Synthesis of Dideoxy Sugars by Triflate Rearrangement

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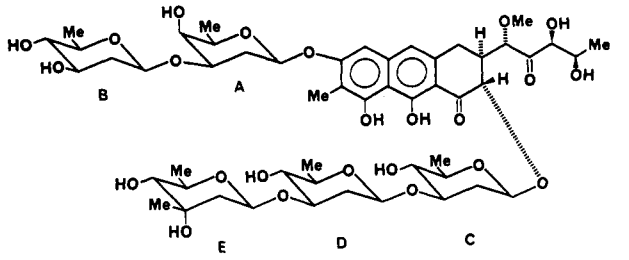
A recently discovered rearrangement of carbohydrate triflates provides a basis for an efficient synthesis of a group of partially protected 2,6-dideoxy sugars, which are potentially useful in the preparation of several anticancer agents. Reaction of methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**4**) with triflic anhydride converts it into the corresponding triflate **12**, a compound that rearranges at room temperature into another extremely reactive triflate **13**. Reaction of **13** with water produces methyl 4-*O*-benzoyl- and 3-*O*-benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranosides (**7** and **8**), while treatment of **13** with tetrabutylammonium nitrate gives methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (**16**). Photolysis of **16** in methanol converts it into methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*xylo*-hexopyranoside (**9**). Reaction of methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**3**) with triflic anhydride produces the corresponding triflate **20**, which rearranges to **21**. Treatment of **21** with water produces methyl 4-*O*-benzoyl- and 3-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranosides (**5** and **6**), respectively.

A number of naturally occurring, biologically active compounds contain 2,6-dideoxy sugar residues. These compounds include the anticancer agents mithramycin (**1**), chromomycin A_3, and olivomycin A as well as many of the cardiac glycosides such as digitoxin (**2**) and digoxin.[1,2] The



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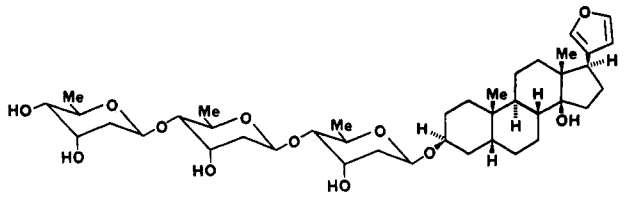

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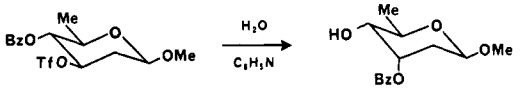
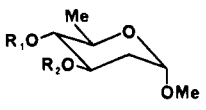
search for more effective and less toxic analogues of these compounds has stimulated interest in their syntheses[3-7] and in the synthesis of related structures.[7,8] Such projects can require significant quantities of partially protected 2,6-dideoxy-D-hexoses. Since it is desirable that partial protection in these hexoses include a base removable group attached to O-3 or O-4, synthesis of *O*-benzoyl derivatives of the four possible methyl 2,6-dideoxy-D-hexopyranosides was undertaken. There were two reasons for choosing these particular compounds, other than their satisfying the basic structural requirements. First, a procedure for synthesis of significant quantities of one of them, methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**3**),[9] already was in use in our laboratory.[10] Second, a recently reported rearrangement involving carbohydrate triflates in which simultaneous inversion of configuration and *O*-benzoyl migration were taking place (eq 1)[10,11] promised relatively simple conversion of **3** into most of the desired compounds (**4**–**10**).



(1)

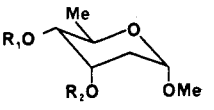
Results and Discussion

It appeared from the outset that compound **3** could be converted (by rearrangement analogous to that shown in eq 1) directly into the 2,6-dideoxy-α-D-*ribo* system found in the hexopyranosides **5** and **6**. It was less certain, however, that **3** could be converted easily into the re-



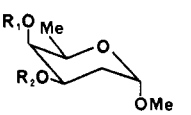
3 R_1 = Bz, R_2 = H

4 R_1 = H, R_2 = Bz



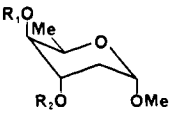
5 R_1 = Bz, R_2 = H

6 R_1 = H, R_2 = Bz



7 R_1 = Bz, R_2 = H

8 R_1 = H, R_2 = Bz



9 R_1 = Bz, R_2 = H

10 R_1 = H, R_2 = Bz

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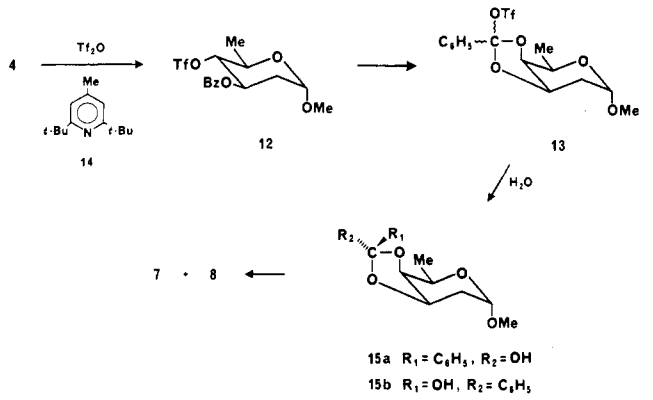
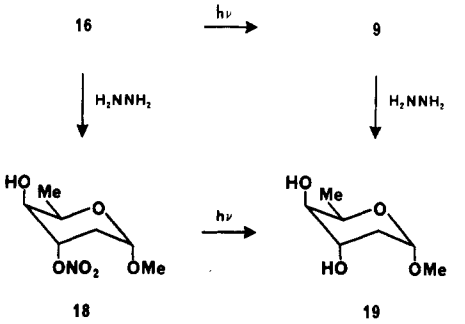
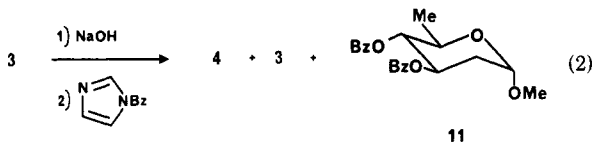
Scheme I



Scheme II



maining compounds, unless the *O*-benzoyl group could be moved to the adjacent oxygen atom [i.e., **3** transformed into methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**4**)]. In that event, a combination of triflate rearrangement, nucleophilic substitution, and photochemical reaction appeared likely to produce the dideoxy sugar derivatives **7–10**. An essential step, therefore, was to establish a convenient procedure for conversion of **3** into **4**. This transformation was accomplished by de-*O*-benzoylation of **3** followed by regioselective reintroduction of the benzoyl group at O-3 using *N*-benzoylimidazole, according to the procedure reported by Carey and Hodgson[12] (eq 2). This process gave **4** in 85% yield along with minor amounts of compound **3** (5%) and methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**11**; 9%).

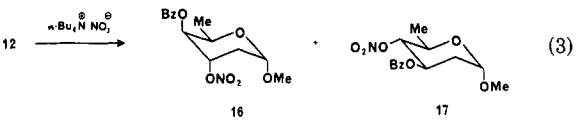


(2)

Treatment of **4** with triflic anhydride quantitatively formed methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-[(trifluoromethyl)sulfonyl]-α-D-*arabino*-hexopyranoside (**12**), a compound that rearranged at room temperature into the new and quite reactive triflate **13** (Scheme I). Compound **13** reacted rapidly even with weak nucleophiles and, therefore, was generated in the absence of moisture and in the presence of the nonnucleophile base 2,6-di-*tert*-butyl-4-methylpyridine (**14**). Even under these conditions decomposition of **13** into a black insoluble material occurred in 2 days. Reaction of **13** with water resulted in the formation of two compounds, methyl 4-*O*-benzoyl- and 3-*O*-benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranosides (**7** and **8**), in 70% and 21% yields, respectively (Scheme I). The preferential formation of **7**, a product with an axial benzoyloxy group, was expected since transformations such as that shown in Scheme I, where an ortho acid is a probable intermediate, are known to proceed in this manner.[10,11,13,14] The explanation for the regioselectivity in this reaction is that the ortho acid formed in greatest amount should have the benzylic hydroxyl group exo to the pyranoid ring (as in compound **15a**) and that ring opening from such a compound (**15a**) should favor, on the basis of stereoelectronic effects, the structure with an axial benzoyloxy group, that is, compound **7**.[15]

Although the nonnucleophilic base **14** was used in the reactions shown in Scheme I, this base was necessary only if direct observation of the triflate **13** was desired, otherwise, a simpler procedure was followed. This alternate approach involved pyridine as the base and called for the addition of water to the reaction mixture as soon as formation of the triflate **12** was complete. The yield of **7** and **8** by either procedure was the same.

Reaction of **12** with tetrabutylammonium nitrate gave methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (**16**) in 84% yield along with a small amount (7%) of methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-nitro-α-D-*arabino*-hexopyranoside (**17**) (eq 3). Although direct



(3)

displacement of the triflyloxy group in **12** by the nitrate ion was a possibility, the location of the substituents and the stereochemistry at C-3 and at C-4 in compounds **16** and **17** precluded such a reaction. Formation of these products required rearrangement to **13** prior to nucleophilic attack. Regioselective formation of the 3-*O*-nitro derivative **16** would be predicted from reaction of nitrate ion at the sterically less hindered 3-position in **13**.

Photolysis of nitrates, an established procedure for their deprotection,[16] was used to complete the synthesis of **9**. Irradiation of **16** in methanol gave methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*xylo*-hexopyranoside (**9**) as the sole reaction product (Scheme II). This reaction provided a clear example of the value of photochemical deprotection of nitrates, because the nitro group was removed while the benzoyl group remained in place. Nucleophilic reagents commonly are used for nitrate deprotection; however, these reagents (e.g., hydrazine) generally react more rapidly with carboxylic acid esters than with nitrates. This situation is illustrated by the treatment of **16** with hydrazine, which regioselectively removes the benzoyl group to produce methyl 2,6-dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (**18**); thus, complete flexibility exists in the order in which *O*-benzoyl and *O*-nitro groups can be removed for compound **16**. Finally, photolysis of **18** gave methyl 2,6-dideoxy-α-D-*xylo*-hexopyranoside (**19**) (Scheme II), as does prolonged treatment of **9** with hydrazine.

The final compounds to be synthesized were methyl 4-*O*-benzoyl- and 3-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranosides (**5** and **6**, respectively). Although it seemed likely, on the basis of the reaction shown in eq 1, that

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Table I. ^{1}H NMR Spectral Data

	4	5	6	7	8	9	12	13	16	17	18
					Chemical Shifts[a]						
H-1	4.79	4.86	4.70	4.89	4.86	4.92	4.77	4.77	4.86	4.81	4.71
H-2a	1.87	2.15–	1.98	1996	2.30	2.19	1.86	2.80	2.35	1.90	2.31
H-2e	2.32	2.04	2.31	1.96	1.96	1.89	2.53	2.34	2.06	2.54	1.95
H-3	5.33	4.22	5.38	4.30	5.40	3.98	5.64	6.37	5.24	5.51	5.13
H-4	3.39	4.76	3.55	5.28	3.92	5.01	4.77	6.17	5.12	5.12	3.59
H-5	3.77	4.29	4.12	4.04	4.03	4.41	4.08	4.36	4.35	3.96	4.18
H-6	1.35	1.28	1.32	1.20	1.29	1.24	1.41	1.33	1.23	1.34	1.24
OMe	3.35	3.42	3.36	3.364	3.35	3.43	3.37	3.35	3.39	3.36	3.55
Ar	8.15–8.01	8.16–8.04	8.10–8.00	8.16–8.04	8.10–7.98	8.15–9.03	8.13–8.01	8.34–7.51	8.16–8.04	8.01–8.00	
	7.53–7.26	7.53–7.26	7.50–7.41	7.56–7.41	7.92–7.40	7.55–7.26	7.53–7.41		7.57–7.45	7.50–7.41	
					Coupling Constants (Hz)						
1,2a	3.6		3.4	2.0	3.5	3.4	3.7	6.1	4.0	3.6	4.1
1,2e	1.4		1.4	2.4	1.3		1.1	6.8	1.0	1.3	1.0
2a,2e	12.9		15.2		12.7	14.6	13.0	17.0	15.5	13.0	15.8
2a,3	11.5		3.1	8.5	11.5	3.4	11.4	2.5	4.0	11.1	4.0
2e,3	5.4		3.6	8.5	6.1	3.0	5.5	2.5	4.0	5.3	3.5
3,4	9.0	2.8	3.4	2.9	2.7	3.0	8.9	9.0	3.4	9.8	3.0
4,5	9.3	9.8	9.5			1.4	9.5	1.0		9.6	1.0
5,6	6.0	6.2	6.3	6.6	6.6	6.6	6.2	6.3	6.6	6.2	6.7

[a] Chemical shifts are relative to Me_4Si (δ 0).

Table II. ^{13}C NMR Spectral Data

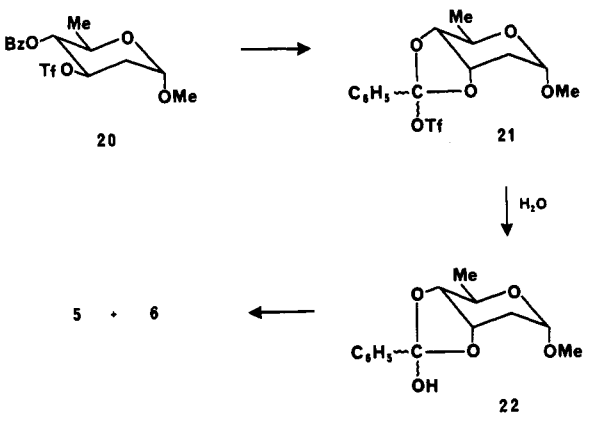
	3	4	5	6	7	8	9	11	12	13	16	17	18
C-1	98.03	97.51	98.50	96.87	98.95	98.51	99.03	98.08	97.67	96.15	96.72	97.82	96.76
C-2	37.82	34.83	35.33	33.47	33.00	29.32	30.62	35.53	35.98	37.43	28.30	35.89	27.36
C-3	66.94[a]	74.87[a]	61.22	72.14[a]	65.03[a]	70.14[a]	60.63	70.00	68.95	89.40[a]	68.13	69.16	77.76
C-4	79.05	72.64[a]	75.39	69.93[a]	73.56	69.13[a]	72.06	75.09	87.25	87.01[a]	75.13	83.22	61.98
C-5	65.27[a]	67.52	65.55	64.23	64.88[a]	65.68	65.32	65.94	64.87	62.77	61.59	64.42	66.73
C-6	17.41	17.39	17.54	17.64	16.89	16.64	16.47	17.73	17.64	14.95	16.30	17.57	16.07
OMe	54.42	54.11	55.10	54.99	54.93	54.88	55.21	54.86	55.08	55.29	55.33	55.00	55.27
C=O	166.49	166.37	165.72	166.55	167932	166.00	165.59	165.87	167.52		165.47		
Ar	128.12	127.89	128.25	128.30	128.44	128.41	128.34	128.31	128.46	130.30	128.65	128.54	
Ar	129.50	129.31	129.64	129.75	129.74	129.72	129.63	128.36	130.01	133.69	129.92	129.66	
Ar	132.96	129.61	129.91	133.00	129.90	133.14	133.08	129.69	133.44	140.99	133.67	133.37	
Ar		132.66	132.99		133.24			132.93					

[a] These assignments in each column may be reversed.

methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**6**) would be formed by reaction of methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-[(trifluoromethyl)sulfonyl]-α-D-*arabino*-hexopyranoside (**20**) with water (Scheme III), it was possible that the presence of the α-methoxy group at C-1 in **22** might make the formation of **6** sufficiently difficult that methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**5**) would be produced. When **20** was formed, allowed to rearrange, and then treated with water, **5** and **6** both were isolated (in 15 and 80% yields, respectively); thus, while the configuration at C-1 in **22** may have had some effect on final product formation, the influence was not large. As with other reactions of this type, the major product had the benzoyloxy group with an axial orientation.

The situation with respect to synthesis of the eight possible methyl *O*-benzoyl-2,6-dideoxy-α-D-hexopyranosides (**3–10**) can be summarized in the following way. All but one of these compounds (**10**) now has been prepared. Triflate rearrangement in combination with nucleophilic substitution and photochemical reaction provides an attractive procedure for formation of several of the potentially most useful of these hexopyranosides. For example, the lyxo derivative **7** has the proper stereochemistry and group protection to be introduced as ring A in the synthesis of mithramycin (**1**) and related compounds, while the ribo derivative **6** is suited for incorporation into the synthesis of digitoxin (**2**) and its analogues. In fact, other than compound **3**, the only member of this group of hexopyranosides (**3–10**) that has been prepared previously (by a different route) is compound **6**, which was synthesized to study formation of digitoxin (**2**) analogues.[17]

Scheme III



Experimental Section

^{1}H and ^{13}C NMR spectra were obtained from a Varian FT-80A spectrometer and are given in Tables I and II, respectively. Photochemical reactions were conducted under nitrogen using a Rayonet RPR-100 photochemical reactor equipped with 16 RPR-2537 A lamps. Chromatography was done on a 2.5 × 15 cm column packed with Baker 230–400mesh silica gel and eluted with

(17) Garegg, P. J.; Kopper, S.; Ossowski, P.; Thiem, J. *J. Carbohydr. Chem.* **1986**, *5*, 59.

hexane–ethyl acetate (3:1), unless otherwise noted. Thin-layer chromatography was done using Whatman MK6F silica gel plates, which were developed with hexane–ethyl acetate (3:1).

Synthesis of Methyl 3-*O*-Benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (4). Methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside[9] (3; 6.04 g, 0.0227 mol) was dissolved in 100 mL of methanol, and 0.4 g of NaOH was added. The reaction mixture was stirred and monitored by TLC. After 1 h, 2.0 g of Dowex 50W-X8 (acidic ion-exchange resin) was added, and stirring was continued until the reaction mixture was no longer basic (litmus). The ion-exchange resin was removed by filtration, and the solvent was distilled under reduced pressure. After the methanol had been removed, the residue was dissolved in 100 mL of anhydrous dichloromethane, and 5.2 g (0.03 mol) of *N*-benzoylimidazole, prepared according to the procedure of Carey and Hodgson,[12] in 100 mL of dichloromethane was added slowly to the reaction mixture, which was stirred and monitored by TLC. After 5 h, 2-mL of water was added, and the reaction mixture was stirred vigorously for an additional 10 min. The reaction mixture then was extracted twice with 25-mL portions of 5% HCl and twice with 25-mL portions of saturated sodium bicarbonate and filtered through Celite, and the solvent was evaporated. Chromatography of the residue under the standard conditions, except that a 5 × 15 cm column was used, gave three substances. The first compound eluted from the column (R_f 0.87) was methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (11; (0.75 g, 2.0 mmol, 9%), mp 91–93 °C (lit.[18] mp 93–94 °C). The ^{1}H NMR spectrum of this material was the same as that reported in ref 18. The second product (R_f 0.64) was methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (4; 5.13 g, 19.3 mmol, 85%), which solidified and was recrystallized from hexane; mp 86–88 °C. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.91; H, 6.77. The ^{1}H NMR spectrum of 4 was the same as that reported for its enantiomer.[19] The final material obtained from the column (R_f 0.44) was compound 3 (0.29 g, 1.1 mmol, 5%).

Synthesis and Rearrangement of Methyl 3-*O*-Benzoyl-2,6-dideoxy-4-*O*-[(trifluoromethyl)sulfonyl]-α-D-*arabino*-hexopyranoside (12). Compound 4 (0.32 g, 1.2 mmol) and 0.42 g (2.0 mmol) of 2,6-di-*tert*-butyl-4-methylpyridine (14) were dissolved in 3 mL of $CDCl_3$. Triflic anhydride (0.42 g, 1.5 mmol) in 1 mL of $CDCl_3$ was added slowly to the stirred reaction mixture, which was maintained at 20 °C. After 15 min, TLC revealed that the starting material had reacted. The solution was filtered, and NMR spectra of the reaction mixture were obtained immediately. Only a single new compound, identified as methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-[(trifluoromethyl)sulfonyl]-α-D-*arabino*-hexopyranoside (12), could be detected from analysis of these spectra (Tables I and II). Compound 12 was an unstable material that after 8 h had rearranged to compound 13, an extremely reactive new triflate that also was identified by analysis of its NMR spectra.

Synthesis of Methyl 4-*O*-Benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (7) and Methyl 3-*O*-Benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (8). A. From Compound 13. Addition of water to the solution of 13, prepared as described above, caused immediate reaction. Evaporation of the solvent under reduced pressure and chromatography of the residue gave two compounds, in addition to the base 14. The first compound eluted from the column (R_f 0.27), mp 90–91 °C, was identified as methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (8; 67 mg, 0.25 mmol, 21%) on the basis of its NMR spectra and its analytical data. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.99;, H, 6.90. This material had an ^{1}H NMR spectrum identical with that reported for its enantiomer.[20] The second compound eluted from the column was methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (7; 223 mg, 0.84 mmol, 70%). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.22; H 6.90.

B. From Compound 4. Compound 4 (1.50 g, 5.6 mmol) and 2.5 mL of pyridine were dissolved in 20 mL of dichloromethane. The reaction mixture was cooled to −20 °C (dry ice and carbon tetrachloride), and a solution of 2.26 g (8.0 mmol) of triflic anhydride in 5 mL of dichloromethane was added dropwise to the stirred solution. After addition was complete, the cooling bath was removed and the reaction mixture allowed to warm to room temperature over a period of 1 h. Water (1 mL) was added to the reaction mixture and stirring was continued for 24 h. The solvent was evaporated under reduced pressure and the residue chromatographed as described above to give compounds 7 and 8 in 70 and 21% yields, respectively.

Synthesis of Methyl 4-*O*-Benzoyl-2,6-dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (16) and Methyl 3-*O*-Benzoyl-2,6-dideoxy-4-*O*-nitro-α-D-*arabino*-hexopyranoside (17). Compound 4 (1.47 g, 6.5 mmol) and 1.5 mL of pyridine were dissolved in 20 mL of dichloromethane and cooled to −20 °C. Triflic anhydride (2.82 g, 10 mmol) in 10 mL of dichloromethane was added dropwise to the stirred solution. After the addition was complete and the reaction mixture had warmed to room temperature (1 h), 3.0 g (10 mmol) of solid tetrabutylammonium nitrate was added to the reaction mixture in one addition. The reaction mixture was stirred until solution was complete and then allowed to stand for 24 h. After distillation of the solvent under reduced pressure, the residue was dissolved in 100 mL of ethyl ether and extracted with water (3 × 25 mL). The ether solution was filtered through a 2-cm bed of silica gel, which was washed with 50 mL of ether, and the solvent distilled to leave a yellow liquid. Chromatography of the liquid in the standard manner, except that the ratio of hexane to ethyl acetate was 9:1, separated it into two components. The first compound (R_f 0.37) was identified as methyl 3-*O*-benzoyl-2,6-dideoxy-4-*O*-nitro-α-D-*arabino*-hexopyranoside (17; 0.14 g, 0.46 mmol, 7%) from analysis of its NMR spectra and its subsequent conversion into 4. The second compound (R_f 0.25) was identified as methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (16; 1.65 g, 5.46 mmol, 84%) from analysis of its NMR spectra, its conversion into compound 9 (see below), and its elemental analysis. Anal. Calcd for $C_{14}H_{17}NO_7$: C, 54.01; H, 5.52. Found: C, 53.76; H, 5.55.

Synthesis of Methyl 4-*O*-Benzoyl-2,6-dideoxy-α-D-*xylo*-hexopyranoside (9). Compound 16 (1.50 g, 4.81 mmol) and 0.40 g (4.80 mmol) of sodium bicarbonate were dissolved in 200 mL of methanol, purged with nitrogen for 1 h, and irradiated for 5 h with continued purging. After irradiation, the solvent was distilled under reduced pressure and the residue extracted with chloroform. The chloroform extract was filtered through a 1-cm bed of silica gel, which was washed with chloroform. The solvent was distilled under reduced pressure to give 1.15 g (4.33 mmol, 90%) of methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*xylo*-hexopyranoside (9), mp 71–73 °C. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.35; H, 6.90. The structure of this material was determined by analysis of its NMR spectra and was confirmed by conversion of 9 into methyl 2,6-dideoxy-α-D-*xylo*-hexopyranoside[21] (19) as described below.

Reaction of Methyl 4-*O*-Benzoyl-2,6-dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (16) with Hydrazine. Compound 16 (0.75 g, 2.4 mmol) was dissolved in a mixture of 2 mL of hydrazine hydrate and 18 mL of methanol. The reaction mixture was stirred for 10 h, the solvent removed under reduced pressure, and the residue chromatographed in the standard fashion to give methyl 2,6-dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (18; 0.27 g, 1.3 mmol, 55%), mp 96–97 °C. This material was identified from its NMR spectra and its conversion into methyl 2,6-dideoxy-α-D-*xylo*-hexopyranoside (19), as described below. When reaction was conducted in the same fashion except that the reaction time was extended to 7 days, 16 gave 19 (0.13 g 0.082 mmol, 34%), identical in NMR spectra with that reported.[21]

Photolysis of Methyl 3-*O*-Benzoyl-2,6-dideoxy-4-*O*-nitro-α-D-*arabino*-hexopyranoside (17) and of Methyl 2,6-Dideoxy-3-*O*-nitro-α-D-*xylo*-hexopyranoside (18). Photolysis of compound 17, under the same conditions as those described above for photolysis of 16, produced compound 4. Photolysis of compound 18 in a like manner produced 19.

Synthesis of Methyl 4-*O*-Benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (5) and Methyl 3-*O*-Benzoyl-2,6-dideoxy-

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α-D-*ribo*-hexopyranoside (6). Compound 3 (1.33 g, 5.0 mmol) and 1.8 mL (15 mmol) of pyridine were dissolved in 30 mL of dichloromethane and cooled to −20 °C. Triflic anhydride (2.0 g, 70 mmol) in 10 mL of dichloromethane was added dropwise to the stirred solution. After addition was complete, the reaction mixture was allowed to warm to room temperature over a period of 1 h, and 1 mL of water was added. Stirring was continued for 14 h, and then the solvent was removed by distillation under reduced pressure. The residue was separated by chromatography into two components. The first of these (R_f 0.35) was a syrup, identified as methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (6; 1.07 g, 4.0 mmol, 80%) on the basis of its NMR spectra and its elemental analysis. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.19; H, 6.99. The second compound (R_f 0.26) was identified as methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (5; 21 mg, .8 mmol, 16%) on the basis of its NMR spectra.

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Total Synthesis of 2,6-Dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol Hydrochloride: A Potent Inhibitor of α-Glucosidases†

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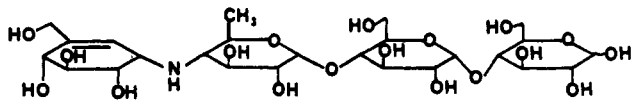
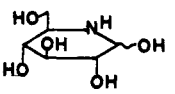
2,6-Dideoxy-2,6-imino-7-*O*-β-D-glucopyranosyl-D-*glycero*-L-*gulo*-heptitol hydrochloride (8), a potent inhibitor of α-glucosidases, has been synthesized. Homologation at C1 coupled with amination at C5 of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1) furnished the protected amine 4. A stereospecific intramolecular cyclization of compound 4, catalyzed by mercuric acetate, constituted the key step of the reaction sequence. Glycosylation of the aglycon 6 with acetobromoglucose yielded, after deprotection, the target glucoside 8.

Introduction

The inhibition of intestinal α-glucosidases has recently been demonstrated to be a useful adjunctive therapy for serum glucose control in diabetes mellitus.[1] Several potent α-glucosidase inhibitors had been isolated from bacterial sources,[2] e.g., acarbose (Bayer g 5421) from *Actinoplanes* SE 50 and nojirimycin from *Streptomyces roseochromogenes* R-468.



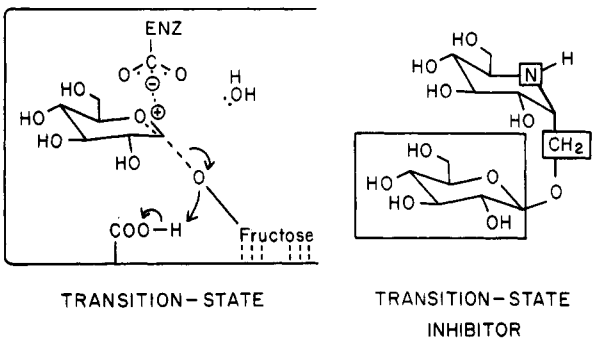
Acarbose



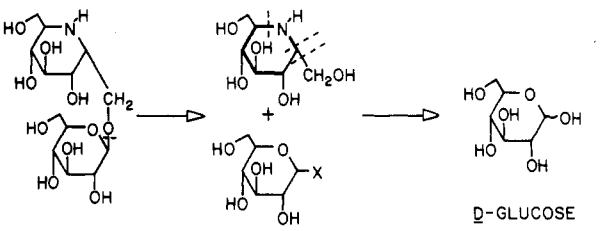
Nojirimycin

The putative mechanism of the enzymatic hydrolysis of disaccharides involves (a) formation of an oxycarbocation, (b) cleavage of the glycosidic linkage, and (c) charge neutralization by water (Scheme I).[3] A carboxylic function at the "active site" of the enzyme is responsible for stabilizing the electron-deficient transition state. We designed, as our prototype transition-state analogue, compound 8, which encompasses the following structural features: (i) replacement of the ring oxygen in glucose by nitrogen as in nojirimycin to facilitate favorable polar–polar interactions with the catalytically important carboxylate at the active site, (ii) insertion of a "methylene" between the two saccharide rings to mimic the lengthening of the severing glycosidic linkage, (iii) a "β"-glycosidic bond to enhance its stability toward enzymatic hydrolysis. The synthesis of this novel α-glucosidase inhibitor utilizing the

Scheme I



Scheme II



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