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Effect of complexation of silver ion with the glycosyl donor and acceptor on the regio- and stereo-selectivity in the β-mannopyranosylation of 1,3-di-*N*-benzyloxycarbonyl-2-deoxystreptamine using silver triflate as a promoter in tetrahydrofuran

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ABSTRACT

A pseudodisaccharide, a 5-*O*-(β-D-mannopyranosyl)-2-deoxystreptamine derivative, was obtained preferentially when 2,3,4-tri-*O*-allyl-6-*O*-benzyl-α-D-mannopyranosyl chloride (**1**) was used as the glycosyl donor for coupling with 1,3-di-*N*-benzyloxycarbonyl-2-deoxystreptamine (**2**) using silver triflate as a promoter in tetrahydrofuran. Complexation of the glycosyl acceptor and the allyl protecting group of the glycosyl donor with the promoter proved important for the regio- and stereo-selective formation of the β-mannopyranosyl linkage.

INTRODUCTION

In the course of total synthesis[1,2] of Destomycin C we found that the pseudodisaccharide **3** having a β-mannopyranosyl linkage was formed preferentially upon coupling 2,3,4-tri-*O*-allyl-6-*O*-benzyl-α-D-mannopyranosyl chloride[1,2] (**1**) with 1,3-di-*N*-benzyloxycarbonyl-2-deoxystreptamine[3] (**2**) using silver triflate in tetrahydrofuran (THF), as shown in Scheme 1. This glycosylation is noteworthy in two respects.‡ First, silver triflate has never been used for the formation of the β-mannopyranosyl linkage, because this promoter is generally considered[5] to favor the formation of the α linkage *via* an S_N1-like mechanism.

Second, the β-linkage was formed preferentially only when THF was used as the solvent. The glycosyl acceptor **2** becomes soluble in THF in the presence of silver triflate, and this phenomenon may be correlated with the foregoing result. Furthermore, the structural analogy of the pseudo-disaccharide **3** with 2-acetamido-2-deoxy-4-*O*-(β-D-

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‡ A preliminary report[4] gave similar results in the successful use of silver triflate as a promoter in THF for the β-selective glycosylation of di-*N*-benzyloxycarbonylactinamide with the enol benzoate of α-D-actinospectosyl chloride.

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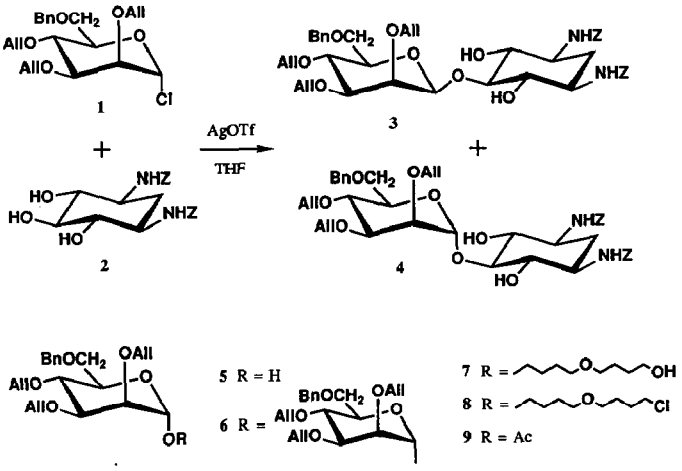


Scheme 1

mannopyranosyl)-D-glucose, the common core structure of the carbohydrate chain in *N*-glycosyl type glycoproteins, a most-challenging synthetic target[6], prompted our study of this glycosylation reaction in detail.

RESULTS AND DISCUSSION

In order to optimize formation of the β-glycosidic linkage in the coupling of **1** and **2**, various conditions were examined and the results are summarized in Table I. In the standard reactions, the glycosyl donor **1** (1.2–1.7 equiv.) and glycosyl acceptor **2** (1 equiv.) were coupled in the presence of silver triflate (7.0–7.3 equiv.) in THF. Only the (1→5)-linked pseudodisaccharide were obtained, except at higher temperatures, and traces of the (1→4)- or (1→6)-linked regioisomers were also obtained (entry 1 and 2). Besides the pseudodisaccharides, the donor **1** was recovered even after 5 h in most cases, together with 2,3,4-tri-*O*-allyl-6-*O*-benzyl-D-mannose[2] (**5**) and the trehalose-type disaccharide[2] (**6**). Furthermore, such byproducts as **7** (ref. 2) and **8** (ref. 2) formed by participation of THF were also isolated in some cases in up to 30% yield. Acetolysis of **8** gave the corresponding 1-acetate **9** in good yield, confirming the structure of **8**.

The β-selectivity increased at lower temperatures (compare entries 1–5 in Table I), although the maximum total yield was attained at −30°. However, the longer reaction-time at −30° led to polymerization of THF, making purification of the products difficult. In contrast, at −78° the longer reaction-time (5 h) and especially higher concentrations of the reactants, increased the total yields remarkably (entries 8–10). With 2.7-times higher concentrations (entry 9), the formation of the β-glycoside **3** increased as expected *via* the S_N2 mechanism, whereas the yield of α-glycoside (**4**) remained unchanged. With 10-times higher concentrations (entry 10) the yield of α-glycoside **4** increased, presumably due to the higher concentration of silver ion, resulting in a slightly lower ratio of β- to α-glycoside.

TABLE I

Mannopyranosylation[a] of **2** with the glycosyl donor **1** in the presence of AgOTf

Entry	*Temperature(°) and time (h)*	*Molar ratio*[b] **1**	*AgOTf*	*Yields (%) of products* **3**	**4**	*Total*	*Remarks*
1	20, 0.5	1.4	7.0	5	17	22	regioisomers[c]
2	0, 0.5	1.2	7.2	10	30	40	regioisomers[c]
3	−30, 0.5	1.7	7.0	37	39	76	
4	−50, 0.5	1.6	7.3	36	27	63	
5	−78, 0.5	1.5	7.0	13	6	19	
6	−30, 0.5	1.5	16.3	14	20	34	
7	−78, 5.0	1.5	3.8	20	15	35	
8	−78, 5.0	1.4	7.0	26	16	42	
9	−78, 5.0	1.5	7.0	52	14	66	higher conc. (x2.7)[d]
10	−78, 5.0	1.7	6.8	55	26	81	higher conc. (x10)[e]
11	−78, 5.0	2.1	6.2	0	27	27	CH_2Cl_2[f]
12	−78, 5.0	1.9	6.0	22	31	53	THF:CH_2Cl_2 = 1:1[f]
13	−78, 5.0	2.1	5.8	30	19	49	THF:toluene = 1:1[f]
14	−78, 5.0	1.5	7.1	16	4	20	collidine(1.0)[g]
15	−78, 5.0	1.5	7.0	16	9	25	Et_3N(1.0)[g]

[a] Unless otherwise stated, the reaction was carried out in THF (concentration of **2**: 0.15M. [b] Glycosyl acceptor **2** as 1.0. [c] (1→4) and/or (1→6)-linked pseudodisaccharides were obtained in traces. [d] The concentration of **2** was 0.40M. [e] The concentration of **2** was 1.5M. [f] Solvent. [g] Additive and its molar ratio.

In this glycosylation reaction, THF and silver triflate play critical roles. The acceptor **2** does not dissolve in THF until silver triflate is added. Such conventional glycosylation solvents as dichloromethane and toluene scarcely dissolve **2**, and give only the α-glycoside **4** (entry 11) and none of the other products. However, when THF was mixed with these solvents, considerable amounts of the glycosides were obtained (entries 12 and 13). 1,4-Dioxane, a cyclic ether like THF, also dissolves **2**, but gave very low yield* of **4**. This result suggested an additional role for THF, such as participation in the complexation of **2** with silver triflate. The complexation was further investigated by a ^{109}Ag-n.m.r. study. A 0.8 mM solution of silver triflate in tetrahydrofuran gave a sharp singlet at −35.6 p.p.m. (silver nitrate in D_2O as the external reference). In the presence of the glycosyl acceptor **2** (0.14 mM) at −77° in tetrahydrofuran-d_8, this signal changed to a broad singlet for the coordinated silver ion at 15.5 p.p.m. to lower field. However, at 27° no singal was observed. These facts may indicate the existence of a distinct silver ion-coordinated species at the lower temperature. Judging from the observed regioselective glycosylation at O-5 of **2**, a symmetrical chelation of two molecules of silver ion with the hydroxyl and substituted amino groups as depicted in Fig. 1 seems to be the most plausible.

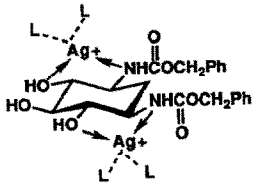


Fig. 1. Proposed chelation of silver ion to **2**.

In relation to this fact, it was found that the optimum amount of silver triflate was ~6–7 equivs. With lower (entry 7, see also Table II, entries 6 and 8) and higher amounts (entry 6) of silver triflate, both the yields and selectivities were notably decreased.

The addition of such conventionally used amines as collidine and triethylamine significantly decreased the yields (entries 14 and 15), suggesting that these amines interfere with the postulated complexation.

The regioselectivity of this glycosylation seems to be correlated with the complexation, which retards the attack of the glycosyl donor at O-4 and O-6 of **2**. The selectivity, however, was affected by even slight changes in the substituents of the glycosyl donor. The effect of substituents on the activity of the glycosyl donor may be explained by the electronic, that is the inductive effect of the substituents, including the recently proposed through-bond effect[7]. The foregoing results suggest that coordination of the substituents to silver ion has a considerable influence on the reactivity as well as on the regioselectivity. In order to investigate this effect, the glycosyl donors **12**, **15**, **19**, and **22**, were synthesized as shown in Scheme 2.

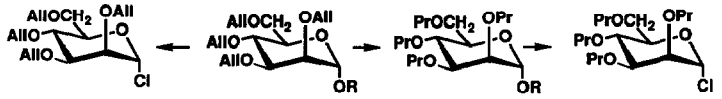
* Only the α-glycoside **4** was obtained, in 9% yield, after 5 h at 10–15°. This temperature was selected because of the higher freezing point of this solvent.

TABLE II

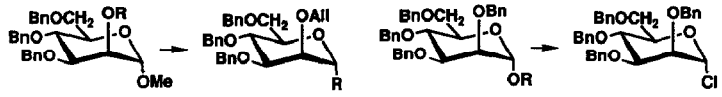
Mannopyranosylation of **2** with several glycosyl donors in the presence of AgOTf in THF

Entry	*Temperature (°) and time (h)*	*Molar ratio*[a] *Glycosyl donors*		*AgOTf*	*Yields (%) of products* α		β		*Total*	*Additive regioisomers*		
1	−30, 0.5	**12**	1.5	7.2	**23aα**	32	**23aβ**	20	52	**24a**	19	
2	−78, 5.0	**12**	1.6	7.1	**23aα**	28	**23aβ**	18	46	**24a**	10	
3	−78, 5.0	**12**	1.6	7.0	**23aα**	20	**23aβ**	21	41	**24a**	10	AllOBn(1.0)[a]
4	−78, 5.0	**12**	1.6	7.0	**23aα**	10	**23aβ**	9	19	**24a**	9	AllOBn(7.0)[a]
5	−78, 5.0	**12**	1.6	6.9	**23aα**	7	**23aβ**	7	14	**24a**	7	AllOBn(14.0)[a]
6	−78, 5.0	**19**	1.6	3.3	**23bα**	4	**23bβ**	7	11	**24b**	8	
7	−78, 5.0	**19**	1.5	7.1	**23bα**	21	**23bβ**	22	43	**24b**	16	
8	−78, 5.0	**22**	1.5	3.3	**23cα**	3	**23cβ**	3	6	**24c**	3	
9	−78, 5.0	**22**	1.6	6.8	**23cα**	20	**23cβ**	15	35	**24c**	22	
10	−30, 0.5	**15**	1.5	7.1	**23dα**	12	**23dβ**	5	17	**24d**	16	
11	−78, 5.0	**15**	1.5	7.0	**23dα**	12	**23dβ**	9	21	**24d**	29	

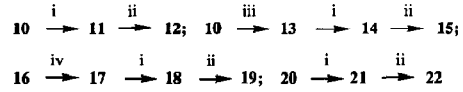
[a] The glycosyl acceptor **2** as 1.0.



12 | 10 R = Me, 11 R = Ac | 13 R = Me, 14 R = Ac | 15



16 R = H, 17 R = All | 18 R = OAc, 19 R = Cl | 20 R = Me, 21 R = Ac | 22



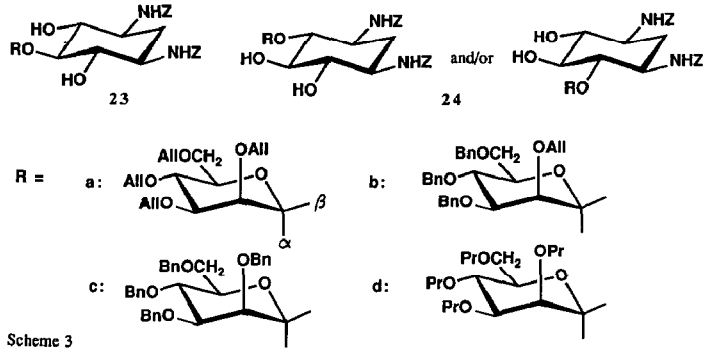
i : Ac_2O–AcOH–H_2SO_4; ii : HCl–Et_2O; iii : H_2, Pd-C, AcOH–EtOH
iv : NaH–DMF; AllCl

Scheme 2

TABLE III

Chemical shifts and coupling constants of H-4 and H-6 of acetylated pseudodisaccharides **3**, **4** and **23** measured in pyridine-d_5 at 500 MHz

Pseudodisaccharide	*Chemical shift (p.p.m.) and coupling constant (Hz)*			
3	5.57 t	(10.5),	5.55 t	(10.1)
4	5.51 t	(10.0),	5.49 t	(10.0)
23aβ	5.58 t	(10.3),	5.56 t	(10.3)
23aα	5.53 t	(9.8),	5.51 t	(9.8)
23bβ	5.59 t	(9.8),	5.56 t	(10.5)
23bα	5.57 t	(10.3),	5.54 t	(10.0)
23cβ	5.66 t	(10.5),	5.62 t	(10.3)
23cα	5.56 t	(9.8),	5.54 t	(9.3)
23dβ	5.53 t	(9.8),	5.52 t	(9.6)
23dα	5.55 t	(11.1),	5.53 t	(10.7)



Scheme 3

Glycosylation of **2** with the glycosyl donors **12**, **15**, **19**, and **22** under the standard conditions gave a mixture of regioisomeric glycosides (**23** and **24**), as shown in Table II and Scheme 3. The position of the glycosidic linkage was determined after acetylation by the chemical shifts of methine protons where free hydroxyl groups had been present (Table III). The signals were assigned with the aid of data reported for 4,5,6-tri-*O*-acetyl-*N*,*N*-dibenzyloxycarbonyl-2-deoxystreptamine[8]: δ 5.61 (H-4 and H-6) and 5.85 (H-5).

It is noteworthy that even the difference of one substituent in the glycosyl donor (compare **1** and **12** as well as **19** and **22**), affects the stereoselectivity, that is, the α to β ratio of (1→5)-linked pseudodisaccharide, and the regioselectivity [namely, the ratio of (1→4)-linked + (1→6)-linked) to (1→5)-linked pseudodisaccharide], as summarized in Table IV.

TABLE IV

Stereo- and regio-selectivity of the glycosylation of **2** with several mannopyranosyl chlorides[a]

Glycosyl donor	*Yield (%) of 5-glycoside*		*Yield (%) of regioisomers*	*Regioisomers /5-glycoside*	*Total yield (%) of glycosides*
	$\alpha+\beta$	β/α			
1	42	1.6	0	0	42
1[b]	76	0.95	0	0	76
12	46	0.7	10	0.2	56
12[b]	52	0.6	19	0.4	71
15	21	0.8	29	1.4	50
15[b]	17	0.8	16	0.9	33
19	43	1.0	16	0.4	59
22	35	0.8	22	0.6	57

[a]At −78°: see Table I and II. [b]At −30°.

These results may be explained rationally by considering the coordination of π electrons of the substituents to silver ion. It is reasonable to assume that the α- and β-glycosides are in these glycosylations are formed solely by the SN1 and SN2 mechanisms, respectively, because both neither steric nor electronic factors favor formation of the β-glycoside via the S_N1 mechanism. The coordination of allyl and/or benzyl groups to silver ion was also confirmed by the glycosylation in the presence of allyl benzyl ether[9] (AllOBn: Table II, entries 3–5), where an increase of AllOBn was shown to retard the glycosylation.

The coordination to silver ion may confer more electron-withdrawing character on these groups. If we assume that silver ion has much more affinity to the alkenic bond (allyl group) than to the aromatic ring (benzyl group), the following order of reactivity in the SN1 (α-glycoside-forming) reaction may be expected: **15** > **22** > **19** > **1** > **12**.

On the other hand, the relative rate of the SN2 (β-glycoside-forming) reaction can not be deduced readily,[10,11] because the electron-withdrawing substituent may cause opposite effects on two concerted processes of the SN2 reaction, namely the bond-

forming one (acceleration through decrease of electron density at the anomeric carbon atom) and the bond-cleaving one (retardation through suppression of C–Cl bond polarization). Consequently, the β:α ratio (SN2: SN1) is deduced to be controlled mainly by the order of reactivity in the SN1 reaction, and expected to be in reverse order from the one described for the SN1 reaction.

This order is in fundamental good accorded with the β:α ratios and the yields of regioisomers shown in Table IV. The remarkable discrepancy of the order observed between **12** and **1** may be explained by the through-bond effect, which suggests that the substituents at C-4 and C-6 have opposite effects[7], namely, the electron-withdrawing groups at C-4 and C-6 respectively retard and accerelate the SN1 reaction. The 6-*O*-allyl group in **12** behaves as electron-withdrawing substituent and facilitates the SN1 reaction, resulting in a lower β:α ratio than in **1**.

These results show a remarkable effect of the coordination of such substituents as the allyl group to silver ion on the regio- and stereo-selectivity of glycosylation. These glycosylations further present an interesting supporting example for the through-bond effect.

The glycosylating system described here was also applied with another glycosyl acceptor, namely, cyclohexanol. A higher temperature was required in order to obtain the same β:α ratio and yield of β-glycoside, indicating that the glycosyl acceptor **2** was more reactive than cyclohexanol, as a consequence of complexation with silver ion. It may be interesting to determine whether this kind of activation is also effective for glycosyl acceptors that are less reactive.

EXPERIMENTAL

General methods. — All melting points are uncorrected. Solutions were evaporated under diminished pressure below 50° (bath). Optical rotations were measured with a Jasco DIP-4 polarimeter. I.r. spectra were recorded with a Hitachi EPI-G2 grating spectrometer. ^{1}H-N.m.r. spectra were recorded with a JEOL PS-100 or GX-500 spectrometer in $CDCl_3$ (internal Me_4Si), unless otherwise stated. ^{13}C-N.m.r. spectra were recorded with a JEOL FX-90Q spectrometer in $CDCl_3$, unless otherwise stated. Both conventional and flash chromatography were performed on Kieselgel 60 (Merck), and preparative t.l.c. on Kieselgel 60HF (Merck).

Methyl 2,3,4,6-tetra-O-*allyl*-α-D-*mannopyranoside*[12] (**10**). — To a suspension of NaH (50%; 74 g, 1.5 mol) in dry *N*,*N*-dimethylformamide (DMF, 200 mL) was added dropwise a solution of methyl α-D-mannopyranoside (50 g, 0.26 mol) in DMF (300 mL). To the mixture stirred overnight at room temperature was added allyl chloride (84 mL, 1.5 mol). After ~12 h at room temperature, the mixture was poured into ice–water and extracted with ether. Conventional processing of the extract and flash column chromatography (10:1 hexane–acetone gave **10** quantitatively, as a syrup; $[\alpha]_D^{27}$ +51.5° (*c* 1.2, $CHCl_3$); ^{1}H-n.m.r.: δ 6.10–5.66 (m, 4 H, 4 =CH), 5.38–4.97 (m, 8 H, 4 $=CH_2$), 4.67 (d, $J_{1,2}$ 2.0 Hz, H-1), 4.44–3.90 (m, 8 H, 4 OCH_2), 3.65 (bs, 6 H, H-2,3,4,5,6a,6b), and 3.32 (s, 3 H, OMe); ^{13}C-n.m.r.: δ 99.2 (C-1).

Anal. Calc. for $C_{19}H_{30}O_6$: C, 64.37; H, 8.55. Found: C, 64.07; H, 8.53.

1-O-Acetyl-2,3,4,6-tetra-O-allyl-α-D-mannopyranose (**11**). — To a solution of **10** (317 mg, 0.89 mmol) in Ac_2O (3 mL) was added a mixture of AcOH (1 mL) and conc. H_2SO_4 (2 μL). After 130 min at room temperature, the mixture was poured into ice–water containing $NaHCO_3$, and extracted with $CHCl_3$. The residue obtained by conventional processing of the extract was purified by flash column chromatography on silica gel (15:1 hexane–EtOAc) to give **11** (284 mg, 83%) as a syrup; $[\alpha]_D^{20}$ +42.9° (*c* 1.7, $CHCl_3$); ν_{max} 1750 cm^{-1} (ester); ^{1}H-n.m.r.: δ 6.15 (d, $J_{1,2}$ 1.5 Hz, H-1), 6.20–5.75 (m, 4 H, 4 =CH), 5.44–5.08 (m, 8 H, 4 $=CH_2$), 4.50–4.00 (m, 8 H, 4 OCH_2), 3.84–3.64 (m, 6 H, H-2,3,4,5,6a,6b), and 2.08 (s, 3 H, OAc); ^{13}C-n.m.r.: δ 170.6 (C=O), and 92.3 (C-1).

Anal. Calc. for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91. Found: C, 62.47; H, 8.10.

2,3,4,6-Tetra-O-allyl-α-D-mannopyranosyl chloride (**12**). — An ice–cold solution of **11** (2.0 g, 5.6 mmol) in dry ether (40 mL) was saturated with HCl, stored for 1 h at 0°, and then diluted with ether, washed with cold water, cold aq. $NaHCO_3$, and cold water, dried, and evaporated to give **12** quantitatively as a syrup; ^{1}H-n.m.r.: δ 6.10 (d, $J_{1,2}$ 2.0 Hz, H-1), 6.1–5.71 (m, 4 H, 4 =CH), 5.46–5.06 (m, 8 H, 4 $=CH_2$), and 4.50–3.66 (m, 14 H, 4 OCH_2, H-2,3,4,5,6a,6b); ^{13}C-n.m.r.: δ 91.8 (C-1).

Methyl 2,3,4,6-tetra-O-propyl-α-D-mannopyranoside[12] (**13**). — A solution of **10** (497 mg, 1.40 mmol) in EtOH (5 mL) containing 1 drop of AcOH was hydrogenolyzed in the presence of 10% Pd–C for 2.5 h. Conventional processing and no further purification afforded **13** quantitatively; $[\alpha]_D^{29}$ +40.2° (*c* 1.8, $CHCl_3$); ^{1}H-n.m.r.: δ 4.76 (s, H-1), 3.94–3.26 (m, 14 H, 4 OCH_2, H-2,3,4,5,6a,6b), 3.38 (s, 3 H, OMe), 1.84–1.34 (m, 8 H, 4 CCH_2), and 1.08–0.80 (m, 12 H, 4 CMe); ^{13}C-n.m.r.: δ 99.3 (C-1).

Anal. Calc. for $C_{19}H_{38}O_6$: C, 62.94; H, 10.59. Found: C, 62.86; H, 10.61.

1-O-Acetyl-2,3,4,6-tetra-O-propyl-α-D-mannopyranose (**14**). — To a solution of **13** (501 mg, 1.38 mmol) in Ac_2O (9 mL) was added a mixture of AcOH (3 mL) and conc. H_2SO_4 (6 μL). After 40 min at room temperature, this mixture was processed in the same manner as described for **11** to give **14** quantitatively; $[\alpha]_D^{27}$ +46.3° (*c* 1.9, $CHCl_3$); ν_{max} 1740 cm^{-1} (ester); ^{1}H-n.m.r.: δ 6.16 (d, $J_{1,2}$ 1.8 Hz, H-1), 3.96–3.28 (m, 14 H, 4 OCH_2, H-2,3,4,5,6a,6b), 2.09 (s, 3 H, OAc), 1.84–1.40 (m, 8 H, 4 CCH_2), and 1.08–0.80 (m, 12 H, 4 CMe); ^{13}C-n.m.r.: δ 169.1 (C=O), and 92.5 (C-1).

Anal. Calc. for $C_{20}H_{38}O_7$: C, 61.50; H, 9.83. Found: C, 61.35; H, 9.90.

2,3,4,6-Tetra-O-propyl-α-D-mannopyranosyl chloride (**15**). — An ice-cold solution of **14** (1.95 g, 4.99 mmol) in dry ether (50 mL) was saturated with HCl, stored for 45 min at 0°, and processed as described for **12** to give **15** quantitatively; ^{1}H-n.m.r.: δ 6.07 (d, $J_{1,2}$ 2.0 Hz, H-1), 3.96–3.22 (m, 14 H, 4 OCH_2, H-2,3,4,5,6a,6b), 1.80–1.36 (m, 8 H, 4 CCH_2), and 1.08–0.80 (m, 12 H, 4 CMe); ^{13}C-n.m.r.: δ 92.3 (C-1).

Methyl 2-O-allyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**17**). — To a suspension of NaH (50%, 716 mg, 14.9 mmol) in dry DMF (3 mL) was added dropwise a solution of methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside[13] (**16**) (5.33 g, 11.5 mmol) in DMF (8 mL). To the mixture stirred for 10 h at room temperature was added allyl chloride (1.2 mL, 14.7 mmol). After stirring for 2 h, the mixture was processed as described for **10** to give **17** (4.88 g, 84%) as a syrup; $[\alpha]_D^{29}$ +39.5° (*c* 1.6, $CHCl_3$);

^{1}H-n.m.r.: δ 7.4–7.0 (m, 15 H, 3 Ph), 6.07–5.68 (m, 1 H, =CH), 5.36–5.04 (m, 2 H, $=CH_2$), 4.84, 4.59 (ABq, J 11.0 Hz, $PhCH_2$), 4.70 (d, $J_{1,2}$ 1.8 Hz, H-1), 4.63 (s, 2 H, $PhCH_2$), 4.63, 4.44 (ABq, J 10.5 Hz, $PhCH_2$), 4.20–4.08 (m, 2 H, OCH_2), 3.94–3.60 (m, 6 H, H-2,3,4,5,6a,6b), and 3.32 (s, 3 H, OMe); ^{13}C-n.m.r.: δ 99.1 (C-1).

Anal. Calc. for $C_{31}H_{36}O_6$: C, 73.77; H, 7.20. Found: C, 73.42; H, 7.03.

1-O-Acetyl-2-O-allyl-3,4,6-tri-O-benzyl-α-D-mannopyranose (**18**). — To a solution of **17** (548 mg, 1.08 mmol) in Ac_2O (12 mL) and AcOH (20 mL) was added a mixture of AcOH (8 mL) and conc. H_2SO_4 (16 μL). After 50 min at room temperature, the mixture was processed as described for **11** to give **18** in 66% yield as a syrup; $[\alpha]_D^{28}$ +46.4° (c 1.1, $CHCl_3$); ν_{max} 1750 cm^{-1} (ester); ^{1}H-n.m.r.: δ 7.4–7.0 (m, 15 H, 3 Ph), 6.06 (d, $J_{1,2}$ 2.0 Hz, H-1), 6.08–5.68 (m, 1 H, =CH), 5.39–5.05 (m, 2 H, $-CH_2$), 5.02–4.38 (m, 6 H, 3 $PhCH_2$), 4.32–4.08 (m, 2 H, OCH_2), 4.06–3.44 (m, 6 H, H-2,3,4,5,6a,6b), and 1.98 (s, 3 H, OAc); ^{13}C-n.m.r.: δ 168.7 (C=O) and, 92.1 (C-1).

Anal. Calc. for $C_{32}H_{36}O_7$: C, 72.15; H, 6.83. Found: C, 72.02; H, 6.71.

2-O-Allyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl chloride (**19**). — The same processing of **18** as described for **12** followed by purification on a column of silica gel (12:1 hexane–EtOAc) gave **19** in 63% yield; ^{1}H-n.m.r.: δ 7.4–7.0 (m, 15 H, 3 Ph), 6.06 (d, $J_{1,2}$ 1.8 Hz, H-1), 6.08–5.66 (m, 1 H, =CH), 5.37–5.07 (m, 2 H, $=CH_2$), 4.84, 4.48 (ABq, J 10.5 Hz, $PhCH_2$), 4.67 (s, 2 H, $PhCH_2$), 4.62, 4.44 (ABq, J 12.0 Hz, $PhCH_2$), and 4.24–3.66 (m, 8 H, OCH_2, H-2, 3,4,5,6a,6b); ^{13}C-n.m.r.: δ 91.8 (C-1).

*1-O-Acetyl-2,3,4,6-tetra-O-benzyl-α-D-*mannopyranose (**21**). — To a solution of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside[14] (**20**, 0.30 g, 0.54 mmol) in Ac_2O (4.5 mL) and AcOH (7.5 mL) was added a mixture of AcOH (3 mL) and conc. H_2SO_4 (6 μL). After 80 min at room temperature, this mixture was processed as described for **11** to give **21** in 83% yield as a syrup; $[\alpha]_D^{27}$ + 29.3° (c, 1.3 $CHCl_3$); ν_{max} 1740 cm^{-1} (ester); ^{1}H-n.m.r.: δ 7.50–6.92 (m, 20 H, 4 Ph), 6.18 (d, $J_{1,2}$ 2.0 Hz, H-1), 5.04–4.43 (m, 8 H, 4 $PhCH_2$), 4.36–3.68 (m, 6 H, H-2,3,4,5,6a,6b), and 1.98 (s, 3 H, OAc); ^{13}C-n.m.r.: δ 168.9 (C=O), and 91.9 (C-1).

Anal. Calc. for $C_{36}H_{38}O_7$: C, 74.19; H, 6.59. Found: C, 74.31; H, 6.61.

*2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl chloride** (**22**). — The same processing of **21** as described for **12** followed by purification on a column of silica gel (10:1 hexane–EtOAc) gave **22** in 55% yield; ^{1}H-n.m.r.: δ 7.40–7.06 (m, 20 H, 4 Ph), 6.04 (d, $J_{1,2}$ 2.0 Hz, H-1), 4.86, 4.50 (ABq, J 11.0 Hz, $PhCH_2$), 4.66 (s, 2 H, $PhCH_2$), 4.58 (d, 2 H, J 1.0 Hz, $PhCH_2$), 4.63, 4.44 (ABq, J 12.5 Hz, $PhCH_2$), and 4.24–3.60 (m, 6 H, H-2,3,4,5,6a,6b); ^{13}C-n.m.r.: δ 91.7 (C-1).

Standard procedure[1,2] *for glycosylation of* **2** *with substituted* α-D-*mannopyranosyl chlorides* (**1**, **12**, **15**, **19** and **22**). — To a suspension of **2** (0.35 mmol) in dry tetrahydrofuran (THF) or other solvents (20 mL) was added, in the dark, dry silver triflate (2.5 mmol) and additives, if needed. Then to the solution kept at the specified temperature, was added dropwise a solution of the glycosyl chloride (0.42 mmol) in dry THF or other dry solvents (4 mL) during 5 min. After 30 min or 5 h, the mixture was poured into an

* Preparation from the corresponding 1-*O*-*p*-nitrobenzoyl chloride has been reported[15].

ice–cold 1:1 mixture of saturated aq. $NaHCO_3$ and NaCl, filtered, and extracted with $CHCl_3$. The residue obtained by usual processing of the extract was fractionated by flash chromatography (hexane–EtOAc) to give anomeric and/or regioisomeric mixture of pseudodisaccharides, whose yields and ratios are given in the tables. In the reactions at higher concentration (Table 1, entries 9 and 10), the total amount of solvent was 9 and 2.4 mL, respectively. In most cases beside the pseudo-disaccharides, by-products derived from the glycosyl donor, were also obtained. For instance, the following by products **5–8**, were derived from **1**.

2,3,4-Tri-O-*allyl-6*-O-*benzyl*-α-D-*mannopyranose* (**5**): $[\alpha]_D^{20}$ +28.1° (*c* 0.9, $CHCl_3$); ν_{max} 3400 cm^{-1} (OH); ^{1}H-n.m.r.: δ 7.4–7.2 (m, 5 H, Ph), 6.1–5.6 (m, 3 H, 3 =CH), 5.4–5.0 (m, 7 H, H-1, 3 $=CH_2$), 4.50, 4.48 (ABq, *J* 12.0 Hz, $PhCH_2$), and 4.4–3.3 (m, 12 H, H-2,3,4,5,6a,6b, 3 OCH_2); ^{13}C-n.m.r.: δ 92.9 (C-1).

Anal. Calc. for $C_{22}H_{30}O_6$: C, 67.66; H, 7.76. Found: C, 67.48; H, 7.65.

2,3,4-Tri-O-*allyl-6*-O-*benzyl*-α-D-*mannopyranosyl 2,3,4-tri*-O-*allyl-6*-O-*benzyl*-α-D-*mannopyranoside* (**6**): $[\alpha]_D^{20}$ +57.5° (*c* 1.1, $CHCl_3$); ^{1}H-n.m.r.: δ 7.32 (m, 10 H, Ph), 6.16–5.64 (m, 6 H, 6 =CH), 5.42–5.02 (m, 14 H, H-1,1′, 6–CH_2), 4.64, 4.52 (ABq, *J* 12.0 Hz, 2 $PhCH_2$), 4.44–3.88 (m, 12 H, 6 OCH_2), and 3.88–3.40 (m, 12 H, H-2,3,4,5,6a,6b,2′,3′,4′,5′,6′a,6′b); ^{13}C-n.m.r. δ 93.5 (C-1, C-1′).

Anal. Calc. for $C_{44}H_{58}O_{11}$: C, 69.26; H, 7.68. Found: C, 69.22; H, 7.65.

11-Hydroxy-6-oxaundecyl 2,3,4-tri-O-*allyl-6*-O-*benzyl*-α-D-*mannopyranoside* (**7**): $[\alpha]_D^{14}$ +39.9° (*c* 0.93, $CHCl_3$); ν_{max} 3450 cm^{-1} (OH); ^{1}H-n.m.r.: δ 7.30 (bs, 5 H, Ph), 6.15–5.60 (m, 3 H, 3 –CH), 5.42–4.96 (m, 6 H, 3 –CH_2), 4.81 (s, H-1), 4.64, 4.52 (ABq, *J* 12.0 Hz, $PhCH_2$), 4.40–3.80 (m, 6 H, 3 OCH_2), 3.84–3.20 (m, 14 H, H-2,3,4,5,6a,6b, 4 OCH_2), 2.54 (broad, 1 H, OH), and 1.8–1.5 (m, 8 H, 4 CCH_2); ^{13}C-n.m.r.: δ 98.1 (C-1).

Anal. Calc. for $C_{30}H_{46}O_8$: C, 67.38; H, 8.69. Found: C, 67.09; H, 8.93.

11-Chloro-6-oxaundecyl 2,3,4-tri-O-*allyl-6*-O-*benzyl*-α-D-*mannopyranoside* (**8**): $[\alpha]_D^{20}$ +32.0° (*c* 1.0, $CHCl_3$); ^{1}H-n.m.r.: δ 7.5–7.2 (m, 5 H, Ph), 6.2–5.7 (m, 3 H, 3 =CH), 5.5–5.0 (m, 6 H, 3 $=CH_2$), 4.83 (s, H-1), 4.62, 4.58 (ABq, *J* 12.0 Hz, $PhCH_2$), 4.4–3.3 (m, 18 H, H-2,3,4,5,6a,6b, 6 OCH_2), 3.55 (t, 2 H, *J* 6.2 Hz, CH_2Cl), and 2.0–1.5 (m, 8 H, 4 CCH_2); ^{13}C-n.m.r.: δ 98.1 (C-1), and 44.9 (CH_2 Cl); Beilstein reaction positive.

5-O-(*2,3,4,6-Tetra*-O-*allyl*-β-D-*mannopyranosyl*)-*1,3-di*-N-*benzyloxycarbonyl-2-deoxystreptamine* (**23aβ**): m.p. 182–183° (from hexane–acetone), $[\alpha]_D^{25}$ −10.5° (*c* 0.9, $CHCl_3$); ν_{max} 3700–3150 (OH and NH), and 1690 cm^{-1} (urethane); ^{1}H-n.m.r.: δ 7.4–7.1 (m, 10 H, 2 Ph), 6.10–5.60 (m, 4 H, 4 =CH), 5.38–4.90 (m, 14 H, 4 –CH_2, 2 $PhCH_2$, 2 NH), 4.57 (s, H-1′), 4.32–3.84 (m, 9 H, 4 OCH_2, H-5), 3.80–3.18 (m, 11 H, H-1,3,4,6,2′,3′,4′,5′,6′a,6′b, one of OH), 2.52 (m, H-2*e*), and 1.32 (m, H-2*a*); ^{13}C-n.m.r.: δ 156.8, 156.3 (2 s, C=O) and 102.1 (d, $J_{C\text{-}1',H\text{-}1'}$ 157.1 Hz, C-1′).

Anal. Calc. for $C_{40}H_{52}N_2O_{12}$: C, 63.80; H, 6.98; N, 3.72. Found: C, 64.03; H, 7.28; N, 3.49.

5-O-(*2,3,4,6-Tetra*-O-*allyl*-α-D-*mannopyranosyl*)-*1,3-di*-N-*benzyloxycarbonyl-2-deoxystreptamine* (**23aα**): $[\alpha]_D^{23}$ +23.9° (*c* 0.8, $CHCl_3$); ν_{max} 3600–3150 (OH and NH), 1730 and 1700 cm^{-1} (urethane); ^{1}H-n.m.r.: δ 7.4–7.1 (m, 10 H, 2 Ph), 6.10–5.64 (m, 4 H, 4 =CH), 5.40–4.90 (m, 15 H, 4 $=CH_2$, 2 $PhCH_2$, 2 NH, H-1′), 4.40–3.16 (m, 21 H, 4

OCH_2, H-1,3,4,5,6,2′,3′,4′,5′,6′a,6′b, 2 OH), 2.48 (m, H-2*e*), and 1.24 (m, H-2*a*); ^{13}C-n.m.r.: δ 156.7, 156.3 (2 s, C=O), and 100.0 (d, $J_{C\text{-}1',H\text{-}1'}$ 169.2 Hz, C-1′).

Anal. Calc. for $C_{40}H_{52}N_2O_{12}$: C, 63.80; H, 6.98; N, 3.72. Found: C, 63.54; H, 7.03; N, 3.33.

*5-O-(2-O-Allyl-3,4,6-tri-O-benzyl-β-*D*-mannopyranosyl)-1,3-di-*N*-benzyloxycarbonyl-2-deoxystreptamine* (**23bβ**): m.p. 243–245° (from hexane–acetone), $[\alpha]_D^{26}$ −33.0° (*c* 1.0, pyridine); ν_{max} 3650–3100 (OH and NH), and 1680 cm^{-1} (urethane); ^{1}H-n.m.r.: δ 7.6–7.0 (m, 25 H, 5 Ph), 6.20–5.76 (m, 1 H, =CH), 5.40–3.20 (m, 30 H, –CH_2, 5 $PhCH_2$, 2 NH, OCH_2, 2 OH, H-1,3,4,5,6,1′,2′,3′,4′,5′,6′a,6′b), 2.55 (m, H-2*e*), and 1.25 (m, H-2*a*); ^{13}C-n.m.r.: δ 156.9, 156.3 (2 s, C=O), and 102.1 (d, $J_{C\text{-}1',H,1'}$ 159.3 Hz, C-1′).

Anal. Calc. for $C_{52}H_{58}N_2O_{12}$: C, 69.15; H, 6.49; N, 3.10. Found: C, 68.97; H, 6.45; N, 3.13.

*5-O-(2-O-Allyl-3,4,6-tri-O-benzyl-α-*D*-mannopyranosyl)-1,3-di-*N*-benzyloxycarbonyl-2-deoxystreptamine* (**23bα**): $[\alpha]_D^{25}$ +20.3° (*c* 1.3, $CHCl_3$), ν_{max} 3600–3150 (OH and NH) and 1690 cm^{-1} (urethane); ^{1}H-n.m.r.: δ 7.4–7.0 (m, 25 H, 5 Ph), 6.12–5.66 (m, 1 H, =CH), 5.40–3.10 (m, 30 H, $=CH_2$, 5 $PhCH_2$, 2 NH, OCH_2, 2 OH, H-1,3,4,5,6,1′,2′,3′,4′,5′,6′a,6′b), 2.46 (m, H-2*e*), and 1.25 (m, H-2*a*); ^{13}C-n.m.r.: δ 156.7, 156.3 (2 s, C=O) and 100.0 (d, $J_{C\text{-}1',H\text{-}1'}$ 169.2 Hz, C-1′).

Anal. Calc. for $C_{52}H_{58}N_2O_{12}$: C, 69.15; H, 6.49; N, 3.10. Found: C, 68.99; H, 6.63; N, 2.72.

*5-O-(2,3,4,6-Tetra-O-benzyl-β-*D*-mannopyranosyl)-1,3-di-*N*-benzyloxycarbonyl-2-deoxystreptamine* (**23cβ**): m.p. 237–238.5° (from hexane–EtOAc), $[\alpha]_D^{25}$ +5.5° (*c* 1.37, $CHCl_3$); ^{1}H-n.m.r.: δ 7.4–7.0 (m, 30 H, 6 Ph), 5.10–4.28 (m, 15 H, 6 $PhCH_2$, 2 NH, H-1′), 4.08–3.14 (m, 13 H, H-1,3,4,5,6,2′,3′,4′,5′,6′a,6′b, 2 OH), 2.54 (m, H-2*e*), and 1.26 (m, H-2*a*); ^{13}C-n.m.r.: δ 156.9, 156.3 (2 s, C=O), and 102.3 (d, $J_{C\text{-}1',H,1'}$ 154.9 Hz, C-1′).

Anal. Calc. for $C_{56}H_{60}N_2O_{12}$: C, 70.56; H, 6.36; N, 2.94. Found: C, 70.35; H, 6.33; N, 2.97.

*5-O-(2,3,4,6-Tetra-O-benzyl-α-*D*-mannopyranosyl)-1,3-di-*N*-benzyloxycarbonyl-2-deoxystreptamine* (**23cα**): $[\alpha]_D^{23}$ +17.8° (*c* 1.7, $CHCl_3$), ν_{max} 3600–3150 (OH and NH) and 1700 cm^{-1} (urethane); ^{1}H-n.m.r.: δ 7.4–7.0 (m, 30 H, 6 Ph), 5.16–4.20 (m, 15 H, 6 $PhCH_2$, 2 NH, H-1′), 4.20–3.04 (m, 13 H, H-1,3,4,5,6,2′,3′,4′,5′,6′a,6′b, 2 OH), 2.38 (m, H-2*e*), and 1.20 (m, H-2*a*); ^{13}C-n.m.r.: δ 156.8, 156.4 (2 s, C=O), and 99.8 (d, $J_{C\text{-}1',H\text{-}1'}$ 169.2 Hz, C-1′).

Anal. Calc. for $C_{56}H_{60}N_2O_{12}$: C, 70.56; H, 6.36; N, 2.94. Found: C, 70.31; H, 6.20; N, 2.95.

*1,3-Di-*N*-benzyloxycarbonyl-5-O-(2,3,4,6-tetra-O-propyl-β-*D*-mannopyranosyl)-2-deoxystreptamine* (**23dβ**): m.p. 221.5–222° (from hexane–acetone), $[\alpha]_D^{24}$ −15.6° (*c* 1.1, $CHCl_3$); ν_{max} 3700–3150 (OH and NH), and 1690 cm^{-1} (urethane); ^{1}H-n.m.r.: δ 7.40–7.20 (bs, 10 H, 2 Ph), 5.20–5.00 (m, 6 H, 2 $PhCH_2$, 2 NH), 4.65 (s, H-1′), 3.91–3.21 (m, 20 H, 4 OCH_2, H-1,3,4,5,6,2′,3′,4′,5′,6′a,6′b, one of OH), 2.64–2.20 (m, 3 H, H-2*e*, one of OH), 1.83–1.20 (m, 9 H, 4 CCH_2, H-2*a*), and 1.09–0.80 (m, 12 H, 4 CMe); ^{13}C-n.m.r.: δ 156.9, 156.3 (2 s, C=O), and 102.0 (d, $J_{C\text{-}1',H\text{-}1'}$ 159.3 Hz, C-1′).

Anal. Calc. for $C_{40}H_{60}N_2O_{12}$: C, 63.13; H, 7.96; N, 3.68. Found: C, 62.85; H, 7.73; N, 3.63.

*1,3-Di-*N*-benzyloxycarbonyl-5-*O*-(2,3,4,6-tetra-*O*-propyl-α-*D*-mannopyranosyl)-2-deoxystreptamine* (**23dα**): $[\alpha]_D^{23}$ +27.3° (*c* 0.6, $CHCl_3$); ν_{max} 3600–3200 (OH and NH), 1730 and 1700 cm^{-1} (urethane); ^{1}H-n.m.r.: δ 7.4–7.1 (m, 10 H, 2 Ph), 5.12–4.86 (m, 7 H, 2 $PhCH_2$, 2 NH, H-1′), 4.20–3.10 (m, 21 H, 4 OCH_2, H-1,3,4,5,6,2′,3′,4′,5′,6′a,6′b, 2 OH), 2.46 (m, H-2*e*), 1.78–1.24 (m, 9 H, 4 CCH_2, H-2*a*), and 1.08–0.72 (m, 12 H, 4 CMe); ^{13}C-n.m.r.: δ 156.6, 156.3 (2 s, C=O), 100.1 (d, $J_{C\text{-}1',H\text{-}1'}$ 169.2 Hz, C-1′).

Anal. Calc. for $C_{40}H_{60}N_2O_{12}$: C, 63.13; H, 7.96; N, 3.68. Found: C, 62.96; H, 7.98; N, 3.76.

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REFERENCES

1 J. Yoshimura, S. Horito, J. Tamura, and H. Hashimoto, *Chem. Lett.*, (1985) 1335–1338.
2 J. Tamura, S. Horito, H. Hashimoto, and J. Yoshimura, *Carbohydr. Res.*, 174 (1988) 181–199.
3 S. Umezawa and Y. Ito, *Bull. Chem. Soc. Jpn.*, 34 (1961) 1540–1541.
4 E. Cuny and F. W. Lichtenthaler, *Int. Carbohydr. Symp., 12th*, Utrecht, July 1984, Abstr. 131.
5 H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, 21 (1982) 155–173.
6 J. Montreuil, *Adv. Carbohydr. Chem. Biochem.*, 37 (1980) 157–223.
7 C. A. A. van Boeckel, T. Beetz, and S. F. van Aelst, *Tetrahedron*, 40 (1984) 4097–4107.
8 H. Paulsen and E. Sumfleth, *Chem. Ber.*, 113 (1980) 1723–1745.
9 W. H. Watanabe, L. E. Conlon, and J. C. H. Hwa, *J. Org. Chem.*, 23 (1958) 1666–1668.
10 J. A. L. Jorge, N. Z. Kiyan, Y. Miyata, and J. Miller, *J. Chem. Soc., Perkin Trans*, II (1981) 100–103.
11 V. P. Vitullo, J. Grabouski, and S. Sridharan, *J. Chem. Soc., Chem. Commun.*, (1981) 737–738.
12 B. I. Mikhant'ev, V. L. Lapenko, and V. E. Sopina, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.* 12 (1969) 603–605.
13 A. J. Varma and C. Schuerch, *J. Org. Chem.*, 46 (1981) 799–803.
14 S. Koto, N. Morishima, Y. Miyata, and S. Zen, *Bull. Chem. Soc. Jpn.*, 49 (1976) 2639–2640.
15 E. F. Hounsell, M. B. Jones, and J. A. Wright, *Carbohydr. Res.*, 65 (1978) 201–207.