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STEREOSELECTIVE SYNTHESES OF 1,2-*cis*- AND 1,2-*trans*-D-MANNOPYRANOSIDES

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ABSTRACT

3,4,6-Tri-*O*-allyl-β-D-mannose 1,2-(methyl orthoacetate) has been prepared from the corresponding tri-*O*-acetyl derivative and used as a precursor for stereocontrolled synthesis of both the 1,2-*cis*- and *trans*-D-mannopyranosides. The allyl groups were selected and tested as temporary blocking groups which allow suitable deprotection under mild conditions following glycosidation. Hydrolysis of the orthoester ring afforded 3,4,6-tri-*O*-allyl-D-mannose. The latter was converted into 3,4,6-tri-*O*-allyl-2-*O*-mesyl-α-D-mannopyranosyl chloride, whose coupling with methanol and cyclohexanol afforded stereoselectively the β anomers as the major products. Methanolysis of the orthoester afforded the α anomer as the major product. The determination of the anomeric configuration is discussed and the ^{1}H-n.m.r. and ^{13}C-n.m.r. spectral data are correlated.

INTRODUCTION

The current interest in glycoside syntheses is predominantly for the preparation of complex glycosides, especially antibiotics and oligosaccharides of biological importance, having specific anomeric configurations and specific linkages between different or similar sugars. There are four possible types of glycoside (**a**–**d**) having different dispositions of substituents on the anomeric carbon atom and on the adjacent one, which must be considered in synthetic planning[1–5]. Generally, for the synthesis of 1,2-*trans*-linked glycosides of types **a** and **c**, an acyloxy substituent at C-2 will control by neighboring-group participation the stereochemical outcome of glycosidation[6–9]. Broadly useful methods for the stereoselective synthesis of 1,2-*cis* glycosides of type **b** (*gluco* and *galacto* types) have also been reported[1–5]. On the other hand, these methods are not of general utility for the synthesis of 1,2-*cis*-linked mannosides (type **d**). The presence of the β-D-mannopyranosidic linkage in various naturally occurring oligosaccharides[10–15] has directed much attention towards its synthesis.

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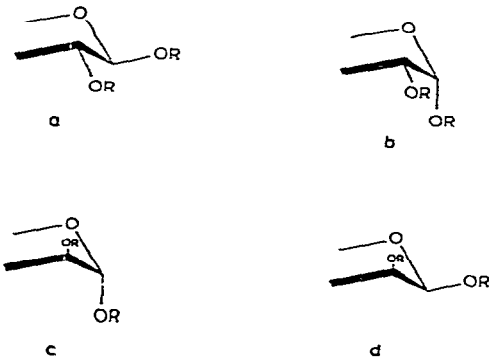
Thus, Perlin, *et al.*[6] and Garegg, *et al.*[17,18] have used glycosyl halides with O-2, O-3-bridging substituents that permit β-attack at C-1. Nevertheless, some deviation in the stereochemical outcome of glycosidation by this method has been described[19]. Another approach for generating the β-D-mannopyranosidic residue has been developed[20–23] by using a suitably protected D-glucopyranosyl halide having a participating group at C-2 to favor the β-linkage, followed by deacylation of O-2, oxidation, and reduction of the resulting ketone to the *manno* epimer. This approach has found wide application in oligosaccharide synthesis. A stereospecific synthesis of β-D-mannopyranosides with the use of insoluble silver catalysts has also been recently reported[24].



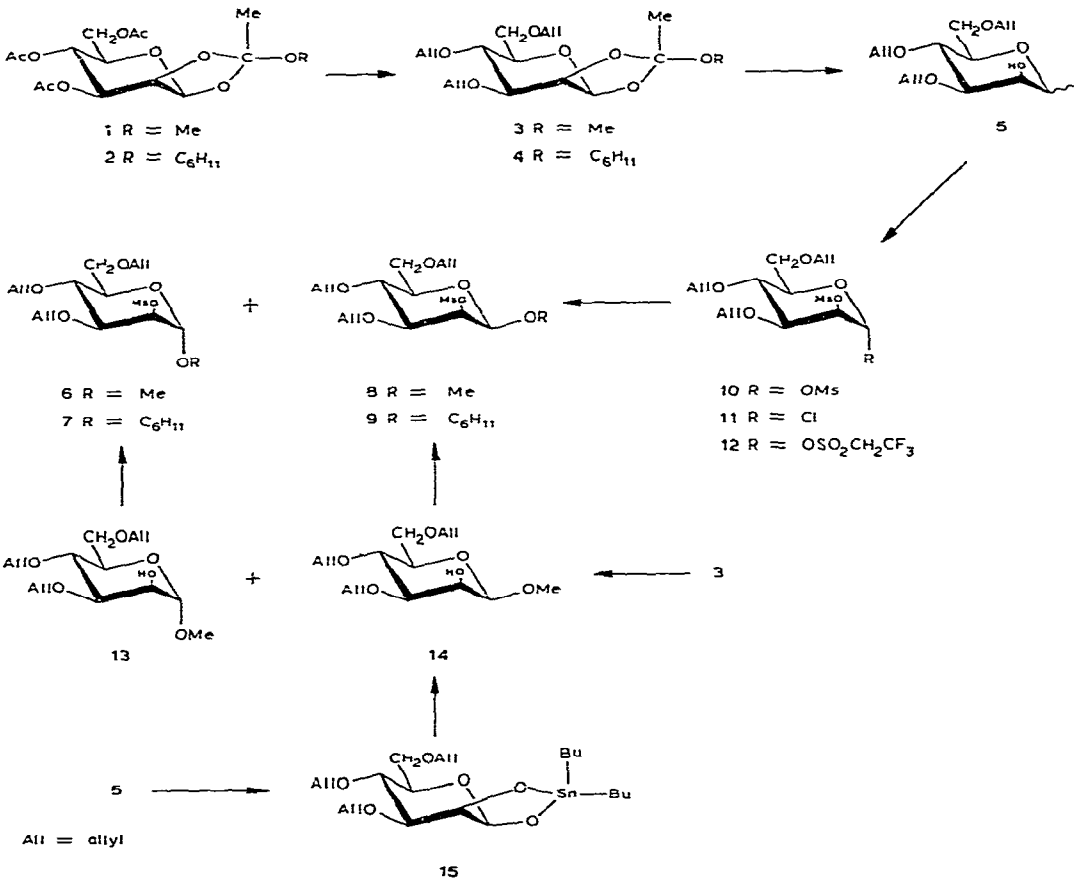
Enhancing the C-2–O dipole by appropriate substitution has also been used to afford a stereoselective synthesis of β-D-mannosides[25], and appears to have promise in glycosidic synthesis as further demonstrated here through a model study with a secondary alcohol. It is also interesting to use simultaneously temporary blocking groups capable of facile deprotection and suitable for possible synthesis of more-complex oligosaccharides.

RESULTS AND DISCUSSION

The marked stability of cyclic 1,2-orthoesters to alkali is well known[26] and it permits the synthesis of derivatives of D-mannose, such as 3,4,6-tri-*O*-methyl-β-D-mannopyranose 1,2-(methyl orthoacetate) and the more useful tri-*O*-benzyl analog (which can be more readily deprotected), for the synthesis of parent oligosaccharides. In the present work, the allyl group is tested as the protecting group.

3,4,6-Tri-*O*-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate)[26–28] **1** was prepared as a mixture of two diasteromers[29] which, on crystallization, gave a crystalline fraction, enriched in one, and a syrupy mother liquor, enriched in the other isomer. Simultaneous deacetylation and allylation of crystalline **1** with powdered potassium hydroxide and allyl bromide gave the corresponding 3,4,6-tri-allyl ether **3** as a syrup. The presence of two diastereomers of **3** was shown by the ^{1}H-n.m.r. spec-

trum, in which two non-equivalent *C*-methyl (at δ 1.68 and 1.52) and *O*-methyl absorptions (at δ 3.30 and 3.47) were found in the ratios of ~7:1. The major isomer has been assigned the *exo* configuration. Similarly the ^{13}C-n.m.r. spectrum showed two signals for *C*-Me at δ 24.5 and 24.1 and for *O*-Me at δ 49.7 and 50.1 for the *exo* and *endo* isomers, respectively. Moreover, the spectrum showed the presence of two signals for the *exo* and *endo* anomeric carbon atoms, at δ 97.8 and 95.2, and also two signals at δ 124.4 and 124.2 for the quaternary carbon atom of the orthoester.



In contrast, the spectrum of the crystalline cyclohexyl orthoester **2** indicated a single isomer, and on deacetylation and allylation **2** was converted into a single diasteromer of **4**, the ^{13}C spectrum of which showed single absorptions for anomeric and quaternary carbon atoms (δ 97.6 and 123.9).

Hydrolysis of **3** by aqueous acetic acid caused the cleavage of the orthoester ring, with the formation of an acetyl derivative, part of which underwent deacetylation, as shown by the n.m.r. spectra. No attempt was made to isolate this acetate, but the mixture was deacetylated by a catalytic amount of sodium methoxide in methanol

to give 3,4,6-tri-*O*-allyl-D-mannose (**5**) as a syrup whose ^{13}C-n.m.r. spectrum in $CDCl_3$ showed a ratio of $\sim 5:2$ of $\alpha:\beta$ anomers, as indicated by the two signals of the anomeric carbon atoms at δ 94.1 and 94.5, respectively. Reaction of **5** with methanesulfonyl chloride in 2,6-lutidine afforded 3,4,6-tri-*O*-allyl-2-*O*-(methylsulfonyl)-α-D-mannopyranosyl chloride (**11**) and 3,4,6-tri-*O*-allyl-2-*O*-(methylsulfonyl)-α-D-mannopyranosyl methanesulfonate (**10**) (identified only by n.m.r. spectroscopy), which presumably was the precursor of **11**. An attempt to force the reaction towards **11** showed, in addition, the formation of a byproduct, probably the β-chloro derivative. On the other hand, treatment of **5** with hydrogen chloride gas

TABLE I

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

Resonance	**2**	**3**[b]	**4**	**5**	**6**	**7**	**8**	**9**	**11**	**13**	**14**
C-1	97.6	97.8	97.6	94.1	99.2	96.4	99.4	96.3	90.6	100.7	101.1
				94.5							
C-2	75.9	77.5	76.4	69.6	74.4	74.7	74.1[c]	74.4[c]	74.8	68.7[c]	68.7[c]
C-3	71.8	79.1	79.0	79.3	77.4[c]	77.9	79.2	79.6	78.9	79.8	81.7
				81.7							
C-4	66.0	74.5[c]	74.5[c]	74.8	77.1[c]	77.9	77.3	78.1	75.9	74.4	74.4
C-5	70.7[c]	73.8[c]	73.9[c]		71.9	72.0	75.8[c]	76.0[c]	73.5	72.6	75.7
C-6 and	62.7	69.2	69.2	69.2	69.1	69.1	69.1	69.6	68.1	69.3[c]	69.5[c]
$-CH_2O-$				69.4							
		71.6	71.6		71.9	72.6	70.8	70.9	72.1	71.1	71.0
		72.4	72.1		72.6	74.2	70.8	72.6	72.5	71.2	72.7
		74.1[c]	74.2[c]		74.1	76.1	72.6	74.3	74.2	74.0	74.1
$-CH_2=$		116.6	116.6	116.7	116.9	116.9	116.9	117.0	117.1	116.6	117.0
		116.7	116.8	117.2	117.0	117.0	117.0	117.8	117.3	117.0	117.5
		117.6	117.7	117.6	117.8		117.7		118.2	117.2	
-CH=		135.0	135.0	135.0	134.5	134.6	134.2	134.6	134.2	135.1	135.1
		135.2	134.8	135.1	135.1	135.1	134.8	135.15	134.8	135.2	135.3
				135.4						135.4	
MeO		49.7			55.1		57.1			54.9	57.0
Ms					38.9	38.9	39.2	39.4	38.9		
Other	20.7	24.5	24.6	70.8		23.8		23.9			
	24.3	124.4	24.9	71.0		24.1		24.0			
	24.7		25.5	72.5		25.7		25.6			
	25.5		34.1	73.9		31.5		31.7			
	33.9		72.4	74.8		33.3		33.4			
	70.3[c]		123.9			77.2		77.2			
	124.4										
CO	169.7										
	170.5										
	170.8										

[a]These assignments are based on estimated shifts from methyl α-D- and β-D-mannopyranosides, respectively: C-1 101.9, 102.2; C-2 71.7, 71.5; C-3 71.71, 74.2; C-4 67.9, 68.0; C-5 73.6, 77.5; C-6 62.1, 62.3 (solvent $CDCl_3$). [b]Data for the *exo* isomer only. [c]These assignments may be interchanged in each vertical column.

in diethyl ether followed by methylsulfonylation afforded the required chloride **11** in crystalline form.

Treatment of chloride **11** with silver 2,2,2-trifluoroethanesulfonate in acetonitrile afforded the 1-*O*-(2,2,2-trifluoroethylsulfonyl) derivative **12** which, upon treatment with 1.1 equiv. of methanol at room temperature, afforded methyl 3,4,6-tri-*O*-allyl-2-*O*-(methylsulfonyl)-β-D-mannopyranoside (**8**) and its α anomer **6** in 7:1 ratio, which were separated by high-pressure liquid chromatography.

The formation of methyl 3,4,6-tri-*O*-allyl-α-D-mannopyranoside (**13**) was accomplished in 85% yield (together with 7% of the β anomer **14**) by methanolysis of orthoester **3**, and mesylation of **13** gave product **6** identical with the byproduct formed by glycosidation of **12** (compare ref. 26). Similarly, methyl tri-*O*-allyl-β-D-mannopyranoside **14** was synthesized in >90% yield by *O*-methylation of the dibutylstannylene complex **15** of 3,4,6-tri-*O*-allyl-D-mannopyranose. Again, mesylation of **14** gave compound **8**, identical with the main product obtained on glycosidation of **12**. Whereas the 2-sulfonates of mannose provide a route to β-mannosides that can be substituted by other sugar residues at O-3, -4, and -6, the orthoester and the stannylene complex may be used in the synthesis of α- and β-mannosides which can more readily be coupled at O-2 to form complex oligosaccharides.

The reaction of sulfonate **12** with cyclohexanol was also studied. The expected product, cyclohexyl 3,4,6-tri-*O*-allyl-2-*O*-(methylsulfonyl)-β-D-mannopyranoside (**9**) was formed, together with its α anomer (**7**). The β configuration was readily assigned by comparison of the optical rotations of the two anomers and by reference to ^{1}H-n.m.r. spectra, which will be discussed later.

The ^{13}C-n.m.r. spectral assignments of these compounds, listed in Table I, were made by applying to the literature values for methyl α- and β-D-mannopyranoside[30] the anticipated shifts due to the particular substitution. The values were consistent with expectations, but were generally not further confirmed. The C-6 resonance in unprotected methyl α- and β-D-mannopyranosides appears at 62.1 and 62.3 p.p.m., respectively. The customary downfield shift (7–10 p.p.m.) on α-etherification[30,31] at O-6 and a small (downfield) shift through γ-substitution at O-4 results in a chemical shift of ~69 p.p.m. for the triallyl derivatives. The C-5 absorption in these derivatives would be expected to be shifted upfield [2 × (1–3 p.p.m.)] by the effect of β-allylation at O-6 and O-4, but the γ-effect of substitution at O-3 should decrease the upfield shift somewhat. It appears that the upfield shift in both α and β series is ~2 p.p.m. In both the parent compounds and the allylated derivatives, the C-5 resonance in the β series is 3–4 p.p.m. downfield from those in the corresponding α series. At C-4, a pronounced downfield shift caused by α-allylation and a smaller upfield shift through β-substitution results in a net downfield shift of 7 p.p.m. for compounds **13** and **14**. Substitution of a 2-*O*-mesyl group results in an additional γ downfield shift of C-4 of ~3 p.p.m. (compare **6** and **8**). As expected, C-4 in the α- and β-anomeric pairs show no pronounced differences. At C-3, the large downfield shift caused by allylation at O-3 and a small, upfield shift through O-4 allylation results in a pronounced, net downfield shift in compounds **13** and **14**. Mesylation at

O-2 results in a β-upfield shift of $\sim$2 p.p.m. in compounds **6** and **8**. The C-3 resonance in the β series appears downfield from that in the α series. The C-2 resonance is shifted upfield by substitution on the other hydroxyl groups, but upon mesylation of its hydroxyl group, a downfield shift is observed. No effect on the shift of the C-2 as a result of anomeric configuration was observed. The chemical shifts given for C-1 are readily assigned from its characteristic position in the spectra. The CH_2O signal of the allyl group appears in the region of the other carbohydrate carbon resonances, and is identified by comparison of its intensity as well as by comparison of the spectra of similar compounds having benzyl groups instead of allyl. The $CH_2=$ and $CH=$ signals are readily assigned by their characteristic downfield chemical shifts. Such other groups as C-Me or O-Ms are readily assigned in the upfield region.

DETERMINATION OF THE ANOMERIC CONFIGURATION

The anomeric configuration of D-mannopyranosides may be established by comparison of the specific rotations of the two anomers if both are available. N.m.r. spectroscopy may provide confirmatory evidence, although the assignment is more difficult than in the *gluco* series. In the ^{1}H-n.m.r. spectrum, for example, the $J_{1,2}$ values for α- and β-D-mannopyranosides correspond to equatorial–equatorial and equatorial–axial arrangements of H-1 and H-2 and generally are too similar to be useful. Similarly, although the chemical shift of the α-anomeric proton is usually downfield of that of a β-anomeric proton, as is observed in the current series (α at δ 4.8–5.00; β at δ 4.4–4.7), variations may occur[32] with some aglycons and under some conditions of measurement, and configuration cannot be firmly assigned on the basis of chemical shift.

In ^{13}C-n.m.r. spectra of D-mannopyranosides, the difference between chemical shifts for C-1 in the α and β series is too small to use in assigning anomeric configuration and, in some cases, a reversal of order is observed. Table I lists four sets of anomers of various modes of substitution that demonstrate this fact. The use of the coupling constant between C-1 and H-1 $J_{C-1,H-1}$ has therefore been suggested[16,32,33] for discrimination, as it is $\sim$10 Hz smaller when H-1 is axial than when it is equatorial. The chemical shifts of C-3 and C-5 in an unsubstituted β-D-mannopyranoside are at substantially lower field than the corresponding α-D-mannopyranosides. This difference is seen in the present series where, in each pair of anomers shown in the table, a downfield shift ($\sim$2–3 p.p.m.) of C-3 and C-5 is found in the β series when compared with the α. Other differences in the ^{13}C-n.m.r. spectra that reflect differences in anomeric configuration are the signals for the methyl aglycon (α $\sim$55, β $\sim$57 p.p.m.) and lesser differences for the 2-*O*-mesyl group.

EXPERIMENTAL

General methods. — ^{1}H-n.m.r. spectra were determined with a Varian A-60-A or XL-100-15 spectrometer for solutions in chloroform-*d* with tetramethylsilane as

internal reference. ^{13}C-N.m.r. spectra were determined with Varian XL-100-15 or CFT-20 spectrometers in 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 model 141 polarimeter in jacketed, 1-dm cells. Melting points were determined with a "Meltemp" apparatus with a 76-mm immersion thermometer. Microanalyses were made by Microanalysis Inc., Wilmington, Delaware. T.l.c. was performed on "Baker-Flex" silica gel 1B-F (2.5 × 7.5 cm) plates; the solvents were ethyl acetate–hexane (1 : 1, solvent *A* or 2 : 1, solvent *B*). High-pressure liquid chromatography (l.c.) was carried out using a Valvco septumless injector (1.0 mL), a Glenco pump, model HPLPS-1, and a Waters differential refractometer R-401. A stainless-steel column (1 × 25 cm inside diameter) containing silica gel (Whatman, Partisil M 9 10/25) was used. Preparative l.c. was performed on a Waters Prep-500 instrument, using a silica gel column. Solutions were dried with anhydrous magnesium sulfate.

3,4,6-Tri-O-allyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (**3**). — A solution of compound[26] **1** (12.5 g, 30 mmol) in benzene (50 mL) and allyl bromide (70 mL) was treated with powdered potassium hydroxide (25 g) and the stirred suspension was boiled under reflux for 5 h. The mixture was cooled, diluted with dichloromethane, and the organic layer was washed with aqueous sodium hydrogencarbonate and then dried. The residual syrup obtained upon evaporation of the solvent was purified by preparative l.c. with 1 : 2 ethyl acetate–hexane as a solvent to give a pure product (10 g, 81% yield); R_F 0.34 (solvent *A*): $[\alpha]_D^{27}$ +6.9° (*c* 1.0, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ ~6.1 (m, 3H, 3 -C*H*=CH_2), 5.42 (d, 1H, *J* ~2 Hz, H-1), ~5.3 (m, 6H, -CH=CH_2), ~4.6 (m, 7H, 3 -OCH_2-CH=CH_2 and H-2), ~3.7 (m, 4H, H-3,-5,-6,-6′), ~3.5 (m, 1H, H-4), 3.47 and 3.30 (2s, 3H, *endo* and *exo* OMe), and 1.68 and 1.52 (2s, 3H, *exo* and *endo* Me).

Anal. Calc. for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.85; H, 8.02.

3,4,6-Tri-O-allyl-β-D-mannopyranose 1,2-(cyclohexyl orthoacetate) (**4**). — A solution of compound[26] **2** (0.9 g, 2.0 mmol) in a mixture of benzene (5 mL) and allyl bromide (5 mL) was treated with powdered potassium hydroxide (1.0 g) and the stirred suspension was processed as for the preparation of compound **3** to afford a product that crystallized from methanol–water (0.5 g, 55%), m.p. 46–48°, $[\alpha]_D^{23}$ +7.9° (*c* 0.8, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ ~6.0 (m, 3H, 3 -C*H*=CH_2), 5.3 (m, 7H, 3 -CH=CH_2, H-1), 4.55 (m, 1H, H-2), ~4.2 (m, 6H, 3 -OCH_2-CH=CH_2), ~3.7 (m, 6H, H-3,-4,-5,-6,-6′, and H-1 of cyclohexyl), 1.72 (s, 3H, Me), and ~1.3 (m, 10H, cyclohexyl).

Anal. Calc. for $C_{23}H_{36}O_7 \cdot 0.5\ H_2O$: C, 63.72; H, 8.60. Found: C, 63.88; H, 8.64.

3,4,6-Tri-O-allyl-D-mannopyranose (**5**). — A solution of **3** (10.0 g, 30 mmol) in acetic acid (135 mL) and water (90 mL) was heated for 3 h on a steam bath, and then kept overnight at room temperature. The mixture was evaporated and toluene was evaporated several times from the residue to remove traces of acetic acid. The resulting syrup was dissolved in chloroform and the solution was washed successively

with sodium hydrogencarbonate and water, and then dried. The chloroform was evaporated off and the syrup deacetylated with a catalytic amount of sodium methoxide in methanol. The solution was made neutral with acetic acid and the solvent removed *in vacuo*. The residue was extracted with ether and the syrup obtained upon evaporation of the ether was purified by preparative l.c. with 2:1 ethyl acetate–hexane as solvent. Evaporation of the solvent gave a pure product (7.0 g, 83% yield); R_F ~0.1 (solvent *A*); $[\alpha]_D^{22}$ +26.3° (*c*, 4.0 chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ ~6.0 (m, 3H, 3 -CH_2-CH=CH_2), ~5.3 (m, >6H, 3 -CH=CH_2, H-1α), 4.7 (bs, <1H, H-1β), 4.5 (bs, 1H, H-2), ~4.1 (m, 8H, 3 -CH_2-CH=CH_2 and H-3, H-5), and ~3.6 (m, 5H, H-4,-6,-6′, and 2-OH).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.14; H, 7.93.

*3,4,6-Tri-*O*-allyl-2-*O*-mesyl-α-*D*-mannopyranosyl chloride* (**11**). — A cooled solution of **5** (1.0 g, 3.3 mmol) in ether (20 mL) was saturated with hydrogen chloride gas and then kept for 5 h at room temperature. The ether was evaporated, the residue dissolved in 2,6-lutidine (10 mL), and the solution cooled to ~0°. Mesyl chloride (1.0 mL) was added dropwise. After stirring for 0.5 h at 0° and for 1 h at room temperature, the mixture was poured onto crushed ice and the product extracted with ether. The extract was washed with water, dried and evaporated to afford a syrup that crystallized from ether–petroleum ether to give **11**; yield 0.8 g (61%); m.p. 45–47°, $[\alpha]_D^{28}$ +81.0° (*c* 5, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.34 (d, 1H, J ~1.5 Hz, H-1), ~6.2 (m, 3H, 3 -CH=CH_2), ~5.4 (m, 7H, 3 -CH=CH_2 and H-2), ~4.2 (m, 9H, 3 -OCH_2-CH=CH_2 and H-3,-4,-5), ~3.8 (m, 2H, H-6,-6′), and 3.20 (s, 3H, Ms).

Anal. Calc. for $C_{16}H_{25}ClO_7S$: C, 48.42; H, 6.35; Cl, 8.93; S, 8.08. Found: C, 48.56; H, 6.22; Cl, 9.59; S, 8.67.

*Methyl 3,4,6-tri-*O*-allyl-2-*O*-mesyl-α-*D*-mannopyranoside* (**6**). — A solution of **13** (0.2 g, 0.6 mmol) in 2,6-lutidine (2 mL) was cooled and then treated with mesyl chloride (0.2 mL). The mixture was refrigerated overnight and then diluted with ice-cold water. The product was extracted with dichloromethane and the organic layer washed successively with water, dilute hydrochloric acid, water, aqueous sodium hydrogencarbonate and water, and then dried. The dichloromethane was evaporated off to give a homogeneous syrup (0.21 g, 84%) that was purified by l.c. with 1:3 ethyl acetate–hexane; $[\alpha]_D^{23}$ + 38.4° (*c* 1.3, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ ~6.0 (m, 3H, 3 -CH=CH_2), ~5.3 (m, 6H, 3 -CH=CH_2), ~4.9 (m, 2H, H-1,-2), ~4.2 (m, 6H, 3 -OCH_2-CH=CH_2), ~3.7 (m, 5H, H-3,-4,-5,-6,-6′), 3.38 (s, 3H, Me), and 3.12 (s, 3H, Ms).

Anal. Calc. for $C_{17}H_{28}O_8S$: C, 52.02, H, 7.17. Found: C, 51.77; H, 7.23.

*Methyl 3,4,6-tri-*O*-allyl-2-*O*-mesyl-β-*D*-mannopyranoside* (**8**). — A solution of **14** (0.1 g, 0.3 mmol) in 2,6-lutidine (1 mL) was mesylated as in the previous experiment to give **8** as a homogeneous syrup (90 mg, 72% yield); $[\alpha]_D^{23}$ −54.0° (*c* 0.6, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ ~6.0 (m, 3H, 3 -CH=CH_2), ~5.3 (m, 7H, 3 -CH=CH_2 and H-2), 4.42 (s, 1H, H-1), 4.2 (m, 6H, 3 -OCH_2-CH=CH_2), ~3.8 (m, 2H, H-3,-5), ~3.5 (m, 3H, H-4,-6,-6′), 3.56 (s, 3H, Me), and 3.14 (s, 3H, Ms).

Anal. Calc. for $C_{17}H_{28}O_8S$: C, 52.04; H, 7.19; S, 8.15. Found: C, 51.33, H, 7.21, S 8.49.

Reaction of 3,4,6-tri-O-allyl-2-O-mesyl-α-D-mannopyranosyl chloride (**11**) *with methanol.* — The chloride **11** (39.6 mg, 0.1 mmol) dissolved in acetonitrile (1.0 mL) was allowed to react with silver trifluoroethanesulfonate to form the corresponding sulfonyl derivative **12**. After 1 h, the solution was filtered from the precipitated silver chloride and then treated with 1.1 equiv of methanol. All operations were performed on a high vacuum rack as described before[34-36]. The mixture was kept overnight, diluted with dichloromethane, and washed with a solution of sodium hydrogencarbonate, sodium thiosulfate, and water. The dried solution was evaporated to a syrup that afforded, after l.c. with 1:4 ethyl acetate–hexane, the main product **8** (32 mg, 82% yield) and the minor product **6** (3 mg, 8% yield).

Reaction of 3,4,6-tri-O-allyl-2-O-mesyl-α-D-mannopyranosyl chloride with cyclohexanol. — The chloride **11** (80 mg, 0.2 mmol) dissolved in acetonitrile (2 mL) was allowed to react with silver trifluoroethanesulfonate to form the corresponding sulfonyl derivative. After 1 h, the solvent was distilled off, and then the sulfonate was dissolved in dimethoxyethane and treated with 1.1 equiv of cyclohexanol. All operations were carried out under high vacuum. After being kept in dark for 3 days, the mixture was processed as before to give a syrup containing a major product that was separated on l.c. with 1:5 ethyl acetate–hexane to give **9** (69 mg, 74% yield), R_F 0.43 (solvent *A*); $[\alpha]_D^{23}$ −51.7° (*c* 1.4, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ ~6.1 (m, 3H, 3 -C*H*=CH_2), ~5.4 (m, 7H, 6 -CH=CH_2 and H-2), 4.95 (d, 1H, H-1), ~4.3 (m, 6H, 3 -OCH_2-CH=CH_2), ~3.8 (m, 6H, H-3,-4,-5,-6,-6′ and H-1 of cyclohexyl), 3.17 (s, 3H, Ms), and 1.7 (m, 10H, cyclohexyl).

Anal. Calc. for $C_{22}H_{36}O_8S$: C, 57.37; H, 7.88; S, 6.97. Found: C, 56.96; H, 7.85; S, 7.04.

A minor product (7 mg, 8% yield) was the fast-moving fraction (R_F 0.4, solvent *A*); $[\alpha]_D^{23}$ +29.6° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ ~6.1 (m, 3H, 3 -C*H*=CH_2), ~5.4 (m, 7H, 6 -CH=CH_2 and H-2), 4.74 (s, 1H, H-1), ~4.3 (m, 6H, 3 -OCH_2-CH=CH_2), ~3.9 (m, 3H, H-3,-5 and H-1 of cyclohexyl), ~3.6 (m, 3H, H-4,-6,-6′), 3.22 (s, 3H, Ms), and 1.7 (m, 10H, cyclohexyl).

Anal. Calc. for $C_{22}H_{36}O_8S$: S, 6.97. Found: S, 7.08.

Methyl 3,4,6-tri-O-allyl-α-D-mannopyranoside (**13**). — A solution of **3** (2.0 g, 5.6 mmol) in abs methanol (50 mL) was treated with acetyl chloride (1 mL) and the mixture was boiled under reflux overnight. T.l.c. indicated that all of the starting material had disappeared with the formation of two new spots; the major one was the faster-moving product (R_F 0.19, solvent *A*) and the other was minor (R_F 0.06, solvent *A*). The methanol was evaporated *in vacuo*, the resulting syrup was dissolved in dichloromethane, and the solution was washed with aqueous sodium hydrogencarbonate and dried. The syrup, obtained upon evaporation of methanol, was subjected to l.c. with 1:2 ethyl acetate–hexane. Evaporation of the fraction enriched with major product afforded 1.5 g(83%) of **13**; $[\alpha]_D^{23}$ +75.1° (*c* 2.6, dichloromethane); ^{1}H-n.m.r. ($CDCl_3$): δ ~5.9 (m, 3H, 3 -C*H*=CH_2), ~5.2 (m, 6H, 3 -CH=CH_2),

4.76 (d, 1H, J <1 Hz, H-1), ~4.1 (m, 7H, 3 -OCH_2-CH=CH_2 and H-2), 3.68 (m, 5H, H-3,-4,-5,-6,-6'), 3.38 (s, 3H, OMe), and 2.6 (s, 1H, OH).

Anal. Calc. for $C_{16}H_{26}O_6 \cdot 0.5\ H_2O$: C, 59.42; H, 8.42. Found: C, 59.69; H, 8.21.

*Methyl 3,4,6-tri-*O*-allyl-β-*D*-mannopyranoside* (**14**). — (*a*) The fraction enriched with the minor product from the previous experiment, upon evaporation, afforded **14** as a syrup (0.13 g, 7% yield); $[\alpha]_D^{23}$ −34.5° (*c*, 0.8, dichloromethane).

(*b*) A suspension of **5** (1.0 g, 3.3 mmol) and dibutyltin oxide (0.83 g, 3.3 mmol) in methanol (100 mL) was heated under reflux until dissolution. After continued heating for 30 min, the methanol was evaporated off and toluene was evaporated from the residue. The residue was suspended in *N*,*N*-dimethylformamide (10 mL) and methyl iodide (0.71 mL), and stirred at 50° until t.l.c. indicated the absence of **5** and the formation of a major product. The mixture was evaporated and the residue extracted with dichloromethane. Evaporation of the solvent and chromatography of the product with 1:2 ethyl acetate–hexane gave **14** (0.95 g, 88%) identical with that obtained by method *a*: ^{1}H-n.m.r. ($CDCl_3$): δ ~6.0 (m, 3H, 3 -CH=CH_2), ~5.3 (m, 6H, 3 -CH=CH_2), 4.34 (s, 1H, H-1), ~4.3 (m, 7H, OCH_2-CH=CH_2 and H-2), ~3.8 (m, 5H, H-3,-4,-5,-6,-6'), 3.56 (s, 3H, OMe), and 2.4 (bs, 1H, OH).

Anal. Calc. for $C_{16}H_{26}O_6 \cdot H_2O$: C, 57.81; H, 8.49. Found: C, 57.91; H, 7.94. Upon further drying: C, 58.61; H, 8.00.

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