Synthesis of β-D-Mannopyranosides and β-L-Rhamnopyranosides by Glycosidation at C-1

Vinai K. Srivastava and Conrad Schuerch*

Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210

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A stereoselective synthesis of β-D-mannopyranosides and β-L-rhamnopyranosides has been achieved by glycosidation at C-1. Treatment of the 1-*O*-tosyl derivative **2** with 1 equiv of methanol in acetonitrile gave methyl 3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-β-D-mannopyranoside (**3**) in over 90% yield (isolated). No α-anomer was formed in a detectable amount. Treatment of **2** with 1 equiv of cyclohexanol afforded 88% of β-anomer **6** and 12% α-anomer **7**. When the 1-*O*-[(2,2,2-trifluoroethyl)sulfonyl] derivative was used in place of 1-*O*-tosyl, **6** was formed in 93% yield along with 7% of the α-anomer. Coupling of **2** with methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**8**) gave a mixture of disaccharides, α-anomer **16** and β-anomer **9** in a 1:5 ratio (α/β). This reaction was also more stereoselective when the 1-*O*-[(2,2,2-trifluoroethyl)sulfonyl] derivative was used in place of 1-*O*-tosyl for methyl 2,3,4-tri-*O*-benzyl-6-*O*-[3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-β-D-mannopyranosyl]-α-D-mannopyranoside (**9**) was formed in over 90% yield. α-anomer **16** was prepared in over 95% yield by glycosidation of **8** with **13** (prepared from 2-*O*-benzoyl-3,4-di-*O*-benzyl-α-D-mannopyranosyl chloride (**12**)). Reduction of the benzyl and methylsulfonyl groups with sodium–liquid ammonia gave methyl 6-*O*-β-D-mannopyranosyl-α-D-mannopyranoside (**10**). Treatment of diol **18** with methylsulfonyl chloride in 2,6-lutidine gave crystalline α- and β-anomers **19** and **20** of 3,4-di-*O*-benzyl-2-*O*-(methylsulfonyl)-L-rhamnopyranosyl chloride in a ratio of 82:18 (α/β). The evidence of ^{1}H NMR indicates that β-anomer **20** does not adopt the $^1C_4$ chair form A as the favored conformation in solution but that its favored conformation in chloroform is the $^4C_1$ chair form B. Treatment of 1-*O*-tosyl derivative **21** with 1.0 equiv of methanol or cyclohexanol afforded mainly β-anomer (>88%) along with small amount of α-anomer. The reaction was more stereoselective and also faster when the 1-*O*-[(2,2,2-trifluoroethyl)sulfonyl] derivative was used in place of the 1-*O*-tosyl derivative. Proof of the structures for all the new compounds is based on ^{1}H NMR, ^{13}C NMR, optical rotations, and elemental analysis.

Although 1,2-trans-related glycosides with either 1-equatorial, 2-equatorial or 1-axial, 2-axial conformations can generally be prepared by similar routes involving participation of a C-2 ester function, different methods are needed for the synthesis of the two corresponding classes of 1,2-cis-related glycosides. A number of methods are available for 1-axial, 2-equatorial glycosides, but the direct stereoselective synthesis of 1-equatorial, 2-axial glycosides on which we have reported earlier[1,2] remains a challenge in spite of the work of Gorin and Perlin[3a] (cf. ref 3b), and Garegg and Iversen[4] on the synthesis of β-D-mannopyranosides. Recently Kasai et al.[5] prepared a few β-L-rhamnopyranosides for ^{13}C NMR studies by a modification of the method of Gorin and Perlin but reported no data on reaction stereoselectivity and gave no other physical constants on the new compounds. A direct stereoselective synthesis of β-L-rhamnopyranosides and β-D-mannopyranosides is badly needed because the β-D-mannopyranosyl linkage is important in glycoproteins, and O-antigenic lipopolysaccharides of *Salmonella* contain β-linked D-mannopyranosyl and β-linked L-rhamnopyranosyl units in their structures.[6a]

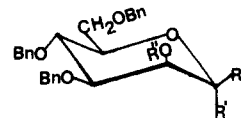
We report the first practical stereoselective synthesis of β-L-rhamnopyranosides and a detailed statement of this new synthesis of β-D-mannopyranosides.[6b] The rationale for this reaction has been discussed in a preliminary communication.[1] Briefly, the β stereoselectivity of these glycosidations is the result of interaction of opposing dipoles of a strongly electronegative nonparticipating substituent on C-2 and a highly reactive electronegative leaving group on C-1. These control the structure of the transition state and influence the rate of reaction and the nature of the products formed.

3,4,6-Tri-*O*-benzyl-2-*O*-(methylsulfonyl)-α-D-mannopyranosyl chloride (**1**; see Chart I) was prepared as a syrup in 54% yield by treatment of 3,4,6-tri-*O*-benzyl-D-mannopyranose with methylsulfonyl chloride in 2,6-lutidine. Treatment of chloride **1** on a high-vacuum rack with silver *p*-toluenesulfonate in acetonitrile afforded the 1-*O*-tosyl derivative **2**, as described for the D-galactopyranosyl and D-glucopyranosyl derivatives.[7-9] Compound **2** was not isolated but was treated directly with 1 equiv of methanol for 36 h at room temperature in the dark. The reaction afforded methyl 3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-β-D-mannopyranoside (**3**) in 90% yield after silica gel chromatography ($[\alpha]^{22}_D$ −39.4° (*c* 0.89, chloroform)); no α-anomer could be detected. H-1$_\beta$ resonated as a singlet at δ 4.42, the mesyl group resonated at δ 3.12 as a singlet, and OMe-β resonated at δ 3.55. To prove the β configuration for **3**, we synthesized the α-anomer of **3** from methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**4**). Mesylation of **4** with MsCl in 2,6-lutidine gave methyl 3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-α-D-mannopyranoside (**5**), $[\alpha]^{24}_D$ +18.4° (*c* 1.7, $CHCl_3$). H-1$_\alpha$ was masked with benzyl methylene protons (δ 5.0–4.55), but no peak was present at δ 4.42. α-Methoxyl resonated at δ 3.36 and mesyl at δ 2.99. ^{13}C NMR data for **3** included resonances for C-1$_\beta$ (99.60 ppm), OMe (57.15 ppm), and Ms (39.3 ppm), while the corresponding values for **5** were C-1$_\alpha$ (99.11 ppm), OMe

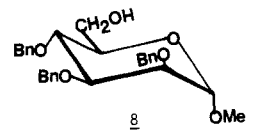
(1) V. K. Srivastava and C. Schuerch, *Carbohydr. Res.*, **79**, C-13 (1980).
(2) V. K. Srivastava and C. Schuerch, *Tetrahedron Lett.*, 3269 (1979).
(3) (a) P. A. J. Gorin and A. S. Perlin, *Can. J. Chem.*, **39**, 2474 (1961). (b) M. A. E. Shaban and R. W. Jeanloz, *Carbohydr. Res.*, **52**, 103 (1976).
(4) P. J. Garegg and T. Iversen, *Carbohydr. Res.*, **70**, C-13 (1979).
(5) R. Kasai, M. Okihara, J. Asakawa, K. Mizutani, and O. Tanaka, *Tetrahedron*, **35**, 1427 (1979).
(6) (a) K. Jann and O. Westphal in "The Antigens", Vol. 3, M. Sela, Ed., Academic Press, New York, 1975, p 1. (b) **Note added in proof**: The method of ref 3a has now been applied to rhamnoside synthesis by L. V. Backinowsky, N. F. Balan, A. S. Shashkov, and N. K. Kochetkov, *Carbohydr. Res.*, **84**, 225 (1980), and the method of ref 4 by T. Iversen and D. R. Bundle, *ibid.*, **84**, C13 (1980).
(7) R. Eby and C. Schuerch, *Carbohydr. Res.*, **34**, 79 (1974).
(8) T. J. Lucas and C. Schuerch, *Carbohydr. Res.*, **39**, 39 (1975).
(9) V. Marousek, T. J. Lucas, P. Wheat, and C. Schuerch, *Carbohydr. Res.*, **60**, 85 (1978).

0022-3263/81/1946-1121$01.25/0

Chart I



1. R = H, R' = Cl, R" = Ms.
2. R = H, R' = OTs, R" = Ms
3. R = OMe, R' = H, R" = Ms
4. R = H, R' = OMe, R" = H
5. R = H, R' = OMe, R" = Ms
6. R = OC_6H_{11}, R' = H, R" = Ms
7. R = H, R' = OC_6H_{11}, R" = Ms
11. R = H, R' = OBz, R" = Bz
12. R = H, R' = Cl, R" = Bz
13. R = H, R' = OTs, R" = Bz



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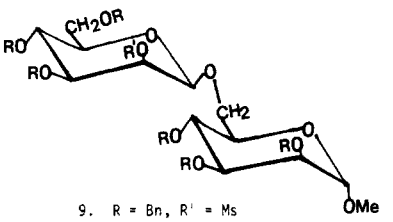
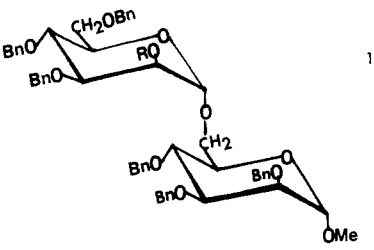


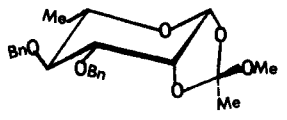
9. R = Bn, R' = Ms
10. R = H, R' = H



14. R = Bz
15. R = OH
16. R = Ms

Bn = $-CH_2C_6H_5$
OTs= $-OSO_2C_6H_4CH_3$
Ms= $-SO_2CH_3$
Bz= $-COC_6H_5$

Chart II



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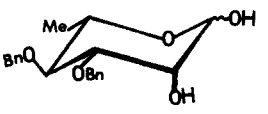

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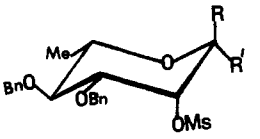


19. R = Cl, R' = H
20. R = H, R' = Cl
21. R = OTs, R' = H
22. R = OMe, R' = H
23. R = H, R' = OMe
24. R = OC_6H_{11}, R' = H
25. R = H, R' = OC_6H_{11}

(55.12 ppm), and Ms (38.8 ppm). ^1H NMR and ^{13}C NMR data and a negative value of optical rotation in comparison to the data for **5** thus supported a β-anomer assignment for **3**.

It was of interest to see whether reaction with a secondary alcohol also would be stereoselective. Therefore, **2** was treated with cyclohexanol in the same fashion, and the reaction afforded 86% β-anomer **6** along with 14% α-anomer **7**. The reaction was more stereoselective, and also faster, when the 1-*O*-[(2,2,2-trifluoroethyl)sulfonyl] derivative was used in place of the 1-*O*-tosyl. β-Anomer **6** was formed in over 93% yield and α-anomer **7** in 7% yield. ^1H NMR (δ units) for **6**: H-1_β, 4.60; Ms, 3.15. ^1H NMR (δ units) for **7**: H-1_α, 4.98; Ms, 3.01.

Reactions of this type can be used to synthesize β-linked mannose disaccharides. Reaction of methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**8**) with **2** was carried out in acetonitrile for 48 h and gave a mixture of two anomers in an α/β ratio of 1:5 (~17% of α-D-anomer) as determined by the ratio of mesyl peak areas in the ^1H NMR spectra: δ 3.02 (s, 0.5 H, Ms-α) and 2.99 (s, 2.5 H, Ms-β). Pure β-anomer **9** was separated as a syrup and its configuration confirmed by ^1H NMR [4.42 (1 H, H-1'β)] and optical rotation.

The reaction of **8** was more selective, and also faster, when the 1-*O*-[(2,2,2-trifluoroethyl)sulfonyl] derivative was used in place of 1-*O*-tosyl. Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-β-D-mannopyranosyl)-α-D-mannopyranoside (**9**) was formed after 18 h in over 90% yield; $[\alpha]^{25}_D$ +7.3° (*c* 1, $CHCl_3$). Its ^1H NMR spectrum was identical with that of the previous preparation. For comparison, α-anomer **16** of **9** was prepared by starting from 1,2-di-*O*-benzoyl-3,4,6-tri-*O*-benzyl-D-mannopyranose (**11**). Chlorination of **11** with HCl in ether afforded 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**12**). Reaction of **12** with silver *p*-toluenesulfonate in acetonitrile afforded the 1-*O*-tosyl derivative **13**, and this tosyl derivative was treated directly with 1 equiv of **8** to afford methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**14**) in over 95% yield. No β-anomer could be detected: $[\alpha]^{22}_D$ +16.9° (*c* 1, $CHCl_3$); H-1'$_\alpha$ resonated at δ 5.12 as a doublet ($J_{1'2'}$ = 2.0 Hz) and H-2' at δ 5.76 (br s, 1 H, H-2'). Debenzoylation of **14** with NaOMe gave 2-hydroxy derivative **15** which on mesylation gave 2'-*O*-methylsulfonyl derivative **16**: $[\alpha]^{24}_D$ +41.80° (*c* 0.68, $CHCl_3$); ^1H NMR δ 5.18 (2 H, H-1'$_\alpha$, H-2'), 3.01 (s, Ms). The above ^1H NMR data and the optical rotation supported a β-anomer assignment to **9**.

The selective removal of the methylsulfonyl group in the presence of benzyl groups was not accomplished. Treatment of **16** with Ni/EtOH at refluxed temperature failed to provide the reduction product **15**, and **16** was isolated. Recently, Jarrell et al.[10] have reduced secondary toluenesulfonyl groups in carbohydrates using sodium naphthalene in THF. Treatment of **5** with sodium–naphthalene reagent failed to give any reduction, and starting material was isolated. This reagent only worked for the reduction of primary *p*-toluenesulfonates in our hands, and secondary sulfonates were not reduced. Heating the reaction mixture resulted in decomposition.

Treatment of **9** with Na/liquid NH_3 afforded methyl 6-*O*-β-D-mannopyranosyl-α-D-mannopyranoside (**10**) as a

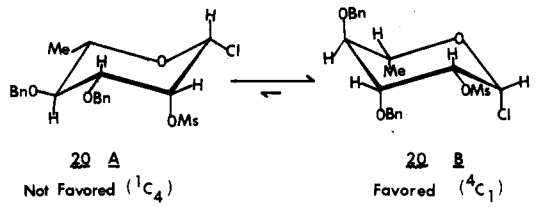
(10) H. C. Jarrell, R. G. S. Ritchie, W. A. Szarek, and J. K. N. Jones, *Can. J. Chem.*, **51**, 1767 (1973).

foam, $[\alpha]^{22}_D$ +49.6° (c 1.6, H_2O). The ^1H NMR spectrum showed no proton signals for aromatic and mesyl protons. ^1H NMR and ^{13}C NMR spectra confirmed the identity of **10**.

β-L-Rhamnopyranosides were prepared by a similar sequence of reactions. 3,4-Di-*O*-benzyl-β-L-rhamnopyranose 1,2-(methyl orthoacetate) (**17**; see Chart II) was prepared in 88% yield by benzylation of 3,4-di-*O*-acetyl-β-L-rhamnopyranose 1,2-(methyl orthoacetate) by the method of Franks and Montgomery.[11] Hydrolysis of **17** with 90% acetic acid on a steam bath gave a 1-*O*-acetyl derivative that on deacetylation with 0.1 M sodium methoxide in methanol afforded crystalline 3,4-di-*O*-benzyl-L-rhamnopyranose (**18**) in 96% yield. Treatment of **18** (1.0 equiv) with methylsulfonyl chloride (2.5 equiv) in 2,6-lutidine for 20 min at 0–5 °C gave (presumably via the 1,2-bis[*O*-(methylsulfonyl)] derivative as intermediate) an anomeric mixture of 3,4-di-*O*-benzyl-2-*O*-(methylsulfonyl)-L-rhamnopyranosyl chlorides **19** and **20** in a 82:18 ratio (α/β). Chromatographic separation on silica gel afforded crystalline **19** and **20**. Optical rotation for the α-anomer was −46.7° and for the β-anomer +52°. The ^1H NMR spectrum of **19** showed H-1_α at δ 6.40 ($J_{1,2}$ = 1.7 Hz) and Ms at δ 3.14. The ^1H NMR spectrum of **20** showed H-1_β at δ 5.42 ($J_{1,2}$ ≤ 0.5 Hz) and Ms at δ 3.16.

The ^1H NMR spectrum of **19** (Table I) was consistent for the $^1C_4$ chair conformation, but the spectrum of **20** (Table I) was not consistent for $^1C_4$ chair conformation as $J_{3,4}$ is 5.5 Hz. If the favored conformation of **20** had been $^1C_4$, the coupling constants for $J_{3,4}$ should be ~8–10 Hz because of 1,2-diaxial proton coupling. The signals for benzyl methylene protons on C-3 and C-4 are observed as the typical eight-line pattern of the AB portion of an ABX multiplet, and the first-order J_{AB} couplings are 11.8 and 12.2 Hz. The fact that both of these couplings are large indicates that the benzyl CH_2 groups at C-3 and C-4 are in a rigid conformation as would be required for the $^4C_1$ conformation B, and the data are consistent with the $^4C_1$ conformation not $^1C_4$.

Two chair conformations are possible for **20**, the thermodynamically less stable anomer: that having four equatorial groups and one axial group ($^1C_4$ conformation, A) and that having four axial groups and one equatorial



20 A Not Favored ($^1C_4$) **20 B** Favored ($^4C_1$)

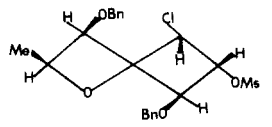
group ($^4C_1$ conformation, B). The above data indicate that, in chloroform solution, the $^4C_1$ conformation (B) having four axial groups is the favored form. It its therefore evident that the magnitude of the anomeric effect (an unfavorable polar interaction between electron clouds of the ring oxygen atom and the equatorial G(1)–Cl dipole) and a similar interaction with the C(2)–mesyl dipole in this system together exceed the combined steric destabilizing influence of four axial groups and one *syn*-diaxial interaction. It is, however, probable that the spectrum observed is the time-averaged spectrum of both conformers A and B (and possibly a skew conformer like C) in rapid equilibrium, with B in preponderance. A small proportion of the less favored conformers (A and C), in rapid equilibrium

(11) N. E. Franks and R. Montgomery, *Carbohydr. Res.*, 6, 286 (1968).
(12) S. Josephson and D. R. Bundle, *Can. J. Chem.*, 57, 662 (1979).

Table I. ^1H NMR Spectral Data[a] of L-Rhamnopyranosyl Derivatives

compd	chemical shift								
	H-1	H-2	H-3	H-4	H-5	H-6	CH_2	Ms	OMe or OC_6H_{11}
19	6.4 (d, $J_{1,2}$ = 1.7)	5.33 (dd, $J_{2,3}$ = 3.0)	4.45 (dd, $J_{3,4}$ = 10.1)	3.62 (t, $J_{4,5}$ = 10.1)	4.15 (m)	1.4 (d, $J_{5,6}$ = 6.8)	5.27–4.77 (m)	3.14 (s)	
20	5.42 (br s, $J_{1,2}$ = <0.5)	5.23 (dd, $J_{2,3}$ = 1.7, $J_{1,2}$ = ~0.5)	3.75 (q, $J_{3,4}$ = 5.5)	3.52 (m)		1.37 (d, $J_{5,6}$ = 5.4)	5.07, 4.87 (AB, J_{AB} = 10.8), 4.75, 4.54 (AB, J_{AB} = 12.2)	3.16 (s)	
22	~4.9	5.02 (dd, $J_{2,3}$ = 3.0, $J_{1,2}$ = 1.5)	3.98 (q, $J_{3,4}$ = 9.0)	3.86–3.49 (m)		1.31 (d, $J_{5,6}$ = 6.0)	4.93–4.55 (m)	3.01 (s)	3.35 (s)
23	4.44 (s)	5.20 (d, $J_{2,3}$ = 1.8)		3.69–3.37		1.36 (d, $J_{5,6}$ = 5.6)	5.1, 4.91 (AB, J_{AB} = 11.0), 4.77, 4.57 (AB, J_{AB} = 12.5)	3.16 (s)	3.58 (s)
24	~4.9	5.02 (m)	3.99 (q, $J_{3,4}$ = 9.6, $J_{2,3}$ = 3.0)	3.40 (t, $J_{4,5}$ = 9.6)	3.91–3.75 (m)	1.29 (d, $J_{5,6}$ = 6.2)	4.96–4.58 (m)	3.02 (s)	3.72 (br m), 1.94–1.08 (m)
25	4.60 (s)	5.07 (d, $J_{2,3}$ = 2.4)		3.59–3.32		1.34 (d, $J_{5,6}$ = 5.8)	4.98, 4.88 (AB, J_{AB} = 10.8), 4.63, 4.51 (AB, J_{AB} = 11.6)	3.18 (s)	3.62 (br m), 2.06–1.12 (m)

[a] In parts per million of solutions in $CDCl_3$. Multiplicities and *J* values (in hertz) are given in parentheses.



20 C

Skew

with B, would not greatly affect the magnitudes of the first-order couplings observed. The possibility that **20** adopts a skew C conformation in the flexible cycle could not be confirmed as $J_{4,5}$ could not be calculated. (H-4 and H-5 signals overlapped in a 400-MHz ^{1}H NMR spectrum and could not be separated.) Horton et al.[13,14] have reported that the preferred conformation for tri-*O*-acetyl-β-D-xylopyranosyl chloride in chloroform is similarly that chair form in which the halogen atom is axial.

In a recent publication, Josephson and Bundle[15] have reported an ABX pattern for the benzyl CH_2 in the ^{1}H NMR spectra of 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride (J_{AB} = 10.6 and 10.2 Hz). These workers isolated this chloro derivative as a syrup and claimed 95% purity, but it seems probable that their preparation of that chloro derivative had a significant amount of β-anomer in the $^4C_1$ conformation.

Treatment of chloride **19** on a high-vacuum rack with silver *p*-toluenesulfonate in acetonitrile afforded the α-1-*O*-tosyl derivative **21** as indicated by ^{1}H NMR. H-1 was observed as a doublet centered at δ 6.07 ($J_{1,2}$ = 2.2 Hz). No β-anomer could be detected. It was of interest to see if β-chloro derivative **20** would also give the more thermodynamically stable α-tosyl derivative. Thus, reaction of β-chloro derivative **20** with silver *p*-toluenesulfonate in the same manner afforded only α-tosyl derivative **21**. Compound **21** was not isolated but was treated directly with 1.1 equiv of methanol for 40 h at room temperature in the dark. The reaction afforded mainly β-L-rhamnopyranoside **23** in 93% yield and α-anomer **22** in 7% yield. Pure α- and β-anomers were obtained after liquid chromatography on silica gel (1:4 v/v ethyl acetate–hexane). The optical rotation for α-anomer was −1.2° and for the β-anomer was +81.6°.

^{1}H NMR (Table I) and ^{13}C NMR (Table II) of **22** are consistent with the α-anomer in the $^1C_4$ chair conformation. Comparison of ^{1}H NMR and ^{13}C NMR spectra of **22** and **23** indicates that H-1_α resonated downfield in **22** compared to H-1_β in **23**. Methoxyl and mesyl protons resonated at higher field in **22** than in **23**. C-1, methoxyl, and mesyl carbons resonated at higher field in **22** than in **23**. These shifts are consistent with the α- and β-anomeric configurations of these glycosides. Optical rotations also confirmed the anomeric configurations of **22** and **23**. However, the ^{1}H NMR spectrum of **23** was not consistent for the $^1C_4$ chair conformation. The signals for the benzyl CH_2 protons on C-3 and C-4 are observed as the typical eight-line pattern of the AB portion of an ABX multiplet similar to that obtained for β-chloro derivatives **20**, and the first-order J_{AB} couplings are 11.0 and 12.5 Hz. Unfortunately, coupling constants of $J_{3,4}$ and $J_{4,5}$ could not be obtained as proton resonances of H-3, H-4, H-5, and OMe overlapped in the 100-MHz spectrum. It is surprising that at C-1 a methoxyl group would have any strong unfavorable polar

Table II. ^{13}C NMR Shifts[a] (Proton Decoupled)

	compound											
	3	**5**	**6**	**7**	**8**	**9**	**10**[b]	**14**	**16**	**22**	**23**	**25**
C-1	99.60	99.11	96.39	96.36	99.46	98.88	101.0	98.99	99.11	99.05	99.41	96.06
C-2	74.40	75.20	74.44	75.38	74.94	*d*	70.90	*d*	*d*	75.51	75.68	75.68
C-3	79.80	77.94	79.98	78.14	80.26	80.98	71.8, 70.2[c]	80.40	80.39	77.9	79.57	79.79
C-4	77.20	76.47	78.19	77.52	79.94	*d*	68.3, 67.3[c]	*d*	*d*	80.03	79.57	79.61
C-5	76.0	71.95	75.95	72.18	72.17	*d*	73.3	*d*	*d*	68.06	71.92	71.77
C-6	69.30	69.01	69.50	69.23	62.33	68.43	66.96	68.89	67.04	17.86	17.87	17.99
C-1′						99.76	101.42	98.29	98.57			
C-2′						*d*	70.90	*d*	*d*			
C-3′						79.43	71.8, 70.2[c]	77.55	77.11			
C-4′						*d*	68.3, 67.3[c]	*d*	*d*			
C-5′						*d*	76.5	*d*	*d*			
C-6′						69.39	61.48	69.13	68.88			
OMe	57.15	55.12			54.65	54.94	55.27	54.69	54.83	55.02	57.08	
OC_6H_{11}			77.29, 33.51, 31.75, 25.61, 24.02, 23.90	77.22, 33.31, 31.58, 25.67, 24.07, 23.84								77.11, 33.48, 31.7, 25.63, 24.10, 23.92
Ms	39.30	38.80	39.43	38.92		39.43			38.75	38.85	39.28	39.45

[a] Solutions in $CDCl_3$; shifts given in parts per million. These assignments are tentative based on analogies (see ref 17). [b] In D_2O. [c] Indistinguishable. May be rearranged. [d] Indistinguishable.

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Table III. Reaction of 1-O-Sulfonyl-D-mannopyranosyl and -L-rhamnopyranosyl Derivatives with Alcohols[a]

compd	sulfonyl group	alcohol	solvent	time, h	yield isolated, %	% β-anomer[b]	% α-anomer[b]
2	Ts[c]	MeOH	AcCN	36	90	>95	
2	Ts	$C_6H_{11}OH$	AcCN	40	86	86	14
2	Tre[d]	$C_6H_{11}OH$	AcCN	40	87	93	7
2	Ts	8	AcCN	48	78	83	17
2	Tre	8	AcCN	24	81	95	5
13	Ts	8	AcCN	36	83		>95
21	Ts	MeOH	AcCN	40	75	93	7
21	Tre	MeOH	AcCN	24	78	95	5
21	Ts	MeOH	THF	40		58	42
21	Ts	MeOH	DME	40		78	22
21	Ts	MeOH	C_6H_6	40		72	28
21	Ts	$C_6H_{11}OH$	AcCN	48	77	88	12
21	Tre	$C_6H_{11}OH$	AcCN	24	79	93	7

[a] Reaction carried out at room temperature. [b] α/β ratios were determined by ^1H NMR spectra by measuring the mesyl CH_3 peak and by liquid chromatography by measuring peak area. [c] p-Toluenesulfonyl. [d] 2,2,2-Trifluoroethylsulfonyl.

interaction. However, the opposing dipole of the mesyl group at C-2 combined with C-1 might cause this change in conformation from $^1C_4$ chair to $^4C_1$ chair.

It was of interest to see if the reaction solvent would have some influence on stereoselectivity. In our hands for this type of system, acetonitrile proved to be the best solvent. Results are given in Table III. This reaction also was more stereoselective and faster when the 1-O-[(2,2,2-trifluoroethyl)sulfonyl] derivative was used in place of the 1-O-tosyl derivative.

It was also important to see whether reaction with a secondary alcohol also would be stereoselective as L-rhamnose is β-linked to D-galactose at the C-3 position in some *Salmonella* lipopolysaccharides. Thus, when **21** was treated with cyclohexanol for 48 h, the reaction afforded 88% of cyclohexyl 3,4-di-O-benzyl-2-O-(methylsulfonyl)-β-L-rhamnopyranoside (**25**) along with 12% of α-anomer **24**. In this case also, the 1-O-[(2,2,2-trifluoroethyl)sulfonyl] leaving group gave a more stereoselective reaction. The optical rotation for α-anomer **24** was −9.2° and for the β-anomer was +74.6°. The ^1H NMR spectrum of **24** showed H-1_α around δ 4.9 along with resonances of benzyl methylene protons, mesyl at δ 3.02, and cyclohexyl at δ 1.94–1.08. The ^1H NMR spectrum of β-anomer **25** showed H-1_β at δ 4.60 as a singlet upfield from the corresponding signal in α-anomer **24**. The mesyl and cyclohexyl protons in **25** (Table I) resonated farther downfield than those in **24**. These shifts are consistent with the α- and β-anomeric configurations of these glycosides. In this case also, β-anomer **25** had a similar ABX pattern for its benzyl methylene protons, indicating a change in preferred conformation from $^1C_4$ chair to $^4C_1$ chair.

In conclusion, the nature of the leaving group at C-1 and the nonparticipating substituent at C-2 of D-mannopyranosyl and L-rhamnopyranosyl derivatives controls both the rate and stereoselectivity of reactions at C-1. This reaction provides a practical synthesis of β-D-mannopyranosides and β-L-rhamnopyranosides in high yields and demonstrates the application of sulfonate leaving groups in the synthesis of the last of the four major classes of hexopyranosides.

Experimental Section

General Methods. ^1H NMR spectra were obtained on a Varian A-60-A or XL-100-15 or on a Bruker WH-400 FT spectrometer on solutions in chloroform with tetramethylsilane as internal reference or on solutions in D_2O with acetone (δ 2.07) as reference for deblocked glycosides. ^{13}C NMR spectra were determined 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 with the assumption that the acetone methyl peak is located at 30.6 ppm in deblocked glycosides. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter in jacketed 1-dm cells. Melting points were determined on a Mel-temp apparatus with a 76-mm immersion thermometer. TLC was performed on Baker-Flex silica gel 1B-F (2.5 × 7.5 cm) plates. High-pressure liquid chromatography (LC) was carried out by using a Valvco septumless injector (1.0 mL), a Glenco pump (Model HPLPS-1), and a Waters R-401 differential refractometer. A stainless-steel column (1 × 25 cm i.d.) containing a silica gel column (Whatman, Partisil M 9 10/25) was used at a flow rate of 8.0 mL/min. Water high-pressure LC was carried out with the same injector and pump, a Micromeritics 771 refractive index detector, and a stainless-steel column (0.75 × 29.0 in. o.d., jacketed in circulating 60 °C water) containing Biogel P-2 at a flow rate of 3.0 mL/min. Volume of effluent was recorded in counts of 2 mL.

Spectrograde acetonitrile was dried with CaH_2. Silver p-toluenesulfonate (Eastman Organic Chemicals) was recrystallized from acetonitrile and dried under high vacuum before use. Silver (2,2,2-trifluoroethyl)sulfonate was prepared as described in an earlier publication from this laboratory.[16]

3,4,6-Tri-O-benzyl-2-O-(methylsulfonyl)-α-D-mannopyranosyl Chloride (1). 3,4,6-Tri-O-benzyl-D-mannopyranose[11] (1.0 g) was dissolved in 2,6-lutidine (5 mL) cooled to 0 °C. Methylsulfonyl chloride (0.67 g) was added, and the reaction mixture was allowed to stand for 20 min at 0–5 °C (reaction mixture turns solid and starts developing a pink color). The excess reagent was decomposed with few drops of ice-cold water until a total of 25 mL had been added. The product settled out as a pink gum. The liquid was removed by decantation, the gum was triturated with ice-cold water, and the water was decanted. The gum was dissolved in 15 mL of chloroform, washed with cold water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated to a syrup (1.1 g). TLC (EtOAc/hexane, 1:2 v/v) showed one major product along with two minor slow-moving spots, one of them corresponding to the starting material. Purification on a silica gel column with the same solvent gave chloride **1** (0.65 g) in 54% yield as a syrup, $[\alpha]^{24}_D$ +55.4° (*c* 0.93, $CHCl_3$). Compound **1** was stored in a freezer and decomposed at room temperature if left for a longer time (~4 h): ^1H NMR (chloroform-*d*) δ 7.35–7.29 (15 H, aromatics), 6.25 (d, 1 H, $J_{1,2}$ = 1.8 Hz, H-1), 5.15 (t, 1 H, $J_{2,3}$ = 3.0 Hz, H-2), 4.80–4.58 (6 H, $CH_2C_6H_5$), 4.50–3.93 (3 H, H-3, H-4, H-5), 3.78 (m, 2 H, H-6, H-6′), and 2.99 (s, 3 H, Ms).

Preparation of 3,4,6-Tri-O-benzyl-2-O-(methylsulfonyl)-α-D-mannopyranosyl p-Toluenesulfonate (2) and Its Reaction with Alcohols. The chloride **1** (0.4 mmol) dissolved in acetonitrile (2 mL) was allowed to react with silver p-toluenesulfonate or (2,2,2-trifluoroethyl)sulfonate (0.6 mmol) to form the corresponding sulfonyl derivative under previously described conditions.[7-9] After 1 h, the reaction mixture was stirred and filtered to remove silver chloride. The solution was then

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Table IV. Physical Constants of D-Mannosyl and L-Rhamnosyl Derivatives

compd	mp, °C	$[\alpha]_D$ [a]	mol formula (mol wt)	anal.,[b] % C	H	Cl	S
3		−39.4 (c 0.89)	$C_{29}H_{34}O_8S_1$ (542.59)	64.19 (63.97)	6.32 (6.20)		5.91 (5.72)
5		+18.4 (c 1.7)					
6		−46.4 (c 1.28)	$C_{34}H_{42}O_8S_1$ (610.77)	66.86 (66.43)	6.93 (6.72)		5.25 (5.17)
7		+26.6 (c 1.3)					
9		+7.3 (c 1.0)	$C_{56}H_{62}O_{13}S_1$ (975.16)	68.98 (68.64)	6.40 (6.11)		3.29 (3.04)
14		+16.9 (c 1.0)	$C_{62}H_{64}O_{12}$ (1001.2)	74.38 (74.76)	6.44 (6.47)		
15		+40.1 (c 1.35)					
16		+41.8 (c 0.68)	$C_{56}H_{62}O_{13}S_1$ (975.16)	68.98 (69.21)	6.40 (6.32)		3.29 (3.20)
19	68.5	−46.7 (c 1.95)	$C_{21}H_{25}Cl_1O_6S_1$ (440.94)	57.20 (56.90)	5.72 (5.60)	8.04 (7.95)	7.27 (7.21)
20	140	+52.0 (c 1.01)	$C_{21}H_{25}Cl_1O_6S_1$ (440.94)	57.20 (57.07)	5.72 (5.64)	8.04	7.27
22		−1.2 (c 0.6)					
23		+81.6 (c 0.4)	$C_{22}H_{28}O_7S_1$ (436.53)	60.53 (60.38)	6.46 (6.14)		7.34 (7.02)
24	92	−9.2 (c 0.5)					
25	95	+74.6 (c 0.9)	$C_{27}H_{37}O_7S_1$ (504.65)	64.26 (64.45)	7.19 (7.42)		6.35 (6.21)

[a] In chloroform at 22–24 °C. [b] Calculated value given with experimental value in parentheses.

mixed with 0.4 mmol of an alcohol as in earlier work[7-9] and allowed to react for 18–48 h in the dark at room temperature. Chloroform was added to the reaction mixture after this period, and the solution was washed with sodium thiosulfate (10%), sodium bicarbonate (10%), and water, dried over anhydrous $MgSO_4$, and concentrated to afford crude glycosides as a syrup. The crude glycosides were analyzed by ^1H NMR spectroscopy and liquid chromatography to determine the ratio of α- and β-anomers. Results are shown in Table III. The pure glycosides were obtained after chromatographic separation on silica gel.

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-(methylsulfonyl)-α-D-mannopyranoside (5). 2-Hydroxy derivative 4 was prepared by debenzoylation of methyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside with a catalytic amount of sodium methoxide in absolute methanol as described in an earlier publication.[16] Compound 4 (0.1 g) was dissolved in 2,6-lutidine (2 mL), and methylsulfonyl chloride (0.04 g) was added at 0–5 °C. The reaction mixture was worked up after 30 min in the usual way to afford 5 as a syrup: 0.11 g (94% yield); $[\alpha]^{24}_D$ +18.4° (c 1.7, $CHCl_3$).

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-[3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-α-D-mannopyranosyl]-α-D-mannopyranoside (16). Glycosidation of 13[16] with 8 in the usual way afforded α-linked disaccharide 14 in over 95% yield; $[\alpha]^{22}_D$ +16.9° (c 1, $CHCl_3$). Debenzoylation of 14 with NaOMe and mesylation as described above afforded 16 as syrup, $[\alpha]^{24}_D$ +41.8° (c 0.68, $CHCl_3$).

Methyl 6-*O*-β-D-Mannopyranosyl-α-D-mannopyranoside (10). Disaccharide 9 (0.08 g) was dissolved in dry tetrahydrofuran (1.0 mL) in a flask equipped with a cold finger type condenser filled with dry ice/ethanol slurry. Gaseous ammonia was admitted and condensed to a volume of ~10 mL. The reaction mixture was stirred, and freshly cut sodium was added in small increments until an indigo color persisted for 45 min. The ammonia was evaporated, and methanol was added slowly until all excess metal reacted and the reaction mixture became clear (slight yellow). The reaction mixture was evaporated to dryness, and the residue was dissolved in water (1.0 mL), neutralized with solid CO_2 to pH ~8.0, and deionized by treatment with Amberlite IR 120 H^+ resin. The resulting solution on evaporation gave a syrup. This syrup was further purified by liquid chromatography on Biogel with water as solvent. The title disaccharide 10 was isolated from a single-fraction peak at 13.5 count. This peak fraction on evaporation gave a syrup that on several coevaporations with absolute ethanol afforded 10 as a foam: 0.018 g (65% yield); $[\alpha]^{22}_D$ +49.5° (c 1.6, H_2O). Anal. Calcd for $C_{13}H_{24}O_{11}$ (m/e 356.62): C, 43.82; H, 6.80. Found: C, 43.92; H, 7.30.

3,4-Di-*O*-benzyl-β-L-rhamnopyranose 1,2-(Methyl Orthoacetate) (17). Benzylation of 3,4-di-*O*-acetyl-β-L-rhamnopyranose 1,2-(methyl orthoacetate) (10.0 g) with benzyl chloride (25 mL) and powdered KOH (24.0 g) in toluene (75 mL) as described for the D-mannose derivative by Franks and Montgomery[11] afforded crystalline 17: 11.5 g (88% yield); mp 108–109 °C; $[\alpha]^{22}_D$ +0.7° (c 1.57, $CHCl_3$) [lit.[12] mp 110–111 °C; $[\alpha]_D$ +0.6° (c 1, $CHCl_3$)]; ^1H NMR (chloroform-d) δ 7.34 (s, 10 H, aromatics), 5.31 (d, 1 H, H-1, $J_{1,2}$ = 2.8 Hz), 5.12–4.60 (m, 4 H, 2 CH_2), 4.44 (dd, 1 H, H-2, $J_{2,3}$ = 4.2 Hz), 3.94–3.34 (m, 3 H, H-3, H-4, H-5), 3.28 (s, 3 H, OMe), 1.71 (s, 3 H, CCH_3), 1.30 (d, CH_3 at C-6, $J_{5,6}$ = 6.0 Hz). Anal. Calcd for $C_{23}H_{28}O_6$ (m/e 400.48): C, 68.98; H, 7.05. Found: C, 68.92; H, 7.05.

3,4-Di-*O*-benzyl-L-rhamnopyranose (18). Acid hydrolysis of ortho ester 17 (8.0 g) with 90% acetic acid (50 mL) followed by deacetylation with NaOMe as described[11] for the D-mannose ortho ester afforded crystalline (ether–n-hexane) 18: 6.6 g (96% yield); mp 104–105 °C; $[\alpha]^{21}_D$ −9.4° (c 1.52, $CHCl_3$); ^1H NMR (chloroform-d) δ 7.3 (s, 10 H, aromatics), 5.25 (br s, 0.6 H, H-1_α), 5.02–4.52 (m, 4.4 H, 2 CH_2 and H-1_β), 4.07–3.30 (H-2, H-3, H-4, H-5, and 2-OH), 1.28 (d, 3 H, CH_3, $J_{5,6}$ = 6.0 Hz). Anal. Calcd for $C_{20}H_{24}O_5$ (m/e 344.41): C, 69.75; H, 7.02. Found: C, 69.82; H, 6.95.

3,4-Di-*O*-benzyl-2-*O*-(methylsulfonyl)-D-rhamnopyranosyl Chlorides 19 and 20. Reaction of 18 (1.0 equiv) with methylsulfonyl chloride (2.5 equiv) as described earlier afforded a mixture of α-19 and β-20 chlorides. Liquid chromatographic separation on silica gel (EtOAc–hexane, 1:4 v/v) afforded pure 19 (7 and 8 count) and 20 (9 and 10 count). Physical constants are reported in Table IV.

Glycosidation reactions of 21 were carried out as described for 2 and the results are given in Tables III and IV.

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Registry No. 1, 73938-75-7; 2, 73938-76-8; 3, 73938-77-9; 4, 20672-67-7; 5, 76251-54-2; 6, 76251-55-3; 7, 76251-56-4; 8, 34212-64-1; 9, 76281-97-5; 10, 76332-68-8; 13, 73045-72-4; 14, 76251-57-5; 16, 76251-58-6; 17, 70802-02-7; 18, 76251-59-7; 19, 76251-60-0; 20, 76251-61-1; 21, 76251-62-2; 22, 76251-63-3; 23, 76251-64-4; 24, 76251-65-5; 25, 76251-66-6; 3,4,6-tri-*O*-benzyl-D-mannopyranose, 65827-56-7; methyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside, 68536-57-2; 3,4-di-*O*-acetyl-β-L-rhamnopyranose 1,2-(methylorthoacetate), 70831-95-7; methanol, 67-56-1; cyclohexanol, 108-93-0; 15, 76251-67-7.