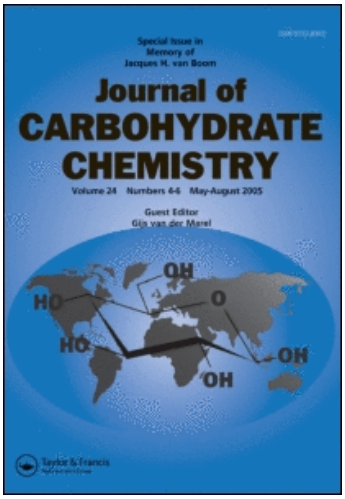

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CONVERSION OF DIGITOXIN (2) INTO SYNTHETICALLY USEFUL DERIVATIVES OF DIGITOXOSE (1) (2,6-DIDEOXY-D-*ribo*-HEXOSE)

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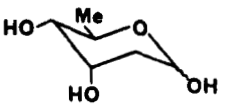
ABSTRACT

An efficient procedure is described for the conversion of digitoxin (2) into 1,3,4-tri-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranose (4). This conversion allows digitoxin (2) to become a viable source of 2,6-dideoxy sugars since the tribenzoate 4 is readily converted into synthetically useful derivatives. One type of derivative, exemplified by *t*-butyl 2,6-dideoxy-β-D-*ribo*-hexopyranoside (17), is an unprotected glycoside and thus easily permits structural modification at C-3 and C-4. A second type of derivative formed from 4 is one capable of glycosidic coupling at the anomeric carbon atom. Examples of this latter type are 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranosyl chloride (7) and ethyl 3,4-di-*O*-benzoyl-2,6-dideoxy-1-thio-β-D-*ribo*-hexopyranoside (13).

INTRODUCTION

2,6-Dideoxy-D-*ribo*-hexose (digitoxose, 1) is a naturally occurring sugar first isolated from the hydrolysis of the cardiac glycoside digitoxin (2).[1] Subsequently, digitoxose (1) was synthesized in the laboratory using other carbohydrates as starting materials.[2-6] Recently, noncarbohydrates also have been converted into digitoxose (1).[7-9]

Our interest in 2,6-dideoxy sugars for use in preparation of carbohydrate-modified analogs of the anticancer agent mithramycin (3), attracted us to digitoxin (2) as a possible source of dideoxy sugars. In order for digitoxin (2) to function in this capacity, several requirements



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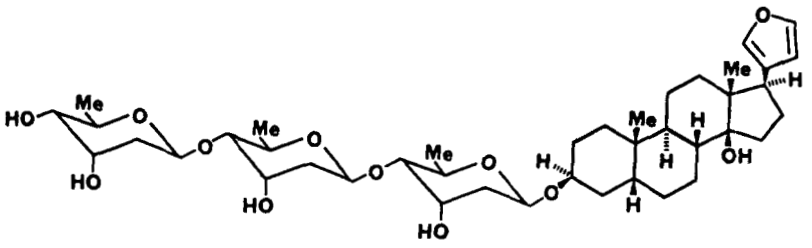

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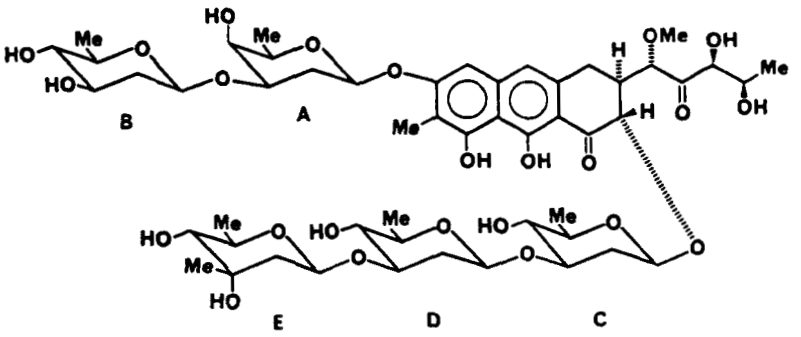

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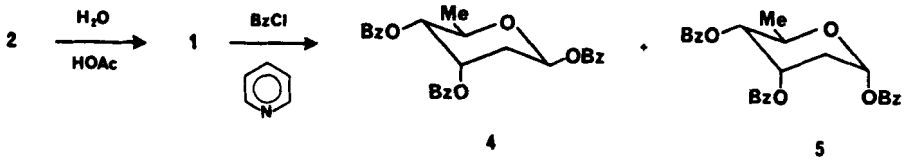
had to be met. First, digitoxin (2) needed to be hydrolyzed into digitoxose (1) in better yield than had been reported previously.[1,10] Digitoxose (1) then had to converted effectively into two types of compounds. One of these was a substance protected only at C-1 so that reactions such as inversion of configuration at C-3 and C-4 would be possible. The second was a derivative (such as a glycosyl halide or thioglycoside) which could be coupled at the anomeric carbon atom to other molecules.

RESULTS AND DISCUSSION

Upon heating in aqueous acetic acid, digitoxin (2) was hydrolyzed to digitoxose (1) in 90% yield. Benzoylation of 1 produced a solid material

which, upon recrystallization, gave 1,3,4-tri-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranoside (4) in 63% yield (Scheme I). Chromatography of the

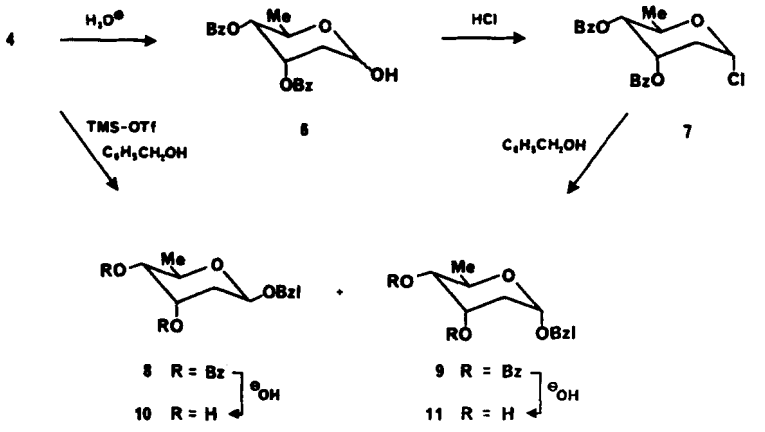
Scheme I



material remaining after recrystallization yielded additional 4 (9%) and 1,3,4-tri-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (5) (12%); thus, the combined tribenzoate yield was 84%. These tribenzoates (4 or 5) appeared to be capable of being converted easily into compounds with the desired reactivity.

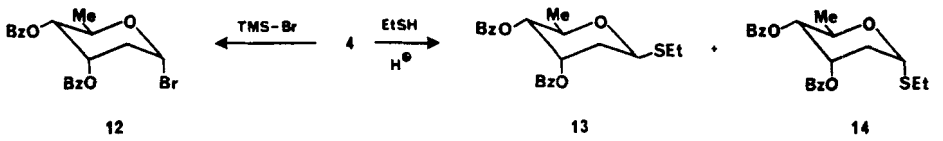
Base-catalyzed deprotection of esters under appropriate conditions is known to remove an *O*-1 acyl group regioselectively.[11-13] Unfortunately, attempted selective deprotection of 4 under basic conditions[14] produced a complex mixture; however, acid-catalyzed hydrolysis of 4 or 5 selectively removed the *O*-1 benzoyl group to give 3,4-di-*O*-benzoyl-2,6-dideoxy-D-*ribo*-hexopyranose (6) (Scheme II). Reaction of 6 with hydrogen

Scheme II



chloride in toluene produced 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranosyl chloride (7), a digitoxose derivative which easily experienced glycosidic coupling, as shown by its reaction with benzyl alcohol to produce benzyl 3,4-di-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranoside (8) and benzyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (9) (Scheme II). Compound 7 is not the only glycosyl halide which is capable of being prepared from the tribenzoate 4. Reaction of 4 with trimethylsilyl bromide has been shown to give 3,4-di-*O*-benzoyl-2,6-dideoxy-α-*D*-*ribo*-hexopyranosyl bromide (12) (Scheme III),[15] a compound which has been demonstrated to be an effective glycosyl donor in oligosaccharide synthesis.[16] It was further possible to convert 4 into two additional compounds useful in glycoside synthesis; that is, the thioglycosides 13 and 14 were prepared by reaction of 4 with ethanethiol in the presence of triflic acid (Scheme III).

Scheme III



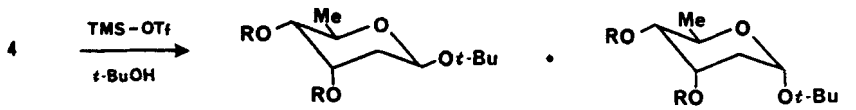
12 13 14

The benzyl glycosides 8 and 9 also were formed by reaction of 4 with benzyl alcohol in the presence of (trimethylsilyl trifluoromethanesulfonate (TMS-triflate) (Scheme II); unfortunately, a difficult chromatographic separation was necessary to isolate these compounds (8 and 9). Although it seemed possible that the desired separation would be easier for the debenzoylated anomers 10 and 11 (Scheme II), this proved not to be the case; thus, more easily separable glycosides were sought.

Previous experience with the chromatography of digitoxose derivatives[17,18] indicated that difficulty in separation also would be encountered with methyl glycosides; however, *t*-butyl glycosides potentially presented a different situation. The *t*-butyl group is sufficiently large that interaction between an adsorbent and an axial C-3 hydroxyl group should be more difficult for an α anomer than for the corresponding β anomer. Such an effect could lead to a considerable difference in R_f values for these two epimers. With this thought in mind, the *t*-butyl

3,4-di-*O*-benzoyl-2,6-dideoxy-D-*ribo*-hexopyranosides **15** and **16** were synthesized (Scheme IV). Since the hydroxyl groups remained protected in

Scheme IV



15 R = Bz **16** R = Bz

17 R = H **18** R = H

these compounds (**15** and **16**), their chromatographic mobilities were, as expected, very similar; however, debenzoylation gave *t*-butyl 2,6-dideoxy-β-D-*ribo*-hexopyranoside (**17**) and *t*-butyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside (**18**), which proved remarkably easy to separate. The difference in R_f values was so great that significant quantities of pure anomers could be obtained easily.

When the ease in preparation and purification of the *t*-butyl glycosides **17** and **18** is combined with the facile synthesis of the glycosyl chloride **7** and the thioglycosides **13** and **14**, pathways have been established leading from digitoxin (**2**) to the derivatives needed for its effective use as a starting material in the preparation of 2,6-dideoxy sugars.

EXPERIMENTAL

General Procedures. TLC was conducted us ing Whatman MK6F silica gel plates. Solvents used for TLC analysis and column chromatography were either 9:1 (solvent A) or 3:1 (solvent B) hexane:ethyl acetate. Column chromatography was done on a 2.5 x 15 cm column of 230-400 mesh silica gel. The molecular sieves used were 3A and were activated prior to use by heating for 20 h at 250 °C. NMR spectra ($CDCl_3$) were determined using a Varian FT80A spectrometer. Spectral data are given in Tables I and II.

Synthesis of 1,3,4-Tri-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranose (**4**) and 1,3,4-Tri-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranose (**5**) from Digitoxin (**2**). Digitoxin (**2**) (6.59 g, 8.61 mmol) was suspended in a solution of 50 mL of acetic acid and 50 mL of water. The mixture was stirred and heated to 83 °C over a period of 25 min to give a homogeneous so-

TABLE I. ^{1}H NMR SPECTRAL DATA

Chemical Shifts[a]

	4	5	7	8	9	10	11	13	14	15	16	17	18
H-1	6.50	6.48	6.25	5.10	5.05	4.88	4.94	5.08	5.37	5.21	5.14	5.03	5.18
H-2a	2.34-	2.45-	2.43-	2.11-	2.32-	1.72	1.87	2.17-	2.55	2.18-	1.82-	1.65-	1.89-
H-2e	2.50	2.60	2.68	2.32	3.22	2.09	2.20	2.34	2.38	2.06	2.25	2.12	2.02
H-3	5.96	5.80	5.81	5.84	5.75	4.02	3.93	5.81	5.76	5.84	5.93	4.08	3.95
H-4	5.15	5.15	5.09	5.04	5.01	3.25	3.13	5.02	5.05	4.99	5.22	3.26	3.09
H-5	4.49	4.75	4.80	4.27	4.59	3.73	3.79	4.26	4.79	4.26	4.84	3.73	3.85
H-6	1.39	1.33	1.32	1.37	1.28	1.30	1.32	1.33	1.30	1.33	1.30	1.28	1.26
CH2				5.00	4.84	4.88	4.72	2.79	2.70				
CH2'				4.45	4.63	4.50	4.45						
CH3								1.32	1.33	1.30	1.27	1.24	1.26
ArH	8.34-	8.13-	8.22-	8.03-	8.14-	7.31	7.31	8.11-	8.26-	8.11-	8.30-		
"	7.25	7.88	7.84	7.82	7.83			7.82	7.82	7.80	8.01		
"		7.54-	7.60-	7.54-	7.53-			7.62-	7.54-	7.60-	7.39-		
"		7.20	7.23	7.24	7.20			7.18	7.30	7.29	7.10		

Coupling Constants[b]

1,2a	7.5		2.8	7.9		9.3	3.4	9.3	5.9	6.5	4.1	8.7	
1,2e	3.8		2.8	3.7		2.6	1.4	4.6	1.1	5.3	1.0	3.1	
2a,3	3.0	3.0	3.0	3.4	3.0	3.0	3.4	3.0	3.4	3.1	3.1	3.2	3.0
2e,3	3.0	3.0	3.0	3.4	3.0	3.2	3.4	3.0	3.8	3.1	3.1	3.2	3.0
3,4	3.0	3.0	2.9	3.0	3.0	3.2	3.2	3.0	3.0	3.2	3.1	3.2	3.2
4,5	8.8	10.1	10.1	9.6		9.2	9.8	9.9	9.6	9.7	9.7	9.4	9.8
5,6	6.3	6.1	6.0	6.2	6.2	6.2	6.1	6.2	6.0	6.4	6.3	6.2	6.3

[a]Chemical shifts are relative to Me_4Si. [b]Coupling constants are in Hertz.

lution. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was partitioned between 100 mL of water and 250 mL of ether. The layers were separated and the ether layer extracted with an additional 100 mL portion of water. The water extracts were combined and the water distilled under reduced pressure. The final traces of moisture were removed using a vacuum pump to give 3.44 g (23.2 mmol, 90%) of digitoxose (1), mp 104-105 °C (lit.[1] 105-107 °C). Typically the digitoxose (1) was not isolated: rather, the residue after solvent removal was dissolved in 100 mL of anhydrous pyridine, cooled in ice bath, and 21.8 g (0.155 mol) of benzoyl chloride was added dropwise to the stirred solution. The reaction mixture was allowed to warm to room temperature and stand overnight. It was again placed in an ice bath and 10 mL of water was added dropwise with vigorous stirring. After 30 min, the entire reaction mixture was added slowly to a stirred solution of 40 g of sodium bicarbonate in 600 mL of water. The precipitate which formed was removed by filtration, washed with 100 mL of water, and recrystall-

TABLE II. ^{13}C NMR SPECTRAL DATA[a]

	4	5	6β	6α	7	8	9	10	11	13	14	15	16	17	18
C-1	91.48	90.76	92.63	90.78	89.05	97.13	95.76	96.83	96.13	77.48	79.31	92.72	90.65	92.21	92.33
C-2	34.26	32.79	37.24	34.09	37.55	35.51	33.85	37.48	34.94	36.29	35.09	37.53	35.21	39.41	36.84
C-3	70.28	66.98	68.83	67.67	66.24	68.05	66.94	69.37	67.11	71.03	67.10	69.19	67.52	69.40	68.32
C-4	72.50	72.58	73.00	72.92	72.33	72.87	73.13	72.77	72.43	72.96	73.28	73.33	73.53	73.15	73.43
C-5	67.57	64.55	68.47	62.53	64.77	68.59	62.31	67.64	64.40	68.26	63.25	68.62	62.18	68.72	64.71
C-6	18.30	17.79	18.14	17.72	17.31	17.94	17.63	17.96	17.58	18.01	17.79	18.53	17.75	18.58	18.10
CH2						70.37	69.80	70.37	69.14	24.54	26.70				
CH3										14.83	15.39	28.83	28.83	28.83	28.83
CMe3												75.67	74.66	75.65	76.29
C=O	165.51	165.89	165.57	165.57	165.37	165.19	165.96			165.19		165.99	165.74		
C=O	164.87	165.37	164.44	165.69		165.06	165.59			165.11		165.74	165.59		
Ar	133.57	133.19	133.21	133.21	133.30	137.21	133.69	137.46	136.72	133.05	133.23	133.00	133.18		
"	133.37	129.85	129.67	129.67	133.20	132.94	133.10	128.20	128.29	132.93	130.26	130.05	129.82		
"	133.30	129.75	128.56	128.56	129.97	132.89	132.79	127.75	127.69	129.39	129.84	128.69	128.42		
"	130.01	128.46	128.36	128.36	128.41	129.34	130.20	127.54		128.32	128.58				
"	129.73	128.31				128.23	129.89			128.10					
"	129.40					128.14	129.72								
"	128.48					128.07	128.32								
"						127.64	128.04								
"						127.51	127.61								

[a]Chemical shifts are relative to Me_4Si.

ized from ethanol (120 mL) to give 6.73 g (14.6 mmol) of 1,3,4-tri-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranose (4), mp 174-175.5 °C (lit.[19] 176-177 °C). The filtrate from the recrystallization was concentrated and chromatographed in the standard fashion (solvent A) to give a fraction (R_f 0.25, solvent A) from which, after dissolving in 50 mL of ethanol, an additional 0.96 g (2.09 mmol) of 4 crystallized to give a total yield for 4 of 72%. The filtrate after crystallization of 4 was concentrated and, upon standing overnight, deposited 1.28 g (2.8 mmol, 12%) of 1,3,4-tri-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranose (5), mp 145-147 °C. Anal. Calcd for $C_{27}H_{24}O_7$: C, 70.42; H, 5.25. Found: C, 70.64; H, 5.26. None of the remaining fractions was analyzed.

Synthesis of 3,4-Di-*O*-benzoyl-2,6-dideoxy-D-*ribo*-hexopyranose (6). 1,3,4-Tri-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranose (4) (4.28 g, 0.0093 mol) was dissolved in a solution consisting of 50 mL of THF, 4 mL of water, and 1 mL of concentrated sulfuric acid. After standing at room temperature for 4 days, 10 g of sodium bicarbonate was added slowly with stirring and the solution was stirred until it was no longer acidic (litmus). The reaction mixture was partitioned between water (100 mL) and ether (150 mL) and the layers were separated. The aqueous layer was extracted with two 100 mL portions of ether and the ether extracts were passed through a 1 cm bed of silica gel (240-400 mesh). Distillation of the solvent left a residue which crystallized slowly and incompletely. This material was chromatographed under standard conditions (solvent B) to give 3.15 g (8.84 mmol, 95%) of 3,4-di-*O*-benzoyl-2,6-dideoxy-D-*ribo*-hexopyranose (6) (R_f 0.24 (solvent B), mp 95-107 °C). ^{13}C NMR analysis of this material indicated it to be a 3.5/1 (β/α) mixture of anomers.

Synthesis of 3,4-Di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranosyl Chloride (7). Compound 6 (1.05 g, 2.95 mmol) was dissolved in 50 mL of anhydrous toluene. This solution was cooled to 0 °C and anhydrous hydrogen chloride was bubbled into the stirred, cooled solution for 20 min. The solvent and the hydrogen chloride were removed under reduced pressure at room temperature. Final traces of solvent were removed using a mechanical pump. The product was an unstable material which reverted to 6 upon exposure to moisture or attempted chromatography. NMR spectra indicated the product to be a 5/1 mixture of two compounds. It was possible to determine from the spectra those resonances (see Tables 1 and 2) arising from the major product, 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranosyl chloride (7).

Synthesis of Benzyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranoside (8) and Benzyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (9).

a. From Compound 4. Compound 4 (0.72 g, 1.56 mmol) and 0.45 g (4.2 mmol) of benzyl alcohol were dissolved in 12 mL of toluene and stored over 3 g of 3A molecular sieves for 20 h. Trimethylsilyl trifluoromethanesulfonate (TMS-triflate) (0.23 g, 1.0 mmol) then was added dropwise to the stirred solution which still contained the molecular sieves. After 3 h, 1 mL of pyridine was added, the mixture was filtered, and the filtrate extracted with 10 mL of saturated sodium bicarbonate solution. The solvent was distilled from the organic phase under reduced pressure and the residue chromatographed in the normal manner (solvent A). The first compound (R_f 0.32, solvent A) eluted from the column was benzyl 3,4-di-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranoside (8) (0.30 g, 0.67 mmol, 43%), mp 107.5-108.5 °C. Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.44; H, 5.81. The second compound obtained (R_f 0.28, solvent A) from the column was benzyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (9) (0.31 g, 0.70 mmol, 45%), mp 74-76 °C. Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.38, H, 5.90.

b. From Compound 7. Compound 7 (3.0 mmol), prepared as described above, was dissolved in 10 mL of toluene which contained 1 g (0.01 mol) of benzyl alcohol and 0.64 g (3.2 mmol) of 2,6-di-*t*-butyl-4-methylpyridine. After two days, the reaction mixture was filtered, the solvent distilled under reduced pressure, and the residue chromatographed. Compounds 8 and 9 were isolated as described in the preceding paragraph in the same yields.

Synthesis of Benzyl 2,6-Dideoxy-β-D-*ribo*-hexopyranoside (10) and Benzyl 2,6-Dideoxy-α-D-*ribo*-hexopyranoside (11). Compound 8 (0.30 g, 0.67 mmol) was dissolved in 20 mL of methanol and 0.3 g (7 mmol) of sodium hydroxide was added. The solution was stirred for 18 h, the solvent distilled under reduced pressure, and the residue partitioned between hexane (10 mL) and water (30 mL). The aqueous phase was extracted with three 25 mL portions of chloroform and the solvent was distilled from the combined chloroform extracts to give 0.15 g (0.63 mmol, 94%) of benzyl 2,6-dideoxy-β-D-*ribo*-hexopyranoside (10), a liquid (R_f 0.31, solvent A). The same procedure was used to convert compound 9 into benzyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside (11), also a liquid (R_f 0.44, solvent A), in quantitative yield. The ^1H NMR spectra of compounds 10 and 11 were the same as those reported for their enantiomers.[20]

Synthesis of Ethyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-1-thio-β-D-*ribo*-hexopyranoside (13) and Ethyl 3,4-Di-*O*-Benzoyl-2,6-dideoxy-1-thio-α-D-*ribo*-hexopyranoside (14). Compound 4 (0.66 g, 1.43 mmol) and 0.6 mL (8.0 mmol) of ethanethiol were dissolved in 10 mL of dichloromethane and a drop of trifluoromethanesulfonic acid was added. After 15 min, the reaction mixture was shaken with 5 mL of saturated sodium bicarbonate solution. The solvent was distilled from the organic phase and the residue was chromatographed (Solvent A) to give 0.35 g (0.82 mmol) of ethyl 3,4-di-*O*-benzoyl-2,6-dideoxy-1-thio-β-D-*ribo*-hexopyranoside (13) (R_f 0.40, solvent A), mp 89-91 °C. Anal. calcd for $C_{22}H_{24}O_5S$: C, 63.44; H, 5.81. Found: C, 63.54; H, 5.58. The second material obtained from chromatography (0.14 g, 0.33 mmol) was ethyl 3,4-di-*O*-benzoyl-2,6-dideoxy-1-thio-α-D-*ribo*-hexopyranoside (14) (R_f 0.33, solvent A), mp 119-121 °C. Anal. calcd for $C_{22}H_{24}O_5S$: C, 63.44; H, 5.81. Found: C, 63.74, H, 5.68.

Synthesis of *t*-Butyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-β-D-*ribo*-hexopyranoside (15), *t*-Butyl 3,4-Di-*O*-benzoyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (16), *t*-Butyl 2,6-dideoxy-β-D-*ribo*-hexopyranoside (17), and *t*-Butyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside (18). Compound 4 (1.09 g, 2.37 mmol) was dissolved in a mixture of 15 mL of *t*-butyl alcohol and 15 mL of tetrahydrofuran and stored over 3 g of molecular sieves for 10 h. TMS-triflate (0.5 mL, 2.5 mmol) was dissolved in 5 mL of tetrahydrofuran and added to the reaction mixture. After 1 h, TLC analysis indicated the reaction to be complete. The solvent was distilled and the residue was chromatographed in the standard manner (solvent A). The material isolated (R_f 0.42, 0.92 g, 2.23 mmol, 94%) was identified, after deprotection, separation, and reprotection, as a 1.2/1 (β/α) mixture of the *t*-butyl 3,4-di-*O*-benzoyl-2,6-dideoxy-D-*ribo*-hexopyranosides 15 and 16, respectively. Reaction of the mixture with sodium hydroxide, as described in the deprotection of compounds 8 and 9 and chromatography (Solvent B) gave 0.25 g (1.23 mmol) of *t*-butyl 2,6-dideoxy-β-D-*ribo*-hexopyranoside (17, R_f 0.05, solvent B) and *t*-butyl 2,6-dideoxy-α-D-*ribo*-hexopyranoside (18, R_f 0.24, solvent B). Benzoylation of compounds 17 and 18 under the conditions used to benzoylate digitoxose (1) gave compounds 15 and 16, respectively. Compound 16 remained a liquid but 15 crystallized, mp 127-129 °C. Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.84, H, 6.80.

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