JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

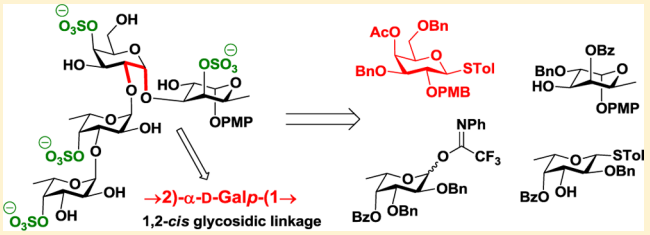
Stereoselective Synthesis of a Sulfated Tetrasaccharide Corresponding to a Rare Sequence in the Galactofucan Isolated from *Sargassum polycystum*

Jun Zhou, Liping Yang, and Wenhao Hu*

Shanghai Engineering Research Centre of Molecular Therapeutics and New Drug Development, and Department of Chemistry, East China Normal University, Shanghai, 200062, PR China

Supporting Information

ABSTRACT: The first chemical synthesis of a highly sulfated tetrasaccharide **1**, as the rare sequence in the galactofucan isolated from the brown alga *Sargassum polycystum*, was achieved in a convergent and stereoselective manner. The key features of the synthetic strategy include construction of multiple contiguous 1,2-*cis* glycosidic bonds and [2 + 2] assembly based on the rationally developed D-galactose building block **6**. The synthesized oligosaccharides were fully characterized using a combination of coupled-HSQC and other 2D NMR techniques.



Fucoidans, a family of complex sulfated polysaccharides extracted from brown algae, have been reported to exhibit various physiological and biological functions[1] such as anticoagulant, antithrombotic, anti-inflammatory, antiviral, and antitumor activities. These polysaccharides have a common backbone[2] built up of sulfated α-L-fucopyranose (Fuc*p*) residues with (1 → 3)- or (1 → 4)-linkages. Nevertheless, depending on the algal species, crude fucoidan extracts may contain minor heteropolysaccharide[3] components with a variety of sugar residues and different linkages. Recently, from brown alga *Sargassum polycystum*, Usov[4] and co-workers isolated a novel galactofucan, in which sequences of 3-linked 4-*O*-sulfated α-L-Fuc*p* residues are interspersed by discontinuous 2-linked 4-*O*-sulfated α-D-galactopyranose (Gal*p*) residue as a distinctive structural feature (Figure 1). It is an unusual naturally occurring [→ 2)-α-D-Gal*p*-(1 →] unit in the seaweed resource and should have influence on conformation and biological activities.

Chemical synthesis is currently an efficient approach to obtain pure fucoidan oligosaccharides with specific structures, which would enable the investigation of structure−activity relationship and potential application to new drug discovery. Several sulfated fucoidan homo-oligosaccharides have been chemically synthesized[5] and showed antitumor activity. However, such a unique type of sulfated galactofucan oligosaccharide containing 2-linked α-D-Gal*p* unit, as reported by Usov, has not been synthesized yet. Herein, we report the first chemical synthesis of a highly sulfated tetrasaccharide **1** corresponding to the rare sequence in the galactofucan isolated from the brown alga *Sargassum polycystum*.

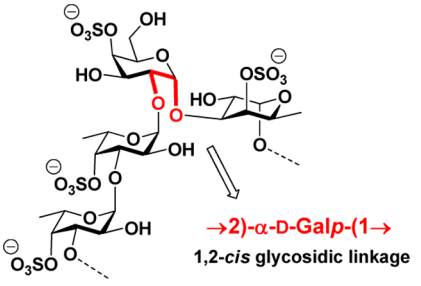


Figure 1. Structure of the rare sequence in the galactofucan isolated from the brown alga *Sargassum polycystum*.

Sulfated tetrasaccharide **1**, which contains four contiguous 1,2-*cis* glycosidic[6] linkages (Figure 2), presents several significant synthetic challenges. The most prominent one is the stereoselective construction of the [→ 2)-α-D-Gal*p*-(1 →] backbone with a highly crowded 1,2-*cis* orientation of two sugar moieties. In this respect, the potent steric effect between the reducing end α-L-fuc*p* residue and the fuco-disaccharide moiety, oriented in a 1,2-*cis* configuration, requires much more attention in convergent synthesis. Moreover, highly selective α-galactosidic[7] and α-fucosidic[8] bond formation without generating inseparable anomeric mixtures is regarded to be challenging in assembly of oligosaccharide. In addition, as in heparin[9] oligosaccharide synthesis, differentiation of hydroxyl groups that would remain free, undergo elongation, or be sulfated is to rely on orthogonality[10] of protecting groups.

As for the construction of (1 → 2)-linked α-D-galactoside unit in nonterminal part of oligosaccharide chain, only a few successful examples have been reported, despite different plausible retrosynthetic disconnections. The use of a type of galactosyl donor,[11] carrying a glycosylated hydroxyl at C-2

Received: March 3, 2014
Published: April 25, 2014

dx.doi.org/10.1021/jo500503r | J. Org. Chem. 2014, 79, 4718−4726

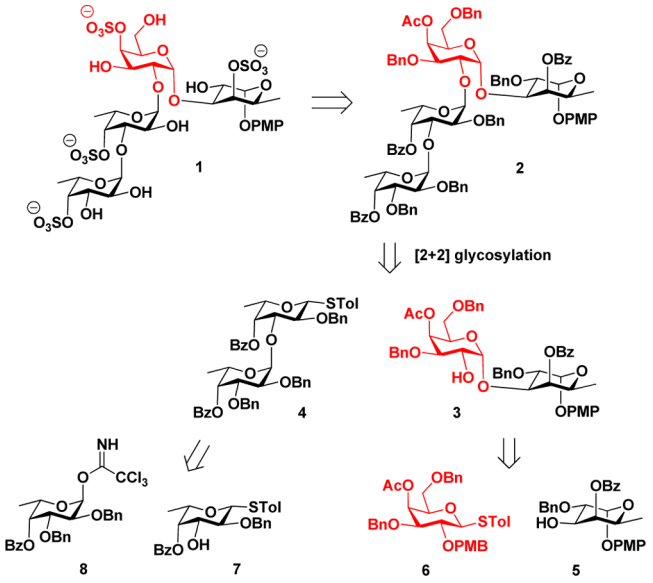


Figure 2. Synthetic plan of the target tetrasaccharide **1**.

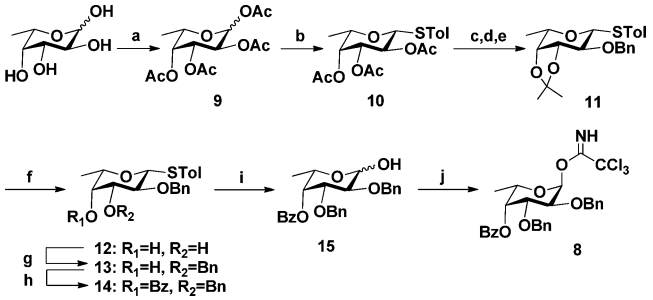
position, led principally to an undesired 1,2-*trans* outcome in glycosylations. From a stereochemical viewpoint, the bulky 2-*O*-glycosyl moiety of the donor sterically hinders incoming acceptor from the α-face, thereby affording a β-linked galactoside or an anomeric mixture. In contrast, 2-OH α-galactoside derivatives[12] have been reported to serve as appropriate acceptors mainly for L-rhamnosylations. However, in order to glycosylate the sterically congested C-2 alcohols for building up [α-L-Rha*p*-(1 → 2)-α-D-Gal*p*-(1 →] units, multiple equivalents[12a−d] of reactive L-rhamnosyl halides or imidates were utilized as donors in combination with stoichiometric amount of heavy metal[12a,d−f] salts or other Lewis acids; in some cases, moderate or even low yields[12e,f] were obtained. Nevertheless, the efficient and stereoselective formation of [α-L-Fuc*p*-(1 → 2)-α-D-Gal*p*-(1 →] disaccharide unit, as required for our target, using 2-OH α-galactoside acceptor and thiofucosyl donor still remains unknown, because it requires an appropriately reactive donor and stereochemical control of 1,2-*cis* fucosylation, which is more difficult than 1,2-*trans* rhamnosylation in the presence of neighboring group participation.

Our synthetic plan (Figure 2) of the sulfated tetrasaccharide **1** suggested a convergent [2 + 2] assembly of tetrasaccharide **2**, employing disaccharide acceptor **3** and thiofucosyl donor **4**, to construct the [α-L-Fuc*p*-(1 → 2)-α-D-Gal*p*-(1 →] backbone through an α-fucosidic bond. Thus, the orthogonally protected thiogalactosyl donor **6** was developed as a crucial and ideal donor to build up the 1,2-*cis*-α-galactosidic linkage of disaccharide **3**. Herein, the 4-*O*-acetyl group of **6** would be expected to confer the remote neighboring group participation effect[13] during the α-galactosidic bond formation. The *p*-methoxybenzyl (PMB) ether group was installed at C-2 position of **6** as a nonparticipating group to facilitate the α-galactosylation, as well as a temporary protection in anticipation of chain elongation. In turn, the α-linked disaccharide **4** can be derived from 1-thio acceptor **7** and imidate donor **8** through an orthogonal glycosylation, minimizing the number of protecting group manipulations.

Strategically, these synthetic precursors were decorated by a carefully selected set of orthogonal protections that enables transformations on selected hydroxyls (Figure 2). Herein, the hydroxyls to be sulfated were masked as benzoyl (Bz) or acetyl (Ac) esters, and benzyl (Bn) ethers were employed to block those that would be free in the target. As described above, 4-*O*-Ac and 2-*O*-PMB of **6** were installed to possess corresponding functions. Capping the reducing end with *p*-methoxyphenyl (PMP) group[14] enables easy cleavage and further conjugate preparation if necessary.

The synthesis of fucosyl imidate donor **8** is outlined in Scheme 1. The known β-thiofucoside **10**,[15] acquired from L-

Scheme 1. Synthesis of Imidate Donor 8[a]

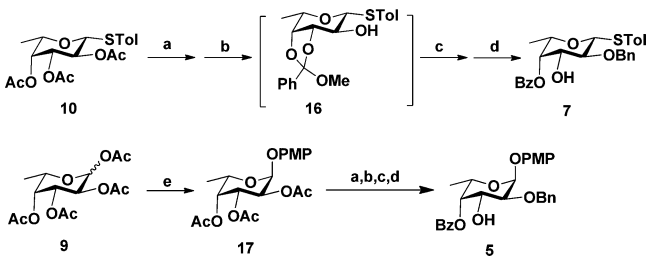


[a]Reagents and conditions: (a) Ac_2O, pyridine, DMAP; (b) *p*-thiocresol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 87% over 2 steps; (c) MeONa, MeOH; (d) 2,2-dimethoxypropane, TsOH, acetone; (e) BnBr, NaH, DMF, 95% over 3 steps; (f) TsOH, MeOH, 90%; (g) Bu_2SnO, toluene then BnBr, TBAI, DMF, 98%; (h) BzCl, Py, DMAP, CH_2Cl_2, 83%; (i) NBS, acetone, H_2O, 87%; (j) Cl_3CCN, DBU, CH_2Cl_2, 75%.

fucose in two steps, underwent deacetylation, 3,4-*O*-isopropylidenation, and 2-*O*-benzylation to provide **11** in 95% yield over three steps. Subsequent cleavage of the acetal in the presence of *p*-toluenesulfonic acid (TsOH) in methanol afforded 3,4-diol **12** in 90% yield. Regioselective 3-*O*-benzylation (98%) of **12** using stannylidene approach followed by 4-*O*-benzoylation (83%) and oxidative hydrolysis (87%) using *N*-bromosuccinimide (NBS) provided 1-hemiacetal **15**, which was converted into the corresponding imidate donor **8** as an α-anomer in 75% yield.

Starting from 2,3,4-triacetate **10**, building block **7** containing a free hydroxyl at C-3 position can be efficiently synthesized through a sequential four-step procedure[16] without purification of intermediates (Scheme 2). Briefly, crude triol generated by deacetylation of **10**, was transformed into cyclic 3,4-*O*-orthobenzoate **16**, which was subjected to sequential 2-*O*-benzylation and regioselective acidic hydrolysis to furnish C-3 alcohol **7** in 82% yield over four steps. Using the similar

Scheme 2. Synthesis of Building Blocks 5 and 7[a]



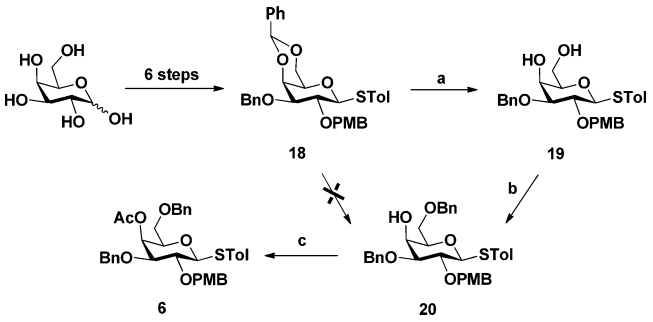
[a]Reagents and conditions: (a) MeONa, MeOH; (b) $PhC(OMe)_3$, camphorsulfonic acid, acetonitrile; (c) BnBr, NaH, DMF; (d) HCl (1 M), 82% for **7**; 70% for **5**; over 4 steps; (e) *p*-methoxyphenol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 78%.

dx.doi.org/10.1021/jo500503r | J. Org. Chem. 2014, 79, 4718−4726

approach, the reducing end building block **5** was prepared from **17** in an overall yield of 70%. Interestingly, condensation of *p*-methoxyphenol with tetra-acetate **9** afforded the fucoside **17**, which was unexpectedly identified as an exclusive α-anomer. This 1,2-*cis* selectivity, as distinct from typical phenolic glycosylation with the assistance of 2-*O*-acyl group, was attributed to reversible in situ anomerization[17] and the stabilizing anomeric effect.

Galactose building block **6** was synthesized from the reported **18**[18] in three steps (Scheme 3). For the purpose of making the

Scheme 3. Synthesis of Building Block 6[a]

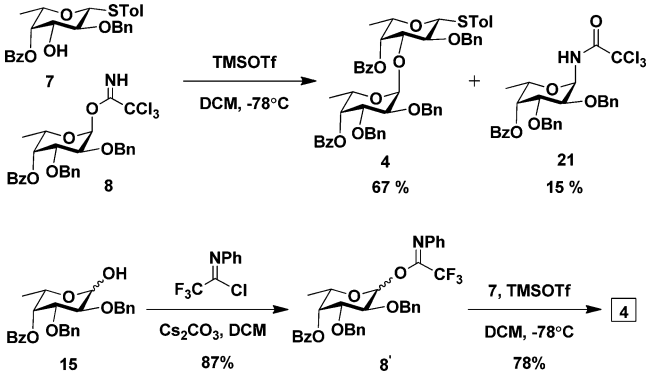


[a]Reagents and conditions: (a) TsOH, MeOH; (b) BnBr, NaOH, Bu_4NHSO_4, H_2O, CH_2Cl_2, 61% over 2 steps; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 88%.

C-4 alcohol **20** from **18**, we initially attempted reductive opening of the benzylidene ring on **18** using Et_3SiH–trifluoroacetic acid (TFA), Et_3SiH–trimethylsilyl triflate (TMSOTf), $NaBH_3CN$–HCl and $NaBH_3CN$–cyanuric chloride[19] combinations, respectively. Unfortunately, the use of these conditions failed to provide **20** and led to degradation of the instable PMB[20] ether in acidic media. To circumvent this difficulty, we resorted to a stepwise approach. The benzylidene acetal on **18** was removed to provide diol **19**, which was selectively benzylated[21] at the primary alcohol under the phase transfer condition to produce 4-OH **20** (61%, over two steps). Acetylation of the resulting alcohol delivered building block **6** in 88% yield.

With all of the building blocks in hand, the assembly of target oligosaccharide was continued, commencing from the synthesis of the nonreducing end disaccharide **4** (Scheme 4). Orthogonal glycosylation[22] of donor **8** and 1-thio acceptor **7** promoted by TMSOTf at −78 °C afforded the α-linked disaccharide **4** in a moderate yield of 67%, which could directly serve as donor in

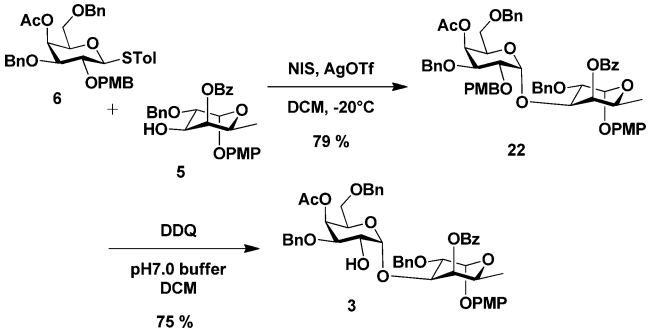
Scheme 4. Synthesis of Disaccharide 4



subsequent [2 + 2] glycosylation. We were also able to isolate 15% of *N*-glycosyl amide **21**, a side product due to fast decomposition of the highly reactive trichloroacetimidate donor **8**, even at very low temperature. To avoid this problem, we opted to convert hemiacetal **15** into *N*-phenyl trifluoroacetimidate[23] donor **8′**, which would be moderately reactive and shelf-stable. Thus, acceptor **7** was glycosylated using **8′** as donor under aforementioned conditions, delivering disaccharide **4** in an improved yield of 78%.

Disaccharide precursor **22** was assembled (Scheme 5) from galactosyl donor **6** and the reducing end acceptor **5** in the

Scheme 5. Synthesis of Disaccharide 3



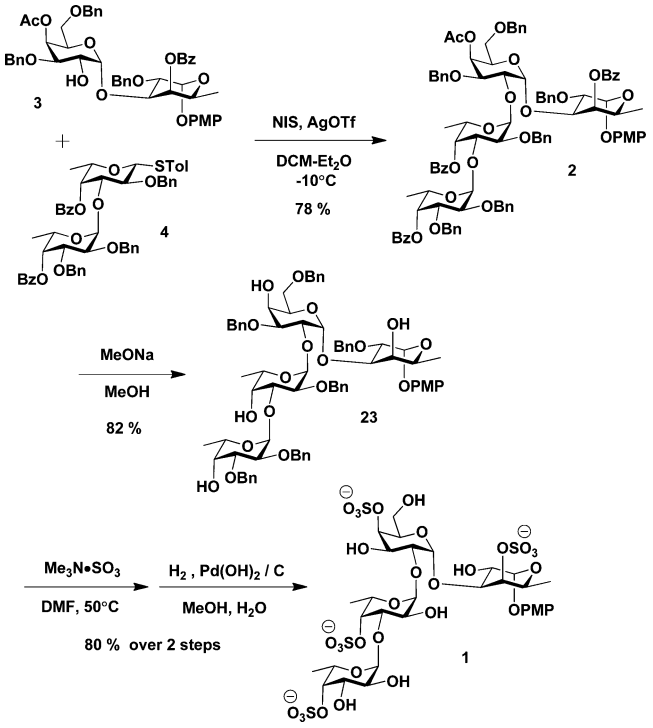
presence of *N*-iodosuccinimide (NIS) and silver triflate (AgOTf) at −20 °C in 79% yield with complete α-selectivity, which may be credited to the remote neighboring group participation[13] by the acetyl group situated at C-4 position of **6**. The $^1J_{C1/H1}$ one-bond heteronuclear coupling constant of 175.5 Hz, measured by coupled-HSQC, on the D-Gal residue was characteristic[24,6b] for the newly formed α-galactosidic bond, which could also be determined by the corresponding $^3J_{1,2}$ value of 3.2 Hz. Next, the temporary 2-*O*-PMB protection was removed by treating with DDQ to obtain disaccharide acceptor **3** in 75% yield.

In general, side reaction of a highly reactive donor due to its fast promotion, especially when coupled with a sterically hindered or an unreactive acceptor, would be a significant issue for glycosylation. Therefore, we decided to carry out the [2 + 2] glycosylation of acceptor **3** with thiofucosyl donor **4** using NIS/AgOTf in a mixed solvent of CH_2Cl_2–Et_2O (Scheme 6). Under this somewhat mild condition, the highly reactive and precious fucosyl donor would be promoted more slowly[25] to suppress its degradation pathways. In addition, α-selectivity would be enhanced by ether solvent effect.[8a,26] As expected, the reaction proceeded smoothly at −10 °C over about 3 h using 1.1 equiv of donor **4** and furnished tetrasaccharide **2** in 78% yield with exclusive α-selectivity. The $^1J_{C1/H1}$ coupling constant of 174.4 Hz on the third sugar residue of **2** confirmed the orientation of the newly generated α-fucosidic bond.

Finally, the fully protected tetrasaccharide **2** was subjected to the cleavage of the benzoyl and acetyl ester groups under Zemplén condition to afford the corresponding tetra-alcohol **23** in 82% yield (Scheme 6). *O*-Sulfation of **23** using SO_3·Me_3N in DMF at 50 °C and subsequent hydrogenolysis over $Pd(OH)_2$/C afforded the crude product, which was subjected to ion-exchange on a Dowex 50WX8 (Na^+ form) column and size-exclusion chromatography on a Sephadex G-25 column to provide target tetrasaccharide **1** as its sodium salt in 80% yield over two steps.

dx.doi.org/10.1021/jo500503r | J. Org. Chem. 2014, 79, 4718–4726

Scheme 6. Synthesis of Target Tetrasaccharide 1



NMR signal assignments of **1** including the identification of anomeric configurations were carried out using a combination of COSY, TOCSY, HSQC, HSQC-TOCSY, HMBC, ROESY, and coupled-HSQC 2D NMR techniques. Herein, HSQC spectrum showed four cross peaks in anomeric region. The appearance of $^{1}J_{C1/H1}$ values (173.8, 176.3, 175.5, 173.0 Hz) in coupled-HSQC proved the presences of four α-glycosidic bonds in Fuc^{I}, Gal^{II}, Fuc^{III} and Fuc^{IV} residues, respectively. Furthermore, one (1 → 2)- and two (1 → 3)- linkages were revealed through inter-residue NOEs observed in ROESY experiment and three-bond correlations in HMBC spectrum as well.

In summary, we have accomplished the first chemical synthesis of a highly sulfated tetrasaccharide **1** as the rare sequence in the galactofucan isolated from the brown alga *Sargassum polycystum* in an efficient and stereoselective way. The orthogonally protected galactose building block **6** was proved to be a crucial and ideal donor to build up the 1,2-*cis*-α-galactosidic bond, and also could enable the convergent [2 + 2] assembly of tetrasaccharide backbone. The construction of the multiple contiguous 1,2-*cis* glycosidic linkages was achieved with exclusive stereoselectivities. In addition, ^{1}H and ^{13}C signals of the synthesized oligosaccharides were fully assigned on the basis of 2D NMR techniques.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on a 400 MHz spectrometer (operating frequencies of 400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C), while probe temperature was kept at 300 K during all experiments. Chemical shifts are in ppm calibrated using TMS, $CDCl_3$ or HOD as internal standards. ^{1}H and ^{13}C signals on carbohydrate rings were fully assigned on the basis of 2D NMR techniques. Gradient COSY, multiplicity-edited HSQC and HMBC were acquired using standard pulse programs. TOCSY and HSQC-TOCSY were measured with a spin lock time of 120 ms. Mixing time in ROESY experiment was set to 400 ms. In coupled-HSQC experiment, ^{13}C decoupler was turned off during acquisition. To designate resonances, the sugar residues were numbered with Roman numerals I, II, III, etc., beginning at the reducing end.

***p*-Tolyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside (10).** To a solution of L-fucose (1.4 g, 7.73 mmol) and DMAP (134 mg, 1.10 mmol) in pyridine (30 mL) at 0 °C was added Ac_2O (15 mL). The mixture was warmed to room temperature, stirred for 12 h and then concentrated. The residue was diluted with EtOAc, washed with 5% citric acid (aq.), $NaHCO_3$ (sat. aq.) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to give crude **9** (2.62 g) as a syrup, which was used without further purification. $BF_3{\cdot}OEt_2$ (1.96 mL, 15.47 mmol) was added dropwise to a solution of crude **9** and *p*-thiocresol (1.15 g, 9.28 mmol) in CH_2Cl_2 (30 mL) under nitrogen at 0 °C. After stirring at 0 °C for 2 h, the mixture was warmed to room temperature, stirred for 12 h and quenched with $NaHCO_3$ (sat. aq.). The organic layer was washed with 5% NaOH (aq.) and brine, dried over $MgSO_4$, filtered and concentrated. Crystallization from a mixture of *i*-PrOH and hexanes provided **10** (2.49 g, 81% over 2 steps) as a white solid: $[\alpha]_D^{20}$ −4.6 (c 0.503, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.38 (m, 2H, ArH), 7.13 (d, J = 7.9 Hz, 2H, ArH), 5.25 (dd, J = 3.3, 0.9 Hz, 1H, H-4), 5.20 (dd, J = 9.9, 9.9 Hz, 1H, H-2), 5.04 (dd, J = 9.9, 3.4 Hz, 1H, H-3), 4.63 (d, J = 9.9 Hz, 1H, H-1), 3.80 (qd, J = 6.3, 0.8 Hz, 1H, H-5), 2.34 (s, 3H, $ArCH_3$), 2.14 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.23 (d, J = 6.4 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.1, 169.5 ($COCH_3$), 138.2, 133.0, 129.6, 129.1 (ArC), 86.9 (C-1), 73.1 (C-5), 72.5 (C-3), 70.4 (C-4), 67.4 (C-2), 21.2 ($ArCH_3$), 20.9, 20.7, 20.6 ($COCH_3$), 16.5 (C-6); HRMS (ESI-TOF) m/z Calcd for $C_{19}H_{24}O_7NaS$ $[M + Na]^+$ 419.1140, found 419.1126.

***p*-Tolyl 2-*O*-benzyl-3,4-*O*-isopropylidene-1-thio-β-L-fucopyranoside (11).** Compound **10** (1.18 g, 2.97 mmol) was dissolved in methanol (20 mL), and MeONa (16 mg, 0.30 mmol) was added. After 12 h, Dowex 50WX8 acidic resin was added to neutralize MeONa. The resin was removed, and the solution was concentrated in vacuo to afford crude triol as a residue. The residue was coevaporated with toluene and dissolved in acetone (20 mL). 2,2-Dimethoxypropane (0.73 mL, 5.932 mmol) and *p*-TsOH (56 mg, 0.30 mmol) were added. After stirring at room temperature for 4 h, triethylamine (5 mL) was added, and the solvent was evaporated. The resulting crude alcohol was dissolved in DMF (10 mL), and NaH (60%, 237 mg, 5.93 mmol) was added in portions at 0 °C. After 30 min, BnBr (0.71 mL, 5.93 mmol) was added, and the mixture was stirred at room temperature for 5 h. The mixture was poured slowly to water and extracted with EtOAc. The organics were dried over $MgSO_4$, filtered and concentrated. Crystallization from hexanes afforded **11** (1.12 g, 95%) as a white solid: $[\alpha]_D^{20}$ −2.0 (c 0.353, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.40 (m, 4H, ArH), 7.36−7.26 (m, 3H, ArH), 7.09 (d, J = 7.9 Hz, 2H, ArH), 4.82 and 4.67 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.52 (d, J = 9.7 Hz, 1H, H-1), 4.21 (dd, J = 5.9, 5.9 Hz, 1H, H-3), 4.03 (dd, J = 5.6, 2.1 Hz, 1H, H-4), 3.79 (qd, J = 6.5, 2.1 Hz, 1H, H-5), 3.48 (dd, J = 9.7, 6.5 Hz, 1H, H-2), 2.32 (s, 3H, $ArCH_3$), 1.41 (s, 3H, CCH_3), 1.39 (d, J = 6.6 Hz, 3H, H-6), 1.35 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.6, 132.8, 129.9, 129.5, 128.3, 128.2, 127.7 (ArC), 109.7 (CMe_2), 86.5 (C-1), 79.9 (C-3), 78.3 (C-2), 76.5 (C-4), 73.5 (CH_2Ar), 72.4 (C-5), 27.9 (CCH_3Me), 26.4 ($CMeCH_3$), 21.1 ($ArCH_3$), 16.9 (C-6); HRMS (ESI-TOF) m/z Calcd for $C_{23}H_{28}O_4NaS$ $[M + Na]^+$ 423.1606, found 423.1599.

***p*-Tolyl 2-*O*-benzyl-1-thio-β-L-fucopyranoside (12).** A solution of **11** (1.11 g, 2.77 mmol) in methanol (25 mL) was treated with *p*-toluenesulfonic acid (53 mg, 0.28 mmol). After stirring at room temperature for 24 h, the mixture was neutralized by triethylamine (5 mL) and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:2:1) afforded **12** (895 mg, 90%) as a white solid: $[\alpha]_D^{20}$ −3.9 (c 0.233, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.1 Hz, 2H, ArH), 7.42−7.27 (m, 5H, ArH), 7.12 (d, J = 7.9 Hz, 2H, ArH), 4.96 and 4.69 (ABq, J_{AB}= 11.0 Hz, 2H, CH_2Ar), 4.53 (d, J = 9.6 Hz, 1H, H-1), 3.72 (dd, J = 5.1, 3.4 Hz, 1H, H-4), 3.66−3.56 (m, 2H, H-3, H-5), 3.50 (dd, J = 9.3, 9.3 Hz, 1H, H-2), 2.48 (d, J = 5.3 Hz, 1H, OH), 2.34 (s, 3H, $ArCH_3$), 2.11 (d, J = 5.3 Hz, 1H, OH), 1.34 (d, J = 6.5 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.8,

dx.doi.org/10.1021/jo500503r | J. Org. Chem. 2014, 79, 4718−4726

132.5, 130.0, 129.7, 128.6, 128.3, 128.1 (ArC), 87.7 (C-1), 78.2 (C-2), 75.3 (C-3), 75.3 (CH_2Ar), 74.4 (C-5), 71.8 (C-4), 21.1 ($ArCH_3$), 16.6 (C-6); HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{24}O_4NaS$ $[M + Na]^+$ 383.1293, found 383.1294.

***p*-Tolyl 2,3-di-*O*-benzyl-1-thio-β-L-fucopyranoside (13).** A mixture of **12** (884 mg, 2.45 mmol) and Bu_2SnO (763 mg, 3.07 mmol) in toluene (40 mL) was heated at 130 °C for 4 h with azeotropic removal of water. The mixture was concentrated to 1/4 of the original volume by continued evaporation and then cooled to 60 °C. DMF (15 mL), BnBr (0.44 mL, 3.68 mmol), CsF (745 mg, 4.90 mmol) and TBAI (272 mg, 0.74 mmol) were added. The reaction was stirred at 60 °C for 12 h and quenched with water. The mixture was portioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:5:1) provided **13** (1.09 g, 98%) as a white solid: $[\alpha]_D^{20}$ −5.8 (*c* 0.243, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.45 (m, 2H, ArH), 7.44−7.39 (m, 2H, ArH), 7.37−7.26 (m, 8H, ArH), 7.10 (d, *J* = 7.9 Hz, 2H, ArH), 4.84 and 4.74 (ABq, J_{AB} = 10.3 Hz, 2H, CH_2Ar), 4.71 and 4.68 (ABq, J_{AB} = 11.6 Hz, 2H, CH_2Ar), 4.53 (d, *J* = 9.6 Hz, 1H, H-1), 3.81 (ddd, *J* = 3.4, 3.4, 0.9 Hz, 1H, H-4), 3.65 (dd, *J* = 9.3, 9.3 Hz, 1H, H-2), 3.58−3.51 (m, 2H, H-3, H-5), 2.32 (s, 3H, $ArCH_3$), 2.23 (dd, *J* = 3.4, 0.7 Hz, 1H, OH), 1.36 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.7, 137.6, 132.7, 123.0, 129.6, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8 (ArC), 87.8 (C-1), 83.0 (C-3), 76.9 (C-2), 75.7 (CH_2Ar), 74.2 (C-5), 72.1 (CH_2Ar), 69.4 (C-4), 21.1 ($ArCH_3$), 16.8 (C-6); HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{30}O_4NaS$ $[M + Na]^+$ 473.1763, found 473.1777.

***p*-Tolyl 4-*O*-benzoyl-2,3-di-*O*-benzyl-1-thio-β-L-fucopyranoside (14).** Benzyol chloride (0.83 mL, 7.20 mmol) was added dropwise to a solution of **13** (1.08 g, 2.40 mmol), pyridine (1.4 mL, 16.79 mmol) and DMAP (59 mg, 0.48 mmol) in CH_2Cl_2 (20 mL) under nitrogen at room temperature. After stirring for 18 h, the mixture was treated with $NaHCO_3$ (sat. aq.). The organic phase was washed with 5% citric acid (aq.), $NaHCO_3$ (sat. aq.) then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Crystallization from methanol afforded **14** (1.1 g, 83%) as a white solid: $[\alpha]_D^{20}$ −8.5 (*c* 0.303, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.01 (m, 2H, ArH), 7.63−7.54 (m, 3H, ArH), 7.48−7.43 (m, 2H, ArH), 7.42−7.37 (m, 2H, ArH), 7.36−7.24 (m, 5H, ArH), 7.24−7.19 (m, 3H, ArH), 7.15 (d, *J* = 7.9 Hz, 2H, ArH), 5.61 (dd, *J* = 3.2, 0.7 Hz, 1H, H-4), 4.79 and 4.52 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.74 and 4.72 (ABq, J_{AB} = 10.4 Hz, 2H, CH_2Ar), 4.60 (d, *J* = 9.4 Hz, 1H, H-1), 3.81 (qd, *J* = 6.4, 0.8 Hz, 1H, H-5), 3.75 (dd, *J* = 9.1, 3.2 Hz, 1H, H-3), 3.67 (dd, *J* = 9.3, 9.3 Hz, 1H, H-2), 2.38 (s, 3H, $ArCH_3$), 1.30 (d, *J* = 6.4 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (C═O), 138.5, 137.9, 137.6, 133.6, 133.2, 130.1, 129.8, 129.6, 129.1, 128.3, 128.2, 128.1, 127.73, 127.70 (ArC), 87.1 (C-1), 81.5 (C-3), 76.2 (C-2), 75.5 (CH_2Ar), 73.4 (C-5), 71.7 (CH_2Ar), 70.3 (C-4), 21.3 ($ArCH_3$), 17.0 (C-6); HRMS (ESI-TOF) m/z Calcd for $C_{34}H_{34}O_5NaS$ $[M + Na]^+$ 577.2025, found 577.2019.

4-*O*-Benzoyl-2,3-di-*O*-benzyl-α/β-L-fucopyranoside (15). To a solution of **14** (208 mg, 0.38 mmol) in acetone/H_2O (9:1, 5 mL) at 0 °C was added NBS (133 mg, 0.75 mmol) in portions. After stirring at 0 °C for 5 h, the mixture was poured into CH_2Cl_2. The organic phase was washed with $NaHCO_3$ (sat. aq.), $Na_2S_2O_3$ (sat. aq.) and then brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:3:1) provided a mixture of **15**α and **15**β (5/3) (146 mg, 87%) as a foam: $[\alpha]_D^{20}$ −126.4 (*c* 0.140, CH_2Cl_2); HRMS (ESI-TOF) m/z Calcd for $C_{27}H_{28}O_6Na$ $[M + Na]^+$ 471.1784, found 471.1805. NMR data for **15**α: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.04 (m, 2H, ArH), 7.59−7.56 (m, 1H, ArH), 7.49−7.45 (m, 2H, ArH), 7.34−7.24 (m, 10H, ArH), 5.64 (dd, *J* = 3.2, 1.0 Hz, 1H, H-4), 5.32 (d, *J* = 3.6 Hz, 1H, H-1), 4.85 and 4.70 (ABq, J_{AB} = 11.6 Hz, 2H, CH_2Ar), 4.83 and 4.59 (ABq, J_{AB} = 11.5 Hz, 2H, CH_2Ar), 4.38 (qd, *J* = 6.6, 0.5 Hz, 1H, H-5), 4.04 (dd, *J* = 9.8, 3.3 Hz, 1H, H-3), 3.90 (dd, *J* = 9.8, 3.6 Hz, 1H, H-2), 2.96 (s, 1H, OH), 1.20 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (C═O), 138.1, 138.0, 133.1, 130.0, 129.9, 128.42, 128.41, 128.3, 128.1, 127.9 (Ar C), 92.2 (C-1), 76.1 (C-3), 75.4 (C-2), 73.8 (CH_2Ar), 71.6 (CH_2Ar), 71.1 (C-4), 65.3 (C-5), 16.4 (C-6); Coupled HSQC anomeric cross peak (400 MHz, $CDCl_3$) δ 5.32/92.2 ($J_{C1/H1}$ = 170.6 Hz). NMR data for **15**β: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.10 (m, 2H, ArH), 7.61−7.58 (m, 1H, ArH), 7.46−7.42 (m, 2H, ArH), 7.28−7.22 (m, 10H, ArH), 5.58 (dd, *J* = 3.3, 1.0 Hz, 1H, H-4), 4.90−4.79 (m, 3H, CH_2Ar, CHHAr), 4.74 (dd, *J* = 7.4, 3.0 Hz, 1H, H-1), 4.57 (B of ABq, J_{AB} = 11.6 Hz, 1H, CHHAr), 3.81 (qd, *J* = 6.3, 0.8 Hz, 1H, H-5), 3.71 (dd, *J* = 9.6, 3.4 Hz, 1H, H-3), 3.63 (dd, *J* = 9.6, 7.4 Hz, 1H, H-2), 3.16 (d, *J* = 4.5 Hz, 1H, OH), 1.27 (d, *J* = 6.4 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (C═O), 137.8, 133.2, 130.0, 129.8, 128.4, 128.2, 128.0, 127.7, 127.7, 127.6 (Ar C), 97.3 (C-1), 79.8 (C-2), 79.5 (C-3), 75.2 (CH_2Ar), 71.8 (CH_2Ar), 70.3 (C-4), 69.6 (C-5), 16.6 (C-6); Coupled HSQC anomeric cross peak (400 MHz, $CDCl_3$) δ 4.74/97.3 ($J_{C1/H1}$ = 163.2 Hz).

4-*O*-Benzoyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl trichloroacetimidate (8). Compound **15** (140 mg, 0.31 mmol) was dissolved in dry CH_2Cl_2 (5 mL). To this solution Cl_3CCN (0.26 mL, 3.0 mmol) and DBU (15 μL, 0.11 mmol) were added at room temperature. After stirring for 5 h, the mixture was concentrated in vacuo. Flash chromatography on triethylamine deactivated silica gel (EtOAc/hexanes 1:20) afforded **8** (138.4 mg, 75%) as a syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, NH), 8.09−8.02 (m, 2H, ArH), 7.62−7.57 (m, 1H, ArH), 7.50−7.43 (m, 2H, ArH), 7.34−7.27 (m, 7H, ArH), 7.25−7.20 (m, 3H, ArH), 6.55 (d, *J* = 3.3 Hz, 1H, H-1), 5.69 (dd, *J* = 3.0, 1.1 Hz, 1H, H-4), 4.82 and 4.63 (ABq, J_{AB}= 11.7 Hz, 2H, CH_2Ar), 4.78 and 4.74 (ABq, J_{AB}= 11.9 Hz, 2H, CH_2Ar), 4.34 (qd, *J* = 6.5, 0.7 Hz, 1H, H-5), 4.15 (dd, *J* = 10.0, 3.1 Hz, 1H, H-2), 4.09 (dd, *J* = 10.0, 3.3 Hz, 1H, H-3), 1.22 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (COPh), 161.3 (C═N), 138.3, 137.9, 133.2, 129.9, 129.8, 128.5, 128.2, 128.2, 127.9, 127.52, 127.51 (ArC), 95.2 (C-1), 91.4 (CCl_3), 75.3 (C-2), 74.7 (C-3), 73.1 (CH_2Ar), 71.7 (CH_2Ar), 70.9 (C-4), 68.0 (C-5), 16.4 (C-6); Coupled HSQC anomeric cross peak (400 MHz, $CDCl_3$) δ 6.55/95.2 ($J_{C1/H1}$ = 177.4 Hz); HRMS (ESI-TOF) m/z Calcd for $C_{29}H_{28}NO_6NaCl_3$ $[M + Na]^+$ 614.0880, found 614.0880.

***N*-Phenyl-*O*-(4-*O*-benzoyl-2,3-di-*O*-benzyl-α/β-L-fucopyranosyl) trifluoroacetimidate (8′).** To a solution of compound **15** (331 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) were added *N*-phenyl trifluoroacetimidoyl chloride (184 mg, 0.89 mmol) and Cs_2CO_3 (481 mg, 1.48 mmol). After stirring for 2 h at room temperature, the mixture was filtered and concentrated. Flash chromatography on triethylamine deactivated silica gel (EtOAc/hexanes 1:15) provided a mixture of **8′**β and **8′**α (4.3/1.0) (396 mg, 87%) as a syrup. Pure anomers were isolated for analysis. Data for **8′**β: $[\alpha]_D^{20}$ −94.0 (*c* 0.350, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.7 Hz, 2H, ArH), 7.64−7.58 (m, 1H, ArH), 7.49 (t, *J* = 7.7 Hz, 2H, ArH), 7.35−7.22 (m, 12H, ArH), 7.14−7.07 (m, 1H, ArH), 6.83 (d, *J* = 7.6 Hz, 2H, ArH), 5.67 (brs, 1H, H-1), 5.58 (s, 1H, H-4), 4.85−4.78 (m, 3H, CH_2Ar, CHHAr), 4.57 (B of ABq, J_{AB} = 11.6 Hz, 1H, CHHAr), 3.90 (dd, *J* = 8.3, 8.3 Hz, 1H, H-2), 3.82−3.55 (m, 2H, H-5, H-3), 1.26 (d, *J* = 6.3 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2 (COPh), 143.5, 137.9, 137.6, 133.3, 130.0, 129.7, 128.7, 128.5, 128.38, 128.35, 128.2, 128.0, 127.9, 127.8, 124.2, 119.3 (ArC), 116.2 (q, $^1J_{C-F}$ = 281.8 Hz, CF_3), 97.21 (C-1), 79.44 (C-3), 77.57 (C-2), 75.63 (CH_2Ar), 71.98 (CH_2Ar), 70.56 (C-5), 69.91 (C-4), 16.33 (C-6); HRMS (ESI-TOF) m/z Calcd for $C_{35}H_{32}F_3NO_6Na$ $[M + Na]^+$ 642.2079, found 642.2093. Data for **8′**α: $[\alpha]_D^{20}$ −114.3 (*c* 0.675, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.7 Hz, 2H, ArH), 7.58 (t, *J* = 7.4 Hz, 1H, ArH), 7.45 (t, *J* = 7.7 Hz, 2H, ArH), 7.35−7.21 (m, 12H, ArH), 7.09 (t, *J* = 7.4 Hz, 1H, ArH), 6.77 (d, *J* = 6.6 Hz, 2H, ArH), 6.53 (brs, 1H, H-1), 5.68 (s, 1H, H-4), 4.83 and 4.63 (ABq, J_{AB} = 11.4 Hz, 2H, CH_2Ar), 4.82 and 4.73 (ABq, J_{AB} = 11.9 Hz, 2H, CH_2Ar), 4.27 (brs, 1H, H-5), 4.11 (d, *J* = 9.6 Hz, 1H, H-3), 4.06 (d, *J* = 9.6 Hz, 1H, H-2), 1.22 (d, *J* = 6.3 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (COPh), 143.7, 138.1, 137.9, 133.2, 129.9, 129.8, 128.7, 128.5, 128.4, 128.3, 127.9, 127.7, 127.7, 127.6, 124.2, 119.6 (ArC), 116.3 (q, $^1J_{C-F}$ = 286.7 Hz, CF_3), 94.5 (C-1), 75.8 (C-3), 74.5 (C-2), 73.6 (CH_2Ar), 71.9 (CH_2Ar), 70.8 (C-4), 68.1 (C-5), 16.4 (C-6); HRMS (ESI-TOF) m/z Calcd for $C_{35}H_{32}F_3NO_6Na$ $[M + Na]^+$ 642.2079, found 642.2098.

dx.doi.org/10.1021/jo500503r | J. Org. Chem. 2014, 79, 4718−4726

***p*-Tolyl 4-*O*-benzoyl-2-*O*-benzyl-1-thio-β-L-fucopyranoside (7).** Deacetylation of **10** (337 mg, 0.85 mmol) provided the crude triol as described in the synthesis of **11**. The crude triol was coevaporated with toluene and dissolved in acetonitrile (10 mL). Trimethyl orthobenzoate (0.29 mL, 1.7 mmol) and DL-10-camphorsulfonic acid (20 mg, 0.085 mmol) were added. After stirring at room temperature for 1 h, triethylamine (5 mL) was added, and the solvent was evaporated. The resulting alcohol was dissolved in DMF (8 mL), and NaH (60%, 68 mg, 1.7 mmol) was added in portions at 0 °C. After 30 min, BnBr (0.2 mL, 1.7 mmol) was added, and the mixture was stirred at room temperature for 12 h. The mixture was treated with 1 N HCl (2.6 mL). After stirring for 1 h, EtOAc and H_2O were added successively to the mixture, and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:5:1) provided **7** (390 mg, 82%) as a syrup: $[\alpha]_D^{20}$ −26.7 (*c* 1.277, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.00 (m, 2H, ArH), 7.65−7.54 (m, 3H, ArH), 7.50−7.43 (m, 2H, ArH), 7.39−7.26 (m, 5H, ArH), 7.19−7.14 (m, 2H, ArH), 5.42 (dd, *J* = 3.4, 0.8 Hz, 1H, H-4), 4.95 and 4.66 (ABq, J_{AB} = 10.8 Hz, 2H, CH_2Ar), 4.61 (d, *J* = 9.6 Hz, 1H, H-1), 3.93 (ddd, *J* = 9.1, 3.6, 3.6 Hz, 1H, H-3), 3.84 (qd, *J* = 6.4, 0.9 Hz, 1H, H-5), 3.63 (dd, *J* = 9.3, 9.3 Hz, 1H, H-2), 2.39 (s, 3H, ArCH3), 2.29 (d, *J* = 3.7 Hz, 1H, OH), 1.28 (d, *J* = 6.4 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C═O), 138.1, 137.8, 133.3, 133.0, 130.1, 129.7, 129.6, 129.4, 128.6, 128.4, 128.2, 128.0 (Ar*C*), 87.0 (C-1), 77.5 (C-2), 75.3 (*C*H$_2$Ar), 74.3 (C-3), 73.5 (C-5), 73.4 (C-4), 21.2 (Ar*C*H$_3$), 16.9 (C-6); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{27}H_{28}O_5NaS$ [M + Na]$^+$ 487.1555, found 487.1578.

***p*-Methoxyphenyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranoside (17).** $BF_3{\cdot}OEt_2$ (0.32 mL, 2.51 mmol) was added dropwise to a solution of crude **9** (417 mg, 1.25 mmol) and *p*-methoxyphenol (234 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) under nitrogen at 0 °C. After stirring at 0 °C for 2 h, the mixture was allowed to warm to room temperature, stirred for 12 h and quenched with $NaHCO_3$ (sat. aq.). The organic layer was separated and washed with 5% NaOH (aq) and brine, dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:9:1) provided **17** (386 mg, 78%) as a syrup: $[\alpha]_D^{20}$ −162.7 (*c* 0.473, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01−6.93 (m, 2H, ArH), 6.86−6.78 (m, 2H, ArH), 5.62 (d, *J* = 3.6 Hz, 1H, H-1), 5.57 (dd, *J* = 10.9, 3.4 Hz, 1H, H-3), 5.37 (dd, *J* = 3.3, 1.1 Hz, 1H, H-4), 5.26 (dd, *J* = 10.9, 3.7 Hz, 1H, H-2), 4.32 (qd, *J* = 6.5, 0.7 Hz, 1H, H-5), 3.77 (s, 3H, OCH_3), 2.19 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 1.14 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.5, 170.1 ($COCH_3$), 155.2, 150.7, 117.8, 114.7 (Ar*C*), 95.7 (C-1), 71.1 (C-4), 69.0 (C-3), 68.0 (C-2), 65.2 (C-5), 55.7 (OCH_3), 20.8, 20.72, 20.65 ($COCH_3$), 15.9 (C-6); Coupled HSQC anomeric cross peak (400 MHz, $CDCl_3$) δ 5.62/95.7 ($J_{C1/H1}$ = 176.4 Hz); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{19}H_{24}O_9Na$ [M + Na]$^+$ 419.1318, found 419.1308.

***p*-Methoxyphenyl 4-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranoside (5).** According to the sequential four-step procedure described in the synthesis of **7**, compound **17** (350 mg, 0.88 mmol) was converted into **5** (298 mg, 70%) as a foam: $[\alpha]_D^{20}$ −136.4 (*c* 0.287, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.04 (m, 2H, ArH), 7.62−7.56 (m, 1H, ArH), 7.50−7.42 (m, 2H, ArH), 7.36−7.26 (m, 5H, ArH), 7.06−7.00 (m, 2H, ArH), 6.87−6.81 (m, 2H, ArH), 5.55 (dd, *J* = 3.4, 1.1 Hz, 1H, H-4), 5.50 (d, *J* = 3.5 Hz, 1H, H-1), 4.71 (s, 2H, CH_2Ar), 4.49 (dd, *J* = 10.0, 3.5 Hz, 1H, H-3), 4.32 (qd, *J* = 6.6, 0.8 Hz, 1H, H-5), 3.96 (dd, *J* = 10.1, 3.5 Hz, 1H, H-2), 3.79 (s, 3H, OCH_3), 2.43 (br.s, 1H, OH), 1.17 (d, *J* = 6.6 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C═O), 155.1, 151.2, 137.7, 133.2, 129.9, 129.8, 128.6, 128.5, 128.12, 128.08, 118.0, 114.7 (Ar*C*), 96.4 (C-1), 76.4 (C-2), 73.5 (C-4), 72.7 (CH_2Ar), 68.3 (C-3), 65.9 (C-5), 55.7 (OCH_3), 16.2 (C-6); Coupled HSQC anomeric cross peak (400 MHz, $CDCl_3$) δ 5.50/96.4 ($J_{C1/H1}$ = 171.0 Hz); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{27}H_{28}O_7Na$ [M + Na]$^+$ 487.1733, found 487.1728.

***p*-Tolyl 3,6-di-*O*-benzyl-2-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (20).** A solution of **18** (300 mg, 0.51 mmol) in methanol (5 mL) was treated with *p*-toluenesulfonic acid (10 mg, 0.05 mmol). After stirring at room temperature for 36 h, the mixture was neutralized by triethylamine (2 mL) and concentrated in vacuo to afford crude *p*-tolyl 3-*O*-benzyl-2-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**19**) as powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 2H, ArH), 7.40−7.26 (m, 7H, ArH), 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 6.90−6.84 (m, 2H, ArH), 4.78 and 4.68 (ABq, J_{AB} = 9.9 Hz, 2H, CH_2Ar), 4.71 (s, 2H, CH_2Ar), 4.57 (d, *J* = 9.7 Hz, 1H, H-1), 4.05−4.00 (m, 1H, H-4), 3.99−3.92 (m, 1H, H-6$_a$), 3.810 (s, 3H, OCH_3), 3.80−3.73 (m, 1H, H-1$_b$), 3.70 (dd, *J* = 9.3, 9.3 Hz, 1H, H-2), 3.56 (dd, *J* = 8.9, 3.3 Hz, 1H, H-3), 3.45 (dd, *J* = 6.5, 4.5 Hz, 1H, H-5), 2.57 (s, 1H, OH), 2.32 (s, 3H, ArCH_3), 2.10 (dd, *J* = 8.6, 3.8 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 137.8, 137.6, 132.6, 130.4, 129.9, 129.7, 128.6, 128.1, 127.9, 113.8 (Ar*C*), 87.9 (C-1), 82.5 (C-3), 78.0 (C-5), 76.8 (C-2), 75.4 (CH_2Ar), 72.3 (CH_2Ar), 67.5 (C-4), 62.8 (C-6), 55.3 (OCH_3), 21.1 (ArCH_3); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{28}H_{32}O_6NaS$ [M + Na]$^+$ 519.1817, found 519.1837.

The crude diol **19**, BnBr (122 μL, 1.03 mmol) and tetrabutylammonium hydrogen sulfate (35 mg, 0.10 mmol) were dissolved in CH_2Cl_2 (10 mL), and then 5% NaOH (aq., 5 mL) was added. After stirring at 50 °C for 30 h, the mixture was diluted with CH_2Cl_2 and H_2O. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Crystallization from methanol afforded **20** (194 mg, 61% over 2 steps) as a white solid: $[\alpha]_D^{20}$ +3.2 (*c* 0.353, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H, ArH), 7.37−7.27 (m, 12H, ArH), 7.05 (d, *J* = 7.9 Hz, 2H, ArH), 6.89−6.84 (m, 2H, ArH), 4.77 (A of ABq, J_{AB} = 9.9 Hz, 1H, C*H*HAr), 4.74−4.65 (m, 3H, CH_2Ar, CH*H*Ar), 4.59−4.52 (m, 3H, H-1, OCH_2Ar), 4.09−4.06 (m, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.83−3.73 (m, 2H, H-6$_a$, H-6$_b$), 3.69 (dd, *J* = 9.3, 9.3 Hz, 1H, H-2), 3.58−3.51 (m, 2H, H-5, H-3), 2.48 (dd, *J* = 2.5, 0.6 Hz, 1H, OH), 2.30 (s, 3H, ArCH_3); ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 159.4, 138.0, 137.8, 137.6, 132.6, 130.5, 130.0, 129.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 113.8 (Ar*C*), 88.1 (C-1), 82.7 (C-3), 77.1 (C-5), 76.8 (C-2), 75.4 (*C*H$_2$Ar), 73.7 (*C*H$_2$Ar), 72.2 (*C*H$_2$Ar), 69.5 (C-6), 67.0 (C-4), 55.3 (OCH_3), 21.1 (ArCH_3); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{35}H_{38}O_6NaS$ [M + Na]$^+$ 609.2287, found 609.2280.

***p*-Tolyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (6).** To a solution of **20** (137 mg, 0.23 mmol), triethylamine (0.39 mL, 2.80 mmol) and DMAP (3 mg, 0.023 mmol) in dry CH_2Cl_2 (5 mL) was added Ac_2O (0.11 mL, 1.17 mmol) at 0 °C. The reaction was stirred at room temperature for 5 h, and then quenched with $NaHCO_3$ (sat. aq.). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:10:1) provided **6** (172 mg, 88%) as a white foam: $[\alpha]_D^{20}$ +14.7 (*c* 0.387, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.44 (m, 2H, ArH), 7.37−7.26 (m, 12H, ArH), 7.05 (d, *J* = 7.9 Hz, 2H, ArH), 6.91−6.83 (m, 2H, ArH), 5.61 (d, *J* = 1.7 Hz, 1H, H-4), 4.77 and 4.49 (ABq, J_{AB} = 11.0 Hz, 2H, CH_2Ar), 4.70 and 4.65 (ABq, J_{AB} = 9.8 Hz, 2H, CH_2Ar), 4.64−4.57 (m, 1H, H-1), 4.54 and 4.45 (ABq, J_{AB} = 11.7 Hz, 2H, CH_2Ar), 3.80 (s, 3H, OCH_3), 3.71 (dd, *J* = 6.3, 6.3 Hz, 1H, H-5), 3.64−3.57 (m, 3H, H-3, H-2, H-6$_a$), 3.51 (dd, *J* = 9.6, 6.7 Hz, 1H, H-6$_b$), 2.30 (s, 3H, ArCH_3), 2.08 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C═O), 159.4, 137.71, 137.70, 137.6, 132.5, 130.5, 129.94, 129.91, 129.6, 128.44, 128.42, 128.2, 128.0, 127.84, 127.82, 113.8 (Ar*C*), 88.2 (C-1), 81.3 (C-3), 76.6 (C-2), 75.9 (C-5), 75.4 (*C*H$_2$Ar), 73.7 (*C*H$_2$Ar), 72.0 (*C*H$_2$Ar), 68.3 (C-6), 67.0 (C-4), 55.3 (OCH_3), 21.1 (ArCH_3), 20.9 ($COCH_3$); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{37}H_{40}O_7NaS$ [M + Na]$^+$ 651.2392, found 651.2381.

***p*-Tolyl (4-*O*-benzoyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-(1 → 3)-4-*O*-benzoyl-2-*O*-benzyl-1-thio-β-L-fucopyranoside (4) and *N*-(4-*O*-Benzoyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-trichloroacetamide (21).** Trichloroacetimidate donor **8** (133 mg, 0.224 mmol) and acceptor **7** (87 mg, 0.187 mmol) were azeotroped with toluene at 20 °C and dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 1 h under nitrogen. The reaction mixture was cooled to −78 °C and TMSOTf (3.4 μL, 18.7 μmol) was added dropwise. After stirring for 20 min at −78 °C, the mixture was allowed to warm to 0 °C over 0.5 h. The mixture was

dx.doi.org/10.1021/jo500503r | J. Org. Chem. 2014, 79, 4718−4726

treated with $NaHCO_3$ (sat. aq.), diluted with CH_2Cl_2 and filtered through a pad of Celite. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:10:2) afforded disaccharide **4** (112 mg, 67%) and side product **21** (17 mg, 15%) as white foam. Glycosylation of acceptor **7** (52 mg, 0.112 mmol) using trifluoroacetimidate **8′** (84 mg, 0.135 mmol) under the activation of TMSOTf (2 μL, 11.2 μmol) in anhydrous CH_2Cl_2 (3 mL) was conducted at −78 °C over 2.5 h with the same procedure, providing disaccharide **4** (79 mg, 78%).

Data for ***4****.* $[\alpha]_D^{20}$ −162.7 (*c* 0.117, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.98 (m, 2H, ArH), 7.96−7.87 (m, 2H, ArH), 7.66−7.59 (m, 2H, ArH), 7.59−7.49 (m, 2H, ArH), 7.45−7.28 (m, 9H, ArH), 7.22−7.06 (m, 12H, ArH), 5.67 (d, *J* = 2.9 Hz, 1H, H-4^I), 5.28 (d, *J* = 3.4 Hz, 1H, H-1^{II}), 5.16 (dd, *J* = 3.0, 0.9 Hz, 1H, H-4^{II}), 5.02 and 4.55 (ABq, J_{AB} = 10.5 Hz, 2H, CH_2Ar), 4.65 (d, *J* = 9.5 Hz, 1H, H-1^I), 4.63 and 4.41 (ABq, J_{AB} = 11.1 Hz, 2H, CH_2Ar), 4.52 and 4.43 (ABq, J_{AB} = 12.1 Hz, 2H, CH_2Ar), 4.12 (qd, *J* = 6.4, 0.8 Hz, 1H, H-5^{II}), 4.01 (dd, *J* = 9.5, 3.2 Hz, 1H, H-3^I), 3.90 (dd, *J* = 10.1, 3.2 Hz, 1H, H-3^{II}), 3.86−3.77 (m, 3H, H-2^I, H-2^{II}, H-5^I), 2.41 (s, 3H, ArCH_3), 1.28 (d, *J* = 6.4 Hz, 3H, H-6^I), 0.91 (d, *J* = 6.5 Hz, 3H, H-6^{II}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (C═O), 166.2 (C═O), 138.3, 138.24, 138.23, 137.9, 133.4, 133.2, 132.9, 130.2, 130.0, 129.8, 129.7, 129.6, 129.2, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.3, 127.2 (ArC), 93.4 (C-1^{II}), 87.3 (C-1^I), 76.1 (C-3^{II}), 75.8 (C-2^I), 75.7 (C-3^I), 75.5 (CH_2Ar), 74.0 (C-2^{II}), 73.6 (C-5^I), 72.7 (CH_2Ar), 71.5 (CH_2Ar), 71.3 (C-4^{II}), 68.8 (C-4^I), 65.0 (C-5^{II}), 21.3 (ArCH_3), 17.0 (C-6^{II}), 16.0 (C-6^{II}); Coupled HSQC anomeric cross peaks (400 MHz, $CDCl_3$) δ 4.65/87.3 ($J_{C1/H1}$ = 153.3 Hz, residue I), 5.28/93.4 ($J_{C1/H1}$ = 172.1 Hz, residue II); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{54}H_{54}O_{10}NaS$ $[M + Na]^+$ 917.3335, found 917.3351.

Data for ***21****.* $[\alpha]_D^{20}$ −76.7 (*c* 0.333, CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.05 (m, 2H, ArH), 7.63−7.58 (m, 1H, ArH), 7.51−7.44 (m, 2H, ArH), 7.36−7.26 (m, 11H, ArH, NH), 5.67 (dd, *J* = 5.4, 5.4 Hz, 1H, H-1), 5.64 (dd, *J* = 3.3, 1.7 Hz, 1H, H-4), 4.84 and 4.59 (ABq, J_{AB} = 11.5 Hz, 2H, CH_2Ar), 4.76 and 4.61 (ABq, J_{AB} = 11.5 Hz, 2H, CH_2Ar), 4.08 (dd, *J* = 9.2, 5.2 Hz, 1H, H-2), 4.04 (qd, *J* = 6.5, 1.6 Hz, 1H, H-5), 3.79 (dd, *J* = 9.2, 3.3 Hz, 1H, H-3), 1.27 (d, *J* = 6.5 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (COPh), 162.4 (COCCl_3), 137.5, 137.2, 133.4, 129.9, 129.6, 128.6, 128.5, 128.4, 128.2, 127.96, 127.95, 127.8 (ArC), 92.5 (CCl_3), 77.2 (C-1), 76.1 (C-3), 73.49 (C-2), 73.45 (CH_2Ar), 71.9 (CH_2Ar), 69.9 (C-4), 66.9 (C-5), 16.2 (C-6); Coupled HSQC anomeric cross peak (400 MHz, $CDCl_3$) δ 5.67/77.2 ($J_{C1/H1}$ = 169.4 Hz); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{29}H_{28}NO_6NaCl_3$ $[M + Na]^+$ 614.0880, found 614.0859.

***p*-Methoxyphenyl [4-*O*-acetyl-3,6-di-*O*-benzyl-2-*O*-(4-methoxybenzyl)-α-D-galactopyranosyl]-(1 → 3)-4-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranoside (22).** Donor **6** (159 mg, 0.253 mmol) and acceptor **5** (98 mg, 0.211 mmol) were azeotroped with toluene and dissolved in anhydrous CH_2Cl_2 (5 mL). Freshly activated 4 Å molecular sieves (500 mg) were added, and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was cooled to −20 °C and treated successively with NIS (57 mg, 0.253 mmol) and AgOTf (5 mg, 21.1 μmol) under nitrogen. After stirring for 1 h at −20 °C, the mixture was treated with $NaHCO_3$/$Na_2S_2O_3$ (sat. aq.), diluted with EtOAc and filtered through a pad of Celite. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:5:1) afforded disaccharide **22** (162 mg, 79%) as a white foam: $[\alpha]_D^{20}$ +149.4 (*c* 0.027, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.03 (m, 2H, ArH), 7.63−7.57 (m, 1H, ArH), 7.49−7.42 (m, 2H, ArH), 7.37−7.32 (m, 2H, ArH), 7.30−7.19 (m, 13H, ArH), 7.01−6.95 (m, 4H, ArH), 6.85−6.79 (m, 2H, ArH), 6.68−6.62 (m, 2H, ArH), 5.60 (dd, *J* = 2.8, 1.1 Hz, 1H, H-4^{II}), 5.50 (dd, *J* = 3.4, 0.8 Hz, 1H, H-4^I), 5.46 (d, *J* = 3.2 Hz, 1H, H-1^{II}), 5.34 (d, *J* = 3.6 Hz, 1H, H-1^I), 4.64−4.45 (m, 9H, H-5^{II}, H-3^I, C*H*HAr, 3 × CH_2Ar), 4.28 (B of ABq, J_{AB} = 11.1 Hz, 1H, CH*H*Ar), 4.12 (qd, *J* = 6.6, 0.7 Hz, 1H, H-5^I), 4.05 (dd, *J* = 10.1, 3.6 Hz, 1H, H-2^I), 3.78 (s, 3H, OCH_3), 3.77−3.73 (m, 2H, H-3^{II}, H-2^{II}), 3.72 (s, 3H, OCH_3), 3.62−3.57 (m, 2H, H-6$_a^{II}$, H-6$_b^{II}$), 2.03 (s, 3H, $COCH_3$), 1.02 (d, *J* = 6.5 Hz, 3H, H-6^I); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 ($COCH_3$), 166.5 (COPh), 158.8, 155.0, 151.1, 138.4, 138.3, 138.2, 133.2, 130.8, 130.1, 129.9, 128.9, 128.5, 128.32, 128.29, 128.2, 127.9, 127.7, 127.6, 127.5, 127.4, 118.1, 114.6, 113.4 (ArC), 98.9 (C-1^{II}), 97.0 (C-1^I), 76.1 (C-3^{II}), 75.9 (C-2^I), 74.6 (C-2^{II}), 74.2 (C-4^I), 73.4 (CH_2Ar), 72.6 (CH_2Ar), 72.4 (C-3^I), 72.1 (CH_2Ar), 72.0 (CH_2Ar), 69.5 (C-6^{II}), 68.9 (C-4^{II}), 68.7 (C-5^{II}), 65.8 (C-5^I), 55.7 (OCH_3), 55.2 (OCH_3), 20.9 ($COCH_3$), 16.1 (C-6^I); Coupled HSQC anomeric cross peaks (400 MHz, $CDCl_3$) δ 5.34/97.0 ($J_{C1/H1}$ = 171.0 Hz, residue I), 5.46/98.9 ($J_{C1/H1}$ = 175.5 Hz, residue II); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{57}H_{60}O_{14}Na$ $[M + Na]^+$ 991.3881, found 991.3931.

***p*-Methoxyphenyl (4-*O*-acetyl-3,6-di-*O*-benzyl-α-D-galactopyranosyl)-(1 → 3)-4-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranoside (3).** DDQ (41 mg, 0.19 mmol) was added to a solution of compound **22** (157 mg, 0.16 mmol) in a mixed solvent (CH_2Cl_2/pH7.0 phosphate buffer = 20/1, 5 mL) at 0 °C. After stirring for 2 h at 0 °C, the reaction was quenched by adding $NaHCO_3$ (sat. aq.) and CH_2Cl_2. The organic phase was washed consecutively with $NaHCO_3$ (sat. aq.) and brine, dried over MgSO4, filtered and concentrated. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:5:1) afforded **3** (103 mg, 75%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.01 (m, 2H, ArH), 7.65−7.57 (m, 1H, ArH), 7.50−7.43 (m, 2H, ArH), 7.36−7.20 (m, 15H, ArH), 7.03−6.96 (m, 2H, ArH), 6.87−6.79 (m, 2H, ArH), 5.57 (d, *J* = 2.4 Hz, 1H, H-4^{II}), 5.53 (d, *J* = 2.7 Hz, 1H, H-4^I), 5.43 (d, *J* = 3.5 Hz, 1H, H-1^I), 5.39 (d, *J* = 3.9 Hz, 1H, H-1^{II}), 4.71 and 4.61 (ABq, J_{AB} = 11.6 Hz, 2H, CH_2Ar), 4.66 and 4.26 (ABq, J_{AB} = 11.3 Hz, 2H, CH_2Ar), 4.59 and 4.50 (ABq, J_{AB} = 11.8 Hz, 2H, CH_2Ar), 4.52 (dd, *J* = 10.1, 3.5 Hz, 1H, H-3^I), 4.40 (dd, *J* = 6.2, 6.2 Hz, 1H, H-5^{II}), 4.18 (q, *J* = 6.3 Hz, 1H, H-5^I), 4.04 (dd, *J* = 10.2, 3.5 Hz, 1H, H-2^I), 3.89 (ddd, *J* = 10.0, 8.1, 3.9 Hz, 1H, H-2^{II}), 3.79 (s, 3H, OCH_3), 3.62−3.51 (m, 2H, H-6$_a^{II}$, H-6$_b^{II}$), 3.48 (dd, *J* = 10.0, 3.2 Hz, 1H, H-3^{II}), 2.14 (d, *J* = 8.1 Hz, 1H, OH), 2.04 (s, 3H, $COCH_3$), 1.07 (d, *J* = 6.5 Hz, 3H, H-6^I); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 ($COCH_3$), 166.3 (COPh), 155.1, 151.1, 138.2, 137.9, 137.6, 133.4, 129.8, 128.6, 128.5, 128.33, 128.28, 128.2, 128.0, 127.9, 127.7, 127.6, 118.1, 114.6 (ArC), 100.4 (C-1^{II}), 96.6 (C-1^I), 76.7 (C-3^{II}), 75.9 (C-2^I), 73.8 (C-3^{II}), 73.7 (C-3^I), 73.4 (CH_2Ar), 72.6 (CH_2Ar), 71.6 (CH_2Ar), 68.9 (C-5^{II}), 68.8 (C-6^{II}), 68.6 (C-2^{II}), 67.7 (C-4^{II}), 65.8 (C-5^I), 55.7 (OCH_3), 20.8 ($COCH_3$), 16.1 (C-6^I); Coupled HSQC anomeric cross peaks (400 MHz, $CDCl_3$) δ 5.43/96.6 ($J_{C1/H1}$ = 171.9 Hz, residue I), 5.39/100.4 ($J_{C1/H1}$ = 174.4 Hz, residue II); HRMS (ESI-TOF) *m*/*z* Calcd for $C_{49}H_{52}O_{13}Na$ $[M + Na]^+$ 871.3306, found 871.3295.

***p*-Methoxyphenyl (4-*O*-benzoyl-2,3-di-*O*-benzyl-α-L-fucopyranosyl)-(1 → 3)-(4-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranosyl)-(1 → 2)-(4-*O*-acetyl-3,6-di-*O*-benzyl-α-D-galactopyranosyl)-(1 → 3)-4-*O*-benzoyl-2-*O*-benzyl-α-L-fucopyranoside (2).** A solution of donor **4** (65.1 mg, 72.7 μmol) and acceptor **3** (55 mg, 64.8 μmol) in a mixed anhydrous solvent (CH_2Cl_2/ether = 1/1, 4 mL) containing freshly activated 4 Å molecular sieves (400 mg) was stirred at room temperature for 1 h under nitrogen. The mixture was cooled to −10 °C and treated successively with NIS (18 mg, 78.8 μmol) and AgOTf (2 mg, 6.5 μmol). After stirring for 3 h at −10 °C, the mixture was treated with triethylamine and filtered through a pad of Celite. The filtrate was concentrated in vacuo to residue. Flash chromatography on silica gel (EtOAc/hexanes/CH_2Cl_2 1:10:1) provided tetrasaccharide **2** (82 mg, 78%) as a white foam: $[\alpha]_D^{20}$ −141.6 (*c* 0.243, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.05 (m, 2H, ArH), 8.00−7.93 (m, 2H, ArH), 7.91−7.84 (m, 2H, ArH), 7.66−7.60 (m, 1H, ArH), 7.59−7.52 (m, 1H, ArH), 7.51−7.39 (m, 7H, ArH), 7.39−7.19 (m, 10H, ArH), 7.18−7.07 (m, 14H, ArH), 7.07−7.01 (m, 2H, ArH), 7.01−6.92 (m, 4H, ArH), 6.87 (d, *J* = 7.2 Hz, 2H, ArH), 6.82−6.75 (m, 2H, ArH), 5.66 (d, *J* = 2.4 Hz, 1H, H-4^{II}), 5.57 (d, *J* = 2.7 Hz, 1H, H-4^I), 5.46 (d, *J* = 3.5 Hz, 1H, H-1^I), 5.44 (d, *J* = 3.6 Hz, 1H, H-1^{II}), 5.40 (d, *J* = 3.7 Hz, 1H, H-1^{III}), 5.18 (d, *J* = 3.0 Hz, H-1^{IV}), 5.12−5.08 (m, 2H, H-4^{III}, H-4^{IV}), 4.81 and 4.77 (ABq, J_{AB} = 12.5 Hz, 2H, CH_2Ar), 4.71 (A of ABq, J_{AB} = 11.4 Hz, 1H, C*H*HAr), 4.68−4.59 (m, 3H, H-3^I, H-5^{II}, C*H*HAr), 4.53 and 4.38 (ABq, J_{AB} = 12.2 Hz, 2H, CH_2Ar), 4.52 (B of ABq, J_{AB} = 11.7 Hz, 1H, CH*H*Ar), 4.47 (A of ABq, J_{AB} = 11.5 Hz, 1H, C*H*HAr), 4.36 (A of ABq, J_{AB} = 12.0 Hz, 1H,

dx.doi.org/10.1021/jo500503r | J. Org. Chem. 2014, 79, 4718−4726

CHHAr), 4.33−4.10 (m, 8H, H-5^{III}, H-3^{III}, 3 × CHHAr, H-2^{II}, H-2^{I}, H-5^{I}), 3.94 (dd, J = 10.3, 3.2 Hz, 1H, H-3^{II}), 3.88−3.73 (m, 7H, H-5^{IV}, H-2^{III}, H-2^{IV}, H-3^{IV}, OCH_3), 3.66−3.60 (m, 2H, H-6$_a^{II}$, H-6$_b^{II}$), 2.08 (s, 3H, $COCH_3$), 1.03 (d, J = 6.5 Hz, 3H, H-6^{I}), 0.94 (d, J = 6.5 Hz, 3H, H-6^{III}), 0.72 (d, J = 6.5 Hz, 3H, H-6^{IV}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 ($COCH_3$), 166.6 (COPh), 166.3 (COPh), 166.0 (COPh), 155.1, 151.2, 138.6, 138.38, 138.36, 138.3, 138.2, 138.0, 133.4, 132.9, 132.8, 130.2, 129.94, 129.91, 129.89, 129.84, 129.83, 128.7, 128.6, 128.3, 128.2, 128.1, 128.02, 128.01, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 118.0, 114.6 (ArC), 99.8 (C-1^{II}), 97.7 (C-1^{III}), 96.2 (C-1^{I}), 92.8 (C-1^{IV}), 76.2 (C-3^{II}), 76.1 (C-3^{IV}), 75.9 (C-2^{I}), 74.2 (C-2^{IV}), 73.9 (C-4^{I}, C-2^{III}), 73.5 (CH_2Ar), 72.3 (CH_2Ar), 72.1 (C-3^{I}), 71.6 (C-2^{II}, C-4^{IV}), 71.5 (CH_2Ar), 71.3 (CH_2Ar), 71.0 (CH_2Ar), 70.9 (CH_2Ar), 69.5 (C-6^{II}), 69.4 (C-4^{III}), 69.3 (C-3^{III}), 69.0 (C-5^{II}), 68.2 (C-4^{II}), 65.8 (C-5^{I}) 65.2 (C-5^{IV}), 64.61 (C-5^{III}), 55.7 (OCH_3), 20.9 ($COCH_3$), 16.3 (C-6^{III}), 16.1 (C-6^{I}), 15.9 (C-6^{IV}); Coupled HSQC anomeric cross peaks (400 MHz, $CDCl_3$) δ 5.46/96.2 ($J_{C1/H1}$ = 171.9 Hz, residue I), 5.44/99.8 ($J_{C1/H1}$ = 176.9 Hz, residue II), 5.40/97.7 ($J_{C1/H1}$ = 174.4 Hz, residue III), 5.18/92.8 ($J_{C1/H1}$ = 171.9 Hz, residue IV); HRMS (ESI-TOF) m/z Calcd for $C_{96}H_{98}O_{23}Na$ [M + Na]$^+$ 1641.6397, found 1641.6345.

***p*-Methoxyphenyl (2,3-di-*O*-benzyl-α-L-fucopyranosyl)-(1 → 3)-(2-*O*-benzyl-α-L-fucopyranosyl)-(1 → 2)-(3,6-di-*O*-benzyl-α-D-galactopyranosyl)-(1 → 3)-2-*O*-benzyl-α-L-fucopyranoside (23).** To a solution of tetrasaccharide **2** (74 mg, 45.4 μmol) in methanol (5 mL) was added MeONa (12 mg, 230 μmol). The mixture was heated at 50 °C for 3 d. Dowex 50WX8 acidic resin was added to neutralize MeONa. The resin was removed, and the solution was concentrated in vacuo. Flash chromatography on silica gel (MeOH/CH_2Cl_2 1:100) provided tetraol **23** (47 mg, 82%) as a white powder: $[\alpha]_D^{20}$ −100.1 (c 0.817, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.10 (m, 30H, ArH), 7.01−6.95 (m, 2H, ArH), 6.85−6.79 (m, 2H, ArH), 5.37 (d, J = 3.7 Hz, 1H, H-1^{I}), 5.26 (d, J = 3.3 Hz, 1H, H-1^{II}), 5.02 (d, J = 3.6 Hz, 1H, H-1^{III}), 4.92 and 4.84 (ABq, J_{AB} = 12.8 Hz, 2H, CH_2Ar), 4.76 and 4.62 (ABq, J_{AB} = 11.8 Hz, 2H, CH_2Ar), 4.74−4.67 (m, 2H, CH_2Ar), 4.68 (A of ABq, J_{AB} = 11.7 Hz, 1H, CHHAr), 4.63 (A of ABq, J_{AB} = 11.6 Hz, 1H, CHHAr), 4.59−4.54 (m, 1H, H-4^{II}), 4.54−4.45 (m, 5H, H-1^{IV}, CH_2Ar, CHHAr, CHHAr), 4.28 (qd, J = 5.9, 0.8 Hz, 1H, H-5^{III}), 4.14−4.06 (m, 2H, H-3^{I}, H-5^{IV}), 4.06−4.00 (m, 2H, H-4^{I}, H-5^{II}), 4.00−3.88 (m, 5H, H-5^{I}, H-2^{II}, H-2^{I}, H-3^{II}, H-3^{III}), 3.88−3.71 (m, 7H, H-6$_a^{II}$, H-3^{IV}, H-2^{III}, OCH_3, H-2^{IV}), 3.71−3.63 (m, 2H, H-6$_b^{II}$, H-4^{IV}), 3.22 (br.s, 1H, OH), 3.19 (d, J = 1.7 Hz, 1H, H-4^{III}), 2.58 (s, 1H, OH), 2.32 (s, 1H, OH), 1.62 (br.s, 1H, OH), 1.36 (d, J = 6.5 Hz, 3H, H-6^{III}), 0.94 (d, J = 6.6 Hz, 3H, H-6^{IV}), 0.81 (d, J = 6.5 Hz, 3H, H-6^{I}); ^{13}C NMR and DEPT135 (100 MHz, $CDCl_3$) δ 154.7, 151.6, 138.8, 138.5, 138.3, 138.0, 137.9, 136.8, 128.61, 128.57, 128.5, 128.34, 128.25, 128.23, 128.18, 128.00, 127.98, 127.83, 127.76, 127.7, 127.6, 127.5, 127.4, 117.6, 114.6 (ArC), 101.0 (C-1^{III}), 99.8 (C-1^{II}), 97.3 (C-1^{I}), 94.0 (C-1^{IV}), 81.7 (C-3^{I}), 80.4 (C-2^{II}), 78.3 (C-3^{IV}), 75.0 (C-2^{IV}), 75.0 (C-2^{III}), 74.4 (C-3^{III}), 74.12 (C-3^{II}), 74.10 (2 × CH_2Ar), 73.53 (C-2^{I}), 73.51 (CH_2Ar), 72.7 (CH_2Ar), 72.4 (CH_2Ar), 72.2 (CH_2Ar), 71.2 (C-6^{II}), 70.7 (C-4^{I}), 69.9 (C-4^{IV}), 69.4 (C-4^{II}), 69.3 (C-5^{II}), 68.0 (C-4^{III}), 66.7 (C-5^{I}), 65.9 (C-5^{III}), 65.6 (C-5^{IV}), 55.7 (OCH_3), 17.2 (C-6^{III}), 15.9 (C-6^{I}, C-6^{IV}); Coupled HSQC anomeric cross peaks (400 MHz, $CDCl_3$) δ 5.37/97.3 ($J_{C1/H1}$ = 172.6 Hz, residue I), 5.26/99.8 ($J_{C1/H1}$ = 168.2 Hz, residue II), 5.02/101.0 ($J_{C1/H1}$ = 169.7 Hz, residue III), 4.52/94.0 ($J_{C1/H1}$ = 168.3 Hz, residue IV); HRMS (ESI-TOF) m/z Calcd for $C_{73}H_{84}O_{19}Na$ [M + Na]$^+$ 1287.5505, found 1287.5526.

***p*-Methoxyphenyl (4-*O*-sodium sulfonato-α-L-fucopyranosyl)-(1 → 3)-(4-*O*-sodium sulfonato-α-L-fucopyranosyl)-(1 → 2)-(4-*O*-sodium sulfonato-α-D-galactopyranosyl)-(1 → 3)-4-*O*-sodium sulfonato-α-L-fucopyranoside (1).** A solution of **23** (24 mg, 19.0 μmol) and SO_3·Me_3N complex (53 mg, 379 μmol) in anhydrous DMF (1 mL) was heated at 50 °C under nitrogen for 3d, after which HRMS analysis showed complete conversion. The reaction was stopped by adding triethylamine and H_2O at 0 °C. The mixture was treated with Na_2CO_3 (36 mg, 341 μmol), stirred for another 12 h and then concentrated. The residue was treated by passing through a column packed with Dowex 50WX8 (Na^+ form) resin to afford crude tetra-*O*-sulfated derivative: HRMS (ESI-TOF) m/z Calcd for $C_{73}H_{80}O_{31}Na_3S_4$ [M + 3Na]$^-$ 1649.3260, found 1649.3213.

A solution of this crude product in a mixed solvent (MeOH/H_2O = 1/2, 6 mL) containing 20% Pd(OH)$_2$/C (450 mg) was degassed and equipped with a hydrogen balloon. After stirring at room temperature for 2 days, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was subjected to a Dowex 50WX8 (Na^+ form) column followed by size-exclusion chromatography on a Sephadex G-25 column eluted with H_2O. The appropriate fractions were lyophilized to provide final compound **1** (17 mg, 80% as tetrasodium salt) as a white fluffy solid: ^{1}H NMR and HSQC (400 MHz, D_2O, 300 K) δ 7.14 (d, J = 9.1 Hz, 2H, ArH), 7.01 (d, J = 9.0 Hz, 2H, ArH), 5.51 (d, J = 3.8 Hz, 1H, H-1^{I}), 5.37 (d, J = 3.7 Hz, 1H, H-1^{II}), 5.29 (d, J = 3.9 Hz, 1H, H-1^{III}), 5.19 (d, J = 3.9 Hz, 1H, H-1^{IV}), 4.80−4.75 (overlapped by HOD, 3H, H-4^{III}, H-4^{II}, H-4^{I}), 4.64 (d, J = 2.7 Hz, 1H, H-4^{IV}), 4.52 (dd, J = 8.5, 3.6 Hz, 1H, H-5^{II}), 4.50−4.36 (m, 5H, H-5^{IV}, H-5^{III}, H-5^{I}, H-3^{I}, H-3^{II}), 4.18 (dd, J = 10.5, 3.9 Hz, 1H, H-2^{I}), 4.14 (dd, J = 10.5, 2.7 Hz, 1H, H-3^{III}), 4.05 (dd, J = 10.6, 3.1 Hz, 1H, H-3^{IV}), 4.00 (dd, J = 10.5, 3.8 Hz, 1H, H-2^{II}), 3.93 (dd, J = 10.4, 3.9 Hz, 1H, H-2^{III}), 3.89−3.76 (m, 6H, H-6$_a^{II}$, OCH_3, H-2^{IV}, H-6$_b^{II}$), 1.30 (d, J = 6.5 Hz, 6H, H-6^{III}, H-6^{IV}), 1.25 (d, J = 6.5 Hz, 3H, H-6^{I}); ^{13}C-APT NMR (100 MHz, D_2O, 300 K) δ 154.7, 150.3, 119.1, 115.2 (ArC), 100.0 (C-1^{III}), 99.4 (C-1^{II}), 98.4 (C-1^{I}), 97.6 (C-1^{IV}), 80.8 (C-4^{IV}), 80.0 (C-4^{I}), 78.9 (C-4^{III}), 78.2 (C-4^{II}), 75.4 (C-3^{III}), 73.8 (C-2^{II}), 73.0 (C-3^{I}), 71.1 (C-5^{II}), 69.0 (C-3^{IV}), 68.6 (C-2^{IV}), 68.1 (C-2^{I}), 67.9 (C-3^{II}), 67.2 (C-2^{III}), 67.1 (C-5^{I}), 66.4 (C-5^{III}), 66.3 (C-5^{IV}), 61.5 (C-6^{II}), 55.8 (OCH_3), 15.90 (C-6^{III}), 15.86 (C-6^{IV}), 15.8 (C-6^{I}); Coupled HSQC anomeric cross peaks (400 MHz, D_2O) δ 5.51/98.4 ($J_{C1/H1}$= 173.8 Hz, residue I), 5.37/99.4 ($J_{C1/H1}$ = 176.3 Hz, residue II), 5.29/100.0 ($J_{C1/H1}$ = 175.5 Hz, residue III), 5.19/97.6 ($J_{C1/H1}$ = 173.0 Hz, residue IV); HRMS (ESI-TOF) m/z Calcd for $C_{31}H_{44}O_{31}Na_3S_4$ [M + 3Na]$^-$ 1109.0443, found 1109.0490.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and 2D NMR spectra of synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: whu@chem.ecnu.edu.cn. Fax: +86-021-62221235.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We wish to thank the NSFC (21125209, 21332003), the MOST of China (2011CB808600), and STCSM (12JC1403800) for financial support.

■ REFERENCES

(1) (a) Senthilkumar, K.; Manivasagana, P.; Venkatesan, J.; Kim, S. K. *Int. J. Biol. Macromol.* **2013**, *60*, 366−74. (b) Wijesinghea, W. A. J. P.; Jeon, Y. J. *Carbohydr. Polym.* **2012**, *88*, 13−20.

(2) Patankar, M. S.; Oehninger, S.; Barnett, T.; Williams, R.; Clark, G. *J. Biol. Chem.* **1993**, *268*, 21770−21776.

(3) (a) Duarte, M. E.; Cardoso, M. A.; Noseda, M. D.; Cerezo, A. S. *Carbohydr. Res.* **2001**, *333*, 281−293. (b) Li, B.; Wei, X. J.; Sun, J. L.; Xu, S. Y. *Carbohydr. Res.* **2006**, *341*, 1135−1146. (c) Bilan, M. I.; Grachev, A. A.; Shashkov, A. S.; Kelly, M.; Sanderson, C. J.; Nifantiev, N. E.; Usov, A. I. *Carbohydr. Res.* **2010**, *345*, 2038−2047.

(4) Bilana, M. I.; Grachev, A. A.; Shashkov, A. S.; Thuy, T. T. T.; Van, T. T. T.; Ly, B. M.; Nifantiev, N. E.; Usov, A. I. *Carbohydr. Res.* **2013**, *377*, 48−57.

(5) (a) Zong, C. L.; Li, Z. Z.; Sun, T. T.; Wang, P.; Ding, N.; Li, Y. X. *Carbohydr. Res.* **2010**, *345*, 1522−1532. (b) Hua, Y. X.; Gu, G. F.; Du, Y. G. *Carbohydr. Res.* **2004**, *339*, 867−872. (c) Hua, Y. X.; Du, Y. G.;

Yu, G. L.; Chu, S. D. *Carbohydr. Res.* **2004**, *339*, 2083−2090. (d) Ustyuzhanina, N.; Krylov, V.; Grachev, A.; Gerbst, A.; Nifantiev, N. *Synthesis* **2006**, *23*, 4017−4031. (e) Nakayasu, S.; Soegima, R.; Yamaguchi, K.; Oda, T. *Biosci., Biotechnol., Biochem.* **2009**, *73*, 961−964.

(6) (a) Boltje, T. J.; Buskas, T.; Boons, G. J. *Nat. Chem.* **2009**, *1*, 611−622. (b) Boltje, T. J.; Kim, J. H.; Park, J.; Boons, G. J. *Nat. Chem.* **2010**, *2*, 552−557. (c) Kim, J. H.; Yang, H.; Park, J.; Boons, G. J. *J. Am. Chem. Soc.* **2005**, *127*, 12090−12097. (d) Boltje, T. J.; Zhong, W.; Park, J.; Wolfert, M. A.; Chen, W. X.; Boons, G. J. *J. Am. Chem. Soc.* **2012**, *134*, 14255−14262. (e) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900−1934. (f) Mydock, L. K.; Demchenko, A. V. *Org. Biomol. Chem.* **2010**, *8*, 497−510. (g) Demchenko, A. V. *Synlett* **2003**, *9*, 1225−1240. (h) Walvoort, M. T. C.; Lodder, G.; Mazurek, J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Am. Chem. Soc.* **2009**, *131*, 12080−12081. (i) Walvoort, M. T. C.; van den Elst, H.; Plante, O. J.; Kröck, L.; Seeberger, P. H.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4393−4396. (j) Geng, Y. Q.; Qin, Q.; Ye, X. S. J. *Org. Chem.* **2012**, *77*, 5255−5270. (k) Manabe, S.; Ishii, K.; Ito, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10666−10667. (l) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144−1153.

(7) (a) Werz, D. B.; Castagner, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2007**, *129*, 2770−2771. (b) Wang, Y. H.; Huang, X. F.; Zhang, L. H.; Ye, X. S. *Org. Lett.* **2005**, *6*, 4415−4417. (c) Wang, Z.; Zhou, L. Y.; El-Boubbou, K.; Ye, X. S.; Huang, X. F. *J. Org. Chem.* **2007**, *72*, 6409−6420. (d) Kakita, K.; Tsuda, T.; Suzuki, N.; Nakamura, S.; Nambu, H.; Hashimoto, S. *Tetrahedron* **2012**, *68*, 5005−5017. (e) Chen, L. Q.; Shi, S. D.; Liu, Y. Q.; Gao, Q. J.; Yi, X.; Liu, K. K.; Liu, H. *Carbohydr. Res.* **2011**, *346*, 1250−1256. (f) Tilve, M. J.; Gallo-Rodriguez, C. *Carbohydr. Res.* **2011**, *346*, 2838−2848.

(8) (a) Fujiwara, R.; Horito, S. *Carbohydr. Res.* **2011**, *346*, 2098−2103. (b) Vermeer, H. J.; van Dijk, C. M.; Kamerling, J. P.; Vliegenthart, J. F. G. *Eur. J. Org. Chem.* **2001**, *2001*, 193−203.

(9) (a) Polat, T.; Wong, C. H. *J. Am. Chem. Soc.* **2007**, *129*, 12795−12800. (b) Hu, Y. P.; Lin, S. Y.; Huang, C. Y.; Zulueta, M. M. L.; Liu, J. Y.; Chang, W.; Hung, S. C. *Nat. Chem.* **2011**, *3*, 557−563. (c) Zulueta, M. M. L.; Lin, S. Y.; Lin, Y. T.; Huang, C. J.; Wang, C. C.; Ku, C. C.; Shi, Z. H.; Chyan, C. L.; Irene, D.; Lim, L. H.; Tsai, T. I.; Hu, Y. P.; Arco, S. D.; Wong, C. H.; Hung, S. C. *J. Am. Chem. Soc.* **2012**, *134*, 8988−8995. (d) Arungundram, S.; Al-Mafraji, K.; Asong, J. K.; Leach, F. E., III; Amster, I. J.; Venot, A.; Turnbull, J. E.; Boons, G. J. *J. Am. Chem. Soc.* **2009**, *131*, 17394−17405. (e) Noti, C.; de Paz, J. L.; Polito, L.; Seeberger, P. H. *Chem.—Eur. J.* **2006**, *12*, 8664−8686. (f) Codée, J. D. C.; Stubba, B.; Schiattarella, M.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *J. Am. Chem. Soc.* **2005**, *127*, 3767−3773. (g) Chen, J. F.; Zhou, Y.; Chen, C.; Xu, W. C.; Yu, B. *Carbohydr. Res.* **2008**, *343*, 2853−2862. (h) Zhou, Y.; Lin, F.; Chen, J. F.; Yu, B. *Carbohydr. Res.* **2006**, *341*, 1619−1629.

(10) (a) Boltje, T. J.; Li, C. X.; Boons, G. J. *Org. Lett.* **2010**, *12*, 4636−4639. (b) Prabhu, A.; Venot, A.; Boons, G. J. *Org. Lett.* **2003**, *5*, 4975−4978.

(11) (a) Kalikanda, J.; Li, Z. T. *Carbohydr. Res.* **2011**, *346*, 2380−2383. (b) Kashiwagi, G. A.; Mendoza, V. M.; de Lederkremer, R. M.; Gallo-Rodriguez, C. *Org. Biomol. Chem.* **2012**, *10*, 6322−6332. (c) Mendoza, V. M.; Agusti, R.; Gallo-Rodriguez, C.; de Lederkremer, R. M. *Carbohydr. Res.* **2006**, *341*, 1488−1497. (d) van Well, R. M.; Collet, B. Y. M.; Field, R. A. *Synlett* **2008**, *14*, 2175−2177.

(12) (a) Pozsgay, V. *J. Am. Chem. Soc.* **1995**, *117*, 6673−6681. (b) Pozsgay, V. *Angew. Chem., Int. Ed.* **1998**, *37*, 138−142. (c) Pozsgay, V. *J. Org. Chem.* **1998**, *63*, 5983−5999. (d) Pozsgay, V.; Pannell, L. *Carbohydr. Res.* **1994**, *258*, 105−122. (e) Pozsgay, V.; Coxon, B. *Carbohydr. Res.* **1994**, *257*, 189−215. (f) Doboszewski, B.; Zamojski, A. *Carbohydr. Res.* **1984**, *132*, 29−38. (g) Schmid, U.; Waldmann, H. *Chem.—Eur. J.* **1998**, *4*, 494−501.

(13) (a) Demchenko, A. V.; Rousson, E.; Boons, G. J. *Tetrahedron Lett.* **1999**, *40*, 6523−6526. (b) Li, Z. T.; Zhu, L. S.; Kalikanda, J. *Tetrahedron Lett.* **2011**, *52*, 5629−5632. (c) Kalikanda, J.; Li, Z. T. *J. Org. Chem.* **2011**, *76*, 5207−5218. (d) Ma, Y. Y.; Lian, G. Y.; Li, Y.; Yu, B. *Chem. Commun.* **2011**, *47*, 7515−7517.

(14) Verma, P. R.; Mukhopadhyay, B. *RSC Adv.* **2013**, *3*, 201−207.

(15) Chao, C. S.; Chen, M. C.; Lin, S. C.; Mong, K. K. T. *Carbohydr. Res.* **2008**, *343*, 957−964.

(16) (a) Mukhopadhyay, B.; Field, R. A. *Carbohydr. Res.* **2003**, *338*, 2149−2152. (b) Turek, D.; Sundgren, A.; Lahmann, M.; Oscarson, S. *Org. Biomol. Chem.* **2006**, *4*, 1236−1241.

(17) (a) Tang, Y.; Li, J. K.; Zhu, Y. G.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2013**, *135*, 18396−18405. (b) Crich, D.; Vinod, A. U. *J. Org. Chem.* **2005**, *70*, 1291−1296. (c) Yang, L.; Ye, X. S. *Carbohydr. Res.* **2010**, *345*, 1713−1721. (d) Boysen, M.; Gemma, E.; Lahmann, M.; Oscarson, S. *Chem. Commun.* **2005**, 3044−3046. (e) Olsson, J. D. M.; Eriksson, L.; Lahmann, M.; Oscarson, S. J. *Org. Chem.* **2008**, *73*, 7181−7188. (f) Satoh, H.; Manabe, S.; Ito, Y.; Lüthi, H. P.; Laino, T.; Hutter, J. *J. Am. Chem. Soc.* **2011**, *133*, 5610−5619. (g) Malik, S.; Shah, K. J.; Kartha, K. P. R. *Carbohydr. Res.* **2010**, *345*, 867−871. (h) Pilgrim, W.; Murphy, P. V. *J. Org. Chem.* **2010**, *75*, 6747−6755. (i) Vidadala, S. R.; Pimpalpalle, T. M.; Linker, T.; Hotha, S. *Eur. J. Org. Chem.* **2011**, 2426−2430. (j) Forsman, J. J.; Wärnå, J.; Murzin, D. Y.; Leino, R. *Carbohydr. Res.* **2009**, *344*, 1102−1109.

(18) Ding, N.; Li, C. X.; Liu, Y. P.; Zhang, Z. H.; Li, Y. X. *Carbohydr. Res.* **2007**, *342*, 2003−2013.

(19) Tatina, M.; Yousuf, S. K.; Mukherjee, D. *Org. Biomol. Chem.* **2012**, *10*, 5357−5360.

(20) (a) Ma, Y. Y.; Cao, X.; Yu, B. *Carbohydr. Res.* **2013**, *377*, 63−74. (b) Li, Y.; Liu, X. Y. *Chem. Commun.* **2014**, *50*, 3155−3158.

(21) Takeo, K. I.; Nakaji, T.; Shinmitsu, K. *Carbohydr. Res.* **1984**, *133*, 275−288.

(22) (a) Yamada, H.; Harada, T.; Miyazaki, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3979−3982. (b) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213−4216. (c) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769−782. (d) Wang, Y. Y.; Ye, X. S.; Zhang, L. H. *Org. Biomol. Chem.* **2007**, *5*, 2189−2200.

(23) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405. (b) Yu, B.; Sun, J. S. *Chem. Commun.* **2010**, *46*, 4668−4679. (c) Yang, X. Y.; Fu, B. Q.; Yu, B. *J. Am. Chem. Soc.* **2011**, *133*, 12433−12435. (d) Wu, Z. T.; Wei, G.; Lian, G. Y.; Yu, B. *J. Org. Chem.* **2010**, *75*, 5725−5728. (e) Wang, Z.; Chinoy, Z. S.; Ambre, S. G.; Peng, W. J.; McBride, R.; de Vries, R. P.; Glushka, J.; Paulson, J. C.; Boons, G. J. *Science* **2013**, *341*, 379−383. (f) Martin, C. E.; Broecker, F.; Oberli, M. A.; Komor, J.; Mattner, J.; Anish, C.; Seeberger, P. H. *J. Am. Chem. Soc.* **2013**, *135*, 9713−9722.

(24) (a) Podlasek, C. A.; Wu, J.; Stripe, W. A.; Bondo, P. B.; Serianni, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 8635−8644. (b) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *J. Org. Chem.* **2004**, *69*, 1174−1179. (c) Boonyarattanakalin, S.; Liu, X.; Michieletti, M.; Lepenies, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 16791−16799.

(25) (a) Fridman, M.; Soloman, D.; Yogev, S.; Baasov, T. *Org. Lett.* **2002**, *4*, 281−283. (b) Lahmann, M.; Oscarson, S. *Org. Lett.* **2000**, *2*, 3881−3882.

(26) Ishiwata, A.; Munemura, Y.; Ito, Y. *Tetrahedron* **2008**, *64*, 92−102.