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Carbohydrate Research 338 (2003) 2779–2792
CARBOHYDRATE RESEARCH
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A new synthesis of the oligosaccharide domain of acarbose

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Received 25 July 2003; accepted 9 September 2003

Abstract

Synthesis of the oligosaccharide domain of acarbose was reinvestigated and was optimally performed using a maltosidic acceptor, already bearing a α-D-Glc-(1→4)-D-Glc bond, and a new D-fucopyranosyl donor. The crucial glycosylation step was improved by varying three different parameters and notably by focusing on the C-4 protecting group of the fucosyl residue, solvent and promoter. The resulting trisaccharide was further transformed into an electrophilic species in order to open further derivatization perspectives for designing new acarbose analogues. Substitution reactions were efficiently carried out with azide and thiocyanate anions. Two other potentially interesting trisaccharidic compounds were also synthesized, i.e. the C-4^{III} amine and the corresponding isothiocyanate.

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Keywords: Acarbose; Maltose; D-Fucose; Thioglycosides; Glycosylation reactions

1. Introduction

Acarbose is one of the most famous hypoglycemic agents. Owing to its inhibiting effects on α-glucosidases, it is frequently used for the treatment of type II insulin-independent diabetes.[1] Acarbose history began in 1975 with its isolation from *Actynomycetals* species.[2] Since that time, numerous projects have been instigated on the basis of both its biological properties and its particular chemical structure so that more than 100 related studies have been published in the last 5 years. Moreover, concomitant increasing number of patients suffering from diabetes—150 million people in 2000, but twice that in 2025 estimates the World Health Organization—continuously supports further research works for finding new drugs for the treatment of this incurable disease and also more efficient preparation procedures. While acarbose shows high selectivity and activity toward α-glucosidases, structural modifications are able to alter the initial biological property. These observations were interestingly reviewed by Nishimura in the 1990s.[3] More recently, transfer of acarviosine–glucose residue from acarbose to various mono- and disaccharidic acceptors under the action of *Bacillus stearothermophilus* maltogenic amylase allowed Robyt and coworkers to prepare acarbose analogues containing isomaltose, cellobiose and lactose structures.[4] The latter derivative was indeed a potent competitive inhibitor for β-glucosidase but no more for α-glucosidase. This result demonstrates that modification of the reducing part, two or three glycosyl units far away from the cyclitol moiety, involves serious biological changes. Actually, structural variations were generally introduced directly on acarbose either on the terminal valienamine or on the reducing residue. On this basis, acarbose **1** can be viewed as a pseudotetrasaccharide built with an aminocyclitol and a trisaccharide domain which is characterized by a linear connection between one rare quinovosyl residue and two glucosyl entities (Fig. 1). Moreover, previous total synthesis of acarbose suggested that the final key-step consists in binding a valienamine derivative to a trisaccharidic building block.[5–7] In this context, we have initiated a

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doi:10.1016/j.carres.2003.09.004

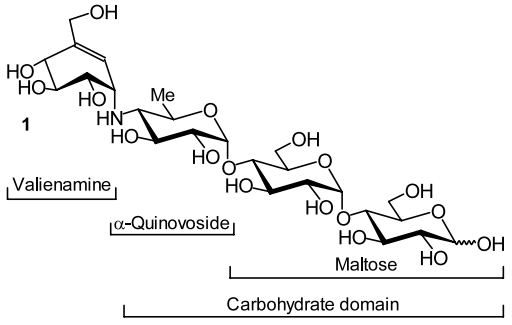
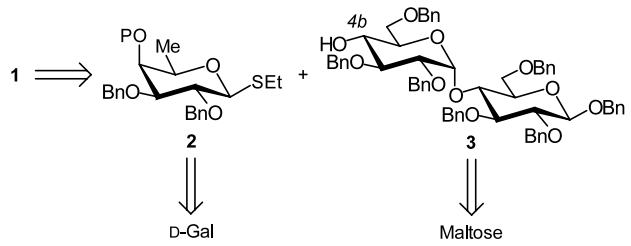


Fig. 1. Structure of acarbose **1**.

program devoted to a novel route for synthesizing acarbose along with new derivatives. Since valienamine can be produced according to different methods,[8] we first focused on the preparation of the carbohydrate domain. Ogawa's approach relies on a pre-formed maltotriosyl compound[5] further transformed into an epoxide. However, introduction of the valienamine part on the trisaccharidic epoxide was not regiospecific. In a second possibility, Danishefsky and coworkers used α-glycal epoxides and glycosyl fluorides as donors for the construction of two new glycosidic linkages.[6] The third known synthesis was proposed by Schmidt and Laesecke who performed a coupling reaction between a maltosidic acceptor and an extremely rare quinovosyl trichloroacetimidate.[7] Unfortunately, the two latter methodologies were achieved without total diastereocontrol of the glycosylation reactions. In consideration of these precedents, the choice of glycosyl donor(s) proves to be crucial to success in this project.

Numerous studies have shown that the reactivity of both donor and acceptor is closely connected with the nature and the position of protecting groups present on these substrates. Amongst the most popular donors, we turned to thioglycosides owing to their easy availability and their compatibility with various protecting group manipulations. Conversely, Wong and coworkers were able to establish a reactivity database of thioglycosides in which the more reactive donor is a perbenzylated 1-thio-L-fucopyranoside.[9] Moreover, other authors reported that 1,2-*cis*-L-fucosides are often obtained with excellent stereoselectivities using non-participating benzyl ether groups.[10] Therefore, we assumed that a similar behavior occurs starting from the enantiomeric 1-thio-D-fucopyranosyl donor. For our purpose, further carbohydrate domain elongation requires an orthogonal protecting group at the axial hydroxyl on the donor, and the effect of four groups was examined (Scheme 1). Since D-fucose is an expensive raw material, preparation of the required donor **2** was best achieved starting from D-galactose. Finally, in order to limit glycosylation reactions, we selected the 4^{II}-OH free maltoside **3** as an acceptor since it can be obtained in a few steps from maltose, a common and easily available disaccharide



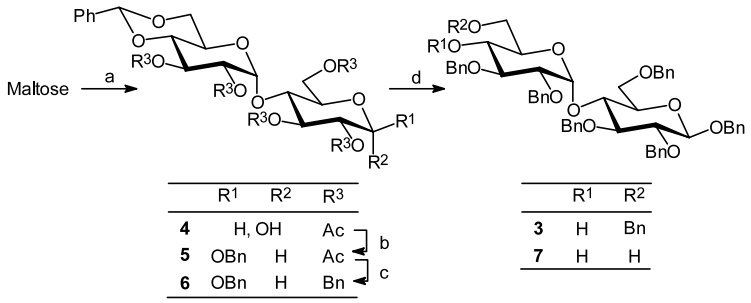
Scheme 1. Proposed retrosynthetic scheme for **2** and **3**.

already possessing an appropriate α-D-Glc-(1→4)-D-Glc linkage.

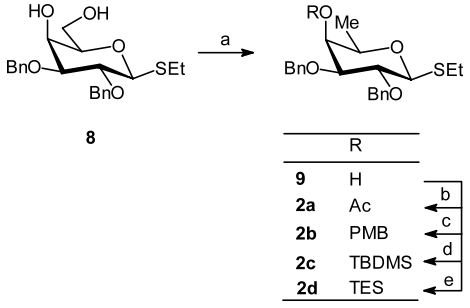
2. Results and discussion

Acceptor **3** has been prepared as a mixture of α,β-anomers from maltose in only three steps.[11] However, we anticipated that the resulting α,β-mixture would significantly complicate NMR assignments after fucosylation reaction since two or four different diastereoisomers could theoretically be obtained. Therefore, the structurally well defined compound **3**, presenting a reducing unit with an anomeric β configuration, was prepared according to a multi-step approach by first acetalizing maltose in dimethylsulfate–dimethylformamide mixture at 70 °C.[12] This procedure cleanly afforded the 4^{II},6^{II}-benzylidene maltose in 67% yield. Acetylation under standard conditions followed by selective anomeric deacylation under the action of morpholine afforded the hemiacetal **4** (Scheme 2). The key 1-*O*-benzylation was further achieved in a similar fashion as that already described for the preparation of methyl maltoside.[13] Using silver(I) oxide as a base in dichloromethane, the kinetically favored β-anomer **5** was isolated in 83% yield and exclusively obtained as revealed the NMR spectrum and more particularly the coupling constant value of 7.6 Hz between H-1a and H-2a. Subsequent Zemplén transesterification followed by standard benzylation furnished **6** which was submitted to reductive opening of the benzylidene ring. The latter reaction proved to be tightly dependent on both the reductive agent and the proton source. First attempted opening by the borane–tetrahydrofuran complex in the presence of methanesulfonic acid gave the undesired 4-OBn, 6-OH maltoside in 65% yield along with 16% of diol **7**. Although this by-product could not be totally avoided, the required compound **3** was synthesized using the borane–trimethylamine complex and aluminum trichloride, or better still, methanesulfonic acid. The maltosidic acceptor **3** was thus chromatographically isolated in 56% and 68% yield, respectively.

Our attention was further turned to the synthesis of the D-fucopyranosyl donor. Its preparation started from known thiogalactopyranoside **8**[14] (Scheme 3). This latter substrate was obtained in our laboratory in five steps



Scheme 2. Preparation of maltosidic acceptor **3**. Conditions: (a) i. PhCHO, Me_2SO_4, DMF (67%); ii. Ac_2O, Pyr (94%); iii. morpholine, CH_2Cl_2 (88%); (b) BnBr, Ag_2O, CH_2Cl_2 (83%); (c) i. NaOMe, MeOH; ii. BnBr, NaH, DMF (88%); (d) BH_3:NMe_3, $MeSO_3H$, THF (**3**: 68%; **7**: 17%).



Scheme 3. Synthesis of D-fucopyranosyl donors **2a**–**d**. Conditions: (a) i. MsCl, Et_3N, CH_2Cl_2; ii. $LiAlH_4$, THF (80%); (b) Ac_2O, Pyr, DMAP (97%); (c) PMBCl, NaH, DMF (69%); (d) TBDMSCl, imidazole, DMF (84%); (e) TESCl, imidazole, DMF (99%).

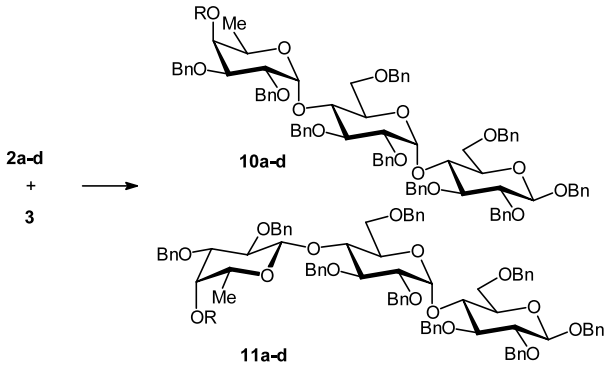
from peracetyl D-galactose (thioglycosidation under Ferrier conditions, Zemplén deacetylation, acido-catalyzed transbenzylidenation, benzylation and acidic hydrolysis) in 64% overall yield. Regiospecific activation of the primary position yielded a mesylate which was reduced by lithium aluminum hydride. The resulting monohydroxylated thiofucopyranoside **9** was subsequently protected either with electron-withdrawing group, i.e., acetyl (→**2a**), or as ethers, i.e., *p*-methoxybenzyl (PMB, →**2b**), *t*-butyldimethysilyl (TBDMS, →**2c**) and triethylsilyl (TES, →**2d**). During this work, a similar procedure was proposed by Floss et al. starting from a 2-(trimethylsilyl)ethyl galactopyranoside.[15]

With acceptor **3** and donors **2a**–**d** in hand, optimization of both stereoselectivity and yield of the glycosylation step was carried out considering three parameters: (i) the solvent; (ii) the nature of C-4 protecting group on the donor and; (iii) the promoter. On the basis of our experiment relative to the preparation of 1,2-*cis*-hexofuranosides from perbenzylated thiofuranosyl donors,[16] the coupling reactions were promoted by a small excess of *N*-iodosuccinimide (NIS) in the presence of a catalytic amount of an added Lewis acid, tin(II) trifluoromethanesulfonate [$Sn(OTf)_2$]. Since S_N2 type reactions are favored in solvents with low polarity, glycosylations were also performed in dichloromethane or in toluene. Conversely, it was shown that electron-donating solvent such as ethers are able to stabilize an intermediate oxycarbenium and so strengthen the α-directed introduction of the nucleophile.[17] First coupling was achieved from 4-*O*-acetylated fucosyl donor **2a** and acceptor **3** in a 1:2.4 toluene-1,4-dioxane mixture and was promoted by NIS/$Sn(OTf)_2$. After stirring for 45 min at room temperature, standard work-up and chromatography, the desired trisaccharide **10a** and its stereoisomer **11a** presenting a β-D-fucopyranosyl entity were isolated in 63% global yield (Table 1, entry 1). Considering 2D NMR data, the non-reducing fucosides in **10a** and **11a** clearly differed from one another in coupling constant values, $J_{1c,2c}$ 3.8 Hz for the major **10a** while $J_{1c,2c}$ 7.8 Hz for **11a**. These results were corroborated by $J_{C\text{-}1,H\text{-}1}$ values obtained according to a HMQC technique.[18] Indeed, a characteristic difference of 11 Hz between one-bond coupling constants was observed for the C-1–H-1 bond of the fucopyranosyl residues in **10a** and **11a** with a greater value for the α-anomer ($J_{C\text{-}1c,H\text{-}1c}$ 172.9 Hz in **10a** and $J_{C\text{-}1c,H\text{-}1c}$ 161.3 Hz in **11a**).

Improved yields and, more interestingly, better selectivities were observed with donors **2b**–**d** bearing 4-*O*-PMB or 4-*O*-silyl ether groups (entries 2–7). Target trisaccharides **10b**–**d** were thus exclusively obtained in good to excellent yield. It is noteworthy that: (i) reaction times significantly decreased by performing the coupling in dry toluene without molecular sieves (entries 5–7); (ii) using the sterically less demanding TES group and; (iii) substituting the stannous salt by the corresponding copper(II) ditriflate lead to optimum conditions (entry 7). These results highlighted the impact of C-4 protecting group on the stereochemistry of the glycosylation reaction starting from fucopyranosyl donor and the need for a C-4-electron-donating group to ensure the target α-stereodirection.[19] Moreover, this procedure proved to be highly reproducible so that the required trisaccharide **10d** was stereospecifically prepared on a multi-gram scale and isolated in 95% yield.

Carrying out this project involved further inversion of the C-4c configuration on the trisaccharide. Consequently, selective removal of silyl group by fluoride

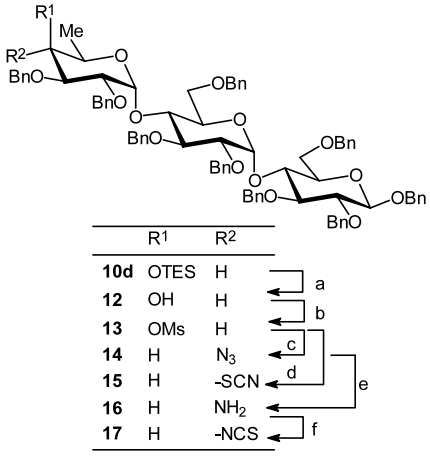
Table 1
Optimization of glycosidic coupling starting from **12a**–**d** as donors and **3** as acceptor



Entry	Donor	Promoter (equiv.)	Time (min)	Solvent (v/v)	Products (selectivity) [a]	R	Yield (%)
1	**2a**	NIS (1.2), $Sn(OTf)_2$ (0.2)	45	Toluene-1,4-dioxane (1:2.4) [b]	**10a/11a** (5.2:1)	Ac	63
2	**2b**	NIS (1.2), $Sn(OTf)_2$ (0.2)	45	CH_2Cl_2 [b]	**10b/11b** (19.4:1)	PMB	73
3	**2b**	NIS (1.2), $Sn(OTf)_2$ (0.2)	45	Toluene-1,4-dioxane (1:2.4) [b]	**10b/11b** (1:0)	PMB	75
4	**2c**	NIS (1.2), $Sn(OTf)_2$ (0.2)	45	Toluene-1,4-dioxane (1:2.4) [b]	**10c/11c** (1:0)	TBDMS	81
5	**2c**	NIS (1.2), $Sn(OTf)_2$ (0.2)	10	Toluene	**10c/11c** (1:0)	TBDMS	70
6	**2d**	NIS (1.2), $Sn(OTf)_2$ (0.2)	5	Toluene	**10d/11d** (1:0)	TES	60
7	**2d**	NIS (1.2), $Cu(OTf)_2$ (0.2)	15	Toluene	**10d/11d** (1:0)	TES	95

[a] Selectivities were established on the integrating values corresponding to H-1c.
[b] Reactions were carried out in the presence of 4 Å molecular sieves.

anions led to derivative **12** (Scheme 4). According to previous results on the synthesis of β-acarbose,[20] displacement of an axial triflate group by a nucleophilic aminocyclitol resulted in β-elimination. On this consideration, a mesyl group was preferred to a triflate one. However, owing to the low reactivity of the axial hydroxyl, mesylation required addition of a nucleophilic catalyst. Thus, in the presence of *N*,*N*-dimethylaminopyridine (DMAP), target compound **13** was isolated in 90% yield. Subsequently, and in order to mimic mesylate substitution by a free amino-valienamine, the primary cyclohexylamine ($CyNH_2$) was chosen as a nucleophile. After refluxing **13** in pure $CyNH_2$ for 3 days, no reaction occurred. In a second attempt, displacement was performed with the corresponding lithium amide (CyNHLi) in dry THF. Unfortunately, even at $-60\,^{\circ}C$, substitution was performed on the sulfur atom so that trisaccharide **12** was finally isolated in 70% yield. These results may be ascribed to some hindrance of the



Scheme 4. Synthesis of scaffolds **12**–**17**. Conditions: (a) TBAF, THF (95%); (b) MsCl, DMAP, CH_2Cl_2 (90%); (c) NaN_3, TBABr, DMF (95%); (d) KSCN, TBABr, DMF (65%); (e) i. PPh_3, toluene; ii. H_2O, NaOH (90%); (f) $CSCl_2$, DMAP, CH_2Cl_2 (90%).

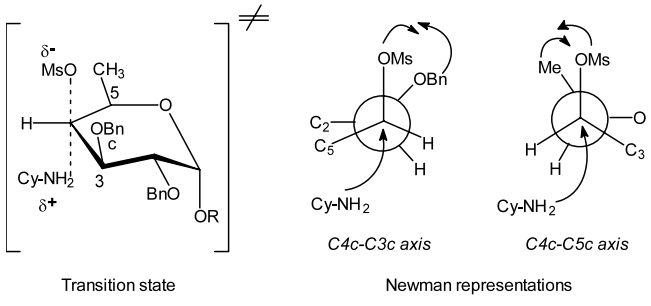


Fig. 2. Conformation constrain during the nucleophilic substitution.

incoming nucleophile and to some increased energy in the transition state following on required ring distortion and consequently eclipsing between mesylate group and 3-*O*-benzyl and 6-methyl ones (Fig. 2). Therefore, we assumed that less sterically demanding but good nucleophile species could be more suitable. Thus, the azide and ambivalent thiocyanate anions[21] were reacted with **13** to give the desired trisaccharidic azide **14** and thiocyanate **15** exclusively. The structure of the resulting thiocyanato derivative was unambiguously established on the basis of a band at 2152 cm^{-1} obtained by IR spectroscopy. Although the yields in **14** and **15** were significant, 95% and 65%, respectively, the reactions required heating and a phase transfer catalyst such as tetrabutylammonium bromide (TBABr), strengthening the idea that a nucleophilic substitution at the axial C-4c position was energetically demanding. Two other synthons, potentially interesting for the preparation of acarbose and analogues, were also obtained from azide **14**. The amine **16** was synthesized by chemoselective reduction under Staudinger procedure. Since this trisaccharidic amine could act as a nucleophile for further linking to an electrophilic cyclitol derivative, our approach complements well that proposed by Danishefsky[6] in which the carbohydrate domain was used as an electrophile. Moreover, this amine **16** was further transformed into the new thiocyanato derivative **17** under the action of thiophosgene and DMAP. The IR spectra of the product differ from those of **15** and results in a typical absorption band at 2050 cm^{-1}. Both amine **16** and thiocyanate **17** were isolated in excellent 90% yield.

In conclusion, we have designed a new strategy for the synthesis of the carbohydrate domain of acarbose. We therefore prepared attractive and new trisaccharidic synthons which could be used as precursors for the total synthesis of the therapeutic pseudotetrasaccharide. The crucial glycosylation reaction in this approach involved a maltosidic acceptor, easily available from maltose in a few steps, and a D-fucopyranosyl donor specifically prepared from D-galactose. Various parameters were improved and this allowed us to select toluene as solvent, NIS/$Cu(OTf)_2$ as a promoter and more importantly a silyl protecting group at the axial hydroxyl on the fucosyl donor. Because of its low steric bulk, the TES group was straightforwardly introduced on the less reactive 4-OH and was also efficiently removed after glycosylation. Moreover, we have prepared an amino trisaccharide, for further reacting with a precursor of the valienamine part, and three trisaccharidic building blocks, an azide, a thiocyanate and an isothiocyanate, which are likely to be elongated for the preparation of novel families of acarbose analogues. Such a project is currently developed in our laboratory and results will be published in due time.

3. Experimental

3.1. General methods

Melting points were determined on a Reichert microscope and are uncorrected. TLC analyses were conducted on E. Merck 60 F_{254} silica gel non-activated plates and compounds were revealed using a 5% soln of H_2SO_4 in EtOH followed by heating. For column chromatography, E. Merck 60H (5–40 μm) silica gel was used. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. ^1H, ^{13}C, HETCOR and COSY NMR spectra were recorded in $CDCl_3$ on a Brüker ARX 400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C analyses. Chemical shifts are given in δ-units measured downfield from Me_4Si. Assignments of ^1H and ^{13}C for carbohydrate residues of compounds **2**–**17** are given in Tables 2–7. Microanalyses were performed by the Service de Microanalyse de l'ICSN (Gif sur Yvette, France) and by the Service de Microanalyse de l'Institut de Chimie de Rennes (CRMPO, Rennes, France).

3.2. 2,3-Di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-(α,β)-D-glucopyranose (4)

Maltose (5 g, 13.14 mmol) and benzaldehyde (3.07 mL, 30 mmol) were successively added at rt to a soln of dimethylsulfate (2.5 mL, 26.28 mmol) in DMF (10 mL). The mixture was then heated to 70 °C for 12 h and cooled to rt before quenching with Et_3N (3.66 mL, 52.56 mmol). Excess of the base was evaporated under diminished pressure and the residue was diluted with water (200 mL), extracted with CH_2Cl_2 (3150 mL) and with 1:1 EtOAc–*n*-BuOH (5200 mL). The organic layers were concentrated and purification by flash chromatography (22:3 CH_2Cl_2–MeOH) gave a white solid (4 g, 67%).

A soln of the latter compound (47.8 g, 111 mmol) and Ac_2O (75.4 mL, 800 mmol) in pyridine (250 mL, 3.5 mol) was stirred at rt for 24 h. The reaction media was further concentrated under diminished pressure and then poured into water (1.5 L). After 10 h, the white precipitate was filtered and then dissolved with CH_2Cl_2 (1 L), washed with water (2500 mL), dried ($MgSO_4$) and concentrated under diminished pressure to give a colorless solid (71 g, 94%).

To a soln of this solid (8.6 g, 12.6 mmol) in dry CH_2Cl_2 (40 mL) was added morpholine (4.4 ml, 50 mmol). The reaction media was heated to 40 °C for 20 h and then diluted with CH_2Cl_2 (200 mL). The mixture was successively washed with 5% aq HCl (100 mL), 5% aq $NaHCO_3$ (50 mL) and water (100 mL), dried ($MgSO_4$) and concentrated. The residue was triturated in cyclohexane (200 mL) and finally filtered to give **4**

(7.07 g, 88%) as a white solid: mp 218 °C; $[\alpha]_D^{20}$ +73° (*c* 1.0, $CHCl_3$); TLC (1:1 petroleum ether–EtOAc): R_f = 0.3; **4α**: ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 2), 7.37–7.25 (m, 5 H, C_6H_5), 5.42 (s, 1 H, OC*H*Ph), 2.13 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.02 (s, 3 H, OAc); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 3), 171.0, 170.9, 170.6, 170.4, 170.1 (CO), 136.4 (C_{ipso}), 129.0, 128.0, 126.0 (C_6H_5), 101.5 (O*C*HPh), 20.8–20.3 (CO*C*H_3); **4β**: ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 2), 7.37–7.25 (m, 5 H, C_6H_5), 5.42 (s, 1 H, OC*H*Ph), 2.13 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.02 (s, 3 H, OAc); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 3), 171.0, 170.9, 170.6, 170.4, 170.1 (CO), 136.4 (C_{ipso}), 129.0, 128.0, 126.0 (C_6H_5), 101.5 (O*C*HPh), 20.8–20.3 (CO*C*H_3). Anal. Calcd for $C_{29}H_{36}O_{16}$: C, 54.37; H, 5.66. Found: C, 54.00; H, 5.75.

3.3. Benzyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (5)

To a soln of **4** (1.21 g, 1.9 mmol) in CH_2Cl_2 (25 mL) was added freshly prepared Ag_2O (800 mg, 3.8 mmol). The mixture was stirred in the dark for 30 min before adding BnBr (452 mL, 3.8 mmol). The media was stirred for a further 10 h, filtered through a bed of celite and concentrated under diminished pressure. Flash column chromatography with 3:2 light petroleum–EtOAc afforded **5** (1.15 g, 83%) as a white solid: mp 218 °C; $[\alpha]_D^{20}$ +2° (*c* 1.0, $CHCl_3$); TLC (3:2 petroleum ether–EtOAc): R_f = 0.4; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 2), 7.30–7.15 (m, 10 H, C_6H_5), 4.78 (d, 1 H, *J* 12.2 Hz, OCH_2Ph), 5.39 (s, 1 H, OC*H*Ph), 4.51 (d, 1 H, OCH_2Ph), 2.04 (s, 3 H, OAc), 1.95 (s, 6 H, OAc), 1.91 (s, 3 H, OAc), 1.90 (s, 3 H, OAc); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 3), 170.9, 170.4, 170.3, 170.8 (CO), 136.7, 136.7 (C_{ipso}), 129.2, 128.5, 128.3, 128.1, 127.9, 126.2 (C_6H_5), 101.6 (O*C*HPh), 70.7 (O*C*H_2Ph), 21.0, 20.9, 20.8, 20.7 (CO*C*H_3). Anal. Calcd for $C_{36}H_{42}O_{16}$: C, 59.17; H, 5.79. Found: C, 59.62; H, 5.79.

3.4. Benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (6)

To a soln of **5** (3.7 g, 5.06 mmol) in dry MeOH (37 mL) was added sodium (20 mg, 0.9 mmol). After stirring at rt for 3 h, the reaction was neutralized with IR-120 (H^+-form), filtered and concentrated under diminished pressure. To the resulting residue diluted with DMF (56 mL) and cooled to 0 °C were successively added a 60% dispersion of NaH in mineral oil (2.3 g, 57.5 mmol) and BnBr (3.1 mL, 26.2 mmol). The mixture was allowed to stir at rt for 10 h, quenched with MeOH (5 mL) and concentrated under diminished pressure. Purification by flash chromatography (7:3 light petroleum–EtOAc) lead to **6** (3.74 g, 88%) as a colorless solid: mp 92 °C; $[\alpha]_D^{20}$ −3° (*c* 1.0, $CHCl_3$); TLC: (4:1 petroleum ether–EtOAc): R_f = 0.6; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 2), 7.55–7.15 (m, 35 H, C_6H_5), 5.58 (s, 1 H, OC*H*Ph), 5.03–4.55 (m, 14 H, OCH_2Ph); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 3), 138.7, 138.6, 138.2, 138.1, 137.8, 137.5, 137.4 (C_{ipso}), 128.8–126.0 (C_6H_5), 101.1 (O*C*HPh), 75.3, 74.7, 73.8, 73.7, 73.4, 71.0 (O*C*H_2Ph). Anal. Calcd for $C_{61}H_{62}O_{11}$: C, 75.44; H, 6.44. Found: C, 75.64; H, 6.51.

3.5. Benzyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (3)

To a soln of **6** (37.74 g, 38.9 mmol) in dry THF (350 mL) were successively added BH_3:NMe_3 (16.8 g, 220.8 mmol) and fractions of $MeSO_3H$ (14.28 mL, 220.8 mmol) in THF (50 mL). The mixture was stirred for 12 h, neutralized with Et_3N (28 mL, 220.8 mmol) and then concentrated under diminished pressure. The residue was diluted with CH_2Cl_2 (500 mL) and successively washed with 1N aq H_2SO_4 (150 mL), 5% aq $NaHCO_3$ (150 mL) and water (200 mL). The organic layer was dried ($MgSO_4$), concentrated and flash chromatographed (4:1 light petroleum–EtOAc) to yield **3** (25.7 g, 68%) as a colorless oil and diol **7** (5.85 g, 17%). **3**: $[\alpha]_D^{20}$ +13° (*c* 1.0, $CHCl_3$); TLC: (7:3 petroleum ether–EtOAc): R_f = 0.4; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 2), 7.42–7.14 (m, 35 H, C_6H_5), 4.97–4.39 (m, 14 H, OCH_2Ph); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 3), 138.7, 138.4, 138.2, 137.9, 137.8, 137.4 (C_{ipso}), 128.5–126.6 (C_6H_5), 75.3, 74.6, 73.8, 73.5, 73.2, 73.0, 70.9 (OCH_2Ph). Anal. Calcd for $C_{61}H_{64}O_{11}$: C, 75.29; H, 6.63. Found: C, 75.14; H, 6.69; **7**: mp: 107 °C; $[\alpha]_D^{20}$ + 13° (*c* 1.0, $CHCl_3$); TLC: (3:2 petroleum ether–EtOAc): R_f = 0.2; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 2), 7.42–7.14 (m, 30 H, C_6H_5), 4.98–4.50 (m, 12 H, OCH_2Ph); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 3), 137.6, 137.5, 137.0, 136.7, 136.3 (C_{ipso}), 127.5–125.5 (C_6H_5), 74.2, 73.6, 72.8, 72.4, 72.0, 69.9 (OCH_2Ph). Anal. Calcd for $C_{54}H_{58}O_{11}$: C, 73.45; H, 6.62. Found: C, 73.51; H, 6.61.

3.6. Ethyl 2,3-di-*O*-benzyl-1-thio-β-D-fucopyranoside (9)

To a soln of **8** (1.7 g, 4.2 mmol) in CH_2Cl_2 (7.5 mL) were successively added Et_3N (1.17 mL, 8.4 mmol) and MsCl (365 μl, 5.04 mmol) at 0 °C. After 1 h at rt, the reaction media was diluted with CH_2Cl_2 (80 mL), washed with aq satd NH_4Cl (230 mL) and water (40 mL), dried

Table 2
^{1}H NMR (400 MHz) chemical shifts and coupling constants (^{1}H–^{1}H) for maltosidic derivatives **3**–**7**

Compound	δ (ppm), J (Hz)													
	H-1a ($J_{1a,2a}$)	H-2a ($J_{2a,3a}$)	H-3a ($J_{3a,4a}$)	H-4a ($J_{4a,5a}$)	H-5a ($J_{5a,6a}$)	H-6a ($J_{6a,6'a}$)	H-6′a ($J_{5a,6'a}$)	H-1b ($J_{1b,2b}$)	H-2b ($J_{2b,3b}$)	H-3b ($J_{3b,4b}$)	H-4b ($J_{4b,5b}$)	H-5b ($J_{5b,6b}$)	H-6b ($J_{6b,6'b}$)	H-6′b ($J_{5b,6'b}$)
4α	5.18	4.72–4.66	5.53	3.96–3.91	4.22–4.15	4.50–4.43	4.22–4.15	5.33–5.30	4.81	5.41–5.36	3.49	3.80–3.76	4.22–4.15	3.72–3.66
	(nd)	(nd)	(9.4)	(9.4)	(nd)	(nd)	(nd)	(4.3)	(10.2)	(9.7)	(9.7)	(nd)	(nd)	(nd)
4β	4.72–4.66	4.72–4.66	5.22–5.18	4.00–3.95	3.72–3.66	4.50–4.43	4.22–4.15	5.33–5.30	4.81	5.41–5.36	3.49	3.80–3.76	4.22–4.15	3.72–3.66
	(3.8)	(9.5)	(9.5)	(nd)	(nd)	(nd)	(nd)	(4.1)	(10.2)	(9.7)	(9.7)	(nd)	(nd)	(nd)
5	4.47	3.83–3.75	5.13	3.95	3.60–3.55	4.50–4.46	4.20–4.14	5.30–5.24	3.83–3.75	5.36	3.58	3.78–3.74	4.20–4.14	3.64
	(7.6)	(9.1)	(9.1)	(9.1)	(nd)	(nd)	(nd)	(3.1)	(12.5)	(9.9)	(9.7)	(4.3)	(4.3)	(10.4)
6	4.42	3.55–3.45	3.71–3.64	4.02	3.55–3.45	3.74	3.71–3.64	5.60	3.38	3.87	3.55–3.45	3.76	4.06	3.55–3.45
	(7.6)	(nd)	(8.9)	(9.1)	(3.8)	(nd)	(10.9)	(3.8)	(9.4)	(9.4)	(nd)	(4.8)	(nd)	(10.2)
3	4.55	3.62–3.56	3.82–3.75	4.09	3.62–3.56	3.62–3.56	3.50	5.67	3.45	3.74	3.65	3.82–3.75	3.85	3.82–3.75
	(7.6)	(nd)	(9.1)	(9.1)	(nd)	(3.8)	(10.2)	(3.6)	(9.4)	(9.1)	(2.3	(nd)	(4.8)	(11.2)
7	4.46	3.60–3.50	3.75–3.68	4.02	3.60–3.50	3.75	3.75–3.68	5.59	3.31	3.63	3.41	3.60–3.50	3.60–3.50	3.60–3.50
	(7.6)	(nd)	(nd)	(nd)	(3.8)	(nd)	(11.4)	(3.8)	(9.7)	(9.1)	(8.6)	(nd)	(nd)	(nd)

nd: not determined.

Table 3
^{13}C NMR (400 MHz) chemical shifts for maltosidic derivatives **3**–**7**

Compound	δ (ppm)											
	C-1a	C-2a	C-3a	C-4a	C-5a	C-6a	C-1b	C-2b	C-3b	C-4b	C-5b	C-6b
4α	94.2	73.5	75.5	72.5	71.9	62.7	96.1	70.7	68.4	78.5	63.5	68.2
4β	94.2	73.5	75.5	72.5	71.9	62.7	96.1	70.7	68.4	78.5	63.5	68.2
5	98.7	72.2	75.6	72.7	72.2	62.6	96.4	70.8	68.5	78.8	63.7	68.5
6	102.4	82.4	85.0	72.0	74.3	68.8	97.3	78.7	78.9	82.3	63.3	69.0
3	102.4	82.3	84.9	72.5	74.6	69.7	96.6	79.0	81.3	71.4	70.7	69.2
7	102.3	82.2	84.9	72.2	74.6	68.6	96.4	79.1	81.2	70.4	71.9	62.3

($MgSO_4$) and finally concentrated under diminished pressure. The resulting crude oil was diluted with THF (25 mL) and added dropwise to a cooled (0 °C) suspension of LAH (478 mg, 12.6 mmol) in THF (15 mL). After 30 min at 0 °C and diluting with THF (50 mL), acetone (5 mL) and 10% NaOH (1.2 mL) were successively and carefully added to give a white precipitate that could be filtered and washed with EtOAc (100 mL). The organic layer was washed with aq satd NH_4Cl (250 mL) and water (250 mL), dried ($MgSO_4$) and concentrated under diminished pressure. Flash chromatography (73:27 light petroleum–EtOAc) gave **9** (1.22 g, 75%) as a white solid: mp: 67–70 °C; $[\alpha]_D^{20}$ −3° (*c* 1, $CHCl_3$); TLC (7:3 toluene–Et_2O): $R_f = 0.4$; ^1H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 4), 7.42–7.39 (m, 2 H, C_6H_5), 7.36–7.29 (m, 8 H, C_6H_5), 4.88 (d, 1 H, *J* 10.3 Hz, OC*H*$_2$Ph), 4.77 (d, 1 H, *J* 10.3 Hz, OC*H*$_2$Ph), 4.73 (d, 1 H, *J* 12.4 Hz, OC*H*$_2$Ph), 4.70 (d, 1 H, *J* 12.4 Hz, OC*H*$_2$Ph), 3.81 (ddd, 1 H, $J_{4,OH}$ 2.2 Hz, H-4), 2.83–2.67 (m, 2 H, C*H*$_2$CH$_3$), 1.31 (t, 3 H, *J* 7.4 Hz, CH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 5), 138.2, 137.8 (C_{ipso}), 128.5–127.8 (C_6H_5), 75.8 (O*C*H$_2$Ph), 72.1 (O*C*H$_2$Ph), 24.7 (*C*H$_2$CH$_3$), 15.0 (CH$_2$*C*H$_3$). Anal. Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26. Found: C, 68.29; H, 7.27.

Table 5
^{13}C NMR (400 MHz) chemical shifts for derivatives **2a**–**d**, **8** and **9**

Compound	δ (ppm)					
	C-1	C-2	C-3	C-4	C-5	C-6
8	85.6	78.2	82.6	67.8	78.2	62.9
9	84.7	77.8	82.7	69.5	74.1	16.7
2a	84.9	77.7	81.0	69.4	72.9	15.0
2b	84.9	78.4	84.5	75.8	74.5	17.2
2c	83.5	76.1	82.6	70.9	73.9	16.7
2d	84.8	77.6	83.6	72.1	75.0	17.4

3.7. Ethyl 2,3-di-*O*-benzyl-4-*O*-acetyl-1-thio-β-D-fucopyranoside (2a)

A soln of monohydroxylated fucoside **9** (2.5 g, 6.4 mmol), Ac_2O (3 mL, 32.2 mmol) and DMAP (16 mg, 0,13 mmol) in dry pyridine (25 mL) was stirred over-

Table 4
^1H NMR (400 MHz) chemical shifts and coupling constants (^1H–^1H) for derivatives **2a**–**d**, **8** and **9**

Compound	δ (ppm), *J* (Hz)						
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6 ($J_{6,6'}$)	H-6′ ($J_{5,6'}$)
8	4.43	3.67	3.55	4.05	3.46	3.92	3.78
	(9.7)	(9.0)	(3.3)	(0.9)	(6.5)	(4.6)	(11.8)
9	4.39	3.62	3.56–3.53	3.81	3.56–3.53	1.34	
	(9.6)	(9.1)	(3.2)	(0.9)	(6.5)		
2a	4.45	3.58	3.62	5.38	3.65	1.22	
	(9.1)	(9.0)	(3.0)	(1.0)	(6.4)		
2b	4.38	3.81	3.55	3.53	3.45	1.16	
	(9.7)	(9.4)	(2.9)	(0.9)	(6.3)		
2c	4.34	3.75	3.41	3.81	3.49	1.23	
	(9.5)	(9.3)	(2.4)	(< 1.0)	(6.2)		
2d	4.29	3.67	3.33	3.76	3.4	1.23	
	(9.7)	(9.4)	(2.3)	(< 1.0)	(6.4)		

night at rt. After removal of the solvent, the crude oil was diluted in CH_2Cl_2 and purified by chromatography eluting with 9:1 petroleum ether–EtOAc. Compound **2a** (2.69 g) was obtained in 97% yield: mp: 61 °C; $[\alpha]_D^{20}$ + 21° (*c* 1, $CHCl_3$); TLC (9:1 petroleum ether–EtOAc): $R_f = 0.2$; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 4), 7.41–7.37 (m, 2 H, C_6H_5), 7.36–7.24 (m, 8 H, C_6H_5), 4.83 (d, 1 H, *J* 10.2 Hz, OCHPh), 4.77 (d, 1 H, *J* 10.3 Hz, OCHPh), 4.74 (d, 1 H, *J* 11.3 Hz, OCHPh), 4.52 (d, 1 H, *J* 11.3 Hz, OCHPh), 2.76 (qd, 2 H, ^2J 12.5 Hz, *J* 7.4 Hz, CH_2CH_3), 2.18 (s, 3 H, CH_3CO), 1.32 (t, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 5), 171.0 (CO), 137.7, 138.2 (C_{ipso}), 128.4–127.8 (C_6H_5), 75.8 (OCH_2Ph), 71.8 (OCH_2Ph), 24.9 (CH_2CH_3), 21.0 (CH_3CO), 16.7 (CH_2CH_3). Anal. Calcd for $C_{22}H_{28}O_4S$: C, 65.95; H, 7.00. Found: C, 66.68; H, 6.96.

3.8. Ethyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-fucopyranoside (2b)

To a soln of **9** (300 mg, 0.77 mmol) in freshly distilled DMF (5 mL) cooled at 0 °C were successively added *p*-methoxybenzyl chloride (209 μL, 1.54 mmol) and a 60% suspension of sodium hydride in oil (62 mg, 1.54 mmol). The media was slowly warmed to rt and stirred for 3 h. After diluting with CH_2Cl_2 (20 mL), the soln was washed with aq satd NH_4Cl (10 mL) and water (20 mL), the organic layer dried ($MgSO_4$) and concentrated. Purification by chromatography (9:1 light petroleum–EtOAc) yielded the desired donor **2b** (271 mg, 69%): mp: 61 °C; $[\alpha]_D^{20}$ −11° (*c* 1, $CHCl_3$); TLC (7:3 petroleum ether–EtOAc): $R_f = 0.5$; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 4), 7.42–7.24 (m, 12 H, C_6H_5), 6.87–6.82 (m, 2 H, C_6H_5), 4.91 (d, 1 H, *J* 11.5 Hz, OCH_2Ph), 4.90 (d, 1 H, *J* 10.2 Hz, OCH_2Ph), 4.80 (d, 1 H, *J* 10.2 Hz, OCH_2Ph), 4.76 (d, 1 H, *J* 11.8 Hz, OCH_2Ph), 4.72 (d, 1 H, *J* 11.8 Hz, OCH_2Ph), 4.64 (d, 1 H, *J* 11.5 Hz, OCH_2Ph), 3.79 (s, 3 H, OCH_3), 2.73 (qd, 2 H, *J* 12.5, *J* 7.4 Hz, CH_2CH_3), 1.29 (t, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 5), 159.1, 138.5, 138.4 (C_{ipso}), 130.8–113.5 (C_6H_5), 75.7 (OCH_2Ph), 74.0 (OCH_2Ph), 72.8 (OCH_2Ph), 55.2 (OCH_3), 24.7 (CH_2CH_3), 15.0 (CH_2CH_3). Anal. Calcd for $C_{30}H_{36}O_5S$: C, 70.83; H, 7.13. Found: C, 70.83; H, 7.17.

3.9. Ethyl 2,3-di-*O*-benzyl-4-*O*-*t*-butyldimethysilyl-1-thio-β-D-fucopyranoside (2c)

A suspension of fucopyranoside **9** (300 mg, 0,77 mmol) and imidazole (209 mg, 3,08 mmol) in dry DMF (6 mL) containing 3 Å molecular sieves (300 mg) was stirred at rt and under N_2 for 30 min. *t*-Butyldimethysilyl chloride (700 mg, 4,64 mmol) was then added and the resulting mixture was heated at 90 °C for 24 h. After cooling and diluting with CH_2Cl_2, the molecular sieves were removed by filtration over a bed of Celite. The filtrate was finally washed with aq satd NaCl (10 mL) and water (20 mL), dried ($MgSO_4$) and chromatographed (7:3 petroleum ether–EtOAc) to afford target **2c** (325 mg, 84%) as a white amorphous solid: mp: 49 °C; $[\alpha]_D^{20}$ +3° (*c* 1, $CHCl_3$); TLC (7:3 petroleum ether–EtOAc): $R_f = 0.3$; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 4), 7.41–7.24 (m, 10 H, C_6H_5), 4.89 (d, 1 H, *J* 10.2 Hz, OCH_2Ph), 4.78 (d, 1 H, *J* 10.2 Hz, OCH_2Ph), 4.75–4.68 (m, 2 H, OCH_2Ph), 2.72 (qd, 2 H, *J* 12.5, *J* 7.4 Hz, CH_2CH_3), 1.30 (t, 3 H, CH_2CH_3), 0.92 [s, 9 H, $C(CH_3)_3$], 0.09 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 5), 137.3 (C_{ipso}), 127.4, 127.2, 126.7, 126.6, 126.4 (C_6H_5), 74.4 (OCH_2Ph), 72.0 (OCH_2Ph), 25.1 [$C(CH_3)_3$], 22.6 (CH_2CH_3), 17.5 [$C(CH_3)_3$], 14.1 (CH_2CH_3), −4.9 (CH_3Si), −5.6 (CH_3Si). Anal. Calcd for $C_{28}H_{42}O_4SSi$: C, 66.89; H, 8.42. Found: C, 67.02; H, 8.45.

3.10. Ethyl 2,3-di-*O*-benzyl-4-*O*-triethylsilyl-1-thio-β-D-fucopyranoside (2d)

To a soln of **9** (6.9 g, 17.86 mmol) in DMF (35 mL) cooled to 0 °C were successively added imidazole (2.4 g, 35.72 mmol) and then Et_3SiCl (4.5 mL, 26.79 mmol). After stirring at rt for 12 h, the reaction media was diluted with Et_2O (200 mL), washed with aq satd NH_4Cl (100 mL) and water (100 mL), dried ($MgSO_4$) and finally concentrated under diminished pressure. Flash chromatography eluting with 9:1 light petroleum–EtOAc gave **2d** (8.10 g, 90%) as a colorless oil: $[\alpha]_D^{20}$ + 8° (*c* 1, $CHCl_3$); TLC (9:1 petroleum ether–EtOAc): $R_f = 0.5$; ^{1}H NMR ($CDCl_3$): δ carbohydrate ring protons (see Table 4), 7.42–7.25 (m, 10 H, C_6H_5), 4.88 (d, 1 H, *J* 10.2 Hz, OCH_2Ph), 4.77 (d, 1 H, *J* 10.2 Hz, OCH_2Ph), 4.74–4.70 (m, 2 H, OCH_2Ph), 2.84–2.68 (qd, 2 H, *J* 12.6, *J* 7.4 Hz, CH_2CH_3), 1.31 (t, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 5), 138.5, 138.0 (C_{ipso}), 128.6–127.6 (C_6H_5), 75.5 (OCH_2Ph), 75.0 (OCH_2Ph), 24.3 (CH_2CH_3), 15.1 (CH_2CH_3). Anal. Calcd for $C_{28}H_{42}O_4SSi$: C, 66.89; H, 8.42. Found: C, 66.75; H, 8.35.

3.11. Benzyl 2,3-di-*O*-benzyl-4-*O*-acetyl-α-D-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (10a) and benzyl 2,3-di-*O*-benzyl-4-*O*-acetyl-β-D-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (11a)

Donor **2a** (80 mg, 0.18 mmol) and acceptor **3** (180 mg, 0.18 mmol) diluted in toluene (5 mL) were rotoevapo-

rated into dryness. To the mixture was further added 1:2.4 toluene-1,4-dioxane (3.4 mL), activated 4 Å molecular sieves (380 mg), NIS (48 mg, 0.22 mmol) and tin(II) ditrifluoromethanesulfonate (13 mg, 0.03 mmol). After completion of the reaction (45 min at rt), acids were neutralized by $NaHCO_3$ (150 mg). Finally, the reaction media was filtered, diluted with toluene (14 mL), washed with 20% aq $Na_2S_2O_3$, water (10 mL), dried ($MgSO_4$), concentrated and chromatographed (19:1 toluene–Et_2O) to afford **10a** (109 mg) and **11a** (21 mg) in 63% overall yield; **10a**: TLC R_f (9:1 toluene–Et_2O): 0.5; $[\alpha]_D^{20}$ +49.1° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–7.03 (m, 45 H, C_6H_5), 4.97 (d, 1 H, ^2J 11.8 Hz, OCH_2Ph), 4.94 (d, 1H, ^2J 11.3 Hz, OCH_2Ph), 4.93 (d, 1 H, ^2J 10.9 Hz, OCH_2Ph), 4.85 (d, 1 H, ^2J 11.6 Hz, OCH_2Ph), 4.76 (d, 1 H, ^2J 11.6 Hz, OCH_2Ph), 4.75 (d, 1 H, ^2J 11.6 Hz, OCH_2Ph), 4.68 (d, 1 H, ^2J 12.0 Hz, OCH_2Ph), 4.66 (d, 1 H, ^2J 11.4 Hz, OCH_2Ph), 4.64 (d, 1 H, ^2J 10.9 Hz, OCH_2Ph), 4.63 (d, 1 H, ^2J 10.8 Hz, OCH_2Ph), 4.58 (d, 1 H, ^2J 12.2 Hz, OCH_2Ph), 4.54 (d, 1 H, ^2J 12.3 Hz, OCH_2Ph), 4.50 (d, 1 H, ^2J 13.0 Hz, OCH_2Ph), 4.47 (d, 1 H, ^2J 11.9 Hz, OCH_2Ph), 4.45 (d, 1 H, ^2J 12.3 Hz, OCH_2Ph), 4.42 (d, 1 H, ^2J 12.0 Hz, OCH_2Ph), 4.39 (d, 1 H, ^2J 12.0 Hz, OCH_2Ph), 4.37 (d, 1 H, ^2J 11.0 Hz, OCH_2Ph), 2.10 (s, 3 H, CH_3CO); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 170.0 (CO), 137.8, 137.4, 137.2, 137.0, 136.7, 136.4, (C_{ipso}), 127.4–125.6 (C_6H_5), 73.7, 72.9, 72.8, 72.5, 72.2, 72.0, 70.8, 70.0 (OCH$_2$Ph); HMQC ($CDCl_3$): $J_{C\text{-}1a,H\text{-}1a}$ 159.7 Hz, $J_{C\text{-}1b,H\text{-}1b}$ 174.5 Hz, $J_{C\text{-}1c,H\text{-}1c}$ 172.9 Hz. Anal. Calcd for $C_{83}H_{88}O_{16}$: C, 74.31; H, 6.61. Found: C, 74.33; H, 6.68; **11a**: TLC (9:1 toluene–Et_2O): R_f 0.4; $[\alpha]_D^{20}$ +28.4° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.34–7.05 (m, 45 H, C_6H_5), 5.00 (d, 1 H, ^2J 10.5 Hz, OCH_2Ph), 4.87 (d, 1 H, ^2J 10.8 Hz, OCH_2Ph), 4.84 (d, 1 H, ^2J 10.8 Hz, OCH_2Ph), 4.83 (d, 1 H, ^2J 11.6 Hz, OCH_2Ph), 4.72 (d, 1 H, ^2J 11.5 Hz, OCH_2Ph), 4.69 (d, 1 H, ^2J 11.5 Hz, OCH_2Ph), 4.67 (d, 1 H, ^2J 11.5 Hz, OCH_2Ph), 4.62–4.57 (m, 4 H, OCH_2Ph), 4.53 (d,1 H, ^2J 11.8 Hz, OCH_2Ph), 4.43 (d, 1 H, ^2J 12.2 Hz, OCH_2Ph), 4.39 (d,1 H, ^2J 12.9 Hz, OCH_2Ph), 4.39 (d, 1 H, ^2J 11.6 Hz, OCH_2Ph), 4.38 (d, 1 H, ^2J 11.4 Hz, OCH_2Ph), 4.31 (d, 1 H, ^2J 12.0 Hz, OCH_2Ph), 4.10 (d, 1 H, ^2J 12.1 Hz, OCH_2Ph), 2.10 (s, 3 H, CH_3CO); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 170.0 (CO), 138.3, 137.8, 137.4, 137.2, 136.7, 136.9, 136.4 (C_{ipso}), 127.4–125.7 (C_6H_5), 74.0, 73.9, 73.7, 73.1, 72.6, 72.4, 72.1, 70.7, 69.9 (OCH$_2$Ph), 19.8 (CH$_3$CO); HMQC ($CDCl_3$): $J_{C\text{-}1a,H\text{-}1a}$ 159.7 Hz, $J_{C\text{-}1b,H\text{-}1b}$ 174.2 Hz, $J_{C\text{-}1c,H\text{-}1c}$ 161.3 Hz. Anal. Calcd for $C_{83}H_{88}O_{16}$: C, 74.31; H, 6.61. Found: C, 74.04; H, 6.67.

3.12. Benzyl 2,3-di-*O*-benzyl-4-*O*-*p*-methoxybenzyl-α-D-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (10b)

This glycosylation reaction was performed as described for **10a** starting from donor **2b** (46 mg, 0.09 mmol), acceptor **3** (88 mg, 0.09 mmol), NIS (24 mg, 0.11 mmol) and tin(II) ditrifluoromethanesulfonate (8 mg, 0.02 mmol) in 1:2.4 toluene-1,4-dioxane (1.4 mL). After work-up and chromatographic purification (24:1 toluene–Et_2O), the target trisaccharide **11b** (93 mg) was isolated in 73% yield; TLC (9:1 toluene–Et_2O): R_f 0.6; $[\alpha]_D^{20}$ +39.6° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.46–7.06 (m, 47 H, C_6H_5), 6.88–6.86 (m, 2 H, C_6H_5), 5.00 (d, 1 H, ^2J 11.9 Hz, OCH_2Ph), 4.98–4.96 (m, 2 H, OCH_2Ph), 4.89 (d, 1 H, ^2J 11.7 Hz, OCH_2Ph), 4.87 (d, 1 H, ^2J 11.2 Hz, OCH_2Ph), 4.82 (d, 1 H, ^2J 12.5 Hz, OCH_2Ph), 4.79 (d, 1 H, ^2J 12.3 Hz, OCH_2Ph), 4.72 (d, 1 H, ^2J 12.0 Hz, OCH_2Ph), 4.69–4.65 (m, 5 H, OCH_2Ph), 4.64–4.58 (m, 4 H, OCH_2Ph), 4.54–4.43 (m, 3 H, OCH_2Ph), 3.83 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 159.2, 138.8, 138.7, 138.5, 138.4, 138.2, 137.7, 137.4 (C_{ipso}), 130.7–126.5 (C_6H_5), 113.5 (C_6H_5), 74.6, 74.1, 74.0, 73.8, 73.4, 73.3, 73.2, 72.9, 72.8, 70.9 (OCH$_2$Ph), 55.2 (OCH_3); HMQC ($CDCl_3$): $J_{C\text{-}1a,H\text{-}1a}$ 159.5 Hz, $J_{C\text{-}1b,H\text{-}1b}$ 171.5 Hz, $J_{C\text{-}1c,H\text{-}1c}$ 172.7 Hz. Anal. Calcd for $C_{89}H_{94}O_{16}$: C, 75.30; H, 6.67. Found: C, 75.56; H, 6.81.

3.13. Benzyl 2,3-di-*O*-benzyl-4-*O*-*t*-butyldimethylsilyl-α-D-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (10c)

This glycosylation reaction was performed as previously described for **11a** starting from donor **2c** (80 mg, 0.16 mmol), acceptor **3** (155 mg, 0.16 mmol), NIS (43 mg, 0.19 mmol) and tin(II) ditrifluoromethanesulfonate (13 mg, 0.03 mmol) in 1:2.4 toluene-1,4-dioxane (3.4 mL). After work-up and chromatographic purification (24:1 toluene–Et_2O), the target trisaccharide **10c** (183 mg) was obtained in 81% yield; TLC (19:1 toluene–Et_2O): R_f 0.4; $[\alpha]_D^{20}$ +46.7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.41–7.10 (m, 45 H, C_6H_5), 4.97 (d, 1 H, ^2J 12.1 Hz, OCH_2Ph), 4.94 (d, 1 H, ^2J 13.0 Hz, OCH_2Ph), 4.84 (d, 1 H, ^2J 11.9 Hz, OCH_2Ph), 4.79 (d, 1 H, ^2J 11.5 Hz, OCH_2Ph), 4.68 (d, 1 H, ^2J 11.9 Hz, OCH_2Ph), 4.66 (d, 1 H, ^2J 10.9 Hz, OCH_2Ph), 4.64 (d, 1 H, ^2J 10.8 Hz, OCH_2Ph), 4.62–4.54 (m, 8 H, OCH_2Ph), 4.54 (d, 1 H, ^2J 12.5 Hz, OCH_2Ph), 4.52 (d, 1 H, ^2J 12.7 Hz, OCH_2Ph), 4.48 (d, 1 H, ^2J 11.9 Hz, OCH_2Ph), 4.46 (d, 1 H, ^2J 12.1 Hz, OCH_2Ph), 0.84 [s, 9 H, C(CH_3)$_3$], −0.01 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon

Table 6
^{1}H NMR (400 MHz) chemical shifts and coupling constants (^{1}H–^{1}H) for trisaccharides **10**–**17**

Compound δ (ppm), J (Hz)	**10a**	**11a**	**10b**	**10c**	**10d**	**12**	**13**	**14**	**15**	**16**	**17**
H-1a ($J_{1a,2a}$)	4.55 (7.7)	4.45 (7.8)	4.57 (7.4)	4.62–4.54 (nd)	4.70 (7.6)	4.53 (7.6)	4.55 (9.1)	4.55 (7.6)	4.55 (7.9)	4.55 (8.0)	4.56 (7.6)
H-2a ($J_{2a,3a}$)	5.01–3.74 (nd)	(9.5)	3.82–3.49 (8.8)	3.95–3.81 (9.1)	3.58 (8.6)	3.63–3.55 (nd)	3.63–3.56 (8.9)	3.63–3.5 (nd)	3.63–3.51 (nd)	3.63–3.51 (8.8)	3.62 (8.9)
H-3a ($J_{3a,4a}$)	5.01–3.74 (nd)	4.00 (8.8)	4.09 (8.8)	3.78 (8.9)	3.76 (8.9)	3.80–3.72 (8.9)	3.78 (8.9)	3.82–3.73 (8.9)	3.80–3.74 (nd)	3.78 (8.9)	3.83–3.75 (9.4)
H-4a ($J_{4a,5a}$)	5.01–3.74 (nd)	3.82–3.67 (nd)	4.06–3.86 (nd)	4.07 (8.9)	4.05 (9.1)	4.07 (9.1)	4.09 (9.1)	4.07 (9.1)	4.15–3.93 (nd)	4.09 (9.1)	4.12 (9.4)
H-5a ($J_{5a,6a}$)	3.63–3.46 (nd)	3.54–3.34 (nd)	3.82–3.49 (nd)	3.73–3.55 (nd)	3.66–3.55 (nd)	3.63–3.55 (nd)	3.63–3.56 (nd)	3.63–3.51 (3.8)	3.63–3.51 (4.1)	3.63–3.51 (3.2)	3.65–3.56 (nd)
H-6a ($J_{6a,6'a}$)	3.63–3.46 (nd)	3.54–3.34 (nd)	3.82–3.49 (nd)	3.73–3.55 (nd)	3.66–3.55 (nd)	3.63–3.55 (nd)	3.63–3.56 (nd)	3.65 (nd)	3.86 (nd)	3.76 (nd)	3.93–3.86 (nd)
H-6′a ($J_{5a,6'a}$)	3.63–3.46 (nd)	3.54–3.34 (nd)	3.82–3.49 (nd)	3.73–3.55 (nd)	3.66–3.55 (nd)	3.63–3.55 (nd)	3.53–3.48 (nd)	3.63–3.51 (11.9)	3.80–3.74 (10.9)	3.63–3.51 (10.5)	3.65–3.56 (nd)
H-1b ($J_{1b,2b}$)	6.55 (3.7)	5.60 (3.9)	5.56 (3.6)	3.95–3.81 (3.5)	5.65 (3.6)	5.55 (3.6)	5.57 (3.6)	5.60 (3.6)	5.60 (3.6)	5.59 (3.6)	5.62 (3.6)
H-2b ($J_{2b,3b}$)	5.01–3.74 (nd)	3.22 (9.6)	3.82–3.49 (nd)	3.49 (9.3)	3.48 (9.4)	3.51 (nd)	3.53–3.48 (nd)	3.63–3.55 (nd)	3.63–3.51 (9.6)	3.63–3.51 (nd)	3.56–3.50 (nd)
H-3b ($J_{3b,4b}$)	5.01–3.74 (nd)	3.82–3.67 (nd)	4.06–3.86 (nd)	3.95–3.81 (nd)	3.97 (8.1)	4.00–3.92 (nd)	4.02–3.87 (nd)	3.98–3.90 (nd)	4.05 (8.6)	4.03–3.97 (nd)	4.08–3.97 (nd)
H-4b ($J_{4b,5b}$)	5.01–3.74 (nd)	3.82–3.67 (nd)	3.82–3.49 (nd)	3.95–3.81 (nd)	3.95–3.82 (nd)	4.00–3.92 (nd)	4.02–3.87 (nd)	3.98–3.90 (nd)	4.15–3.93 (nd)	4.03–3.97 (nd)	4.08–3.97 (nd)
H-5b ($J_{5b,6b}$)	5.01–3.74 (nd)	3.82–3.67 (nd)	3.82–3.49 (nd)	3.95–3.81 (nd)	3.95–3.82 (nd)	4.00–3.92 (3.8)	4.02–3.87 (nd)	3.84–3.76 (4.2)	4.15–3.93 (nd)	3.96–3.90 (nd)	3.93–3.86 (nd)
H-6b ($J_{6b,6'b}$)	3.63–3.46 (nd)	3.54–3.34 (nd)	3.82–3.49 (nd)	3.73–3.55 (nd)	3.95–3.82 (nd)	3.90 (nd)	4.02–3.87 (nd)	3.84–3.76 (1.5)	4.15–3.93 (nd)	3.90–3.86 (nd)	3.83–3.75 (nd)
H-6′b ($J_{5b,6'b}$)	3.63–3.46 (nd)	3.54–3.34 (nd)	3.82–3.49 (nd)	3.73–3.55 (nd)	3.95–3.82 (nd)	3.90–3.80 (10.9)	3.87–3.80 (nd)	3.75–3.67 (11.1)	3.63–3.51 (nd)	3.88 (nd)	3.56–3.50 (nd)
H-1c ($J_{1c,2c}$)	5.67 (3.8)	4.22 (7.8)	5.70 (3.9)	3.95–3.81 (nd)	5.85 (3.6)	5.64 (nd)	5.65 (3.6)	5.55 (3.6)	5.74 (3.6)	5.55 (3.6)	5.57 (3.6)
H-2c ($J_{2c,3c}$)	5.01–3.74 (nd)	(10.0)	4.06–3.86 (nd)	3.73–3.55 (9.0)	3.66–3.55 (nd)	3.80–3.72 (nd)	3.64 (10.9)	3.40 (9.7)	3.43 (9.4)	3.43 (9.7)	3.33 (9.7)
H-3c ($J_{3c,4c}$)	5.01–3.74 (nd)	3.93 (2.9)	4.06–3.86 (nd)	3.99 (9.0)	3.66–3.55 (nd)	3.80–3.72 (nd)	3.75 (2.8)	3.82–3.73 (9.8)	4.15–3.93 (10.4)	3.52 (9.4)	3.83–3.75 (nd)
H-4c ($J_{4c,5c}$)	5.23 (1.1)	5.12 (<1)	4.06–3.86 (nd)	3.95–3.81 (nd)	3.72–3.69 (nd)	3.73–3.69 (nd)	4.77–3.74 (nd)	3.04 (9.8)	2.50 (10.4)	2.44 (9.4)	3.35–3.28 (nd)
H-5c ($J_{5c,6c}$)	3.63–3.46 (6.5)	3.17 (6.4)	3.82–3.49 (6.4)	3.73–3.55 (6.0)	3.66–3.55 (6.4)	3.80–3.72 (6.4)	3.87–3.80 (7.4)	3.63–3.51 (6.4)	4.15–3.93 (6.1)	3.63–3.51 (6.2)	3.83–3.75 (6.1)
H-6c	0.96	0.97	0.99	1.02	1.15	1.12	1.00	1.13	1.22	1.10	1.12

(nd): not determined.

atoms (see Table 7), 139.0, 138.9, 138.6, 138.5, 138.3, 137.8, 137.5 (C_{ipso}), 128.5–126.6 (C_6H_5), 74.7, 74.1, 73.9, 73.5, 73.3, 73.2, 73.0, 71.0 (OCH_2Ph), 26.1 [$C(CH_3)_3$], 18.6 [$C(CH_3)_3$], −3.9, −4.5 (CH_3Si); HMQC ($CDCl_3$): $J_{C\text{-}1a,H\text{-}1a}$ 159.7 Hz; $J_{C\text{-}1b,H\text{-}1b}$ 175.0 Hz; $J_{C\text{-}1c,H\text{-}1c}$ 175.0 Hz. Anal. Calcd for $C_{87}H_{100}O_{15}Si$: C, 73.91; H, 7.13. Found: C, 74.21; H, 7.14.

3.14. Benzyl 2,3-di-*O*-benzyl-4-*O*-triethylsilyl-α-D-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (10d)

To a soln of donor **2d** (6 g, 11.93 mmol) and maltosidic acceptor **3** (9.6 g, 9.94 mmol) in dry toluene (200 mL) were successively added at 0 °C and under vigorous stirring NIS (2.68 g, 11.93 mmol) followed by copper(II) ditrifluoromethanesulfonate (719 mg, 2 mmol). Complete consumption of both substrates was attained after 10 min so that acidic media could be neutralized by adding NEt_3 and further partitioned between Et_2O (200 mL) and aq $Na_2S_2O_3$. The resulting organic layer was washed with water (2200 mL) and dried ($MgSO_4$). After removal of the solvent, the product was chromatographed (6.7:1 light petroleum–EtOAc) and isolated in 95% yield (13.3 g); TLC (9:1 light petroleum–EtOAc): R_f 0.2; $[\alpha]_D^{20}$ +42.1° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–7.00 (m, 45 H, C_6H_5), 4.90–4.41 (m, 18 H, OCH_2Ph), 0.87 (t, 9 H, *J* 7.9 Hz, CH_2CH_3), 0.55 (qd, 8 H, *J* 1.8 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 139.0, 138.9, 139.6, 138.6, 138.5, 138.4, 138.3, 137.8, 137.5 (C_{ipso}), 128.5–126.5 (C_6H_5), 74.7, 74.1, 74.0, 73.5, 73.4, 73.3, 73.2, 73.0, 71.1 (OCH_2Ph), 7.1 (CH_2CH_3), 5.2 (CH_2CH_3). Anal. Calcd for $C_{87}H_{100}O_{15}Si$: C, 73.91; H, 7.13. Found: C, 73.62; H, 7.12.

3.15. Benzyl 2,3-di-*O*-benzyl-α-D-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (12)

To a soln of silylated trisaccharide **10d** (6.7 g, 4.67 mmol) was added a molar soln of tetrabutylammonium fluoride in THF (7 mL, 7 mmol). After 1 h at rt, the reaction media was partitioned between Et_2O (300 mL) and aq satd NH_4Cl (150 mL). The organic layer was then washed with water (150 mL), dried ($MgSO_4$), concentrated under diminished pressure and purified by flash chromatography (3:1 light petroleum–EtOAc). Compound **12** was thus isolated in 95% yield as a colorless oil (5.76 g); TLC (4:1 light petroleum–EtOAc): R_f 0.2; $[\alpha]_D^{20}$ +46.8° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–7.04 (m, 45 H, C_6H_5), 4.97–4.41 (m, 18 H, OCH_2Ph); 2.33 (s, 1 H, $J_{4c\text{-}OH} < 1$ Hz, OH-4c); ^{13}C NMR ($CDCl_3$): δ

Table 7
^{13}C NMR (400 MHz) chemical shifts for trisaccharides **10**–**17**

Compound	δ (ppm)															
	C-1a	C-2a	C-3a	C-4a	C-5a	C-6a	C-1b	C-2b	C-3b	C-4b	C-5b	C-6b	C-1c	C-2c	C-3c	C-4c	C-5c	C-6c
10a	101.3	83.6[b]	81.0[b]	80.6[b]	78.4[b]	68.0	96.2[a]	73.8[b]	73.6[b]	72.4[b]	71.3[b]	68.0	95.3[a]	75.3[b]	69.7[b]	69.6[b]	64.0	15.1
11a	101.3[c]	83.8[e]	81.4[e]	79.2[e]	78.5[e]	68.2[d]	95.9[e]	78.1[e]	77.5[e]	75.0[e]	73.7[e]	67.1[d]	101.1[c]	72.0[e]	70.0[e]	68.7[e]	67.6	15.3
10b	102.3	82.0[f]	84.6[f]	72.5[f]	76.6[f]	69.2[f]	96.5	79.3[f]	81.6[f]	75.7[f]	70.8[f]	69.1	97.1	76.6[f]	79.5[f]	70.8[f]	66.8	16.7
10c	102.4	82.1[h]	84.7	74.7[h]	75.2[h]	69.3[g]	96.6	78.4[h]	73.9[h]	73.0[h]	72.8[h]	69.2[g]	97.1	79.3	81.5	70.9[h]	67.8	17.2
10d	102.4	82.1	84.7	73.7	74.8	69.3	96.5	79.4	81.5	72.8	70.1	69.3	97.6	75.4	78.3	72.8	67.7	16.8
12	102.4	82.1	84.6	73.6	74.7	69.2	96.4	79.3	81.5	72.7	70.3	69.2	96.9	75.0	78.0	70.0	65.7	16.3
13	102.4	82.1	84.7	73.5	74.7	69.1	96.4	79.4	81.6	72.4	70.7	69.1	96.6	74.6	76.0	81.7	65.2	16.6
14	102.4	82.1	84.6	73.1	74.7	68.7	96.3	79.4	81.7	72.4	70.7	68.9	96.2	79.7	79.7	68.2	66.7	18.6
15	102.4	82.1	84.7	73.4	74.7	68.7	96.4	79.4	81.9	72.1	70.5	68.5	96.1	81.1	77.3	55.5	67.3	19.0
16	102.4	82.1	84.7	73.4	74.7	69.0	96.5	79.2	81.6	73.2	70.9	69.0	96.9	80.4	81.3	58.7	69.3	18.3
17	102.4	82.1	84.7	73.0	74.7	68.6	96.2	79.4[i]	81.6	72.4	70.5	68.9	96.1	79.2	79.3[i]	64.2	68.8	18.3

(a), (b), (c), (d), (e), (f), (g), (h), (i): Signals may be reversed within the same line.

carbohydrate ring carbon atoms (see Table 7), 138.8, 138.4, 138.3, 138.2, 138.0, 137.7, 137.4, (C_{ipso}), 128.5–126.6 (C_6H_5), 74.7, 74.0, 73.9, 73.7, 73.5, 73.2, 73.0, 72.3, 71.1 (OCH_2Ph). Anal. Calcd for $C_{81}H_{86}O_{15}$: C, 74.86; H, 6.67. Found: C, 75.14; H, 6.71.

3.16. Benzyl 2,3-di-*O*-benzyl-4-*O*-methanesulfonyl-α-D-fucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (13)

Mesylation was performed by mixing a soln of **12** (6.07 g, 4.67 mmol) in dry CH_2Cl_2 (60 mL) containing 4-*N*,*N*-dimethylaminopyridine (776 mg, 6.35 mmol) to a soln of methanesulfonyl chloride (435 μL, 6 mmol) in dry CH_2Cl_2 (5 mL). The reaction was completed after 10 min stirring at rt. The media was diluted with additional CH_2Cl_2 (200 mL) and successively washed with aq satd NH_4Cl (270 mL) and water (100 mL), dried ($MgSO_4$), concentrated and finally chromatographed (4:1 light petroleum–EtOAc). The desired product **13** was thus isolated in 90% yield as a colorless oil (5.47 g); R_f 0.6 (3:1 light petroleum–EtOAc); $[\alpha]_D^{20}$ +48.5° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–7.04 (m, 45 H, C_6H_5), 5.00–4.41 (m, 18 H, OCH_2Ph), 2.85 (s, 3 H, SO_2CH_3); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 138.1, 138.8, 138.4, 138.3, 138.0, 137.9, 137.7, 137.5, 137.4 (C_{ipso}), 128.5–126.5 (C_6H_5), 74.8, 74.0, 73.9, 73.7, 73.4, 73.0, 71.1 (OCH_2Ph), 39.0 (SO_2CH_3). Anal. Calcd for $C_{82}H_{88}O_{17}S$, $1H_2O$: C, 70.56; H, 6.50. Found: C, 70.84; H, 6.52.

3.17. Benzyl 4-azido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (14)

To a soln of mesylate **13** (2.4 g, 1.74 mmol) in DMF (20 mL) were added TBABr (112 mg, 0.35 mmol) and sodium azide (340 mg, 5.22 mmol). The reaction was allowed to warm at 85 °C and stirred for 3 days. The mixture was further partitioned between Et_2O (150 mL) and aq satd tetrabutylammonium chloride (100 mL). The resulting organic layer was then washed with water (100 mL), dried ($MgSO_4$) and the solvent removed under diminished pressure. A flash chromatography (87:13 light petroleum–EtOAc) finally yielded **14** (2.21 g, 95%) as a colorless oil; TLC (9:1 light petroleum–EtOAc): R_f 0.3; $[\alpha]_D^{20}$ +55.2° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–7.04 (m, 45 H, C_6H_5), 5.00–4.41 (m, 18 H, OCH_2Ph); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 138.8, 138.3, 138.0, 137.9, 137.7, 137.5, 137.4 (C_{ipso}), 128.5–126.6 (C_6H_5), 75.5, 74.7, 74.0, 73.4, 73.0, 72.8, 71.1 (OCH_2Ph). Anal. Calcd for $C_{81}H_{85}N_3O_{14}$: C, 73.45; H, 6.47; N, 3.17. Found: C, 73.59; H, 6.54; N, 2.92.

3.18. Benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-thiocyanato-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (15)

Mesylate **13** (100 mg, 0.07 mmol), potassium thiocyanate (40 mg, 0.4 mmol) and TBABr (3 mg, 0.007 mmol) were combined into DMF (1 mL) and warmed at 140 °C for 5 h. After cooling at rt and diluting with Et_2O (20 mL), the mixture was washed with water (28 mL). The resulting organic layer was finally dried ($MgSO_4$), concentrated and submitted to chromatographic purification (4.3:1 light petroleum–EtOAc). The product **15** was thus obtained as a colorless oil (60 mg) in 65% yield; TLC (4:1 light petroleum–EtOAc): R_f 0.4; $[\alpha]_D^{20}$ +2.2° (*c* 1, $CHCl_3$); IR: *v* 2152 (SCN) cm^{-1}; ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–7.04 (m, 45 H, C_6H_5), 4.98–4.40 (m, 18 H, OCH_2Ph); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 138.9, 138.4, 138.3, 138.8, 138.7, 137.6, 137.5 (C_{ipso}), 128.5–126.4 (C_6H_5). 110.1 (SCN), 76.3, 74.7, 73.9, 73.4, 73.2, 73.0, 72.9, 71.0 (OCH_2Ph). Anal. Calcd for $C_{82}H_{85}NO_{14}S$: C, 73.46; H, 6.39. Found: C, 73.30; H, 6.54.

3.19. Benzyl 4-amino-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (16)

A soln of azide **14** (1.7 mg, 1.28 mmol) and triphenylphosphine (673 mg, 2.56 mmol) in dry toluene (10 mL) was stirred at rt for 12 h. The resulting iminophosphorane was hydrolyzed in situ by adding 10% aq NaOH (10 mL) and by heating at 90 °C for 12 h. After cooling at rt, the media was diluted with Et_2O (20 mL) and washed with water until neutral pH. The organic layer was then dried over $MgSO_4$ and the solvent removed under diminished pressure. Chromatography (3:2 light petroleum–EtOAc) of the crude oil afforded the desired trisaccharidic amine **16** (1.5 g, 90%); TLC (3:2 light petroleum–EtOAc): R_f 0.2; $[\alpha]_D^{20}$ +33.0° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–6.91 (m, 45 H, C_6H_5), 4.90–4.35 (m, 18 H, OCH_2Ph); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 139.0, 138.9, 138.7, 138.4, 138.3, 138.1, 137.8, 137.5 (C_{ipso}), 128.5–126.6 (C_6H_5), 75.4, 74.7, 74.1, 74.0, 73.4, 73.3, 73.0, 72.4, 71.0 (OCH_2Ph). Anal. Calcd for $C_{81}H_{87}NO_{14}$: C, 74.92; H, 6.75. Found: C, 75.23; H, 6.82.

3.20. Benzyl 2,3-di-*O*-benzyl-4,6-dideoxy-4-isothiocyanato-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (17)

To a soln of **16** (100 mg, 0.07 mmol) in dry CH_2Cl_2 (1.5 mL) cooled at −20 °C were successively added 4-*N*,*N*-dimethylaminopyridine (39 mg, 0.31 mmol) and thiophosgene (8.4 μL, 0.11 mmol). After complete disappearance of the substrates and heating to rt, the solvent was removed and the crude oil purified on silica gel (4:1 light petroleum–EtOAc). Compound **17** was thus obtained in 90% yield (91 mg) as a colorless oil; R_f 0.3 (4:1 light petroleum–EtOAc); $[\alpha]_D^{20}$ +30.0° (*c* 1, $CHCl_3$); IR: *v* 2050 (NCS) cm^{-1}; ^1H NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 6), 7.40–7.04 (m, 45 H, C_6H_5), 5.00–4.43 (m, 18 H, OCH_2Ph); ^{13}C NMR ($CDCl_3$): δ carbohydrate ring carbon atoms (see Table 7), 138.8–137.4 (C_{ipso}), 135.4 (NCS), 128.5–126.5 (C_6H_5), 75.8, 74.7, 74.0, 73.9, 73.4, 73.0, 72.9, 71.1 (OCH_2Ph). Anal. Calcd for $C_{82}H_{85}NO_{14}S$: C, 73.46; H, 6.39. Found: C, 73.37; H, 6.27.

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