Me).

Anal. Calcd for $C_8H_{15}NO_8S$ (285.3): C, 33.68; H, 5.30, S, 11.24. Found: C, 33.80; H, 5.30; S 11.39.

Methyl 2,3,6-Trideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (12). A solution of **11** (700 mg) in benzene (5 ml, dried over CaH_2) and dry sodium bicarbonate (2.5 g) were heated overnight at reflux. The mixture was allowed to cool, then filtered, and the filter residue was washed twice with chloroform. The combined filtrate was evaporated to give a brown syrup that was decolorized by passage through a 15-g silica gel column with ether. Evaporation of the effluent gave crude crystalline **12** which was recrystallized from chloroform–petroleum ether. The yield of pure **12** was 427 mg (92%), mp 124–125 °C (reported[17] for the L enantiomer, 124–125 °C). The NMR data of **12** were identical with those described[17] for its L enantiomer.

Methyl 3,6-Dideoxy-2,4-di-*O*-methylsulfonyl-3-nitro-α-D-glucopyranoside (14). The glucoside[15] **13** (200 mg) in dichloromethane (10 ml) was treated with MsCl (0.08 ml, 1 molar equiv) and triethylamine (0.14 ml) as described for previous experiments. After a reaction time of 5 min there was no change visible in TLC (solvent A). Therefore, five additional 0.08-ml portions of MsCl and equivalent amounts of triethylamine were added in 5-min intervals, without cooling. Eventually progress of reaction resulting in complete consumption of **13** was noted. Ether was then added to the reaction mixture to precipitate salt which was removed. On evaporation the filtrate gave a brownish residue which was repeatedly evaporated with 1-propanol until the smell of MsCl was no longer noticeable. The residue then crystallized copiously upon trituration with ice water. The material was washed with cold water, dissolved in ethyl acetate, dried with Na_2SO_4, and recrystallized by addition of petroleum ether. The yield was 260 mg (74%): mp 132–132.5 °C; $[\alpha]_D$ +110.5° (*c* 0.4, chloroform); ν_{max} 1555 (NO_2), 1170 cm^{-1} (OMs); NMR δ 4.7–5.1 (4 H, ill resolved, H-1, -2, -3, -4), 3.93 (octet, 1 H, H-5, $J_{4,5}$ = 10, $J_{5,6}$ = 6 Hz), 3.51 (s, 3 H, OMe), 3.01 and 3.03 (2 s, 6 H, 2 OMs), 1.44 (d, 3 H, J = 6 Hz, C-Me).

Anal. Calcd for $C_9H_{17}NO_{10}S_2$ (363.4): C, 29.74; H, 4.71; S, 17.64. Found: C, 29.73; H, 4.79; S, 17.66.

Methyl 3,6-Dideoxy-2-*O*-methylsulfonyl-3-nitro-α-L-galactopyranoside (16). The galactoside[16] **15** (300 mg) in dichloromethane (7 ml) was treated with MsCl (0.1 ml) and triethylamine (0.2 ml in 1 ml of dichloromethane). The mixture was stirred for 90 min at 25 °C, after which period TLC (solvent A) indicated reaction to be incomplete. When the TLC pattern remained unchanged after 4 h, a second and a third set of MsCl and TEA were added with a 30-min interval. This caused the reaction to become nearly complete, with only a trace of **15** remaining. Final addition of a fourth set of reagent portions resulted in complete disappearance of **15.** There was one major product spot (**16**) and a quite strong spot that migrated faster (and was seen, by application of another solvent, to be inhomogeneous). The reaction mixture was partially evaporated to a volume of 5 ml, ether (10 ml) was added, and the mixture was kept in a refrigerator for 2 h and then filtered. The filtrate was evaporated with several additions of 1-propanol, and the resulting syrup was chromatographed on silica gel (10 g) using chloroform as eluent. Fractions containing fast-moving material yielded a thick oil (135 mg) which was seen by TLC (with chloroform) to consist of two components moving close together. The NMR spectrum of the oil suggested the presence of two nonmesylated, unsaturated glycosides, one of which appeared to preponderate. There were signals (total intensity 1 H) in the δ 7.0–7.3 region (nitro olefinic protons), unresolved signals (4 H) at δ 3.6–5.3, two 3 H signals close together near δ 3.5 (OCH_3), and two overlapping 3 H doublets centered at δ 1.5 (C–CH_3). Further elution of the column gave syrupy **16** which crystallized on standing for a few hours: large plates (200 mg, 48%); mp 175–176 °C; $[\alpha]_D$ −206.6° (*c* 0.2, chloroform); ν_{max} 3570 (OH), 1555 (NO_2), 1160–1170 cm^{-1} (OMs); NMR δ 5.30 (1 H, q, $J_{1,2}$ = 3.7, $J_{2,3}$ = 11 Hz, H-2), 5.13 (1 H, d, H-1), 4.92 (1 H, q, $J_{3,4}$ = 3 Hz, H-3), 4.4 (1 H, m, H-4), 4.13 (1 H, q, H-5), 3.50 (3 H, s, OCH_3), 3.14 (3 H, s, OMs), 1.32 (3 H, d, J = 7 Hz, C–CH_3).

Anal. Calcd for $C_8H_{15}NO_8S$ (285.3): C, 33.68; H, 5.30; S, 11.24. Found: C, 33.54; H, 5.19; 11.12.

Attempted elimination of the mesyloxy group by refluxing **16** in the presence of sodium bicarbonate in benzene or toluene for 6 h was unsuccessful. The compound remained unchanged.

Methyl 4-*O*-Acetyl-2,3,6-trideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (20). The 4-acetate[15] **19** (100 mg) in anhydrous ether (5 ml) and MsCl (0.02 ml) were stirred for 15 min after which triethylamine (0.5 ml) was added with water cooling. Stirring was continued for 45 min at room temperature. Processing of the mixture as previously described furnished crude **20** as a yellowish syrup which after purification by passage through silica gel (5 g) gave crystalline **20** (60 mg, 65%), mp 81–82 °C (reported[17] for L enantiomer, 81–81.5 °C).

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Registry No.—**1**, 38150-01-5; **2**, 59790-62-4; **3**, 51254-77-4; **4**, 3650-60-0; **5**, 25541-57-5; **6**, 16697-51-1; **7**, 25541-58-6; **8**, 59734-05-3; **9**, 59790-63-5; **10**, 59790-64-6; **11**, 59790-65-7; **12**, 59790-66-8; **13**, 43138-55-2; **14**, 59790-67-9; **15**, 22224-31-3; **16**, 59790-68-0; **19**, 59790-69-1; **20**, 59790-70-4; methanesulfonyl chloride 124-63-0.

References and Notes

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(10) Thin layer chromatography of the reaction mixture showed two major, poorly separated spots which most likely represented isomeric monomesyl nitro olefins. In addition there were some minor spots.
(11) An enhanced tendency for dehydration in the 3-deoxy-3-nitro galactopyranose system, to give 2,3 unsaturation, has been noted and commented upon previously: H. H. Baer and W. Rank, *Can. J. Chem.*, **47**, 2811 (1969).
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(15) We prepared methyl 3,6-dideoxy-3-nitro-α-D-glucopyranoside (**13**) and its α-D-manno isomer from methyl 6-deoxy-α-D-glucopyranoside according to the method detailed for the corresponding L enantiomers (ref 16). Their 4-acetates **9** and **19** were then prepared also as described for the respective L enantiomers (ref 17).
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Solid-State Conformations of Vitamin D_3

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Discoveries within the last 10 years of active metabolites and synthetic analogues of vitamins D_2 (ergocalciferol) and D_3 (cholecalciferol) have stimulated much research in this area