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Synthesis of chlorodeoxy trisaccharides related to the *Shigella flexneri* Y polysaccharide *

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ABSTRACT

Chloromethoxylation of di-*O*-acetyl-L-rhamnal has been employed as a convenient route to methyl 3,4-di-*O*-acetyl-2-chloro-2-deoxy-α-L-rhamnopyranoside **7**, which was converted into an ethyl thioglycoside **10**, suitable for use as a glycosyl donor. It and a disaccharide analogue **20** were effective donors in *N*-iodosuccinimide–triflic acid promoted glycosylations of a 2-acetamido-2-deoxy-D-glucopyranoside acceptor **22**. Chlorodeoxy saccharides have previously been shown to be suitable derivatives to probe oligosaccharide–protein interactions, and this synthetic strategy provided three monochlorodeoxy trisaccharide congeners of the native *Shigella flexneri* epitope **2**, α-L-Rha*p*-(1 → 3)-α-L-Rha*p*-(1 → 3)-β-D-GlcNAc*p*-(1 → O)-Me.

INTRODUCTION

Binding of the polymeric *Shigella flexneri* variant Y O-antigen[1]

[→ 2)-α-L-Rha*p*-(1 → 2)-α-L-Rha*p*-(1 → 3)-α-L-Rha*p*-(1 → 3)-β-D-GlcNAc*p*-(1 →]

to monoclonal antibodies is inhibited by a 2′-monodeoxytrisaccharide **1** with a relative activity $\Delta(\Delta G)$ in the range −1.5 to −2.0 kcal/mol compared to native tri- and penta-saccharide epitopes **2** and **3** (refs 2 and 3). The precise origin of this enhanced binding is not clear but is thought to arise from the acceptance of the epitope in the binding site with its OH-2′ group oriented toward a relatively hydrophobic pocket. Replacement of –OH by –H would relieve unfavourable polar/nonpolar interactions, as well as steric contacts. Related enhancements, although of somewhat lower magnitude, were reported in mapping the interactions between blood group epitopes and antibodies or lectins[4,5]; however, in certain instances comparable or larger effects were observed when the corresponding monochlorodeoxy or monodeoxyfluoro analogues were studied[4,5]. Consequently it was of interest to synthesize and assay the activity of monochlorodeoxy analogues

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of epitopes **1** and **2**, since the electronegativity and van der Waals radii of the –Cl and –OH groups are comparable[6]. Since the Fab of one antibody that binds the *S. flexneri* epitope has recently crystallized with bound haptens, it is also possible to envision cocrystallization with enhanced and functionally modified inhibitors, thereby providing insight at atomic resolution into the possibility for the rational design of improved oligosaccharide inhibitors of carbohydrate–protein interactions. This was considered to be especially relevant since deoxyfluoro analogues have been used by several groups[7], and recent crystallographic data highlight potential problems that can arise due to the size and extreme electronegativity of the $-CH_2F$ functionality[8].

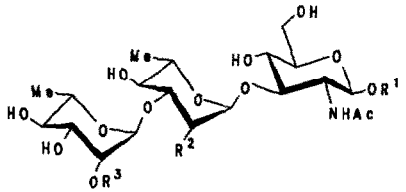
An essential synthon for the chemical synthesis of chlorodeoxy analogues of **1** was a suitably activated derivative of 2-chloro-2-deoxy-L-rhamnose. An appealing and direct route to compounds of this type could be envisioned following the well-known chloromethoxylation chemistry established for D-glucal by Lemieux and Fraser-Reid[9], followed by conversion of the methyl 2-chloro-2-deoxy-L-rhamnopyranoside to an ethyl thioglycoside.

The investigation of this synthetic strategy is reported together with the synthesis of a trisaccharide containing a 2-acetamido-6-chloro-2,6-dideoxy-β-D-glucopyranosyl residue, a compound designed to probe the role of the GlcNAc hydroxymethyl group in hydrogen bonding with an antibody[3].

RESULTS

Halogenomethoxylation of D-glucal triacetate was reported[9,10] to give a mixture of methyl 2-deoxy-2-halogeno-D-hexopyranoside isomers in a ratio that depended upon the configuration at C-4 and the type of halogen atom introduced. Chloromethoxylation of D-glucal triacetate led to a mixture of α-D-*manno*-, β-D-*gluco*-, and α-D-*gluco*-methyl 2-chloro-2-deoxy-hexopyranosides in which the 1,2-*trans*-diaxial (α-D-*manno*) product was preponderant[9]. A similar reaction applied to isomers in the L-series should afford the same distribution of product. In the case of 6-deoxy-L-glucal (**4**), it was expected that the absence of a bulky acetoxy group at C-6 should further favor the attack of a chlorine atom at the *endo* side of the molecule, leading to an increased ratio of the desired 1,2-*trans*-diaxial target, the 2-chloro-2-deoxy-α-L-rhamnopyranoside (**7**). However, this was not the case as the β-L-gluco isomer **5** was isolated (36%) by crystallization of the crude chloromethoxylation mixture, while chromatography of the mother liquors gave a homogeneous (TLC) mixture (~ 85 : 15) of the α-L-*manno* **7** (30%) and α-L-*gluco* **6** (5%) isomers. Although the composition of the crude mixture was not determined with precision, it is clear that the compound having the β-L-*gluco* and not the α-L-*manno* configuration was the major product. Nevertheless, chloromethoxylation of **4** remained the method of choice to prepare 3,4-di-*O*-acetyl-2-chloro-2-deoxy-α-L-rhamnopyranoside (**7**), since it could be purified from isomer **6** by crystallization. Acetolysis of the methyl pyranoside **7** gave a mixture (9 : 1) of the

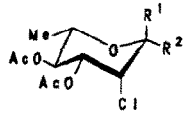
α-L- and β-L-rhamnopyranoses **8** and **9** that was treated with ethanethiol in the presence of $BF_3 \cdot Et_2O$ to yield the α-L- and β-L-ethyl 1-thio-L-rhamnopyranosides **10** and **11**, easily separated by chromatography. Selective acid-catalyzed methanolysis[11] of the 3-*O*-acetyl group of **10** was investigated as a possible route to a glycosyl acceptor selectively protected at O-4. Methanolysis of **10** (HCl–MeOH) was conducted either at 50°C and quenched when TLC analysis of the mixture showed an equal amount of diol **14** and starting diacetate **10** (1.75 h), or left overnight (16 h) at room temperature, after which time no diacetate was left. Workup and chromatography gave (Table IV) in both cases a mixture of the monoacetylated compounds **12** and **13** in which the alcohol **12** was preponderant



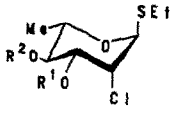
1 R^1=Me, R^2=R^3=H
2 R^1=Me, R^2=OH, R^3=H
3 R^1= →2)-α-L-Rhap R^2=OH, R^3=α-L-Rhap

4

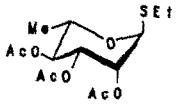
5 R^1=H, R^2=OMe
6 R^1=OMe, R^2=H



7 R^1=OMe, R^2=H
8 R^1=OAc, R^2=H
9 R^1=H, R^2=OAc
10 R^1=SEt, R^2=H
11 R^1=H, R^2=SEt



12 R^1=H, R^2=Ac
13 R^1=Ac, R^2=H
14 R^1=R^2=H
15 R^1=Ac, R^2=Bz
16 R^1=Bz, R^2=Ac
17 R^1=H, R^2=Bz
18 R^1=Bz, R^2=H



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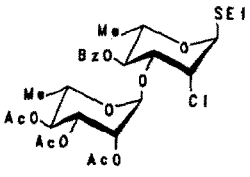
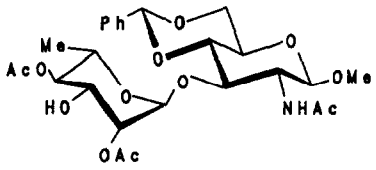


20

(9:1). Despite the rather good selectivity of the acid-catalyzed methanolysis of the 3-*O*-acetyl group, this reaction was not optimized because the glycosyl acceptor **12** could not be isolated free of alcohol **13**. Sequential acetylation–benzoylation steps were then envisioned as a route to access a rhamnopyranoside derivative that could be selectively deprotected at O-3. Saponification of the diacetate **10** gave the unstable diol **14** that was treated in a one-pot synthesis, first at 0°C with one equiv of acetyl chloride, then at 20°C with an excess of benzoyl chloride. As expected[12], acetylation occurred mainly at O-3, but once again the 3-acetate **15** (59%) could not be separated from the 4-acetate **16** (9%). Methanolysis[11] of the homogeneous (TLC) mixture of **15** and **16** provided access to the monobenzoylated alcohol **17** that could be obtained free of isomer **18**. Finally, silver triflate promoted glycosylation of the alcohol **17** by the ethyl thioglycoside **19** (ref 13) activated with



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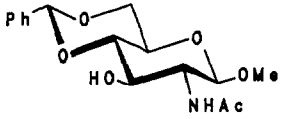

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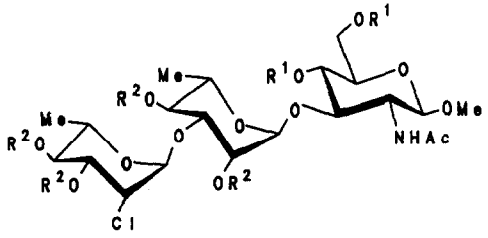
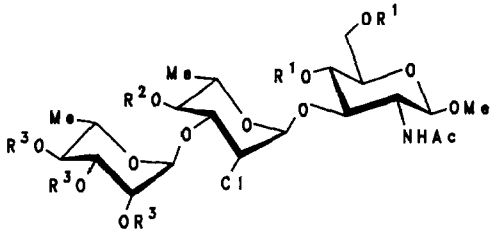
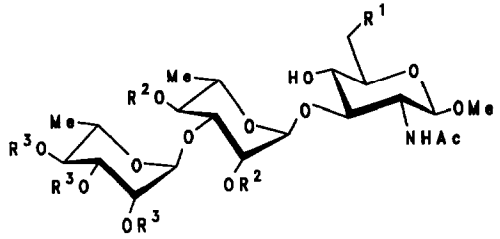


23 R^1 = >CHPh, R^2 = Ac
24 $R^1 = R^2 = H$



25 R^1 = >CHPh, R^2 = Bz, R^3 = Ac
26 $R^1 = R^2 = R^3 = H$



27 R^1-OH, R^2-Bz, R^3-Ac
28 R^1-Cl, R^2-Bz, R^3-Ac
29 R^1-Cl, R^2-R^3-H

bromine[14] gave the disaccharide glycosyl donor **20** (71%). Thus the 2-chloro-2-deoxy mono- and di-saccharides **10** and **20** could be used as glycosyl donors in sequential or block-extension reactions.

Thioglycosides **10** and **20**, activated with iodonium ions generated in situ from *N*-iodosuccinimide and triflic acid[15,16], reacted with the known glycosyl acceptors **21** (ref 17) and **22** (ref 18) to give the 2″- and 2′-monochloro-trisaccharides **23** and **25**. In order to minimize the risk of acid-catalyzed 2′ → 3′ *O*-acetyl migration[17] during the glycosylation of **21** by the 2-chloro-2-deoxyglycosyl donor **10**, the reaction was performed with 0.26 equiv of triflic acid. Since **10** cannot form orthoesters, the previously noted tendency for orthoacetate formation under mildly acidic conditions[17] did not arise, but the glycosylation did not reach completion. After further addition of acid and extended reaction time, the trisaccharide **23** was obtained in moderate yield (39%), while unreacted disaccharide **21** was recovered (19%). As no acetyl migration was likely to occur when monosaccharide **22** was used as the glycosyl acceptor, its condensation with disaccharide **20** was performed using more triflic acid than that used for the preparation of **23**, and trisaccharide **25** was isolated in 64% yield. Trisaccharides **23** and **25** were deprotected by acid hydrolysis of the benzylidene acetal and transesterification of the acyl groups to give the 2″-chloro- and 2′-chloro-trisaccharides **24** (78%) and **26** (86%).

Introduction of a chlorine atom at C-6 of the glucosamine unit D was accomplished using the trisaccharide **27** as starting material[17]. Selective chlorination[19] at C-6 of **27** was accomplished using conditions analogous to those used for its bromination[17]. The chlorinated trisaccharide **28** (56%) was subsequently deprotected by transesterification of the acyl groups to give the 6-chloro analogue **29** (86%).

DISCUSSION

While there are numerous methods for the preparation of chlorodeoxy hexopyranosides[19–31], synthesis of 2-chloro-2-deoxy glycopyranosides by nucleophilic substitution is a notoriously difficult challenge[32], and the few reports of such

displacements have involved powerful leaving groups[27,33]. Routes to chlorodeoxy glycosides have involved one-pot syntheses with methanesulfonyl chloride[20], sulfuryl chloride[21,22], Vilsmeier-type reagents[23,25], triphenylphosphine–carbon tetrachloride–pyridine[26], or imidazole[19], as well as two-step procedures via the nucleophilic displacement of isolated chlorosulfates[27], imidazolyl-[28], or trifluoromethanesulfonate groups[29–31]. In these reactions that are often sensitive to steric hindrance[28,29], and in some cases selective for primary hydroxyl groups[19,20,24,26], the nucleophilic substitution of a leaving group via an S_N2 type mechanism leads to the chloro sugar with inversion of configuration. Although appropriate for the preparation of the 2-acetamido-6-chloro-2,6-dideoxy-D-glucose residue **29**, this type of reaction is unsuitable for the preparation of a 2-chloro-2-deoxy-L-rhamnopyranoside (**7**), since either the use of a selectively substituted 6-deoxy-L-glucopyranoside or a double-inversion strategy at C-2 of a L-rhamnopyranoside derivative would be required. The number of steps and the pronounced resistance to displacement of O-2 leaving groups underscored the attraction of a strategy that utilized methyl 3,4-di-*O*-acetyl-2-chloro-2-deoxy-α-L-rhamnopyranoside (**7**) prepared from commercially available 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**4**).

Reaction of the glucal **4** with a glycosyl acceptor in the presence of *N*-iodosuccinimide was reported[2,34] to give an epimeric mixture of 1,2-*trans*-2-deoxy-2-iodoglycosides in which the α-L-*manno* configuration was preponderant. However, the lower reactivity of *N*-chlorosuccinimide as an halogenating agent[25] led us to investigate the chloroalkoxylation of **4** under the conditions described by Lemieux and Fraser-Reid[9] using chlorine in the presence of silver acetate as the chlorinating reagent. Although the formation of both *trans* adducts **5** and **7** was anticipated[10], it is not clear why the 1,2-*trans*-diequatorial glycoside **5** was the major product, while D-glucal gave predominantly the 1,2-*trans*-diaxial adduct[9]. Nevertheless, the easy conversion of the methyl glycoside **7** to the ethyl thioglycoside donor **10** (2 steps, 72% overall yield) rendered chloromethoxylation of **4** an acceptable route to **10**.

Regioselective deacetylations of peracetylated sugars have been reported using either chemical[35–40] or enzymatic[41] reactions during which selectivity towards the primary[41], anomeric[35–39], or 2-acetates[38] were observed. Consequently the selective *O*-deacetylation under acid conditions, which results in the formation of alcohol **12** as the major product when diacetate **10** was treated with methanolic HCl, was a surprising observation even though selective *O*-deacetylation in the presence of benzoate esters has been demonstrated[11]. To the best of our knowledge this is the first reported regioselective *O*-deacetylation of a 3,4-di-*O*-acetylglycopyranoside. Although the reaction was not optimized, it provides an attractive route to L-rhamnopyranoside derivatives such as alcohol **12**, selectively protected at O-4. In contrast, selective acetylation of diol **14** (acetylchloride–pyridine) constitutes a straightforward method to prepare a derivative selectively protected at O-3.

TABLE I

NMR data for compounds **5**–**18**. [a]

Atom	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12** [b]	**13** [b]	**14** [b]	**15**	**16**	**17**	**18**
Proton (J, Hz)														
H-1	4.35	4.74	4.76	6.15	5.86	5.29	4.81	5.35	5.29	5.30	5.35–5.48		5.42	5.37
($J_{1,2}$)	(8.5)	(3.5)	(1.0)	(1.5)			(1.0)	(1.0)	(1.0)					
H-2	3.68	3.88	4.35	4.35	4.51	4.53	4.57	4.47	4.56	4.45	4.61	4.72	4.53	4.66
($J_{2,3}$)	(10.0)	(10.0)	(3.5)	(3.5)	(3.5)	(3.5)	(3.5)	(4.0)	(3.5)	(~3)		(~3.0)	(3.5)	(3.5)
H-3	5.15	5.37	5.28	5.28	5.04	5.18	4.96	4.00	5.05	3.96	5.35–5.48		4.18	5.36
($J_{3,4}$)	(10.0)	(10.0)	(10.0)	(10.0)	(10.0)	(10.0)	(10.0)	(9.5)	(11.5)	(~10.0)			(9.5)	(9.5)
H-4	4.70	4.71	5.13	5.19	5.15	5.14	5.14	4.90	3.73	3.52	5.35–5.48		5.17	3.93
($J_{4,5}$)	(9.5)	(9.5)	(10.0)	(10.0)	(10.0)	(10.0)	(10.0)	(9.5)	(9.5)	(~10.0)	(9.5)		(9.5)	
H-5	3.57	3.91	3.86	3.95	3.64	4.21	3.51	4.19	4.16	4.02	4.40	4.33	4.37	4.21
($J_{5,6}$)	(6.0)	(6.0)	(6.0)	(6.5)	(6.0)	(6.5)	(6.5)	(6.0)	(6.0)	(~6)	(6.0)	(6.0)	(6.5)	(6.5)
H-6	1.22	1.17	1.22	1.22	1.26	1.20	1.25	1.22	1.22	1.29	1.28	1.28	1.29	1.40
OCH_3	3.55	3.42	3.38											
SCH_2CH_3						2.61	2.71	2.63	2.63	2.60	2.67	2.67	2.68	2.67
SCH_2CH_3						1.26	1.28	1.27	1.33	1.24	1.31	1.31	1.32	1.31
OAc	2.00	1.99	2.03	2.05	2.04	2.01	2.02	2.10	2.13		1.95	1.97		
OAc	2.05	2.02	2.05	2.08	2.08	2.02	2.06							
OAc				2.13	2.14									
Carbons [c]														
C-1			100.7	93.0	90.3	84.2	83.1							
($J_{C,H}$)			(174)	(180)	(163)	(170)	(151)							
C-2			57.8	56.8	58.6	60.1	61.4							
C-3			69.7	69.9	71.6	70.2	72.9							
C-4			70.5	69.3	69.6	70.6	69.9							
C-5			66.7	69.3	71.9	67.4	75.4							
C-6			17.4	17.5	17.4	17.3	17.7							

[a] Spectra were determined at 500 and 125 MHz, respectively, for ^1H and ^{13}C unless otherwise noted. Solutions were ~2% in $CDCl_3$ with Me_4Si as internal standard. [b] Spectrum recorded at 200 MHz. [c] The numbers in parentheses denote the one-bond ^{13}C–^1H coupling constants for the anomeric carbon atoms (Hz).

TABLE II

^{1}H NMR chemical shifts for compounds **20**, **23–26**, **28** and **29**

Protons (J, Hz)	**20** [a]	**23** [a]	**24** [b]	**25** [a]	**26** [b]	**28** [a]	**29** [b]
α-L-Rha Unit B							
H-1	4.84	4.98	5.23	4.85	4.99	4.92	5.01
($J_{1,2}$)	(2.0)	(1.5)					
H-2	4.86	4.26	4.50	4.83	4.05	4.88	4.05
($J_{2,3}$)	(3.5)		(3.5)	(3.5)	(3.5)	(3.5)	(3.5)
H-3	5.18	5.10	4.13	5.16	3.79	5.04	3.81
($J_{3,4}$)	(9.5)		(9.5)	(9.5)	(10.0)	(10.0)	(10.0)
H-4	4.96	5.06	3.55	4.95	3.47	4.84	3.46
($J_{4,5}$)	(9.5)		(10.0)	(10.0)	(9.5)	(10.0)	(9.5)
H-5	4.13	3.84	3.87	4.12	3.88	3.74	3.77
($J_{5,6}$)	(6.0)	(6.0)	(6.5)	(6.5)	(6.5)	(6.0)	(6.0)
H-6	1.18	1.13	1.33	1.20	1.31	0.95	1.30
α-L-Rha Unit C							
H-1	5.36	4.80	4.81	5.06	5.07	5.04	4.81
($J_{1,2}$)	(1.5)						
H-2	4.50	5.05	3.87	4.30	4.23	5.36	3.86
($J_{2,3}$)	(3.5)	(3.5)	(3.5)		(3.5)	(3.5)	(3.0)
H-3	4.22	4.03	3.80	4.26	4.04	4.35	3.77
($J_{3,4}$)	(9.5)	(10.0)	(9.5)	(9.5)	(9.5)	(10.0)	(9.5)
H-4	5.39	4.92	3.53	5.21	3.60	5.47	3.52
($J_{4,5}$)	(9.5)	(10.0)	(10.0)	(9.5)	(9.5)	(9.5)	(9.5)
H-5	4.31	3.93	4.03	4.21	4.12	4.26	4.03
($J_{5,6}$)	(6.0)	(6.0)	(6.5)	(6.0)	(6.5)	(6.5)	(6.0)
H-6	1.28	0.56	1.24	0.78	1.27	1.29	1.24
β-D-GlcNAc Unit D							
H-1		4.86	4.47	4.63	4.48	4.70	4.53
($J_{1,2}$)		(8.0)	(8.5)		(8.5)	(8.5)	(8.5)
H-2		3.25	3.81	3.71	3.84	3.51	3.84
($J_{2,3}$)		(9.0)	(9.5)		(9.5)		(9.0)
H-3		4.37	3.58	4.21	3.61	4.02	3.61
($J_{3,4}$)		(9.0)	(9.0)	(9.0)	(9.0)		
H-4		3.49	3.52	3.62	3.53	3.48	3.68
($J_{4,5}$)				(9.0)	(10.0)		
H-5		3.52	3.47	3.52	3.47	3.48	3.68
($J_{5,6}$)		(10.0)	(6.0)	(10.0)	(6.0)		
H-6		3.73	3.75	3.78	3.75	3.70	3.88
($J_{6,6'}$)		(10.0)	(12.5)	(10.5)	(12.0)	(11.5)	(12.0)
H-6′		4.33	3.93	4.36	3.94	3.89	3.97
($J_{5,6'}$)		(4.5)	(1.5)	(4.9)	(2.0)		
OCH_3		3.45	3.52	3.47	3.52	3.48	3.51
NH		5.88		5.74		6.10	
NAc		1.98	2.05	2.01	2.06	2.05	2.05
OAc	1.86	2.00		1.85		1.81	
OAc	1.93	2.01 (6H)		1.93		1.81	
OAc	2.00	2.09		2.00		1.90	
C*H*Ph		5.48		5.55			
SCH_2CH_3	2.66						
SCH_2CH_3	1.30						

[a] In $CDCl_3$. [b] In D_2O.

In an earlier paper[17] we have reported that activation of thioglycosides by *N*-iodosuccinimide–triflic acid was a convenient and efficient procedure for the synthesis of oligosaccharides containing α-L-Rha residues, even though complications due to orthoester formation may arise. The oligosaccharide synthesis described here supports these general observations, but, since the glycosyl donor **10** cannot form orthoester intermediates, the moderate yields observed in sequential chain-extension reactions compared to the higher yields in block synthesis point to a delicate balance in the reactivity of donor–acceptor pairs, and possibly also the relative amounts of the triflic acid used as catalyst.

EXPERIMENTAL

General Methods.—The methods employed were described in an earlier publication[17]. NMR data are presented in Table I for monosaccharide derivatives and in Tables II (^{1}H) and III (^{13}C) for di- and tri-saccharides.

Methyl 3,4-di-O-acetyl-2-chloro-2,6-dideoxy-β-L-glucopyranoside (**5**), *methyl 3,4-di-O-acetyl-2-chloro-2,6-dideoxy-α-L-glucopyranoside* (**6**), *and methyl 3,4-di-O-acetyl-*

TABLE III

^{13}C NMR chemical shifts [a] for compounds **20**, **23–26**, **28** and **29**

Carbon ($J_{C,H}$)	**20** [b]	**23** [b]	**24** [c]	**25** [b]	**26** [c]	**28** [b]	**29** [c]
α-L-Rha Unit B							
C-1	99.8	100.9	102.6	99.3	103.6	99.1	103.2
($J_{C,H}$)	(171)	(173)	(177)	(172)	(171)	(172)	(172)
C-2	69.9	57.7	62.1	70.0	70.9	69.5	70.9
C-3	68.5	69.5	69.7	68.5	71.1	68.4	70.9
C-4	71.0	70.1	72.5	71.1	72.7	70.9	72.8
C-5	67.6	67.7	70.5	67.5	70.5	67.2	69.8
C-6	17.3	17.3	17.4	17.3	17.4	17.1	17.35
α-L-Rha Unit C							
C-1	84.3	97.4	102.2	100.0	101.7	99.6	102.2
($J_{C,H}$)	(170)	(175)	(170)	(177)	(175)	(173)	(170)
C-2	62.2	71.5	71.2	59.9	61.6	72.1	71.3
C-3	78.1	75.6	79.5	77.0	78.6	75.6	78.9
C-4	72.3	72.1	72.0	71.9	71.4	72.3	72.0
C-5	68.0	66.4	69.8	67.3	70.5	68.1	69.8
C-6	17.5	16.4	17.2	16.9	17.3	17.7	17.3
β-D-GlcNAc Unit D							
C-1		100.9	102.2	101.5	102.1	100.7	102.3
($J_{C,H}$)		(164)	(163)	(164)	(162)	(164)	(162)
C-2		58.5	55.9	57.4	55.9	56.1	55.9
C-3		75.4	82.7	75.6	83.0	85.1	82.2
C-4		80.3	69.3	79.8	69.2	71.0	75.3
C-5		66.1	76.9	66.2	76.8	75.0	69.7
C-6		68.8	61.6	68.8	61.5	44.3	44.6

[a] The numbers in parentheses denote the one-bond ^{13}C–^{1}H coupling constants for the anomeric carbon atoms (Hz). [b] In $CDCl_3$. [c] In D_2O.

2-chloro-2-deoxy-α-L-rhamnopyranoside (**7**).—Chlorine was bubbled through a cold (0°C) mixture of the glucal **4** (17 g, 79 mmol) and silver acetate (19 g, 1.5 mol equiv) in anhyd MeOH (500 mL) for 45 min, and the mixture was stirred for a further 30 min at room temperature. The solids were filtered off and rinsed with MeOH (100 mL). The combined filtrate and washings were concentrated, and the residue was dissolved in EtOAc (500 mL) and was washed with satd aq $NaHCO_3$ (3 × 300 mL) and satd aq NaCl (3 × 300 mL). The aqueous washings were reextracted with EtOAc (2 × 200 mL), and the combined organic phases were dried and concentrated. The β-L-glucoside **5** crystallized on standing and was filtered off in a mixture of 9:1 hexanes–EtOAc (8 g, 36%); mp 112.4–113.5°C, $[\alpha]_D^{25}$ −70.2° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}ClO_6$: C, 47.1; H, 6.1. Found: C, 47.1; H, 6.2.

Concentration of the mother liquors and flash chromatography (9:1 hexanes–EtOAc) gave a mixture (7.8 g) of *α-L-rhamno* **7** and *α-L-gluco* **6** isomers in the ratio 85:15 as evaluated by NMR spectroscopy. The target α-L-rhamnopyranoside **7** was crystallized (5.7 g, 25%) in hexanes; mp 93.8–94.7°C; $[\alpha]_D^{25}$ −46.4° (*c* 0.7, $CHCl_3$). Anal. Found: C, 46.9; H, 5.9.

1,3,4-Tri-O-acetyl-2-chloro-2-deoxy-α- and -β-L-rhamnopyranosides (**8** and **9**).—A solution of H_2SO_4 in glacial acetic acid (0.5 M, 9 mL) was added dropwise to a solution of methyl glycoside **7** (4.3 g, 15.3 mmol) in a mixture of 3:7 glacial acetic acid-Ac_2O (320 mL) stirred at 20°C (water bath). After 5 h, more acid solution (3 mL) was added to the stirred mixture, and after an additional 2 h at 20°C the solution was poured slowly into a stirred ice-cold aq satd solution of $NaHCO_3$ (400 mL) and extracted with CH_2Cl_2 (2 × 500 mL). The organic phases were washed with water (2 × 200 mL), combined, dried, and concentrated at 40°C under high vaccuum. Residual traces of Ac_2O were coevaporated with toluene (2 × 100 mL), and chromatography (7:3, hexanes–EtOAc) gave a mixture (9:1) of the α-L- and β-L-rhamnopyranosides **8** and **9** (4.5 g, 96%).

Ethyl 3,4-di-O-acetyl-2-chloro-2-deoxy-1-thio-α-L-rhamnopyranoside (**10**) *and ethyl 3,4-di-O-acetyl-2-chloro-2-deoxy-1-thio-β-L-rhamnopyranoside* (**11**).—A solution of the anomers **8** and **9** (4.5 g, 14.6 mmol) in anhyd CH_2Cl_2 (265 mL) containing ethanethiol (1.4 mL, 1.3 mol equiv) and $BF_3 \cdot Et_2O$ (2.35 mL, 1.3 mol equiv) was stirred overnight at room temperature. Et_3N (2.6 mL) was added dropwise, and the solution was concentrated. The residue was dissolved in EtOAc (300 mL) and washed successively with aq satd $NaHCO_3$ (150 mL), M HCl (100 mL), satd aq $NaHCO_3$ (100 mL), and satd aq NaCl (100 mL). The washings were reextracted with EtOAc (100 mL), and the combined organic phases were dried and concentrated. Chromatography (9:1 hexanes–EtOAc, 1500 mL) gave the ethyl 1-thio-α-L-rhamnoside **10** (3.4 g, 75.5%) as a colourless oil; $[\alpha]_D^{25}$ −122.6° (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{12}H_{19}ClO_5S$: C, 46.4; H, 6.2. Found: C, 46.3; H, 6.2.

Further elution of the column (hexanes–EtOAc; 8:2, 500 mL; 7:3, 500 mL) gave the ethyl 1-thio-β-L-rhamnoside **11** (970 mg, 21%) that crystallized on standing; mp 111.7–112.6°C; $[\alpha]_D^{25}$ +90.0° (*c* 0.8, $CHCl_3$). Anal. Found: C, 46.3; H, 6.1.

Ethyl 4-O-acetyl-2-chloro-2-deoxy-1-thio-α-L-rhamnopyranoside and ethyl 3-O-

TABLE IV

Acid-catalyzed methanolysis of diacetate **10**

Entry	Time (h)	Temperature (°C)	Products		
			Diacetate **10**	Monoacetates (ratio **12**/**13**)	Diol **14**
A	1.75	50	22%	46% (88/12)	16%
B	16	20	0%	55% (94/6)	34%

*acetyl-2-chloro-2-deoxy-1-thio-α-*L*-rhamnopyranoside* (**12** and **13**).—A solution of the diacetate **10** (56 mg, 0.18 mmol) in methanolic HCl (0.4 M, 5 mL) was stirred 1.75 h at 50°C. Et_3N (1 mL) was added to the solution which was concentrated. Chromatography (8:2 hexanes–EtOAc) gave the diacetate **10** (13 mg, 22%), and a mixture (88:12, 22 mg) of the monoacetates **12** (40%) and **13** (6%). Further elution (6:4 hexanes–EtOAc) gave the diol **14** (7 mg, 16%).

Another sample of diacetate **10** (56 mg, 0.18 mmol) was treated for 16 h at room temperature under the same conditions. Separation of the products as described above gave the mixture (94:6, 27 mg) of **12** (52%) and **13** (3%), and the diol **14** (14 mg, 34%).

*Ethyl 2-chloro-2-deoxy-1-thio-α-*L*-rhamnopyranoside* (**14**).—A solution of the diacetate **10** (3.4 g, 11 mmol) in methanolic NaOMe (0.03 M, 330 mL) was stirred for 40 min at room temperature and deionized with Amberlite IR-120 (H^+) resin. The resin was filtered off, rinsed with MeOH (100 mL), and the combined filtrates were concentrated to dryness. Chromatography (6:4 hexanes–EtOAc) gave the pure diol **14** as a colourless oil (2.4 g, 98%) that decomposed upon standing at room temperature. The diol **14** was therefore rechromatographed, characterized by NMR spectroscopy, and used immediately in the protection reactions.

*Ethyl 3-O-acetyl-4-O-benzoyl-2-chloro-2-deoxy-1-thio-α-*L*-rhamnopyranoside* (**15**) *and ethyl 4-O-acetyl-3-O-benzoyl-2-chloro-2-deoxy-1-thio-α-*L*-rhamnopyranoside* (**16**).—A solution of the diol **14** (1.84 g, 8.1 mmol) in anhyd CH_2Cl_2 (100 mL) and anhyd pyridine (30 mL) containing activated powdered 4A molecular sieves (7 g) was stirred at room temperature 1 h, cooled to 0°C under N_2, and acetyl chloride (580 μL, 1 mol equiv) was added dropwise. After 1 h at 0°C, more acetyl chloride (30 μL, 0.05 mol equiv) was added, and the mixture was stirred an additional hour. After acetylation, TLC (7:3 hexanes–EtOAc) showed a single product (R_f 0.5). Benzoyl chloride (1.9 mL, 2 mol equiv) was added to the mixture, which was stirred overnight at room temperature. MeOH (1 mL) was added to destroy excess benzoyl chloride, solids were filtered off, rinsed with CH_2Cl_2 (20 mL), and the combined filtrates were concentrated. A solution of the residue in EtOAc (200 mL) was washed successively with M HCl (100 mL), satd aq $NaHCO_3$ (100 mL), and satd aq NaCl (100 mL). The aqueous washings were reextracted with EtOAc (2 × 100 mL), and the combined organic phases were dried and concentrated. Flash chromatography (97:3 hexanes–EtOAc) gave the mixed monoacetates **15**

(59%) and **16** (9%) (2.04 g, 87:13). Further elution of the column (9:1 hexanes–EtOAc) gave the diacetate **10** (230 mg, 9%).

Ethyl 4-O-benzoyl-2-chloro-2-deoxy-1-thio-α-L-rhamnopyranoside (**17**) *and ethyl 3-O-benzoyl-2-chloro-2-deoxy-1-thio-α-L-rhamnopyranoside* (**18**).—The mixture of rhamnosides **15** and **16** (87:13, 2.04 g) was dissolved in a methanolic solution of HCl (0.4 M, 100 mL) and stirred at room temperature 6 h and then at 50°C 2 h. Following addition of Et_3N (10 mL), the cooled mixture was concentrated. A solution of the residue in EtOAc (200 mL) was washed successively with water (100 mL), M HCl (100 mL), satd aq $NaHCO_3$ (100 mL), and satd aq NaCl (100 mL). The washings were reextracted with EtOAc (100 mL), and the combined organic phases were dried and concentrated. Flash chromatography (hexanes–EtOAc, 95:15, 700 mL; 90:10, 500 mL) gave first a 47:53 mixture (421 mg) of **16** (yield 75%, based on estimated starting **16**) and **15** (yield 13%, based on estimated starting **15**); then pure alcohol **17** (1.31 g, 79% yield based on estimated starting **15**), and finally a mixture (35:65, 86 mg) of **17** (yield 1.9%, based on estimated starting **15**) and **18** (yield 24%, based on estimated starting **16**). The alcohol **17** was isolated as a colourless oil; $[\alpha]_D^{25}$ −140.1° (*c* 1.4, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}ClO_4S$: C, 54.4; H, 5.8. Found: C, 54.0; H. 5.7.

Ethyl 4-O-benzoyl-2-chloro-2-deoxy-1-thio-3-O-(2',3',4'-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**20**).—Bromine (20 μL, 0.39 mmol) was added to a solution of **19** (ref 13) (136 mg, 0.41 mmol) in anhyd CH_2Cl_2 (2 mL), and after 1 h at room temperature cyclohexene (80 μL, 0.80 mmol) was added. The resulting glycosyl bromide solution was added dropwise to a mixture of the acceptor **17** (102 mg, 0.31 mmol), silver triflate (174 mg, 2.2 mol equiv), and activated powdered 4A molecular sieves (2 g) in anhyd CH_2Cl_2 (10 mL) and was stirred in the dark under N_2 at −50°C. The mixture was allowed to reach −35°C over 2 h, then cooled to −45°C, and more silver triflate (80 mg, 1 mol equiv) was added. After 1 h at −45°C, Et_3N (120 μL) was added, and solids were filtered off and rinsed with CH_2Cl_2 (20 mL). The combined filtrates were washed successively with water (20 mL), M HCl (20 mL), and satd aq $NaHCO_3$ (20 mL). The aqueous phases were reextracted with CH_2Cl_2 (20 mL), and the combined organic solutions were dried and concentrated. Flash chromatography (hexanes–EtOAc; 80:20, 250 mL; 70:30, 100 mL) gave the disaccharide **20** (130 mg, 71%) as a colourless glass; $[\alpha]_D^{25}$ −52.7° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{27}H_{35}ClO_{11}S$: C, 53.8; H, 5.8. Found: C, 53.9; H, 5.9.

Methyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-[2',4'-di-O-acetyl-3'-O-(3'',4''-di-O-acetyl-2''-chloro-2''-deoxy-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl]-β-D-glucopyranoside (**23**).—A mixture of the acceptor **21** (ref 17) (100 mg, 0.18 mmol) and the thioglycoside **10** (70 mg, 1.25 mol equiv) in anhyd CH_2Cl_2 (7 mL) containing powdered activated 4A molecular sieves (650 mg) was stirred under N_2 overnight at room temperature. *N*-Iodosuccinimide (56 mg, 1.4 mol equiv) and a satd solution of triflic acid in CH_2Cl_2 (0.15 M, 320 μL, 0.26 mol equiv) were added, and the mixture was protected from light and stirred at room temperature

for 3 h. More acid (100 μL, 0.08 mol equiv) was added, and stirring was maintained for another 24 h. Again more acid (200 μL, 0.16 mol equiv) was added, the reaction was allowed to proceed for an additional 24 h, at the end of which time it was quenched by addition of Et_3N (100 μL). Solids were filtered off, rinsed with CH_2Cl_2 (20 mL), and the combined filtrates were washed successively with aq sodium thiosulfate (10%, 2 × 30 mL), M HCl (20 mL), aq satd $NaHCO_3$ (20 mL) and water. The washings were reextracted with CH_2Cl_2 (20 mL), and the organic phases were combined, dried, and concentrated. Chromatography (20:1 $CHCl_3$–MeOH) gave only partial purification of the trisaccharide **23**. The combined impure fractions (80 mg, 90% of desired product as estimated by TLC, R_f 0.25, solvent as above) were concentrated and rechromatographed (60:1 $CHCl_3$–MeOH) to give the pure trisaccharide **23** (56 mg, 39%), $[\alpha]_D^{25}$ −47.3° (*c* 0.4, $CHCl_3$). Anal. Calcd for $C_{36}H_{48}ClNO_{17}$: C, 53.9; H, 6.0; N, 1.8. Found: C, 53.6; H, 6.0; N, 1.9.

Further washing of the solids with 10:1 $CHCl_3$–MeOH, concentration, and chromatography (30:1 $CHCl_3$–MeOH) of the residue gave 19 mg (19%) of unreacted glycosyl acceptor **21**.

Methyl 2-acetamido-3-O-[3'-O-(2"-chloro-2"-deoxy-α-L-rhamnopyranosyl)]-α-L-rhamnopyranosyl]-2-deoxy-β-D-glucopyranoside (**24**).—A solution of the protected trisaccharide **23** (48 mg, 0.06 mmol) in 60% acetic acid (3 mL) was stirred for 45 min at 100°C and concentrated. Residual acid was coevaporated with a mixture of 3:2 toluene–methanol (3 × 5 mL), and the residue was dissolved in anhyd MeOH (2 mL). A solution of NaOMe in MeOH (M, 60 μL) was added, and the mixture was stirred at room temperature 21 h and deionized with Amberlite IR-120 (H^+) resin. The resin was filtered off, rinsed with MeOH (3 mL), and the combined filtrates were concentrated. Chromatography (8:1.2:1 EtOAc–MeOH–H_2O) gave trisaccharide **24** that was finally purified on a Bio-Gel P-2 column (water) and isolated as a white powder (26 mg, 78%); $[\alpha]_D^{25}$ −87.6° (*c* 0.4, MeOH). Anal. Calcd for $C_{21}H_{36}ClNO_{13}$: C, 46.2; H, 6.6; N, 2.6. Found: C, 45.9; H, 6.6; N, 2.4.

Methyl 2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-[4'-O-benzoyl-2'-chloro-2'-deoxy-3'-O-(2",3",4"-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl]-β-D-glucopyranoside (**25**).—A mixture of the acceptor **19** (ref 18) (53 mg, 0.16 mmol), the thioglycoside **20** (116 mg, 1.18 mol equiv), and activated powdered 4A molecular sieves (500 mg) in anhyd CH_2Cl_2 (7.5 mL) was stirred overnight under N_2 at room temperature. *N*-Iodosuccinimide (53 mg, 1.4 mol equiv) and a satd solution of triflic acid in CH_2Cl_2 (0.15 M, 520 μL, 0.48 mol equiv) were added to the mixture that was protected from the light, and stirred under N_2 at room temperature. After 6 h Et_3N was added (50 μL), and workup of the reaction was carried out as described for the preparation of **23**. Chromatography (60:1 $CHCl_3$–MeOH) gave the pure trisaccharide **25** (90 mg, 64%) as a colourless glass; $[\alpha]_D^{25}$ −74.6° (*c* 0.8, $CHCl_3$). Anal. Calcd $C_{41}H_{50}ClNO_{17}$: C, 57.0; H, 5.8; N, 1.6. Found: C, 57.2; H, 5.8; N, 1.6.

Methyl 2-acetamido-3-O-[2'-chloro-2'-deoxy-3'-O-(α-L-rhamnopyranosyl)-α-L-rhamnopyranosyl]-2-deoxy-β-D-glucopyranoside (**26**).—Trisaccharide **25** (81 mg, 0.09

mmol) was deprotected as described for the preparation of **24**, but transesterification was allowed to proceed for 2.5 days before workup. Flash chromatography (8:1.2:1 EtOAc–MeOH–H_2O) gave trisaccharide **26** that was purified on a Bio-Gel P-2 column (water) and obtained as a colourless glass (44 g, 86%) by coconcentration with MeOH; $[\alpha]_D^{25}$ −74.8° (*c* 0.4, MeOH). Anal. Calcd for $C_{21}H_{36}ClNO_{13}$: C, 46.2; H, 6.6; N, 2.6. Found: C, 46.0; H, 6.8; N, 2.5.

*Methyl 2-acetamido-6-chloro-2,6-dideoxy-3-*O*-[2',4'-di-*O*-benzoyl-3'-*O*-(2",3",4"-tri-*O*-acetyl-α-*L*-rhamnopyranosyl)-α-*L*-rhamnopyranosyl]-β-*D*-glucopyranoside* (**28**). —A solution of the diol **27** (ref 17) (150 mg, 0.17 mmol) in a mixture of anhyd 1:1 MeCN–anhyd pyridine (4 mL) containing CCl_4 (200 μL, 10 mol equiv), triphenylphosphine (89 mg, 2 mol equiv), and imidazole (51 mg, 4.1 mol equiv), was stirred at room temperature 24 h. MeOH (200 μL) was added and the mixture was concentrated. A solution of the residue in CH_2Cl_2 (120 ml) was washed successively with M HCl (50 mL), satd aq $NaHCO_3$ (50 mL) and water (50 mL). The washings were reextracted with dichloromethane (2 × 50 mL), and the combined organic phases were dried and concentrated. Flash chromatography (1:1 EtOAc–toluene) of the residue gave the chlorinated trisaccharide **28** pure (79 mg, 52%) as a colourless glass; $[\alpha]_D^{25}$ −44.0° (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{41}H_{50}ClNO_{18}$: C, 55.9; H, 5.7; N, 1.6. Found: C, 56.1; H, 5.6; N, 1.5.

*Methyl 2-acetamido-6-chloro-2,6-dideoxy-3-*O*-[3'-*O*-(α-*L*-rhamnopyranosyl)-α-*L*-rhamnopyranosyl]-β-*D*-glucopyranoside* (**29**).—A solution of the chlorinated trisaccharide **28** (70 mg, 0.8 mmol) in methanolic NaOMe (0.03 M, 2 mL) was stirred for 3 days at room temperature and deionized with Amberlite IR 120 (H^+) resin. The resin was filtered off and rinsed with MeCOH, and the combined filtrate and washings were concentrated. Chromatography (8:1.2:1 EtOAc–MeOH–H_2O) of the residue gave trisaccharide **29** that was finally purified on a Bio-Gel P-2 column (water) and isolated as a colourless glass by coconcentration with MeOH (36 mg, 86%), $[\alpha]_D^{25}$ −83.7° (*c* 0.4, MeOH). Anal. Calcd for $C_{21}H_{36}ClNO_{13}$: C, 46.2; H, 6.6; N, 2.6. Found: C, 45.9; H, 6.8; N, 2.4.

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