A Through-process for the Preparation of Methyl Per-*O*-acetyl 1-Thio-glycosides from Aldoses

Shinkiti Koto,* Toyosaku Yoshida, Kazuhiro Takenaka, and Shonosuke Zen

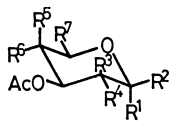
School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108

(Received May 4, 1982)

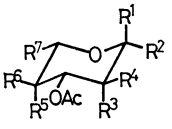
Synopsis. D-Glucose, D-galactose, D-mannose, D-xylose, L-arabinose, L-fucose, L-rhamnose, maltose, cellobiose, lactose, D-glucosamine, D-galactosamine, and D-mannosamine were converted into the corresponding methyl per-*O*-acetyl 1-thioglycopyranosides by way of a three-step (acetobromination, methylthioation, and acetylation) through-process in a single vessel.

The alkyl thio group is useful for protecting the anomeric center of carbohydrate in the sequential glycoside synthesis.[1] Continuing our methodologic study of oligosaccharide synthesis,[1a,2] a handy procedure for introducing the methylthio group at the anomeric center of a given saccharide was developed.

D-Glucose was smoothly acetobrominated through reaction with acetyl bromide (AcBr) in acetic acid (AcOH). The use of the AcOH solvent prevents any occasional sudden evolution of HBr such as occurs in the direct use of AcBr for the acetobromination of free sugar. The reaction was so clean that the evaporation of excess AcBr and AcOH gave 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide ready for immediate use. The subsequent conversion to the methylthio compound was conveniently carried out by a reaction with commercially available aq sodium methanethiolate (MeSNa) in acetone. Because of the concurrent de-*O*-acetylation during mercaptolysis, a reacetylation process was required. The chromatography of the reaction mixture afforded methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**1**) in a ≈60% yield. The whole process from D-glucose to **1** could be done in a single vessel.

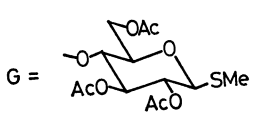


1—5, 8—13



6, 7

Compd	R^1	R^2	R^3	R^4	R^5	R^6	R^7
1	H	SMe	H	OAc	H	OAc	CH_2OAc
2	H	SMe	H	OAc	OAc	H	CH_2OAc
3	SMe	H	OAc	H	H	OAc	CH_2OAc
4	H	SMe	H	OAc	H	OAc	H
5	H	SMe	H	OAc	OAc	H	H
6	H	SMe	H	OAc	OAc	H	Me
7	SMe	H	OAc	H	H	OAc	Me
8	G	H	H	OAc	H	OAc	CH_2OAc
9	H	G	H	OAc	H	OAc	CH_2OAc
10	H	G	H	OAc	OAc	H	CH_2OAc
11	H	SMe	H	NHAc	H	OAc	CH_2OAc
12	H	SMe	H	NHAc	OAc	H	CH_2OAc
13	SMe	H	NHAc	H	H	OAc	CH_2OAc



Using this through-process, D-galactose, D-mannose, D-xylose, L-arabinose, L-fucose, and L-rhamnose were readily converted into the corresponding acetates of methyl 1-thioglycopyranosides. In the cases of the 6-deoxy sugars, however, a careful control of the temperature for the evaporation of excess AcBr was essential.

Disaccharides, maltose, cellobiose, and lactose, were also suitable; their inter-glycoside linkage was not cleaved at all during acetobromination.

In the case of D-glucosamine, the acetobromination took a much longer time[3] compared to those described above. Nevertheless, methyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (**11**) was obtained in a ≈50% yield. Other amino sugars, D-galctosamine, and D-mannosamine were derived into the thioglycoside derivatives.

Thus, the through-process presented is so simple and economical that its rather low yields do not make it disadvantageous in comparison with the previously known methods for preparing methyl 1-thioglycoside.[4]

Experimental

General. See the preceeding report.[5]

General Procedure for Obtaining the Data in Table 1. Cooled AcOH (0.5 ml) was added into a suspention of aldose (with or without water of crystallization) or glycosamine hydrochloride (1.0 mmol) in AcBr (1.0 ml) under stirring at 0 °C. The mixture was then stirred at room temperature for 2 h (but for 3 d for amino sugar). The excess reagents were then evaporated off at 25—35 °C, followed by evaporation with toluene. Cold aq MeSNa (Tokyo Kasei, 15%, 2.0 ml) was added into a solution of the acetobromo sugar thus obtained in acetone (3.5 ml) under stirring at 0 °C; in the case of aminosugar, the amount of aq MeSNa was doubled. The mixture was then stirred for 18 h at room temperature. Evaporation at 45—55 °C gave a solid material which was heated in Ac_2O (3.0 ml) containing NaOAc (0.1 g) under stirring at 100 °C. Evaporation on a boiling-water bath and subsequent chromatography on silica gel using the toluene–2-butanone system (gradient) gave totally acetylated methyl 1-thioglycopyranoside.

An Example of Large-scale Preparation. D-Mannose (10 g, 0.056 mol) was added at once into well-cooled AcBr (56 ml) under good stirring at 0 °C. Soon after this, cold AcOH (28 ml) was added to the suspension. During the next 10 min, all the sugar dissolved, with a fairly violent evolution of HBr. After the evolution had been set aside, the ice-bath was removed and the solution was stirred for 1.5 h at the ambient temperature. The excess reagents were evaporated under reduced pressure at 23—35 °C and then co-evaporated with toluene three times. The heavy syrup thus obtained was evacuated for 0.5 h and dissolved in cold Me_2CO (80 ml). Cold aq NaSMe (15%, 86 ml) was then added to the stirred solution at 0 °C. After the ice bath had been removed, the mixture was vigorously stirred at the ambient temperature for 18 h. After the evaporation of volatile ma-

TABLE 1. PHYSICAL AND ANALYTICAL DATA

Compd	Yield %	Mp θ_m/°C	$[\alpha]_D^{25}$/°(c, $CHCl_3$)	Mol formula	Calcd(%) C	Calcd(%) H	Calcd(%) N	Found(%) C	Found(%) H	Found(%) N	Lit
1	61	99—100	−15(0.9)	$C_{15}H_{22}O_9S$	47.61	5.86		47.58	5.92		a
2	49	111—112	+2(0.7)					47.53	5.84		b
3	59	122—124	+102(0.8)					47.69	5.91		c
4	56	90—92	−74(0.5)	$C_{12}H_{18}O_7S$	47.05	5.92		46.90	5.88		d
5	40	80—81	+6(0.3)					46.92	5.90		e
6	57	149—150	+2(1.0)	$C_{13}H_{20}O_7S$	49.76	6.12		48.96	6.36		
7	34	—	−114(2.1)					49.50	6.40		
8	46	130—132	+50(0.5)	$C_{27}H_{38}O_{15}S$	48.64	5.75		48.46	5.70		f
9	59	200—202	−20(0.8)					48.65	5.82		g
10	45	128—130	−8(0.5)					48.34	5.81		h
11	54	199—200	−37(0.9)	$C_{15}H_{23}NO_8S$	47.74	6.14	3.71	47.92	6.24	3.66	
12	34	208—210	−33(0.3)					47.53	6.18	3.60	
13	34	—	+125(1.6)					47.76	6.18	3.68	

a) Ref. 4c; mp 96 °C, $[\alpha]_D$ −12.2°(c 1.2, $CHCl_3$). Ref. 4d; mp 91 °C, $[\alpha]_D$ −12.0°(c 1.0, $CHCl_3$). b) Ref. 4b; mp 108 °C, $[\alpha]_D^{17}$ +2.85°(c 1.3, $CHCl_3$). Ref. 4f; mp 109—111 °C, $[\alpha]_D$ +3.7($CHCl_3$). c) Ref. 4f; mp 123—125 °C, $[\alpha]_D$ +93.1°($CHCl_3$). d) Ref. 4e; mp 87.5—90 °C, $[\alpha]_D$ −73.4±2°(c 0.49, $CHCl_3$). e) Ref. 4b; mp 73—74 °C, $[\alpha]_D^{18}$ +6.2°(c, 1.95, $CHCl_3$). f) Ref. 4f; mp 133—135 °C, $[\alpha]_D$ +56.0°($CHCl_3$). g) Ref. 4a; mp 200 °C, $[\alpha]_D^{20}$ −20.3°(c 1.6, $CHCl_3$). h) Ref. 4f; mp 124—125 °C, $[\alpha]_D$ −9.0($CHCl_3$).

TABLE 2. ^{1}H NMR DATA[a)]

Compd	H-1(J/Hz)	MeS, Ac	MeC(J/Hz)
1	4.38(9)	1.98 2.00 2.04 2.06 **2.16**	
2	4.39(9)	1.98 2.03 2.06 2.15 **2.17**	
3	5.17(≈1)	1.97 2.04 2.09 2.14(6H)	
4	4.37(9)	2.02(6H) (2.06 2.15)	
5	4.39(8.5)	2.01 2.06 2.13 2.17	
6	4.35(10)	1.96 2.05 2.15 2.17	1.21(7.6)
7	5.07(≈1)	1.96 2.03 2.14(6H)	1.25(7.0)
8	4.43(10)	1.99 2.00 2.01 2.02 2.04 2.09 2.13(6H)	
9	4.35(10)	1.96 2.00 2.02(6H) 2.05 2.08 2.11 2.13	
10	4.37(10)	1.95 2.03(12H) 2.10 2.13(6H)	
11	4.58(10)	1.96 2.02 2.03 2.07 2.19	
12	4.59(10)	1.93 1.95 2.02 2.15 2.19	
13	5.11(1.5)	1.98 2.04 2.05 2.09 2.13	

a) The spectra were determined at 90 MHz in $CDCl_3$ with Me_4Si.

terials at 45—55 °C, the residue thus obtained was stirred in Ac_2O (168 ml) containing AcONa (5.8 g) at 100 °C for 2 h. Evaporation on a boiling water bath and subsequent chromatography gave **3** (8.4 g, 40%).

References

1) a) S. Koto, T. Uchida, and S. Zen, *Bull. Chem. Soc. Jpn.*, **46**, 2520 (1973); b) P. J. Pfaffli, S. H. Hixon, and L. Anderson, *Carbohydr. Res.*, **23**, 195 (1972); M. A. Nashed, M. Kiso, C. W. Slife, and L. Anderson, *ibid.*, **90**, 71 (1981).

2) S. Koto, N. Morishima, C. Kusuhara, S. Sekido, T. Yoshida, and S. Zen, *Bull. Chem. Soc. Jpn.*, **55**, 2995 (1982).

3) G. Fodor and L. Ötvös, *Chem. Ber.*, **89**, 701 (1956); Y. Ito, S. Koto, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **35**, 1618 (1962).

4) F. Wrede and O. Hettche, *Z. Physiol. Chem.*, **172**, 169 (1927); B. Helferich, H. Grunewald, and F. Langenhoff, *Chem. Ber.*, **86**, 873 (1953); M. Cerny and J. Pacak, *Chem. Listy*, **52**, 2090 (1958); M. Sakata, M. Haga, S. Tejima, and M. Akagi, *Chem. Pharm. Bull.*, **12**, 652 (1964); J. Stanek, M. Sindlerova, and M. Cerny, *Coll. Czech. Chem. Commun.*, **30**, 297 (1965); T. Ogawa and M. Matsui, *Carbohydr. Res.*, **54**, C17 (1977).

5) S. Koto, N. Morishima, R. Kawahara, K. Ishikawa, and S. Zen, *Bull. Chem. Soc. Jpn.*, in press.

TABLE 3. ^{13}C NMR DATA[a)]

Compd	C-1′	C-1	C-2—C-6 (and C-2′—C-6′)										CH_3CON	CH_3-5	CH_3S
1	—	83.0	76.2	74.1	69.3	68.5	62.3						—	—	11.3
2	—	83.6	74.7	72.1	67.5	66.7	61.6						—	—	11.5
3	—	83.7	71.0	69.7	69.1	66.5	62.6						—	—	13.6
4	—	83.6	72.8	69.3	69.0	66.1							—	—	11.6
5	—	84.2	71.2	68.2	67.6	66.8							—	—	12.0
6	—	83.3	73.4	72.5	70.7	66.9							—	**16.5**	11.5
7	—	83.6	71.4	70.8	69.6	67.1							—	**17.5**	13.8
8	95.8	82.8	76.4(2)	72.9	70.2(2)	69.5	68.7	68.1	63.1	61.6			—	—	11.5
9	101.1	83.1	77.0	76.6	73.7	73.1	72.2	71.8	69.7	68.0	62.3	61.7	—	—	11.6
10[b)]	101.3	83.0	77.0	76.4	73.9	71.2	70.9	69.7	69.3	66.8	62.4	61.0			11.5
11	—	84.5	76.2	74.2	68.6	62.5	52.6						23.3	—	11.7
12	—	85.1	74.7	72.2	67.5	62.3	48.6						22.8	—	11.9
13	—	85.0	69.7	68.7	66.5	62.7	51.3						23.4	—	13.6

a) The spectra were determined at 25.1 MHz, in $CDCl_3$ with Me_4Si. b) in $CDCl_3$-$(CD_3)_2CO$.