First Intramolecular Aglycon Delivery onto a D-Fucofuranosyl Entity for the Synthesis of α-D-Fucofuranose-Containing Disaccharides

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Intramolecular aglycon delivery was performed for the first time starting from *n*-pentenyl glycofuranoside as a donor. *p*-Methoxybenzyl-assisted aglycon transfer required very mild reaction conditions and was promoted by *N*-iodosuccinimide without assistance of any Lewis acid catalyst. As a result, rare α-D-fucofuranose-containing disaccharides were obtained. Moreover, structure elucidation led to the conclusion that an *N*-succinimidyl residue was still present in the resulting products.

Introduction

Among the numerous carbohydrates involved in biological pathways, L-fucose holds a special and prominent place. In fact, natural oligosaccharides containing L-fucopyranosyl residues are of particular interest for determinants of A and H blood groups[1] and for Lewis derivatives.[2] Therefore, chemical synthesis and structure−activity relationships of compounds that embody this 6-deoxy sugar have been widely investigated. In our laboratory, we have developed a program directed toward the preparation of glycoconjugates bearing uncommon hexofuranosyl entities.[3] Generally speaking, hexofuranosides are found in archaebacteriae[4] that are able to survive under extreme conditions, or as membrane components of various pathogenic microorganisms[5,6] wherein they act as epitopes and warrant cell survival. Processes by which galacto-, gluco-,[7] and fucofuranosides,[8] and their conjugates, are biosynthesized or metabolized have not yet been clearly elucidated. Nevertheless, the biological action and the structure of enzymes, such as the uridine diphosphogalactopyranose mutase[9] and some galactofuranosidases,[10] are currently being studied. To the best of our knowledge, mammalian hexofuranoconjugates have yet to be identified. Consequently, the hexofuranose-containing conjugates are expected to be antigenic,[6] which offers interesting prospects for the design of new pharmacophores and of new molecular tools for enzymatic studies.

In this context, we became interested in the preparation of extremely rare fucofuranosides. Unlike mammalian cells that biosynthesize L-fucopyranose-containing oligosaccharides, microorganisms such as *Chaetoceros curvisetus*[8a] and *Eubacterium saburreum*[8c] are able to incorporate the D-fucose enantiomer − in the furanose configuration − into heterogeneous polysaccharides. The latter bacterium has been detected in approximal dental plaque,[8d] and its T19 strain may settle in the human oral cavity and produce a cell-surface polysaccharide antigen of unique chemical composition.[8c] The structural backbone of this heteroglycan **1** is built of a linear chain of branched β-D-glycero-D-galactoheptopyranosyl residues with a difucofuranoside as an antenna (Figure 1). Moreover, both fucofuranosyl entities are characterized by an α-anomeric configuration.

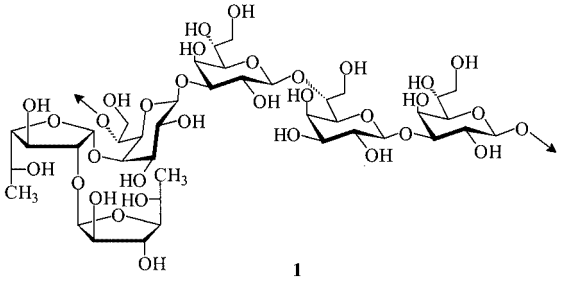

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Figure 1. Polysaccharide antigen **1** produced by the T19 strain of *E. saburreum*

To study the chemical synthesis of the nonreducing end of this backbone structure, we first designed a simplified trisaccharide-mimicking compound **2** (Scheme 1) in which the heptaoside was replaced by a galactopyranoside bearing an ω-amino chain for further linkage to a carrier. The 1,2-*cis* relationship, however, was preserved for the furanosyl entities. The difficulties connected with this endeavor are (i)

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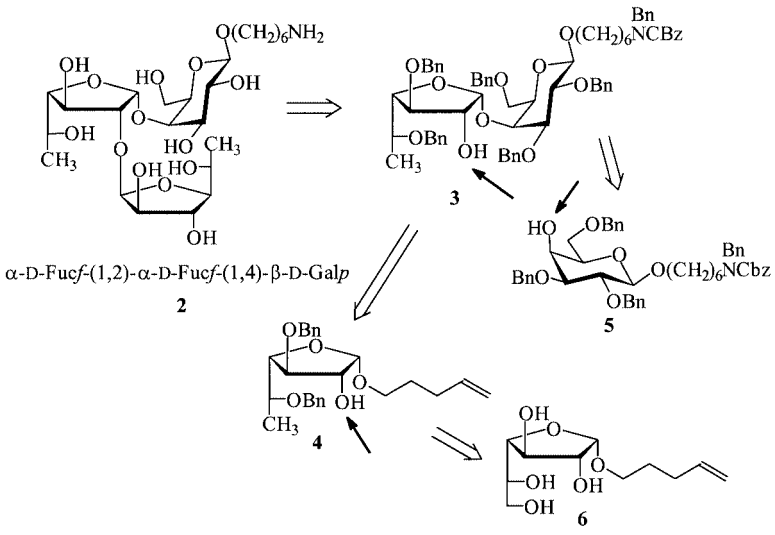


Scheme 1. Targeted mimic structures and retrosynthetic approach

the glycosylation of the less reactive axial hydroxy group 4-OH of the D-galactopyranosyl unit, (ii) the preparation of new D-fucofuranosyl donors, and (iii) the preparation of α-linked furanosides (i.e., 1,2-*cis*-furanosides). We anticipated that the glycosylation reaction could be more easily performed using an intramolecular aglycon delivery (IAD) approach.[11] The acetal approach requires the discrimination of the 2-position on both the acceptor and the donor and, thus, the preparation of the disaccharidic acceptor **3** and the fucofuranosyl donor **4**. This disaccharide **3** may also be obtained from the same donor **4** and the galactopyranoside **5**. Therefore, we have synthesized the *n*-pentenyl fucofuranoside **4** bearing a free 2-OH group, which could be prepared from the corresponding galactofuranoside **6**, and the glycosyl acceptor **5**. We describe herein the preparation of new fucofuranosyl donors, α-D-Fuc*f*-(1,4)-β-D-Gal*p* and α-D-Fuc*f*-(1,6)-α-D-Glc*p* disaccharides, and mechanistic considerations to explain the formation of unexpected intermediates obtained during the aglycon transfer.

Results and Discussion

Among the few D-fucofuranosides previously prepared,[10c,12] no 1,2-*cis* derivatives have been specifically synthesized. The IAD concept generally involves the introduction of an orthogonal protecting group at 2-O on the glycosyl donor. Considering our strategy starting from D-galactofuranosides, first we needed the protection of the primary hydroxy group by a sterically demanding group. We then expected that discrimination between the three remaining secondary functions could be attained by the increasing 2-O nucleophilicity by an intramolecular hydrogen bond between[13] 2-OH and an exocyclic heteroatom at C-1 (Figure 2). On this assumption, donors characterized by a relative 1,2-*cis* configuration were required. Although α-thiofuranosides are readily available,[14] ethyl 1-thio-α-D-galactofuranoside proved to be unsuitable for further protection and deprotection steps, even under moderately acidic conditions.

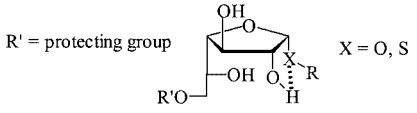
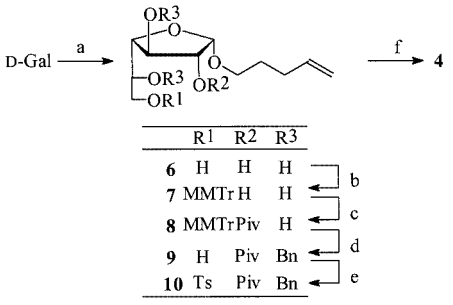


Figure 2. Increased nucleophilicity of 2-OH by intramolecular hydrogen bonding

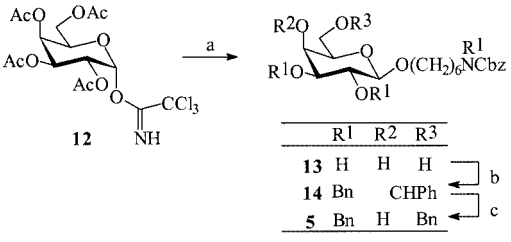
On this consideration, although *n*-pentenyl glycosides have never been used in an IAD approach,[11d] we were attracted towards these widespread compounds as potential donors[15,16] since (i) they allow protecting group manipulations and (ii) α-D-galactofuranosides can be synthesized stereospecifically in one step from free galactose.[17] Thus, we prepared the *n*-pentenyl α-D-galactofuranoside (**6**) by 1-*O*-alkylation of unprotected D-galactose with 4-penten-1-yl bromide in *N*,*N*′-dimethylpropyleneurea (DMPU) in the presence of sodium iodide (Scheme 2). Owing to its high solubility in water, the resulting galactofuranoside was purified by a quantitative peracetylation/deacylation sequence. Subsequent monotritylation of the primary hydroxy group, using (4-methoxyphenyl)diphenylmethyl chloride (MMTrCl) in the presence of sodium hydride and a catalytic amount of 4-(dimethylamino)pyridine (DMAP), afforded **7**. As we expected, **7** was pivaloylated specifically at position 2 in the presence of triethylamine, and 2,6-diprotected galactofuranoside **8** was isolated in 77% yield. The free hydroxy groups of **8** were then benzylated under basic conditions. The resulting product was not isolated, however, since simple neutralization by addition of IR-120 resin (H^+ form) allowed in situ detritylation and gave **9**. After efficient 6-*O*-tosylation, reduction of **10** was smoothly performed with sodium borohydride,[18] followed by a one-pot removal of the ester protecting group with sodium meth-

oxide. This sequence afforded **4** in 36% yield for the last five steps.



Scheme 2. Synthesis of α-D-fucofuranoside **4**: (a) 4-penten-1-yl bromide, NaH, DMPU; Ac_2O, Pyr; MeONa, MeOH (37%); (b) MMTrCl, DMAP, Pyr (75%); (c) PivCl, Pyr (77%); (d) BnBr, TBAI, NaH, CH_2Cl_2; IR 120 (H^+ form) (85%); (e) TsCl, Et_3N, DMAP, CH_2Cl_2 (94%), (f) $NaBH_4$, DMF; MeONa, MeOH (77%)

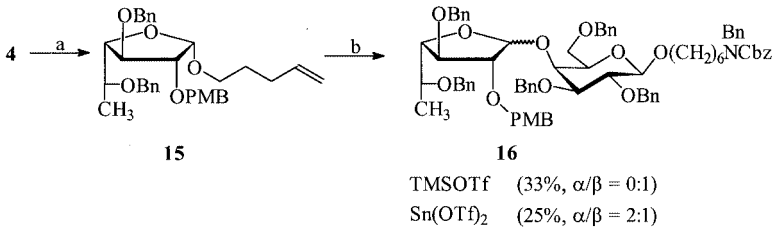
Next we considered the synthetic route to galactopyranoside acceptor **5** (Scheme 3). The preparation began with the galactosylation of the *N*-protected aminohexanol **11**.[19] Amongst peracetylated galactopyranosyl donors (i.e., the bromide, trichloroacetimidate, and thioglycoside derivatives) best results were obtained with the known trichloroacetimidate **12**.[20] It is interesting to note that the use of tin(II) bis(trifluoromethanesulfonate) [$Sn(OTf)_2$] as a very mild Lewis acid catalyst provided a fine tuning between the reactivities of both substrates **11** and **12** and resulted in the optimal coupling yield. Finally, the glycosylation procedure was significantly improved by a one-pot transesterification/deprotection step under Zemplen conditions so that the yield of this two-step sequence was raised to 87%. Ensuing 4,6-*O*-benzylidenation with benzaldehyde dimethylacetal in the presence of camphorsulfonic acid (CSA), followed by standard benzylation, yielded the fully *O*- and *N*-protected compound **14**. Finally, selective opening of the benzylidene ring was performed with sodium cyanoborohydride in the presence of trifluoromethanesulfonic acid (TfOH) and provided the target acceptor **5** in 73% yield.



Scheme 3. Synthesis of β-D-galactopyranoside **5**: (a) $HO(CH_2)_6NHCbz$ (**11**), $Sn(OTf)_2$, CH_2Cl_2; MeONa, MeOH (87%); (b) $PhCH(OMe)_2$, CSA, DMF; BnBr, NaH, DMF (54%); (c) $NaBH_3CN$, TfOH, THF (73%)

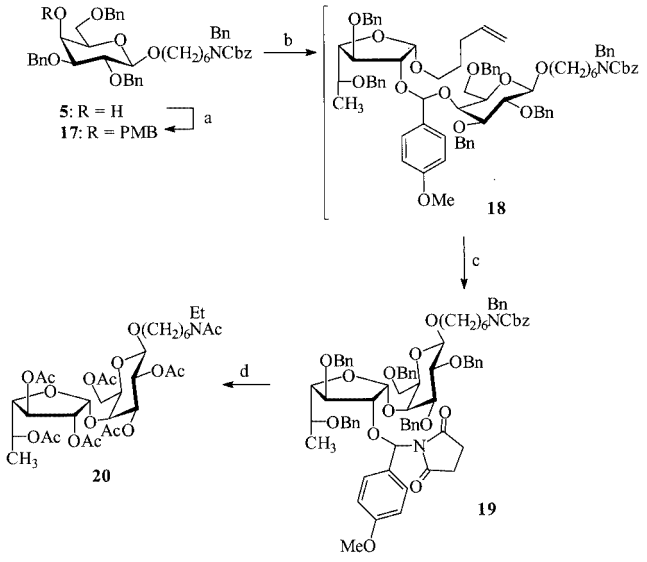
Having the fucofuranosyl donor and the acceptor in hand, first we investigated intermolecular fucosylation of **5** to estimate the nucleophilic potential of **5** toward our fucofuranosyl donor. Thus, fucoside **4** was treated with *p*-methoxybenzyl chloride (PMBCl) to afford **15** (Scheme 4) bearing a nonparticipating group at 2-O also suitable for further tethering. The selectivity of the coupling reaction promoted by *N*-iodosuccinimide (NIS) depended on the nature of Lewis catalyst. Thus, the disaccharide **16** presenting a β-interglycosidic bond was obtained diastereospecifically in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and isolated in 33% yield, while the milder Lewis acid $Sn(OTf)_2$ gave an inseparable α,β-mixture of **16** in a slightly lower yield (25%) with the α-isomer being the major fucofuranoside. These results showed that the 1,2-*cis* anomer could be obtained under mild conditions. The α-furanosyl configuration was established on the basis of the ^{13}C NMR chemical shift of the anomeric center of the nonreducing fucosyl residue. In fact, α-O-linked furanosides give resonances at lower fields than do the corresponding β-products.[21] Our observations were consistent with this assignment since a difference in chemical shifts of 5.8 ppm was obtained for C-1b ($\delta_{16\alpha}$ = 101.2 ppm; $\delta_{16\beta}$ = 107.0 ppm).

Encouraged by the latter result, we further examined this approach, this time by connecting the acceptor and donor through a bifunctional group. The preparation of a silicon-tethered disaccharide was first performed, but the resulting silyl acetal unit proved to be chemically too sensitive. Therefore, our attention was turned to the use of an acetal as tether; more specifically, a *p*-methoxybenzyl acetal.[11c] Oxidation of 2-*O*-PMB fucoside **15** by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in the presence of **5** went to completion slowly, owing to the low reactivity of the axial hydroxy group of **5**. Nevertheless, the alternative route, consisting in oxidation of 4-*O*-PMB-protected galactopyranoside **17** with C-2-unprotected fucofuranosyl donor **4** mediated by DDQ, successfully afforded the desired intermediate **18** (Scheme 5). Although the tether was rather unstable, **18** could be purified by flash chromatography and characterized by ^1H and ^{13}C NMR analysis. The structural assignment was based on the notably downfield chemical shift of the PMB methylene carbon atom (from δ = 73.0 ppm for **17** to δ = 104.5 ppm for **18**). Attempted activation of the pentenyl donor by NIS and a catalytic amount of either TMSOTf or $Sn(OTf)_2$ resulted in degradation of both the donor and acetal linkages, with the release of the acceptor even in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). Nevertheless, when using NIS only,[22] *p*-methoxybenzyl-assisted aglycon delivery occurred efficiently. After workup and purification, we isolated a disaccharide whose structure was assigned on the basis of significant signals in NMR spectra. Structure elucidation was complicated, however, since the creation of a new stereogenic center was manifested by the splitting of signals. Nevertheless, spectral analysis led us to the following observations: (i) the signals of the *n*-pentenyl chain had disappeared; (ii) three ^{13}C NMR signals are present at δ = 104.0/103.9 and 99.9 ppm, signifying β-Gal*p* and α-Fuc*f* configurations, respectively; (iii) a methoxy group is present (δ_{OCH3} = 55.1



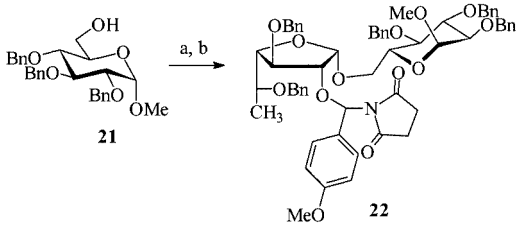
Scheme 4. Intermolecular glycosidic coupling: (a) PMBCl, NaH, DMF (91%); (b) **5**, NIS, Lewis catalyst, CH_2Cl_2

and 55.2 ppm); (iv) a signal at δ = 176.4 ppm characterizes carbonyl functions. On the basis of this analysis, we presume that aglycon transfer was efficient and that subsequent trapping of the intermediate benzylic cation by the poorly nucleophilic *N*-succinimidyl anion resulted in the formation of an O,N-acetal at position 2b. To obtain clear proof of the stereoorientation of the intramolecular glycosylation, hydrogenolysis of **19** in the presence of catalytic amount of palladium acetate was carried out under a high pressure of hydrogen, then followed by standard peracetylation, to yield **20**.[23] The chemical structure of this disaccharide was deduced by high-resolution mass spectrometry (*m*/*z* = 777.3249 for $[C_{34}H_{53}NO_{17} + Na]^+$) and from the correlated ^1H-^{13}C signals at δ = 5.14 ppm and 102.1 ppm, respectively. The latter value, quite different from that obtained for **16β** ($\delta_{C\text{-}1b}$ = 107.0 ppm) but similar to **16α** ($\delta_{C\text{-}1b}$ = 101.2 ppm), and a high coupling constant between 1b-H and 2b-H ($J_{1b,2b}$ = 4.6 Hz), are consistent with an α-configuration for the nonreducing fucofuranosyl unit.



Scheme 5. Tethering and intramolecular aglycon transfer: (a) PMBCl, NaH, DMF (90%); (b) **4**, DDQ, CH_2Cl_2; (c) NIS, CH_2Cl_2 (34% for two steps); (d) H_2 (30 atm), $Pd(OAc)_2$; Ac_2O, Py (25%)

To be certain of the proposed structure and mechanism, we also synthesized a second α-fucofuranose-containing disaccharide according to a similar procedure, but starting from fucofuranoside **15** and the glucopyranoside acceptor **21** bearing a free primary hydroxy group (Scheme 6). The tethering was carried out with DDQ and intramolecular glycosylation occurred smoothly under the action of NIS over 19 h at room temperature. Once again, the resulting disaccharide **22**, isolated in a moderate 21% yield, was characterized by the presence of an *N*-succinimidyl residue linked to the methylene carbon atom of the PMB group. The α-configuration of the reducing entity is suggested by both the chemical shift of C-1a ($\delta_{C\text{-}1a}$ = 97.7 ppm) and a small coupling constant between 1a-H and 2a-H ($J_{1a,2a}$ = 3.6 Hz). When considering the nonreducing carbohydrate residue, the similar chemical shifts for C-1b in fucofuranosides **22** ($\delta_{C\text{-}1b}$ = 100.5 ppm) and fucofuranosides previously synthesized during this study indicate the same α-configuration for all products. This conclusion was unambiguously corroborated by a value for $J_{1b,2b}$ of 4.0 Hz. The presence of a substituted PMB group was established by the specific signals at δ = 5.65 ppm (s, 1 H) in the ^1H NMR spectrum and at δ = 80.0 ppm in the ^{13}C NMR spectrum. The large upfield shift of the benzylic carbon atom signal ($\Delta\delta_{CHPhOMe} = \delta_{18} - \delta_{22}$ = 34 ppm) is more indicative of an O,N-acetal than of an O,O-acetal. The succinimidyl moiety was identified owing to its carbonyl and methylene functions. These observations were also corroborated by high-resolution mass spectrometry. The molecular ion of **22** was characterized as its sodium adduct (*m*/*z* = 1030.4354 for $[C_{60}H_{65}NO_3 + Na]^+$) and as its cation having lost one hydrogen atom (*m*/*z* = 1006.4380 for $[C_{60}H_{64}NO_3]^+$). Moreover, a fragment was measured at 909.4213, corresponding to the departure of a $C_4H_4NO_2$ entity. Finally, an abundant fragment ion at 218.0819, resulting from the release of a $C_{12}H_{12}NO_3$ residue, enabled us to deduce the presence of a covalent link between the *N*-succinimide unit and the benzylic carbon atom of the PMB group.



Scheme 6. Synthesis of α-D-fucofuranoside **22**: (a) **15**, DDQ, CH_2Cl_2; (b) NIS, CH_2Cl_2 (21% for 2 steps)

Conclusions

The synthesis of α-D-fucofuranose-containing disaccharides was investigated by using an internal glycosylation procedure. Our strategy relied on the mild activation of an *n*-pentenyl fucosyl donor by *N*-iodosuccinimide. To promote *p*-methoxybenzyl-assisted aglycon transfer, any traces of a Lewis acid other than NIS were prohibited. This mildly activated reaction highlights a new mechanistic pathway in which the poorly nucleophilic *N*-succinimidyl anion quenches the benzylic cation after intramolecular aglycon delivery. This study resulted in the formation and characterization of mixed α-fucofuranosides presenting an O,N-acetal function at position 2 of the donor moiety. Our observations underline (i) the requirement for finding tuned reactive species as glycosyl donors and acceptors in every glycosylation reaction and (ii) that substantial efforts are still needed to efficiently synthesize complex glycoconjugates bearing 1,2-*cis*-hexofuranosyl entities.

Experimental Section

General Remarks: Dichloromethane and *N*,*N*-dimethylformamide (DMF) were dried with phosphorus pentoxide and distilled, while tetrahydrofuran (THF) and toluene were dried with sodium/benzophenone before distilling. Anhydrous pyridine and methanol were obtained after drying and distilling from calcium hydride and magnesium, respectively. Chemicals and the solvent DMPU were commercially available and used as received. All reactions were performed under nitrogen. Thin layer chromatographic (TLC) analyses were carried out on precoated nonactivated plates (E. Merck 60 F_{254}) with detection by UV absorption (254 nm), when applicable, and charring with 5% H_2SO_4 in EtOH. For column chromatography, E. Merck 60H (5−40 μm) Silica Gel was used. Filtrations were performed with Celite 521. Optical rotations were determined with a Perkin−Elmer 341 polarimeter at 20 °C using a 1-dm cell. ^1H and ^{13}C NMR spectra were recorded with a Bruker ARX 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts are given in ppm (δ) and coupling constants (*J*) in Hertz (Hz). The terms m, s, d, and t signify multiplets, singlets, doublets, and triplets, respectively. $CDCl_3$ and tetramethylsilane were used as solvent and internal standard, respectively. In order to avoid ambiguity, we consistently use these designations: C-1a = C atom 1 of ring a; C-2b = C atom 2 of ring b; 1a-H = H atom at C atom 1 of ring a; 2b-H = H atom at C atom 2 of ring b; 6-Ha = H atom a at C atom 6; 6-Hb = H atom b at C atom 6; etc. Microanalyses were performed by the Service de Microanalyses de l'ICSN (Gif sur Yvette, France).

Preparation of D-Fucofuranosides

α-D-Galactofuranoside 6: A 60% suspension of sodium hydride in oil (0.88 g, 21.9 mmol), *n*-pentenyl bromide (2.6 mL, 21.9 mmol) and sodium iodide (3.28 g, 21.9 mmol) were successively added to a suspension of D-galactose (3.95 g, 21.9 mmol) in DMPU (120 mL). After 5 d at room temperature, one-pot acetylation was carried out by adding at 0 °C dry pyridine (83 mL, 1.03 mol) and acetic anhydride (83 mL, 0.90 mmol) and then stirring for 24 h. The reaction mixture was further diluted with ethyl acetate (300 mL), washed with 20% aqueous HCl and a saturated solution of aqueous NaCl. The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, eluting with light petroleum/ethyl acetate (3:2), gave the peracetylated galactofuranoside (TLC: R_f = 0.45), which was then deacetylated in methanolic sodium methoxide (0.1 M, 46 mL, 4.6 mol). Neutralization with IR 120 (H^+ form) after 2 h at room temperature, filtering, and concentration, provided **4** (2.01 g) in 37% yield. TLC: R_f = 0.53 (dichloromethane/methanol, 4:1). $[\alpha]_D^{20}$ = +67.3 (*c* = 1.0, dichloromethane). ^1H NMR (CD_3OD): δ = 1.62−1.74 (m, 2 H, CH_2), 2.11−2.17 (m, 2 H, CH_2), 3.46 (dt, ^2J = 9.7, ^3J = 7.1 Hz, 1 H, OCH_2CH$_2$), 3.54 (dd, $J_{6a,6b}$ = 12.2, $J_{5,6b}$ = 8.1 Hz, 1 H, 6-Hb), 3.59−3.65 (m, 1 H, 5-H), 3.63 (dd, 1 H, $J_{5,6a}$ = 4.6 Hz, 6-Ha), 3.71 (dd, $J_{3,4}$ = 7.1, $J_{4,5}$ = 5.6 Hz, 1 H, 4-H), 3.82 (dt, ^2J = 9.7, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.94 (dd, $J_{1,2}$ = 4.6, $J_{2,3}$ = 7.6 Hz, 1 H, 2-H), 4.09 (t, *J* = 6.3 Hz, 1 H, 3-H), 4.84 (d, 1 H, 1-H), 4.92−4.97 (m, 1 H, CH=CH_2), 5.00−5.06 (m, 1 H, CH=CH_2), 5.84 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.6 Hz, 1 H, CH=CH$_2$) ppm. ^{13}C NMR (CD_3OD): δ = 30.0, 31.3 [$(CH_2)_2$], 64.1 (C-6), 68.9 (OCH$_2$CH$_2$), 74.5 (C-5), 76.3 (C-3), 78.8 (C-2), 83.4 (C-4), 102.8 (C-1), 115.2 (CH=CH$_2$), 139.5 (CH=CH$_2$) ppm. $C_{11}H_{20}O_6$ (248.28): calcd. C 53.22, H 8.12; found C 52.83, H 8.21.

α-D-Galactofuranoside 7: DMAP (0.47 g, 3.87 mmol) and (4-methoxyphenyl)diphenylmethyl chloride (11.94 g, 38.7 mmol) were added to a solution of compound **6** (3.20 g, 12.9 mmol) in dry pyridine (60 mL). After 2 h, the mixture was diluted with ethyl acetate and washed with 20% aqueous HCl, a saturated solution of aqueous $NaHCO_3$, and finally a saturated solution of aqueous NaCl. The aqueous layers were extracted twice with ethyl acetate and the combined organic layers dried ($MgSO_4$) and concentrated. Purification by flash chromatography (light petroleum/ethyl acetate, 13:7) afforded **7** (5.03 g) in 75% yield. TLC: R_f = 0.48 (dichloromethane/methanol, 9:1). $[\alpha]_D^{20}$ = +24.5 (*c* = 1.0, dichloromethane). ^1H NMR ($CDCl_3$ + D_2O): δ = 1.64−1.71 (m, 2 H, CH_2), 2.05−2.11 (m, 2 H, CH_2), 3.15 (dd, $J_{6a,6b}$ = 9.6, $J_{5,6b}$ = 6.6 Hz, 1 H, 6-Hb), 3.30 (dd, 1 H, $J_{5,6a}$ = 6.1 Hz, 6-Ha), 3.47 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.73 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.78 (s, 3 H, OMe), 3.75−3.79 (m, 1 H, 5-H), 3.94 (dd, $J_{3,4}$ = 7.1, $J_{4,5}$ = 4.6 Hz, 1 H, 4-H), 4.06 (dd, $J_{1,2}$ = 4.6, $J_{2,3}$ = 7.6 Hz, 1 H, 2-H), 4.16 (t, *J* = 7.1 Hz, 1 H, 3-H), 4.88 (d, 1 H, 1-H), 4.95−5.04 (m, 2 H, CH=CH_2), 5.77 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.6 Hz, 1 H, CH=CH$_2$), 6.83 (d, ^3J = 9.2 Hz, 2 H, *o*-H of C_6H_4OMe), 7.19−7.45 (m, 12 H, C_6H_5, C_6H_4) ppm. ^{13}C NMR ($CDCl_3$ + D_2O): δ = 28.6, 30.1 [$(CH_2)_2$], 55.2 (OMe), 64.7 (C-6), 68.6 (OCH$_2$CH$_2$), 70.7 (C-5), 75.8 (C-3), 77.8 (C-2), 82.9 (C-4), 86.8 (CPh$_2$C$_6$H$_4$OMe), 101.1 (C-1), 113.2 (C-*o* of C_6H_4OMe), 115.2 (CH=CH$_2$), 127.0, 127.9, 128.2, 128.3, 130.3 (C_6H_5, C_6H_4), 135.3 (C-*p* of C_6H_4OMe), 137.7 (CH=CH$_2$), 144.0, 144.1 (C-*i* of PhC), 158.5 (C-*i* of C_6H_4OMe) ppm. $C_{31}H_{36}O_7$ (520.63): calcd. C 71.51, H 6.97; found C 71.40, H 7.01.

α-D-Galactofuranoside 8: Triethylamine (1.4 mL, 10.0 mmol), DMAP (61 mg, 0.50 mmol) and (dropwise) pivaloyl chloride (0.59 mL, 4.81 mmol) were successively added to a solution of **7** (1.67 g, 3.21 mmol) in THF (5 mL) at 0 °C. After stirring at this temperature for 1 h, the reaction mixture was diluted with ethyl acetate (50 mL), washed with 20% aqueous HCl, a saturated solution of aqueous $NaHCO_3$, and brine. The aqueous layers were extracted with ethyl acetate, then the resulting organic layers were combined, dried with $MgSO_4$, and concentrated. Flash chromatography provided **8** (1.49 g) in 77% yield. TLC: R_f = 0.30 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D^{20}$ = +30.1 (*c* = 1.0, dichloromethane). ^1H NMR ($CDCl_3$ + D_2O): δ = 1.23 [s, 9 H, C$(CH_3)_3$], 1.56−1.63 (m, 2 H, CH_2), 2.02−2.07 (m, 2 H, CH_2), 3.13 (dd, $J_{6a,6b}$ = 9.2, $J_{5,6b}$ = 7.1 Hz, 1 H, 6-Hb), 3.31 (dd, 1 H, $J_{5,6a}$ = 5.6 Hz, 6-Ha),

3.36 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.64 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.78 (s, 3 H, OMe), 3.77−3.80 (m, 1 H, 5-H), 4.09 (dd, $J_{3,4}$ = 6.1, $J_{4,5}$ = 4.6 Hz, 1 H, 4-H), 4.51 (t, J = 6.9 Hz, 1 H, 3-H), 4.76 (dd, $J_{1,2}$ = 4.6, $J_{2,3}$ = 7.1 Hz, 1 H, 2-H), 4.94−5.10 (m, 2 H, CH=CH_2), 5.15 (d, 1 H, 1-H), 5.75 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.6 Hz, 1 H, CH=CH$_2$), 6.83 (d, ^3J = 8.6 Hz, 2 H, *o*-H of C$_6$H$_4$OMe), 7.19−7.46 (m, 12 H, C$_6$H$_5$, C$_6$H$_4$) ppm. ^{13}C NMR (CDCl$_3$ + D$_2$O): δ = 27.1 [C(CH$_3$)$_3$], 28.6, 29.9 [(CH$_2$)$_2$], 38.6 [C(CH$_3$)$_3$], 55.2 (OMe), 64.7 (C-6), 68.4 (OCH$_2$CH$_2$), 70.7 (C-5), 73.2 (C-3), 79.8 (C-2), 83.1 (C-4), 86.8 (CPh$_2$C$_6$H$_4$OMe), 100.3 (C-1), 113.1 (C-*o* of C$_6$H$_4$OMe), 115.1 (CH=CH$_2$), 126.9, 127.9, 128.2, 128.3, 130.3 (C$_6$H$_5$, C$_6$H$_4$), 135.3 (C-*p* of C$_6$H$_4$OMe), 137.6 (CH=CH$_2$), 144.1, 144.2 (C-*i* of Ph), 158.5 (C-*i* of C$_6$H$_4$OMe), 178.8 [COC(CH$_3$)$_3$] ppm. C$_{36}$H$_{44}$O$_8$ (604.75): calcd. C 71.50, H 7.73; found C 71.38, H 7.45.

α-D-Galactofuranoside 9: Benzyl bromide (5.0 mL, 42.0 mmol), tetrabutylammonium iodide (0.155 g, 0.42 mmol) and a 60% suspension of sodium hydride in oil (0.168 g, 4.20 mmol) were added successively to a solution of **8** (1.27 g, 2.10 mmol) in dichloromethane (13 mL), cooled to 0 °C. The reaction mixture was heated under reflux for 24 h, cooled to 0 °C for a second addition of sodium hydride (0.168 g, 4.20 mmol), and then heated under reflux for an additional 4 d. After quenching with some drops of methanol, a one-pot detritylation was performed using IR 120 resin (H$^+$ form, pH = 1) over a period of 1 h. Filtration, neutralization with triethylamine, and concentration, afforded a crude product that was purified by chromatography, eluting with light petroleum/ethyl acetate (4:1), to give **9** (0.915 g, 85%) as a colorless oil. TLC: R_f (light petroleum/ethyl acetate, 4:1) = 0.26. $[\alpha]_D^{20}$ = +63.7 (c = 1.0, dichloromethane). ^{1}H NMR (CDCl$_3$ + D$_2$O): δ = 1.26 [s, 9 H, C(CH$_3$)$_3$], 1.54−1.61 (m, 2 H, CH$_2$), 2.01−2.07 (m, 2 H, CH$_2$), 3.33 (dt, ^2J = 9.7, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.54−3.58 (m, 1 H, 5-H), 3.63 (dd, $J_{5,6b}$ = 5.1, $J_{6a,6b}$ = 11.7 Hz, 1 H, 6-Hb), 3.69 (dt, ^2J = 9.7, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.73 (dd, 1 H, $J_{5,6a}$ = 3.6 Hz, 6-Ha), 4.10 (t, J = 6.8 Hz, 1 H, 4-H), 4.41 (t, J = 7.1 Hz, 1 H, 3-H), 4.50−4.73 (m, 4 H, OCH_2Ph), 4.92 (dd, $J_{1,2}$ = 4.6, $J_{2,3}$ = 7.6 Hz, 1 H, 2-H), 4.93−5.01 (m, 2 H, CH=CH_2), 5.25 (d, 1 H, 1-H), 5.76 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.6 Hz, 1 H, CH=CH$_2$), 7.25−7.37 (m, 10 H, C$_6$H$_5$) ppm. ^{13}C NMR (CDCl$_3$ + D$_2$O): δ = 27.1 [C(CH$_3$)$_3$], 28.7, 30.1 [(CH$_2$)$_2$], 38.5 [C(CH$_3$)$_3$], 61.5 (C-6), 67.8 (OCH$_2$CH$_2$), 72.3, 72.8 (OCH$_2$Ph), 78.8 (C-2), 79.9 (C-3), 80.2 (C-4), 80.5 (C-5), 100.1 (C-1), 114.9 (CH=CH$_2$), 127.7, 127.8, 127.9, 128.1, 128.4, 128.5 (C$_6$H$_5$), 137.3 (CH=CH$_2$), 137.9, 138.3 (C_{ipso}Ph), 177.7 [COC(CH$_3$)$_3$] ppm. C$_{30}$H$_{40}$O$_7$ (512.65): calcd. C 70.29, H 7.86; found C 70.04, H 7.86.

α-D-Galactofuranoside 10: Triethylamine (0.58 mL, 7.11 mmol), DMAP (9 mg, 0.07 mmol) and tosyl chloride (0.407 g, 2.13 mmol) were successively added to a solution of **9** (0.730 g, 1.42 mmol) in dichloromethane (7.3 mL). The mixture was heated under reflux for 4 h, then cooled to room temperature, diluted with dichloromethane (50 mL), and washed successively with water, a saturated aqueous solution of ammonium chloride, and brine. The organic layer was dried (MgSO$_4$) and concentrated, and the residue purified by chromatography (light petroleum/ethyl acetate, 19:1 → 9:1). The desired product **10** (0.893 g) was isolated in 94% yield. TLC: R_f = 0.39 (light petroleum/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = +39.2 (c = 1.0, dichloromethane). ^{1}H NMR (CDCl$_3$): δ = 1.25 [s, 9 H, C(CH$_3$)$_3$], 1.46−1.54 (m, 2 H, CH$_2$), 1.96−2.01 (m, 2 H, CH$_2$), 2.40 (s, 3 H, CH_3C$_6$H$_4$SO$_2$), 3.22 (dt, ^2J = 9.6, ^3J = 7.1 Hz, 1 H, OCH_2CH$_2$), 3.57 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.68−3.72 (m, 1 H, 5-H), 3.89 (dd, $J_{3,4}$ = 7.1, $J_{4,5}$ = 5.1 Hz, 1 H, 4-H), 4.08 (dd, $J_{6a,6b}$ = 10.7, $J_{5,6b}$ = 7.1 Hz, 1 H, 6-Hb), 4.20 (dd, 1 H, $J_{5,6a}$ = 4.1 Hz, 6-Ha), 4.33 (t, J = 7.3 Hz, 1 H, 3-H), 4.39−4.62 (m, 4 H, OCH_2Ph), 4.85 (dd, $J_{1,2}$ = 4.6, $J_{2,3}$ = 7.6 Hz, 1 H, 2-H), 4.91−4.98 (m, 2 H, CH=CH_2), 5.15 (d, 1 H, 1-H), 5.73 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.6 Hz, 1 H, CH=CH$_2$), 7.24−7.31 (m, 12 H, C$_6$H$_5$, C$_6$H$_4$), 7.73 (d, ^3J = 8.2 Hz, 2 H, C$_6$H$_5$, C$_6$H$_4$) ppm. ^{13}C NMR (CDCl$_3$): δ = 21.6 (CH$_3$PhSO$_2$), 27.0 [C(CH$_3$)$_3$], 28.5, 30.0 [(CH$_2$)$_2$], 38.4 [C(CH$_3$)$_3$], 67.4 (OCH$_2$CH$_2$), 69.7 (C-6), 72.2, 73.7 (OCH$_2$Ph), 77.3 (C-5), 78.8 (C-2), 78.9 (C-4), 79.1 (C-3), 99.7 (C-1), 114.8 (CH=CH$_2$), 127.6−128.4, 129.8 (C$_6$H$_5$, C$_6$H$_4$), 132.7 (C-*p* of C$_6$H$_4$SO$_2$), 137.3 (CH=CH$_2$), 137.9, 138.0 (C-*i* of Ph), 144.8 (C-*i* of C$_6$H$_4$SO$_2$), 177.6 [COC(CH$_3$)$_3$] ppm. C$_{37}$H$_{46}$O$_9$S (666.84): calcd. C 66.64, H 6.95; found C 66.66, H 7.05.

α-D-Fucofuranoside 4: Sodium borohydride (0.570 g, 15.0 mmol) was added to a solution of galactofuranoside **10** (2.50 g, 3.75 mmol) in DMF (50 mL). After stirring at room temperature for 44 h, sodium methoxide in methanol (0.5 M, 15 mL, 7.5 mmol) was added, and the mixture stirred for an additional 2 h. The basic mixture was neutralized by the addition of acetic acid in methanol, and then diluted with water (50 mL) and extracted with diethyl ether (4 × 20 mL). The combined organic layers were then dried (MgSO$_4$), concentrated and purified by chromatography, eluting with light petroleum/ethyl acetate (9:1), to afford the desired fucofuranoside **4** (1.20 g) in 77% yield. TLC: R_f = 0.35 (light petroleum/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = +11.6 (c = 1.0, dichloromethane). ^{1}H NMR (CDCl$_3$ + D$_2$O): δ = 1.17 (d, $J_{5,6}$ = 6.6 Hz, 3 H, 6-H), 1.60−1.68 (m, 2 H, CH$_2$), 2.04−2.09 (m, 2 H, CH$_2$), 3.43 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.51−3.57 (m, 1 H, 5-H), 3.77 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.84 (t, J = 6.3 Hz, 1 H, 3-H), 3.87 (t, J = 6.3 Hz, 1 H, 4-H), 4.24 (t, J = 5.3 Hz, 1 H, 2-H), 4.51−4.85 (m, 4 H, OCH_2Ph), 4.93 (d, $J_{1,2}$ = 4.6 Hz, 1 H, 1-H), 4.94−5.03 (m, 2 H, CH=CH_2), 5.78 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.6 Hz, 1 H, CH=CH$_2$), 7.24−7.35 (m, 10 H, C$_6$H$_5$) ppm. ^{13}C NMR (CDCl$_3$ + D$_2$O): δ = 15.6 (C-6), 28.6, 30.3 [(CH$_2$)$_2$], 67.7 (OCH$_2$CH$_2$), 71.1, 71.7 (OCH$_2$Ph), 76.3 (C-5), 77.8 (C-2), 83.8 (C-3), 84.3 (C-4), 101.2 (C-1), 114.9 (CH=CH$_2$), 127.4, 127.6, 127.7, 127.9, 128.2, 128.3 (C$_6$H$_5$), 137.9, 138.0, 138.7 (C-*i* of Ph, CH=CH$_2$) ppm. C$_{25}$H$_{32}$O$_5$ (412.53): calcd. C72.79, H 7.82; found C 72.74, H 7.82.

α-D-Fucofuranoside 15: A 60% suspension of sodium hydride in oil (0.087 g, 2.18 mmol) and *p*-methoxybenzyl chloride (316 μL, 2.18 mmol) were successively added to a solution of **4** (0.748 g, 1.81 mmol) in DMF (15 mL), cooled to 0 °C. After stirring at room temperature for 1.5 h, water was carefully added at 0 °C and the mixture was extracted with diethyl ether (5 × 15 mL). The combined organic layers were then washed with saturated aqueous ammonium chloride and brine, dried (MgSO$_4$), and concentrated under reduced pressure. The resulting crude oil was submitted to chromatographic purification, eluting with light petroleum/ethyl acetate (9:1), to give **15** (0.877 g) in 91% yield. TLC: R_f = 0.43 (light petroleum/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = +38.2 (c = 1.0, dichloromethane). ^{1}H NMR (CDCl$_3$): δ = 1.16 (d, $J_{5,6}$ = 6.6 Hz, 3 H, 6-H), 1.62−1.70 (m, 2 H, CH$_2$), 2.06−2.12 (m, 2 H, CH$_2$), 3.31 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.55−3.61 (m, 1 H, 5-H), 3.69 (dt, ^2J = 9.6, ^3J = 6.6 Hz, 1 H, OCH_2CH$_2$), 3.80 (s, 3 H, OMe), 4.04 (dd, $J_{1,2}$ = 4.1, $J_{2,3}$ = 5.3 Hz, 1 H, 2-H), 3.84 (t, J = 7.1 Hz, 1 H, 4-H), 4.11 (t, J = 5.3 Hz, 1 H, 3-H), 4.48−4.79 (m, 6 H, OCH_2Ph), 4.84 (d, 1 H, 1-H), 4.94−5.04 (m, 2 H, CH=CH_2), 5.80 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.6 Hz, 1 H, CH=CH$_2$), 6.86−6.89 (m, 2 H, *o*-H of C$_6$H$_4$OMe), 7.24−7.36 (m, 12 H, C$_6$H$_5$, C$_6$H$_4$) ppm. ^{13}C NMR (CDCl$_3$): δ = 15.5 (C-6), 28.6, 30.3 [(CH$_2$)$_2$], 55.3 (OMe), 67.2 (OCH$_2$CH$_2$), 71.1, 72.0, 72.2 (OCH$_2$Ph), 77.3 (C-5), 82.0 (C-3), 83.5 (C-4), 84.1 (C-2), 100.0 (C-

1), 113.8 (C-*o* of C_6H_4OMe), 114.8 (CH=CH_2), 127.4−129.8 (C_6H_5, C_6H_4), 138.1, 138.2, 138.8 (C-*i* of Ph, CH=CH_2), 159.4 (C-*i* of C_6H_4OMe) ppm. $C_{33}H_{40}O_6$ (532.68): calcd. C 74.41, H 7.57; found C 7.14, H 7.61.

Preparation of the Glycosyl Acceptor

β-D-Galactopyranoside 13: The trichloroacetimidate **12** (4.77 g, 9.7 mmol) and tin(II) ditrifluoromethanesulfonate (0.404 g, 0.97 mmol) were successively added to a solution of **11** (4.87 g, 19.4 mmol) in dichloromethane (96 mL) containing 4-Å molecular sieves (4.8 g) at 0 °C. After stirring for 10 min, the reaction mixture was neutralized by adding a few drops of triethylamine. A methanolic solution of sodium methoxide (0.1 M, 78 mL) was added to the mixture without further workup. Neutralization was carried out by adding IR 120 (H^+ form) and then stirring for 1 h at room temperature. After filtration and concentration, chromatographic purification, eluting with dichloromethane/methanol (9:1 → 17:3), gave the product **13** (3.48 g) which was isolated in 87% yield. TLC: R_f = 0.15 (dichloromethane/methanol, 9:1). $[\alpha]_D^{20}$ = −8.3 (*c* = 1.0, methanol). ^{1}H NMR (CD_3OD): δ = 1.31−1.44 (m, 2 H, CH_2), 1.46−1.53 (m, 2 H, CH_2), 1.58−1.65 (m, 2 H, CH_2), 3.10 (t, ^2J = 9.7 Hz, 2 H, ^3J = 6.8 Hz, CH_2CH_2NH), 3.44 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 3.48−3.50 (m, 2 H, 5-H, 2-H), 3.51 (dt, 1 H, ^2J = 9.6 Hz, ^3J = 6.6 Hz, OCH_2CH_2), 3.71 (dd, $J_{6a,6b}$ = 11.7, $J_{5,6b}$ = 5.6 Hz, 1 H, 6-Hb), 3.74 (dd, 1 H, $J_{5,6a}$ = 7.1 Hz, 6-Ha), 3.82 (dd, 1 H, $J_{4,5}$ < 1 Hz, 4-H), 3.89 (dt, ^2J = 9.7, ^3J = 6.7 Hz, 1 H, OCH_2CH_2), 4.19 (d, $J_{1,2}$ = 7.1 Hz, 1 H, 1-H), 5.49 (s, 2 H, OCH_2Ph), 7.28−7.34 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (CD_3OD): δ = 26.7, 27.6, 30.7, 30.8 [$(CH_2)_4$], 41.7 (CH_2CH_2NH), 62.5 (C-6), 67.3 (OCH_2Ph), 70.3 (C-4), 70.6 (OCH_2CH_2), 72.6 (C-2), 75.0 (C-3), 76.6 (C-5), 105.0 (C-1), 128.7, 128.9, 129.4, (C_6H_5), 138.5 (C-*i* of C_6H_5), 158.9 (NHCO) ppm. $C_{20}H_{31}NO_8$ (413.47): calcd. C 58.10, H 7.56; found C 58.32, H 7.70.

β-D-Galactopyranoside 14: Benzaldehyde dimethylacetal (1.3 mL, 8.70 mmol) and monohydrated camphorsulfonic acid (0.169 g, 0.73 mmol) were successively added to a solution of **13** (3.00 g, 7.30 mmol) in DMF (30 mL). After stirring at 50 °C for 3 h, then cooling and quenching with some drops of triethylamine, the mixture was diluted with DMF (30 mL). A 60% suspension of sodium hydride in oil (1.04 g, 26.1 mmol) and benzyl bromide (3.1 mL, 26.1 mmol) were then added. After 2 h at room temperature, neutralization was effected by the addition of methanol. After concentration under reduced pressure at 50 °C, the resulting oil was partitioned between ethyl acetate (75 mL) and water (75 mL). The organic layer was washed with water and a brine, dried ($MgSO_4$), concentrated and chromatographed (light petroleum/ethyl acetate, 7:3 → 13:7) to afford target **14** (3.02 g) in 54% overall yield. TLC: R_f = 0.20 (light petroleum/ethyl acetate, 7:3). $[\alpha]_D^{20}$ = +23.1 (*c* = 1.0, dichloromethane). ^{1}H NMR ($CDCl_3$): δ = 1.16−1.65 [m, 8 H, $(CH_2)_4$], 3.13−3.20 (m, 1 H, CH_2CH_2N), 3.20−3.27 (m, 1 H, CH_2CH_2N), 3.29 (s, 1 H, 5-H), 3.42−3.52 (m, 1 H, OCH_2CH_2), 3.54 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.6 Hz, 1 H, 3-H), 3.82 (dd, 1 H, $J_{1,2}$ = 7.8 Hz, 2-H), 3.91−3.98 (m, 1 H, OCH_2CH_2), 4.00 (d, $J_{6a,6b}$ = 12.3 Hz, 1 H, 6-Hb), 4.09 (d, 1 H, 4-H), 4.29 (d, 1 H, 6-Ha), 4.35 (d, 1 H, 1-H), 4.47 (d, ^2J = 9.6 Hz, 2 H, NCH_2Ph), 4.76−4.92 (m, 4 H, OCH_2Ph), 5.16 (d, ^2J = 6.7 Hz, 2 H, $OCOCH_2Ph$), 5.49 (s, 1 H, CHPh), 7.23−7.39 (m, 23 H, C_6H_5), 7.54−7.57 (m, 2 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.8, 26.6, 27.6, 28.0, 29.6 [$(CH_2)_4$], 46.1, 47.1 (CH_2CH_2N), 66.3 (C-5), 50.0, 50.4 (NCH_2Ph), 67.1 (NCO_2CH_2Ph), 69.2 (C-6), 69.8 (OCH_2CH_2), 71.9 (OCH_2Ph), 74.0 (C-4), 75.2 (OCH_2Ph), 78.4 (C-2), 79.1 (C-3), 101.3 (CHPh), 103.6 (C-1), 126.5−128.9 (C_6H_5), 137.8, 137.9, 138.4, 138.9 (C-*i* of C_6H_5), 156.1, 156.6 (NC=O) ppm. $C_{48}H_{53}O_8N$ (771.96): calcd. C 74.68, H 6.92; found C 74.81, H 7.01.

β-D-Galactopyranoside 5: Sodium cyanoborohydride (0.581 g, 9.25 mmol) and trifluoromethanesulfonic acid (818 μL, 9.25 mmol) were successively added to a solution of **14** (1.02 g, 1.32 mmol) in THF (20 mL) containing 4-Å molecular sieves (1.00 g) cooled to 0 °C. After stirring for 15 min, neutralization was effected by the addition of triethylamine. The mixture was filtered through a bed of Celite, eluting with dichloromethane, then washed with water and brine, dried ($MgSO_4$), and concentrated. Chromatographic purification (light petroleum/ethyl acetate, 3:1) gave **5** (0.743 g) in 73% yield. TLC: R_f = 0.63 (light petroleum/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +0.5 (*c* = 1.0, dichloromethane). ^{1}H NMR ($CDCl_3$ + D_2O): δ (ppm):; 1.17−1.40 [m, 4 H, $(CH_2)_2$], 1.41−1.66 [m, 4 H, $(CH_2)_2$], 3.13−3.20 (m, 1 H, CH_2CH_2N), 3.20−3.28 (m, 1 H, CH_2CH_2N), 3.42−3.49 (m, 1 H, OCH_2CH_2), 3.48 (dd, $J_{2,3}$ = 9.4, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 3.55 (t, *J* = 6.0 Hz, 1 H, 5-H), 3.63 (dd, 1 H, $J_{1,2}$ = 7.7 Hz, 2-H), 3.72 (dd, 1 H, $J_{6a,6b}$ = 9.8 Hz, 6-Hb), 3.79 (dd, 1 H, 6-Ha), 3.86−3.94 (m, 1 H, OCH_2CH_2), 4.01 (d, 1 H, 4-H), 4.33 (d, 1 H, 1-H), 4.47 (d, ^2J = 8.0 Hz, 2 H, NCH_2Ph), 4.58−4.90 (m, 6 H, OCH_2Ph), 5.16 (d, ^2J = 6.4 Hz, 2 H, $OCOCH_2Ph$), 7.13−7.34 (m, 25 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$ + D_2O): δ = 25.9, 26.6, 27.6, 28.0, 29.6 [$(CH_2)_4$], 46.1, 47.1 (CH_2CH_2N), 50.1, 50.4 (NCH_2Ph), 66.7 (C-4), 67.1 (NCO_2CH_2Ph), 69.1 (C-6), 69.8 (OCH_2CH_2), 72.4 (OCH_2Ph), 73.0 (C-5), 73.7, 75.1 (OCH_2Ph), 78.9 (C-2), 80.5 (C-3), 103.6 (C-1), 127.1−128.5 (C_6H_5), 136.8, 137.9, 137.9, 138.6 (C-*i*), 156.2, 156.7 (NC=O) ppm. $C_{48}H_{55}O_8N$ (773.97): calcd. C 74.49, H 7.16; found C 74.65, H 7.19.

β-D-Galactopyranoside 17: This compound was obtained as described previously for **15**, but starting from **5** (0.630 g, 0.81 mmol) in DMF (13 mL) and using a 60% suspension of sodium hydride in oil (0.041 g, 0.97 mmol) and *p*-methoxybenzyl chloride (150 μL, 0.97 mmol). After stirring at room temperature, workup and chromatography (light petroleum/ethyl acetate, 17:3), the desired galactoside **17** (0.651 g) was isolated in 90% yield. TLC: R_f = 0.65 (light petroleum/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = +4.3 (*c* = 1.0, dichloromethane). ^{1}H NMR($CDCl_3$ + D_2O): δ = 1.17−1.40 [m, 4 H, $(CH_2)_2$], 1.41−1.63 [m, 4 H, $(CH_2)_2$], 3.13−3.26 (m, 2 H, CH_2CH_2N), 3.42−3.47 (m, 1 H, OCH_2CH_2), 3.48 (dd, $J_{2,3}$ = 7.1, $J_{3,4}$ = 2.6 Hz, 1 H, 3-H), 3.49−3.52 (m, 1 H, 5-H), 3.53−3.57 (m, 2 H, 6-H), 3.76 (s, 3 H, OMe), 3.79 (dd, 1 H, $J_{1,2}$ = 7.6 Hz, 2-H), 3.86 (d, 1 H, 4-H), 3.85−3.90 (m, 1 H, OCH_2CH_2), 4.31 (d, 1 H, 1-H), 4.45−4.48 (m, 2 H, NCH_2Ph), 4.38−4.91 (m, 8 H, OCH_2Ph), 5.15−5.17 (m, 2 H, $OCOCH_2Ph$), 6.77−6.83 (m, 2 H, H-*o* of C_6H_4OMe), 7.13−7.33 (m, 27 H, C_6H_5, C_6H_4) ppm. ^{13}C NMR ($CDCl_3$ + D_2O): δ = 25.9, 26.6, 27.7, 28.0, 29.6 [$(CH_2)_4$], 46.2, 47.1 (CH_2CH_2N), 50.1, 50.4 (NCH_2Ph), 55.2 (OMe), 67.1 (NCO_2CH_2Ph), 68.8 (OCH_2CH_2), 68.9 (C-6), 72.8 (C-4), 73.0 ($OCH_2C_6H_4OMe$), 73.4 (C-5), 73.5, 73.9, 75.1 (OCH_2Ph), 79.8 (C-2), 82.2 (C-3), 103.9 (C-1), 113.8 (C-*o* of C_6H_4OMe), 127.2−130.8 (C_6H_5, C_6H_4), 137.9, 138.6, 138.8 (C-*i* of Ph), 156.2, 156.7 (NC=O), 159.1 (C-*i* of C_6H_4OMe) ppm. $C_{56}H_{63}O_9N$ + 0.5 H_2O (903.13): calcd. C 74.48, H 7.14; found C 74.36, 6.97.

Glycosidic Coupling Reactions

Disaccharide 16: NIS (0.014 g, 0.06 mmol) and a Lewis acid [0.01 mmol, either TMSOTf (2 μL) or $Sn(OTf)_2$ (4 mg)] were added to a solution of **15** (0.032 g, 0.06 mmol) and **5** (0.039 g, 0.05 mmol) in dichloromethane (1 mL) in the presence of 4-Å molecular sieves (0.1 g). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 22 h, and then quenched by adding triethyl-

amine. After filtration through a bed of Celite, the resulting solution was concentrated and chromatographed (light petroleum/ethyl acetate, 4:1) to afford either stereochemically pure **16β** (0.020 g, 33%) or a mixture of **16α,β** (0.015 g, 25%). **16β**: TLC: R_f = 0.40 (light petroleum/ethyl acetate, 7:3). ^{1}H NMR ($CDCl_3$): δ = 1.15 (d, $J_{5b,6b}$ = 6.1 Hz, 3 H, 6-Hb), 1.18−1.55 [m, 8 H, $(CH_2)_4$], 3.11−3.27 (m, 2 H, CH_2CH_2N), 3.49 (dd, $J_{2a,3a}$ = 6.6, $J_{3a,4a}$ = 2.5 Hz, 1 H, 3a-H), 3.50−3.52 (m, 1 H, 5a-H), 3.53−3.56 (m, 2 H, 6-Ha), 3.59−3.64 (m, 1 H, 5b-H), 3.78 (s, 3 H, OMe), 3.76−3.79 (m, 1 H, 2a-H), 3.86 (dd, $J_{4b,5b}$ = 3.6, $J_{3b,4b}$ = 8.2 Hz, 1 H, 4b-H), 3.84−3.88 (m, 1 H, OCH_2CH_2), 3.93 (dd, 1 H, $J_{2b,3b}$ = 4.1 Hz, 3b-H), 3.92−3.96 (m, 1 H, OCH_2CH_2), 4.11 (dd, 1 H, $J_{1b,2b}$ = 1.0 Hz, 2b-H), 4.14 (d, 1 H, 4a-H), 4.31 (d, $J_{1a,2a}$ = 7.1 Hz, 1 H, 1a-H), 4.21−4.95 (m, 12 H, OCH_2Ph), 5.16 (d, ^3J = 5.1 Hz, 2 H, $OCOCH_2Ph$), 5.49 (d, 1 H, 1b-H), 6.76−6.81 (m, 2 H, *o*-H of C_6H_4OMe), 7.06−7.34 (m, 37 H, C_6H_5, C_6H_4) ppm. ^{13}C ($CDCl_3$): δ = 16.1 (C-6b), 25.9, 26.6, 27.7, 28.1, 29.6 [$(CH_2)_4$], 46.1, 47.1 (CH_2CH_2N), 50.1, 50.4 (NCH_2Ph), 55.3 (OMe), 67.1 (NCO_2CH_2Ph), 68.9 (C-6a), 70.1 (OCH_2CH_2), 71.2, 71.3, 71.9 (OCH_2Ph), 72.5 (C-4a), 73.0 (C-4b), 73.5 (OCH_2Ph), 73.7 (C-5a), 74.2 (C-5b), 75.0 (OCH_2Ph), 79.6 (C-2a), 82.2 (C-3a), 83.3 (C-3b), 88.1 (C-2b), 103.9 (C-1a), 107.0 (C-1b), 113.4 (C-*o* of C_6H_4OMe), 127.2−130.0 (C_6H_5, C_6H_4), 138.0−138.8 (C-*i* of CH_2Ph), 159.2 (C-*i* of C_6H_4OMe) ppm. **16α**: TLC: R_f = 0.40 (light petroleum/ethyl acetate, 7:3). Characteristic data obtained from the anomeric mixture: ^{13}C NMR ($CDCl_3$): δ = 15.8 (C-6b), 25.9, 26.6, 27.6, 28.0, 29.7 [$(CH_2)_4$], 46.1, 47.1 (CH_2CH_2N), 50.0, 50.3 (NCH_2Ph), 55.2 (OMe), 67.1 (NCO_2CH_2Ph), 69.2 (C-6a), 69.9 (OCH_2CH_2), 71.2 (OCH_2Ph), 72.1 (C-4a), 72.2, 73.4 (OCH_2Ph), 73.7 (C-5a), 75.1 (OCH_2Ph), 77.1 (C-5b), 79.4 (C-2a), 80.7 (C-3b), 81.4 (C-3a), 83.1 (C-4b), 84.1 (C-2b), 101.2 (C-1b), 104.0 (C-1a), 113.8 (C-*o* of C_6H_4OMe), 127.2−129.9 (C_6H_5, C_6H_4), 137.9−138.3 (C-*i* of CH_2Ph), 159.3 (C-*i* of C_6H_4OMe) ppm.

Disaccharide 20: DDQ (0.029 g, 0.127 mmol) was added to a solution of fucofuranosyl donor **4** (0.035 g, 0.085 mmol) and galactopyranoside **17** (0.091 g, 0.102 mmol) in dry dichloromethane (2 mL) containing 4-Å molecular sieves (0.2 g) and cooled to 0 °C. After stirring at room temperature for 1 h, the reaction was quenched by adding an aqueous solution (0.50 mL) of ascorbic acid (0.7%), citric acid (1.3%) and sodium hydroxide (0.9%).[24] The mixture was filtered through a bed of Celite and the resulting solution was washed with an aqueous solution of ascorbic acid (0.7%), citric acid (1.3%) and sodium hydroxide (0.9%), then with saturated aqueous sodium bicarbonate, and then finally with brine. The combined aqueous layers were extracted with dichloromethane and the resulting organic solution was dried ($MgSO_4$) and concentrated. For spectral assignments, the desired tether **18** was purified through a short bed of silica gel eluting with light petroleum/ethyl acetate (4:1). This eluent was complemented with 1% of triethylamine to neutralize the acidic centers of the chromatographic material and so to limit degradation of labile tether **18**. This procedure allowed us to record ^{1}H and ^{13}C NMR spectra. Nevertheless, we recommend that crude **18** be used without further purification. In this case, **18** was first dried by co-evaporation with dry toluene under reduced pressure at 50 °C. The resulting oil was then dissolved in dichloromethane (2 mL) containing 4-Å molecular sieves (0.2 g). After cooling at 0 °C, NIS (0.023 g, 0.10 mmol) was added and the mixture was warmed slowly to room temperature. After stirring for 19 h, the mixture was neutralized (triethylamine), filtered through a bed of Celite (dichloromethane), and finally purified by chromatography (light petroleum/ethyl acetate, 7:3 → 13:7). Compound **19** was isolated in 34% yield. Subsequent hydrogenolysis was carried out with **19** (0.036 g, 0.028 mmol) in a solution of acetic acid (0.024 mL, 0.041 mmol) in ethanol (4 mL) in the presence of palladium acetate (36 mg). After stirring under hydrogen (1 atm) at room temperature for 6 d and then for an additional 24 h under a higher pressure of hydrogen (30 atm), the mixture was neutralized (acetic acid), filtered, and concentrated. The resulting crude oil was then acetylated [acetic anhydride (2 mL), pyridine (2 mL)] at 50 °C for 5 h. The solution was diluted with ethyl acetate (10 mL), successively washed with 20% aqueous HCl, saturated aqueous sodium bicarbonate, and brine. After drying ($MgSO_4$) and removal of the solvent, chromatographic purification gave **20** (0.005 g) in 25% yield. **Tethered Disaccharide 18:** TLC: R_f = 0.55 (light petroleum/ethyl acetate/triethylamine, 4:1:0.05). ^{1}H NMR ($CDCl_3$): δ = 1.04 (d, $J_{5b,6b}$ = 6.1 Hz, 3 H, 6b-Ha), 1.08−1.54 [m, 10 H, $(CH_2)_4$, CH_2], 1.91−1.97 (m, 2 H, CH_2), 2.99 (dt, ^2J = 9.2, ^3J = 7.1 Hz, 1 H, $OCH_2C_4H_7$), 3.04−3.19 (m, 2 H, CH_2CH_2N), 3.28 (dd, $J_{2a,3a}$ = 9.7, $J_{3a,4a}$ = 3.0 Hz, 1 H, 3a-H), 3.32−3.39 (m, 1 H, $OCH_2C_5H_{10}$), 3.42−3.50 (m, 3 H, 5a-H, 5b-H, $OCH_2C_4H_7$), 3.52 (dd, 1 H, $J_{1a,2a}$ = 7.6 Hz, 2a-H), 3.65 (dd, $J_{5a,6'a}$ = 5.6, $J_{6a,6'a}$ = 9.6 Hz, 1 H, H-6a-Hb), 3.70 (s, 3 H, OMe), 3.69−3.71 (m, 1 H, 4b-H), 3.76−3.84 (m, 1 H, $OCH_2C_5H_{10}$), 3.91 (dd, 1 H, 6a-Ha), 3.95−3.97 (m, 2 H, 2b-H, 3b-H), 4.21 (d, 1 H, 1a-H), 4.23−4.26 (m, 2 H, 4a-H, 1b-H), 4.36−4.38 (m, 2 H, NCH_2Ph), 4.39−4.71 (m, 10 H, OCH_2Ph), 4.86−4.94 (m, 2 H, $CH=CH_2$), 5.08 (br. s, 2 H, $OCOCH_2Ph$), 5.65 (s, 1 H, $CHPhOMe$), 5.69 (ddt, $J_{4',5'a}$ = 16.8, $J_{4',5'b}$ = 10.2, $J_{3',4'}$ = 6.1 Hz, 1 H, $CH=CH_2$), 6.68−6.71 (m, 2 H, *o*-H of C_6H_4OMe), 7.12−7.25 (m, 37 H, C_6H_5, C_6H_4) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.5 (C-6b), 25.8, 26.6, 27.6, 28.0, 29.6 [$(CH_2)_4$], 28.8, 30.3 [$(CH_2)_2$], 46.1, 47.1 (CH_2CH_2N), 50.1, 50.4 (NCH_2Ph), 55.3 (OMe), 67.2 ($OCH_2C_4H_7$, NCO_2CH_2Ph), 69.2 (C-6a), 69.9 ($OCH_2C_5H_{10}$), 71.2 (OCH_2Ph), 71.5 (C-4a), 72.6, 72.9, 73.4 (OCH_2Ph), 73.7 (C-5a), 75.0 (OCH_2Ph), 77.0 (C-5b), 79.2 (C-2a), 81.5, 81.8 (C-2b, C-3b), 82.0 (C-3a), 82.9 (C-4b), 99.9 (C-1b),103.9 (C-1a), 104.5 (CHC_6H_4OMe), 113.1 (C-*o* of C_6H_4OMe), 114.7 ($CH=CH_2$), 127.3−128.5 (C_6H_5, C_6H_4), 132.0−138.8 (C-*i* of Ph, $CH=CH_2$), 155.9, 156.7 (NC=O), 159.7 (C-*i* of C_6H_4OMe) ppm. **Disaccharide 19:** Selected ^{13}C NMR spectroscopic data ($CDCl_3$): δ = 15.5 (C-6b), 25.9−29.7 (CH_2), 46.2, 47.1 (CH_2CH_2N), 50.1, 50.4 (NCH_2Ph), 55.1, 55.2 (OMe), 69.1 (C-6a), 73.2 (C-5a), 73.5, 75.0 (OCH_2Ph), 76.5 (C-5b), 79.2 (C-2a), 80.3, 80.7, 82.2, 83.0 (C-2b, C-3b, C-4b, C-3a), 100.0 (C-1b), 103.9, 104.0 (C-1a), 113.1 (C-*o* of C_6H_4OMe), 158.9 (NC=O), 159.6 (C-*i* of C_6H_4OMe), 176.4 (CH_2CO) ppm. **Disaccharide 20:** TLC: R_f = 0.28 (dichloromethane/methanol, 19:1). ^{1}H NMR ($CDCl_3$): δ = 1.25−1.35 [m, 4 H, $(CH_2)_2$], 1.38 (d, $J_{5b,6b}$ = 6.6 Hz, 3 H, 6b-Ha), 1.47−1.57 [m, 4 H, $(CH_2)_2$], 1.96, 1.98, 2.00, 2.01, 2.03, 2.07, 2.11 (7 s, 21 H, $OCOCH_3$), 3.08−3.14 (m, 2 H, NCH_2CH_2), 3.29 (t, J = 7.6 Hz, 1 H, 5a-H), 3.40−3.46 (OCH_2CH_2), 3.65 (s, 1 H, NH), 3.75 (t, $J_{4b,5b}$ = 6.6 Hz, 1 H, 5b-H), 3.84−3.90 (m, 2 H, OCH_2CH_2, 4b-H), 4.02 (d, $J_{3a,4a}$ = 3.0 Hz, 1 H, 4a-H), 4.12 (dd, $J_{6'a,6a}$ = 11.2, $J_{5a,6'a}$ = 6.1 Hz, 1 H, 6a-Hb), 4.39 (d, $J_{1a,2a}$ = 8.2 Hz, 1 H, 1a-H), 4.41−4.46 (m, 1 H, 6-Ha), 4.76 (dd, 1 H, $J_{2a,3a}$ = 10.7 Hz, 3a-H), 4.96−4.99 (m, 2 H, 1b-H, 5b-H), 5.14 (dd, $J_{2b,3b}$ = 8.6, $J_{1b,2b}$ = 4.6 Hz, 1 H, 2b-H), 5.42 (dd, 1 H, 2a-H), 5.57−5.62 (m, 1 H, 3b-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.5 (C-6b), 20.5, 20.7, 20.8, 20.9, 21.0, 21.3, ($OCOCH_3$), 22.2 ($NHCOCH_3$), 27.0, 27.1, 29.4, 29.5 [$(CH_2)_4$], 40.8 (NCH_2CH_2), 62.4 (C-6a), 68.4 (C-5b), 69.0 (C-2a), 70.0 (OCH_2CH_2), 71.8 (C-5a), 72.3 (C-3b), 73.2 (C-3a), 75.9 (C-2b), 76.5 (C-4a), 80.3 (C-4b), 101.7 (C-1a), 102.1 (C-1b), 168.8−171.2 (C=O) ppm. HRMS: *m*/*z* ($[M + Na]^+$, $C_{34}H_{53}NO_{17}Na$): calcd. 770.3211; found 770.3249.

Disaccharide 22: The reaction was performed according to a procedure similar to that described for **19** but using, for the preparation of the intermediate acetal, fucofuranoside **15** (0.040 g,

0.075 mmol), glucopyranoside **21** (0.029 g, 0.063 mmol) and DDQ (0.029 g, 0.127 mmol), and for the aglycon transfer, NIS (0.070 g, 0.31 mmol). The resulting disaccharide **22** (0.013 g) was isolated after chromatography (light petroleum/ethyl acetate, 3:2) in 21% yield. TLC: R_f = 0.42 (light petroleum/ethyl acetate, 3:2). ^{1}H NMR ($CDCl_3$): δ = 1.14 (d, $J_{5b,6b}$ = 6.6 Hz, 3 H, 6-Hb), 2.65 [s, 4 H, $(CH_2)_2$], 3.08 (dd, $J_{1a,2a}$ = 3.6, $J_{2a,3a}$ = 9.7 Hz, 1 H, 2a-H), 3.30 (s, 3 H, 1a-OCH_3), 3.36 (dd, $J_{4a,5a}$ = 9.2, $J_{3a,4a}$ = 5.1 Hz, 1 H, 4a-H), 3.48−3.52 (m, 1 H, 5b-H), 3.53−3.57 (m, 1 H, 5a-H), 3.59 (s, 3 H, $C_6H_4OCH_3$), 3.74 (dd, 1 H, $J_{6a,6'a}$ = 12.2, $J_{5a,6'a}$ = 2.0 Hz, 6a-Hb), 3.77 (dd, 1 H, $J_{5a,6a}$ = 2.5 Hz, 6a-Ha), 3.78 (dd, 1 H, 3a-H), 3.87 (dd, $J_{3b,4b}$ = 7.1, $J_{4b,5b}$ = 7.6 Hz, 1 H, 4b-H), 4.06 (dd, $J_{1b,2b}$ = 4.0, $J_{2b,3b}$ = 7.1 Hz, 1 H, 2b-H), 4.16 (t, 1 H, 3b-H), 4.59 (d, 1 H, 1a-H), 4.42−4.87 (m, 10 H, OCH_2Ph), 5.37 (d, 1 H, 1b-H), 6.42 (s, 1 H, CHC_6H_4OMe), 6.77−6.79 (m, 2 H, *o*-H of C_6H_4OMe), 7.13−7.31 (m, 27 H, C_6H_5, C_6H_4) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.6 (C-6b), 28.1 [$(CH_2)_2$], 55.0, 55.1 ($C_6H_4OCH_3$, 1a-OCH_3), 64.9 (C-6a), 70.5 (C-5a), 71.2, 71.8, 73.1, 74.7, 75.3 (OCH_2Ph), 77.2 (C-4a), 77.3 (C-5b), 79.9 (CHC_6H_4OMe), 80.1 (C-2a), 81.2 (C-3b), 81.8 (C-3a), 81.9 (C-2b), 84.0 (C-4b), 113.7 (C-*o* of C_6H_4OMe), 97.7 (C-1a), 100.5 (C-1b), 127.0−128.3 (C_6H_5, C_6H_4), 137.9, 138.4, 138.8, 139.2 (C-*i* of Ph), 152.6 (C-*i* of C_6H_4OMe), 176.2 (C=O) ppm. HRMS: $[M + Na]^+$, ($C_{60}H_{65}NO_{13}Na$) calcd. *m*/*z* = 1030.4354, found 1030.4362; $[M - H]^+$ ($C_{60}H_{64}NO_{13}$) calcd. *m*/*z* = 1006.4378; found 1006.4380; $[M - C_4H_4NO_2]^+$ ($C_{56}H_{61}O_{11}$) calcd. *m*/*z* = 909.4214; found 909.4213: $[C_{12}H_{12}NO_3]^+$ calcd. *m*/*z* = 218.0817; found 218.0819.

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