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Complex Oligosaccharide Investigations: Synthesis of an Octasaccharide Incorporating the Dimeric Le^x Structure of PSGL-1

Jie Xia,† James L. Alderfer, Robert D. Locke, Conrad F. Piskorz, and Khushi L. Matta*

Molecular and Cellular Biophysics, Roswell Park Cancer Institute, Buffalo, New York 14263

khushi.matta@roswellpark.org

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The synthesis of an octasaccharide containing the dimeric Le^x oligosaccharide structure found in PSGL-1 carbohydrate chains is reported. Several approaches were investigated employing regioselective and stereoselective glycosylation procedures, and a novel Lewis^x trisaccharide donor, **7**, was prepared and utilized as a key intermediate building block in the scheme developed for the construction of octasaccharide **3**. Toward the preparation of **7**, investigations into the influence of different protecting groups upon the relative reactivities of disaccharide acceptor moieties, **25** or **26**, and the fucosyl donors, **10** and **11**, were conducted using similar glycosylating conditions. Dramatic differences were noted between the effects of electron-donating and electron-withdrawing groups upon the reactivity of the acceptor hydroxyl. A similar effect upon the glycosylating capability of the donor molecule was, likewise, observed. The repeat use of donor **7** was instrumental in the synthesis of the desired dimeric octasaccharide structure **3**. The structure and purity of **3** and important intermediates were fully characterized by DQF-COSY, TOCSY, ROESY, and ESI mass spectroscopy.

Introduction

The outer surface of mammalian cells is dominantly occupied by glycoproteins and glycolipids. Their carbohydrate moieties play a very essential role in many fundamental biological processes.[1] Aberrant glycosylation and overexpression of carbohydrate antigens is one of the most characteristic features of tumor cells.[2] Well established examples of terminal carbohydrate structures related to tumor antigens are sialyl-Lewis^x, sialyl-Lewis^a, Lewis^x, Lewis^a, sialyl-TN, GM_2, and Gobo-H.[3] A large variety of carbohydrate structures (sialylated, sulfated, sialylated and sulfated oligosaccharide molecules) are also found to bind to E- and P-selectins.[4] Structural studies of O-linked carbohydrate chains present in P-selectin glycoprotein ligand-1 (PSGL-1) and mucin-like core 2 structures (GlyCAM-1) indicate the presence of the sialylated Lewis^x tetrasaccharide structure.[5] Oligosaccharide containing the sialyl Lewis^x dimer (SLe^x−Le^x) was shown to strongly bind with E-selectin under static conditions,[6] suggesting that the sialylated Lewis^x core structure should be a good candidate in the search for selectin inhibitors.

The development of purely chemical synthetic procedures[7] would provide a valuable complementary method for controlling the primary sequence of carbohydrate molecules. A synthetic-based approach would offer an opportunity to directly incorporate desired sugar residues along with structural and functional modifications of the oligosaccharide backbone and provide for structural diversity. Considering all these prescribed factors, ef-

* Corresponding author.
† Current address: Medicinal Chemistry Department, ISIS Pharmaceuticals, Inc., Carlsbad, CA 92008. E-mail: jxia@isisph.com.

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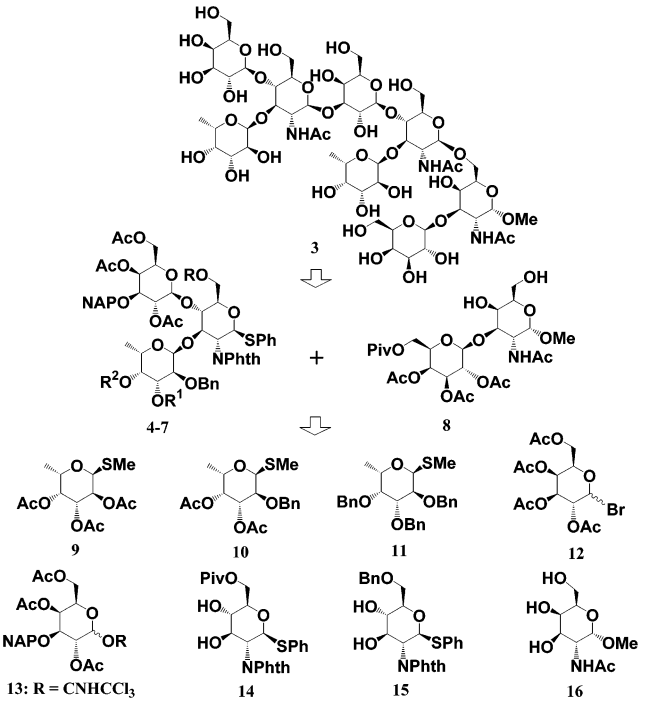
ficient synthetic protocols for the assembly of highly functional carbohydrate molecules would prove to be greatly beneficial to organic chemistry, glycobiology, and medicinal studies. We herein describe our synthetic investigations leading to the efficient synthesis of a highly complex octasaccharide **3** that is representative of the carbohydrate chains of PSGL-1.

Results and Discussion

PSGL-1 is a mucin-like protein that contains a disialylated and monofucosylated core 2 tetrasaccharide, NeuAcα2→3Galβ1→4(Fucα1→3)GlcNAcβ1→6(NeuAcα2→3Galβ1→3)GalNAcOH (**1**), and a monosialylated, trifucosylated glycan having a polyactosamine backbone, NeuAcα2→3Galβ1→4(Fucα1→3)GlcNAcβ1→3Galβ1→4-(Fucα1→3)GlcNAcβ1→3Galβ1→4(Fucα1→3)GlcNAcβ1→6-(Galβ1→3)GalNAcOH (**2**). The strategy planned for the synthesis of our title compound, wherein a highly complex carbohydrate molecule is constructed through the assembly of key oligosaccharide building blocks, was previously employed by our laboratory for the synthesis of structure **1** of the PSGL-1 oligosaccharides.[8] Upon careful analysis of the carbohydrate structures of PSGL-1, a synthetic scheme was planned. The retrosynthetic analysis of that strategy is outlined in Scheme 1. Octasaccharide **3** is constructed of two Lewis^x trisaccharide fragments and a disaccharide fragment. The starting point for our synthesis was the preparation of the Lewis^x trisaccharide donors, **4**−**7**, with proper protecting patterns. In consideration of the potential difficulty in obtaining detailed structural information on complex oligosaccharides by NMR methodology, trisaccharide donors **4**−**6** were designed with simple protection patterns in order to make the structural elucidation of these complex intermediates easier. Also, the placement of an acetyl group at the C^4-position of L-fucopyranoside[9] can impart neighboring group participation toward high α-anomeric selectivity in fucosylation[10] reactions using

SCHEME 1. Retrosynthetic Analysis of Target 3 and Building Blocks Required for Construction of Key Intermediate Compounds 4−7



n-Bu_4NI−$CuBr_2$ as the promoter. Fucosyl donor **10**[11] was prepared and employed for the syntheses of novel Lewis^x trisaccharide donors **4** and **6**. The synthesis of **10** is illustrated in Scheme 2. Removal of the acetyl group from known compound **9** provided compound **17**, which was treated with dimethoxylpropane in the presence of CSA at room temperature to give compound **18** in good yield. Benzylation of **18** with benzyl bromide and powdered potassium hydroxide in the presence of 18-crown-6 as the phase transfer catalyst in dry THF gave compound **19** in high yield (78%). Compound **19** was treated with hot 60% acetic acid, followed by complete acetylation to give the novel fucosyl donor, **10**, in high yield (80%) in two steps. Preparation of imidate donor **13** was performed as illustrated in Scheme 2. Reaction of known bromide donor **12** with 2-trimethylsilylethanol in the presence of mercuric oxide (HgO) and a catalytic amount of mercuric bromide ($HgBr_2$) was conducted at room temperature to afford compound **21**,[12] which upon removal of acetyl group provided compound **22**. Introduction of the naphthylmethyl (NAP) group at the 3-position of galactopyranoside **22**, mediated by Bu_2SnO in the presence of Bu_4NI and naphthylmethyl bromide in dry benzene, afforded compound **23** (86%). This was then treated with anhydrous acetic anhydride/pyridine in the presence of DMAP at room temperature to provide compound **24** in reasonable yield (49%). The trimethylsilylethanyl protecting group could be efficiently removed from compound **24** with 33% TFA in dry dichloromethane at room temperature over a period of 40 min without causing any loss of the NAP group from the galactose residue.

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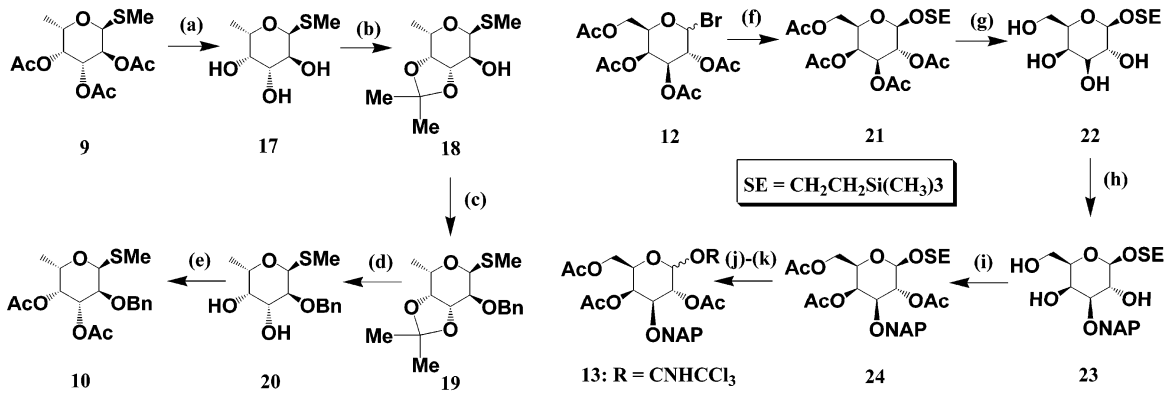
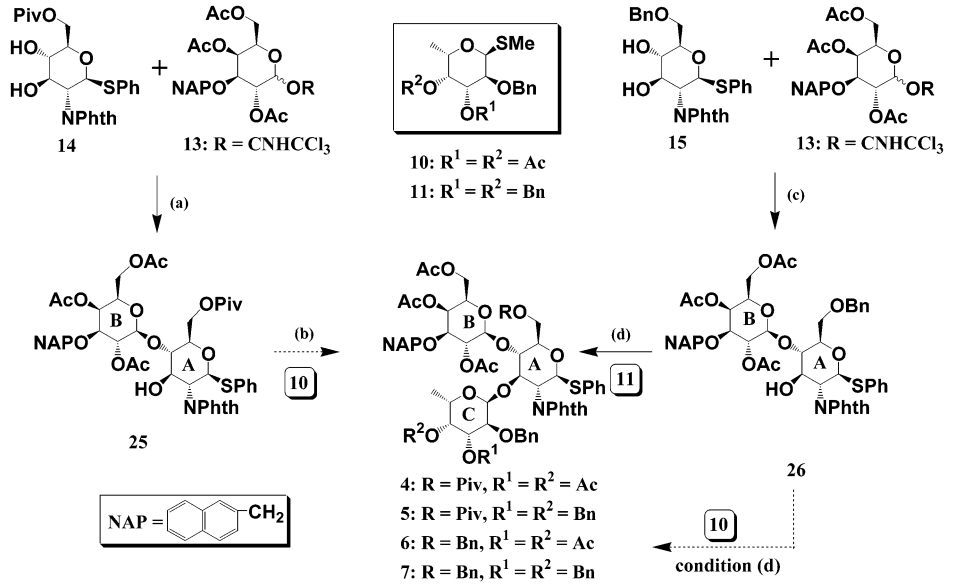
SCHEME 2[a]



[a] Reaction Conditions: (a) 1 M $CH_3ONa-CH_3OH/CH_2Cl_2$-CH_3OH, rt, 1 h; (b) $Me_2C(OMe)_2$, CSA, pH = 3.0, rt, 1 h, 94% in two steps; (c) KOH/18-crown-6/THF, rt, 40 min, then BnBr, rt, 3−4 h, 78%; (d) 60% HOAc, 65 °C, 1.5 h; (e) Ac_2O−pyridine (1:1)/DMAP, rt, 12 h, 80% in two steps; (f) $HgO-HgBr_2/CH_2Cl_2$, SEOH, 4 Å MS, rt, 12 h; (g) 1 M $CH_3ONa-CH_3OH/CH_2Cl_2-CH_3OH$, rt, 1 h, in two steps 90%; (h) Bu_2SnO−benzene, reflux, then *n*-Bu_4NI/NAPBr, 80 °C, 48 h, 86%; (i) Ac_2O−pyridine (1:1)/DMAP, rt, 12 h, 49% in two steps; (j) TFA−CH_2Cl_2 (2:1), rt, 40 min, 90%; (k) $CCl_3CN/DBU/CH_2Cl_2$, 0−25 °C, 1 h, 93%.

SCHEME 3[a]



[a] Reaction conditions: (a) $TMSOTf/CH_2Cl_2$, 4 Å MS, from −65 to −60 °C, 2 h, 65%; (b) $CuBr_2$-*n*-$Bu_4NBr/DMF-ClCH_2CH_2Cl$ (1:5), rt, 48 h, donor **10** or **11**, no reaction; (c) $TMSOTf/CH_2Cl_2$, 4 Å MS, from −65 to −60 °C, 2 h, 70%; (d) $CuBr_2$-*n*-$Bu_4NBr/DMF-ClCH_2CH_2Cl$ (1:5), rt, 48 h, donor **11**, 93%.

However, release of NAP from galactose was observed when treatment was continued for more than 1 h. The imidate donor **13** was then obtained in 93% yield by standard methods. Construction of Lewis^x trisaccharide donors **4**−**7** is summarized in Scheme 3. First, regioselective glycosylation of diol **14** with imidate donor **13** was performed under standard glycosylation conditions using TMSOTf as the catalyst[13] to provide in 60% yield the β-(1→4) linkage of disaccharide **25**. The structure of disaccharide **25** was fully characterized by two-dimensional NMR techniques (2D DQF-COSY, TOCSY, and ROESY). The β(1→4) linkage of disaccharide **25** was indicated by a strong cross-peak between H^B-1 from galactose residue **B** and H^A-4 from glucosamine residue **A** in a 2D ROESY experiment. The disaccharide **25**, when fucosylated with either the novel fucosyl donor **10** or the traditional donor **11** using *n*-$Bu_4NBr-CuBr_2$ as a promoter, failed to yield trisaccharide donors **4** or **5**. We turned our attention to diol **15** which had an electron-donating, benzyl protecting group at the 6-position of its glucosamine residue. Diol **15** was regioselectively glycosylated with imidate donor **13** under standard conditions to provide the β(1→4) linkage of disaccharide **26** in good yield (70%). The structure of disaccharide **26** was fully confirmed by two-dimensional NMR techniques (2D DQF-COSY, TOCSY, and ROESY). The β(1→4) linkage of disaccharide **26** was confirmed by observation of a strong cross-peak between H^B-1 and H^A-4 in the disaccharide. The 4-hydroxyl group of diol **15** was seemingly activated by electron-donating benzyl groups during glycosylation. Treatment of disaccharide **26** with the novel fucosyl donor **10** under *n*-$Bu_4NBr-CuBr_2$ catalysis also failed to provide trisaccharide

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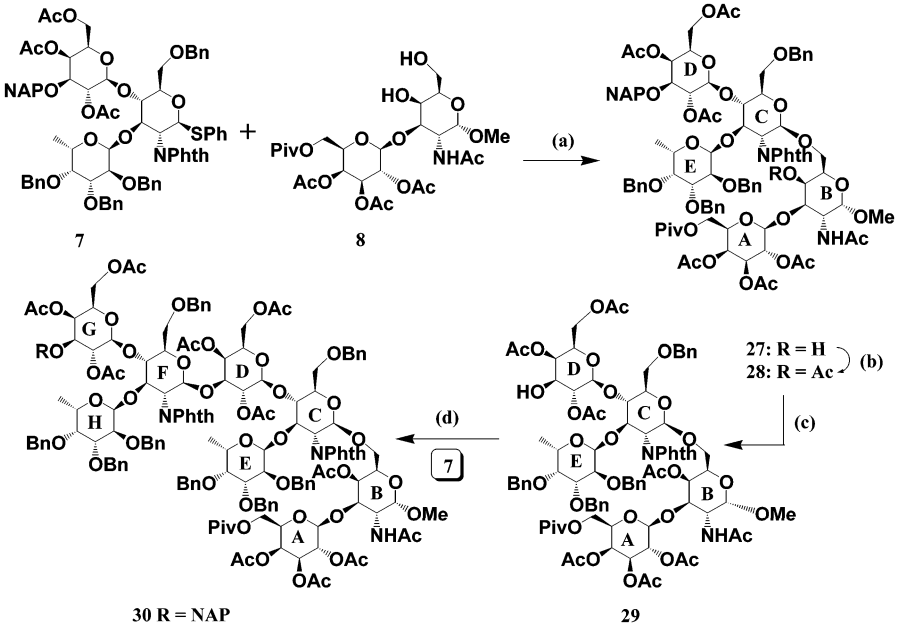
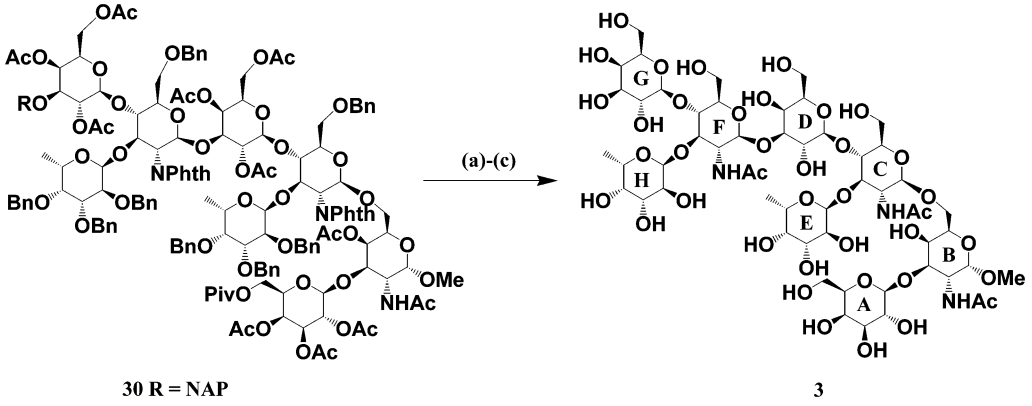
SCHEME 4[a]



[a] Reaction conditions: (a) NIS-TfOH/CH_2Cl_2, 4 Å MS, from −70 to −65 °C, 1 h, 76%; (b) Ac_2O−pyridine (1:1)/DMAP, rt, 12 h; (c) DDQ/CH_2Cl_2−H_2O, rt, 24 h, 58% or CAN/CH_3CN−H_2O (10:1), rt, 48 h, 65%; (d) NIS-TfOH/CH_2Cl_2, 4 Å MS, from −65 to −60 °C, 1 h, 46%.

SCHEME 5[a]



[a] Reaction conditions: (a) Pd-C(10%)/CH_2Cl_2−MeOH (2:1), H_2, r, 12 h; (b) NH_2-NH_2·H_2O−CH_3OH (1:5), 95 °C, 16 h, then Ac_2O−pyridine (1:1)/DMAP, rt, 12 h; (c) 1 M CH_3ONa−CH_3OH/CH_3OH−H_2O (1:1), rt, overnight, 42% over three steps.

donor **6**. Fortunately, when the disaccharide **26** was reacted with the traditional fucosyl donor **11** under the same glycosylation conditions, trisaccharide donor **7** was obtained in good yield (76%). Therefore, the electron-donating/withdrawing properties of protecting groups located at the 6-position of the glucosamine residue in disaccharides **25** and **26** were critical to the fucosylation reaction under Bu_4NBr−$CuBr_2$ glycosylation conditions. The reactivity of donors **10** and **11** became quite different when a simple change of acetyl to benzyl protection at their 3- and 4-positions occurred and when Bu_4NBr−$CuBr_2$ was used as the promoter. Construction of target octasaccharide **3** is outlined in Schemes 4 and 5. Regioselective glycosylation of the 6-hydroxyl group of disaccharide acceptor **8**[8] with trisaccharide **7** under controlled glycosylation conditions provided pentasaccharide **27** as the only glycosylation product in a high yield (76%). The structure of pentasaccharide **27** was fully confirmed by a variety of two-dimensional NMR experiments (2D DQF-COSY, TOCSY and ROESY). Compound **27** was then treated overnight with anhydrous acetic anhydride/pyridine in the presence of a catalytic amount of DMAP at room temperature to provide compound **28**. Removal of naphthylmethyl (NAP) protection from the acetylated **28** was effected with DDQ methodology developed in our laboratory.[14] The efficiency of this protocol was fully confirmed by other researchers.[15] The desired acceptor **29** was obtained in a reasonable yield (56%). Alternatively, when compound **28** was treated with a large excess of CAN in acetonitrile/water (10:1) for 48 h at room temperature, the desired acceptor **29** was produced in good yield (65%). Acceptor **29** was coupled with an excess

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of trisaccharide donor **7** promoted by (NIS-TfOH)[16] at low temperatures to provide octasaccharide **30** in a reasonable yield (46%) based on the recovery of acceptor **29**. Octasaccharide **30** was systematically deprotected (Scheme 5) by the removal of benzyl group with Pd−C (10%) under a hydrogen atmosphere, removal of two Phth groups with $NH_2-NH_2 \cdot H_2O$ and methanol, complete acetylation with Ac_2O-pyridine, and finally the removal of acetyl groups with 1 M sodium methoxide−methanol in the presence of water−methanol to provide the target octasaccharide **3** in 42% yield. The structure and purity of octasaccharide **3** were fully characterized by DQF-COSY, TOCSY, ROESY, and ESI mass spectroscopy.

Conclusion

In summary, a convergent synthesis of octasaccharide **3** incorporating the Le^x-Le^x dimer found in PSGL-1 carbohydrate chains was accomplished through systematic and investigative synthetic studies of novel Lewis^x trisaccharide donors **4**−**7**. These studies will provide valuable protocols for use in the syntheses of other more complex oligosaccharide molecules.

Experimental Section

General Procedures. TLC was conducted on glass plates precoated with a 0.25 mm layer of silica gel 60 F-254 (Analtech GHLF uniplates). The compounds were visualized either by exposure to UV light or by spraying with 10% H_2SO_4 and 0.2% *p*-anisaldehyde in a solution of ethanol and heating or both. Solutions were concentrated under reduced pressure at <40 °C. The silica gel used for column chromatography was Baker analyzed (60−200 mesh). ^{1}H NMR spectra were recorded at 400 or 600 MHz. The values of δ (parts per million) are given relative to the signal (δ 0) for internal Me_4Si for solutions in CD_2Cl_2, $CDCl_3$, and CD_3OD. ^{13}C NMR spectra were recorded at 100.6 MHz using $CDCl_3$ (77.0 ppm), CD_2Cl_2 (54.15 ppm), and CD_3OD (49.15 ppm) as references. First-order chemical shifts and coupling constants (J, hertz) were obtained from one-dimensional spectra, and assignments of proton resonance were based on 2D DQF-COSY, 2D ROESY, and 2D TOCSY. Two-dimensional double-quantum-filtered phase-sensitive ^{1}H−^{1}H correlated spectra (DQF ^{1}H−^{1}H COSY) and rotating-frame nuclear Overhauser enhancement spectroscopy (ROESY) were recorded at 400 or 600 MHz. For ROESY experiments, the mixing time was set at 400 ms. All samples submitted for elemental analyses were dried for 48 h under vacuum over P_2O_5 at room temperature. Elemental analyses were performed by the Robertson Laboratory, Madison, New Jersey. Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane were kept over 4 Å molecule sieves. Pyridine was redistilled over potassium hydroxide.

Methyl 3,4-*O*-Isopropylidene-1-thio-*β*-L-fucopranoside (18). To a solution of compound **9** (5.6 g, 18.13 mmol) in dichloromethane/methanol (20 mL, 1:1) was added 1 M sodium methoxide−methanol until the pH of the solution was equal to 10, and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized with H^+-resin and the filtrate concentrated under reduced pressure to a crude residue that was treated with dimethoxylpropane (120 mL) in the presence of CSA (500 mg) at room temperature for 1 h. The reaction mixture was then neutralized with triethylamine and concentrated to a crude residue that was applied to a column of silica gel eluted with hexane/ethyl acetate (2:1) to give a pure compound **18** (4.0 g, 94%) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.14 (d, 1 H, J = 9.3 Hz, H-1), 4.06−4.04 (m, 2 H), 3.89−3.87 (m, 1 H), 3.57−3.56 (m, 1 H), 2.93 (d, 1 H, OH), 2.21 (s, 3 H, SCH_3), 1.53 (s, 3 H, CH_3), 1.41 (d, 3 H, J = 6.5 Hz, CH_3), 1.37 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 109.78 (ketal carbon), 85.09 (C-1), 79.36, 76.51, 72.92, 71.48, 28.34, 26.35, 16.84, 11.72. Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74. Found: C, 51.36; H, 7.46.

Methyl 2-*O*-Benzyl-3,4-*O*-isopropylidene-1-thio-*β*-L-fucopranoside (19). To a solution of compound **18** (4.35 g, 18.59 mmol) and 18-crown-6 (520 mg) in dry THF (50 mL) was added powdered potassium hydroxide (12.0 g, 0.21 mol). The mixture was stirred at room temperature for 40 min. Benzyl bromide (3.31 mL) was then added, and stirring was continued at the same temperature for 2 h. The filtrate was concentrated and passed through a column of silica gel eluted with hexane/ethyl acetate (3:1) to yield pure compound **19** (6.0 g, 78%) as a green yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43−7.41 (m, 2 H, ArH), 7.34−7.25 (m, 3 H, ArH), 4.85 (d, 1 H, J = 11.4 Hz, OCH_APh, ABq), 4.74 (d, 1 H, J = 11.7 Hz, OCH_BPh, ABq), 4.26 (d, 1 H, J = 10.0 Hz, H-1), 4.18 (dd, 1 H, J = 6.1, 6.2 Hz), 4.01 (dd, 1 H), 3.78−3.76 (ddd, 1 H), 3.45−3.41 (m, 1 H), 2.18 (d, 3 H, SCH_3), 1.45 (s, 3 H, CH_3), 1.37 (d, 3 H, J = 6.7 Hz, CH_3), 1.36 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 138.00, 128.34, 128.30, 127.74, 109.59 (ketal carbon), 84.17 (C-1), 79.85, 78.81, 76.59, 73.42, 72.56, 28.08, 26.44, 16.78, 12.67. Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.93; H, 7.46. Found: C, 62.62; H, 8.41.

Methyl 2-*O*-Benzyl-3,4-di-*O*-acetyl-1-thio-*β*-L-fucopyranoside (10). A solution of compound **19** (6.0 g, 18.52 mmol) in 60% acetic acid (30 mL) was stirred at 65 °C for 1.5 h. The reaction mixture was concentrated under reduced pressure to a crude residue that was treated with acetic anhydride (20 mL) and dry pyridine (20 mL) in the presence of a catalytic amount of DMAP (5 mg) at room-temperature overnight. The reaction mixture was concentrated to a crude residue that was applied to a column of silica gel eluted with hexane/ethyl acetate (1:1) to give a pure compound **10** as an oil (5.43 g, 80%) in two steps. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73−7.27 (m, 5 H, ArH), 4.84 (d, 1 H, J = 10.3 Hz, $PhCH_AO$, ABq), 4.62 (d, 1 H, J = 10.9 Hz, $PhCH_BO$, ABq), 4.42 (d, 1 H, J = 9.7 Hz, H-1), 3.71−3.62 (m, 2 H, H-5, H-2), 2.25 (s, 3 H, Ac), 2.13 (s, 3 H, Ac), 1.94 (s, 3 H, Ac), 1.17 (d, 3 H, J = 5.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.54 (C=O), 170.50 (C=O), 137.98, 128.37, 128.01, 127.86, 85.61 (C-1), 75.92, 75.42, 74.50, 72.82, 71.04, 20.74 (Ac), 20.71 (Ac), 16.40, 13.12. Anal. Calcd for $C_{18}H_{24}O_6S$: C, 58.68; H, 6.56. Found: C, 58.55; H, 6.51.

2′-Trimethylsilylethanyl 2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranoside (21).[12] A solution of 2,3,4,6-tetra-*O*-D-galactosyl bromide **12** (12.0 g) and trimethylsilylethanol (7.1 mL) in dry dichloromethane (100 mL) containing 4 Å MS (20 g) was stirred at room temperature under an N_2 atmosphere for 2 h. HgO (6.32 g) and $HgBr_2$ (57 mg) were then added, and stirring was continued overnight at the same temperature. The filtrate was concentrated under reduced pressure to a crude residue that was applied to a column of silica gel eluted with hexane/ethyl acetate (4:1) to give a pure compound **21** (10 g, 90%) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.36 (d, 1 H, J = 3.2 Hz, H-4), 5.18 (d, 1 H, J = 8.0, 8.1 Hz, H-2), 5.00 (d, 1 H, J = 3.0, 10.4 Hz, H-3), 4.49 (d, 1 H, J = 8.0 Hz, H-1), 4.17−4.12 (m, 2 H), 4.04−3.90 (m, 2 H), 3.57−3.55 (m, 1 H), 2.13 (s, 3 H, Ac), 2.02 (s, 6 H, 2 Ac), 1.95 (s, 3 H, Ac), 0.97−0.89 (m, 2 H, 0.00 (s, 9 H, 3 CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 183.00 (C=O), 180.44 (C=O), 180.36 (C=O), 180.20 (C=O), 100.07 (C-1), 70.50, 69.94, 68.42, 66.79, 66.57, 60.70, 20.12 (Ac), 19.96 (2Ac), 19.88 (Ac), 17.33 (CH_3Si), −2.07 ($3CH_3$).

2′-Trimethylsilylethanyl 3-Naphthylmethyl-2,4,6-tri-*O*-acetyl-*β*-D-galactopyranoside (24). A catalytic amount of 1 M sodium methoxide−methanol solution was added to a solution of compound **21** (10.0 g, 10 mmol) in methanol−dichloromethane (50 mL, 1:1). The reaction mixture was stirred at room temperature for 2 h and then concentrated to a crude residue that was applied to a short column of silica gel eluted with dichloromethane/methanol (40:1) to give a pure

(16) (a) Veeneman, G. H.; Van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331. (b) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313.

compound **22** for direct application to the next reaction. Tributyl tin oxide (3.32 g, 13.34 mmol) was added to a solution of compound **22** (5.07 g, 13.34 mmol) in dry benzene (150 mL) and stirred under refluxing temperature for 4 h. The temperature was adjusted to 75−80 °C, and then *n*-Bu_4NI (5.9 g, 16.0 mmol) and naphthylmethyl bromide (3.54 g, 16.0 mmol) were added in one portion; stirring was maintained at this same temperature for 24 h. The mixture was concentrated and applied to a column of silica gel eluted with dichloromethane−methanol (60:1) to give a pure compound **23** (6.0 g, 86%), which was directly treated with dry pyridine−acetic anhydride (50 mL, 1:1) in the presence of a catalytic amount of DMAP (50 mg) at room temperature overnight. The reaction mixture was concentrated and applied to a column of silica gel eluted with hexane−ethyl acetate (4:1) to give a pure compound **24** (3.7 g, 49%) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 −7.76 (m, 3 H, ArH), 7.72−7.68 (s, 1 H, ArH), 7.48−7.40 (m, 2 H, ArH), 7.40−7.32 (dd, 1 H, ArH), 5.28 (d, 1 H, J = 4.4 Hz, H-4), 5.11 (dd, 1 H, J = 7.4, 8.4 Hz, H-2), 4.82 (d, 1 H, J_{gem} = 12.4 Hz, $C_{10}H_7CHO$, ABq), 4.54 (d, 1 H, J_{gem} = 12.6 Hz, $C_{10}H_7CHO$, ABq), 4.32 (d, 1 H, J = 8.1 Hz, H-1), 4.15 (d, 2 H), 3.95−3.88 (m, 1 H), 3.75 (ddd, 1 H), 3.55−3.48 (m, 2 H), 2.14 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 1.99 (s, 3 H, Ac), 1.00−0.80 (m, 2 H), 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.60 (2C═O), 169.42 (C═O), 135.13, 133.91, 133.20, 128.29, 127.97, 127.84, 126.80, 126.34, 126.15, 125.89, 100.86, 76.74, 71.44, 70.95, 70.71, 67.36, 66.09, 62.08, 21.23 (Ac), 20.96 (Ac), 20.82 (Ac), 18.06, − 1.32 ($SiCH_3$). Anal. Calcd for $C_{28}H_{38}O_9Si$: C, 61.52; H, 7.01; Si, 5.13. Found: C, 61.13; H, 6.54; Si, 5.23.

***O*-3-*O*-Naphthylmethyl-2,4,6-tri-*O*-acetyl-α-D-galactopyranosyl Trichloroacetimidate (13).** TFA (8 mL) was added to a solution of compound **24** (2.47 g, 3.82 mmol) in dry dichloromethane (20 mL) and stirred at room temperature for 40 min. The reaction mixture was concentrated under reduced temperature to a crude residue that was coevaporated with toluene and then dried under high vaccum to completely remove TFA. The residue was treated with trichloroacetonitrile (2.3 mL) and DBU (115 μL) in dry dichloromethane (20 mL) at 0−5 °C for 2 h. The reaction mixture was concentrated and applied to a silica gel column eluted with hexane−ethyl acetate (4:1) to give pure compound **13** as an amorphous solid (2.4 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (s, 1 H, $CNHCCl_3$), 7.84−7.72 (m, 4 H, ArH), 7.48−7.36 (m, 3 H, ArH), 5.70 (d, 1 H, J = 3.4 Hz, H-1, α-form), 5.31 (dd, 1 H, J = 2.8 Hz, 10.3 Hz, H-2), 4.89 (d, 1 H, J_{gem} = 11.1 Hz, $C_{10}H_7CH_AO$, ABq), 4.66 (d, 1 H, J_{gem} = 12.0 Hz, $C_{10}H_7CH_BO$, ABq), 4.35 (t, 1 H, J = 6.8, 6.9 Hz, H-5), 4.25−4.20 (dd, 1 H, H-3), 4.12−4.05 (m, 2 H), 2.16 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.98 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.26 (C═O), 170.05 (C═O), 160.77 (C═O), 134.86, 133.24, 133.12, 128.17, 127.87, 127.33, 126.87, 126.26, 126.10, 125.81, 94.00 (C-1), 72.43, 71.77, 69.67, 68.90, 66.79, 61.96, 20.78 (Ac), 20.70 (Ac), 20.66 (Ac).

Phenyl (3-*O*-Naphthylmethyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-6-*O*-trimethylacetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (25). A solution of acceptor **14** (843 mg, 1.74 mmol) and imidate donor **13** (1.23 g, 1.82 mmol) in dry dichloromethane (10 mL) containing 4 Å MS (8.0 g) was stirred at −65 °C for 2 h under a N_2 atmosphere. TMSOTf (67 μL) in dichloromethane (0.5 mL) was added dropwise, and the reaction was stirred at temperatures between −45 and −40 °C for 1 h. The solids were filtered off and the filtrate washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated to a crude residue that was applied to a silica gel column eluted with hexanes−ethyl acetate (2:1) to give a pure compound **25** (1.1 g, 60%) as an amorphous solid. R_f = 0.35 (hexanes−ethyl acetate (2:1)). ^{1}H NMR ($CDCl_3$, 400 MHz, DQF-COSY, TOCSY, and ROESY): δ 7.88−7.64 (m, 7 H, ArH), 7.52−7.44 (m, 2 H, ArH), 7.44−7.32 (m, 4 H, ArH), 7.28−7.16 (m, 3 H, ArH), 5.63 (d, 1 H, $J_{1,2}$ = 10.5 Hz, H^A-1), 5.49 (d, 1 H, J = 3.5 Hz, H^B-4), 5.18 (dd, 1 H, J = 9.4, 10.5 Hz, H^B-2), 4.80 (d, 1 H, J_{gem} = 12.4 Hz, $C_{10}H_7CH_AO$, ABq), 4.53 (d, 1 H, J = 12.4 Hz, $C_{10}H_7CH_BO$, ABq), 4.43−4.40 (m, 3 H, H^A-3, H^B-1, $J_{1,2}$ = 10.3 Hz, H^A-6b), 4.21−4.11 (m, 2 H, H^A-2, H^B-6b), 4.03−3.96 (m, 2 H, H^B-6a, H^A-6a), 3.87−3.79 (m, 2 H, H^B-5, H^A-5), 3.40 (dd, 1 H, J = 3.4, 9.9 Hz, H^B-3), 3.45−3.41 (m, 1 H, H^A-4), 2.14 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 1.86 (s, 3 H, Ac), 1.14 (s, 9 H, t-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.10 (C═O), 135.03, 133.60, 129.81, 129.35, 128.93, 128.81, 128.73, 127.93, 127.35, 127.20, 126.69, 124.53, 124.33, 103.29 (C^B-1), 84.56 (C^A-1), 84.33, 78.31, 76.85, 72.59, 72.53, 71.94, 71.03, 66.45, 64.22, 63.03, 55.82, 28.15 ($3CH_3$), 21.79 (Ac), 21.69 (Ac), 21.19 (Ac). Anal. Calcd for $C_{47}H_{48}O_{15}SN$: C, 62.79; H, 5.38; N, 1.57. Found: C, 62.66; H, 5.51; N, 1.49.

Phenyl (3-*O*-Naphthylmethyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (26). A solution of acceptor **15** (1.0 g, 2.04 mmol) and imidate donor **13** (1.44 g, 2.14 mmol) in dry dichloromethane (10 mL) containing 4 Å MS (8.0−10.0 g) was stirred at −65 °C for 2 h under a N_2 atmosphere. TMSOTf (78 μL) in dichloromethane (0.5 mL) was added dropwise, and the reaction was stirred at temperatures between −45 and −40 °C for 1 h. The solids were filtered off, and the filtrate was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated to a crude residue that was applied to a silica gel column eluted with hexanes−ethyl acetate (2:1) to give a pure compound **26** (1.29 g, 70%) as an amorphous solid. R_f = 0.25 (hexanes−ethyl acetate (2:1)). ^{1}H NMR ($CDCl_3$, 400 MHz, DQF-COSY, TOCSY, and ROESY): δ 7.90−7.65 (m, 9 H, ArH), 7.51−7.30 (m, 5 H, ArH), 7.29−7.10 (m, 7 H, ArH), 5.60 (d, 1 H, $J_{1,2}$ = 9.8 Hz, H^A-1), 5.47 (d, 1 H, J = 3.0 Hz, H^B-4), 5.14 (dd, 1 H, J = 7.9, 7.3 Hz, H^B-2), 4.81 (d, 1 H, J_{gem} = 12.5 Hz, $C_{10}H_7CH_AO$, ABq), 4.63 (d, 1 H, J_{gem} =11.5 Hz, $PhCH_AO$, ABq), 4.53 (d, 1 H, J_{gem} = 12.5 Hz, $C_{10}H_7CH_BO$, ABq), 4.47 (d, 1 H, J_{gem} = 12.6 Hz, $PhCH_BO$, ABq), 4.41−4.37 (m, 2 H, H^A-3, H^B-1, $J_{1,2}$ = 8.8 Hz), 4.22 (t, 1 H, J = 10.1 Hz, H^A-2), 4.16 (s, 1 H, OH^A-3), 4.12 (dd, 1 H, J = 4.3, 11.3 Hz, H^B-6b), 4.02 (dd, 1 H, J = 8.6, 8.1 Hz, H^B-6a), 3.81−3.77 (m, 1 H, H^B-5), 3.75−3.60 (m, 3 H, H^A-5, H^A-6b, H^A-6a), 3.50 (dd, 1 H, J = 3.6, 10.4 Hz, H^B-3), 2.15 (s, 3 H, Ac), 1.98 (s, 3 H, Ac), 1.90 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.73 (C═O), 170.47 (C═O), 170.44 (C═O), 169.31 (C═O), 134.25, 132.87, 129.00, 128.47, 128.05, 128.03, 127.92, 127.77, 126.99, 126.54, 126.38, 125.86, 123.71, 123.47, 101.92 (C^B-1), 83.56 (C^A-1), 82.15, 78.37, 76.58, 73.74, 71.69, 71.51, 71.04, 70.45, 68.43, 65.76, 62.13, 55.35, 21.08 (Ac), 20.90 (Ac), 20.49 (Ac). Anal. Calcd for $C_{49}H_{46}O_{14}SN$: C, 65.02; H, 5.12; N, 1.55. Found: C, 65.10; H, 5.52; N, 1.38.

Phenyl (3-*O*-Naphthylmethyl-2,4,6-tri-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-[(2,3,4-*O*-tri-benzyl-α-L-fucopyranosyl)-(1→3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (7). A solution of disaccharide acceptor **26** (1.21 g, 0.97 mmol), methyl tri-*O*-benzyl-1-thio-β-D-fucopyranoside **11** (1.9 g), and tetrabutylammonium bromide (1.55 g) in dry 1,2-dichloroethane−DMF (15 mL, 5:1) containing 4 Å MS (10.0 g) was stirred at room temperature for 2 h under a N_2 atmosphere. $CuBr_2$ (1.26 g) was then added, and stirring was continued for 48 h. Solids were filtered off, and the filtrate was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated to a crude residue that was applied to a silica gel column eluted with hexanes−ethyl acetate (4:1) to give pure compound **7** (1.32 g, 93%) as an amorphous solid. R_f = 0.46 (hexanes−ethyl acetate (2:1)). ^{1}H NMR ($CDCl_3$, 600 MHz, DQF-COSY, TOCSY, and ROESY): δ 7.85 −7.81 (m, 2 H, ArH), 7.73−7.69 (m, 2 H, ArH), 7.50−7.49 (m, 2 H, ArH), 7.36−7.32 (m, 3 H, ArH), 7.28−7.00 (m, 23 H, ArH), 5.47 (d, 1 H, $J_{1,2}$ = 10.9 Hz, H^A-1), 5.40 (d, 1 H, J = 2.9 Hz, H^B-4), 4.98 (dd, 1 H, H^B-2), 4.82 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H^C-1), 4.81−4.78 (m, 2 H, $C_{10}H_7CH_AO$, ABq, $PhCH'_AO$, ABq), 4.75−4.68 (m, 2 H, H_A-3, $PhCH''_AO$, J_{gem} = 11.6 Hz, ABq), 4.63−4.59 (m, 2 H, H^C-5, H^B-1, $J_{1,2}$= 8.5 Hz), 4.56 (d, 1 H, J_{gem} = 11.0 Hz, $PhCH_BO$, ABq), 4.51−4.46 (m, 2 H, H^A-2, $C_{10}H_7CH_BO$), 4.42 (d, 1 H, J_{gem} = 11.4 Hz, $PhCH'''_AO$, ABq), 4.36 (d, 1 H, J_{gem} = 11.3 Hz, $PhCH''_BO$, ABq), 4.26 (d, 1 H, J_{gem} = 12.9 Hz, $PhCH'''_BO$, ABq), 4.16−4.08 (m, 2 H, H^B-6b, H^A-4, J = 9.5, 8.7 Hz), 3.97 (dd, 1

H, J = 6.0, 10.5 Hz, H^B-6a), 3.89 (dd, 1 H, J = 1.3, 9.8 Hz, H^C-3), 3.85−3.74 (m, 3 H, H^A-6b, H^A-6a, H^C-2), 3.63 (d, 1 H, H^C-4), 3.55 (t, 1 H, H^A-5), 3.48−3.42 (m, 1 H, H^B-5), 3.31 (dd, 1 H, J = 3.8, 9.9 Hz, H^B-3), 2.04 (s, 3 H, Ac), 1.99 (s, 3 H, Ac), 1.86 (s, 3 H, Ac), 1.20 (d, 3 H, J = 6.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.47 (C═O), 170.30 (C═O), 169.99 (C═O), 134.48, 132.74, 129.12, 128.70, 128.54, 128.47, 128.40, 128.30, 128.27, 128.15, 128.06, 128.01, 127.98, 127.73, 127.49, 127.43, 127.31, 126.84, 126.41, 125.93, 123.99, 100.03, 97.83, 84.65, 80.09, 79.92, 77.17, 75.31, 74.97, 74.54, 73.81, 73.71, 73.28, 72.66, 71.33, 70.92, 70.86, 68.28, 66.90, 65.93, 61.20, 55.90, 21.25 (Ac), 21.05 (Ac), 21.01 (Ac), 17.01 (CH_3). Anal. Calcd for $C_{76}H_{74}O_{18}NS$: C, 69.07; H, 5.64; N, 1.06. Found: C, 70.35; H, 5.72; N, 1.07.

Methyl (3-*O*-Naphthylmethyl-2,4,6-tri-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)-(1→6)-[(2,3,4,-tri-*O*-acetyl-6-*O*-trimethylacetyl-*β*-D-galactopyranosyl)-(1→3)]-2-acetamido-2-deoxy-α-D-galactopyranoside (27). A solution of acceptor **8** (50 mg. 0.082 mL), trisaccharide donor **7** (128 mg, 0.097 mmol), and NIS (175 mg) in dry dichloromethane (4 mL) containing 4 Å MS (2.0 g) was stirred at temperatures between −65 and −60 °C for 2 h under a N_2 atmosphere. TfOH (17 μL) in dry dichloromethane (0.5 mL) was added dropwise, and stirring was continued at the same temperature for 1.5 h. Solids were filtered off, and the filtrate was washed with saturated $NaHCO_3$ and 10% Na_2SO_3, dried (Na_2SO_4), and concentrated to a crude residue that was passed through a column of silica gel eluted with dichloromethane−methanol (60:1) to give a pure compound **27** (113 mg, 76%) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 600 MHz, DQF-COSY, TOCSY, and ROESY): δ 7.84−7.42 (m, 10 H, ArH), 7.40−6.84 (m, 21 H, ArH), 5.35 (d, 1 H, J = 2.6 Hz, H^A-4), 5.31 (d, 1 H, J = 10.5 Hz, NHAc), 5.16−5.06 (m, 2 H, H^B-2, H^C-1, $J_{1,2}$ = 8.6 Hz), 4.96−4.93 (m, 2 H, H^D-2, H^A-2), 4.81−4.75 (m, 3 H, H^E-1, $C_{10}H_7CH_AO$, Ph-CH_AO), 4.74−4.69 (m, 2 H, $PhCH_A'O$, H^C-3), 4.65 (m, 1 H, H^E-5), 4.56 (d, 1 H, J_{gem} = 12.3 Hz, $PhCH_BO$, ABq), 4.53 (d, 1 H, $J_{1,2}$ = 8.3 Hz, H^D-1), 4.50 (d, 1 H, $J_{1,2}$ = 7.6 Hz, H^A-1), 4.49 (d, 1 H, J_{gem} = 12.6 Hz, $C_{10}H_7CH_BO$, ABq), 4.44 (d, 1 H, $PhCH_A''O$), 4.43−4.30 (m, 4 H, H^C-2, H^B-2, $PhCH_A'''O$, Ph-$CH_B''O$), 4.27 (d, 1 H, J_{gem} = 13.00 Hz, $PhCH_B'''O$, ABq), 4.18 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H^B-1), 4.16−4.02 (m, 3 H, H^D-6b, H^C-4), 4.01−3.72 (m, 8 H, H^D-6a, H^B-6b, H^E-3, H^A-5, H^B-4, H^C-6b, H^E-2, H^C-6a), 3.68−3.48 (m, 5 H, H^B-5, H^E-4, H^B-6a, H^B-3, H^C-5), 3.39 (t, 1 H, H^D-5), 3.24 (dd, 1 H, H^D-3), 2.84 (s, 3 H, OCH_3), 2.12 (s, 3 H, Ac), 2.05 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.99 (s, 3 H, Ac), 1.95 (s, 3 H, Ac), 1.91 (s, 3 H, Ac), 1.85 (s, 3 H, Ac), 1.20 (d, 3 H, J = 6.1 Hz, CH^E_3), 1.15 (s, 9 H, t-Bu). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.38 (C═O), 17.30 (C═O), 170.25 (C═O), 170.20 (C═O), 169.52 (C═O), 169.50 (C═O), 169.39 (C═O), 168.40 (C═O), 139.10, 138.95, 138.20, 138.10, 135.10, 134.10, 129.35, 128.65, 128.41, 128.38, 128.31, 128.17, 128.11, 128.05, 128.00, 127.98, 127.62, 127.34, 127.31, 127.20, 126.69, 126.54, 126.37, 125.81, 101.91, 99.90, 99.24, 98.48, 97.49, 79.98, 78.00, 75.40, 75.31, 74.78, 74.43, 73.67, 72.92, 72.53, 72.30, 71.60, 71.08, 70.84, 70.71, 70.37, 68.92, 68.84, 66.97, 66.68, 65.58, 61.27, 61.06, 56.83, 54.83, 27.31, 21.14 (Ac), 20.95 (Ac), 20.93 (Ac), 20.89 (Ac), 20.80 (Ac), 20.74 (Ac), 20.67 (Ac), 18.85 (CH_3). Anal. Calcd for $C_{96}H_{109}O_{33}N_2$: C, 63.39; H, 6.04; N, 1.55. Found: C, 64.11; H, 6.08; N, 1.54.

Methyl (3-*O*-Naphthylmethyl-2,4,6-tri-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)]-(1→6)-[(2,3,4,-tri-*O*-acetyl-6-*O*-trimethylacetyl-*β*-D-galactopyranosyl)-(1→3)]-2-acetamido-4-*O*-acetyl-2-deoxy-α-D-galactopyranoside (28). A solution of compound **27** (223 mg) was treated with anhydrous acetic anhydride (5 mL) and dry pyridine (5 mL) in the presence of a catalytic amount of DMAP (5 mg) at room-temperature overnight. The reaction mixture was concentrated and applied to a column of silica gel eluted with dichloromethane−ethanol (80:1) to give a pure compound **28** in quantitative yield as an amorphous solid. ^{1}H NMR ($CDCl_3$, 600 MHz, DQF-COSY, TOCSY, and ROESY): δ 8.00−7.00 (m, 31 H, ArH), 5.41−5.39 (m, 2 H, H^D-4, J = 2.8 Hz, NHAc, J = 9.4 Hz), 5.28 (d, 1 H, J = 2.7 Hz, H^A-4), 5.16 (d, 1 H, J = 2.3 Hz, H^B-4), 5.05−5.01 (m, 2 H, H^A-2, H^C-1, $J_{1,2}$ = 8.8 Hz), 4.98−4.89 (m, 2 H, H^D-2, H^A-3), 4.81−4.73 (m, 4 H, H^E-1, $C_{10}H_7CH_AO$, $PhCH_AO$, $PhCH'_AO$, J_{gem} = 12. 3 Hz), 4.69−4.65 (m, 4 H, $PhCH_2O$, H^C-3, H^E-5), 4.56 (d, 1 H, J_{gem} = 12.0 Hz, $C_{10}H_7CH_BO$, ABq), 4.52 (d, 1 H, $J_{1,2}$ = 7.7 Hz, H^D-1), 4.48 (d, 1 H, J_{gem} = 12.4 Hz, $PhCH_BO$, ABq), 4.46 (d, 1 H, $J_{1,2}$ = 7.8 Hz, H^A-1), 4.42 (d, 1 H, J_{gem} = 12.9 Hz, $PhCH''_AO$, ABq), 4.39−4.28 (m, 3 H, H^C-2, H^B-2, $PhCH'_BO$, J_{gem} = 12.1 Hz, ABq), 4.23 (d, 1 H, J_{gem} = 12.1 Hz, $PhCH''_BO$, ABq), 4.17−4.09 (m, 4 H, H^B-1, H^C-4, H^D-6b, H^A-6b), 4.06−3.95 (m, 2 H, H^A-6a, H-6a), 3.93−3.88 (m, 2 H, H^B-6b, H^E-3), 3.86−3.70 (m, 5 H, H^C-6b, H^E-2, H^B-5, H^C-6a, H^B-3), 3.62 (d, 1 H, J = 2.8 Hz, H^E-4), 3.51−3.45 (m, 1 H, H^C-5), 3.37 (t, 1 H, J = 7.3, 7.4 Hz, H^D-5), 3.28−3.20 (m, 2 H, H^B-6a, H^D-3), 2.85 (s, 3 H, OCH_3), 2.13 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.00 (s, 3 H, Ac), 1.94 (s, 3 H, Ac), 1.92 (s, 3 H, Ac), 1.20 (d, 3 H, J = 6.7 Hz, CH_3), 1.15 (s, 9 H, t-Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.65 (C═O), 17.20 (C═O), 169.74 (C═O), 169.62 (C═O), 128.65, 128.42, 128.38, 128.30, 128.16, 128.08, 128.02, 127.97, 127.61, 127.32, 127.19, 126.54, 126.32, 101.28, 99.89, 99.14, 98.35, 97.53, 79.99, 77.01, 75.48, 75.16, 74.73, 74.42, 73.68, 73.66, 72.93, 72.54, 72.34, 71.61, 70.95, 70.82, 70.68 (2C), 69.98, 68.70, 68.00, 66.74, 66.68, 65.81, 61.05, 60.80, 56.57, 54.94, 48.92, 27.23 ($3CH_3$), 23.63 (NHAc), 21.13 (Ac), 20.99 (Ac), 20.94 (Ac), 20.91 (Ac), 20.87 (Ac), 20.83 (Ac), 16.87 (CH_3). Anal. Calcd for $C_{98}H_{111}O_{34}N_2$: C, 63.25; H, 6.01; N, 1.51. Found: C, 63.25; H, 5.98; N, 1.46.

Methyl (2,4,6-Tri-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)]-(1→6)-[(2,3,4,-tri-*O*-acetyl-6-*O*-trimethylacetyl-*β*-D-galactopyranosyl)-(1→3)]-2-acetamido-4-*O*-acetyl-2-deoxy-α-D-galactopyranoside (29). A solution of compound **28** (167 mg) in a mixture of dichloromethane−methanol−water (trace) (7 mL, 4:1) was added DDQ (28 mg), and the reaction mixture was stirred at room temperature for 21 h. The mixture was concentrated and taken up in dichloromethane (50 mL), which was washed with saturated $NaHCO_3$ (2 × 50 mL), dried (Na_2SO_4), and concentrated. The crude residue was applied to a column of silica gel eluted with dichloromethane−ethyl acetate (4:1) to give a pure compound **29** (66 mg, yield 58% based on the recovery of 40 mg of starting material). ^{1}H NMR ($CDCl_3$, 600 MHz, DQF-COSY, TOCSY, and ROESY): δ 7.80−6.80 (m, 24 H, ArH), 5.38 (d, 1 H, J = 9.1 Hz, NHAc), 5.29 (d, 1 H, J = 2.1 Hz, H^A-4), 5.17 (d, 1 H, J = 4.9 Hz, H^B-4), 5.16 (d, 1 H, J = 2.9 Hz, H^D-4), 5.06−5.02 (m, 2 H, J = 8.7 Hz, H^C-1, H^A-2), 4.92 (dd, 1 H, J = 3.2, 10.3 Hz, H^A-3), 4.84 (d, 1 H, J_{gem} = 12.3 Hz, $PhCH_AO$, ABq), 4.79 (d, 1 H, $J_{1,2}$ = 3.1 Hz, H^E-1), 4.76 (d, 1 H, J_{gem} = 11.8 Hz, $PhCH_A'O$, ABq), 4.75 (dd, 1 H, H^D-2), 4.74 (dd 1 H, H^D-2), 4.68 (t, 1 H, H^C-3), 4.63 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H^D-1), 4.58 (ddd, 1 H, H^E-5), 4.55 (d, 1 H, J_{gem} = 12.3 Hz, $ArCH_B'O$, ABq), 4.51 (d, 1 H, J_{gem} = 12.1 Hz, $ArCH_A''O$, ABq), 4.47 (d, 1 H, H^A-1), 4.45 (d, 1 H, J_{gem} = 12.8 Hz, $ArCH_BO$, ABq), 4.41 (d, 1 H, J_{gem} = 11.8 Hz, $ArCH_A'''O$, ABq), 4.36 (t, 1 H, H^C-2), 4.32 (ddd, 1 H, H^B-2), 4.22 (d, 1 H, J_{gem} = 12.4 Hz, $ArCH_B'''O$, ABq), 4.16 (d, 1 H, $J_{1,2}$ = 2.8 Hz, H^B-1), 4.15−3.73 (m, 12 H, H^B-6b, H^A-6b, H^D-6b, H^A-6a, H^C-6b, H^B-6a, H^D-6a, H^E-3, H^C-6a, H^E-2, H^B-3), 3.60−3.20 (m, 5 H, H^E-4, H^C-5, H^D-5, H^D-3), 2.87 (s, 3 H, OCH_3), 2.14 (s, 3 H, Ac), 2.09 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 1.94 (s, 3 H, Ac), 1.93 (s, 3 H, Ac), 1.86 (s, 3 H, Ac), 1.16−1.13 (m, 12 H, t-Bu, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.90 (C═O), 17.65 (C═O), 170.33 (C═O), 169.73 (C═O), 169.70 (C═O), 139.01, 134.25, 128.79, 128.51, 128.44, 128.37, 128.31, 128.18, 128.07, 127.64, 127.35, 127.20, 101.28, 99.37, 99.18, 98.36, 97.80, 80.00, 77.44, 75.47, 75.34, 74.72, 74.41, 73.78, 73.69, 73.10, 72.98, 72.88, 72.57, 71.33, 70.94, 70.82, 70.71, 69.99, 69.49, 68.97, 68.72, 68.00, 66.74, 66.64, 60.93, 60.80, 56.52, 54.76, 48.93, 27.23,

23.62 (Ac), 21.31 (Ac), 21.00 (Ac), 20.87 (Ac), 20.73 (Ac), 16.95 (CH_3). Anal. Calcd for $C_{87}H_{103}O_{34}N_2$: C, 60.72; H, 6.03; N, 1.64. Found: C, 60.79; H, 6.28; N, 1.60.

Methyl {(2,4,6-Tri-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)]-(1→3)]-(2,4,6-tri-*O*-acetyl-*β*-D-galactopyranosyl)-(1→4)-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-6-*O*-benzyl-2-deoxy-2-phthalimido-*β*-D-glucopyranosyl)}-(1→6)-[(2,3,4,-tri-*O*-acetyl-6-*O*-trimethylacetyl-*β*-D-galactopyranosyl)-(1→3)]-2-acetamido-4-*O*-acetyl-2-deoxy-α-D-galactopyranoside (30). A solution of pentasaccharide acceptor **29** (120 mg, 0.064 mmol), trisaccharide donor **7** (150 mg, 0.102 mmol), and NIS (116 mg, 0.51 mmol) in dry dichloromethane (10 mL) containing 4 Å MS (3.0 g) was stirred at temperatures between −65 and −60 °C for 1−1.5 h under a N_2 atmosphere. TfOH (32 μL) in dry dichloromethane (0.5 mL) was added dropwise, and stirring was continued at the same temperature for 1.5 h. Additional portions of trisaccharide donor **7** (80 mg) and TfOH (16 μL) were added again, and stirring was continued for another 1 h at the same temperature. The solids were filtered off, and the filtrate was washed with saturated $NaHCO_3$ and 10% Na_2SO_3, dried (Na_2SO_4), and concentrated to a crude residue, which was passed through a column of silica gel eluted with dichloromethane−methanol (60:1) to give pure compound **30** (66 mg, 46% based on the recovery of acceptor **29**, 40 mg) as an amorphous solid. ^{1}H NMR ($CDCl_3$, 600 MHz, DQF-COSY, TOCSY, and ROESY): δ 8.00−7.00 (m, 55 H, ArH), 5.45 (d, 1 H, J = 2.8 Hz, H^H-4), 5.35 (d, 1 H, J = 10.1 Hz, NHAc), 5.29 (d, 1 H, J = 4.3 Hz, H^E-4), 5.28 (d, 1 H, H^A-4), 5.15 (d, 1 H, J = 2.4 Hz, H^G-1), 5.03 (dd, 1 H, H^E-2), 5.01 (dd, 1 H, H^H-2), 5.00 (d, 1 H, $J_{1,2}$ = 8.8 Hz, H^C-1), 4.93 (d, 1 H, $J_{1,2}$ = 8.7 Hz, H^F-1), 4.88 (dd, 1 H, H^E-3), 4.82−4.72 (m, 5 H, 4 ArCHO, H^D-1), 4.71 (dd, H^C-3), 4,69 (d,1 H, J = 2.8 Hz, H^B-4), 4.64 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H^H-1), 4.62 (m, 1 H, H^D-5), 4.61 (dd, 1 H, H^A-2), 4.57 (d, 1 H, J_{gem} = 12.4 Hz, ArCHO), 4.50−4.48 (m, 3 H, 2 ArCHO, H^F-3), 4.46 (d, 1 H, H^E-1), 4.42 (m, 1 H, H^G-5), 4.38−4.32 (m, 4 H, 3 ArCHO, H^A-1), 4.29 (dd, 1 H, H^B-2), 4.28 (dd, 1 H, H^F-2), 4.25 (dd, 1 H, H^C-3), 4.20−4.18 (m, 3 H, 2ArCHO, H^H-6b), 4.16−3.69 (m, 13 H, H^B-1, H^C-4, H^F-4, H^H-6a, H^E-6b, H^F-6b, H^G-3, H^F-6a, H^E-6a, H^B-3, H^G-2), 3.60−3.20 (m, 6 H, H^H-5, H^C-5, H^A-3, H^H-3, H^F-5, H^E-5), 2.83 (s, 3 H, OCH_3), 2.13 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 2.05 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 1.94 (s, 3 H, Ac), 1.92 (s, 3 H, Ac), 1.91 (s, 3 H, Ac), 1.89 (s, 3 H, Ac), 1.72 (s, 3 H, Ac), 1.20 (d, 3 H, J = 6.7 Hz, CH_3), 1.16 (s, 9 H, t-Bu), 0.90 (d, 3 H, J = 6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.63 (C═O), 170.40 (C═O), 170.35 (C═O), 170.30 (C═O), 170.20 (C═O), 170.00 (C═O), 169.80 (C═O), 169.70 (C═O), 169.60 (C═O), 169.20 (C═O), 168.95 (C═O), 168.83 (C═O), 168.80 (C═O), 168.48 (C═O), 168.41 (C═O), 140.00, 139.20, 138.52, 138.50, 134.23, 132.07, 128.78, 128.66, 128.61, 128.48, 128.41, 128.36, 128.31, 128.27, 128.16, 128.10, 128.08, 128.04, 127.93, 127.90, 127.63, 127.56, 127.35, 127.31, 127.26, 127.17, 126.76, 126.49, 126.29, 125.86, 123.53, 101.30, 100.90, 99.51, 99.05, 98.39, 98.30, 97.50, 800.00, 79.80, 75.45, 74.64, 74.56 (2C), 74.42 (2C), 73.91 (2C), 73.75, 73.68, 72.90, 72.82, 72.64 (2C), 72.40, 71.70 (2C), 71.19, 70.93 (3C), 70.81 (3C), 69.98, 68.96, 68.67, 66.72, 66.57, 61.08, 61.07, 60.80, 56.52, 50.48, 56.30, 54.72, 48.90, 27.23 ($3CH_3$), 23.62 (NHAc), 21.15 (Ac), 20.99 (Ac), 20.95 (2Ac), 20.87 (2Ac), 20.82 (2Ac), 20.72 (2Ac), 20.62 (Ac), 16.91 ($2CH_3$). Anal. Calcd for $C_{157}H_{171}O_{52}N_3$: C, 64.31; H, 5.88; N, 1.44. Found: C, 64.35; H, 5.89; N, 1.60.

Methyl {(*β*-D-Galactopyranosyl)-(1→4)-[(α-L-fucopyranosyl)-(1→3)]-2-deoxy-2-acetamido-*β*-D-glucopyranosyl)-(1→3)]-(*β*-D-galactopyranosyl)-(1→4)-[(α-L-fucopyranosyl)-(1→3)]-2-deoxy-acetamido-*β*-D-glucopyranosyl)-(1→6)}-[*β*-D-galactopyranosyl)-(1→3)]-2-acetamido-2-deoxy-α-D-galactopyranoside (3). A solution of octasaccharide **30** (37 mg, 0.01 mmol) and Pd-C(10%) (37 mg) in dichloromethane−methanol (6 mL, 2:1) was stirred under a hydrogen atmosphere at room-temperature overnight. Solids were filtered out, and the filtrate was concentrated to a dry residue that was treated with anhydrous pyridine (3 mL)/acetic anhydride (3 mL) at room temperature overnight. The reaction mixture was concentrated and applied to a short silica gel column eluted with dichloromethane−methane (60:1) to give a pure compound (30 mg) that was directly treated with NH_2−NH_2·H_2O−MeOH (12 mL, 1:5) at 95 °C for 16 h. The mixture was concentrated, coevaporated with toluene (3 × 10 mL) and dried under high vacuum, and then treated with a mixture of Ac_2O−pyridine (10 mL, 1:1) in the presence of DMAP (3 mg) at room-temperature overnight. The reaction mixture was concentrated and applied to a short silica gel column eluted with dichloromethane−methanol (40:1) to give the peracetylated compound. The acetylated compound was then treated with 1 M CH_3ONa−CH_3OH (50 μL) in methanol−water (2 mL, 1:1) at room-temperature overnight and concentrated. It was then applied to a short silica gel column eluted with n-C_4H_9OH−HOAc−H_2O (2:1:1) to give a pure compound **3** (6 mg, 42%) as a white solid. R_f = 0.32 (n-C_4H_9OH−HOAc−H_2O (2:1:1)). ^{1}H NMR (D_2O, 600 MHz, DQF-COSY, TOCSY, and ROESY): δ 5.11 (d, 1 H, $J_{1,2}$ = 3.8 Hz, H^{Fuc}-1), 5.08 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H ^{Fuc}-1), 4.80 (m, 2 H, 2 H^{Fuc}-5), 4.73 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H^B-1), 4.64 (d, 1 H, $J_{1,2}$ = 8.3 Hz, H-1), 4.54 (d, 1 H, $J_{1,2}$ = 8.2 Hz, H-1), 4.45−4.40 (ddd, 3 H, H^A-1, H^D-1, H^G-1), 4.29 (dd, 1 H, J = 3.7, 10.9 Hz, H^B-2), 4.17 (d, 1 H, J = 3.0 Hz, H^B-4), 4.08−3.80 (m, 18 H), 3.80−3.54 (m, 20 H), 3.52−3.46 (m, 3 H, H^A-2, H^D-2, H^G-2), 3.32 (s, 3 H, OCH_3), 2.05 (s, 3 H, Ac), 2.00 (s, 3 H, Ac), 1.98 (s, 3 H, Ac), 1.18 (d, 3 H, J = 6.7 Hz, CH_3), 1.12 (d, 3 H, J = 6.8 Hz, CH_3). ^{13}C NMR (D_2O, 100.6 MHz): δ 174.60 (C═O), 174.20 (C═O), 173.40 (C═O), 104.00, 101.80, 101.15 (2C), 100.80, 98.00, 97.98, 97.60, 80.97, 76.40, 74.60, 74.40, 74.25 (2C), 74.00, 73.98, 72.40, 71.98, 71.20, 70.40, 70.00, 69.99, 69.40, 68.42 (2C), 68.20, 67.99, 67.61, 67.42, 67.01, 67.00, 66.00, 60.25, 60.00, 58.41, 58.40, 54.45, 54.40, 54.15, 48.00, 21.60 (Ac), 21.20 (2Ac), 14.62 (CH_3), 14.60 (CH_3). ESIMS (negative mode) Calcd for $C_{55}H_{93}O_{39}N_3$: 1419 (M). Found: 1419.

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Supporting Information Available: One-dimensional ^{1}H NMR and ^{13}C NMR spectra for compounds **3**, **7**, **10**, **13**, **18**, **19**, **21**, **23**, and **25**−**30**; two-dimensional TOCSY, DQF-COSY, and ROESY spectra for compounds **3** and **25**−**30**; and two-dimensional TOCSY and ROESY spectra for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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