ELSEVIER

Carbohydrate Research 300 (1997) 271–277

CARBOHYDRATE RESEARCH

Note

Synthesis of methyl 4-thio-β-cellobioside. A reinvestigation

Vincent Moreau, Jens Chr. Norrild [1], Hugues Driguez *

Centre de Recherches sur les Macromolécules Végétales, CNRS [2], B.P. 53, F-38041 Grenoble, France

Received 17 October 1996; in revised form 30 January 1997

Abstract

The best yield for the synthesis of the title compound was obtained by nucleophilic displacement of the 4-*O*-triflyl group in methyl tri-*O*-benzyl-4-*O*-triflyl-β-D-galactopyranoside by 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose in HMPA in the presence of diethylamine. Under these conditions, the formation of unsaturated side products was decreased. © 1997 Elsevier Science Ltd.

Keywords: Thioglycosides; Methyl 4-thio-β-cellobioside; E2-Elimination; S_N2 substitution

1. Introduction

Methyl hepta-*O*-acetyl-4-thio-α-cellobioside **3** was first obtained in 52% yield by the action of the sodium salt of methyl 4-thio-α-D-glucopyranoside (**2**) on tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1** and acetylation (Pathway 1, Scheme 1) [1]. The hemibenzoylated analog **4** was later on prepared (75% yield) by displacement of the triflate group in methyl 2,3,6-tri-*O*-benzoyl-4-*O*-triflyl-α-D-galactopyranoside (**7**) by the sodium salt of 1-thio-β-D-glucopyranose (**5**) (Pathway 2, Scheme 1) [2], and then more recently [3] from 1-thio-β-D-glucose pentaacetate **6** by in situ *S*-deacetylation and activation in the presence of 2-aminoethanethiol (cysteamine, 73% yield) [4]. However, when this synthetic approach involved **6** and methyl 2,3,6-tri-*O*-benzoyl-4-*O*-triflyl-β-D-galactopyranoside **15a** [5], the expected disaccharide **16a** was obtained in a disappointingly low yield (21%), the main product of the reaction being methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-L-*threo*-hex-4-enopyranoside **18a** (46%) (Table 1, entry 1, Scheme 2).

When this condensation was conducted in *N*,*N*-dimethylformamide, in the presence of diethylamine [6], a slight improvement was observed, the disaccharide **16a** being obtained in 38% yield, but the elimination product **18a** was still the major product of the reaction (44%, Table 1, entry 2).

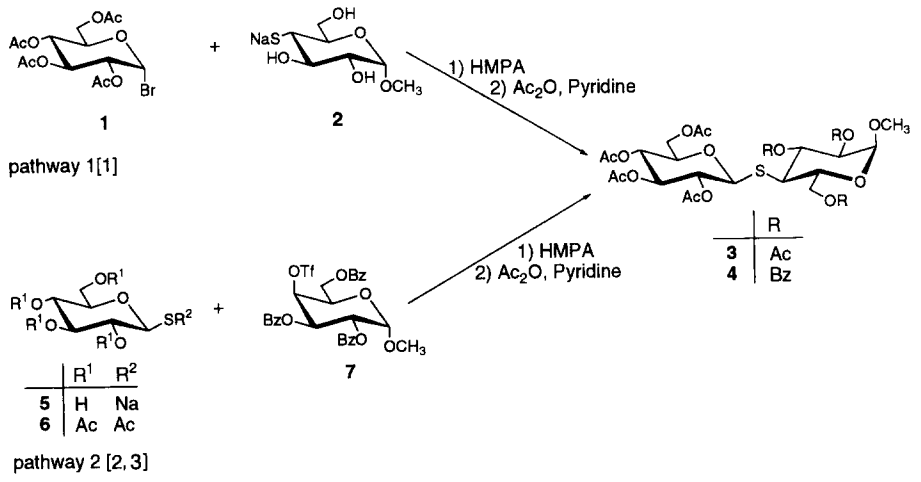
In view of the interest in 4-thio-oligosaccharide analogs as tools in glycobiology [7], we decided to investigate the steric and stereoelectronic influence of the protecting groups at C-6, C-3 and C-2 on the course of the reaction.

* Corresponding author.

[1] Permanent address: Department of Chemistry, the Technical University of Denmark, DK-2800 Lyngby, Denmark.

[2] Affiliated to Université Joseph Fourier Grenoble I.

0008-6215/97/$17.00 © 1997 Elsevier Science Ltd. All rights reserved.
PII S0008-6215(97)00046-3

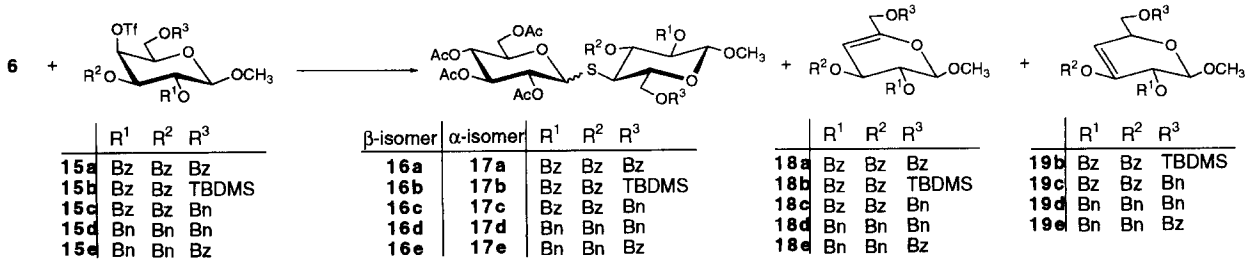


Scheme 1.

Table 1

Entries	Donor	Acceptor	Conditions	4-Thio-β-disaccharides (yield)	Unsaturated compounds (yield)	4-Thio-α-disaccharides (yield)
1	**6**	**15a**	cyst., DTE, HMPA	**16a** (21)	**18a** (46)	
2	**6**	**15a**	Et_2NH, DMF	**16a** (38)	**18a** (44)	
3	**6**	**15b**	Et_2NH, DMF	**16b** (46)	**18b** + **19b** (30)	**17b** (9)
4	**6**	**15c**	Et_2NH, DMF	**16c** (45)	**18c** + **19c** [a] (41)	**17c** (6)
5	**6**	**15d**	Et_2NH, DMF	**16d** (57)	**18d** + **19d** [a] (20)	**17d** (11)
6	**6**	**15d**	Et_2NH, HMPA	**16d** (69)	**18d** + **19d** [a] (21)	**17d** (2)
7	**6**	**15d**	cyst., DTE, HMPA	**16d** (75)	**18d** + **19d** [a] (19)	
8	**6**	**15e**	Et_2NH, DMF	**16e** (41)	**18e** + **19e** [a] (15)	
9	**6**	15e	Et_2NH, HMPA	**16e** (45)	**18e** + **19e** [a] (18)	**17e** (2)
10	**1**	**21**	Et_2NH, DMF	**16a** (27)		
11	**1**	**21**	Cs_2CO_3, DMF	**16a** (32)		

[a] A 1:1 ratio as estimated by ^1H NMR. No further characterisation was undertaken.



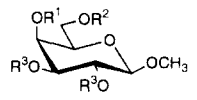
	R^1	R^2	R^3
15a	Bz	Bz	Bz
15b	Bz	Bz	TBDMS
15c	Bz	Bz	Bn
15d	Bn	Bn	Bn
15e	Bn	Bn	Bz

β-isomer	α-isomer	R^1	R^2	R^3
16a	**17a**	Bz	Bz	Bz
16b	**17b**	Bz	Bz	TBDMS
16c	**17c**	Bz	Bz	Bn
16d	**17d**	Bn	Bn	Bn
16e	**17e**	Bn	Bn	Bz

	R^1	R^2	R^3
18a	Bz	Bz	Bz
18b	Bz	Bz	TBDMS
18c	Bz	Bz	Bn
18d	Bn	Bn	Bn
18e	Bn	Bn	Bz

	R^1	R^2	R^3
19b	Bz	Bz	TBDMS
19c	Bz	Bz	Bn
19d	Bn	Bn	Bn
19e	Bn	Bn	Bz

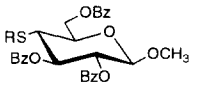
Scheme 2.



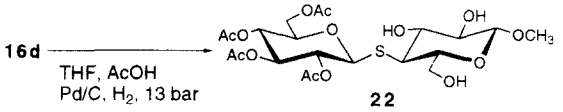
	R^1	R^2	R^3
8	H	Bz	Bz
9	-CHPh-		Bz
10	H	H	Bz
11	H	TBDMS	Bz
12	H	Bn	Bz
13	H	Bn	Bn
14	H	Bz	Bn

Starting from the readily available methyl 2,3-di-*O*-benzoyl-β-D-galactopyranoside **10** [8], selective protection at *O*-6 with a *tert*-butyldimethylsilyl group gave the 6-*O*-*tert*-butyldimethylsilyl protected derivative **11** (86%). In a similar approach, reductive ring-opening of the 4,6-benzylidene acetal in the dibenzoyl derivative **9** led to the 6-*O*-benzyl derivative **12** in 88% yield. Finally, the C-4 free hydroxyl group in **11**, **12**, in the already known tri-*O*-benzyl galactoside **13** [9] and in the 2,3-di-*O*-benzyl-6-*O*-benzoyl analog **14** [10] was converted into the triflates **15b–15e**, respectively, by reaction with triflic anhydride in CH_2Cl_2 and pyridine. Coupling of triflates **15b–15e** with peracetylated 1-thio-β-D-glucose **6**, activated either by diethylamine (entries 3–6,8,9) or cysteamine (entry 7), is reported in Table 1.

Under these conditions, we did not succeed to avoid totally the formation of the unsaturated by-products **18** and **19**, but a benzyl group at C-3 of the acceptor seemed to limit their formation (from ~ 40 to 20%, entries 1–4 and 5–9 respectively). In addition to the expected disaccharide **16** and elimination products **18** and **19**, the thio-α-disaccharide **17** was also isolated in variable amounts (2–11%). From these results, the formation of this 1,2-*cis*-disaccharide is more important in *N*,*N*-dimethylformamide than in hexamethylphosphorotriamide (entries 5 and 6) or in the presence of diethylamine (entries 6, 7). However, cysteamine cannot be used in these coupling reactions since *N*-acetyl-cysteamine was found as contaminant of the disaccharide **16d** after chromatographic purification.



	R
20	CN
21	H



Scheme 3.

In view of these results, the alternative synthesis involving the reaction of **1** and the 4-thiolate generated from **21** was investigated. Treatment of **15a** with potassium thiocyanate afforded the thiocyanate **20** in quantitative yield. Reduction of the thiocyanate group with zinc in acetic acid gave the thiol acceptor **21** (91%). However, glycosylation of **21** with **1** in the presence of diethylamine or cesium carbonate gave, quite surprisingly, the expected disaccharide **16a** in only low to moderate yield (27 and 32% respectively). It is worth to mention that Magnusson et al. [11] have recently used the same procedure for the synthesis in very high yield of a thiogalabiose derivative.

In conclusion, when methyl 4-*O*-triflyl-tri-*O*-benzyl-β-D-galactopyranoside (**15d**) was the acceptor in the 4-thiodisaccharide coupling reaction, the yield of the methyl 4-thio-β-cellobioside derivative **16d** was considerably improved. Hydrogenation using a large excess of catalyst afforded the debenzylated hemiacetylated thiodisaccharide **22** (Scheme 3) in 80% yield.

2. Experimental

General methods.—NMR spectra were recorded in D_2O (external reference) or in $CDCl_3$ (internal Me_4Si) with a Bruker 300 AC spectrometer. Low mass measurement was performed on a Nermag R-1010C mass spectrometer, NH_3-isobutane as ionisation gas and glycerol as matrix were respectively used for DCI and FAB(+) ionisation modes. Optical rotations were measured at room temperature (20 °C) with a Perkin–Elmer 241 polarimeter. For flash and open chromatographies, E. Merck Silica Gel 60 (0.040–0.063 mm) and (0.063–0.2 mm) were used respectively. Light petroleum refers to the 60–80 °C fraction. Hexamethylphosphorotriamide, which is a known carcinogen, was exclusively handled in a fume-hood and disposable gloves were worn.

*Methyl 2,3-di-*O*-benzoyl-6-*O*-tert-butyldimethylsilyl-β-D-galactopyranoside* (**11**).—To a soln of methyl 2,3-di-*O*-benzoyl-β-D-galactopyranoside **10** [8] (530 mg, 1.32 mmol) in dry pyridine (11 mL) at −5 °C was added *tert*-butyldimethylsilyl chloride (320 mg, 2.12 mmol). After stirring for 10 min at −5 °C and

then for 3 h at room temperature, the reaction mixture was quenched at 0 °C with MeOH (3 mL) and concd under reduced pressure. The residue was diluted with toluene and concd again (3 ×). It was then purified by column chromatography (4:1 petroleum ether–EtOAc) to yield **11** (584 mg, 86%), mp 121–122 °C (from EtOAc–petroleum ether), $[\alpha]_D^{20}$ +72° (*c* 0.83, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 7.98–7.31 (m, Ar), 5.75 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 10.3 Hz, H-2), 5.28 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3), 4.59 (d, 1 H, H-1), 4.38 (ddd, 1 H, $J_{4,5}$ 3.3, $J_{4,OH}$ 4.1 Hz, H-4), 4.01 (dd, 1 H, $J_{6a,6b}$ 10.6, $J_{6a,5}$ 5.7 Hz, H-6a), 3.93 (dd, 1 H, $J_{6b,5}$ 4.6 Hz, H-6b), 3.67 (m, 1 H, H-5), 3.5 (s, 3 H, OCH_3), 2.89 (d, 1 H, OH), 0.89 (s, 9 H, $C(CH_3)_3$), 0.1–0.09 (2 s, 6 H, $Si(CH_3)_2$); ^{13}C ($CDCl_3$): δ 165.9–165.4 (CO), 133.3–128.1 (Ar), 102.2 (C-1), 74.5, 74.0, 69.6, 68.1 (C-2, -3, -4, -5), 62.8 (C-6), 56.5 (OCH_3), 25.8 ($C(CH_3)_3$), 18.25 ($C(CH_3)_3$), -5 ($Si(CH_3)_2$); FAB$^+$MS (NBA + NaCl): *m/z* 539 $[M + Na]^+$. Anal. Calcd for $C_{27}H_{36}O_8Si$: C, 62.79; H, 6.97. Found: C, 62.69; H, 7.11.

Methyl 2,3-di-O-benzoyl-6-O-benzyl-β-D-galactopyranoside (**12**).—The 4,6-*O*-benzylidene derivative **9** [8] (250 mg, 0.51 mmol) was dissolved in dry THF (15 mL) containing 3 Å molecular sieves. Sodium cyanoborohydride (260 mg, 4.1 mmol) was added and the soln was stirred at room temperature for 15 min, after which a freshly prepared soln of HCl (6 M) in dry Et_2O was added dropwise until the evolution of gas ceased and the pH remained acidic. After 15 min, the reaction mixture was diluted in CH_2Cl_2 (50 mL) and washed with ice-cold water, ice-cold satd aq $NaHCO_3$ (2 ×) and brine. The organic soln was dried (Na_2SO_4) and concd. Column chromatography of the residue (3:2 petroleum ether–EtOAc) afforded **12** (220 mg, 88%), $[\alpha]_D^{20}$ +70° (*c* 0.42, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 8.0–7.25 (m, Ar), 5.77 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.3 Hz, H-2), 5.29 (dd, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 4.61 (d, 1 H, H-1), 4.59 (s, 2 H, CH_2Ph), 4.36 (m, 1 H, OH), 3.86–3.80 (m, 4 H, H-4, -5, -6a, -6b), 3.52 (s, 3 H, OCH_3); ^{13}C ($CDCl_3$): δ 165.9, 165.3 (CO); 133.3–127.7 (Ar); 102.2 (C-1); 74.4, 73.7, 69.6, 69.2 (C-2, -3, -4, -5); 73.3 (CH_2Ph); 68.0 (C-6); 56.7 (OCH_3); DCIMS (NH_3 + isobutane): *m/z* 510 $[M + NH_4]^+$, 461 $[M-OMe]^+$. Anal. Calcd for $C_{28}H_{28}O_8$: C, 68.28; H, 5.72. Found: C, 68.44; H, 5.46.

General procedure for the thiodisaccharide coupling reactions: methyl 4-O-triflyl-β-D-galactopyranoside derivatives **15a – 15e**.—Compounds **8**, **11**, **12** and **13** [9], **14** [10] (0.27 mmol) were dissolved in a mixture of CH_2Cl_2 (5 mL) and pyridine (0.6 mL) and triflic anhydride (0.41 mL, 2.5 mmol) was added at 0 °C. After stirring at 0 °C for 30 min and then at room temperature for 1 h, the reaction mixture was concd. The residue was dissolved in CH_2Cl_2, washed with ice-cold 10% aq $KHSO_4$, ice-cold satd aq $NaHCO_3$, ice-cold water, dried (Na_2SO_4) and concd to an oily product which was pure by TLC and used without further characterization.

Entries 1 and 7.—To a soln of **15a** or **15d**, freshly prepared from the corresponding alcohols **8** and **13** (0.27 mmol) in HMPA (4 mL), **6** (110 mg, 0.27 mmol), dithioerythritol (42 mg, 0.27 mmol) and cysteamine (21 mg, 0.27 mmol) were added. The reaction mixture was stirred at room temperature overnight (15 h) and then diluted with EtOAc, washed with H_2O (3 ×) and dried (Na_2SO_4). The residue obtained after concn was then purified by column chromatography.

Entries 2–5, 8.—To a soln of **15a–15d** or **15e** (0.27 mmol) in DMF (3 mL), the thioacetate **6** (110 mg, 0.27 mmol) and Et_2NH (0.44 mL, 4.25 mmol) were added. The soln was stirred at room temperature overnight, and concd. The residue was dissolved in CH_2Cl_2 and washed with H_2O, dried (Na_2SO_4) and concd. The crude product was purified by column chromatography.

Entries 6 and 9.—Compound **6** (0.27 mmol) and Et_2NH (0.16 mL, 1.54 mmol) were added to a soln of **15d** or **15e** in HMPA (3 mL). The reaction mixture was then treated as described above for compounds **15a** or **15d**.

General procedure for the purification of the reaction mixtures.—Flash chromatography allowed the separation of the elimination products **18** and **19** (eluent 2:1 petroleum ether–EtOAc or 3:1 petroleum ether–EtOAc for **16d**, **16e**) from the thiodisaccharides **16** (and **17** when formed). The mixtures of **16** and **17** were resolved further by chromatography on an open column using 2.5:1 petroleum ether–EtOAc.

Methyl 2,3,6-tri-O-benzoyl-4-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (**16a**).—Mp 195 °C (from EtOH), $[\alpha]_D^{20}$ +25° (*c* 0.98, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 8.0–7.29 (m, Ar), 5.65 (dd, 1 H, $J_{2,3}$ 9.4, $J_{3,4}$ 10.9 Hz, H-3), 5.38 (dd, 1 H, $J_{1,2}$ 7.9 Hz, H-2), 5.13 (dd, 1 H, $J_{2,3}$ 8.8 Hz, H-3′), 4.95–4.82 (m, 4 H, H-1′, -2′, -4′, -6a), 4.76 (dd, 1 H, $J_{6a,6b}$ 10.7, $J_{6b,5}$ 4.5 Hz, H-6b), 4.59 (d, 1 H, H-1), 4.14–4.10 (m, 2 H, H-5, -6′a), 4.00 (dd, 1 H, $J_{6a,6b}$ 12.3, $J_{6b,5}$ 5.9 Hz, H-6′b), 3.72 (m, 1 H, H-5′), 3.45 (s, 3 H, OCH_3), 3.29 (dd, 1 H, $J_{4,5}$ 10.9 Hz, H-4), 2.02, 1.98, 1.91, 1.54 (s, 12 H, $COCH_3$); ^{13}C ($CDCl_3$): δ 170.0, 169.7, 169.2, 169.1

($COCH_3$), 165.8, 165.5, 165.0 (COC_6H_5), 133.3–128.2 (C Ar), 101.8 (C-1), 81.2 (C-1'), 75.4, 74.2, 73.4, 73.1, 70.1, 69.7, 68.2 (C-2, -3, -5, -2', -3', -4', -5'), 63.8, 62.2 (C-6, -6'), 56.6 (OCH_3), 46.5 (C-4), 20.4, 20.3, 19.7 ($COCH_3$); DCIMS (NH_3 + isobutane): *m/z* 871 $[M + NH_4]^+$. Anal. Calcd for $C_{42}H_{44}O_{17}S$: C, 59.15; H, 5.19; S, 3.75. Found: C, 58.99; H, 5.15; S, 3.91.

*Methyl 2,3-di-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-4-thio-β-*D*-glucopyranoside* (**16b**).—Mp 155–157 °C (from EtOH), $[\alpha]_D^{20}$ +32° (*c* 0.62, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 7.94–7.28 (m, Ar), 5.53 (dd, 1 H, $J_{2,3}$ 9.4, $J_{3,4}$ 11.0 Hz, H-3), 5.26 (dd, 1 H, $J_{1,2}$ 7.9 Hz, H-2), 5.16 (dd, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3'), 4.96 (d, 1 H, $J_{1,2}$ 10.0 Hz, H-1'), 4.92 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4'), 4.85 (dd, 1 H, H-2'), 4.52 (d, 1 H, H-1), 4.18 (dd, 1 H, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 11.6 Hz, H-6a), 4.06–4.00 (m, 3 H, H-6b, -6'a, -6'b), 3.73–3.63 (m, 2 H, H-5, -5'), 3.45 (s, 3 H, OCH_3), 3.29 (dd, 1 H, $J_{4,5}$ 11.0 Hz, H-4), 2.04, 1.99, 1.92, 1.70 (s, 12 H, $COCH_3$), 0.94 (s, 9 H, $(C(CH_3)_3)$), 0.13, 0.12 (s, 6 H, $Si(CH_3)_2$); ^{13}C ($CDCl_3$): δ 170.3, 169.9, 169.3, 169.1 ($COCH_3$), 165.7, 165.2, (COC_6H_5), 133.1–128.2 (C, Ar), 101.5 (C-1), 82.1 (C-1'), 76.6, 75.5, 73.8, 73.2, 70.8, 70.0, 68.4 (C-2, -3, -5, -2', -3', -4', -5'), 62.5, 62.4 (C-6, -6'), 56.3 (OCH_3), 45.6 (C-4), 25.7 ($C(CH_3)_3$), 20.6, 20.4, 20.1 ($COCH_3$), 18.4 ($SiC(CH_3)_3$), −4.9, −5.0 ($Si(CH_3)_2$); DCIMS (NH_3 + isobutane): *m/z* 882 $[M + NH_4]^+$. Anal. Calcd for $C_{41}H_{54}O_{16}SSi$: C, 57.06; H, 6.30; S, 3.70. Found: C, 56.59; H, 6.29; S, 3.69.

*Methyl 2,3-di-*O*-benzoyl-6-*O*-*tert*-butyldimethylsilyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl)-4-thio-β-*D*-glucopyranoside* (**17b**).—$[\alpha]_D^{20}$ +195° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.87–7.28 (m, Ar), 5.72 (d, 1 H, $J_{1,2}$ 5.8 Hz, H-1'), 5.66 (dd 1 H, $J_{2,3}$ 9.6, $J_{3,4}$ 10.7 Hz, H-3), 5.20 (dd, 1 H, $J_{1,2}$ 7.9 Hz, H-2), 5.17 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 9.9 Hz, H-3'), 5.01 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-4'), 4.89 (dd, 1 H, H-2'), 4.55 (d, 1 H, H-1), 4.37–4.26 (m, 2 H, H-6'a, -5'), 4.14–3.96 (m, 3 H, H-6a, -6b, -6'b), 3.55 (m, 1 H, $J_{4,5}$ 10.7 Hz, H-5), 3.46 (s, 3 H, OCH_3), 3.25 (dd, 1 H, H-4), 2.08, 1.97 (s, 6 H, OCH_3), 0.92 (s, $C(CH_3)_3$), 0.12, 0.10, (s, 6 H, $Si(CH_3)_2$); DCIMS (NH_3 + isobutane): *m/z* 882 $[M + NH_4]^+$.

*Methyl 2,3,6-tri-*O*-benzoyl-4-deoxy-α-*L*-threo-hex-4-enopyranoside* (**18a**).—$[\alpha]_D^{20}$ +86° (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.2–7.35 (m, Ar), 5.54–5.50 (m, 2 H, H-2, -3), 5.43 (d, 1 H, $J_{3,4}$ 4.2 Hz, H-4), 5.21 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 4.89 (d, 1 H, $J_{6a,6b}$ 13.4 Hz, H-6a), 4.81 (d, 1 H, H-6b), 3.56 (s, 3 H, OCH_3); DCIMS (NH_3 + isobutane): *m/z* 506 $[M + NH_4]^+$.

*Methyl 2,3-di-*O*-benzoyl-4-deoxy-6-*O*-tert-butyldimethylsilyl-α-*L*-threo-hex-4-enopyranoside* (**18b**) *and methyl 2,3-di-*O*-benzoyl-4-deoxy-6-*O*-tert-butyldimethylsilyl-β-*D*-erythro-hex-3-enopyranoside* (**19b**).—The ratio **18b**/**19b** was 2:1 (^1H NMR). Compound **18b**: ^1H NMR: δ 8.0–7.25 (m, Ar) 5.56 (m, 1 H, H-3), 5.50 (dd, 1 H, $J_{1,2} = J_{2,3} = 4.5$ Hz, H-2), 5.26 (d, 1 H, $J_{3,4}$ 4.5 Hz, H-4), 5.13 (d, 1 H, H-1), 4.13 (s, 2 H, H-6a, -6b), 3.53 (s, 3 H, OCH_3), 0.89 (s, $(C(CH_3)_3)$), 0.08 (s, $Si(CH_3)_2$). Compound **19b**: ^1H NMR: δ 8.0–7.25 (m, Ar), 6.13 (d, 1 H, $J_{4,5}$ 3.0 Hz, H-4), 5.71 (m, 1 H, H-2), 4.90 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 4.58 (m, 1 H, H-5), 3.86 (dd, 1 H, $J_{6a,6b}$ 9.6, $J_{5,6a}$ 5.5 Hz, H-6a), 3.70 (dd, 1 H, $J_{5,6b}$ 8.2 Hz, H-6b), 3.50 (s, 3 H, OCH_3), 0.89 (s, $[C(CH_3)_3]$, 0.08 (s, $Si(CH_3)_2$); DCIMS (NH_3 + isobutane): *m/z* 516 $[M + NH_4]^+$, 467 $[M-OMe]^+$.

*Methyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-4-thio-β-*D*-glucopyranoside* (**16c**).—Mp 125–127 °C (from Et_2O), $[\alpha]_D^{20}$ +26° (*c* 0.76, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 7.92–7.27 (m, Ar), 5.54 (dd, 1 H, $J_{2,3}$ 7.9, $J_{3,4}$ 11.3 Hz, H-3), 5.33 (dd, 1 H, $J_{1,2}$ 7.9 Hz, H-2), 5.11 (dd, 1 H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3'), 4.91–4.77 (m, 3 H, H-1', -2', -4'), 4.71, 4.56 (d, 4 H, J_{ab} 11.7 Hz, CH_2Ph), 4.52 (d, 1 H, H-1), 4.08–3.90 (m, 4 H, H-6a, -6b, -6'a, -6'b), 3.82 (m, 1 H, H-5), 3.48 (s, 3 H, $COCH_3$), 3.44 (m, 1 H, H-5'), 3.37 (dd, 1 H, $J_{3,4} = J_{4,5} = 11.3$ Hz, H-4), 1.99, 1.93 (s, 12 H, $COCH_3$); ^{13}C ($CDCl_3$): δ 170.3, 170.0, 169.3, 169.1 ($COCH_3$), 165.7, 165.2, (COC_6H_5), 133.2–127.8 (C, Ar), 101.9 (C-1), 81.8 (C-1'), 76.4, 75.4, 73.8, 73.2, 70.8, 68.3 (C-2, -3, -5, -2', -3', -4', -5'), 73.6 (CH_2Ph), 69.1 (C-6'), 62.4 (C-6), 56.8 (OCH_3), 45.9 (C-4), 20.6, 20.5, 20.2 ($COCH_3$); FAB$^+$MS (NBA + NaCl): *m/z* 861 $[M + Na]^+$. Anal. Calcd for $C_{42}H_{46}O_{16}S$: C, 60.14; H, 5.48, S, 3.81. Found: C, 60.48; H, 5.60; S, 3.57.

*Methyl 2,3-di-*O*-benzoyl-6-*O*-benzyl-4-*S*-(2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosyl)-4-thio-β-*D*-glucopyranoside* (**17c**).—$[\alpha]_D^{20}$ +148° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.92–7.25 (m, Ar), 5.71 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1'), 5.70 (dd, 1 H, $J_{2,3}$ 9.6, $J_{3,4}$ 10.8 Hz, H-3), 5.24 (dd, 1 H, $J_{1,2}$ 7.9 Hz, H-2), 5.17 (dd, 1 H, $J_{2,3} = J_{3,4} = 10.1$ Hz, H-3'), 4.96 (dd, 1 H, $J_{4,5}$ 10.1 Hz, H-4'), 4.87 (dd, 1 H, H-2'), 4.67 (s, 2 H, CH_2Ph), 4.55 (d, 1 H, H-1), 4.24–4.19 (m, 2 H, H-5', -6'a), 3.93–3.86 (m, 3 H, H-6a, -6b, -6b'), 3.70 (m, 1 H, H-5), 3.48 (s, 3 H, OCH_3), 3.34 (dd, 1 H, $J_{4,5}$ 10.8 Hz, H-4), 1.99, 1.93 (s, 12 H,

$COCH_3$) DCIMS (NH_3 + isobutane): *m/z* 856 $[M + NH_4]^+$.

Methyl 2,3,6-tri-O-benzyl-4-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (**16d**).—$[\alpha]_D^{20}$ −8.5° (*c* 1.4, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 7.40–7.21 (m, Ar), 5.09–4.49 (m, 10 H, H-1′, -2′, -3′, -4′, 3 × CH_2Ph), 4.23 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 4.06 (dd, 1 H, $J_{6a,6b}$ 12.3, $J_{5,6a}$ 7.1 Hz, H-6′a), 3.97–3.84 (m, 3 H, H-6′b, -6a, -6b), 3.55 (s, 3 H, OCH_3), 3.52 (m, 1 H, H-5), 3.42 (m, 2 H, H-2, -3), 3.21 (m, 1 H, H-5′), 3.15 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 10.8 Hz, H-4), 1.98, 1.97, 1.96, 1.89 ($COCH_3$); ^{13}C ($CDCl_3$): δ 170.0, 169.3, 169.1 ($COCH_3$), 136.3–127.5 (C, Ar), 104.6 (C-1), 82.9, 82.7, 80.3, 76.3, 75.4, 75.2, 74.8, 73.9, 73.4, 70.5, 69.3, 68.1, 62.0 (C-2, -3, -5, -6, -1′, -2′, -3′, -4′, -5′, -6′, 3 × CH_2Ph), 56.9 (OCH_3), 47.3 (C-4), 20.5, 20.4 ($COCH_3$); DCIMS (NH_3 + isobutane): *m/z* 828 $[M + NH_4]^+$. Anal. Calcd for $C_{42}H_{50}O_{14}S$: C, 62.22; H, 6.17, S, 3.95. Found: C, 61.89; H, 6.19; S, 3.33.

Methyl 2,3,6-tri-O-benzyl-4-S-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (**17d**).—$[\alpha]_D^{20}$ +110° (*c* 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35–7.21 (m, Ar), 5.93 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1′), 5.27 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 10.0 Hz, H-3′), 5.08 (dd, 1 H, H-2′), 5.00 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4′), 4.95–4.57 (m, 6 H, 3 × CH_2Ph), 4.26 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.24 (m, 1 H, H-5′), 4.13 (dd, 1 H, $J_{6a,6b}$ 12.5, $J_{5,6a}$ 4.1 Hz, H-6′a), 3.90–3.78 (m, 3 H, H-6a, -6b, -6′b), 3.60 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 10.8 Hz, H-3), 3.54 (s, 3 H, OCH_3), 3.46 (m, 1 H, H-5), 3.37 (dd, 1 H, H-2), 2.99 (dd, 1 H, $J_{4,5}$ 10.8 Hz, H-4), 2.0, 1.94, 1.82 ($COCH_3$) DCIMS (NH_3 + isobutane): *m/z* 828 $[M + NH_4]^+$.

Methyl 2,3-di-O-benzyl-6-O-benzoyl-4-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (**16e**).—$[\alpha]_D^{20}$ −3° (*c* 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.03–7.23 (m, Ar), 5.07–4.80 (m, 10 H, H-2′, -3′, -4′, -6a, 3 × CH_2Ph), 4.69–4.60 (m, 4 H, H-1′, -6b, CH_2Ph), 4.3 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 4.01 (m, 2 H, H-6′a, -6′b), 3.80 (m, 1 H, H-5), 3.58–3.42 (m, 6 H, H-2, -3, -5′, OCH_3), 3.06 (dd, 1 H, $J_{3,4} = J_{4,5}$ = 10.6 Hz, H-4), 1.98, 1.96, 1.93, 1.84 ($COCH_3$); ^{13}C ($CDCl_3$): δ 170.2, 169.9, 169.2, 169.1 ($COCH_3$), 165.9 (COC_6H_5), 138.1–127.6 (Ar), 104.5 (C-1), 83.1, 82.1, 79.6, 75.7, 73.9, 73.7, 70.4, 68.0 (C-2, -3, -5, -1′, -2′, -3′, -4′, -5′), 75.3, 74.7 (CH_2Ph), 64.2, 62.1 (C-6, C-6′), 56.8 (OCH_3), 47.9 (C-4), 20.5, 20.4, 20.3 ($COCH_3$). FAB$^+$MS (NBA + NaCl): *m/z* 847 $[M + Na]^+$. Anal. Calcd for $C_{42}H_{48}O_{15}S$: C, 61.16; H, 5.82; S, 3.88. Found: C, 59.81; H, 5.77; S, 3.84.

Methyl 2,3-di-O-benzyl-6-O-benzoyl-4-S-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (**17e**).—$[\alpha]_D^{20}$ +106° (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.05–7.20 (m, Ar), 5.91 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1′), 5.22 (dd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 8.9 Hz, H-3′), 5.11 (dd, 1 H, H-2′), 4.99 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4′), 4.95 (d, 2 H, J_{ab} 11.1 Hz, CH_2Ph), 4.85 (m, 3 H, H-6a, CH_2Ph), 4.79 (d, 2 H, J_{ab} 11.1 Hz, CH_2Ph), 4.59 (d, 2 H, J_{ab} 11 Hz, CH_2Ph), 4.44 (dd, 1 H, $J_{6a,6b}$ 11.7, $J_{5,6a}$ 6.7 Hz, H-6b), 4.30 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.20 (dd, $J_{6a,6b}$ 12.4, $J_{5,6a}$ 4.7 Hz, H-6′a), 3.95 (dd, 1 H, $J_{5,6b}$ 2.0 Hz, H-6′b), 3.70 (m, 1 H, H-5), 3.62 (dd, 1 H, $J_{2,3}$ 8.75, $J_{3,4}$ 10.6 Hz, H-3), 3.48 (s, 3 H, OCH_3), 3.39 (dd, 1 H, H-2), 2.94 (dd, 1 H, $J_{4,5}$ 10.6 Hz, H-4), 2.03, 1.97, 1.94, 1.78 ($COCH_3$). FAB$^+$MS (NBA + NaCl): *m/z* 847 $[M + Na]^+$.

Methyl 4-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (**22**).—Compound **16d** (190 mg, 0.23 mmol) was dissolved in anhyd THF (45 mL) and AcOH (1 mL), 10% Pd/C (250 mg) was added. The mixture was stirred in a hydrogen atmosphere (1.4 kPa) at 25 °C for 72 h. The catalyst was removed by filtration and washed with EtOAc, and the combined filtrates were evaporated to dryness. Chromatography of the residue (98:2 EtOAc–MeOH) afforded **22** (101 mg, 80%), mp 182–184 °C (from pentane–EtOAc), $[\alpha]_D^{20}$ −18.5° (*c* 0.74, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 5.20 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 10.0 Hz, H-3′), 5.03 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4′), 4.96 (dd, 1 H, $J_{1,2}$ 10.0 Hz, H-2′), 4.68 (d, 1 H, H-1′), 4.21 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.15 (m, 2 H, H-6′a, -6′b), 3.90–3.86 (m, 3 H, H-6a, -6b, OH), 3.76 (m, 1 H, H-5′), 3.59 (s, 1 H, OH), 3.52 (s, 3 H, OCH_3), 3.48 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 10.6 Hz, H-3), 3.38–3.33 (m, 2 H, H-2, -5), 2.92 (s, 1 H, OH), 2.88 (dd, 1 H, H-4), 2.06, 2.03, 1.98, 1.96 ($COCH_3$); ^{13}C ($CDCl_3$): δ 170.7, 170.0, 169.5, 169.1 ($COCH_3$), 103.4 (C-1), 83.9 (C-1′), 75.7, 75.5, 74.8, 74.5, 73.5, 70.4, 68.1 (C-2, -3, -5-, -2′, -3′, -4′, -5′), 62.5, 61.9 (C-6, -6′), 57.1 (OCH_3), 49.2 (C-4), 20.6, 20.5, 20.4 ($COCH_3$); DCIMS (NH_3 + *isobutane*): *m/z* 558 $[M + NH_4]^+$. Anal. Calcd for $C_{21}H_{32}O_{14}S$: C, 46.66; H, 5.96; S, 5.93. Found: C, 46.58; H, 5.89; S, 6.01.

Methyl 2,3,6-tri-O-benzoyl-4-deoxy-4-thiocyanato-β-D-glucopyranoside (**20**).—The triflate **15a** obtained from **8** (3.75 g, 7.4 mmol) and KSCN (2.2 g, 22 mmol), was dissolved in DMF (40 mL) and the mixture was stirred for 15 h at room temperature. After evaporation to dryness, the residue was dissolved in CH_2Cl_2, washed with 10% aq $KHSO_4$ and water, dried, concentrated and purified by column

chromatography (1:1 petroleum ether–EtOAc). The compound **20** was obtained (4 g, 98%), mp 136–137 °C (from EtOH), $[\alpha]_D^{20}$ −28.1° (*c* 0.48, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 8.09–7.29 (m, Ar), 5.87 (dd, 1 H, $J_{3,4}$ 10.5, $J_{2,3}$ 9.0 Hz, H-3), 5.48 (dd, 1 H, $J_{1,2}$ 7.8 Hz, H-2), 4.85–4.83 (m, 2 H, H-6a, -6b), 4.75 (d, 1 H, H-1), 4.22 (m, 1 H, H-5), 3.51 (s, 3 H, OCH_3), 3.48 (dd, 1 H, $J_{4,5}$ 10.5 Hz, H-4); ^{13}C ($CDCl_3$): δ 165.8, 165.2, 165.0 (CO), 133.5–128.2 (Ar), 108.1 (NCS), 101.7 (C-1), 72.9, 72.5, 71.6 (C-2, -3, -5), 63.2 (C-6), 56.7 (OCH_3), 47.4 (C-4); DCIMS (NH_3 + isobutane): *m/z* 565 $[M + NH_4]^+$. Anal. Calcd for $C_{29}H_{25}O_8NS$: C, 63.61; H, 4.60; N, 2.55; S, 5.85. Found: C, 63.21; H, 4.60; N, 2.50; S, 5.83.

Methyl 2, 3, 6 - tri - O - benzoyl - 4 - thio - β - D - glucopyranoside (**21**).—To a soln of **20** (3.5 g, 6.4 mmol) in AcOH (110 mL) was added Zn (13 g). The mixture was heated at 130 °C for 3 h, cooled to 25 °C and filtered. The filtrate was diluted with $CHCl_3$ (500 mL), extracted with cold satd aq $NaHCO_3$, brine, and dried (Na_2SO_4). The residue obtained after concn was chromatographed (4:1 petroleum ether–EtOAc) and gave **21** (3.0 g, 91%), mp 121 °C (from 1-propanol), $[\alpha]_D^{20}$ +71° (*c* 1.42, $CHCl_3$); NMR: ^1H ($CDCl_3$): δ 8.10–7.27 (m, Ar), 5.55 (dd, 1 H, $J_{3,4}$ 10.5, $J_{2,3}$ 9.6 Hz, H-3), 5.38 (dd, 1 H, $J_{1,2}$ 7.8 Hz, H-2), 4.86 (dd, 1 H, $J_{6a,6b}$ 12.1, $J_{5,6a}$ 2.3 Hz, H-6a), 4.75 (dd, 1 H, $J_{5,6b}$ 4.9 Hz, H-6b), 4.67 (d, 1 H, H-1), 3.89 (m, 1 H, H-5), 3.48 (s, 3 H, OCH_3), 3.25 (dd, 1 H, $J_{4,5}$ 10.5 Hz, H-4); ^{13}C ($CDCl_3$): δ 166.1–165.9, 165.2 (CO), 133.2–128.2 (Ar), 101.9 (C-1), 76.1, 75.5, 72.7 (C-2, -3, -5), 64.1 (C-6), 56.8 (OCH_3), 41.0 (C-4); DCIMS (NH_3 + isobutane): *m/z* 540 $[M + NH_4]^+$. Anal. Calcd for $C_{28}H_{26}O_8S$: C, 64.36; H, 4.98; S, 6.13. Found: C, 64.29; H, 4.95; S, 6.13.

Methyl 2,3,6-tri-O-benzoyl-4-S-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-thio-β-D-glucopyranoside (**16a**).—(Entries 10 and 11). To the thiol **21** (78 mg, 0.15 mol) and Cs_2CO_3 (50 mg, 0.15 mol) or Et_2NH (0.29 mL, 2.8 mol) in DMF (2 mL), the bromide **1** (62 mg, 0.15 mmol) was added. The mixture was stirred for 5 h and 15 h respectively at room temperature and concd. Work-up and purification, as already described, afforded **16a** in 27–32% yield.

Acknowledgements

We are grateful to Prof. C. Pedersen (the Technical University of Denmark, Lyngby) for his interest to this work.

References

[1] M. Blanc-Muesser, J. Defaye, and H. Driguez, *Carbohydr. Res.*, 67 (1978) 305–328.
[2] C. Orgeret, E. Seillier, C. Gautier, J. Defaye, and H. Driguez, *Carbohydr. Res.*, 224 (1992) 29–40.
[3] V. Moreau, thèse de Doctorat de l'Université de Grenoble I, 1995.
[4] M. Blanc-Muesser and H. Driguez, *J. Chem. Soc., Perkin Trans. I*, (1988) 3345–3351.
[5] P.J. Garegg and S. Oscarson, *Carbohydr. Res.*, 137 (1985) 270–275.
[6] S. Bennett, M. von Itzstein, and M.J. Kiefel, *Carbohydr. Res.*, 259 (1994) 293–299.
[7] H. Driguez, in J. Thiem and H. Driguez (Eds.), *Top. Curr. Chem.*, 187 (1997) 85–116 and refs cited therein.
[8] J.S.D. Bacon, D.J. Bell, and H.W. Kosterlitz, *J. Chem. Soc.*, (1939) 1248–1250.
[9] P.J. Garegg, H. Hultberg, and S. Wallin, *Carbohydr. Res.*, 108 (1982) 97–101.
[10] J.S. Brimacombe and O.A. Ching, *J. Chem. Soc. (C)*, (1968) 1642–1646.
[11] U. Nilsson, R. Johansson, and G. Magnusson, *Chem. Eur. J.*, 2 (1996) 295–302.