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# Use of the methylsulfenyl cation as an activator for glycosylation reactions with alkyl (aryl) 1-thioglycopyranosides: synthesis of methyl *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→6)-*O*-α-D-glucopyranosyl-(1→2)-α-D-glucopyranoside, a derivative of the core trisaccharide of *E. coli* K12*†

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ABSTRACT

Methylsulfenyl bromide (MSB) and methylsulfenyl trifluoromethanesulfonate (MST) have been used to prepare 1,2-*cis*-linked disaccharides. Ethyl (phenyl) 1-thio-β-D-gluco- and galacto-pyranosides having non-participating (benzyloxy) protecting groups were used as the donors. The αβ-ratio of the products depended on the promoter and conditions of reaction. Intimate ion-pairs, formed initially, may be responsible for the steric outcome of the glycosylations. Thus, with ethyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside as a donor, moderate quantities of the *β-linked* disaccharide could be produced using MSB as the activator. The synthesis of the title trisaccharide glycoside that contains 1,2-*cis* and 1,2-*trans*-linkages is described.

## INTRODUCTION

Several reagents are in use at present for the activation of thioglycosides during oligosaccharide synthesis[1–15], and most of those that are suitable for the formation of 1,2-*trans* glycosidic bonds have participating acyl groups at postion 2. However, application of similar activation techniques for the formation of 1,2-*cis* glycosidic bonds have generally afforded poor αβ-stereoselectivity. Thus, although methyl triflate (MT) and dimethyl(methylthio)sulfonium triflate (DMTST) have found wide application for 1,2-*trans* coupling reactions, their applications for thioglycoside-mediated 1,2-*cis* coupling reactions have remained limited[16,17]. Considerable quantities of β-linked products were isolated during DMTST-mediated coupling of ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**1**) with HO-6 and HO-2 of monosaccharide acceptors in our laboratory. In fact, the β-linked disaccharide was the major product (85%) when

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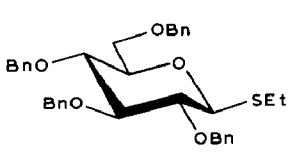
DMTST was used for a reaction[16] between **1** and 1,2,3,4-tetra-*O*-benzoyl-β-D-glucopyranose (**11**) in MeCN at −30°. Benzeneselenyl triflate (PhSeTf), which seemed to be an alternative to MT and DMTST, showed anomalous results with thioglycosides having benzyl ether functions on C-2, and afforded the β-linked isomer as the major product[15].

Recently, alkylsulfenyl triflate was introduced as an alternative to MT and DMTST for activating thioglycosides during oligosaccharide synthesis[1]. We now report on the application of methylsulfenyl triflate (MST) and methylsulfenyl bromide (MSB) for promoting the formation of 1,2-*cis* glycosides, using thioglycosides.

## RESULTS AND DISCUSSION

*1,2-cis-Glycosides.* — The thioglycosides **1**–**4** that have a benzyl group in position 2 were chosen as donors. Various conditions for the coupling reactions were investigated in order to determine the optimum conditions and obtain information on the pathway of reaction. The results from the reactions between **1** and **6** (Table I) indicated that (*a*) the best yield and stereoselectivity was obtained with MSB (10 mol) as the promoter (entry 1), (*b*) the presence of $Bu_4NBr$ adversely affected the yield without improving the stereoselectivity (entries 4 and 5), (*c*) the use of ether did not improve the yield or stereoselectivity (entry 2), and (*d*) MST afforded poorer αβ-ratios of products, especially at lower temperatures (entries 6 and 7). Based on these observations, MSB and the conditions as noted under entry 1 (Table I) were used for the coupling of **1** and **7**, **1** and **8**, **1** and **9**, **2** and **6**, and **3** and **6** (Table II). In these reactions, the following 1,2-*cis*- or the α-linked disaccharides were the major products: methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**12**), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**13**), methyl 3-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**14**), methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**15**), and methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-glucopyranoside (**16**). T.l.c. of the reaction mixtures revealed that, on the addition of MSB, even at −30°, the donor disappeared and a major component having a much lower $R_F$ value appeared. As the reaction progressed, products started to appear with simultaneous disappearance of acceptor and the slow-moving material. Generally the αβ-ratio was in the range 3–5:1. Ethyl (**2**) and phenyl 1-thio-β-D-galactopyranoside (**3**) coupled with comparable efficiency. Addition of excess of $Et_3N$ at the end of the reaction was essential when acid-labile groups were present. When this was not done, the product, for example, from the reaction between **1** and **8** was **14**, in which the 4,6-*O*-benzylidene group had undergone hydrolysis. The disaccharide products **12**–**16** and their corresponding β-linked isomers were identified from the $^{13}C$-n.m.r. data (Table II).

The entries 1–4 in Table I for the reaction between **1** and **6** indicated that, whereas excess of MSB was required for efficient coupling, addition of excess of bromide in the form of $Bu_4NBr$ did not increase the proportion of α-linked product in the reaction

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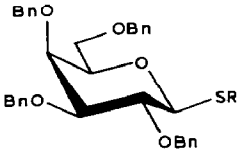
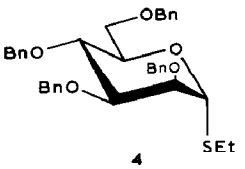



2 R = Et

3 R = Ph

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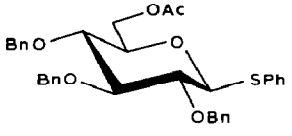


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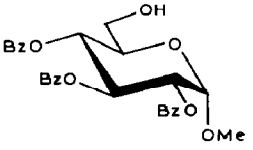


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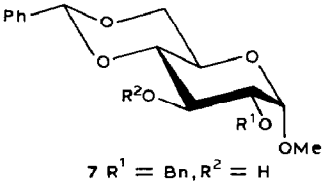
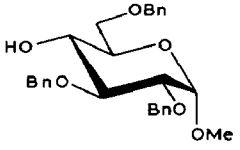



7 $R^1$ = Bn, $R^2$ = H

8 $R^1$ = H, $R^2$ = Bn

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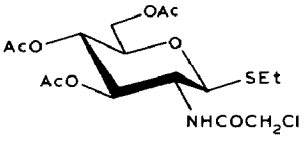


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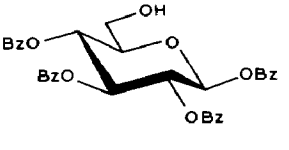


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TABLE I

Reactions between **1** and **6** to give methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside and its β-linked isomer

| *Entry* | *Promoter*[a] | *Temp.(°)/Time* | *Yield*[b] *(%)* | *αβ-Ratio* |
|---|---|---|---|---|
| 1 | MSB | 22/15 h | 97 | 4.7:1[d] |
| 2 | MSB | 22/15 h[e] | 73 | 2.0:1[c] |
| 3 | MSB | −30/1 h:10/3 h:22/15 h | 68 | 3.3:1[c] |
| 4 | MSB–ST–QBr | 22/62 h | 41 | 3.5:1[c] |
| 5 | MSB–QBr | 22/10 d | 40–50 | – |
| 6 | MST | 22/1 h | 89 | 3.8:1[d] |
| 7 | MST | −20 to −10/1 h | 98 | 2.0:1[c] |

[a] MSB, methylsulfenyl bromide; MST, methylsulfenyl triflate; ST, silver triflate; QBr, $Bu_4NBr$. [b] After column chromatography. [c] From the ratio of the intensities of the signals for C-1. [d] After separation of the individual isomer. [e] Reaction in ether.

mixture (entry 5). Likewise, there was no improvement when $Bu_4NBr$ was used together with MST (entry 4). These observations, together with the fact that the MSB-mediated α-coupling required comparatively short reaction times, indicated that the reaction did not proceed through the classical common-ion intermediate[18]. Moreover, with MST as

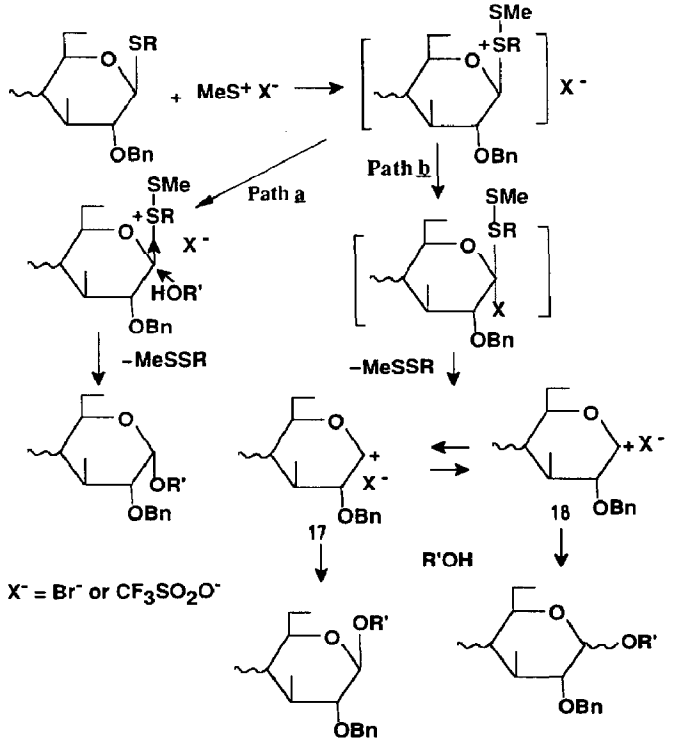
TABLE II

1,2-*cis* Coupling reactions[a] using methylsulfenyl bromide

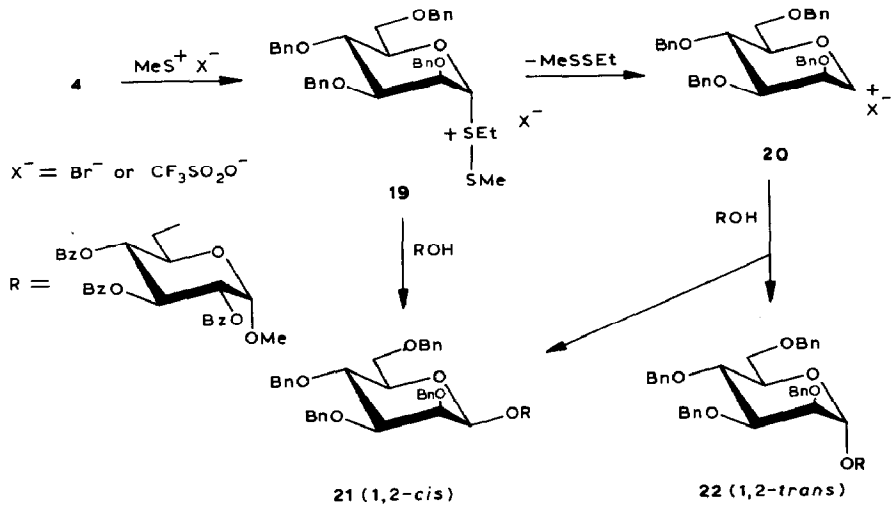
| *No.* | *Donor* | *Acceptor* | *Yield*[b] *(%)* | *αβ-Ratio*[c] | *Product* | $[\alpha]_D^{22}$ (c, $CHCl_3$) | $\delta_C$ ($J_{C\text{-}1,H\text{-}1}$ *in Hz*) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *α-Product (major)* | | *β-Product* | |
| | | | | | | | *C-1* | *C-1'* | *C-1* | *C-1'* |
| 1 | **1** | **6** | 89 | 4.7[d]:1 | **12** | +67°[e] (1.9) | 96.8 (175.9) | 97.2 (168.6) | 96.9 (175.9) | 104.2 (162.1) |
| 2 | **1** | **7** | 79 | 3.1:1 | **13** | +49° (2.6) | 98.5 (~167) | 96.1 (~167) | 98.7 (172.2) | 102.5 (163.2) |
| 3 | **1** | **8** | 79 | 4:1 | **14** | +59° (1.4) | 96.5 (168.6) | 94.1 (168.6) | 99.9 (166.8) | 104.1 (161.3) |
| 4 | **1** | **9** | 57 | 2.1:1 | **15** | +38° (0.8) | 96.7 (172.2) | 97.8 (168.6) | 96.9 (174.2) | 104.2 (157.7) |
| 5 | **2** | **6** | 94 | 2.7:1 | **16** | +62° (1.7) | 96.8 (172.3) | 97.9 (168.6) | 96.7 (175.9) | 104.3 (161.3) |
| 6 | **3** | **6** | 86 | 2.6:1 | | | | | | |

[a]At 22° for 15 h. [b]Based on acceptor used, after column chromatography. [c]After isolation of each isomer. [d]Based on $^{13}C$-n.m.r. data. [e]Determined on the product isolated (entry 6, Table I).

the sole activating reagent, the steric outcome of glycosylation could be affected by manipulating the temperature of the reaction (entries 6 and 7). Thus, the counter ions, $Br^-$ and triflate, appeared to play a role in determining the configuration at the new glycosidic centre. The sequence in Scheme 1, based on the formation of intimate ion-pairs[19], could explain the formation of *α* and *β* products and predict the effect of temperature and solvent. According to Scheme 1, it should be possible to obtain major *α*- or *β*-linked products by choosing the appropriate reagent and reaction conditions. If the reaction proceeded mainly through path *a*, more *α*-linked product would result, whereas path *b* would result in non-stereoselective glycosylation. The results of coupling using MSB (Table II) indicated that both the paths *a* and *b* were followed, to afford a mixture of products in which the 1,2-*cis*-linked isomer preponderated. The ratio of products formed indicated that path *a* was the major route. However, when a more polar solvent (ether) was used, reaction by path *b* increased, thereby affording more *β*-linked product (entry 2, Table I). Glycosylation in the presence of MST accentuated path *b*, in which ion pairs **17** and **18** were involved (Scheme 1). At lower temperatures, the triflate formed a larger proportion of the closely associated ion-pair **17**, which resulted in the formation of increased amount of the *β* isomer (entry 7, Table I). A similar mechanism may be invoked for the DMTST-mediated coupling between **1** and




Scheme 1. Formation of *α*- and *β*-glycosides during glycosylation using methylsulphenyl (bromide or triflate).




Scheme 2. Formation of $\alpha$- and $\beta$-D-mannopyranosides during alkylsulfenyl-mediated glycosylation.

**11** in MeCN at $-30°$, when the $\beta$-linked product was formed almost exclusively[16]. The possibility that, with MSB, part of the reaction involved the formation of a thermodynamically unstable and more reactive $\beta$-glycosyl bromide intermediate, cannot be ruled out.

If such a mechanism were operative, then ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-$\alpha$-D-mannopyranoside (**4**) would also behave in a similar manner (Scheme 2). A concerted pathway analogous to path *a* in Scheme 1 should afford the 1,2-*cis* glycoside (**21**) via **19**, whereas formation of an ion pair (**20**) would afford more of the 1,2-*trans*-linked product **22**. Thus, by analogy with the earlier observations, MST should form more of the ion-pair intermediate and consequently afford, compared to MSB, less 1,2-*cis*-linked product. Also, for a reaction to follow path *a*, as in the MSB-mediated reaction, larger quantities of acceptor should be used. Indeed, reactions between **4** and **6** in the presence of MSB and MST afforded major glycosidation products (**21** and **22**) with opposite anomeric configurations, under the same reaction conditions (Table III); the same ratio of **4** to **6** was used in these reactions. Thus, MSB, in conjunction with a suitable alkyl 1-thio-$\alpha$-D-mannopyranoside as donor, should afford relatively larger proportions of the $\beta$-D-mannopyranoside. Reaction between **4** and **7** in the presence of MSB gave 80% of a mixture of disaccharide derivatives ($\alpha\beta$-ratio 1:1.6) from which the $\beta$-linked product, methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-$\beta$-D-mannopyranosyl)-$\alpha$-D-glucopyranoside (**23**), was isolated (Table III).

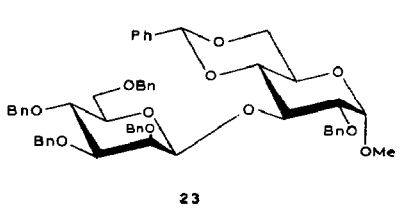
*Synthesis of the trisaccharide methyl glycoside* **29**. — Successive deacetylation, tritylation, benzylation, detritylation, and acetylation of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-$\beta$-D-glucopyranoside[20] afforded compound **5**, suitable for $\alpha$-coupling and having HO-6 temporarily protected with an acetyl group. Coupling between **5** and **8** in the presence of MSB gave an $\alpha\beta$-mixture of disaccharides (95%) from which the $\alpha$-linked derivative **24** was isolated (80% overall yield). The presence of the acetyl group

TABLE III

Reaction of **4** with acceptors **6** and **7**

| *Acceptor* | *Reagent* | *Yield (%)* | *aβ-Ratio*[c] | $[\alpha]_D^{22}$ (c, *CHCl₃*) | | *δ (J$_{C,H}$ in Hz)* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Major product* | | *Minor product* | |
| | | | | *β* | *α* | C-1 | C-1′ | C-1 | C-1′ |
| **6** | MSB | 84[a] | 1.0:2.4 | −1.0° (1.6) | +56.4° (1.9) | 96.9 (172.3) | 102.3 (153.9) | | |
| **6** | MST | 90 | 1.8:1.0 | | | 96.9 (174) | 98.3 (168.6) | | |
| **7** | MSB | 80[b] | 1.0:1.6 | −18° (1.9) | +13.2° (1.6) | 98.5 (169) | 101.9 (157.6) | 97.7 | 98.8 (172.3) |

[a] Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-*α*- and -*β*-D-mannopyranosyl)-*α*-D-glucopyranoside. [b] Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-*α*- and -*β*-D-mannopyranosyl)-*α*-D-glucopyranoside. [c] After separation of the individual isomer.

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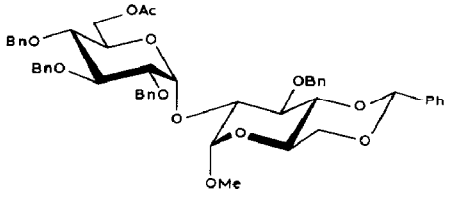


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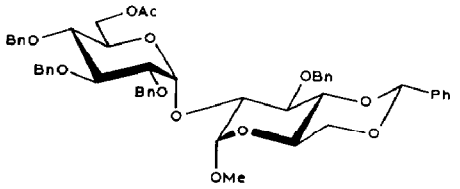


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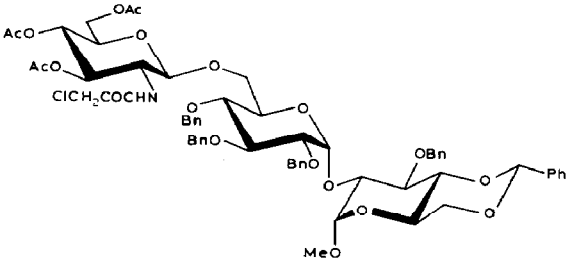


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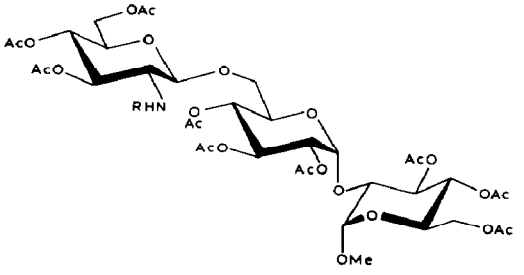
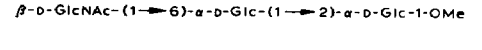



27 R = $COCH_2Cl$

28 R = Ac

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at position 6 in **5** could explain the high $\alpha$-selectivity. Deacetylation of **24** gave **25**, which reacted with an equimolar proportion of **10** (refs. 20 and 22), using MST as the activator, to give **26**. Hydrogenation of **26** followed by acetylation afforded **27** together with a minor product. Reduction of the chloroacetamido function in **27** with zinc and acetic acid in refluxing oxolane gave the deca-acetate **28**, the $^{13}$C- and $^{1}$H-n.m.r. spectra of which matched those of the minor product noted above. Therefore, hydrogenation had resulted in partial reduction of the chloroacetamido function of **26**. Although this reaction was not unexpected, similar phenomena were not observed in the earlier work using sugars containing the 2-*N*-chloroacetamido function[22]. Compound **28** was deacetylated to afford the trisaccharide methyl glycoside **29** the $^{13}$C- and $^{1}$H-n.m.r. spectra of which indicated the structure assigned.

## EXPERIMENTAL

*General methods.* — Melting points are corrected. Optical rotations were determined on solutions in chloroform with a Perkin–Elmer 141 polarimeter. The $^{1}$H- and $^{13}$C-n.m.r. spectra were recorded with a JEOL GSX270 spectrometer on solutions in $CDCl_3$ (internal $Me_4Si$). Decoupling was done as required to identify $^{1}$H signals. Elemental analyses were performed by Mikro Kemi AB (Uppsala, Sweden) or Analytische Laboratorien (Gummerbach, F.R.G.). The f.a.b.–mass. spectra were kindly provided by BioCarb (Lund, Sweden).

Thioglycosides **1–4** were prepared from the respective 1,2-*trans* acetates, using ferric chloride[20]. All reactions were carried out under nitrogen. Methylsulfenyl bromide (MSB) was prepared as described[1]. T.l.c. was performed on Silica Gel 60 G (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on dry Silica Gel 60 (Merck, 230–400 mesh, 50–80 g/g of mixture).

*Coupling reactions.* — *(a) Using MSB.* A dry mixture of the appropriate quantities of donor and the acceptor was dissolved in dichloromethane (1–2 mL per 100 mg), powdered molecular sieve type 4A (0.5 g per 100 mg) was added, and the slurry was stirred for 30–45 min. A solution of MSB (10 mol) in dichloroethane was injected through a septum into the stirred mixture, and reaction was allowed to continue at room temperature for 12–15 h when t.l.c. generally indicated a major conversion into products. Excess of triethylamine was added, the mixture was filtered through Celite, the filter cake was washed with dichloromethane, and the combined filtrate and washings were washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), filtered, and concentrated. The syrupy product was immediately subjected to column chromatography.

*(b) Using MST.* The method adopted was that reported[1].

*(c) Using MSB–$Bu_4NBr$.* A dry mixture of the donor, acceptor, and $Bu_4NBr$ (5 mol) was dissolved in dichloromethane, and powdered molecular sieve 4A was added to the stirred solution (45 min). MSB (3 mol) was injected through a septum into the mixture and the reaction was continued until t.l.c. indicated no further progress. The mixture was then worked-up as in (*a*).

*(d) Using MST–$Bu_4NBr$.* MSB (3 molar) was injected through a septum into a stirred slurry of $Bu_4NBr$ (5 mol) and molecular sieve 4A in dichloromethane. Silver trifluoromethanesulfonate (triflate) (3 mol) was added to the mixture and, after 5–10 min, a solution of donor and acceptor in dichloromethane was introduced. Stirring was continued until t.l.c. indicated no further reaction. The mixture was then worked-up as in (*a*).

*Phenyl 6-O-acetyl-2,3,4-tri-O-benzyl-β-D-glucopyranoside* (**5**). — Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[20] (5.2 g) was deacetylated conventionally (NaOMe–methanol), and the solution was neutralised with Amberlyst 15 ($H^+$) resin, filtered, and concentrated to dryness. Tritylation[23] of the residue (2.98 g) afforded the 6-*O*-trityl compound, which was benzylated[24] and then detritylated using aqueous 80% acetic acid at 100° (12 h). Column chromatography (40:1 and 50:1 toluene–acetone) of the crude product (6.7 g) gave phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (3 g) that was acetylated immediately with 2:1 pyridine–acetic anhydride (8 mL). Conventional work-up and crystallization of the product from ether–hexane afforded **5** (3.2 g), m.p. 69.5–70.5°, $[\alpha]_D^{22}$ +10° (*c* 1.3). $^{13}$C-N.m.r. data: δ 170.6 (CO), 138.2, 137.9, 137.6 (3 C-1-Ph), 87.5 (C-1), 63.3 (C-6), 20.8 ($OCOCH_3$), 86.7, 80.9, 77.5, 77.3, 75.8, 75.5, 75.0. Mass spectrum: *m/z* 585.3 ($M^+ + 1$) and 607.4 ($M^+ + 23$).

*Anal.* Calc. for $C_{35}H_{36}O_6S$ (584.698): C, 71.9; H, 6.2; S, 5.5. Found: C, 71.6; H, 6.3; S, 5.5.

*Methyl 2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside* (**12**). — Thioglycoside **1** (86 mg, 0.14 mmol) and the acceptor **6**[25] (60 mg, 0.12 mmol) were reacted[1] using MSB (0.19 mL, 0.18 mmol) and silver trifluoromethanesulfonate (triflate) (52 mg, 0.2 mmol). The product (115 mg, 89%) was eluted from a column of silica gel (80 g), using 40:1 (60 mL) and 60:1 toluene–acetone, to give **12**, eluted first and isolated as a syrup (79 mg). $^{13}$C-N.m.r. data: δ 165.8, 165.2 (2:1, 3 CO), 138.9, 138.6, 138.4, 137.9 13.3, 132.9 (C-1-Ph), 129.9–127.5 (aromatic), 55.6 ($OCH_3$), 81.7, 80.0, 77.6, 75.5, 74.8, 73.4, 73.1, 72.25, 70.7, 70.3, 69.7, 68.6, 68.3, 66.7.

*Anal.* Calc. for $C_{62}H_{60}O_{14}$ (1029.086): C, 72.35; H, 5.88. Found: C, 71.99; H, 5.90.

Continued elution afforded an αβ-mixture (34 mg, αβ-ratio 1:2) followed by some β-linked disaccharide (4.5 mg, 18.6%), $[\alpha]_D^{22}$ +41° (*c* 0.7).

Compound **12** was also synthesized, using MSB, MSB–silver triflate–$Bu_4NBr$, and MSB–$Bu_4NBr$ in the manner described above, from **1** and **6** in a molar ratio of 1.2:1.0. The results are summarized in Table I.

*Methyl 2-O-benzyl-4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside* (**13**). — A solution of **1** (92.5 mg, 0.16 mmol) and **7** (ref. 26) (64.3 mg, 0.17 mmol) in dichloromethane (1.5 mL) was treated with MSB (1.6 mL, 1.6 mmol) as in the general procedure. T.l.c. (double elution, 4:1 and 6:1 hexane–ethyl acetate) indicated the presence of two products. Column chromatography (silica gel, 80 g) of the crude product with 4:1 (60 mL), 8:1 (100 mL), and 6:1 hexane–ethyl acetate gave, first, the β-linked product, isolated as a syrup (22.8 mg), followed by **13**, isolated as a syrup (71 mg). $^{13}$C-N.m.r. data: δ 138.9, 138.8, 138.0, 137.8, 137.4, 137.1 (C-1-Ph), 129.4–126.4 (aromatic), 102.1 (PhCH), 55.3 ($OCH_3$), 82.9, 81.6, 78.7, 77.9, 75.5, 74.8,

73.4, 72.7, 71.1, 69.8, 69.2, 68.1, 61.8. Mass spectrum: *m/z* 895 ($M^+ + 1$).

Further elution afforded some **7**.

*Methyl 3-O-benzyl-2-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside* (**14**). — A mixture of **1** (118 mg, 0.2 mmol), **8** (ref. 26) (61 mg, 0.16 mmol), and MSB (1.8 mL, 1.8 mmol) was reacted by the general procedure. T.l.c. (double elution, 3:1 and 6:1 hexane–ethyl acetate) indicated the formation of a minor ($R_F$ 0.44) and a major ($R_F$ 0.34) product and **8** ($R_F$ 0.17). After work-up, without the addition of $Et_3N$, t.l.c. (4:1 hexane–ethyl acetate) revealed none of the known products. T.l.c. (double elution, 4:1 and 6:1 toluene–acetone) showed two products ($R_F$ 0.25 and 0.19). Column chromatography [4:1 (30 mL) and 6:1 toluene–acetone] of the product afforded, first the β-linked isomer, then **14** (34 mg). $^{13}$C-N.m.r. data: δ 138.7, 138.55, 138.37, 138.15, 137.85 (5 C-1-Ph), 128.6–127.5 (aromatic), 54.9 ($OCH_3$), 82.1, 80.5, 79.05, 77.6, 76.1, 75.7, 74.9, 74.4, 73.3, 72.9, 70.9, 70.7, 70.3, 68.2, 62.45.

*Methyl 2,3,6-tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside* (**15**). — Compounds **1** (59 mg, 0.1 mmol) and **9** (ref. 22) (69.3 mg, 0.15 mmol) were coupled in dichloromethane (1.0 mL), using MSB (1.8 mL, 1.8 mmol). Column chromatography of the products, using 20:1 (30 mL), 30:1 (40 mL), and 40:1 toluene–acetone, provided **15** (18 mg), isolated as a syrup. $^{13}$C-N.m.r. data: δ 138.0–126.7 (C-1-Ph and aromatic), 55.2 ($OCH_3$) and 82.05, 80.2, 79.5, 77.7, 75.5, 74.9, 74.4, 73.4, 73.3, 73.2, 72.4, 72.1, 70.9, 69.6, 69.05, 68.2.

Further elution gave a 1:1 αβ-mixture (24.4 mg), then the β-linked disaccharide isolated as a syrup (11.4 mg), $[\alpha]_D^{22}$ +13° (*c* 1.1). Continued elution gave **9** (25.4 mg).

*Methyl 2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-α-D-glucopyranoside* (**16**). — Compounds **2** (106.7 mg, 0.18 mmol) and **6** (73.6 mg, 0.15 mmol) were reacted in dichloromethane (1.5 mL), using MSB (1.6 mL, 1.6 mmol). Column chromatography of the products, using 30:1 (70 mL) and 5:1 toluene–acetone, gave **16**, isolated as a syrup (89 mg). $^{13}$C-N.m.r. data: δ 165.8, 165.3 (2:1, CO), 138.9, 138.8, 138.1, 133.3, 133.0 (C-1-Ph), 129.9–127.4 (aromatic), 55.4 ($OCH_3$), 78.6, 76.5, 75.2, 74.8, 73.25, 73.1, 72.9, 72.2, 70.7, 69.6, 69.3, 68.75, 68.5, 66.6. Mass spectrum: *m/z* 1029 ($M^+ + 1$) and 1051 ($M^+ + 23$).

Further elution gave a 3:2 αβ-mixture (25.4 mg) followed by the β-linked isomer of **16** (25.6 mg), $[\alpha]_D^{22}$ +26° (*c* 1.7). $^{13}$C-N.m.r. data: δ 165.85, 165.7, 165.5 (CO), 138.8–127.5 (aromatic), 55.4 ($OCH_3$), 82.0, 79.65, 75.1, 74.5, 73.4, 73.1, 72.2, 70.55, 70.0, 68.9, 68.6.

*Reactions between* **4** *and* **6**. — *(a) Using MSB.* Compounds **4** (84.2 mg, 0.14 mmol) and **6** (127.2 mg, 0.25 mmol) were dissolved in dichloromethane (2 mL) and the reaction was conducted in the presence of MSB (1.6 mL, 1.6 mmol) for 12 h. T.l.c. (double elution, 30:1 and 50:1 toluene–acetone) indicated complete absence of the donor, a mixture of products ($R_F$ 0.32 and 0.25), and **6**. Column chromatography on silica gel (120 g), using 30:1 (150 mL), 60:1 (30 mL), and 50:1 toluene–acetone, gave methyl2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (**22**), isolated as a syrup (36.3 mg). $^{13}$C-N.m.r. data: δ 165.8, 165.1 (2:1, CO), 138.74, 138.63, 138.52, 138.44, 133.34, 133.23, 133.0 (C-1-Ph), 129.9–127.38

(aromatic), 55.5 ($OCH_3$), 79.9, 74.9, 74.87, 74.8, 73.2, 72.6, 72.1, 71.98, 70.6, 69.8, 69.1, 68.1, 66.2.

Continued elution afforded a mixture (5 mg) of products and then methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)-α-D-glucopyranoside (**21**), isolated as a syrup (87.4 mg). $^{13}$C-N.m.r. data: δ 165.9, 165.8, 165.5 (CO), 138.9–127.4 (aromatic), 55.4 ($OCH_3$), 82.2, 76.06, 75.1, 74.75, 74.1, 73.9, 73.4, 72.2, 71.4, 70.58, 69.53, 69.45, 68.94, 68.6.

*Anal.* Calc. for $C_{62}H_{60}O_{14}$ (1029.086): C, 72.35; H, 5.88. Found: C, 72.21; H, 6.02.

*(b) Using MST.* Coupling of **4** (93.8 mg, 0.16 mmol) and **6** (128.4 mg, 0.25 mmol) in dichloromethane (2.5 mL), using silver triflate (80.8 mg, 0.31 mmol) and MSB (0.16 mL, 0.16 mmol) followed by work-up as in (*a*), afforded **22** (97.4 mg) and **21** (55 mg).

*Reaction between* **4** *and* **7** using MSB. — Compounds **4** (84.3 mg, 0.14 mmol) and **7** (104 mg, 0.28 mmol) were dissolved in dichloromethane (1.5 mL) and treated with MSB (1.6 mL, 1.6 mmol). Column chromatography of the products, using 40:1 (60 mL) and 60:1 toluene–acetone, gave methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-α-D-glucopyranoside (45.9 mg). $^{13}$C-N.m.r. data: δ 139.1, 138.7, 138.6, 138.3, 137.58, 137.2 (C-1-Ph), 129.4–126.23 (aromatic), 101.86 (Ph*C*H, $J_{C,H}$ 166.8 Hz), 55.35 ($OCH_3$), 82.75, 79.67, 77.9, 74.86, 74.7, 74.2, 73.5, 73.2, 71.67, 71.5, 69.1, 68.9, 61.89.

Further elution afforded the β-linked isomer **23**, isolated as a syrup (62.5 mg). $^{13}$C-N.m.r. data: δ 139.2–137.36 (6 C-1-Ph), 128.8–126.2 (aromatic), 101.4 ($J_{C,H}$ 165 Hz), 55.3 ($OCH_3$), 82.6, 80.2, 80.16, 76.59, 76.02, 75.1, 74.75, 73.9, 73.59, 73.29, 71.64, 69.43, 68.94, 62.5.

*Anal.* Calc. for $C_{55}H_{58}O_{11}\cdot H_2O$ (913.018): C, 72.35; H, 6.40. Found: C, 71.99; H, 6.54.

*Methyl 2-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl)-3-*O*-benzyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**24**). — A solution of **5** (840 mg, 1.4 mmol) and **8** (784.5 mg, 2.1 mmol) in dichloromethane (4 mL) containing molecular sieve 4A (2 g) was treated with freshly prepared[1] MSB (1.9 g). T.l.c. (double elution, 10:1 and 20:1 toluene–acetone) indicated a minor ($R_F$ 0.36) and a major ($R_F$ 0.29) product along with unreacted acceptor ($R_F$ 0.17). Column chromatography on silica gel (200 g), using 20:1 (300 mL) and 40:1 toluene–acetone, gave a minor product (148 mg) followed by **24** (1.01 g, 83%), m.p. 110–111° (from dichloromethane–hexane), $[\alpha]_D^{22}$ +37.3° (*c* 1.7). $^{13}$C-N.m.r. data: δ 170.5 (CO), 138.7, 138.3, 137.9, 137.4 (1:2:1:1, C-1-Ph), 128.9–126 (aromatic), 101.3 (Ph*C*H, $J_{C,H}$ 161.3 Hz), 97.2 (C-1, $J_{C,H}$ 166.8 Hz), 94.3 (C-1′, $J_{C,H}$ 166.8 Hz), 62.5, 62.3 (C-6,6′), 54.9 ($OCH_3$), 20.8 ($OCOCH_3$), 82.6, 81.9, 79.3, 77.2, 76.8, 75.7, 75.6, 74.9, 74.5, 72.9, 69.0, 68.7. Mass spectrum: *m/z* 847 ($M^+ + 1$) and 869 ($M^+ + 23$).

Analysis was carried out after deacetylation.

*Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl-α-*D*-glucopyranoside* (**25**). — A solution of **24** (0.6 g) in 2:1 methanol–dichloromethane (4.5 mL) was deacetylated with NaOMe (10 mg). T.l.c. (10:1 toluene–acetone) indicated conversion into one product ($R_F$ 0.17). More dichloromethane (3 mL) was added, and the solution was neutralized with Amberlyst 15 ($H^+$) resin, filtered, and

concentrated to dryness. The residue was crystallized from dichloromethane–hexane to afford **25** (0.54 g), m.p. 175–176, $[\alpha]_D^{22}$ +53° (*c* 0.6). $^{13}$C-N.m.r. data: signals due to $COCH_3$ were absent, and those for H-6,6′ and C-6′ were shifted upfield.

*Anal.* Calc. for $C_{48}H_{52}O_{11}$ (804.885): C, 71.62; H, 6.51. Found: C, 71.79; H, 6.41.

*Methyl* O-*(3,4,6-tri*-O-*acetyl-2-chloroacetamido-2-deoxy-β*-D-*glucopyranosyl)-(1→6)*-O-*(2,3,4-tri*-O-*benzyl-α*-D-*glucopyranosyl)-(1→2)-3*-O-*benzyl-4,6*-O-*benzylidene-α*-D-*glucopyranoside* (**26**). — Coupling between **25** (413 mg, 0.5 mmol) and **10** (refs. 20 and 22) (108 mg, 0.13 mmol) was conducted in dichloromethane (5 mL) in the presence of MSB (0.14 mL, 0.14 mmol) and silver triflate (140 mg, 0.54 mmol). More **10** (110 mg and 39 mg; total, 267 mg, 0.31 mmol) was added at intervals of 1 h along with MSB (0.14 mL and 0.04 mL; total, 0.32 mL, 0.32 mmol) and silver triflate (89 mg and 41 mg, total 270 mg, 1.08 mmol). T.l.c. (double elution, 4:1 and 8:1 toluene–acetone) revealed one major product ($R_F$ 0.31). After the usual work-up, the product was eluted from a column of silica gel (200 g), using, successively, 4:1 (250 mL), 10:1 (600 mL), 8:1 (200 mL), 6:1 (250 mL), and 5:1 toluene–acetone to give **26** (322 mg, 66%), m.p. 160–162° (from ether–hexane), $[\alpha]_D^{22}$ +23° (*c* 2.5). N.m.r. data: $^1$H, $\delta$ 7.6–7.0 (aromatic) 6.5 (d, 1 H, *J* 8.5 Hz, NH), 5.58 (s, 1 H, PhC*H*), 5.34, 5.0 (2 t, 2 H, *J* 9.9 Hz, 9.2 Hz, H-3″,4″), 3.45 (s, 3 H, OMe), 2.04, 2.0, 1.99 (3 s, 9 H, 3Ac); $^{13}$C, $\delta$ 170.6, 169.3, 166.2 (CO), 138.8, 138.7, 138.3, 138.1, 137.4 (C-1-Ph), 101.3 (Ph*C*H, $J_{C,H}$ 159.4 Hz), 99.9 (C-1″, $J_{C,H}$ 166.8 Hz), 97.5 (C-1′, $J_{C,H}$ 166.7 Hz), 94.1 (C-1, $J_{C,H}$ 168.6 Hz), 42.3 (C-2″), 29.3 (NHCO*C*H$_2$Cl), 20.8, 20.6 (1:2, OCO*C*H$_3$), 82.3, 81.9, 78.9, 77.15, 75.7, 75.6, 74.6, 74.2, 72.9, 71.8, 71.5, 69.3, 68.9, 68.6, 67.4, 62.3, 62.1, 55.3, 54.9.

*Anal.* Calc. for $C_{62}H_{70}ClNO_{19}$ (1168.636): C, 63.72; H, 6.04; Cl, 3.03; N, 1.20. Found: C, 64.06; H, 6.05; Cl, 3.38; N, 1.27.

Some unreacted acceptor was recovered (~5 mg).

*Methyl* O-*(3,4,6-tri*-O-*acetyl-2-chloroacetamido-2-deoxy-β*-D-*glucopyranosyl)-(1→6)*-O-*(2,3,4-tri*-O-*acetyl-α*-D-*glucopyranosyl)-(1→2)-3,4,6-tri*-O-*acetyl-α*-D-*glucopyranoside* (**27**). — A solution of **26** (314.2 mg) in 1:1 ethanol–dichloromethane (5 mL) was hydrogenated over 10% Pd–C (300 mg) under atmospheric pressure for 12 h. T.l.c. (4:1 and 2:1 toluene–acetone) then showed no **26**. The solution was filtered through Celite and concentrated to dryness, and the residue was acetylated with pyridine–acetic anhydride (2:1, 4 mL). T.l.c. indicated the formation of a major ($R_F$ 0.39) and a minor ($R_F$ 0.18) product. Pyridine and acetic anhydride were removed by repeated co-concentration with toluene, and the products were isolated by column chromatography using 2:1 (50 mL) and 4:1 toluene–acetone. Compound **27** was the major product (189.4 mg, 72.5%), m.p. 125–126° (from ether–hexane, softens at 112°), $[\alpha]_D^{22}$ +126° (*c* 0.9). $^{13}$C-N.m.r. data: $\delta$ 170.6, 170.1, 169.9, 169.8, 169.4, 166.8 (CO), 100.6 (C-1″, $J_{C,H}$ 168.6 Hz), 96.9 (C-1′, $J_{C,H}$ 168.6), 94.8 (C-1, $J_{C,H}$ 174.1 Hz), 42.6 (C-2″), 29.4 (NHCO*C*H$_2$Cl), 20.8–20.6 (OCO*C*H$_3$).

Further elution gave **28** as the minor product (36.2 mg).

*Methyl* O-*(2-acetamido-3,4,6-tri*-O-*acetyl-2-deoxy-β*-D-*glucopyranosyl)-(1→6)*-O-*(2,3,4-tri*-O-*acetyl-α*-D-*glucopyranosyl)-(1→2)-3,4,6-tri*-O-*acetyl-α*-D-*glucopyranoside* (**28**). — Compound **27** (172 mg) was dissolved in oxolane (5 mL), glacial

acetic acid (0.15 mL) and activated zinc[27] (1 g) were added, and the mixture was heated under reflux with vigorous stirring. Fresh zinc (6 x 1 g) and acetic acid (3 x 0.12 mL) were added at regular intervals up to 30–36 h, when t.l.c. (2:1 toluene–acetone) showed almost complete conversion into a product ($R_f$ 0.18). The mixture was diluted with dichloromethane (10 mL), filtered through Celite, washed with water, dried ($MgSO_4$), filtered, and repeatedly co-concentrated with toluene to remove acetic acid. Column chromatography of the crude product, using 2:1 toluene–acetone, afforded **28** (125 mg, 75%), m.p. 123–125° (from ether–hexane), $[\alpha]_D^{22}$ +125° (*c* 1.2). $^{13}$C-N.m.r. data: $\delta$ 170.6, 170.1, 169.8, 169.4 (CO), 101.0 (C-1″), 96.9, 94.8 (C-1′,1), 55.5, 54.5 (C-2″, $OCH_3$), 23.1 ($NHCOCH_3$), 20.7 ($OCOCH_3$), 75.4, 72.7, 71.9, 71.5, 71.1, 70.0, 68.6, 68.2, 67.2, 66.8, 62.1, 61.9.

*Anal.* Calc. for $C_{39}H_{55}NO_{25}$ (937.813): C, 49.90; H, 5.91; N, 1.49. Found: C, 50.02; H, 5.79; N, 1.44.

Some unchanged **27** (4.9 mg) was recovered.

*Methyl* O-*(2-acetamido-2-deoxy-β-*D*-glucopyranosyl)-(1→6)*-O-*(α-*D*-glucopyranosyl)-(1→2)-α-*D*-glucopyranoside* (**29**). — A solution of **28** (120 mg) in 1:1 dichloromethane–methanol (8 mL) was deacetylated using sodium methoxide (< 5 mg). T.l.c. (12:3:3:2 and 12:3:6:3 ethyl acetate–acetic acid–methanol–water) showed only one product ($R_f$ 0.1 and 0.34, respectively). The solution was neutralized with Amberlyst 15 ($H^+$) resin, filtered through Celite, and concentrated to dryness, to give **29** (66.7 mg). The product, isolated by freeze-drying an aqueous solution in deionized water, had $[\alpha]_D^{22}$ +74° (*c* 0.55, water). N.m.r. data ($D_2O$): $^1$H, $\delta$ 5.0, 4.97 (2 d, 2 H, *J* 3.8 and 3.6 Hz, H-1,1′), 4.5 (d, 1 H, *J* 8.5 Hz, H-1″), 3.4 (s, 3 H, OMe), 2.04 (s, 3 H, NAc); $^{13}$C, $\delta$ 175.3 (CO), 102.4 (C-1″), 97.3 (C-1,1′), 56.3 (C-2″), 55.6 ($OCH_3$), 23.1 ($NHCOCH_3$), 76.6, 74.6, 73.5, 72.3, 72.1, 71.4, 70.7, 70.4, 70.1, 68.8, 61.4. Mass spectrum: *m/z* 560 ($M^+ + 1$) and 582 ($M^+ + 23$).

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