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Note

Synthesis of some disaccharide derivatives containing a β-L-rhamnopyranosidic bond

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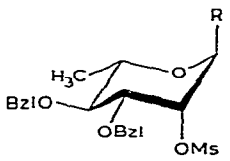
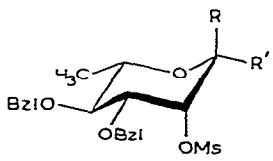
We have reported[1,2] a practical, stereoselective synthesis of β-D-mannopyranosides and β-L-rhamnopyranosides. The β-stereoselectivity of these glycosidations is the result[1] of the interaction of opposing dipoles of a strongly electronegative, non-participating substituent on C-2, and a highly reactive, electronegative leaving-group on C-1. A systematic study of the synthesis of oligosaccharides containing β-L-rhamnosyl residues is needed because this structural unit occurs in bacterial antigens[3,4]. Recently, Kochetkov and his co-workers[5] and Iversen and Bundle[6] reported syntheses of β-L-rhamnopyranosides that involve approaches that have been used previously for the preparation of β-D-mannopyranosides[7–10]. We now report on the synthesis of β-L-rhamnopyranosidic disaccharides by our alternative method[1,2].

3,4-Di-*O*-benzyl-2-*O*-methylsulfonyl-α-L-rhamnopyranosyl chloride (**1**) and the corresponding 1-*O*-(2,2,2-trifluoroethylsulfonyl) (tresyl) derivative **2** were prepared as described earlier[1,2]. The reaction of methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**8**) with **2** in acetonitrile for 48 h gave a mixture of two anomers having



1 R = Cl
2 R = OTres



3 α R′ = H,R derived from 8
3 β R = H,R′ derived from 8
4 α R′ = H,R derived from 9
4 β R = H,R′ derived from 9
5 α R′ = H,R derived from 11
5 β R = H,R′ derived from 11
6 β R = H,R′ derived from 12
7 β R = H,R′ derived from 13

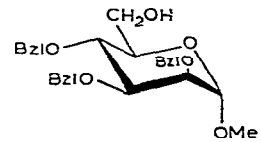


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TABLE I

SOME PHYSICAL PROPERTIES OF THE DISACCHARIDES

	3α	3β	4α	4β	5α	5β	6β	7β	16α	16β
$[\alpha]_D^{22-25}$ (degrees)	−3.5	+45	+29	+67	−3	+33	+46	+91	+27.5	−18[e]
(concentration)[a]	2.0	1.6	0.4	0.5	0.4	0.62	1.1	1.05	0.75	0.4
Mol. formula	$C_{49}H_{56}O_{12}S$		$C_{49}H_{56}O_{12}S$		$C_{49}H_{56}O_{12}S$		$C_{51}H_{62}O_{15}S$	$C_{51}H_{56}O_{13}S$	$C_{50}H_{62}O_{13}S$	
Anal. Calc: C,H,S	67.72; 6.50; 3.69		67.72; 6.50; 3.69		67.72; 6.50; 3.69		64.67; 6.60; 3.39	67.38; 6.21; 3.53	68.97; 6.41; 3.29	
Found: C,H,S	—	67.64; 5.90; 3.69	—	67.23; 5.97; 3.37	67.26; 6.18; 3.74		64.31; 6.30; 3.08	67.40; 6.17; 4.0	68.52; 5.99; 3.54	—
Yield (%)[b]		~71		~90	~84		~85[d]	~84[d]	90	
Anomeric ratio (α:β, %)		27:73		16:84	67:33		[d]	[d]	75:25	
^{1}H-N.m.r. data										
H-1 (δ)	4.87	4.86	[c]	[c]	4.80	4.80	4.83	5.26	[c]	[c]
$J_{1,2}$ (Hz)	0.6	0.5			1.8	1.80	1.4	2.0		
H-1′ (δ)	4.91	4.53	5.16	4.55	5.01	4.46	4.26	4.76	[c]	4.61
$J_{1',2'}$ (Hz)	1.4	—	2.2	—	4.2	—	—	—		
OMe (δ)	3.32	3.30	3.38	3.38	3.37	3.35	—	—	3.27	3.25
OMs (δ)	3.01	2.95	3.10	2.92	2.98	3.01	2.70	2.77	2.92	3.05

[a]In chloroform. [b]Of pure compound. [c]Protons indistinguishable (masked by signals for benzyl methylenes). [d]The α anomer was present in a very small amount. [e]Contains some α anomer.

TABLE II

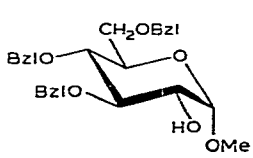
^{13}C-N.M.R. SHIFTS (PROTON-DECOUPLED, P.P.M., IN $CDCl_3$)[a,b]

	3α	3β	4α	4β	5α	5β	6β	7β	16α	16β
C-1	98.17	98.46	100.37	100.38	98.50	99.16	97.61	96.01	99.85	99.80
C-1′	99.10	99.93	99.10	99.65	97.05	100.55	99.89	100.42	99.85	100.10
C-5	[c]	[c]	[c]	[c]	[c]	[c]	68.60	[c]	71.11 [d]	71.06
C-5′	68.25	71.72	68.78	72.05	69.44	71.40	72.53	72.82	71.88	76.21
C-6	67.04	67.89	68.78	69.40	68.51	69.03	17.59 [d]	68.72	69.48 [d]	69.72 [d]
C-6′	17.82	17.95	17.93	18.06	17.81	17.82	17.75	18.00	69.30	69.40
OMe	54.90	54.97	55.06	55.14	54.94	54.77	—	—	54.82	55.02
OMs	38.86	39.53	38.85	39.25	38.58	39.53	38.37	38.21	38.76	39.19

[a]These assignments are tentative, based on analogies. [b]C-2,3,4,2′,3′,4′ and benzyl CH_2 resonances could not be identified, but the total number of carbons was accounted for. [c]Indistinguishable from remaining carbons. [d]Assignment may be reversed.

an αβ-ratio of 27:73, as determined by the ratio of mesyl peak-areas in the ^{1}H-n.m.r. spectra. The anomers were isolated by chromatography on silica gel, to afford 2,3,4-tri-*O*-benzyl-6-*O*-(3,4-di-*O*-benzyl-2-*O*-methylsulfonyl-α- and -β-L-rhamnopyranosyl)-α-D-mannopyranosides (**3β** and **3α**). Optical rotation, ^{1}H-n.m.r. (Table I), and ^{13}C-n.m.r. data (Table II) confirmed the anomeric configurations.

Reactions of this type were carried out to synthesize disaccharides containing β-L-rhamnopyranosidic bonds linked at secondary positions (O-2, O-3, and O-4) of aglycons. Thus, the reaction of methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**9**) with **2** afforded methyl 3,4,6-tri-*O*-benzyl-2-*O*-(3,4-di-*O*-benzyl-2-*O*-methylsulfonyl-β-L-rhamnopyranosyl)-α-D-glucopyranoside (**4β**) along with its α anomer **4α** in the ratio 84:16. The β-anomeric assignment to **4β** was made on the basis of optical rotation (+66.6°), ^{1}H-n.m.r. (Table I), and ^{13}C-n.m.r. data (Table II). Similarly, the reaction of **2** with aglycon **12** [8-(methoxycarbonyl)octyl 2,4-di-*O*-benzoyl-α-L-rhamnopyranoside[11]] afforded mainly 8-(methoxycarbonyl)octyl 2,4-di-*O*-benzoyl-3-*O*-(3,4-di-*O*-benzyl-2-*O*-methylsulfonyl-β-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**6β**) in 85% yield. The α anomer was formed in very small proportion and could not be isolated pure.



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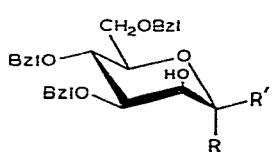
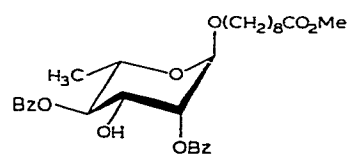


10 R = H, R′ = OAllyl
11 R = OMe, R′ = H



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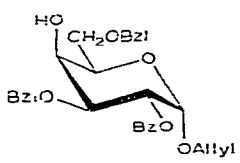
In an attempt to see whether reaction with an axial HO-2 would also be stereoselective, allyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside[12] (**10**) was treated with **2**,

but no reaction occurred. This failure may be due to strong, steric shielding of HO-2 by the β-allyl group at C-1. To avoid the problem of the β configuration, methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**11**) was treated with **2** for 48 h. In this case, the major product was the α anomer **5α**, with methyl 3,4,6-tri-*O*-benzyl-2-*O*-(3,4-di-*O*-benzyl-2-*O*-methylsulfonyl-β-L-rhamnopyranosyl)-α-D-mannopyranoside (**5β**) obtained in lesser amount (αβ-ratio 2:1). Dichloromethane or tetrahydrofuran gave no better stereoselectively than acetonitrile when used as reaction solvent. The use of a more reactive leaving-group, trifluoromethanesulfonate, gave other side-products and the stereoselectivity was not as good as with the tresyl derivative **2**.

In order to alter any specific steric or dipole interactions that might be hindering β-glycosidation, the reaction was performed on the same "aglycon" (**10**) with the corresponding derivative of D-mannose, namely, 3,4,6-tri-*O*-benzyl-2-*O*-methylsulfonyl-1-*O*-tresyl-α-D-mannopyranose[1,2] (**15**). In this case, an S_N2-like transition state leading to a β linkage would be essentially diasteromeric with that involved in the β-glycosidation of the L-rhamnose derivative **2**. Nevertheless, in this case also, an α-linked disaccharide **16α** was the main product, and methyl 3,4,6-tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-methylsulfonyl-β-D-mannopyranosyl)-α-D-mannopyranoside (**16β**) was minor (α,β-ratio 3:1). The similarity of this result to that of the preceding reaction of **2** suggests that these reactions probably pass through an essentially planar, cationic intermediate and the higher preference for α-stereoselectivity is thermodynamic and due to the favorable relationship between the dipoles of the C-1-O and C-2-O bonds[13].



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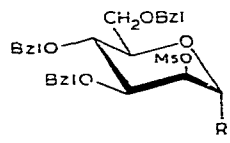
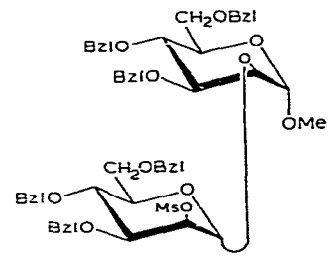


14 R = Cl
15 R = OTres



16β β-anomer
16α α-anomer

In contrast, the reaction of **2** with the unreactive, axial HO-4 of allyl 2-*O*-benzoyl-3,6-di-*O*-benzyl-α-D-galactopyranoside[14] (**13**) afforded mainly allyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-4-*O*-(3,4-di-*O*-benzyl-2-*O*-methylsulfonyl-β-L-rhamnopyranosyl)-α-D-galactopyranoside (**7**) in ~84% yield. The α anomer was present in very small amount and could not be obtained pure. It is surprising that the pathway to the formation of an axial 2-*O*-β-glycosyl linkage is apparently more hindered than that leading to an axial 4-*O*-β-coupling.

Determination of the anomeric configuration

The anomeric configuration of the disaccharides **3β**, **4β**, **5β**, and **16β** was

established by comparison of the specific rotations with those of their α anomers. Disaccharides **6** and **7** had high, positive values, as expected for β-L compounds, but the configuration could not be confirmed by direct comparison, since the α anomers of these disaccharides were not available.

In the ^{1}H-n.m.r. spectra, coupling constants could not be used for determination of anomeric configuration in the present series, as $J_{1,2}$ values for α- and β-L-rhamnopyranosides and α- and β-D-mannopyranosides correspond to a gauche ($\varphi_{1,2}$ ~60°) relationship (*eq-eq* and *ax-eq*). Chemical shifts of β-anomeric protons are usually to higher field than those of corresponding α-anomeric protons. This relationship is observed in the current series (α at δ 5.16–4.80; β at δ 4.26–4.76), and the H-1′ chemical shifts for **6** and **7** lie in the appropriate range for β linkages.

In the ^{13}C-n.m.r. spectra of β-linked L-rhamnopyranosyl and D-mannopyranosyl disaccharides, the difference between chemical shifts for C-1 in the α- and β-series is too small to use in establishing anomeric configuration. Generally, a β-anomeric C-1′ resonates downfield of an α-anomeric C-1′, as is observed in the current series. However, a reversal of this order may occur[15,16] with some aglycons, and therefore, configuration cannot be assigned completely on this basis of chemical shifts. Nevertheless, they can support an assignment based on other evidence. The chemical shifts of C-5 in unsubstituted β-D-mannopyranosides and β-L-rhamnopyranosides are at substantially lower field[16,17] (~4.0 p.p.m.) than for the corresponding α anomers. This difference is seen in the present series (and has been observed by other workers[6,15]). For each pair of anomers shown in Table II, a downfield shift (~2–3 p.p.m. for β-L-rhamnopyranosides and 4.33 p.p.m. for β-D-mannopyranoside) for C-5′ is found in the case of the β anomer compared to the α anomer. Chemical shifts for C-5′ can therefore be used to establish the anomeric configuration in the L-rhamnose and D-mannose series. The chemical shifts of the C-5′ signals for disaccharides **6** and **7** are at 72.53 and 72.82 p.p.m., in close agreement with those observed for other β anomers in the present series. Other differences in the ^{13}C-n.m.r. spectra which reflect differences in the anomeric configuration are the chemical shift of the 2-*O*-mesyl group. Usually, the signal for the mesyl group of the β anomer is downfield to that of the α anomer. The configuration at C-1′ in all products reported can therefore be considered established by the weight of the cumulative evidence cited.

EXPERIMENTAL

General. — ^{1}H-N.m.r. spectra were recorded with a Varian A-60-A or XL-100-15 spectrometer for solutions in chloroform with tetramethylsilane as the internal reference. ^{13}C-N.m.r. spectra were recorded with a Varian XL-100-15 spectrometer in the pulsed Fourier-transform/proton noise-decoupled mode on similar solutions. The spectra are reported with chemical shifts downfield from Me_4Si. Optical rotations were determined with a Perkin–Elmer 141 polarimeter in jacketed 1-dm cells. T.l.c. was performed on "Baker-Flex" silica gel 1B-F (2.5 × 7.5 cm) plates. High-pressure liquid chromatography (h.p.l.c.) was performed with a Valvco septumless injector

(1.0 ml), a Glenco pump (model HPLPS-1), and a Waters differential refractometer R-401. A stainless-steel column (25 × 1 cm inside diameter) containing silica gel (Whatman, Partisil M 9 10/25) was used at a flow rate of 8.0 ml/min.

Spectrograde acetonitrile was dried with CaH_2. Silver 2,2,2-trifluoroethanesulfonate was prepared as described earlier[18]. 3,4-Di-*O*-benzyl-3-*O*-methylsulfonyl-α-L-rhamnopyranosyl chloride (**1**) and 3,4,6-tri-*O*-benzyl-2-*O*-methylsulfonyl-α-D-mannopyranosyl chloride (**14**) were prepared as described in earlier papers[1,2]. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[19] (**8**), methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside[12] (**9**), allyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside[12] (**10**), methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside[18] (**11**), and 8-(methoxycarbonyl)-octyl 2,4-di-*O*-benzoyl-α-L-rhamnopyranoside[11] (**12**) were prepared by literature procedures. Aglycon **13** was prepared by Mr. H. A. El Shenawy[14] of this laboratory.

General method of glycosidation. — α-L-Rhamnopyranosyl chloride (**1**) or α-D-mannopyranosyl chloride (**14**) was treated with 1.5 equiv. of silver 2,2,2-trifluoroethanesulfonate or trifluoromethanesulfonate in acetonitrile to form the sulfonate, as described earlier[1,2]. The glycosyl sulfonate solution in acetonitrile or other solvent (dichloromethane or tetrahydrofuran) was allowed to react with 1 equiv. of aglycon for 40–48 h at room temperature. All operations were performed on a high-vacuum rack. The mixtures were isolated, and the crude product was analyzed by ^{1}H-n.m.r. spectroscopy and h.p.l.c. The anomeric mixture was fractionated by chromatography on silica gel with ethyl acetate–hexane (1:4 or 1:3).

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