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Note

A single-step synthesis of methyl 3-*O*-methyl-α-D-manno-, -α-D-galacto-, -α-L-rhamno-, and -α-L-fuco-pyranoside †

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Mycobaterial polysaccharides [1] and antibiotics [2] often contain some partially methylated monosaccharide units. Thus, 3-*O*-methylated methyl glycopyranosides are useful as authentic samples for structure determinations, or as intermediates for the synthesis of some natural products.

Several methods have been developed for the syntheses of the 3-methyl ethers of methyl glycopyranosides [3–8]. However, the existing procedures are either not highly regioselective, or they involve blocking and deblocking steps, with the result that overall yields of the desired products are not satisfactory. In the present study we have found that the "direct stannylation method" [9,10], by which unprotected glycopyranosides are treated with dibutyltin oxide and then alkylated, is effective for the 3-*O*-methylation of methyl α-D-manno-, α-D-galacto-, α-L-rhamno-, and α-L-fuco-pyranoside. By subjecting the initially formed stannylene derivatives to reaction with methyl iodide at 65°C in a capped flask we achieved good yields with excellent regioselectivity.

The methylated products were identified by the ^{1}H NMR spectra of their acetylated derivatives, all of which gave signals for H-3 upfield and H-2, H-4, and the H-6s (when geminal to oxygen) downfield, clearly indicating 3-*O*-methyl

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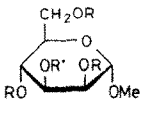
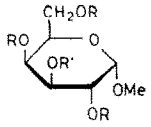
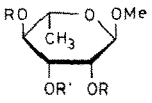
substitution. The optical rotations for all, and melting points for crystalline compounds, were also compared with those reported previously. It was found that methyl 3-*O*-methyl-α-L-fucopyranoside partially changed to its β anomer during the methylation reaction, but after acetylation the two anomers could be separated by column chromatography.



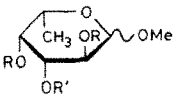
	R	R'
1	H	CH_3
2	Ac	CH_3



	R	R'
3	H	CH_3
4	Ac	CH_3



	R	R'
5	H	CH_3
6	Ac	CH_3



	R	R'
7	H	CH_3 (α)
8	Ac	CH_3 (α)
9	H	CH_3 (β)
10	Ac	CH_3 (β)

1. Experimental

General methods.—See ref 11.

General procedure for 3-O-methylation of methyl glycosides.—A suspension of methyl glycopyranoside (2.6 mmol) and dibutyltin oxide (712 mg, 2.8 mmol) in dry MeOH (30 mL) was boiled under reflux until the solution became homogeneous, after which heating was continued for an additional 1 h. The solvent was evaporated off under diminished pressure, and the residue was dried in vacuo. The resulting white foam was dissolved in *N*,*N*-dimethylformamide (20 mL), and methyl iodide (0.8 mL, 5 molar equiv) was added. The flask was capped and heated at 65°C for 8 h. After cooling, the white precipitate was filtered off. The filtrate was concentrated under diminished pressure to a syrup, which was chromatographed on silica gel with EtOAc as eluent.

General procedure for acetylation of 3-methyl ethers.—This was carried out quantitatively with Ac_2O in pyridine. Methyl 2,4-di-*O*-acetyl-3-*O*-methyl-α-L-fucopyranoside and its β anomer were separated on a silica gel column with 1:4 EtOAc–petroleum ether as eluent. Deacetylation of the two compounds was carried out in 0.02 N NaOMe–MeOH at room temperature (2 h), followed by neutralization with Amberlite IR-120 resin and chromatography on silica gel in EtOAc.

Methyl ethers prepared.—(NMR data are given in Table 1.):

Methyl 3-*O*-methyl-α-D-mannopyranoside (**1**; 390 mg, yield 72%); syrup; $[\alpha]_D$ +53.1° (*c* 0.54, MeOH); lit. [6] $[\alpha]_D$ +57.2° (EtOH). Its triacetate (**2**) was a syrup; $[\alpha]_D$ +28.1° (*c* 0.65, $CHCl_3$).

Methyl 3-*O*-methyl-α-D-galactopyranoside (**3**; 378 mg, yield 70%); syrup; $[\alpha]_D$ +160° (*c* 0.58, MeOH); lit. [4] $[\alpha]_D$ +165° (*c* 2.9, $CHCl_3$). Its triacetate (**4**) was a syrup; $[\alpha]_D$ +132° (*c* 0.77, $CHCl_3$); lit. [12] $[\alpha]_D$ +136° (*c* 1.70, $CHCl_3$).

Table 1
^{1}H NMR data for glycopyranoside 3-methyl ethers and their acetyl derivatives

Compound	Chemical shifts (δ)										Coupling constants (Hz)				
	H-1	H-2	H-3	H-4	H-5	H-6	Me	OMe	OAc	OH	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	J_{5,CH_3}
1	4.80d	3.53				4.20m		3.51,3.38		2.20bs	1.2				
2	4.73d	5.32dd	3.64dd	5.18t	3.88m	4.19m		3.42,3.28	2.08,2.05, 2.04		1.7	3.4	9.8	9.8	
3	4.88d	4.19				3.76m		3.53,3.45		2.22bs	3.9				
4	4.96d	5.04dd	3.69dd	5.53d	4.22	4.04m		3.42,3.40	2.09,2.13, 2.16		3.7	10.5	3.4		
5	4.73d	4.06dd	3.56dd	[a]	3.65m		1.33d	3.43,3.38		2.57bs	1.7	3.2	9.6	9.6	6.1
6	4.64d	5.31dd	3.58dd	4.97t	3.76m		1.21d	3.38,3.34	2.15,2.07		1.7	3.4	9.8	9.8	6.1
7	4.78d	3.90dd	3.40dd	[a]	3.89m		1.32d	3.51,3.43		2.60bs	3.9	9.5	3.4	1.0	6.5
8	4.91d	5.05dd	3.69dd	5.38dd	4.04m		1.08d	3.40,3.38	2.17,2.11		3.7	10.5	3.4	1.2	6.5
9	4.16d	3.63dd	3.20dd	[a]	3.64m		1.40d	3.55,3.53		2.58bs	7.8	9.5	3.4	1.0	6.5
10	4.31d	5.05dd	3.35dd	5.33dd	3.71m		1.22d	3.50,3.36	2.18,2.10		8.1	10.7	3.4	0.7	6.5

[a] First-order splitting was not observed.

Methyl 3-*O*-methyl-α-L-rhamnopyranoside (**5**; 402 mg, yield 81%); syrup; $[\alpha]_D$ −59° (*c* 0.85, MeOH); lit. [13] $[\alpha]_D$ −61° (*c* 1.3). Its diacetate (**6**) had mp 101–103°C; $[\alpha]_D$ −23.8° (*c* 0.77, $CHCl_3$); lit. [13] mp 104–105°C, $[\alpha]_D$ −26° (*c* 0.9).

Methyl 3-*O*-methyl-α-L-fucopyranoside (**7**; 350 mg, yield 70%); mp 99–100°C; $[\alpha]_D$ −133° (*c* 0.85, MeOH); lit. [7] mp 96–97°C, $[\alpha]_D$ −136° (*c* 0.62). Its diacetate (**8**) had mp 115–117°C; $[\alpha]_D$ −177° (*c* 0.77, $CHCl_3$); lit. [14] mp 118–119°C, $[\alpha]_D$ −177° (*c* 1.2).

Methyl 3-*O*-methyl-β-L-fucopyranoside (**9**; 50 mg, yield 10%); mp 100–102°C; $[\alpha]_D$ −10.4° (*c* 0.85, MeOH); lit. [7] mp 104–105°C, $[\alpha]_D$ −12.4° (*c* 0.61). Its diacetate (**10**) had mp 123–125°C; $[\alpha]_D$ −27° (*c* 0.77, $CHCl_3$).

The method was also used for the preparation of allyl 3-*O*-methyl-α-D-mannopyranoside, yield 73%; ^{1}H NMR for its triacetate: δ 6.01–5.82 (m, 1 H, C*H*=CH_2), 5.36–5.13 (m, 4 H, H-2, H-4, CH=CH_2), 4.88 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 4.31–3.86 (m, 5 H, H-5, 2 H-6, CH_2–CH=CH_2), 3.64 (dd, 1 H, $J_{2,3}$ 3.9, $J_{3,4}$ 10.2 Hz, H-3), 3.38 (s, 3 H, OCH_3), 2.08, 2.05, and 2.04 (3 s, 9 H, CH_3CO).

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