Selective monomethylation of O-3 and O-2 of D-mannose with diazomethane in the presence of tin(II) chloride A facile synthesis of methyl 3- and 2-*O*-methyl-α-D-mannopyranosides

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Selective monomethylation of the *cis*-2,3-diol grouping was achieved with diazomethane in the presence of a catalytic amount of tin(II) chloride by blocking of the primary hydroxyl group of methyl α-D-mannopyranoside in the form of its triphenylmethyl ether. In the reaction mixture, the distribution of 2- and 3-*O*-methyl ethers formed depends to a certain extent on the solvent used.

Проведено селективное монометилирование *цис*-2,3-диольной группировки диазометаном в присутствии каталитического количества хлористого олова(II) посредством блокировки первичных гидроксильных групп метил-α-D-маннопиранозида в форме его трифенилметилового эфира. В реакционной смеси соотношение между образующимися 2- и 3-*O*-метиловыми эфирами зависит до некоторой степени от выбора растворителя.

In the studies of both polysaccharide and glycoprotein structures with GLC-mass spectrometry and NMR techniques, the authentic samples of *O*-methyl ethers of the corresponding saccharides are often required. Using classical methods, preparation of these compounds would require multistep, often very laborious procedures with application of several blocking groups. Therefore, in the present decade, considerable attention has been paid to a search for new, selective methods of methylation that could be applied to predetermined sugar hydroxyl groups. With D-mannose, *Srivastava* and *Schuerch* [1] reported selective monomethylation of methyl 6-*O*-triphenylmethyl-α-D-mannopyranoside (*II*) using methyl iodide in the presence of dibutyltin oxide. The main reaction product, methyl 3-*O*-methyl-α-D-mannopyranoside (*VIII*), was obtained in 75 % yield. The latter compound was also prepared in a similar way starting from methyl 4,6-*O*-benzylidene-α-D-mannopyranoside [2]. It has been shown in both cases that a cyclic dibutylstan-

nylene derivative of equatorial O-3 and axial O-2 activates selectively the equatorial oxygen for the subsequent alkylation.

In the previous papers [3—5], we described selective benzylation and methylation of methyl α-L-rhamnopyranoside using tin(II) chloride as the catalyst. We established also a tentative mechanism for complexation, and a possible model of a tin(II) chloride—methyl glycoside intermediate complex, which is preferentially formed through displacement of molecules of the donor solvent coordinated to a tin(II) atom by the favourably *cis*-disposed hydroxyl groups of methyl α-L-rhamnopyranoside. It was of interest to see if the stereospecificity of $SnCl_2$—CH_2N_2 methylation remains preserved also in the presence of a primary hydroxyl group in a sugar moiety. Methyl α-D-mannopyranoside (*I*), having similar spatial arrangement of the hydroxyl groups as methyl α-L-rhamnopyranoside, was selected as the model compound.

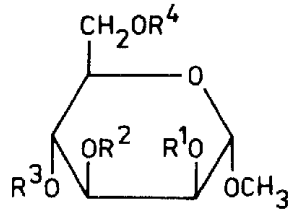
In dry acetone or methanol, compound *I* gave with diazomethane in the presence of tin(II) chloride besides a larger amount (≈38 %) of *VIII* also other products, mainly isomeric di- and tri-*O*-methyl ethers, which pointed to relatively low stereospecificity of the reaction. Considering the fact that analysis of the products of such a methylation of compound *I* may indicate formation of the intermediate tin(II) chloride—methyl glycoside complexes and the sites of coordination of a tin(II) atom to sugar hydroxyl groups [4], the presence of 6-*O*-methylated derivatives (methyl 3,6-, 4,6-di-, and 2,3,6-tri-*O*-methyl-α-D-mannopyranosides) in the reaction mixture in an overall yield of ≈42 % shows that the primary hydroxyl group also participates, to a great extent, in this complexation. We have found [6], however, that a suitable blocking of the group, *e.g.* in the form of triphenylmethyl ether, leads, in the first step, to preferential $SnCl_2$—CH_2N_2 methylation of the *cis*-diol system of the sugar unit, thus enabling a facile preparation of methyl 2- and 3-*O*-methyl-α-D-mannopyranosides (*VII* and *VIII*) in one reaction step.

Table 1

Products of methylation of *II* after detritylation

Solvent	*x*/mole %			
	VII	*VIII*	*IX*	*X*
Ethyl acetate	27.1	67.9	3.8	1.2
Acetone	38.4	53.4	6.1	2.1
Methanol	34.1	62.1	2.9	0.9
N,*N*-Dimethylformamide	24.5	69.8	4.1	1.6
Acetonitrile	41.7	51.7	5.2	1.4

Compound *I* was refluxed in dry pyridine with triphenylmethyl chloride and the subsequent column chromatography on silica gel and crystallization yielded *II*. After dissolution in the selected solvents (Table 1), containing catalytic amounts of tin(II) chloride, methylation of *II* proceeded on addition of an excess of diazomethane in dichloromethane. In 1,4-dioxan, tetrahydrofuran, and pyridine the conversion did not exceed ≈60—70 %. Compounds *VII* and *VIII* together with small amounts of methyl 2,3- and 2,4-di-*O*-methyl-α-D-mannopyranosides (*IX* and *X*; Table 1) were identified in the reaction mixture with GLC—mass spectrometry (see Experimental) after detritylation with a BF_3—MeOH complex [7]. In contrast with methyl α-L-rhamnopyranoside [4], the observed selectivity of methylation was more dependent on the solvents applied. The most suitable distribution of the products for the large-scale preparation of compounds *VII* and *VIII* was found to be in acetonitrile (Table 1). After methylation of *II*, the sirupy material was acetylated and separated on a column of silica gel. Methyl 2,4-di-*O*-acetyl-3-*O*-methyl-6-*O*-trityl- and 3,4-di-*O*-acetyl-2-*O*-methyl-6-*O*-trityl-α-D-mannopyranosides (*III* and *IV*) were obtained, which gave the corresponding *VIII* and *VII* after deacetylation and detritylation [7].



	R^1	R^2	R^3	R^4
I	H	H	H	H
II	H	H	H	$C(C_6H_5)_3$
III	CH_3CO	CH_2	CH_3CO	$C(C_6H_5)_3$
IV	CH_3	CH_3CO	CH_3CO	$C(C_6H_5)_3$
V	CH_3	H	H	$C(C_6H_5)_3$
VI	H	CH_3	H	$C(C_6H_5)_3$
VII	CH_3	H	H	H
VIII	H	CH_3	H	H
IX	CH_3	CH_3	H	H
X	CH_3	H	CH_3	H

In preparation of single *VIII*, $SnCl_2$—CH_2N_2 methylation of *II* was accomplished in ethyl acetate. The mixture of products was then oxidized with a solution of sodium periodate (1,4-dioxan—water) and after deionization and evaporation, the residue was purified on a column of silica gel. Detritylation [7] yielded sirupy *VIII*.

We have mentioned already, that as in the case of methyl α-L-rhamnopyranoside, the flexible *cis*-diol system of compound *II* is sterically more

favourable for coordination with a tin(II) atom than HO-3,4 grouping. It appears, however, that the selectivity of complexation with HO-2,3 is in compound *II* substantially enhanced in comparison with methyl α-L-rhamnopyranoside. While 2-*O*-methyl ether of the latter compound reacted completely in the second step of $SnCl_2$—CH_2N_2 methylation, as the result of tin(II) chloride complexation with HO-3,4 [4], only a part of 2-*O*-methyl ether of compound *II*, in dependence on the solvent used, participated in further complexation — methylation giving *IX* and *X* (Table 1). This can be considered as an evidence [4] for both lower stability and probability of the complex formation at HO-3,4 in compound *II* comparing with methyl α-L-rhamnopyranoside. Besides other factors, the bulky triphenylmethyl group at C-6 evidently has an important role in this connection. The preferential methylation of O-3, which was also observed by other authors [1, 2], can be explained on the basis of better sterical accessibility of the equatorial O-3 position over an axial O-2 and from the different electron density of both oxygens [8]. There are only few data [3—5] available concerning the solvent influence on the complexation tin(II) chloride—sugar unit. The former seems to influence substantially the course of subsequent alkylation.

Finally, the alternative synthesis of *VII* and *VIII* presented enables, in contrast with the previous papers [1, 2] the preparation of both compounds in a single methylation step and their distribution can be influenced to some extent by the selection of a suitable solvent.

Experimental

Optical rotations were measured on solutions in chloroform with a Perkin—Elmer, Model 141, polarimeter at 20 °C. Melting points were determined with a Kofler hot-stage and are uncorrected. TLC was performed on Silufol plates (Kavalier, Votice) with *A* (*V*(chloroform) : *V*(methanol) = 14 : 1), *B* (*V*(light petroleum (b.p. 35—50 °C)) : *V*(acetone) = 6 : 1), *C* (*V*(chloroform) : *V*(actone) = 5 : 1), and *D* (*V*(chloroform) : *V*(methanol) = 6 : 1). Saccharides were detected by charring after spraying the plates with 20 % aqueous ammonium sulfate. Preparative chromatography was accomplished on the dry columns of Silikagel L (40—56 μm; Lachema, Brno).

GLC—mass spectrometry of partially methylated derivatives of *I* was conducted with a JMS-D 100 (Jeol) apparatus, using a column (200 cm × 0.3 cm) packed with 80—100 mesh Gas-Chrom Z coated with 5 % of BDS. The inlet helium pressure was 101.3 kPa, the temperature program 150 °C (8 min)—180 °C at 2 °C/min, and the spectra were determined at 23 eV. ^{13}C NMR spectra were recorded at 20 °C with a Jeol FX-60 instrument in solutions of deuterated chloroform and acetone, with Me_4Si as the internal standard. The following FT techniques were used: noise and off-resonance decouplings with repetition time of 2 s, pulse-width 4 μs (45° flip angle), and 2500 Hz sweep-width (4k real data points). An average number of accumulations was 3000 for noise and 8000 for off-resonance decouplings.

Anhydrous tin(II) chloride was of the same origin as in the previous works [3—5]. All solvents used were purified and dried. Solutions were concentrated at 50 °C under reduced pressure.

Methylation of compound *I* with diazomethane was accomplished as follows. To a solution of compound *I* (5 mg) in dry acetone or methanol (2 cm^3) containing tin(II) chloride (2—5 mmol dm^{-3}), ≈0.6 M-diazomethane (from *N*-nitrosomethyl-urea [9]) in dichloromethane was added slowly at room temperature until a yellow colour persisted. After a complete conversion of the starting compound (≈30 min), the solution was evaporated to dryness, chloroform (250 mm^3) was added and the sample was directly injected onto GLC—mass spectrometry analysis. The partially methylated derivatives of *I* were identified according to [10, 11].

For determination of the product distribution on methylation of *II* in dependence on the solvent used (Table 1), compound *II* (10 mg) was methylated with diazomethane in the selected solvents using the same conditions as described above. The reaction products were then detritylated with the BF_3—MeOH complex [7] and analyzed by GLC—mass spectrometry.

Methyl 6-O-triphenylmethyl-α-D-mannopyranoside (II)

Compound *I* (17 g) was suspended in dry pyridine (170 cm^3) and triphenylchloromethane (34 g) was added under continuous stirring. The reaction mixture was refluxed for 3 h. After cooling, water (300 cm^3) was added and the solution was allowed to stand overnight. The aqueous phase was separated and the residual solution was evaporated. The dry product was dissolved in chloroform, the solution was washed with water (4 × 200 cm^3), dried (Na_2SO_4), and evaporated to a sirup. The product was purified on a column (80 cm × 5 cm) of silica gel using solvent *A* and was crystallized from dichloromethane—hexane. Compound *II* (m = 32 g, yield = 84 %) had m.p. = 94—97 °C, $[\alpha]$ (D, ϱ = 12.4 g dm^{-3}) = +24.2°. Ref. [12] gives m.p. = 92—95 °C, $[\alpha]$ (D, ϱ = 27 g dm^{-3}) = +23.6°.

For $C_{26}H_{28}O_6$ w_i(calc.)/%: (C) 71.54, (H) 6.47; w_i(found)/%: (C) 71.64, (H) 6.62.

Methyl 2,4-di-O-acetyl-3-O-methyl- and 3,4-di-O-acetyl-2-O--methyl-6-O-triphenylmethyl-α-D-mannopyranosides (III and IV)

To a solution of compound *II* (7.5 g) in dry acetonitrile (200 cm^3) containing tin(II) chloride (2—5 mmol dm^{-3}), ≈0.6 M-diazomethane in dichloromethane was added slowly at room temperature until a yellow colour persisted. After ≈40 min, when no starting compound could be detected (TLC, solvent *A*), the reaction mixture was evaporated to dryness, dry pyridine (60 cm^3) and acetic anhydride (60 cm^3) were added and the solution was heated at 90 °C for 1 h. On evaporation, a sirupy material containing two major products (R_f 0.4 and 0.3, TLC, solvent *B*) was obtained. The compounds were isolated by chromatography on a column (70 cm × 5 cm) of silica gel using *B* as the eluant.

Eluted first was *III* (m = 4.3 g, yield = 47 %), m.p. = 182—183 °C (from light petroleum—acetone), $[\alpha]$ (D, ϱ = 9.2 g dm^{-3}) = +11.7°. ^{13}C NMR data: $\delta_{r,i}$/ppm: (CO) 170.4

and 169.5; ($C(C_6H_5)_3$) 143.9—126.8; (C-1) 98.4; (C-2) 70.3; (C-3) 77.1; (C-4) 68.0; (C-5) 74.9; (C-6) 63.0; (CH_3O-3) 57.6; (CH_3O-1) 54.8; (CH_3) 21.1 and 20.7.

For $C_{31}H_{34}O_8$ w_i(calc.)/% : (C) 69.65, (H) 6.41, (CH_3O) 11.61; w_i(found)/% : (C) 69.58, (H) 6.48, (CH_3O) 11.70.

Eluted second was *IV* ($m = 3.5$ g, yield = 38 %), sirup, $[\alpha]$ (D, $\varrho = 11$ g dm^{-3}) = +33.5° ^{13}C NMR data: $\delta_{r,i}$/ppm: (CO) 170.4 and 169.5; ($C(C_6H_5)_3$) 143.9—127.0; (C-1) 98.2; (C-2) 78.2; (C-3) 70.3; (C-4) 67.2; (C-5) 71.9; (C-6) 63.2; (CH_3O-2) 59.5; (CH_3O-1) 54.8; (CH_3) 21.1 and 20.7.

Methyl 2- and 3-O-methyl-6-O-triphenylmethyl--α-D-mannopyranosides (V and VI)

Compound *IV* (3.0 g) was suspended in dry methanol (30 cm^3), 0.22 M-sodium methoxide (10 cm^3) was added and deacetylation was followed by TLC using solvent *B*. After deionization (Dowex 50 W × 8, H^+ form) and usual work up, compound *V* ($m = 2.2$ g, yield = 87 %) was obtained on crystallization from the mixture chloroform—methanol, with m.p. = 145.5—146.5 °C and $[\alpha]$ (D, $\varrho = 10.5$ g dm^{-3}) = +3.8°. ^{13}C NMR data: $\delta_{r,i}$/ppm: ($C(C_6H_5)_3$) 145.4—127.7; (C-1) 99.0; (C-2) 81.3; (C-3) 72.8; (C-4) 69.4; (C-5) 73.2; (C-6) 65.1; (CH_3O-2) 59.3; (CH_3O-1) 54.8.

For $C_{27}H_{30}O_6$ w_i(calc.)/% : (C) 71.98, (H) 6.71, (CH_3O) 13.76; w_i(found)/% : (C) 71.93, (H) 6.80, (CH_3O) 13.85.

Compound *III* (4.0 g) was deacetylated in the same way as in the preceding case. Crystallization (chloroform—methanol) afforded *VI* ($m = 3.1$ g, yield = 92 %) with m.p. = 130—131 °C and $[\alpha]$ (D, $\varrho = 9.8$ g dm^{-3}) = +26.5°. ^{13}C NMR data: $\delta_{r,i}$/ppm: ($C(C_6H_5)_3$) 143.6—127.1; (C-1) 100.3; (C-2) 69.9; (C-3) 80.8; (C-4) 68.6; (C-5) 74.9; (C-6) 66.7; (CH_3O-3) 57.3; (CH_3O-1) 54.8.

For $C_{27}H_{30}O_6$ w_i(found)/% : (C) 71.91, (H) 6.78, (CH_3O) 13.86.

Methyl 2- and 3-O-methyl-α-D-mannopyranosides (VII and VIII)

To a solution of compound *V* (2 g) in dry chloroform (100 cm^3), a BF_3—MeOH complex in methanol ($\varrho = 140$ g dm^{-3}, 5 cm^3) was added at room temperature and the reaction was followed on TLC plates using solvent *C*. After complete detritylation (≈40 min), the reaction mixture was washed with water (3 × 10 cm^3), the organic layer was dried (Na_2SO_4) and sirupy *VII* ($m = 0.9$ g, yield = 98 %) was obtained on evaporation. It had $[\alpha]$ (D, $\varrho = 12$ g dm^{-3}) = +48°; Ref. [2] gives $[\alpha]$ (D, 25 °C, $\varrho = 29$ g dm^{-3} in chloroform) = +51.2°. ^{13}C NMR data: $\delta_{r,i}$/ppm: (C-1) 99.2; (C-2) 81.5; (C-3) 72.6; (C-4) 69.4; (C-5) 74.1; (C-6) 63.2; (CH_3O-2) 59.3; (CH_3O-1) 54.8.

Compound *VI* (3 g) was detritylated similarly as in the preceding case. On evaporation, sirupy *VIII* ($m = 1.3$ g, yield = 94 %) was obtained, with $[\alpha]$ (D, $\varrho = 10.8$ g dm^{-3}) = +56.2°; Ref. [2] gives $[\alpha]$ (D, 25 °C, $\varrho = 18$ g dm^{-3} in chloroform) = +59.6°. ^{13}C NMR

data: $\delta_{C,i}$/ppm: (C-1) 102.1; (C-2, C-4) 67.4; (C-3) 82.5; (C-5) 73.9; (C-6) 63.0; (CH_3O-3) 57.2; (CH_3O-1) 54.8.

Compound *VIII* was also prepared as follows. The sirupy product (2 g), obtained after $SnCl_2$—CH_2N_2 methylation of *II* in ethyl acetate, was dissolved in 0.03 M-sodium periodate (230 cm^3, 1,4-dioxan—water (volume ratio = 1 1)) and the solution was stirred at room temperature overnight. After deionization with the mixed-bed ion exchanger (Ionenaustauscher V) and detritylation, compound *VIII* ($m = 0.6$ g, yield = 95 %) was isolated by chromatography on a column (40 cm × 3.5 cm) of silica gel with solvent *D*.

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