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Benzeneselenenyl triflate as an activator of thioglycosides for glycosylation reactions*

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ABSTRACT

A new method for the activation of thioglycosides was developed by use of benzeneselenenyl triflate (PhSeOTf), which, upon reaction with either a primary or secondary sugar HO-group, afforded *O*-glycosides under extremely mild reaction conditions. The reaction was applicable to various 1-thiohexosides **2-6** as well as to a 2-thioglycoside **20** derived from *N*-acetylneuraminic acid (NeuAc).

INTRODUCTION

The search for new glycosylation reactions has recently become a subject of active research[1], especially since the biomedical potential of glycoconjugates has been recognized[2]. These molecules often carry complex glycan chains composed of a variety of sugar residues with diverse types of interglycosidic linkages. Because of such complexity, it seems to be extremely difficult to find a general solution, based on a single concept, which is applicable to all of the situations encountered in oligosaccharide synthesis. However, recent investigations have revealed the promising features of novel glycosyl donors such as fluorides[3], trichloroacetimidates[4], and 1-thioglycosides[5–15], among other compounds. These substances are relatively stable and can be prepared under mild conditions. Such properties make these methods clearly distinct from the conventional Koenigs–Knorr type process[16], which usually requires the preparation of sensitive halides under rather harsh conditions. Furthermore, improvement in yield and stereoselectivity has quite often been achieved using such modern techniques.

Among these, 1-thioglycosides possess an obvious advantage, particularly in view of synthetic strategy, because they are particularly insensitive to usual protection–deprotection conditions except catalytic hydrogenolysis. In addition, the activation of 1-thioglycosides is possible under specific neutral conditions which do not affect most other functional groups. Accordingly, an *S*-glycosidic linkage can be regarded as a

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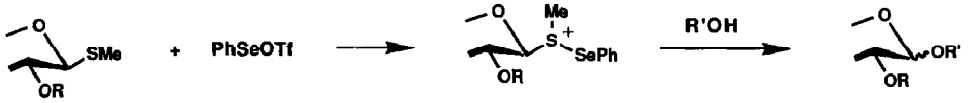
masked reducing end, which is concurrently set armed as an electrophilic entity. In consequence, 1-thioglycoside methodology is an extraordinarily attractive and logical choice for the block synthesis of complex glycan chains.

RESULTS AND DISCUSSION

As a promotor of 1-thioglycosides, thiophilic heavy-metal salts have been investigated. These include Hg(II) (ref. 5), Cu(II) (ref. 6), Ag(I) (ref. 7), and Pb(II) (ref. 7). Although these methods are conceptually quite reasonable, they have not yet found widespread use in the field of oligosaccharide synthesis. Recently, we succeeded in finding a remarkably versatile variant which makes use of $(Bu_4N)_2CuBr_4$ together with co-activators such as AgOTf, $HgBr_2$, and Bu_4NBr (ref 8). By means of this device, we have completed syntheses of complex glycosphingolipids in a highly efficient and stereoselective manner[9]. On the other hand, several recent reports have demonstrated that soft electrophiles such as NBS (ref. 10), methyl triflate[11], dimethyl(methylthio)-sulfonium triflate (DMTST) (ref. 12), aryl sulfenates[13], $NOBF_4$ (ref. 14), and SO_2Cl_2–CF_3SO_3H (ref. 15) are effective as activating agents, among which, DMTST seems to be most promising thus far.

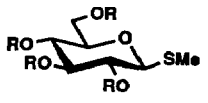
As an extention of this concept, we describe here the use of so called "super-electrophilic" benzeneselenenyl triflate (PhSeOTf) for the activation of thioglycosides. PhSeOTf, which can be easily generated *in situ* from benzeneselenenyl chloride and silver triflate[17], was recently introduced as a selenocyclization reagent. Considering the "soft" nature of a selenium atom, along with the excellent leaving ability of the triflate group, it was anticipated that PhSeOTf would interact readily with a thioglycoside to generate the cationic species **1**, which, in turn, in the presence of a glycosyl acceptor, would afford the *O*-glucoside. As described below, this expectation was realized, and various *O*-glycosides were obtained under extremely mild conditions. After the preliminary account of this work[18] was published, a similar approach, which makes use of alkylsulfenyl triflate (RSOTf), was reported by Garegg and co-workers[19].



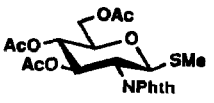
Scheme 1. **1**

Reactions were carried out using 1-thioglycosides **2** (ref. 13), **3** (ref. 20), **4** (ref. 12), **5** (ref. 21), and **6** (ref. 13) and glycosyl acceptors **7** (ref. 22), **8**, **9** (ref. 23), **10** (ref. 24), and **11** (ref. 25) (Scheme 2, Table I). First of all, the benzyl-protected glucose derivative **2** was examined as a glycosyl donor. In order to look into the intrinsic stereochemical bias offered by the compound, toluene was chosen as a relatively nonpolar solvent. The reaction proceeded with remarkable ease and was complete almost instantaneously, even at $-40°$. Interestingly, the major products were revealed to be the β-isomer (entries

1 and 2, Table I). Although a solid rationale to explain this β-selectivity is yet to be ascertained, the following explanation seems appropriate in view of the reverse anomeric effect[29]. Thus, the sulfonium salt **1**, which is first generated, subsequently rearranges either intra- or intermolecularly into the more stable selenonium salt **19**, which then predominantly reacts in an α-form with inversion of configuration to afford the β-D-glycoside. Unfortunately, this stereodirecting effect turned out to be rather sensitive to a



2: R=Bn
3: R=Ac
4: R=Bz



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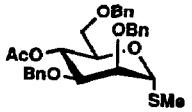

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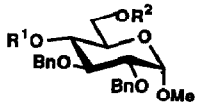
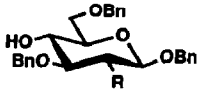
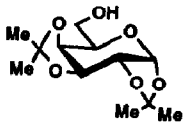


7: R^1=Bn, R^2=H
8: R^1=H, R^2=$SiPh_2{}^tBu$



9: R=OBn
10: R=NPhth



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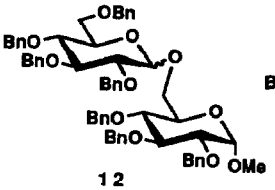

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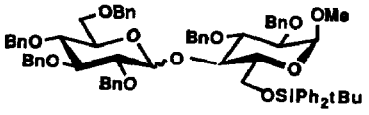

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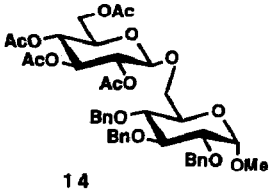

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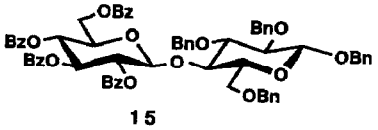

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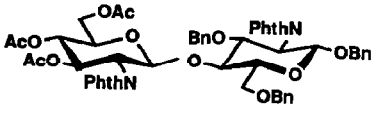

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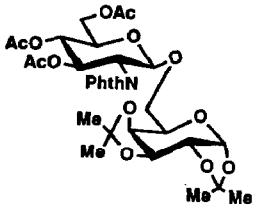

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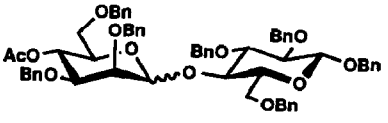

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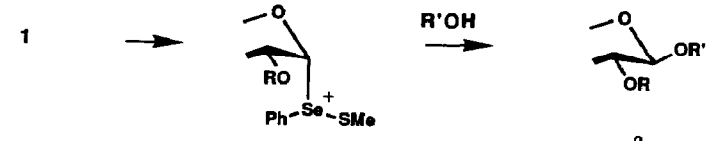


1 19 β

Scheme 2.

TABLE I

Results of glycosylation reactions

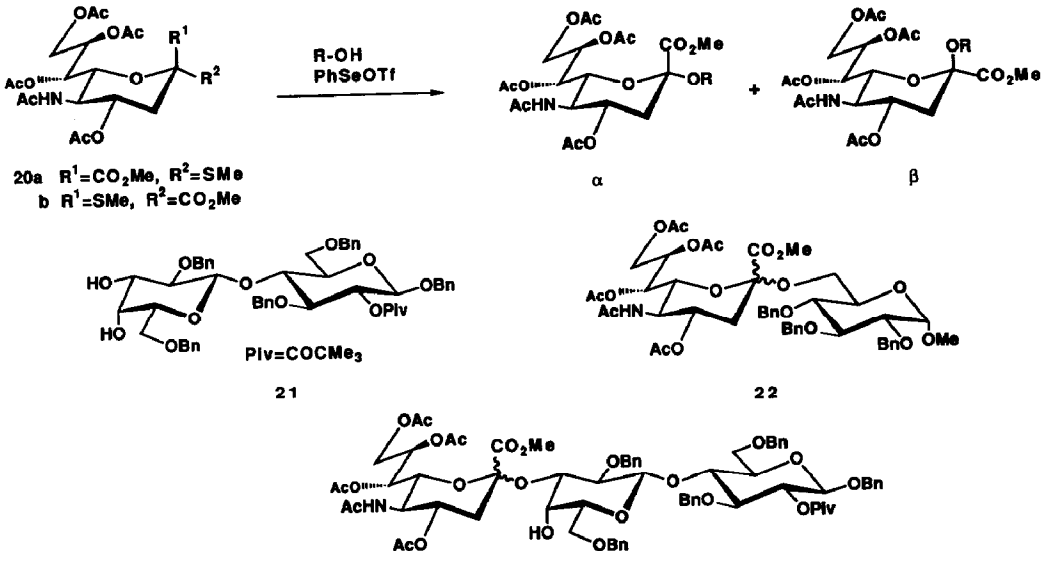
Entry	*Donor*	*Acceptor*	*Solvent*	*Temp. (°)*	*Time (min.)*	*Product*	*Yield (%)*	*β:α*
1	**2**	**7**	toluene	−40	30	**12**[a]	91	88:12
2	**2**	**8**	toluene	−40	60	**13**[b]	74	75:25
3	**3**	**7**	$(CH_2Cl)_2$	0	10	**14**[c]	52	
4	**4**	**9**	$(CH_2Cl)_2$	0	10	**15**[d]	96	
5	**5**	**10**	toluene	−40∼0	60	**16**	91	
6	**5**	**11**	toluene	−40	60	**17**	61	
7	**6**	**9**	toluene	−40	30	**18**[e]	99	16:84

[a] See ref. 26. [b] See ref. 13. [c] See ref. 27. [d] See ref. 12. [e] See ref. 28.

structural deviation, and, to our disappointment, the 1-thiomannoside **6** afforded **18** mainly as an α-D-isomer (entry 7).

On the other hand, 1-thioglycosides **3**, **4**, and **5**, which carry a 1,2-*trans* directing substituent, such as an acyloxy or a phthalimido group, exclusively afforded, as a matter of course, the corresponding β-D-glycosides (entries 3–6). As was frequently pointed out[30], the tetra-*O*-benzoyl derivative **4** afforded a much better result compared with the tetra-*O*-acetyl counterpart **3**. The relatively low yield observed in entry **6** (Table I) might be due to the sensitivity of the acetonide group, since a substantial amount of **5** was recovered while all of the acceptor **11** was consumed.

Considerable effort has been devoted toward developing an effective glycosylation for *N*-acetylneuraminic acid (NeuAc)[31–37]. Being encouraged by the high efficiency of PhSeOTf as an activator, we next examined the reactions of 2-thioglycoside **20** as a NeuAc donor. Recently, work by Hasegawa and co-workers has revealed that the DMTST-promoted reaction of **20a** is superior to conventionally utilized protocol, and a high stereoselectivity, as well as a reasonable yield, was realized under properly established reaction conditions[35]. Our results from the action of PhSeOTf on **20** are summarized in Table II. All reactions proceeded smoothly at low temperature. When 1,2-dichloroethane was used as a solvent, the β-D-glycoside was predominantly obtained, while the stereochemical course could be biased in an α-selective manner by utilizing acetonitrile as the reaction medium. This observed solvent effect is in good agreement with the result reported for DMTST-promoted reactions. A moderate level of α-selectivity was retained in the reaction with the secondary alcohol **21** (ref. 38) (entry 4). The product **23** has already been transformed into ganglioside GM_3 in a high overall yield[39] by taking advantage of the pivaloyl group at the *O*-2a position[40]. Also to be noted is that both the α- and β-anomer of **20** reacted with comparable efficiency. Although we have recently developed a general method for the highly efficient and stereoselective glycosylation of NeuAc[36], the thioglycoside method may be regarded as a valuable alternative, at least for application to relatively simple systems.



Scheme 3.

TABLE II

Reactions of 2-thioglycoside **20**[a]

Entry	**20**	*Acceptor*	*Solvent*	*Temp. (°)*	*Product*	*Yield (%)*	*α:β*
1	**20a**	**7**	$(CH_2Cl)_2$	−23	**22**[b]	63	16:84
2	**20a**	**7**	MeCN	−35	**22**	78	82:18
3	**20b**	**7**	MeCN	−35	**22**	79	78:22
4	**20a**	**21**	MeCN	−35	**23**	25	81:19

[a]Time of reaction = 30 min for each example. [b]See ref. 33.

In summary, PhSeOTf has been shown to play the role of an extremely powerful promotor of thioglycosides. The practicality of this method has been demonstrated by our successful synthesis of cyclomannohexaose, the manno-isomer of α-cyclodextrin[41], by using the PhSeOTf-promoted cyclization as the key transformation. On account of its high efficiency and operational simplicity, the present method should find further practical uses in oligosaccharide synthesis.

EXPERIMENTAL

General. — Melting points were determined with a Büchi 510 melting-point apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter, for solutions in $CHCl_3$ at 20 ± 3°. Column chromatography was performed on Silica Gel-60 (E. Merck, 70–230 mesh A.S.T.M.). Analytical

t.l.c. was performed on Silica Gel-60 F_{254} (E. Merck). Preparative t.l.c. was performed on plates (20 × 20 cm) coated with a 0.5 mm thickness of Silica Gel-60 (E. Merck). ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ with either a JEOL GX400 (400 MHz) or GX500 (500 MHz) spectrometer, unless noted otherwise. The δ-values are expressed in p.p.m. downfield from the signal for internal Me_4Si. All reactions were performed under an atmosphere of dry nitrogen. 1,2-Dichloroethane and acetonitrile were distilled from CaH_2. *N,N*-Dimethylformamide was distilled from P_2O_5 under reduced pressure. Powdered 3A or 4A molecular sieves were purchased from Nakarai Chemicals and activated at 180° under vacuum prior to use. All other solvents and reagents were used as received.

*Methyl 2,3-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-*D*-glucopyranoside* (**8**). — To a stirred solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (1.912 g, 5.106 mmol) and imidazole (550 mg, 8.08 mmol) in *N,N*-dimethylformamide (30 mL) was added dropwise *tert*-butyldiphenylsilyl chloride (1.50 mL, 5.77 mmol) at 0°. The mixture was stirred at 0° to room temperature for 18 h, diluted with ether (150 mL), and washed with water (100 mL). The aqueous layer was extracted with ether (100 mL), and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residue was purified by chromatography on silica gel using 6:1 hexane–AcOEt to afford compound **8** (2.951 g, 94%): $[\alpha]_D$ +13.1° (*c* 1.6); R_f 0.52 (4:1 hexane–AcOEt); ^{1}H-n.m.r. data: δ 4.674 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 3.870 (dd, 1 H, $J_{5,6}$ 3.7, $J_{6,6}$ 10.8 Hz, H-6), 3.820 (dd, 1 H, $J_{5,6}$ 4.6, $J_{6,6}$ 10.8 Hz, H-6'), 3.798 (dd, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 8.3 Hz, H-3), 3.657 (m, 1 H, H-5), 3.571 (ddd, 1 H, $J_{3,4}$ 8.3, $J_{4,5}$ 10.0, $J_{4,OH}$ 2.2 Hz, H-4), 3.499 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.8 Hz, H-2), 3.360 (s, 3 H, OMe), 2.368 (d, 1 H, $J_{OH,4}$ 2.2 Hz, OH), and 1.044 (s, 9 H, *t*-Bu).

Anal. Calc. for $C_{37}H_{44}O_6Si$: C, 72.52; H, 7.24. Found: C, 72.24; H, 7.20.

Generation of PhSeOTf[17]. — To a stirred mixture of PhSeCl (1.0 equiv.) and 3A or 4A molecular sieves (~1.5 g · mmol^{-1}) in a solvent (~6 mL · mmol^{-1}) was added, under positive flush of nitrogen, AgOTf (1.0 equiv.) at 0°. The mixture was stirred for 10 min at 0° to afford a solution of PhSeOTf, which was directly used for glycosylation reactions.

Methyl O-*(2,3,4,6-tetra-*O*-benzyl-α and β-*D*-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranoside* (**12**). — To a stirred suspension of PhSeOTf (0.14 mmol) and 4A molecular sieves (0.25 g) in toluene (1 mL) was added dropwise a solution of compounds **2** (63.4 mg, 0.111 mmol) and **7** (43.0 mg, 0.093 mmol) in toluene (3 mL) at −40°. The mixture was stirred for 30 min at −40° and then diluted with AcOEt (30 mL). Aq. $NaHCO_3$ (5 mL) was added, and the suspension was stirred for 10 min at room temperature and filtered through Celite. The filtrate was washed with water (20 mL), and the aqueous layer was extracted with AcOEt (30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. Chromatography of the residue on silica gel using 5:1 hexane–AcOEt afforded **12** (83.3 mg, 91%), which was shown to be an 88:12 mixture of β- and α-anomers by ^{1}H-n.m.r. analysis: R_f 0.15 (6:1 hexane–AcOEt); ^{1}H-n.m.r. data: δ 4.603 (d, $J_{1,2}$ 3.7 Hz, H-1aβ), 4.345 (d, $J_{1,2}$ 7.8 Hz, H-1bβ), 3.990 (dd, $J_{2,3}$ 9.5, $J_{3,4}$ 9.0 Hz, H-3aβ), 3.826 (m,

H-5bβ), 3.516 (dd, $J_{1,2}$ 3.7, $J_{2,3}$ 9.5 Hz, H-2aβ), 3.426 (m, H-5bβ), 3.348 (s, OMeβ), and 3.323 (s, OMeα).

The pure β-isomer, $[\alpha]_D$ +18.4° (*c* 0.8), m.p. 130–131.5°; lit.[26] $[\alpha]_D$ +17.1° (*c* 0.4), m.p. 133–133.5°, was obtained by crystallization of the mixture from ether–hexane.

Anal. Calc. for $C_{62}H_{60}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.11; H, 6.72.

Methyl O-*(2,3,4,6-tetra*-O-*benzyl-α- and β-*D-*glucopyranosyl)*-(1→4)-*2,3-di*-O-*benzyl-6*-O-tert-*butyldiphenylsilyl-α-*D-*glucopyranoside* (**13**). — The reaction was performed as described for the preparation of compound **12** by using PhSeOTf (0.20 mmol), compound **1** (75.3 mg, 0.132 mmol), compound **8** (89.1 mmol, 0.145 mmol), and 4A molecular sieves (0.25 g). Usual processing and chromatographic purification on silica gel in 10:1 hexane–AcOEt afforded **13** (110.8 mg, 74%) as a 3:1 mixture of β- and α-anomers. An analytical sample of **13** was further separated by preparative t.l.c. in 4:1 hexane–AcOEt to afford pure β- and α-anomers.

The β-anomer had $[\alpha]_D$ +37.2° (*c* 0.8); R_F 0.31 (6:1 hexane–AcOEt); ^{1}H-n.m.r. data: δ 4.752 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1b), 4.613 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1a), 3.408 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.3 Hz, H-2b), 3.309 (s, OMe), and 1.105 (s, 9 H, *t*-Bu).

Anal. Calc for $C_{71}H_{78}O_{11}Si$: C, 75.10, H, 6.92. Found: C, 74.90; H, 6.93.

The α-anomer had $[\alpha]_D$ +33.6° (*c* 1.1); R_F 0.27 (6:1 hexane–AcOEt); ^{1}H-n.m.r. data: δ 5.728 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1b), 4.543 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1a), 3.508 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.5 Hz, H-2a or H-2b), 3.467 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.0 Hz, H-2b or H-2a), 3.350 (s, 3 H, OMe), and 1.030 (s, 9 H, *t*-Bu).

Anal. Found: C, 75.15; H, 6.89.

Methyl O-*(2,3,4,6-tetra*-O-*acetyl-β-*D-glucopyranosyl)-(1→6)-2,3,4-tri-O-*benzyl-α-*D-*glucopyranoside* (**14**). — To a stirred mixture of PhSeOTf (0.26 mmol) and 4A molecular sieves (0.3 g) in 1,2-dichloroethane (1 mL) was added a solution of compounds **3** (80.3 mg, 0.212 mmol) and **7** (82.2 mg, 0.177 mmol) in 1,2-dichloroethane (3 mL) at 0°. The mixture was stirred for 10 min at 0°, processed as usual, and purified by chromatography on silica gel using 3:2 hexane–AcOEt to afford **14** (72.7 mg, 52%): $[\alpha]_D$ +3.0° (*c* 1.4); lit.[27] $[\alpha]_D$ +3.6° (*c* 1.1); R_F 0.24 (3:2 hexane–AcOEt; ^{1}H-n.m.r. data: δ 5.169 (t, 1 H, $J_{2,3}$ 9.5 Hz, H-3b), 5.077 (t, 1 H, $J_{3,4}$, $J_{4,5}$ 9.5 Hz, H-4b), 5.307 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 9.5 Hz, H-2b), 4.578 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1a), 4.516 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1b), 3.510 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.8 Hz, H-2a), 3.355 (s, 3 H, OMe), 2.042, 2.014, 1.990, and 1.949 (4 s, 12 H, 4Ac).

Anal. Calc. for $C_{42}H_{50}O_{15}$: C, 63.47; H, 6.34. Found: C, 63.84; H, 6.52.

Benzyl O-*(2,3,4,6-tetra*-O-*benzoyl-β-*D-*glucopyranosyl)-(1→4)-2,3,6-tri*-O-*benzyl-β-*D-*glucopyranoside* (**15**). — Compound **4** (69.5 mg, 0.110 mmol) was reacted with **9** (50.0 mg, 0.093 mmol) as described for the preparation of compound **14** in the presence of PhSeOTf (0.14 mmol) and 4A molecular sieves (0.3 g). Usual processing and chromatographic purification on silica gel using 15:1 toluene–AcOEt afforded **15** (99.6 mg, 96%), which could be crystallized from ether–hexane: $[\alpha]_D$ −11.0° (*c* 0.8), m.p. 104–105°, lit.[12] $[\alpha]_D$ −9°; R_F 0.47 (10:1 toluene–AcOEt); ^{1}H-n.m.r. data: δ 5.683 (dd, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 9.5 Hz, H-3b), 5.556 (dd, 1 H, $J_{3,4}$ 9.5, $J_{4,5}$ 9.8 Hz, H-4b), 5.471 (dd, $J_{1,2}$ 7.9, $J_{3,4}$ 9.8 Hz, H-2b), 4.959 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1b), 4.397 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1a), 4.228

(dd, 1 H, $J_{5,6}$ 5.0, $J_{6,6}$ 12.0 Hz, H-6b), 4.041 (dd, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 9.5 Hz, H-4a), 3.727 (ddd, 1 H, $J_{4,5}$ 9.8, $J_{5,6}$ 5.0, $J_{5,6}$ 3.4 Hz, H-5b), 3.679 (dd, 1 H, $J_{5,6}$ 3.7, $J_{6,6}$ 11.0 Hz, H-6a), 3.660 (dd, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 9.2 Hz, H-3a), 3.579 (dd, 1 H, $J_{5,6}$ 1.7, $J_{6,6}$ 11.0 Hz, H-6a'), 3.447 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 9.2 Hz, H-2a), and 3.228 (ddd, 1 H, $J_{4,5}$ 9.8, $J_{5,6}$ 3.7, $J_{5,6}$ 1.7 Hz, H-5a).

Anal. Calc. for $C_{68}H_{62}O_{15}\cdot H_2O$: C, 71.82; H, 5.67. Found: C, 71.90; H, 5.55.

Benzyl O-*(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**16**). — To a stirred mixture of PhSeOTf (0.18 mmol) and 4A molecular sieves (0.3 g) in toluene (1 mL) was added dropwise a solution of compounds **5** (68.4 mg, 0.147 mmol) and **10** (71.0 mg, 0.122 mmol) at −40°. The mixture was gradually warmed up to 0° over 1 h. Usual processing, followed by chromatographic purification on silica gel using 2:1 hexane–AcOEt, afforded **16** (111.6 mg, 91%): $[\alpha]_D$ −16.1° (*c*, 1.0); R_F 0.18 (3:2 toluene–AcOEt); ^{1}H-n.m.r. data: δ 5.778 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 9.0 Hz, H-3b), 5.529 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1b), 5.120 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 10.0 Hz, H-4b), 4.953 (d, 1 H, $J_{1,2}$ 8.3 Hz, H-1a), 4.213 (dd, 1 H, $J_{5,6}$ 4.2, $J_{6,6}$ 12.2 Hz, H-6b), 3.935 (dd, 1 H, $J_{5,6}$ 2.3, $J_{6,6}$ 12.2 Hz, H-6b'), 3.606 (dd, 1 H, $J_{5,6}$ 1.2, $J_{6,6}$ 11.2 Hz, H-6a), 3.500 (dd, 1 H, $J_{5,6}$ 3.4, $J_{6,6}$ 11.2 Hz, H-6a'), 1.999, 1.971, and 1.843 (3 s, 9 H, 3 Ac).

Anal. Calc. for $C_{55}H_{52}N_2O_{16}$: C, 66.26; H, 5.26; N, 2.81. Found: C, 66.05; H, 5.28; N, 2.77.

*O-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl)-(1→6)-1,2:-3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**17**). — Compound **4** (90.7 mg, 0.195 mmol) was reacted with **11** (42.3 mg, 0.163 mmol), as described for the preparation of compound **12**, in the presence of PhSeOTf (0.25 mmol) and 4A molecular sieves (0.3 g). Usual processing and chromatographic purification on silica gel using 3:1 toluene–AcOEt afforded **17** (92.5 mg, 61%), together with recovered **4** (42.2 mg).

Compound **17** had $[\alpha]_D$ −23.8° (*c* 1.0); R_F 0.35 (2:1 toluene–AcOEt); m.p. 208–210°; ^{1}H-n.m.r. data (90 MHz): δ 5.84 (dd, 1 H, $J_{2,3}$ 10.6, $J_{3,4}$ 9.0 Hz, H-3b), 5.44 (d, 1 H, $J_{1,2}$ 8.6 Hz, H-1b), 5.15 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 10.1 Hz, H-4b), 5.10 (d, 1 H, $J_{1,2}$ 5,3 Hz, H-1a), 2.10, 2.02, 1.85 (3 s, 9 H, 3 Ac), 1.39, 1.23 (2 s, 6 H, Me_2C), and 1.03 (s, 6 H, Me_2C).

Anal. Calc. for $C_{32}H_{39}NO_{15}$: C, 56.72; H, 5.80; N, 2.07. Found: C, 56.73; H, 5.81; N, 2.03.

Benzyl O-*(4-*O*-acetyl-2,3,6-tri-*O*-benzyl-α and β-*D*-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**18**). — Compound **6** (62.2 mg, 0.115 mmol) was reacted with **9** (51.8 mg, 0.096 mmol) in the presence of PhSeOTf (0.14 mmol) and 4A molecular sieves (0.25 g) as described for the preparation of compound **12**. After usual processing, chromatographic purification on silica gel, followed by separation on preparative t.l.c., both using 6:1 hexane–AcOEt, afforded **18α** (81.8 mg, 83%) and **18β** (15.6 mg, 16%). Physical properties of these compounds were in accordance with those previously reported[28].

Methyl O-*[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-glycero-α and β-*D*-galacto-2-nonuropyranosyl)onate]-(2→6)-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranoside* (**22**). — *Procedure A.* To a mixture of PhSeOTf (0.093 mmol) and 4A molecular

sieves (0.25 g) in 1,2-dichloroethane (1 mL) was added a solution of compounds **20a** (31.9 mg, 0.061 mmol) and **7** (57 mg, 0.12 mmol) in 1,2-dichloroethane (2 mL) at −23°. After stirring for 30 min at −23°, the mixture was processed as usual and separated by chromatography on silica gel using 4:1–2:1 toluene–acetone afforded **22α** (5.9 mg, 10%) and **22β** (30.7 mg, 53%). ^{1}H-N.m.r. data of these products were in full agreement with those reported by Goto and co-workers[34].

Procedure B. To a mixture of PhSeOTf (0.10 mmol) and 3A molecular sieves (0.3 g) in acetonitrile (1 mL) was added a solution of compounds **20a** (35.8 mg, 0.069 mmol) and **7** (48 mg, 0.10 mmol) in acetonitrile (2 mL) at −35°, and the mixture was stirred for 30 min at −35°. Processing and chromatographic separation afforded **22α** (41.4 mg, 64%) and **22β** (8.8 mg, 14%).

Procedure C. Compound **20b** (39.1 mg, 0.075 mmol) was reacted with **7** (52 mg, 0.11 mmol) as described in Procedure B, in the presence of PhSeOTf (0.11 mmol) and 3A molecular sieves (0.3 g) to afford **22α** (43.3 mg, 62%) and **22β** (12.0 mg, 17%).

Benzyl O-*[methyl(5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5,-dideoxy*-D-glycero-*α* and *β*-D-galacto-*2-nonuropyranosyl)onate]-(2→3)*-O-*(2,6-di*-O-*benzyl-β*-D-*galactopyranosyl)-(1→4)-3,6-di*-O-*benzyl-2*-O-*pivaloyl-β*-D-*glucopyranoside* (**23**). — To a stirred mixture of PhSeOTf (0.13 mmol) and 3A molecular sieves (0.3 g) in acetonitrile (1 mL) was added dropwise a solution of compounds **20a** (45.5 mg, 0.087 mmol) and **21** (51.0 mg, 0.058 mmol) in acetonitrile (3 mL) at −35°, and the mixture was stirred for 1 h at −35°. After usual processing, chromatography on Bio Beads S-X3 in toluene, and further separation on preparative t.l.c. using 2:1 toluene–acetone, afforded **23α** (15.7 mg, 20%) and **23β** (3.7 mg, 5%).

Compound **23α** had $[\alpha]_D$ −7.1° (*c* 0.3); R_F 0.12 (10:1 toluene–MeOH); ^{1}H-n.m.r. data: δ 5.397 (m, 1 H, H-8c), 5.308 (dd, 1 H, $J_{6,7}$ 2.1, $J_{7,8}$ 8.1 Hz, H-7c), 5.113 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 9.5 Hz, H-2a), 4.853 (m, 1 H, H-4c), 4.545 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1b), 4.440 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1a), 4.302 (dd, 1 H, $J_{8,9}$ 2.4, $J_{9,9}$ 12.5 Hz, H-9c), 3.998 (dd, 1 H, $J_{5,6}$ 10.7, $J_{6,7}$ 2.1 Hz, H-6c), 3.960 (dd, 1 H, $J_{8,9}$ 6.1, $J_{9,9}$ 12.5 Hz, H-9c), 3.759 (s, 3 H, CO_2Me), 2.503 (dd, 1 H, $J_{3,3}$ 13.2, $J_{3,4}$ 4.4 Hz, H-3c*eq*), 2.081, 2.021, 1.976, 1.904, 1.871 (5 s, 15 H, 5 Ac), and 1.127 (s, 9 H, CMe_3).

Anal. Calc. for $C_{72}H_{87}NO_{24}$: C, 64.04; H, 6.49; N, 1.04. Found: C, 64.11; H, 6.24; N, 0.90.

Compound **23β** had $[\alpha]_D$ −11.7° (*c* 0.4); R_F 0.15 (10:1 toluene–MeOH), ^{1}H-n.m.r. data: δ 5.162 (m, 1 H, H-4c), 5.131 (dd, 1 H, $J_{1,2}$ 8.2, $J_{2,3}$ 9.2 Hz, H-2a), 4.448 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1a), 4.135 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.2 Hz, H-3b), 3.644 (s, 3 H, CO_2Me), 2.527 (dd, 1 H, $J_{3,3}$ 13.2, $J_{3,4}$ 4.8 Hz, H-3c*eq*), 2.110, 2.085, 1.991, 1.979, 1.725 (5 s, 15 H, 5 Ac), and 1.116 (s, 9 H, CMe_3).

Anal. Calc. for $C_{72}H_{87}NO_{24}$: C, 64.04; H, 6.49; N, 1.04. Found: C, 63.94; H, 6.44; N, 0.94.

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