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1,6-Epithio- and 1,6-Episeleno-β-D-glucopyranose: Useful Adjuncts in the Synthesis of 6-Deoxy-β-D-glucopyranosides

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Abstract: The treatment of derivatives of 1,6-epithio- and 1,6-episeleno-β-D-glucopyranose with various carbohydrate alcohols in the presence of *N*-iodosuccinimide/triflic acid gives rise to disulfides and diselenides, respectively, which may be transformed to the desired 6-deoxy-β-D-glucopyranosides.
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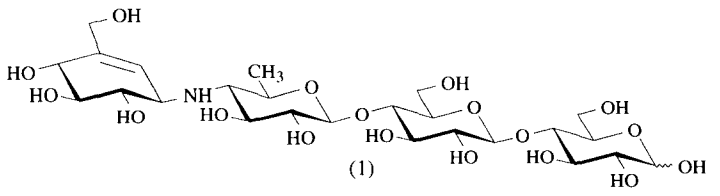
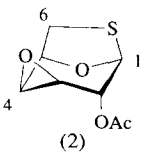
Deoxy sugars are found in many biologically important molecules and are frequently a critical substructure required for carbohydrate-protein recognition processes. 6-Deoxy sugars are important in, for example, the Le^x molecule which contains an L-fucose terminal residue.[1] As well, the cell surface carbohydrates of various bacteria have antigenic determinants possessing a 3,6-dideoxy sugar such as abequose (3,6-dideoxy-D-*xylo*-hexose) or paratose (3,6-dideoxy-D-*ribo*-hexose).[2] Our interest in 6-deoxy sugars stemmed from a desire to synthesize β-acarbose (1), a putative inhibitor of enzymes that process β-D-glucosidic linkages.[3]



(1)

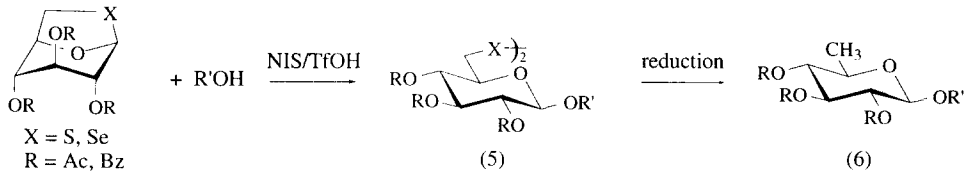


(2)

It occurred to us that a ready synthesis of β-acarbose would pivot on 2-*O*-acetyl-3,4-anhydro-1,6-dideoxy-1,6-epithio-β-D-galactopyranose (2),[4] a molecule beautifully arranged for amination (C4), glycoside formation (C1) and desulfurisation (C6).

This paper reports on our preliminary investigations into the use of derivatives of 1,6-dideoxy-1,6-epithio-β-D-glucopyranose (3),[5] and ultimately of the 1,6-episeleno counterpart (4), for the synthesis of 6-deoxy-β-D-glucopyranosides. The general approach is outlined in Scheme 1 and the results are summarized in the Table.

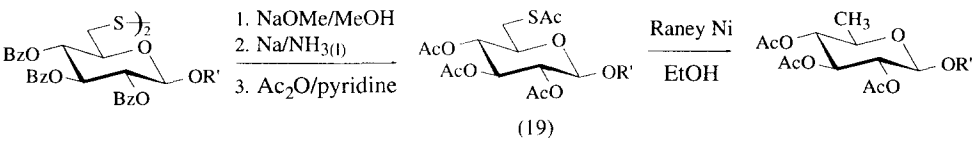
Scheme 1



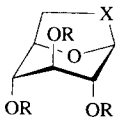
The triacetate (7)[4] was not a successful glycosyl donor for the alcohol (11) (entry 1) – in all reactions attempted, the acetate (18) was formed in up to 35% yield.[6] However, the tribenzoate (8), easily formed from the triacetate (7) in two steps (NaOMe/MeOH; BzCl/pyridine - 89% overall), smoothly converted the alcohols (11) - (16) into the corresponding disulfide (5) (entries 2 - 7). The treatment of (8) with the alcohol (17) (entry 8) gave a complex mixture of products.

The conversion of the intermediate disulfides (5) into the desired deoxy sugars was not straightforward. In only one case (entry 5) was the direct reduction of the disulfide with Raney nickel successful – usually, the reaction was slow and variable and mixtures of products resulted. A reliable procedure, which involved reduction of an intermediate thioacetate (19), finally gave access to the 6-deoxy-β-D-glucopyranosides (Scheme 2).

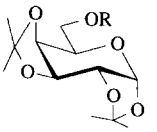
Scheme 2



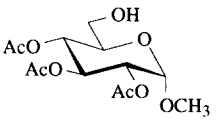
It seemed, at this stage, that some of the deficiencies in the above process might be improved if the sulfur atom of (8) were replaced by selenium. Again, the triacetate (9)[4] was unsatisfactory (entry 9). However, the derived tribenzoate (10) rapidly converted the alcohols (11), (15) and (16) (entries 10 - 12) into a mixture where the diselenide (5) (Scheme 1) appeared to be the major, but not only, selenium-containing product. Now, direct treatment of this mixture of products with tributylstannane gave the desired 6-deoxy-β-D-glucosides (6) in excellent overall yield. Again, and very disappointingly, the treatment of (10) with the alcohol (17) (entry 13) gave a complex mixture of products.



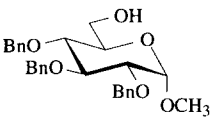
(3) X = S, R = H
(4) X = Se, R = H
(7) X = S, R = Ac
(8) X = S, R = Bz
(9) X = Se, R = Ac
(10) X = Se, R = Bz



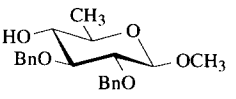
(11) R = H
(18) R = Ac



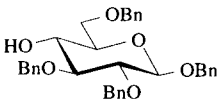
(12)



(13)



(14)



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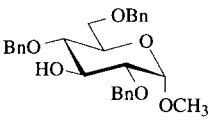
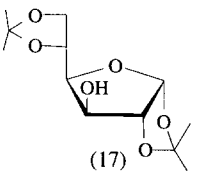


(16)



(17)

Table

Entry	Reactants	Disulfide/Diselenide (5)			6-Deoxy-β-D-glucoside (6)		
		Yield%	m.p. (°C)	$[\alpha]_D$[a]	Yield%	m.p. (°C)	$[\alpha]_D$[a]
1	(7) + (11)	0[b]	-	-	-	-	-
2	(8) + (11)	76	c	+14.2°	56	163-5	–62.8°
3	(12)	92	c	+74.3°	58	158-60	+70.8°
4	(13)	51	c	+51.8°	41	d	d
5	(14)	63	116-9	+60.5°	84	139-40	+7.5°
6	(15)	82	c	+28.3°	33	225-6	+57.7°
7	(16)	69	c	+13.8°	51	190-3	+37.9°
8	(17)	0	-	-	-	-	-
9	(9) + (11)	0[b]	-	-	-	-	-
10	(10) + (11)	e	-	-	73	c	–33.0°
11	(15)	54	c	+49.9°	64[f]	108-12	–17.6°
12	(16)	e	-	-	55	c	–34.2°
13	(17)	0	-	-	-	-	-

[a] 25°C in $CHCl_3$ [b] Only the acetylated acceptor was isolated [c] An oil [d] Identical to the 6-deoxy-β-D-glucoside from entry 3 by ^1H n.m.r. (300 MHz) spectroscopy [e] Not isolated [f] Yield based on (15).

Representative procedures[7]

(a) A solution of NIS (0.28 mmol) and TfOH (0.02 - 0.1 mmol) in dry Et_2O/1,2-dichloroethane (1:1, 4 mL) at 0° was added to a solution of the 1,6-epithio donor (0.24 mmol) and acceptor (0.20 mmol) in dry DCE (2 mL) at 0°. After completion of the reaction (t.l.c.), the solution was quenched with sat. aq. $NaHCO_3$ (1 mL) and aq. $Na_2S_2O_3$ (10%, 1 mL), the organic layer was separated, dried ($MgSO_4$), the solvent evaporated and the residue purified by flash chromatography to give the various disulfides.

(b) In the case of the 1,6-episeleno donors, after glycosylation and workup as in (a), the crude residue was dissolved in dry toluene (4 mL) and treated with Bu_3SnH (0.60 mmol) and AIBN (1 mg) at reflux. After completion of the reaction (t.l.c.), the solvent was evaporated and the residue partitioned between MeCN and petrol. The MeCN layer was separated and evaporated and the residue subjected to flash chromatography to give the various 6-deoxy-β-D-glucopyranosides.

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7. All new compounds gave satisfactory microanalytical and spectral data.

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