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Note

A simple method for avoiding alkylthio group migration during the synthesis of thioglycoside 2,3-orthoesters. An improved synthesis of partially acylated 1-thio-α-L-rhamnopyranosides

Vince Pozsgay

Laboratory of Developmental and Molecular Immunity, National Institute of Child Health and Human Development, and Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892 (USA)

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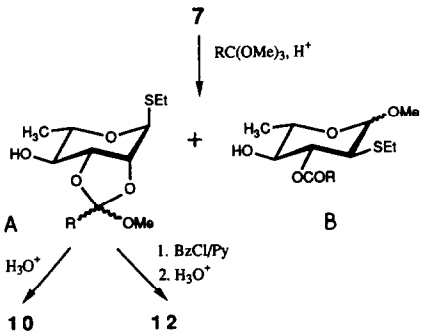
The potential usefulness of alkyl and aryl 1-thioglycosides as intermediates in oligosaccharide synthesis was recognized many years ago[1]. Since the revival of the concept of direct activation of alkyl thioglycosides by Lönn[2] in 1984, such compounds became familiar building blocks in oligosaccharide syntheses either as glycosyl acceptors or glycosyl donors[3].

Although thioglycosides have often been used with success in oligosaccharide syntheses, a number of undesirable transformations were also observed such as glycal formation[2], alkylthio group transfer[2,4,5], and decomposition[5].

Recently, Auzanneau and Bundle[6] reported an additional, serendipitous observation involving a thioglycoside. They found that major structural changes of ethyl 1-thio-α-L-rhamnopyranoside[7] (**7**) occurred when preparation of its cyclic, 2,3-orthoester (**A**, Scheme 1) was attempted, using trialkyl orthoacetates or trialkyl orthobenzoates as reagents, according to the protocol of Garegg and Hultberg[8] that became a standard procedure for the *O*-rhamnopyranosides[9] (Scheme 1). These changes included the stereospecific migration of the anomeric, ethylthio group to C-2 and the attack by the alkoxy group, derived from either the reagent or the product orthoester, at the anomeric carbon to yield the L-*gluco* derivative **B**. The migration could be suppressed by employing an optimized set of reaction conditions. Thus, treatment of the triol **7** under catalysis by 4-toluenesulfonic acid, in *N*,*N*-dimethylformamide as the solvent[8] at 50° for two days, followed by acetic

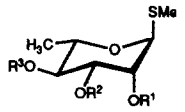
Correspondence to: Dr. V. Pozsgay, National Institutes of Health, Building 8/B1A-25, Bethesda, MD 20892, USA.



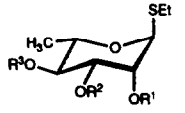
Scheme 1.

acid hydrolysis according to King and Allbutt[10], afforded the 2-benzoate **10** in 54–66% yield. When the intermediate orthoester **A** was treated with benzoyl chloride and pyridine prior to the hydrolytic step, the 2,4-dibenzoate **12** was obtained in 52% yield. If acetonitrile was used as the solvent instead of *N*,*N*-dimethylformamide, the migration became dominant[6]. The concentration of the acid catalyst in the reported procedure[6] seems to be critical, and slight deviations from the "optimized" conditions appear to either prevent the reaction from proceeding, or to favor the formation of the rearranged products. This, and the long reaction times (2.5 days for **12**) make the approach[6] unlikely to be suitable for scale-up. It is noted that compound **12** was previously obtained by Veeneman[11] from the triol **7** in a three-step procedure [(*i*) methoxytritylation, (*ii*) benzoylation, (*iii*) hydrolytic removal of the methoxytrityl group] in an overall yield of 55%.

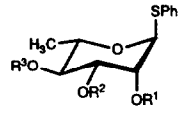
The author reasoned that the most likely cause of the rearrangement, under moderately acidic conditions, is the attack at the anomeric carbon by the alcohol released from the reagent during the formation of the cyclic, 2,3-orthoester instead of a concerted migration of the ethylthio group to C-2 and attack by the alkoxy group at C-1. To test this hypothesis, a mixture containing the triol[7] **7** and trimethyl orthobenzoate in *N*,*N*-dimethylformamide was subjected to vacuum immediately after addition of the acid catalyst (10-camphorsulfonic acid) to remove the volatile by-product methanol. The cyclic orthoester formation was complete within 15 min without the need for heating. It is important to note that rearrangement was negligible ($< 5\%$) with methyl or ethyl thiorhamnoside, even at high acid concentrations (up to 10 mg/mL), and could not be observed at all with the phenyl thiorhamnosides **15** and **23**. Under identical conditions, except that the reactions were carried out under atmospheric pressure, rearranged compounds similar to those described[6] were the major products. This procedure was equally well applicable for the preparation of cyclic orthoacetates using trimethyl orthoacetate as the reagent. Acetic acid catalyzed hydrolysis of the orthoacetates and orthobenzoates, formed from triols **1**, **7**, and **15** gave the 2-acetates **2**, **8**, and **16**, and the 2-benzoates **4**, **10**, and **18**, respectively in 80–88% yields (Table I). It is noted that



	R1	R2	R3
1	H	H	H
2	Ac	H	H
3	H	Ac	H
4	Bz	H	H
5	H	Bz	H
6	Bz	H	Bz



	R1	R2	R3
7	H	H	H
8	Ac	H	H
9	H	Ac	H
10	Bz	H	H
11	H	Bz	H
12	Bz	H	Bz
13	CMe_2		Bz
14	H	H	Bz



	R1	R2	R3
15	H	H	H
16	Ac	H	H
17	H	Ac	H
18	Bz	H	H
19	H	H	Bz
20	Bz	H	Bz
21	CMe_2		H
22	CMe_2		Bz
23	H	H	Bz

Scheme 2.

each of these products contained a varying amount (3–7%) of the isomeric, 3-*O*-acyl derivative, as inferred from their ^{1}H NMR spectra. The relative proportion of the 3-*O*-acyl isomers was not affected by using trifluoroacetic acid in aqueous acetonitrile, instead of aqueous acetic acid, for the hydrolytic step. Although the 3-*O*-acyl isomers were note reported in a related work[6], formation of the *equatorial O*-acyl derivatives, as minor products, in acid-catalyzed opening of cyclic orthoesters is not without precedence[10].

TABLE I

Yields of mixed 2- and 3-mono-*O*-acyl-1-thio-α-L-rhamnopyranosides by Procedure A[a]

Aglycon	% Yield, isolated (compound No.)	
	2/3-*O*-Ac	2/3-*O*-Bz
Me	88 (**2**)/5 (**3**)	81 (**4**)/4 (**5**)
Et	88 (**8**)/3 (**9**)	83 (**10**)/3 (**11**)
Ph	87 (**16**)/7(**17**)	80 (**18**)/5 (**19**)

[a] Isomeric ratios were estimated by ^{1}H NMR spectroscopy at 300 MHz.

TABLE II

Yields and specific rotations of the 2,4-dibenzoates

Compound	% Yield, isolated		$[\alpha]_D^{22}$ in $CHCl_3$ (c)
	Procedure B	Procedure C	
6	79		−20° (1.07)
12	70	86	−27° (0.99) [a]
20	87	89	−95° (0.89)

[a] Lit.[6] −28°, lit.[11] −19.5°.

In situ benzoylation of the cyclic orthobenzoates formed from the triols **1**, **7**, and **15** followed by hydrolysis with 80% acetic acid provided the 2,4-dibenzoates **6**, **12**, and **20** in yields of 70–87% (for the three steps) (Table II). In this case the formation of the isomeric, 3,4-dibenzoates was not observed (^{1}H NMR) indicating that the substituent at HO-4 influences the regioselectivity of the 2,3-cyclic orthoester opening reaction. Again, no rearrangement products could be observed with the phenyl thioglycosides whereas the amount of such by-products was ~ 5% or less for the methyl and ethyl 1-thio-α-L-rhamnosides.

An alternative route to the dibenzoates **12** and **20** used the 4-benzoates **14** and **23** as the starting materials. These were obtained from the triols **7** and **14** by way of a standard protection–deprotection sequence [(*i*) isopropylidenation, (*ii*) benzoylation, (*iii*) hydrolysis]. The diols **14** and **23** were then mixed with trimethyl orthobenzoate as described in general procedure C. Acid-catalyzed, cyclic orthoester formation, followed by acetic acid hydrolysis gave the dibenzoates **12** and **20** in excellent yields (Table II).

It is important to note that no differences were observed in the formation of the cyclic orthoesters when they were prepared, using either *N*,*N*-dimethylformamide or the reagent trimethyl orthobenzoate itself as the solvent. Therefore, it is probable that under moderately acidic conditions the solvent itself has little effect on the ratio of the cyclic orthoester vs. the rearranged product. Apart from the effect of the alcohol released during the cyclic orthoester formation as demonstrated in this study, other structural factors may also play a role. This view is supported by the reported conversion of ethyl 4-*O*-benzyl-1-thio-α-L-rhamnopyranoside to its 2-acetate in 83% yield by way of cyclic orthoester formation in acetonitrile, followed by acetic acid hydrolysis[12]. This finding is in contrast with earlier speculation[6] on the influence of the solvent on the rearrangement vs. cyclic orthoester formation.

In summary, a fast, technically simple and high-yielding procedure is described for the preparation of the 2,3-cyclic orthoesters of methyl, ethyl, and phenyl 1-thio-α-L-rhamnopyranoside. By a 1- or 2-step extension of the procedure these are readily converted into the 2-*O*-acyl derivatives. Considering the high yields, short reaction times and operational simplicity, the method suggested here for the preparation of the 2,4-dibenzoates of various 1-thiorhamnopyranosides is a sub-

TABLE III

^{1}H NMR chemical shifts for partially acylated 1-thio-α-L-rhamnopyranosides [a]

Compound	Chemical shifts (δ)					
	H-1	H-2	H-3	H-4	H-5	H-6
2	5.09	5.20	3.90	3.50	3.98	1.35
3	5.12	nd [b]	5.00	3.63	nd	nd
4	5.23	5.44	4.02	3.64	4.05	1.37
5	5.17	4.24	5.25	3.84	nd	nd
6	5.33	5.50	4.28	5.30	4.39	1.34
8	5.21	5.18	3.90	3.49	4.02	1.34
9	5.24	nd	4.99	3.67	4.02	nd
10	5.35	5.43	4.02	3.64	4.09	1.38
11	5.29	4.27	5.24	3.84	4.20	nd
13	5.61	4.25	4.32	5.19	4.23	1.23
14	5.35	4.11	4.00	5.13	4.34	1.32
15	5.42	4.13	3.68	3.48	4.08	1.31
16	5.44	5.38	3.97	3.57	4.18	1.36
17	5.47	4.31	5.06	3.73	nd	nd
18	5.57	5.62	4.07	3.69	4.25	1.39
19	5.49	4.43	5.28	3.89	4.29	1.38
20	5.66	5.67	4.33	5.47	4.56	1.33
21	5.75	4.35	4.12	3.46	4.08	1.24
22	5.82	4.41	4.42	5.21	4.34	1.17
23	5.58	4.26	4.04	5.17	4.45	1.28

[a] First-order data at 300 K, and 300 MHz, for solutions in $CDCl_3$ for **2–14**, and **16–23**, and in CD_3OD for **15**. [b] Not determined.

stantial improvement over the procedures previously proposed for the synthesis of ethyl 2,4-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside[6,11] (**12**).

EXPERIMENTAL

General methods.—Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured at 22° with a Perkin–Elmer Type 241MC polarimeter in $CHCl_3$, except where indicated otherwise. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). All reagents and solvents were of commercial grade. Anhydrous CH_2Cl_2 and *N*,*N*-dimethylformamide were obtained from Aldrich. The ^{1}H (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded with a Varian Gemini-300 instrument at 300 K, using the software provided by the manufacturer. Chemical shifts are quoted in ppm from Me_4Si. ^{1}H and ^{13}C NMR spectral data for compounds described in this paper are to be found in Tables III and IV, respectively. Elemental analytical data were obtained from Atlantic Microlab Inc. (Norcross, GA) and are presented in Table V.

General procedure A: synthesis of the mono-O-acyl-L-rhamnopyranosides.—A solution of the triol **1** (1 g) in *N*,*N*-dimethylformamide (0.5 mL) was treated with

TABLE IV

^{13}C NMR chemical shifts for partially acylated 1-thio-α-L-rhamnopyranosides [a]

Compound	Chemical shifts (δ)					
	C-1	C-2	C-3	C-4	C-5	C-6
2	83.5	73.9	70.7	73.5	68.5	17.5
4	83.6	74.4	71.1	74.0	68.5	17.6
6	83.5	74.6	69.4	75.8	66.7	17.5
8	82.1	74.2	70.7	73.5	68.5	17.5
10	82.2	74.8	71.1	74.0	68.8	17.6
12	82.2	75.1	69.6	75.8	66.9	17.6
13	79.6	76.8	75.6	75.4	64.7	17.1
14	83.9	72.5	70.8	76.1	66.4	17.5
15	89.7	73.5	72.7	73.9	70.7	17.9
16	86.0	74.0	70.8	73.5	69.3	17.4
18	86.1	74.5	70.8	73.6	69.5	17.6
20	85.7	74.7	69.5	75.5	67.5	17.5
21	83.7	76.5	78.4	75.1	66.8	17.1
22	83.8	76.5 [b]	75.6 [b]	75.1	65.8	17.0
23	87.3	72.4	70.8	76.0	67.2	17.4

[a] At 300 K and 75 MHz for solutions in $CDCl_3$ for **2–14** and **16–23**, and in CD_3OD for **15**. [b] Assignments are interchangeable.

trimethyl orthoacetate (5 mL) or trimethyl orthobenzoate (3.5 mL) then evacuated for 10 min (1 Torr or less). 10-Camphorsulfonic acid (40 mg) was added in one portion and the vacuum was immediately restored. The mixture was stirred for 10 min, then treated with a 0° mixture of acetonitrile (10 mL), water (1 mL) and

TABLE V

Elemental analytical data

Compound	Formula	C		H		S	
		Calcd	Found	Calcd	Found	Calcd	Found
2, 3	$C_9H_{16}O_5S$	45.75	45.82	6.83	6.84	13.57	13.46
4, 5	$C_{14}H_{18}O_5S$	56.36	56.44	6.08	6.13	10.75	10.65
6	$C_{21}H_{22}O_6S$	62.67	62.60	5.51	5.53	7.97	7.79
8, 9	$C_{10}H_{18}O_5S$	47.98	48.07	7.25	7.25	12.81	12.73
10, 11	$C_{15}H_{20}O_5S$	57.67	57.49	6.45	6.49	10.26	10.19
12	$C_{22}H_{24}O_6S$	63.44	63.31	5.81	5.86	7.70	7.70
13	$C_{18}H_{24}O_5S$	61.34	61.25	6.86	6.89	9.10	9.18
14	$C_{15}H_{20}O_5S$	57.67	57.70	6.45	6.50	10.26	10.20
15	$C_{12}H_{16}O_4S$	56.23	56.40	6.29	6.30	12.51	12.38
16, 17	$C_{14}H_{18}O_5S$	56.36	55.29	6.08	6.13	10.75	11.10
18, 19	$C_{19}H_{20}O_5S$	63.31	62.16	5.59	5.54	8.89	9.67
20	$C_{26}H_{24}O_6S$	67.22	67.06	5.21	5.19	6.90	6.87
21	$C_{15}H_{20}O_4S$	60.78	60.85	6.80	6.84	10.82	10.74
22	$C_{22}H_{24}O_5S$	65.99	66.13	6.04	6.09	8.00	7.86
23	$C_{19}H_{20}O_5S$	63.31	63.38	5.59	5.63	8.89	8.96

trifluoroacetic acid (0.2 mL). (Identical results were obtained with 5 mL of aq 80% acetic acid.) After 10 min the mixture was concentrated and the residue was equilibrated in $CHCl_3$ and water. The organic phase was concentrated. The residue was purified by chromatography (2:1 or 1:1 hexane–EtOAc) on silica gel.

General procedure B: synthesis of the 2,4-di-O-benzoyl-L-rhamnopyranosides.—A mixture of the triol **1** (1 g), trimethyl orthobenzoate (3 mL), and *N,N*-dimethylformamide (0.5 mL) was treated with 10-camphorsulfonic acid (40 mg) for 10 min as described in *General procedure A*. Pyridine (2 mL) and benzoyl chloride (2 mL) were added at 0°. The reaction mixture was allowed to reach room temperature (~ 30 min), then cooled to 0° and treated with MeOH (5 mL). After 5 min the volatiles were removed at 25°, under vacuum (1 Torr). The residue was stirred with aq 80% acetic acid at room temperature. After 10 min the mixture was concentrated (vacuum) and the residue purified by silica gel chromatography (7:1 hexane–EtOAc).

General procedure C: synthesis of the 2,4-di-O-benzoyl-L-rhamnopyranosides.—A solution of the 4-benzoate **14** or **23** (3 mM) in CH_2Cl_2 (5 mL) was mixed with trimethyl orthobenzoate (2 mL), then the CH_2Cl_2 was removed at room temperature under vacuum (1 Torr or less). 10-Camphorsulfonic acid (25–50 mg) was added in one portion. The reaction mixture was immediately evacuated (1 Torr or less) and stirred for 13 min under vacuum. A 0° mixture of acetonitrile (20 mL), water (3 mL), and trifluoroacetic acid (0.5 mL) was then added. After 10 min the reaction mixture was concentrated. The residue was partitioned between $CHCl_3$ and water. The organic phase was concentrated. The residue was purified by silica gel chromatography (4–6:1 hexane–EtOAc).

Ethyl 4-O-benzoyl-2,3-O-isopropylidene-1-thio-α-L-rhamnopyranoside (**13**).—A mixture of the triol[7] **7** (5.0 g), 2,2-dimethoxypropane (30 mL), and a catalytic amount of 10-camphorsulfonic acid was stirred at room temperature for 10 min then cooled to 0°. Anhydrous pyridine (10 mL) and benzoyl chloride (4 mL) were added. Stirring was continued for 5 h at room temperature then the mixture was cooled to 0°. Ice–water (300 mL) was added. Crystallization started in 2 min. After an additional 10 min the mixture was filtered and washed with ice–water to yield 8.15 g (96%) of **13**; mp 120–121°; $[\alpha]_D$ −129° (*c* 1.28).

Ethyl-4-O-benzoyl-1-thio-α-L-rhamnopyranoside (**14**).—A solution of compound **13** (7 g) in aq 80% acetic acid (50 mL) was kept at 80° for 30 min, then concentrated under vacuum. The residue was partitioned between $CHCl_3$ and water. The organic phase was dried (Na_2SO_4). Removal of the solvent under vacuum gave the diol **14** (6 g, 97%) as a syrup; $[\alpha]_D$ −194° (*c* 1.18).

Phenyl 1-thio-α-L-rhamnopyranoside (**15**).—A solution of phenyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside[13] (8.5 g) in anhyd MeOH (50 mL) was treated with a catalytic amount of NaOMe at room temperature for 5 h. The solution was neutralized (Dowex 50-X2, H^+) and filtered. Removal of the solvent under vacuum followed by crystallization from diisopropyl ether gave **15** (5.7 g, quant.); mp 89–91°, $[\alpha]_D$ −247° (*c* 0.75, MeOH).

Phenyl 2,3-O-isopropylidene-1-thio-α-L-rhamnopyranoside (**21**).—A mixture of the triol **20** (4.5 g), 2,2-dimethoxypropane (10 mL), and a catalytic amount of 10-camphorsulfonic acid was stirred at room temperature for 20 min. The solution was neutralized with triethylamine and concentrated under vacuum. Silica gel chromatography of the residue (3:1 hexane–EtOAc) gave crystalline **21** (4.1 g, 79%); mp 79–80°; $[\alpha]_D$ −211° (*c* 1.45).

Phenyl 4-O-benzoyl-2,3-O-isopropylidene-1-thio-α-L-rhamnopyranoside (**22**).—Benzoyl chloride (3.3 mL) was added to a stirred solution of the alcohol **21** (3.8 g) in pyridine (10 mL) at 0°. After 15 min ice-cold, aq $NaHCO_3$ was added. The mixture was partitioned between $CHCl_3$ and water. The organic phase was concentrated. Chromatography of the residue on silica gel (20:1 hexane–EtOAc) gave syrupy **22** (4.6 g, 90%) which crystallyzed on standing; mp 76–77°; $[\alpha]_D$ −206° (*c* 1.06).

Phenyl 4-O-benzoyl-1-thio-α-L-rhamnopyranoside (**23**).—Hydrolysis of **22** as described for the preparation of the diol **14** gave the crystalline diol **23** (96%); mp 115–117°; $[\alpha]_D$ −290° (*c* 1.08).

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