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Incidence and avoidance of stereospecific 1,2-ethylthio group migration during the synthesis of ethyl 1-thio-α-L-rhamnopyranoside 2,3-orthoester*

France-Isabelle Auzanneau and David R. Bundle†
Institute for Biological Sciences, National Research Council of Canada, Ottawa, Ontario K1A OR6 (Canada)

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ABSTRACT

The 1,2-migration of an ethylthio group with inversion of configuration at the C-1 and C-2 atoms was observed during the attempted preparation of 2,3-orthoester derivatives of ethyl 1-thio-α-L-rhamnopyranoside. The rearrangement leading to the formation of methyl 2-thio-β-L-glucopyranosides could be avoided by preparing the orthoester in DMF rather than in acetonitrile and by using a controlled amount of acid catalyst.

INTRODUCTION

Thioglycosides are flexible and stable intermediates that are well suited for oligosaccharide synthesis, since the alkylthio group provides effective protection of the anomeric centre, while allowing direct conversion to glycosyl halides under mild conditions or activation by thiophilic reagents[1,2]. However, we demonstrate in this paper that, depending on reaction conditions, alkyl thioglycosides may be susceptible to rearrangement during transformations typically used in the preparations of selectively protected glycosyl donors.

Studies designed to elucidate the molecular recognition of the *Shigella flexneri* Y antigen[3,4], [→2]α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-β-D-GlcNAc*p*-(→], by the binding sites of hybridoma antibodies have necessitated the synthesis of di- to hepta-saccharides[5]. Elaboration of the fine details of this interaction required the synthesis of derivatives of the trisaccharide epitope, α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-β-D-GlcNAc*p*-1→*O*Me (**1**). Synthesis of this trisaccharide was designed to utilize a thioglycoside as the glycosyl donor. Ethyl 2,4-di-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**22**) was chosen as a suitable candidate since it could be used directly either as a glycosyl acceptor for preparation of a disaccharide building block or as a glycosyl donor, following acetylation at O-3. In either case a 4,6-*O*-benzylidene derivative of a suitable 2-acetamido-2-deoxy-D-glucopyranoside derivative **2** would serve as the acceptor for reaction with the thioglycoside or glycosyl halides derived from it.

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† To whom correspondence should be addressed.

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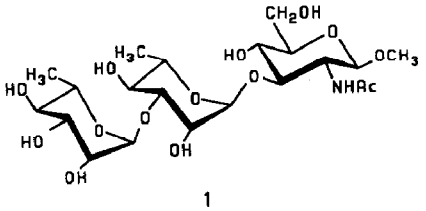
RESULTS AND DISCUSSION

Synthesis of the dibenzoate **22** was envisaged using the tetra-acetate **3** (Ref. 6) as starting material. Thioglycosidation of **3** (EtSH, $BF_3{\cdot}Et_2O$)[2] gave both the α-L (66%) and β-L (15.5%) anomers **4** and **5** (Ref. 7), each separated by crystallisation and subsequently deacylated to give the triols **6** and **7** that were used in the reactions described below.

The synthesis of 2,4-dibenzoates of various α-L-rhamnopyranosides **8** have been previously described[8-10]. These syntheses involved first the formation of the 2,3-*O*-methoxybenzylidene derivative of the corresponding α-L-rhamnopyranoside using trimethyl orthobenzoate and *p*-toluenesulfonic acid in either acetonitrile (CH_3CN)[8] or



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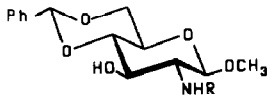

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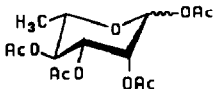

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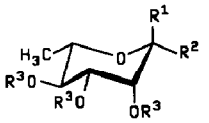
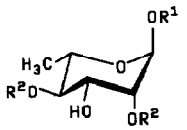
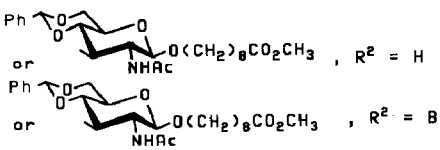


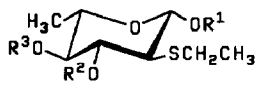
4 $R^1 = SCH_2CH_3$, $R^2 = H$, $R^3 = Ac$
5 $R^1 = H$, $R^2 = SCH_2CH_3$, $R^3 = Ac$
6 $R^1 = SCH_2CH_3$, $R^2 = R^3 = H$
7 $R^1 = R^3 = H$, $R^2 = SCH_2CH_3$



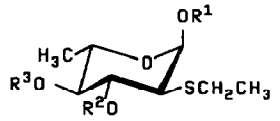


8 $R^1 = CH_3$ or $(CH_2)_8CO_2CH_3$ or , $R^2 = H$

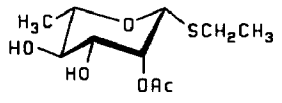
9 $R^1 = CH_3$ or $(CH_2)_8CO_2CH_3$ or , $R^2 = Bz$



10 R^1 = CH_3, R^2 = R^3 = Bz
11 R^1 = CH_3, R^2 = R^3 = H
12 R^1 = CH_3, R^2 = Bz, R^3 = H
13 R^1 = CH_3, R^2 = Ac, R^3 = H
14 R^1 = CH_2CH_3, R^2 = Ac, R^3 = H



15 R^1 = CH_3, R^2 = R^3 = Bz
16 R^1 = CH_3, R^2 = Bz, R^3 = H
17 R^1 = CH_3, R^2 = Ac, R^3 = H
18 R^1 = CH_2CH_3, R^2 = Ac, R^3 = H



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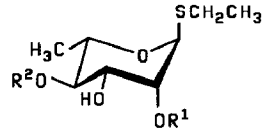
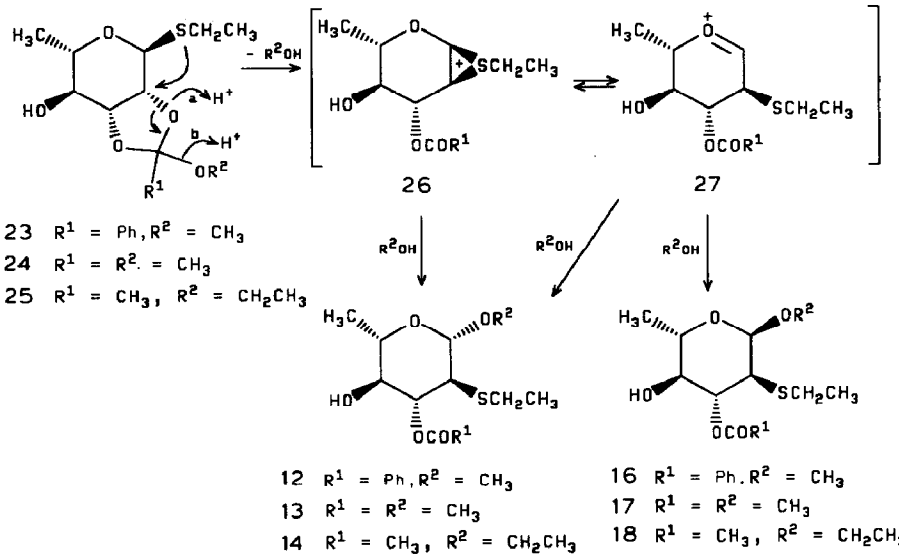


20 R^1 = Ac, R^2 = H
21 R^1 = Bz, R^2 = H
22 R^1 = R^2 = Bz

N,N-dimethylformamide (DMF)[9,10]. Benzoylation of O-4 (BzCl in pyridine), followed by opening of the orthoester in mild acidic medium (80% aqueous acetic acid), gave the dibenzoate **9**. When a solution of the triol **6** in acetonitrile was treated with trimethyl orthobenzoate using a catalytic amount of *p*-toluenesulfonic acid (TsOH), and the crude reaction mixture was subsequently benzoylated, a homogeneous product (t.l.c.) was obtained, which was unexpectedly resistant to acid hydrolysis. ^{1}H-N.m.r. analysis showed that the compound (45%), obtained after chromatography and crystallisation from hexane, was methyl 3,4-di-*O*-benzoyl-6-deoxy-2-*S*-ethyl-2-thio-β-L-glucopyranoside (**10**). Signals integrating for ten protons in the aromatic region that disappeared upon Zemplén deacylation, suggested that the product was *O*-dibenzoylated at O-3 and O-4 as judged by the downfield chemical shifts of H-3 and H-4 (5.40 and 5.18 p.p.m.). Correlated signals at δ 2.66 (2H) and δ 1.14 (3H) provided evidence that the molecule possessed an ethylthio group, while a singlet at δ 3.60 (3H) indicated the presence of an *O*-methyl group. The upfield H-2 resonance at 2.90 p.p.m. suggested that this position was most probably substituted by the ethylthio group, implying that the OCH_3 group was located at the anomeric position. Indeed, the chemical shift (105 p.p.m.) and the heteronuclear $^1J_{C,H}$ coupling constant (160 Hz) measured for the anomeric carbon were consistent with a β-linked *O*-glycoside structure[11]. These data, together with the large ^3J coupling constants ($J_{1,2}$ 8.7, $J_{2,3}$ 11.3, $J_{3,4}$, and $J_{4,5}$ 9.5 Hz) measured for the ring protons confirmed the proposed structure (**10**). Further ^{1}H- and ^{13}C-n.m.r. spectral analysis of the mother liquors revealed that they contained the dibenzoate **10** (6.5%) and the α-L anomer **15** (15%, $^1J_{C\text{-}1,H\text{-}1}$ 170 Hz, $^3J_{1,2}$ 3.3 Hz). Thus, the attempted synthesis of **22**, via a 2,3-orthobenzoate, that was subsequently benzoylated and hydrolysed, resulted in a



Scheme 1

1,2-migration of the anomeric ethylthio group with concommitant inversion of configuration at the C-2 atom.

Intramolecular nucleophilic migrations of alkylthio groups have been previously reported in monosaccharide chemistry[12–15]. In particular, it has been reported[14] that a cyclic acyloxonium ion formed by the protonation of an orthoacid can be opened via the intramolecular migration of a vicinal alkylthio group. In this example, when the synthesis was limited to the first step, *i.e.*, the orthoester formation, the two rearranged monobenzoates anomers **12** (58.5%) and **16** (7.2%) were isolated. The benzoyl group at O-3 and the inversion of configuration at C-2 were consistent with the mechanism presented in Scheme 1. The nucleophilic ethylthio group assists the opening of the protonated orthoester via a "push-pull" mechanism giving the intermediate episulfonium ion **26**, which is subsequently opened through the regiospecific attack on the anomeric carbon by methanol present in the reaction mixture. Moreover, the significant amount of methyl α-L-glycoside isolated suggested that the episulfonium ion **26** was in equilibrium with the oxonium ion **27** that can give both the α-L and the β-L- anomers. It should be noted that this mechanism, which involves intermediates such as **26** and **27**, is very similar to the mechanism proposed by Nicolaou *et al.*[15] to explain the nucleophilic displacement of a good leaving group adjacent to a glycosidic phenylthio group.

When formed under analogous conditions, the orthoacetates **24** and **25** underwent the same rearrangement leading respectively to the acetates **13** (β-L), **17** (α-L) and **14** (β-L), and **18** (α-L) (Table I, entries 2 and 3). As an ethoxy group is more basic than a methoxy group, the somewhat lower yield (Table 1, entry 3) obtained from the ethoxyethylidene derivative **25** prompts us to believe that the initial orthoester protonation occurs at O-2 of the glycoside (Scheme 1, a) rather than on the exocyclic alkoxy group

TABLE I

The influence of reagent, catalyst, and solvent on orthoester stability *vs.* rearrangement

Entry	*mg/mL of Triol*	*Solvent*	*Orthoester*[a] *(Equiv.)*	*TsOH mg/mL*	*Temp.*	*Time*	*Products*		
							Migration products[b]	*2-O-Acyl glycoside*[c]	*Starting material*
1	10(**6**)	CH_3CN	A(1.3)	1	20°	45 min	66%(**12,16**)	—	—
2	10(**6**)	"	B(1.3)	1	"	"	70%(**13,17**)	—	—
3	10(**6**)	"	C(1.3)	1	"	"	56%(**14,18**)	—	—
4	10(**7**)	"	B(1.3)	1	"	90 min	—	75%(**19**)	—
5	10(**6**)	DMF	C(1.3)	1	50°	—	—	—	96%
6	50(**6**)	"	C(1.7)	1	"	50 min	—	96%(**20**)	—
7	50(**6**)	"	B(1.7)	1	"	"	—	92%(**20**)	—
8	50(**6**)	"	C(1.3)	10	"	60 min	60%(**14,18**)	16%(**20**)	—
9	50(**6**)	"	A(6.0)	1	"	48 h	—	54%(**21**)	19%
10	150(**6**)	"	A(3.2)	1-3[d]	"	"	7%(**12,16**)	66%(**21**)	12%

[a] Reagent (mol. equiv.), A: trimethyl orthobenzoate, B: trimethyl orthoacetate, C: triethyl orthoacetate. [b] Total yield of rearranged products (α,β); as determined by ^{1}H-n.m.r. spectrum or chromatographic separation; the ratio α/β was 2:8 in all cases. [c] 2-*O*-Acyl thioglycoside isolated after 80% aqueous acetic acid hydrolysis. [d] Controlled addition of TsOH was performed during the first 24 h.

(Scheme 1, b). This "push-pull" mechanism necessitates a *trans*-diaxial configuration between the ethylthio group and the C-2 orthoester ring linkage. This requirement was confirmed by the exclusive isolation of the monoacetate **19** when the β-L anomer **7** was first reacted with trimethyl orthoacetate and the product hydrolysed in 80% aqueous acetic acid.

A comparison of the reaction of triol **6** with three orthoesters in DMF and in CH_3CN is recorded in Table I. In acetonitrile the methyl 2-deoxy-2-*S*-ethyl-2-thioglycosides were always isolated as the only products formed and detected by t.l.c.. However, in DMF under similar conditions of reagent and acid catalyst concentrations (entry 5), no reaction was observed even when the temperature was raised to 50°. Higher reagent concentrations in DMF gave the stable 2,3-orthoacetate **24** or **25** (entries 6 and 7) that were hydrolysed (80% AcOH), leading to excellent yields of the regioselectively acylated 2-*O*-acetyl-thioglycoside **20**. When the acid catalyst concentration was increased ten fold, the migration products **14** and **18** predominated (entry 8). Attempts to achieve reaction of **6** with trimethyl orthobenzoate required much longer reaction times, but increased reagent and acid concentrations led to the appearance of migration products (entries 9 and 10). Based on these observations, the yield of the 2,4-dibenzoate **22** was optimized by performing the reaction in DMF with a controlled amount of acid catalyst. Side products that resulted from benzoylation of unreacted **6** and rearranged **12** and **16** had to be removed by chromatography.

In rationalising the reactions that occur in CH_3CN and DMF, two factors, solvation and solvent basicity, should be considered[16]. In the strongly solvating environment of DMF, higher reagent concentrations are required to obtain the orthoacetates **24** and **25**, while the basicity of this solvent modulates the influence of acid catalyst on the intramolecular reaction. Eventually, above a certain threshold of acid catalyst concentration, migration/rearrangement was also observed in DMF.

In conclusion, the reported rearrangement of ethyl 1-thio-α-L-rhamnopyranoside under mild conditions of orthoester formation indicates potential problems in the selective protection of 1,2-*trans* thioglycosides having the *manno* configuration. However, these problems are avoided by changing the reaction solvent. As described in the literature, unsymmetric sulfides can be reductively cleaved with tributyltin hydride[17] or Raney nickel[18]. Therefore, this alkylthio migration provides a novel access to 2-deoxy-β-L-glycosides[15].

EXPERIMENTAL

General methods. — ^1H- and ^{13}C-N.m.r. spectra were recorded with Bruker AM 200 and AM 500 spectrometers, for solutions in $CDCl_3$ or in $CDCl_3$ containing 10% CD_3OD, and these were referenced to residual $CHCl_3$ (δ_H 7.24) and $CDCl_3$ (δ_C 77.0) as internal standards. First-order chemical shifts and coupling constants were obtained from the one-dimensional spectra, and assignments of protons resonances were based on COSY experiments. Optical rotations were mesured with a Perkin–Elmer 243 polarimeter, and melting points are uncorrected. T.l.c. was performed on Silica Gel-60

F_{254} (E. Merck) and detected with u.v. light and by charring with sulfuric acid. Silica Gel-60, 70–230 mesh or 230–400 mesh (E. Merck), was used respectively for conventional column chromatography and medium-pressure column chromatography[19]. Solvents were purified and dried according to standard procedures[20], and organic solutions were dried over Na_2SO_4 and concentrated at 40° under reduced pressure.

General procedure A : synthesis of the 3-O-acyl-2-S-ethyl-D-glucopyranoside derivatives. — *p*-Toluenesulfonic acid (1 mg/mL) and trimethyl orthobenzoate, trimethyl or triethyl orthoacetate (1.3 mol. equiv.) were added to a stirred solution of the triol **6** (10 mg/mL) in anhydrous acetonitrile. After 45 min at room temperature, triethylamine (1 mL) was added, and the solution was concentrated to a syrup, which was dissolved in dichloromethane (50 mL) and washed sequentially with M hydrochloric acid (50 mL), saturated aqueous sodium hydrogencarbonate (50 mL), and water (50 mL). The organic phase was dried and concentrated to give an oily residue, which was purified on silica gel.

General procedure B : synthesis of the 2-O-acyl-L-rhamnopyranoside derivatives. — *p*-Toluenesulfonic acid (1 mg/mL) and trimethyl orthobenzoate, trimethyl or triethyl orthoacetate (1.7 mol. equiv.) were added to a stirred solution of the triol **6** (50 mg/mL) in anhydrous *N,N*-dimethylformamide at 50°. The reaction was monitored by t.l.c., and, when necessary, more reagent and TsOH were added, and stirring was maintained at 50° (Table I). After addition of triethylamine (200 μL/mL), the solution was concentrated to give a syrup which was dissolved in 80% aqueous acetic acid (1 mL/50 mg of **6**) and stirred for 30 min at room temperature. The mixture was then concentrated, and the residual solvent was co-evaporated with toluene (3 × 5 mL). The 2-*O*-acyl derivatives were then purified by silica gel chromatography.

Ethyl 2,3,4-tri-O-acetyl-1-thio-α-L-rhamnopyranoside (**4**) and *ethyl 2,3,4-tri-O-acetyl-1-thio-β-L-rhamnopyranoside* (**5**). — Tetra-*O*-acetyl-L-rhamnopyranose[6] (1.41 g, 42 mmol) was treated with ethanethiol (1.5 mol. equiv.) and boron trifluoride etherate (1.2 mol. equiv.) according to a published procedure[2]. Work-up of the reaction mixture as described[2], and crystallisation of the crude reaction products in diethyl ether gave the pure β-L anomer **5** (2.2 g, 15.5%): m.p. 163–164°, $[\alpha]_D^{25}$ +70.5° (*c* 0.9, chloroform) [lit.[7] m.p. 121°, $[\alpha]_D^{24}$ +63.5° (*c* 2.1, chloroform)]. N.m.r. data ($CDCl_3$): ^1H (200.13 MHz), δ 1.22–1.34 (m, 6 H, SCH_2CH_3 and H-6), 1.95, 2.02, 2.16 (3 s, 3 × 3 H, CH_3CO), 2.71 (q, 2 H, SCH_2CH_3), 3.53 (m, 1 H, H-5), 4.72 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 4.98–5.12 (m, 2 H, H-3 and H-4), and 5.47 (dd, 1 H, $J_{2,3}$ 3.1 Hz, H-2); ^{13}C (50.32 MHz), δ 81.9 ($^1J_{C,H}$ 152 Hz, C-1).

Anal. Calc. for $C_{14}H_{22}O_7S$: C, 50.30; H, 6.59. Found: C, 50.47; H, 6.61.

Further crystallisation of the mother liquors in hexane gave the pure α-L anomer **4** (9.4 g, 66%): m.p. 69°, $[\alpha]_D^{25}$ −117.0° (*c* 1.5, chloroform) [lit.[2] m.p. 69–70°, $[\alpha]_D^{25}$ −115° (*c* 2, chloroform), lit.[7] $[\alpha]_D^{24}$ −98° (*c* 2.5, chloroform)]. ^{13}C-N.m.r. data ($CDCl_3$, 50.32 MHz), δ 81.95 ($^1J_{C,H}$ 166 Hz, C-1).

Ethyl 1-thio-α-L-rhamnopyranoside (**6**). — Sodium (450 mg) was added to a solution of the triacetate **4** (10 g, 30 mmol) in methanol (150 mL), and the mixture was stirred 1.5 h at room temperature. Sodium ions were removed with Amberlite IR-120 (H^+), and the resin was filtered off and rinsed with methanol (50 mL). Concentration

and column chromatography (10:1 chloroform–methanol) of the resulting syrup gave the pure triol **6** (6.1 g, 98%): $[\alpha]_D^{25}$ −229.5° (*c* 1.3, methanol). ^{1}H-N.m.r. data ($CDCl_3$–10% CD_3OD, 200.13 MHz), δ 1.16 (m, 6 H, SCH_2CH_3 and H-6), 2.50 (m, 2 H, SCH_2CH_3), 3.32 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.55 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-3), 3.86 (m, 2 H, H-2 and H-5), and 5.10 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1).

Anal. Calc. for $C_8H_{16}O_4S$: C, 46.15; H, 7.69. Found: C, 46.05; H, 7.82.

*Ethyl 1-thio-β-*L*-rhamnopyranoside* (**7**). — Deacetylation of the β-thioglycoside **5** (651 mg, 1.9 mmol), using analogous conditions as those described for the synthesis of **6**, gave the triol **7** (364 mg, 90%) which was purified by crystallisation in diethyl ether–hexane: m.p. 145°, $[\alpha]_D^{25}$ +123.5° (*c* 0.8, methanol). ^{1}H-N.m.r. data ($CDCl_3$–10% CD_3OD, 500.14 MHz), δ 1.17 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3), 1.23 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.63 (m, 2 H, SCH_2CH_3), 3.18 (m, 1 H, H-5), 3.31 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.3 Hz, H-4), 3.41 (dd, 1 H, $J_{2,3}$ 3 Hz, H-3), 3.87 (m, 1 H, $J_{1,2}$ 1 Hz, H-2), and 4.52 (d, 1 H, H-1).

Anal. Calc. for $C_8H_{16}O_4S$: C, 46.15; H, 7.69. Found: C, 46.02; H, 7.75.

*Methyl 3,4-di-*O*-benzoyl-6-deoxy-2-*S*-ethyl-2-thio-β-* and *α-*L*-glucopyranosides* (**10**) and (**15**). — *p*-Toluenesulfonic acid (80 mg) and trimethyl orthobenzoate (350 μL, 1.25 mol. equiv.) were added to a stirred solution of the triol **6** (320 mg, 1.54 mmol) in anhydrous acetonitrile (50 mL). After stirring for 3 h at room temperature, and upon subsequent addition of triethylamine (1 mL), the solution was concentrated to a syrup, which was dissolved in a mixture of anhydrous dichloromethane (40 mL) and anhydrous pyridine (10 mL). Benzoyl chloride (250 μL, 1.3 mol. equiv.) was added dropwise to the solution, and stirring was maintained overnight at room temperature. Following evaporation of the solvents, the residue, dissolved in dichloromethane (70 mL), was washed sequentially with M hydrochloric acid (50 ml), saturated aqueous sodium hydrogencarbonate (50 ml), and water (50 mL). The organic phase was dried and concentrated to a syrup which was purified on silica gel (1:7 ethyl acetate–hexane) to yield 444 mg (67%) of an homogeneous mixture of the anomers **10** and **15** (t.l.c. ethyl acetate–hexane 2:8, R_F 0.62). Crystallisation from hexane gave the pure β-L anomer **10** (301 mg, 45%): m.p. 113–114°, $[\alpha]_D^{25}$ +108.5° (*c* 0.8, chloroform). N.m.r. data ($CDCl_3$): ^{1}H (200.13 MHz), δ 1.14 (t, 3 H, *J* 7.5 Hz, SCH_2CH_3), 1.31 (d, 3 H, $J_{5,6}$ 6.2 Hz, H-6), 2.66 (m, 2 H, SCH_2CH_3), 2.90 (dd, 1 H, $J_{1,2}$ 8.7 Hz and $J_{2,3}$ 11.3 Hz, H-2), 3.60 (s, 3 H, OCH_3), 3.72 (m, 1 H, H-5), 4.43 (d, 1 H, H-1), 5.18 (t, 1 H; $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 5.40 (dd, 1 H, H-3), 7.20–7.52, and 7.83–8.0 (2m, 6 H and 4 H, aromatics); ^{13}C (50.32 MHz), δ 105.4 ($^1J_{C,H}$ 160 Hz, C-1).

Anal. Calc. for $C_{23}H_{26}O_6S$: C, 64.19; H, 6.05. Found: C, 64.40; H, 6.05.

N.m.r. spectral analysis of the mother liquors showed the presence of the β-L anomer **10** (6.5%), together with the α-L anomer **15** (15%). N.m.r. data for **15** ($CDCl_3$): ^{1}H (200.13 MHz), δ 1.10 (t, 3 H, *J* 8 Hz, SCH_2CH_3), 1.23 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.54 (m, 2 H, SCH_2CH_3), 3.02 (dd, 1 H, $J_{1,2}$ 3.3 Hz and $J_{2,3}$ 11.2 Hz, H-2), 3.43 (s, 3 H, OCH_3), 4.09 (m, 1 H, H-5), 4.88 (d, 1 H, H-1), 5.17 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 5.82 (dd, 1 H, H-3), 7.20–7.51, and 7.81–8.0 (2m, 6 H and 4 H, aromatics); ^{13}C (50.32 MHz), δ 101.0 ($^1J_{C,H}$ 170 Hz, C-1).

*Methyl 6-deoxy-2-*S*-ethyl-2-thio-β-*L*-glucopyranoside* (**11**). — Debenzoylation of

the methyl β-L-glycoside **10** (208 mg, 0.48 mmol), using analogous conditions as those described for the synthesis of **6**, gave, after column chromatography (1:1 ethyl acetate–hexane), the pure diol **11** (83 mg, 80%) as an oil that crystallized on standing: m.p. 71°, $[\alpha]_D^{25}$ −40.0° (*c* 1.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$, 200.13 MHz), δ 1.22 (t, 3 H, *J* 8 Hz, SCH_2CH_3), 1.31 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.43–2.80 (m, 3 H, SCH_2CH_3 and H-2), 3.10–3.40 (m, 3 H, H-3, H-4, and H-5), 3.50 (s, 3 H, OCH_3), and 4.21 (d, 1 H, $J_{1,2}$ 8.7 Hz, H-1).

Anal. Calc. for $C_9H_{18}O_4S$: C, 48.65; H, 8.11. Found: C, 49.03; H, 8.21.

Methyl 3-O-benzoyl-6-deoxy-2-S-ethyl-2-thio-β-L-glucopyranoside (**12**) and *methyl 3-O-benzoyl-6-deoxy-2-S-ethyl-2-thio-α-L-glucopyranoside* (**16**). — Reaction of the triol **6** with trimethyl orthobenzoate, using the general procedure A, and purification of the crude mixture by medium-pressure column chromatography (1:5 ethyl acetate–hexane), gave the α-L anomer **16**: (7.2%) $[\alpha]_D^{25}$ −123.5° (*c* 1.0, chloroform). N.m.r. data ($CDCl_3$): ^{1}H (200.13 MHz), δ 1.13 (t, 3 H, *J* 8 Hz, SCH_2CH_3), 1.32 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.59 (m, 2 H, SCH_2CH_3), 2.92 (dd, 1 H, $J_{1,2}$ 3.3 Hz and $J_{2,3}$ 11.1 Hz, H-2), 3.36 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.39 (s, 3 H, OCH_3), 3.80 (m, 1 H, H-5), 4.80 (d, 1 H, H-1), 5.36 (dd, 1 H, H-3), 7.36–7.63, and 7.98–8.13 (2 m, 3 H and 2 H, aromatics); ^{13}C (50.32 MHz), δ 101.0 ($^1J_{C,H}$ 171 Hz, C-1).

Anal. Calc. for $C_{16}H_{22}O_5S$: C, 58.89; H, 6.75. Found: C, 58.92; H, 7.08.

Further elution of the column gave the β-L anomer **12**: (58.7%), $[\alpha]_D^{25}$ −56.0° (*c* 2.0, chloroform). N.m.r. data ($CDCl_3$): ^{1}H (500.14 MHz), δ 1.14 (t, 3 H, *J* 8 Hz, SCH_2CH_3), 1.34 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.57, 2.69 (2 m, 2 H, SCH_2CH_3), 2.76 (dd, 1 H, $J_{1,2}$ 8.8 Hz and $J_{2,3}$ 11.0 Hz, H-2), 3.38 (m, 2 H, H-4 and H-5), 3.52 (s, 3 H, OCH_3), 4.31 (d, 1 H, H-1), 4.95 (dd, 1 H, $J_{3,4}$ 8.7 Hz, H-3), and 7.40, 7.53, and 8.02 (3 m, 5 H, aromatics); ^{13}C (50.32 MHz), δ 105.3 ($^1J_{C,H}$ 160.5 Hz, C-1).

Anal. Found: C, 59.33; H, 6.94.

Methyl 3-O-acetyl-6-deoxy-2-S-ethyl-2-thio-β- and *α-L-glucopyranosides* (**13**) and (**17**). — Reaction of the triol **6** with trimethyl orthoacetate, using the general procedure A and purification of the crude mixture by medium-pressure column chromatography (1:2 ethyl acetate–hexane), gave an homogeneous mixture of the anomers **13** and **17** (70%) in the ratio 2:8 (α:β), as estimated by ^{1}H-n.m.r. spectroscopy. N.m.r. data for the mixture ($CDCl_3$): ^{1}H (200.13 MHz), δ 1.13 (t, 3 H, *J* 8 Hz, α- and β- SCH_2CH_3), 1.22 (d, 3 Hα, $J_{5,6}$ 6 Hz, H-6α), 1.28 (d, 3 Hβ, $J_{5,6}$ 6 Hz, H-6β), 2.06 (s, 3 H, α- and β- CH_3CO), 2.59 (m, 3 H, H-2α, H-2β, $SCH_2CH_3\alpha$, and $SCH_2CH_3\beta$), 3.11–3.39 (m, 1 Hα, 2 Hβ, H-4α, H-4β, and H-5β), 3.30 (s, 3 Hα, $OCH_3\alpha$), 3.47 (s, 3 Hβ, $OCH_3\beta$), 3.65 (m, 1 Hα, H-5α), 4.21 (d, 1 Hβ, $J_{1,2}$ 8.7 Hz, H-1β), 4.65 (dd, 1 Hβ, $J_{2,3}$ 11.7 Hz and $J_{3,4}$ 8.7 Hz, H-3α), 4.68 (d, 1 Hα, $J_{1,2}$ 3.5 Hz, H-1α), and 5.03 (dd, 1 Hα, $J_{2,3}$ 11.2 Hz and $J_{3,4}$ 9.0 Hz, H-3α); ^{13}C (50.32 MHz), δ 100.7 ($^1J_{C,H}$ 170 Hz, C-1α), 105.0 $^1J_{C,H}$ 160 Hz, C-1β).

Anal. Calc. for $C_{11}H_{20}O_5S$: C, 50.00; H, 7.58. Found: C, 50.11; H, 8.03.

Ethyl 3-O-acetyl-6-deoxy-2-S-ethyl-2-thio-β-L-glucopyranoside (**14**) and *ethyl 3-O-acetyl-6-deoxy-2-S-ethyl-2-thio-α-L-glucopyranoside* (**18**). — Reaction of the triol **6** with triethyl orthoacetate, using the general procedure A and purification of the crude mixture by medium-pressure column chromatography (2:7 ethyl acetate–hexane) gave

the α-L anomer **18**: (8%), $[\alpha]_D^{25}$ −64.0° (*c* 0.05, chloroform). N.m.r. data ($CDCl_3$): ^1H (200.13 MHz), δ 1.12–1.32 (m, 9 H, OCH_2CH_3, SCH_2CH_3, and H-6), 2.13 (s, 3 H, CH_3CO), 2.62 (m, 2 H, SCH_2CH_3), 2.72 (dd, 1 H, $J_{1,2}$ 3.4 Hz and $J_{2,3}$ 11.1 Hz, H-2), 3.18 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.3 Hz, H-4), 3.46 (m, 1 H, OCH_2CH_3), 3.71 (m, 2 H, OCH_2CH_3 and H-5), 4.85 (d, 1 H, H-1), and 5.11 (dd, 1 H, H-3); ^{13}C (50.32 MHz), δ 99.7 ($^1J_{C,H}$ 171 Hz, C-1).

Further elution of the column gave the pure β-L anomer **14**: (48%), $[\alpha]_D^{25}$ −4.5° (*c* 1.2, chloroform). N.m.r. data ($CDCl_3$): ^1H (200.13 MHz), δ 1.19 (m, 6 H, SCH_2CH_3 and OCH_2CH_3), 1.30 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.10 (s, 3 H, CH_3CO), 2.61 (m, 3 H, SCH_2CH_3 and H-2), 3.29 (m, 2 H, H-4 and H-5), 3.58, 3.90 (2 m, 2 H, OCH_2CH_3), 4.34 (d, 1 H, $J_{1,2}$ 9 Hz, H-1), and 4.65 (dd, 1 H, $J_{3,2}$ 11.3 Hz and $J_{3,4}$ 8.5 Hz, H-3); ^{13}C (50.32 MHz), δ 104.2 ($^1J_{C,H}$ 160 Hz, C-1).

Anal. Calc. for $C_{12}H_{22}O_5S$: C, 51.80; H, 7.91. Found: C, 51.83; H, 8.03.

Ethyl 2-O-acetyl-1-thio-β-L-rhamnopyranoside (**19**). — *p*-Toluenesulfonic acid (10 mg) and trimethyl orthoacetate (80μL, 1.3 mol. equiv.) were added to a stirred solution of the triol **7** (101 mg, 0.48 mmol) in anhydrous acetonitrile (10 mL). After 1.5 h at room temperature, triethylamine (200 μL) was added to the solution, and the syrup obtained after solvent removal was dissolved in 80% aqueous acetic acid (5 mL) and stirred 30 min at room temperature. The mixture was then concentrated and coevaporated with toluene (3 × 5 mL). Column chromatography (2:1 ethyl acetate–hexane) of the residue gave the diol **19** (91 mg, 75%) which crystallized on standing: m.p. 111–113° $[\alpha]_D^{25}$ +90.5° (*c* 0.8, chloroform). N.m.r. data ($CDCl_3$): ^1H (200.13 MHz), δ 1.26 (t, 3 H, SCH_2CH_3), 1.35 (d, 3 H, $J_{5,6}$ 6 Hz, H-6), 2.13 (s, 3 H, CH_3CO), 2.70 (q, 2 H, SCH_2CH_3), 3.39 (m, 2 H, H-4 and H-5), 3.68 (dd, 1 H, $J_{2,3}$ 3.5 Hz and $J_{3,4}$ 9 Hz, H-3), 4.68 (bs, 1 H, $J_{1,2}$ ~1 Hz, H-1), and 5.33 (bd, 1 H, H-2), ^{13}C (50.32 MHz), δ 81.7 ($^1J_{C,H}$ 152 Hz, C-1).

Anal. Calc. for $C_{10}H_{18}O_5S$: C, 48.00; H, 7.20. Found: C, 47.87; H, 7.29.

Ethyl 2-O-acetyl-1-thio-α-L-rhamnopyranoside (**20**). — Reaction of the triol **6** either with trimethyl or triethyl orthoacetate using the general procedure B, and purification of the crude reaction mixture by column chromatography (10:1 chloroform–methanol), gave the pure diol **20**: (96%, 92%), $[\alpha]_D^{25}$ −135.0° (*c* 1.6, chloroform). N.m.r. data ($CDCl_3$): ^1H (200.13 MHz), δ 1.26 (t, 3 H, SCH_2CH_3), 1.31 (d, 3 H, $J_{5,6}$ 5 Hz, H-6), 2.13 (s, 3 H, CH_3CO), 2.60 (m, 2 H, SCH_2CH_3), 3.46 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.87 (dd, 1 H, $J_{2,3}$ 3.4 Hz, H-3), 4.00 (m, 1 H, H-5), 5.15 (dd, 1 H, $J_{1,2}$ 1.2 Hz, H-2), and 5.18 (bs, 1 H, H-1); ^{13}C (50.32 MHz), δ 81.9 ($^1J_{C,H}$ 169 Hz, C-1).

Anal. Calc. for $C_{10}H_{18}O_5S$: C, 48.00; H, 7.20. Found: C, 47.91; H, 7.37.

Ethyl 2-O-benzoyl-1-thio-α-L-rhamnopyranoside (**21**). — Reaction of the triol **6** with trimethyl orthobenzoate using the general procedure B, and purification of the crude reaction mixture by column chromatography (100:1 chloroform–methanol), gave the pure diol **21**: (66%), $[\alpha]_D^{25}$ −100.0° (*c* 0.85, chloroform). N.m.r. data ($CDCl_3$): ^1H (200.13 MHz), δ 1.26 (t, 3 H, SCH_2CH_3), 1.31 (d, 3 H, $J_{5,6}$ 5 Hz, H-6), 2.60 (m, 2 H, SCH_2CH_3), 3.58 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.4 Hz, H-4), 3.97 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-3), 4.03 (m, 1 H, H-5), 5.29 (bs, 1 H, H-1), 5.38 (dd, 1 H, $J_{1,2}$ 1.4 Hz, H-2), and 7.35–7.60 and 8.0 (2 m, 5 H, aromatics); ^{13}C (50.32 MHz), δ 82.1 ($J_{C,H}$ 166 Hz, C-1).

Anal. Calc. for $C_{15}H_{20}O_5S$: C, 57.69; H, 6.41. Found: C, 57.44; H, 6.65.

Ethyl 2,4-di-O-benzoyl-1-thio-α-L-rhamnopyranoside (**22**). — *p*-Toluenesulfonic acid (2 mg) and trimethyl orthobenzoate (200 μL, 1.5 mol. equiv.) were added to a stirred solution of the triol **6** (160 mg, 0.77 mmol) in anhydrous *N,N*-dimethylformamide (1 mL) at 50°. After 6 h at 50° additional trimethyl orthobenzoate (100 μL) was added, and stirring was maintained overnight at 50°. Additional TsOH (1.4 mg) and trimethyl orthobenzoate (100 μL) were then added, and after 7 h a final amount (50 μL) of trimethyl orthobenzoate was added, and the mixture was stirred at 50° for an additional 16 h. Triethylamine (400 μL) was added, and the solution was concentrated to a syrup which was treated with benzoyl chloride (200 μL, 2.2 mol. equiv.) in anhydrous pyridine (2 mL). After 18 h at room temperature, methanol (300 μL) was added to decompose the excess of benzoyl chloride, and the solution, diluted in dichloromethane (50 mL), was sequentially washed with M hydrochloric acid (50 mL), saturated aqueous sodium hydrogencarbonate (50 mL), and water (50 mL). The organic phase was dried and concentrated to give an oily residue which was dissolved in 80% aqueous acetic acid (2 mL) and stirred for 30 min at room temperature. Concentration, coevaporation with toluene (3 × 5 mL) and chromatography [1:9 ethyl acetate–hexane (80 mL), 2:8 (100 mL)] of the resulting syrup gave the dibenzoate **22** (165 mg, 52%): $[\alpha]_D^{25}$ −28.0° (*c* 1.3, chloroform). N.m.r. data ($CDCl_3$): ^{1}H (200.13 MHz), δ 1.20–1.40 (m, 6 H, SCH_2CH_3 and H-6), 2.68 (m, 2 H, SCH_2CH_3), 4.23 (dd, 1 H, $J_{3,2}$ 3.3 Hz and $J_{3,4}$ 10 Hz, H-3), 4.40 (m, 1 H, H-5), 5.27 (dd, 1 H, $J_{4,5}$ 11 Hz, H-4), 5.43 (bs, 1 H, H-1), 5.47 (dd, 1 H, $J_{1,2}$ 1.5 Hz, H-2), 7.40–7.62, 8.0 (2 m, 10 H, aromatics); ^{13}C (50.32 MHz), δ 82.0 ($^1J_{C,H}$ 166 Hz, C-1).

Anal. Calc. for $C_{22}H_{24}O_6S$: C, 63.46; H, 5.77. Found: C, 63.49; H, 5.79.

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