

## SYNTHESIS OF 1-THIOALDOSIDES HAVING AN AMINO GROUP AT THE AGLYCON TERMINAL\*

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### ABSTRACT

A number of 1-thio- $\beta$ -D-aldosides were prepared, directly or indirectly, from acetylated 1-halides of D-galactose, D-glucose, and 2-amino-2-deoxy-D-glucose. These aldoses have an amino group at the terminal position of the aglycon, in the form of 6-aminohexyl, 6-aminohexanoyl, or *p*-aminophenyl groups.

### INTRODUCTION

Solid matrices carrying biologically specific ligands have been used for affinity chromatography<sup>1</sup> and for investigations of various other biological interactions<sup>2</sup>. In order to study the biological roles of sugars in complex carbohydrates, we have initiated a program to synthesize a series of aldoses having functional groups at the terminal position of the aglycon, and to attach these aldoses to solid matrices for studies of protein–carbohydrate interaction or cellular adhesion.

The present article describes the synthesis of a series of 1-thioaldoses having an amino group at the terminal position of the aglycon. The 1-thioaldoses were chosen in order to avoid the possibility of glycoside cleavage of the matrix-bound aldoses by the action of glycosidases, as 1-thioglycosides are not hydrolyzed by glycosidases.

### EXPERIMENTAL

*General.* — All evaporations were performed under diminished pressure at 20–45° with a rotary evaporator. Melting points were measured with a Fisher–Johns apparatus or a Thomas–Hoover apparatus. Proton magnetic resonance spectra were recorded with either a Varian A-60 or HA-100 spectrometer. Optical rotations were measured at room temperature with a Cary 60 spectropolarimeter. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

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Thin-layer chromatography (t.l.c.) was performed with Silica Gel F<sub>258</sub> (Merck) precoated on aluminum sheets. Generally, t.l.c. sheets were sprayed with 50% sulfuric acid and heated to reveal the components. Ninhydrin reagent<sup>3</sup> (for the amino group), hypochlorite reagent<sup>4</sup> (for the amide group), and periodate-benzidine reagent<sup>5</sup> (for the glycol grouping) were used for group-specific detection of compounds. Solvent systems and *R<sub>F</sub>* values of the compounds presented in this work are shown in Table I.

TABLE I

*R<sub>F</sub>* VALUES OF COMPOUNDS REPORTED IN THIS WORK

Compounds	Solvent systems <sup>a</sup>									
	A	B	C	D	E	F	G	H	I	J
1	0.37		0.72		0.86		0.72			
1a			0.80						0.38	
2	0.81		0.80		0.92		0.80			
2a									0.50	
3	0.87		0.84		0.95		0.81			
3a		0.40	0.81		0.73				0.47	0.57
4		0	0.48		0.44				0.14	0
5	0.71		0.96		0.95		0.96			
5a	0.81	0.26	0.95		0.80		0.76		0.56	0.44
6		0	0.04	0.33		0.16	0	0.03		0
7				0.34		0.19				
8				0.33		0.18				
9	0	0	0.26		0.46		0.70		0	0
10	0.40		0.96		0.96		0.89			
13	0		0.05	0.21	0	0.20	0			

<sup>a</sup>A: Toluene-ethanol-28% ammonia, 200:31:1; B: benzene-ether, 1:1; C: ethyl acetate-acetic acid-water, 8:2:1; D: ethyl acetate-acetic acid-water, 3:2:1; E: ethyl acetate-pyridine-water, 8:2:1; F: butyl alcohol-acetic acid-water, 4:1:5 (upper layer); G: ethyl acetate-propyl alcohol-water, 9:4:2; H: pentyl alcohol-acetic acid-water, 4:1:5 (upper layer); I: benzene-ethanol-28% ammonia, 200:31:1; J: acetone-petroleum ether (b.p. 30-60°), 2:3.

6-(Trifluoroacetyl-amino)-1-hexanol (1). — To a stirred solution of 6-amino-1-hexanol (35 g, 300 mmoles) in water (100 ml) was added *S*-ethyl trifluorothioacetate (52 g, 330 mmoles) during 5 h. The mixture was kept overnight, and then cooled in an ice-bath, and the precipitate that formed was filtered off. The precipitate was dissolved in 95% ethanol, the solution decolorized with charcoal, and compound 1 crystallized by gradual addition of water; yield 48 g (75%); m.p. 52-53° (lit.<sup>6</sup> m.p. 52-53°).

Anal. Calc. for C<sub>8</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>2</sub>: C, 45.06; H, 6.61; F, 26.73; N, 6.57. Found: C, 45.05; H, 6.56; F, 25.76; N, 6.51.

1-(*p*-Tolylsulfonyloxy)-6-(trifluoroacetyl-amino)hexane (2). — To a solution of 1 (42.6 g, 200 mmoles) in dry pyridine (500 ml), cooled to 0°, was added freshly recrystallized *p*-toluenesulfonyl chloride (41.9 g, 220 mmoles). The mixture was kept overnight at 4°, and then poured into ice-water (4 liters) with vigorous stirring.

After further stirring for 30 min, the crude product separated as a solid. After decolorization with charcoal, and crystallization from 95% ethanol, 66.1 g (90%) of crystalline **2** was obtained: m.p. 50–51°; p.m.r. data (CDCl<sub>3</sub>):  $\delta$  1.2–1.8 (m, 8, CH<sub>2</sub>), 2.19 (s, 3, CH<sub>3</sub>–), 3.12 (q, 2, N–CH<sub>2</sub>), 3.96 (t, 2, I–CH<sub>2</sub>), 6.86 (s, 1, NH), 7.22 (d, 2, *m*-ArH), and 7.63 (d, 2, *o*-ArH).

*1-Iodo-6-(trifluoroacetylamino)hexane (3)*. — A mixture of the tosylate **2** (7.34 g, 20 mmoles) and sodium iodide (4.50 g, 30 mmoles) in dry 2-butanone (15 ml) was boiled for 2 h under reflux, and cooled, and the precipitated sodium tosylate was removed by filtration. The filtrate was evaporated to a syrup; this was dissolved in chloroform (25 ml), and the solution was washed with three 25-ml portions of cold water, treated with charcoal, dried (anhydrous sodium sulfate), and concentrated to a small volume. Upon addition of petroleum ether, crystalline **3** was obtained. Recrystallization from ethanol–water gave pure **3** (4.85–5.75 g, 75–89% yield): m.p. 47–47.5°, p.m.r. data (CDCl<sub>3</sub>):  $\delta$  1.2–1.9 (m, 8, C–CH<sub>2</sub>), 3.16 (t, 2, I–CH<sub>2</sub>), 3.30 (q, 2, N–CH<sub>2</sub>), and 6.70 (s, 1, NH).

*6-(Benzyloxycarbonylamino)-1-hexanol (1a)*. — To a solution of 6-amino-1-hexanol (40 g, 341 mmoles) and sodium hydrogen carbonate (95 g, 1.13 moles) in water (1.4 liters) was added dropwise benzyl chloroformate (89 ml, 522 mmoles) during 15 min. The mixture was stirred for 6 h at room temperature, and kept overnight at 4°. The white, gummy precipitate thus obtained was filtered off, washed with cold water, and dissolved in chloroform; the solution was decolorized with charcoal, dried (sodium sulfate), and evaporated to a syrup. Crystallization from ethyl acetate–petroleum ether yielded 80 g (95%) of product **1a**; m.p. 83°; p.m.r. data (CDCl<sub>3</sub>):  $\delta$  1.2–1.8 (m, 8, C–CH<sub>2</sub>); 3.19 (g, 2, N–CH<sub>2</sub>); 3.61 (t, 2, O–CH<sub>2</sub>), 5.11 (s, 2, Ph–CH<sub>2</sub>), and 7.37 (s, 5, C<sub>6</sub>H<sub>5</sub>).

	XNH(CH <sub>2</sub> ) <sub>6</sub> Y	
	X	Y
<b>1</b>	CF <sub>3</sub> CO	OH
<b>2</b>	CF <sub>3</sub> CO	OSO <sub>2</sub> –C <sub>6</sub> H <sub>4</sub> –Me– <u>p</u>
<b>3</b>	CF <sub>3</sub> CO	I
<b>1a</b>	PhCH <sub>2</sub> OCO	OH
<b>2a</b>	PhCH <sub>2</sub> OCO	OSO <sub>2</sub> –C <sub>6</sub> H <sub>4</sub> –Me– <u>p</u>
<b>3a</b>	PhCH <sub>2</sub> OCO	I

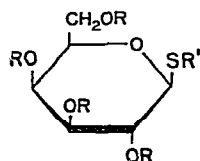
*6-(Benzyloxycarbonylamino)-1-iodohexane (3a)*. — Compound **1a** was treated with *p*-toluenesulfonyl chloride in pyridine (as with **2**), to yield 6-(benzyloxycarbonylamino)-1-(*p*-tolylsulfonyloxy)hexane (**2a**) in 90% yield; m.p. 46–47°. A solution of compound **2a** and sodium iodide in 2-butanone was boiled under reflux (as for **3**), to yield compound **3a** in 75–80% yield: m.p. 43–44.5°; p.m.r. data (CDCl<sub>3</sub>):  $\delta$  3.20 (m, 4, N–CH<sub>2</sub> and I–CH<sub>2</sub>); other peaks were similar to those for **1a**.

**2-S-(2,3,4,6-Tetra-O-acetyl- $\beta$ -D-galactopyranosyl)-2-thiopseudourea hydrobromide (4).** — A mixture of 2,3,4,6-tetra-O-acetyl- $\alpha$ -D-galactopyranosyl bromide (29.9 g, 73 mmol), thiourea (32.9 g, 80 mmol), and dry acetone (30 ml) was boiled under reflux for 15 min, and cooled in an ice bath, and the solid product was separated by filtration. Repeated recrystallization from acetone and then from 2-propanol gave **4** in 80–85% yield; m.p. 171–171.5°; lit.<sup>8</sup> m.p. 169.5°.

**6-Aminohexyl 1-thio- $\beta$ -D-galactopyranoside (6) from compounds 3 and 4.** — To a solution of compound **4** (3.65 g, 7.5 mmol), potassium carbonate (1.2 g, 8.7 mmol), and sodium bisulfite (1.5 g, 14.4 mmol) in water (6 ml) was immediately added compound **3** (1.94 g, 6 mmol) in acetone (6 ml), and the mixture was stirred for 20 min at room temperature. After the reaction was complete, the mixture was diluted with chloroform (25 ml) and water (15 ml), the layers were separated, and the aqueous layer was extracted with chloroform (25 ml). The chloroform layers were combined, washed twice each with 0.5M sulfuric acid and water, dried (sodium sulfate), and evaporated to a syrup (presumably, 6-(trifluoroacetylaminohexyl 2,3,4,6-tetra-O-acetyl-1-thio- $\beta$ -D-galactopyranoside, **5**).

Deacetylation and de(trifluoroacetyl)ation of the syrupy **5** was accomplished in one step by shaking with an excess of Dowex-1 X-8 ( $\text{OH}^-$ ) ion-exchange resin in 50% ethanol for 6 h at room temperature; ~15 ml of the resin was used per mmol of acyl group to be removed. Crystallization from ethanol gave compound **6** in 86% yield; m.p. 147–148°,  $[\alpha]_D^{25}$  -22.5° (water); p.m.r. data ( $\text{D}_2\text{O}$ ):  $\delta$  1.15–1.80 (m, 8, C-CH<sub>2</sub>), 2.48–2.84 (m, 4, N-CH<sub>2</sub> and S-CH<sub>2</sub>), 3.4–3.9 (m, 6, O-CH and O-CH<sub>2</sub>), and 4.40 (d, 1, J 9 Hz).

*Anal.* Calc. for  $\text{C}_{12}\text{H}_{25}\text{NO}_5\text{S}$ : C, 48.78; H, 8.53; N, 4.74; S, 10.85. Found: C, 48.66; H, 8.58; N, 4.67; S, 10.80.



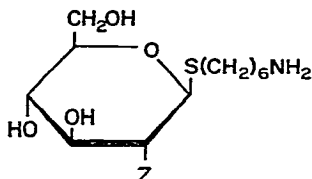
	R	R'
4	Ac	$\text{C}(\text{NH}_2)=\text{NH}\cdot\text{HBr}$
5	Ac	$(\text{CH}_2)_6\text{NHCOCF}_3$
6	H	$(\text{CH}_2)_6\text{NH}_2$
5a	Ac	$(\text{CH}_2)_6\text{NHCOOCH}_2\text{Ph}$
5b	Ac	$(\text{CH}_2)_6\text{NH}_2$
9	H	$\text{C}_6\text{H}_4\text{-NH}_2\text{-p}$
10	Ac	$\text{C}_6\text{H}_4\text{-NH}_2\text{-p}$
11	Ac	$\text{C}_6\text{H}_4\text{-NO}_2\text{-p}$
13	H	$\text{C}_6\text{H}_4\text{-NHCO}(\text{CH}_2)_5\text{NH}_2\text{-p}$

**Compound 6 from compounds 3a and 4.** — The reaction conditions for the preparation of **5a** from compounds **3a** and **4** were identical to those for compounds **3**

and **4** (as already described). The syrupy product of 6-(benzyloxycarbonylamino)hexyl 2,3,4,6-tetra-*O*-acetyl-1-thio- $\beta$ -D-galactopyranoside (**5a**) was obtained in 85–90% yield.

Compound **5a** (2.98 g, 5 mmoles) was treated with 2M hydrobromic acid in glacial acetic acid (6.5 ml) for 15 min, and the reaction was stopped by adding a solution of lithium acetate (2.55 g, 25 mmoles) in acetic acid (6.5 ml). The mixture was applied to a column (5  $\times$  165 cm) of Sephadex LH-20 pre-equilibrated with 90% acetic acid. The column was eluted with 90% acetic acid, and 15-ml fractions were collected. The product appeared in fractions 95–100, which were pooled and evaporated: acetic acid was removed by repeated azeotropic evaporation with toluene. The product, 6-aminohexyl 2,3,4,6-tetra-*O*-acetyl-1-thio- $\beta$ -D-galactopyranoside (**5b**), was obtained as a syrup in 82% yield. Deacetylation of **5b** was accomplished as for compound **5**. The product was crystalline (m.p. 147–148°) and indistinguishable from compound **6** obtained from **5**.

*6-Aminohexyl 1-thio- $\beta$ -D-glucopyranoside (7).* — To a solution of 2-*S*-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl)-2-thiopseudourea hydrobromide<sup>7</sup> (5.37 g, 11 mmoles), potassium carbonate (1.27 g, 12 mmoles), and sodium bisulfite (2.08 g, 20 mmoles) in water (20 ml) was immediately added compound **3** (3.23 g, 10 mmoles) in acetone (20 ml), and the mixture was stirred for 20 min. The mixture was processed as for the D-galactose derivative. The crystalline solid was directly deacetylated in 50% ethanol with Dowex-1 X-8 (OH<sup>−</sup>) ion-exchange resin to give 2.3 g (78%) of **7**; m.p. 127–128.5°,  $[\alpha]_D -52.4^\circ$  (water); p.m.r. data (D<sub>2</sub>O):  $\delta$  1.10–1.75 (m, 8, C-CH<sub>2</sub>), 2.52–2.84 (m, 4, N-CH<sub>2</sub> and S-CH<sub>2</sub>), 3.2–3.9 (m, 6, O-CH and O-CH<sub>2</sub>), and 4.45 (d, 1, *J* 9 Hz).



- 7**      Z = OH  
**8**      Z = NHAc

*6-Aminohexyl 2-acetamido-2-deoxy-1-thio- $\beta$ -D-glucopyranoside (8).* — Compound **8** was prepared analogously from **3** and 2-*S*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\beta$ -D-glucopyranosyl)-2-thiopseudourea hydrochloride<sup>9</sup>. The crystalline product was deacylated with Dowex 1 (OH<sup>−</sup>) ion-exchange resin, to yield crystalline **8** in 84% yield: m.p. 201–202°,  $[\alpha]_D -38.8^\circ$  (water); p.m.r. data (D<sub>2</sub>O):  $\delta$  1.16–1.78 (m, 8, C-CH<sub>2</sub>), 1.96 (s, 3, CH<sub>3</sub>-CO), 2.48–2.78 (m, 4, N-CH<sub>2</sub> and S-CH<sub>2</sub>), 3.28–4.00 (m, 6, O-CH and O-CH<sub>2</sub>), and 4.55 (d, 1, *J* 9 Hz).

*p*-Aminophenyl 1-thio- $\beta$ -D-galactopyranoside (9). — *A. By direct glycosylation.* *p*-Aminobenzenethiol (18.8 g, 150 mmoles) was dissolved in a solution of sodium hydroxide (8.4 g) in water (210 ml) under continuous flushing with nitrogen. A solution of 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-galactopyranosyl bromide (44 g, 107 mmoles) in acetone (310 ml) was then added with stirring, and stirring was continued for 2 h under nitrogen; the mixture was then chilled in an ice-bath, and the product was deposited as a partly crystalline solid, which was collected by filtration. After decolorization, recrystallization of *p*-aminophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio- $\beta$ -D-galactopyranoside (10) was accomplished from ethanol-water: yield 38.9 g (80%), m.p. 135–136°; p.m.r. data (CDCl<sub>3</sub>):  $\delta$  2.00, 2.07, 2.15, 2.20 (each s, 3, Ac), 3.72 (m, 2, O-CH<sub>2</sub>), 4.16 (m, 1, O-CH), 4.60 (d, 1, *J* 9 Hz), 5.1–5.6 (m, 3, AcO-CH), 6.70 (d, 2, *m*-ArH), and 7.43 (d, 2, *o*-ArH).

A solution of compound 10 (2.6 g, 5.7 mmoles) in acetone (25 ml) was diluted with 50% ethanol (100 ml), and stirred with Dowex-1 X-8(OH<sup>−</sup>) (50 ml) for 12 h at room temperature. The resin was removed by filtration, and the filtrate was evaporated to dryness. The product (9) was crystallized from ethanol in almost quantitative yield; m.p. 173–173.5°, [ $\alpha$ ]<sub>D</sub> −49.1° (water); p.m.r. data (D<sub>2</sub>O): 3.5–4.0 (m, 6, O-CH and O-CH<sub>2</sub>), 4.48 (d, 1, *J* 8–9 Hz), 6.78 (d, 2 *m*-ArH), and 7.46 (d, 2, *o*-ArH).

*B. By reduction of p-nitrophenyl-2,3,4,6-tetra-O-acetyl-1-thio- $\beta$ -D-galactopyranoside (11).* Compound 11 was prepared according to Schneider and Lee<sup>10</sup>. Reduction of 11 was effected in a Brown hydrogenator assembled for external generation of hydrogen<sup>11</sup>. Compound 11 (2.2 g, 4.5 mmoles) was suspended in the reaction flask in 90% acetic acid (100 ml) containing 3 g of 5% Pd-BaSO<sub>4</sub>. The generator contained acetic acid (5 ml) in water (50 ml). The buret contained M sodium borohydride in M sodium hydroxide (10 ml). The reaction was monitored by following the uptake of the hydride, and appeared to be complete in 1 h. After 2 h, the mixture was filtered, the filtrate was evaporated, and the product was crystallized from 95% ethanol, to yield 1.95 g (95%) of 9. The product was indistinguishable from that obtained by method *A*.

6-(Trifluoroacetylamino)hexanoic acid (12). — To a solution of 6-amino-hexanoic acid (2.85 g, 21.8 mmoles) in water (30 ml) containing 3 g of potassium carbonate was added *S*-ethyl trifluorothioacetate (3 ml, 23 mmoles), and the solution was stirred for 3 h. Additional *S*-ethyl trifluorothioacetate (3 ml) was added, and the mixture was stirred overnight; acidification with 6M hydrochloric acid, followed by cooling in an ice bath, gave crystalline product (12) in 77% yield; m.p. 87°.

*Anal.* Calc. for C<sub>8</sub>H<sub>12</sub>F<sub>3</sub>NO<sub>3</sub>: C, 42.29; H, 5.33; F, 25.09. Found: C, 42.39; H, 5.38; F, 25.29.

*p*-(6-Aminohexanamido)phenyl 1-thio- $\beta$ -D-galactopyranoside (13). — Compound 10 (287 mg, 1 mmole) was treated with compound 12 (250 mg, 1.1 mmoles) in the presence of 2-ethoxy-*N*-(ethoxycarbonyl)-1,2-dihydroquinoline<sup>12</sup> (EEDQ; 297 mg, 1.2 mmoles) in dry ethanol (15 ml). The mixture was heterogeneous at first, but became clear after being stirred for 2–3 h; it was kept overnight at room temperature. Evaporation of the clear solution gave a brown syrup, which solidified

upon trituration with anhydrous ether. The solid was separated, and dissolved in dry ethanol (15 ml); slow addition of benzene then gave a partly crystalline solid, which was deacylated, in 50% ethanol, with Dowex 1 X-8 ( $\text{OH}^-$ ) as already described. Compound **13** was obtained in 92% yield; m.p. 198–199°,  $[\alpha]_D -41.8^\circ$  (water).

*Anal.* Calc. for  $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_6\text{S}$ : C, 53.97; H, 7.04; N, 6.99; S, 8.00. Found: C, 53.91; H, 7.04; N, 6.89; S, 8.03.

## DISCUSSION

1-Thioaldosides can be prepared<sup>1,3</sup> by (i) *S*-alkylation of 1-thioglycoses, (ii) glycosylation of thiols, (iii) replacement of the 1-acetoxyl group with a thiol group, and (iv) conversion from the sugar dithioacetals. The last two methods require a large excess of the thiol and, hence, are not suitable when the aglycons are not readily available (as in the present work). Method *ii* was found inconvenient, because of instability of the reactants and difficulty in purification of the reaction products (except for the synthesis of **9**). The first method was most satisfactory in our hands for the synthesis of **6**, **7**, and **8**, especially when 1-thio sugars were generated from the corresponding *S*-glycosyl-thiopseudoureas *in situ*. Both the *S*-glycosyl-thiopseudoureas, and the iodides used in the present work were readily prepared in crystalline form and were very stable, even at room temperature.

The pseudothioureia derivatives prepared by the established methods<sup>7–9</sup> were 1-thio- $\beta$ -D-glycosides. Consequently, the 1-thio sugars generated from 1-thioglycosides in the reaction mixture had the  $\beta$ -D configuration. Inspection of the p.m.r. spectra revealed that the signals for the anomeric proton of compounds **6**, **7**, **8**, and **9** all had a rather large splitting-constant ( $J_{1,2}$  8–9 Hz), indicating that they had the  $\beta$ -D configuration. No signal corresponding to an  $\alpha$ -D anomeric proton could be found in any of these spectra.

Of the two *N*-protective groups (trifluoroacetyl and benzyloxycarbonyl), the trifluoroacetyl group was the more convenient to use. Removal of the benzyloxycarbonyl group by catalytic hydrogenolysis was unsuccessful, because of poisoning of the catalyst, and so, hydrogen bromide had to be used; this resulted in extra steps in the synthetic scheme, and lowered the overall yield. On the other hand, trifluoroacetyl groups could be removed under mildly alkaline conditions, and, in our scheme, the use of Dowex 1 X-8 ( $\text{OH}^-$ ) resin facilitated removal of *O*-acetyl groups and the *N*-(trifluoroacetyl) group simultaneously and, the yields were, usually, almost quantitative. The use of the strong, anion-exchange resin was also an improvement over the use of barium (or sodium) methoxide<sup>6</sup>, which was found to give *N*-acetylated byproducts when the compound to be deacetylated had an unprotected amino group (e.g., **5b**). In our hands, these methoxides were also ineffective for de-*N*-(trifluoroacetyl)ation.

Conventionally, *p*-aminophenyl 1-thioaldosides are prepared by first synthesizing the *p*-nitrophenyl 1-thioaldoside and then converting it into the *p*-amino derivative by catalytic reduction. By directly coupling a tetra-*O*-acetylglucosyl

halide with *p*-aminobenzenethiol, an equally good overall yield was obtained in one step. Formation of *N*-glycosylated or *N*-acetylated byproducts was in this case insignificant, presumably because of the lower nucleophilicity of the anilinic amino group.

Although the present study was limited to the synthesis of derivatives of 1-thio-D-galactose and -D-glucose, and 2-acetamido-2-deoxy-1-thio-D-glucose, our scheme should be equally applicable to other sugars. The amino group of the aglycons of these 1-thioaldosides can be utilized to couple these glycosides to such insoluble matrices as Sepharose and Sephadex. The usefulness of such glycoside-bearing, solid matrices has been amply demonstrated in a study of cellular adhesion<sup>14</sup>.

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