Synthesis of the Hexasaccharide Fragment of Landomycin A: Application of Glycosyl Tetrazoles and Phosphites in the Synthesis of a Deoxyoligosaccharide

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Abstract: The synthesis of the hexasaccharide fragment of the antitumor antibiotic landomycin A (**1**) (aka. NSC 639187) is described. The stereocontrolled introduction of key glycoside linkages relies on the combined application of glycosyl tetrazoles and phosphites to establish α and β glycosidic linkages, respectively. Spectral comparison of landomycin A octaacetate (**2**) and hexasaccharide pentaacetate (**3**) serves to corroborate the assigned structure of **1** within the oligosaccharide domain.

Deoxygenated oligosaccharides are ubiquitous among secondary metabolites, particularly within the genus *streptomyces*.[1] Recently, the importance of the oligosaccharide component of these substances in relation to bioactivity has become apparent, particularly evident among the aureolic acid[2] and enediyne antitumor antibiotics.[3] Landomycin A (**1**), a member of the angucycline group of antibiotics, was discovered during the course of screening *Streptomyces* for new antitumor agents and has been characterized as the octaacetate derivative **2**.[4] A particularly striking feature of **1** is the deoxygenated hexasaccharide unit comprising two repeating trisaccharides, each consisting of the sequence α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose. In vitro evaluation of landomycin A (**1**) at the National Cancer Institute under the synonym NSC 639187 revealed a broad spectrum of antitumor activity.[5] However, subsequent in vivo evaluation demonstrated **1** to be overtly cytotoxic, which precluded any further development as a drug candidate. The specific mode of action of landomycin A (**1**) is not known but recent work has indicated **1** inhibits the uptake of tritium labeled thymidine in cell culture, suggesting interference with DNA synthesis to be operative.[6,7] In an effort to more fully elucidate the mode of action of landomycin A as well as to define the relationship between the oligosaccharide structure and antitumor activity we initiated a program directed toward the total synthesis of landomycin A. As a first step, we describe the assembly of hexasaccharide **3**. Further, spectral comparison of **3** to **2** serves to confirm the assigned structure of **1** within the oligosaccharide domain.

From the strategic perspective, bond disconnection about the C1‴−C4″ glycoside linkage reduces the synthesis of **3** to the preparation of trisaccharides **4** and **5**, which possess identical stereochemical as well as constitutional features, and can be assembled in parallel with minor adjustments in the protecting group scheme. In the final merger of **4** and **5**, an activated derivative of trisaccharide **4** would serve as a glycosyl donor, while **5** would serve as the corresponding acceptor. Implicit within this plan was the formidable challenge of merging deoxysugar units to produce 2-deoxy glycosides in the desired stereochemical arrangement. Of the many methods available for the introduction of 2-deoxy-α-glycoside linkages, we chose to take advantage of glycosyl tetrazoles as donors, since these are hydrolytically stable even within 2,3,6-trideoxy sugars.[8,9] On the other hand, the choice of glycosyl donor for the stereocontrolled introduction of the four 2-deoxy-β-glycoside linkages within **3** was less clear. With few exceptions, most β selective glycosylation methods rely on participation of an equatorially disposed C(2) heteroatom within the glycosyl donor, which is subsequently removed following the coupling reaction.[10,11] One notable exception is the use of glycosyl phosphites as donors, which have been reported to afford 2-deoxy-β-

(1) (a) Kennedy, J. F.; White, C. A. *Bioactive Carbohydrates in Chemistry, Biochemistry and Biology*; Ellis Horwood: Chichester, 1983. (b) Kirschning, A.; Bechthold, A.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1.

(2) Aureolic acids: (a) Remers, W. A. In *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1979; Vol. 1, Chapter 3, p 133. (b) Gao, X.; Patel, D. J. *Biochemistry* **1989**, *28*, 751. (c) Banville, D. L.; Keniry, M. A.; Kam, M.; Shafer, R. H. *Biochemistry* **1990**, *29*, 6521. (d) Banville, D. L.; Keniry, M. A.; Shafer R. H. *Biochemistry* **1990**, *29*, 9294. (**e**) Snyder, R. C.; Ray, R.; Blume, S.; Miller, D. M. *Biochemistry* **1991**, *30*, 4290. (f) Sastry, M.; Patel, D. J. *Biochemistry* **1993**, *32*, 6588. (g) Silva, D. J.; Kahne, D. *J. Am. Chem. Soc*. **1993**, *115*, 7962. (h) Silva, D. J.; Kahne, D. *J. Am. Chem. Soc*. **1994**, *116*, 2641.

(3) Enediyne antibiotics: (a) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198. (b) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697. (c) Drak, J.; Iwasawa, N.; Danishefsky, S.; Crothers, D. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 7464. (d) Walker, S.; Landovitz, R.; Ding, W.-D.; Ellestad, G. A.; Kahne, D. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 4608. (e) Aiyar, J.; Danishefsky, S. J.; Crothers, D. M. *J. Am. Chem. Soc.* **1992**, *114*, 7552. (f) Nicolaou, K. C.; Tsay, S.-C.; Suzuki, T.; Joyce, G. F. *J. Am. Chem. Soc*. **1992**, *114*, 7555. (g) Paloma, L. G.; Smith, J. A.; Chazin, W. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1994**, *116*, 6, 3697. (h) Li, T.; Zeng, Z.; Estevez, V. A.; Baldenium, K. U.; Nicolaou, K. C.; Joyce, G. F. *J. Am. Chem. Soc*. **1994**, *116*, 3709. (i) Nicolaou, K. C.; Smith, B. M.; Pastor, J.; Watanabe, Y.; Weinstein, D. S. *Synlett* **1997**, 401.

(4) (a) Henkel, T.; Rohr, J.; Beale, J.; Schwenen, L. *J. Antibiot*. **1990**, 43, 492. (b) Structure Revision: Weber, S.; Zolke, C.; Rohr, J.; Beale, J. *J. Org. Chem.* **1994**, *59*, 4211.

(5) Personal communication. Dr. Anthony B. Mauger, Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD.

(6) Unpublished results of Professor Kenneth Ramos and Dr. Robert Crow, Texas A&M Univeristy, Departments of Chemistry and Veterinary Physiology and Pharmacology.

(7) The cytostatic activity of landomycins A−E is reported to be dependent on the length of the oligosaccharide side-chain. See: Rohr, J.; Wohlert, S.-E.; Oelkers, C.; Kirschning, A.; Ries, M. *J. Chem. Soc., Chem. Commun*. **1997**, 973.

(8) For a review of O-glycosylation methods, see: Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.

(9) (a) Falahatpisheh, N.; Sulikowski, G. A. *Synlett* **1994**, 672. (b) Sobti, K.; Kim, K.; Sulikowski, G. A. *J. Org. Chem*. **1996**, *61*, 6.

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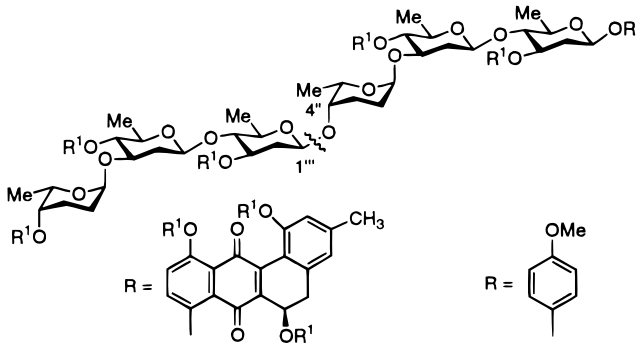
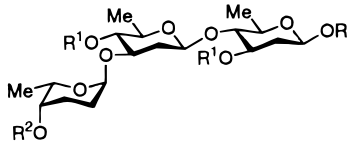
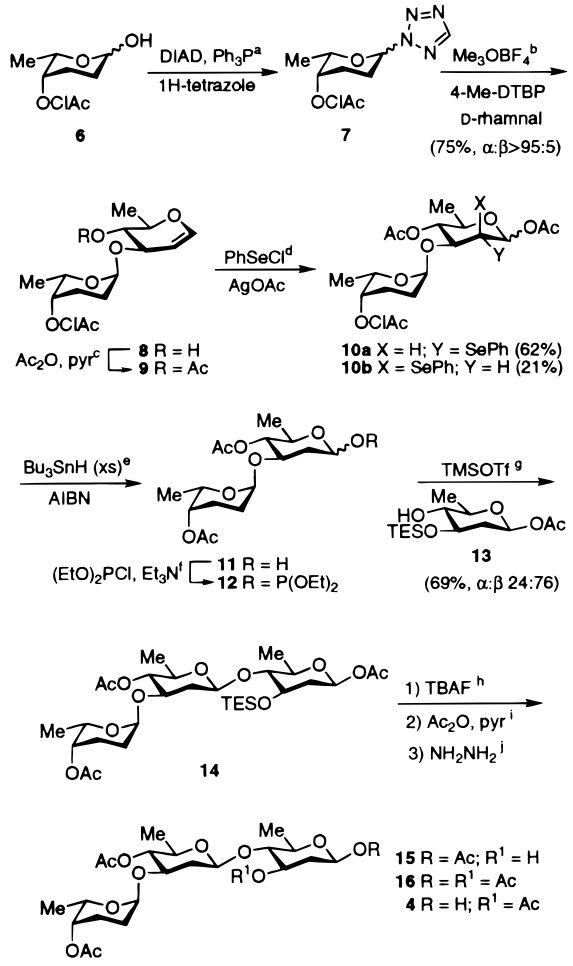




glycosides as the major isomer.[12] Herein we illustrate through the described synthesis of **3** the combined utility of glycosyl tetrazoles and phosphites in the stereocontrolled assembly of deoxygenated oligosaccharides.

Glycosyl tetrazole **7** was obtained by the Mitsunobu reaction of L-rhodinose derivative **6** and 1*H*-tetrazole (Scheme 1).[13,14] Next, glycosyl tetrazole **7** was coupled with D-rhamnal using Me_3OBF_4 as an activating agent and propionitrile as the solvent. Under these conditions a single disaccharide **8** was obtained in 75% yield. Notably, in this coupling reaction no O(4) glycosylation was observed.[15] Acetylation of **8** afforded glycal **9** which was converted to the phenylselenyl acetates **10a** and **10b**. Following a series of failed attempts to engage **10a** (and other derivatives) in a β selective glycosylation we turned our attention to the use of the corresponding 2-deoxy glycosyl phosphite as a β selective glycosyl donor.[12a] To implement this strategy, we initially planned a two-step sequence to remove the phenylselenyl group and anomeric acetate separately. However, when **10a** (or **10b**) was subjected to an excess of tributyltin hydride (with catalytic AIBN), we found the phenylselenyl group and *anomeric acetate* had been removed as well as the choroacetate reduced. Though the mechanism of the process

Scheme 1[a]



[a] (a) THF, 0−20 °C, 70%. (b) C_2H_5CN, 4 Å molecular sieves, −78 to 20 °C, 75%. (c) DMAP, CH_2Cl_2, 20 °C, 91%. (d) $PhCH_3$, 0−20 °C, 83%. (e) $PhCH_3$, reflux, 80%. (f) CH_2Cl_2, −78 °C, 76%. (g) $PhCH_3$, −94 °C, 5 min, 69%. (h) THF, 0 °C, 92%. (i) DMAP, CH_2Cl_2, 20 °C, 93%. (j) MeOH, 20 °C, 78%.

leading to the loss of the anomeric acetate requires further investigation, we were pleased to discover a direct preparation of lactol **11** without the loss of other acetate protecting groups.[16] Disaccharide **11** was converted to glycosyl phosphite **12** in 76% yield.[17] The stage was now set for the crucial coupling between **12** and **13**. In the event, coupling of **12** with acceptor **13** at −94 °C in toluene (cat. TMSOTf) furnished trisaccharide **14** in 69% yield with good β selectivity (α:β 24:76). Following exchange of the C3 silyl ether for an acetate group, the anomeric acetate of trisaccharide **16** was removed by hydrazinolysis to afford **4** in 78% yield.[18]

Having completed the assembly of donor trisaccharide **4**, we next turned our attention to the assembly of acceptor trisaccharide **5**. Roush has illustrated the utility of an equatorially disposed C(2) phenylselenide for the stereocontrolled introduction of a β-arylglycoside using the Mitsunobu protocol.[19] With this in mind we prepared selenide **19**, which was coupled with

(10) (a) Roush, W. R.; Sebesta, D. P.; Bennett, C. E. *Tetrahedron* **1997**, *53*, 8825 and references cited within. (b) Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837 and references cited within. (c) Ramesh, S.; Kaila, N.; Gewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5 and references cited within.

(11) (a) Garegg, P. J.; Ossowski, P. *Acta Chem. Scand., Ser. B* **1983**, *B 37*, 249. (b) Garegg, P. J.; Kopper, S.; Ossowski, P.; Thiem, J. *J. Carbohydr. Chem.* **1986**, *5*, 59. (c) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300. (d) Crich, D.; Ritchie, T. *J. Chem. Soc., Chem. Commun.* **1988**, 1461. (e) Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716. (f) Binkley, R.; Sivik, M. R. *J. Carbohydr. Chem.* **1991**, 10, 399. (g) Marzabadi, C. H.; Franck, R. W. *J. Chem. Soc., Chem. Commun.* **1996**, 2651.

(12) (a) Hashimoto, S.; Sano, A.; Sakamoto, H.; Nakajima, M.; Yanagiya, Y. Ikegabi. S. *Synlett* **1995**, 1271. (b) Peterson, I.; Mcleod, M. *Tetrahedron Lett.* **1995**, *36*, 9065.

(13) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Organic Prepr. and Proced.* **1996**, *28*, 127.

(14) The corresponding N1 isomer of **7** was produced as a minor component contaminated with triphenylphosphine oxide. This material was not utilized in the subsequent coupling reaction.

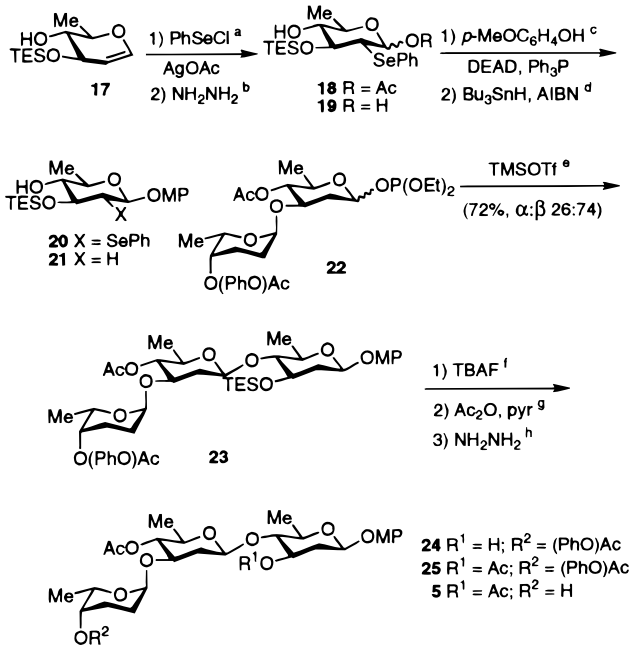
(15) Danishefsky, S. J.; Koseki, K.; Griffith, D. A.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Oriyama, T. *J. Am. Chem. Soc.* **1992**, *114*, 8331.

(16) The reduction of the anomeric acetate proceeds at a slower rate relative to reduction of the C(4′) chloroacetate and C(2) phenylselenide. Also, additional AIBN is required for removal of the anomeric acetate.

(17) The ratio of anomeric phosphites was determined by 121.4 MHz ^{31}P NMR using 85% H_3PO_4 as an internal standard. **12**: 66:34 (α/β) δ = 110.2 and δ = 109.0; **22**: 57:43 (α/β) δ = 140.0 and δ = 138.9; **27**: 58: 42 (α/β) δ = 147.5 and δ = 146.0.

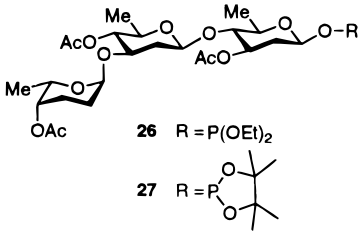
(18) Exoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368.

Scheme 2[a]



[a] (a) $PhCH_3$, 0−20 °C, 85%. (b) MeOH, 20 °C, 74%. (c) $PhCH_3$, 4 Å molecular sieves, 0 °C, 77%. (d) PhH, reflux, 77%. (e) $PhCH_3$, −94 °C, 5 min, 72%. (f) THF, 0 °C, 85%. (g) DMAP, CH_2Cl_2, 20 °C, 90%. (h) MeOH, 20 °C, 72%.

p-methoxyphenol using Mitsunobu reaction conditions to provide **20** with very good β selectivity (α:β 1:10). Reductive removal of the C(2) phenylselenide afforded **21**, which was coupled with glycosyl phosphite **22**[17,20] (prepared starting from the C(4) phenoxyacetate derivative of L-rhodinose). The coupling of **21** and **22** proceeded in 72% yield and with β selectivity (α:β 26:74). Following exchange of the O(3) triethylsilyl group for an acetyl, removal of the O(4″) phenoxyacetyl group afforded trisaccharide **5**.[21]



In our synthetic scheme, the β selective coupling of trisaccharides **4** and **5** depended on derivatization of the former as a glycosyl phosphite. Attempts to prepare the corresponding diethyl phosphite (**26**) proved unworkable presumably due to its hydrolytic instability. However, the corresponding pinacol phosphite **27** was isolable (67% yield) and was observable by ^{31}P NMR.[17] The utility of **27** was demonstrated in the glycosylation of the C(4″) hydroxyl group of acceptor **5** to afford hexasaccharide **3** along with the corresponding α isomer (α:β 52:48, 42% yield). Importantly, the derived spectroscopic data of **3** (^1H and ^{13}C NMR) were found to correlate well in all

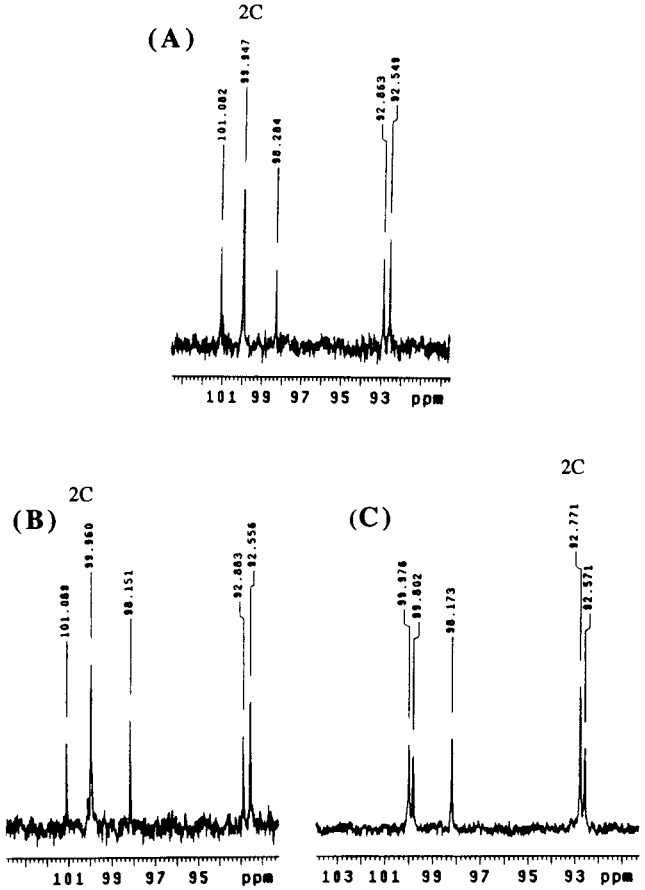


Figure 1. Partial ^{13}C NMR (75 MHz, $CDCl_3$) spectra for landomycin A octaacetate (**2**), hexasaccharide pentaacetate **3**, and hexasaccharide pentaacetate α-**3** in the anomeric carbon region: (A) landomycin A octaacetate (**2**), (B) hexasaccharide pentaacetate **3**, and (C) hexasaccharide pentaacetate α-**3**.

pertinent respects with landomycin A octaacetate (**2**).[22] *Particularly supportive of the assigned structures were the essentially superimposable signals corresponding to the anomeric carbons within the ^{13}C NMR spectrum of hexasaccharide **3** and landomycin A octaacetate (**2**) (Figure 1*).

In conclusion, we have described the synthesis of the hexasaccharide fragment of landomycin A (**3**) using a combination of the glycosyl tetrazole and glycosyl phosphite glycosylation protocols. Currently, we are comparing the biological activity hexasaccharide **3** to landomcyin A as well as continuing the total synthesis of landomcyin A itself.

Experimental Section

General Methods. All reactions were carried out under a nitrogen or argon atmosphere using dry glassware which had been flame-dried under a stream of nitrogen, unless otherwise noted. All necessary solvents were purified prior to use. Tetrahydrofuran and ethyl ether were distilled from sodium/benzophenone; dichloromethane and benzene were distilled from calcium hydride. Pyridine and triethylamine were distilled from calcium hydride and stored over sodium hydroxide. Toluene was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde stain followed by charring on a hot-plate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectro-

(19) (a) Roush, R.; Lin, X.-F. *Tetrahedron Lett*. **1993**, *34*, 6829. (b) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc*. **1995**, *117*, 2236 and references cited within.

(20) In contrast to the reduction of chloroacetate **10** to acetate **11**, the phenoxyacetate was unaffected upon exposure to an excess of tributyltinhydride (cat AIBN, refluxing toluene).

(21) Kocienski, P. *Protecting Groups*; Thieme, New York, 1994; p 24.

(22) We thank Professor Jurgen Rohr (Universitat Gottingen) for kindly providing a sample of landomycin A octaacetate.

scopically pure compounds unless otherwise stated. Melting points are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Varian-200, -300, and -400 spectrometers at ambient temperature. ^{1}H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane. Infrared spectra were recorded on Mattson Galaxy Series FT-IR 5000 or FT-IR 6021 spectrometers. Optical rotations were measured on a Jasco DIP-181 digital polarimeter at ambient temperature. High-performance liquid chromatography (HPLC) was performed with a Rainin sytem. The HPLC system was equipped with a Dynamax method manager, Rainin HPXL solvent delivery system, a Rheodyne injector, and a Dynamax model UV-1 variable-wavelength UV detector. The column measured 21.4 mm × 25 cm with 8-mm, 60 Å normal-phase packing. High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center on a VG Analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer.

Disaccharide 8. Diisopropyl azodicarboxylate (1.44 mL, 7.35 mmol) was added dropwise to a solution of lactol **6** (930 mg, 4.45 mmol), triphenylphosphine (1.93 g, 7.35 mmol), and 1*H*-tetrazole (421 mg, 6.02 mmol) in 20 mL of THF at 0 °C. The resulting mixture was stirred for 75 min at 0 °C and concentrated. Flash chromatography (gradient: 6:1 to 3:1 hexanes−ethyl acetate) of the residue furnished 2.05 g (∼65%) of glycosyl tetrazole **7** contaminated with diethyl hydrazinedicarboxylate**.** This mixture was used in the next reaction without further purification. A sample of α-**7** exhibited the following characteristics: $[\alpha]^{25}_D$ −25.5° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 1730, 1450, 1369, 1284, 1130 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 6.43 (d, J = 4.2 Hz, 1H), 5.05 (br s, 1H), 4.19 (s, 2H), 3.92 (dq, J = 1.5, 6.3 Hz, 1H), 2.70−2.05 (complex m, 4H), 1.16 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9, 152.6, 85.7, 70.3, 68.5, 40.8, 23.0, 21.6, 16.9.

To a solution of tetrazole **7** (∼2.90 mmol) and D-rhamnal (390 mg, 3.00 mmol) in 25 mL of propionitrile were added powered 4 Å mol sieves (ca. 500 mg) and 2,6-di-*tert*-4-methylpyridine (615 mg, 3.00 mmol). The mixture was stirred at room temperature for 30 min and cooled to −78 °C, and trimethyloxomium tetrafluroborate (799 mg, 5.40 mmol) was added. The reaction mixture was allowed to gradually warm to 15 °C (6 h), quenched with solid sodium bicarbonate (ca. 1 g), and filtered through a plug of Celite. The filtrate was concentrated, and the residue purified by flash chromatography (6:1 hexanes−ethyl acetate) to afford 622 mg (67%) of **8** as a white solid: mp 104−105 °C; $[\alpha]^{25}_D$ −91.6° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 3418, 1741, 1655, 1160 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.37 (dd, J = 7.0, 1.6 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 4.95 (d, J = 1.2 Hz, 1H), 4.66 (dd, J = 6.1, 2.1 Hz, 1H), 4.50 (d, J = 2.0 Hz, 1H), 4.29 (dq, J = 1.3, 6.4 Hz, 1H), 4.15 (s, 2H), 4.10 (dt, J = 6.9, 1.6 Hz, 1H), 3.86 (dq, J = 9.9, 6.4 Hz, 1H), 3.41 (ddd, J = 9.9, 6.9, 1.9 Hz, 1H), 2.25−1.55 (complex m, 4H), 1.42 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.0, 145.2, 100.9, 98.1, 80.9 74.4, 73.1, 71.4, 66.2, 40.9, 24.5, 22.6, 17.4, 17.0; HRMS(FAB) *m*/*z* 343.0914 [(M + Na)$^+$, calcd for $C_{14}H_{21}O_6NaCl$ 343.0924].

Acetate 9. To a solution of disaccharide **8** (336 mg, 1.05 mmol) in 5 mL of dichloromethane and 1.2 mL of pyridine cooled to 0 °C was added acetic anhydride (0.4 mL, 4.19 mmol) followed by a catalytic amount (ca. 5 mg) of 4-(dimethylamino)pyridine. The resulting mixture was stirred at room temperature for 5 h, diluted with dichloromethane (25 mL), and sequentially washed with 20% aqueous $CuSO_4$ solution (2 × 15 mL), water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (5:1 hexanes−ethyl acetate) to afford 345 mg (91%) of **9** as a white solid: $[\alpha]^{25}_D$ −91.6° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 3025, 2928, 1737, 1644, 1232, 1124 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (d, J = 6.2 Hz, 1H), 4.97 (br s, 1H), 4.94 (m, 1H), 4.80 (m, overlapping signals, 2H), 4.18 (m, 1H), 4.07 (s, 2H), 4.00 (m, 2H), 2.03 (s, 3H), 2.00−1.41 (complex m, 4H), 1.24 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 167.0, 144.7, 94.4, 93.7, 72.7, 72.4, 71.6, 68.7, 65.0, 40.9, 24.0, 22.5, 10.9, 16.9, 16.5; HRMS(FAB) *m*/*z* 385.1040 [(M + Na)$^+$, calcd for $C_{16}H_{23}O_7$-NaCl 385.1030].

Selenide 10. To a solution of disaccharide **9** (109 mg, 0.30 mmol) in 3 mL of toluene at 0 °C was added phenylselenenyl chloride (86 mg, 0.45 mmol). After stirring at 0 °C for 30 min, silver carbonate (100 mg, 0.60 mmol) was added. The resulting mixture was stirred for 3.5 h and allowed to warm to room temperature. The mixture was filtered through a plug of Celite and concentrated. The residue was purified by flash chromatography (gradient elution: 6:1 to 3:1 hexanes−ethyl acetate) to furnish 106 mg (61%) of **10a** and 35 mg (20%) of **10b**, both amorphous solids. Selenide **10a** exhibited the following characteristics: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2H, arom), 7.26 (m, 3H, arom), 5.69 (d, J = 9.6 Hz, 1H), 5.15 (br s, 1H), 4.84 (br s, 1H), 4.80 (dd, J = 9.0, 9.0 Hz, 1H), 4.10 (s superimposed m, 3H), 3.65 (dd, J = 10.8, 8.7 Hz, 1H), 3.60 (dq, J = 9.6, 6.3 Hz, 1H), 3.25 (dd, J = 10.8, 9.9 Hz, 1H), 2.07 (s, 3H), 1.89 (s, 3H), 2.05−1.69 (m, 4H), 1.15 (d, J = 6.0 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H); HRMS(FAB) *m*/*z* 601.0707 [(M + Na)$^+$, calcd for $C_{24}H_{31}O_9NaSeCl$ 601.0719].

Lactol 11. To a solution of selenide **10a** (550 mg, 0.99 mmol) in 15 mL of toluene was added tributyltin hydride (1.60 mL, 5.94 mmol) followed by a catalytic amount of AIBN (ca. 5 mg). The mixture was refluxed for 12 h with additional AIBN (ca. 5 mg) added every 3 h. After cooling to room temperature, the reaction mixture was concentrated, and the residue purified by flash chromatography (1:1 hexanes−ethyl acetate) to afford 277 mg (81%) of lactol **11** as an amorphous solid: IR ($CHCl_3$) 3427, 1738, 1442, 1376, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (br s), 4.92 (br s), 4.89 (br s), 4.72 (br s), 4.67 (m), 4.19−4.61 (m), 3.43 (superimposed m), 2.18 (m), 2.11 (m), 2.07 (s), 2.06 (s), 2.01 (s), 2.00 (s) 1.16 (d, J = 6.0 Hz), 1.11 (d, J = 6.3 Hz), 1.05 (d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.8, 170.0, 169.8, 93.7, 92.9, 92.5, 91.5, 77.2, 75.7, 74.9, 71.1, 70.2, 69.3, 69.2, 69.1, 65.8, 65.0; HRMS(FAB) *m*/*z* 369.1548 [(M + Na)$^+$, calcd for $C_{16}H_{26}NaO_8$ 369.1525].

Trisaccharide 14. Glycosyl phosphite **12** (220 mg, 0.49 mmol) and glycosyl acceptor **13** (164 mg, 0.54 mmol) were concentrated from benzene (3 × 5 mL). Anhydrous toluene (5 mL) was introduced, and the resultant solution cooled to −94 °C. TMSOTf (10 μL of 0.5 M solution in dichloromethane, 0.005 mmol) was added to the solution, and the mixture was stirred for 5 min and quenched with triethylamine (0.5 mL). The resulting mixture was allowed to warm to 0 °C and poured into a mixture of ethyl acetate and saturated aqueous $NaHCO_3$ (4:1, 50 mL). The aqueous layer was extracted with ethyl acetate (3 × 40 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (gradient elution, 6:1 to 4:1 hexane/ethyl acetate) to afford 161 mg (51%) of trisaccharide **14** and 55 mg (18%) of the corresponding α isomer, both amorphous solids. Trisaccharide **14** exhibited the following characteristics: $[\alpha]^{25}_D$ −12.9° (*c* 0.92, $CHCl_3$); IR(CHCl3) 3019, 2960, 1741, 1375, 1217, 1041; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (dd, J = 9.6, 2.1 Hz, 1H), 4.95 (br s, 1H), 4.77 (br s, 1H), 4.66 (app t, J = 9.6 Hz, 1H), 4.63 (dd, J = 9.6, 1.5 Hz, 1H), 3.92 (dq, J = 0.9, 6.6 Hz, 1H), 3.74 (m, 2H), 3.37 (m, 2H), 3.15 (app t, J = 8.7 Hz, 1H), 2.35 (m, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.92−1.41 (complex m, 7H), 1.27 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.60 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.7, 169.1, 99.4, 92.5, 91.4, 82.1, 75.0, 72.1, 71.1, 70.2, 70.1, 69.1, 65.0, 39.0, 35.5, 23.9, 22.7, 22.6, 21.0, 20.9, 18.3, 17.7, 17.0, 6.7, 4.8; HRMS (FAB) *m*/*z* 655.3133 [(M + Na)$^+$, calcd for $C_{30}H_{52}O_{12}NaSi$: 655.3126].

Characterization data for trisaccharide α-14: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (dd, J = 9.9, 1.8 Hz, 1H), 5.42 (d, J = 3.0 Hz, 1H), 4.89 (br s, 1H), 4.75 (br s, 1H), 4.68 (t, J = 9.3 Hz, 1H), 3.95 (m, overlapping signals, 2H), 3.83 (m, overlapping signals, 2H), 3.40 (dd, J = 9.0 Hz, 6.0 Hz, 1H), 3.15 (app t, J = 8.4 Hz, 1H), 2.22 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.99−1.58 (complex m, 7H), 1.30 (d, J = 6.0 Hz, 3H), 1.12 (d, J = 6.0 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 0.93 (t, J = 7.8 Hz, 9H), 0.57 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.9, 169.2, 98.0, 93.2, 91.3, 81.3, 75.5, 73.0, 71.5, 69.6, 69.3, 66.4, 65.0, 39.2, 34.5, 24.3, 22.7, 21.1, 21.0, 20.9, 18.5, 17.4, 17.0, 6.8, 5.1; HRMS (FAB) *m*/*z* 655.3123 [(M + Na)$^+$, calcd for $C_{30}H_{52}O_{12}NaSi$: 655.3126].

Alcohol 15. To a solution of trisaccharide **14** (266 mg, 0.42 mmol) in 4 mL of THF at 0 °C was added TBAF (0.84 mL of 1 M solution in THF, 0.84 mmol). After 5 min, the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with

ethyl acetate (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1.5:1 hexanes−ethyl acetate) to furnish 196 mg (91%) of **15** as an amorphous solid: $[\alpha]^{25}_D$ −70.9° (*c* 0.96, $CHCl_3$); IR (CHCl3) 3457, 2938, 1737, 1371, 1244, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (dd, J = 10.2, 2.1 Hz, 1H), 4.90 (br s, 1H), 4.70 (br s, 1H), 4.66 (app t, J = 9.6 Hz, 1H), 4.46 (dd, J = 9.9, 2.1 Hz, 1H), 4.40 (s, 1H, −OH), 3.87 (dq, J = 1.2, 6.6 Hz, 1H), 3.76 (m, 1H), 3.60 (m, 1H), 3.46 (dq, J = 9.9, 6.6 Hz, 1H), 3.38 (dq, J = 9.0, 6.0 Hz, 1H), 2.93 (app t, J = 8.7 Hz, 1H), 2.35 (m, 1H), 2.15 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.90−1.38 (complex m, 6H), 1.20 (d, J = 6.3 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 169.5, 169.0, 100.6, 92.5, 91.4, 87.9, 74.2, 71.0, 70.6, 70.4, 69.0, 65.0, 36.6, 35.4, 23.8, 22.5, 20.9, 20.9, 20.8, 17.5, 17.3, 16.9; HRMS (FAB) *m*/*z* 541.2266 [(M + Na)$^+$, calcd for $C_{24}H_{38}NaO_{12}$ 541.2261].

Tetraacetate 16. To a solution of trisaccharide **15** (215 mg, 0.41 mmol) in 4 mL of dichloromethane and 1.2 mL of pyridine was added acetic anhydride (150 μL, 1.60 mmol) followed by a catalytic amount (ca. 5 mg) of 4-(dimethylamino)pyridine. The resulting mixture was stirred at room temperature for 5 h, diluted with dichloromethane (50 mL), and sequentially washed with 20% aqueous $CuSO_4$ solution (2 × 15 mL), water (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (4:1 hexanes−ethyl acetate) to afford 214 mg (92%) of tetraacetate **16** as an amorphous solid: $[\alpha]^{25}_D$ −46.9° (*c* 1.12, $CHCl_3$) IR ($CHCl_3$) 3019, 2936, 1734, 1373, 1748, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (dd, J = 9.9, 2.1 Hz, 1H), 4.98 (m, 1H), 4.86 (br s, 1H), 4.70 (br s, 1H), 4.59 (app t, J = 9.6 Hz, 1H), 4.43 (dd, J = 9.6, 1.8 Hz, 1H), 3.86 (q, J = 6.6 Hz, 1H), 3.57 (m, 1H), 3.47 (m, 1H), 3.34−3.22 (overlapping signals, 2H), 2.20 (m, 2H), 2.04 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H) 1.32−1.18 (complex m, 6H), 1.23 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.8, 169.7, 168.8, 99.7, 92.5, 91.0, 81.1, 74.8, 71.9, 70.9, 69.8, 69.0, 64.9, 35.6, 35.1, 23.8, 22.5, 21.1, 20.9, 20.8, 20.8, 17.8, 17.7, 16.9; HRMS (FAB) *m*/*z* 583.2397 [(M + Na)$^+$, calcd for $C_{26}H_{40}NaO_{13}$ 583.2367].

Trisaccharide 4. To a solution of trisaccharide **16** (76 mg, 0.14 mmol) in 1.2 mL of methanol at 0 °C was added anhydrous hydrazine (1.2 mL of a 0.19 M solution in methanol, 0.23 mmol). The reaction mixture was stirred at 0 °C for 3.5 h and quenched with 20% $CuSO_4$ (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed sequentially with water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (gradient elution: 2:1 to 1:1 hexanes−ethyl acetate) to afford 50 mg (69%) of lactol **4** as an amorphous solid plus recovered starting material (9 mg, 12%). Trisaccharide **4** exhibited the following characteristics: $[\alpha]^{25}_D$ −20.4° (*c* 0.37, $CHCl_3$); IR (CHCl3) 1738, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.34 (m), 5.30 (br s), 4.99 (m), 4.96 (br s) 4.79 (br s) 4.68 (app t, J = 9.6 Hz), 4.51 (d, J = 9.9 Hz), 4.06−3.92 (m), 3.83−3.74 (m), 3.47−3.27 (m), 3.09 (br s −OH), 2.35−1.45 (m), 2.12 (s), 2.06 (s), 2.05 (s), 2.04 (s), 1.30 (d, J = 6.0 Hz), 1.25 (d, J = 7.5 Hz), 1.21 (d, J = 6.3 Hz), 1.11 (d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.1, 169.8, 99.9, 93.5, 92.5, 91.3, 82.4, 81.5, 75.0 74.9, 71.2, 71.1, 71.0, 70.3, 70.0, 69.2, 68.5, 68.8, 65.0, 37.9, 35.7, 35.5, 23.9, 22.7, 21.4, 21.3, 21.0, 20.9, 18.0, 17.8, 17.0; HRMS(FAB) *m*/*z* 541.2274 [(M + Na)$^+$, calcd for $C_{24}H_{38}NaO_{12}$ 541.2261].

Trisaccharide 23. Glycosyl phosphite **22** (108 mg, 0.19 mmol) and glycosyl acceptor **21** (78 mg, 0.21 mmol) were concentrated from benzene (3 × 5 mL). Anhydrous toluene (1.5 mL) was introduced, and the resultant solution cooled to −94 °C. TMSOTf (8 μL of 0.5 M solution in dichloromethane, 0.004 mmol) was added to the solution, and the mixture was stirred for 5 min and quenched with triethylamine (0.5 mL). The resulting mixture was allowed to warm to 0 °C and poured into a mixture of ethyl acetate and saturated aqueous $NaHCO_3$ (4:1, 10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (gradient elution, 8:1 to 5:1 hexane/ethyl acetate) to afford 82 mg (54%) of trisaccharide **23** and 27 mg (18%) of the corresponding α isomer, both amorphous solids. Trisaccharide **23** exhibited the following characteristics: $[\alpha]^{25}_D$ −53.2° (*c* 0.99, $CHCl_3$); IR (CHCl3) 3016, 2872, 1745, 1600, 1508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 7.5 Hz, 2H, arom), 7.01−6.90 (m, 5H, arom), 6.80 (d, J = 9.3 Hz, 2H, arom), 4.95 (overlapping signals, 3H), 4.70 (overlapping signals, 4H), 3.98 (q, J = 6.3 Hz, 1H), 3.79 (s superimposed m, 5H), 3.40 (m, 2H), 3.22 (app t, J = 8.7 Hz, 1H), 2.27 (m, 2H), 2.06 (s, 3H), 1.99−1.41 (m, 6H), 1.34 (d, J = 6.0 Hz, 3H), 1.23 (d, J = 6.0 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H), 0.99 (t, J = 7.8 Hz, 9H), 0.66 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 168.6, 157.6, 154.8, 151.1, 129.4, 121.6, 117.6, 114.5, 114.3, 99.4, 98.0, 92.5, 82.4, 75.0, 71.3, 71.2, 70.7, 70.4, 70.3, 65.1, 64.8, 55.5, 40.4, 35.6, 23.8, 22.6, 18.4, 17.6, 16.9, 6.8, 4.8; HRMS (FAB) *m*/*z* 811.3729 [(M + Na)$^+$, calcd for $C_{41}H_{60}NaO_{13}Si$: 811.3701].

Characterization data for trisaccharide α-23: ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 7.5 Hz, 2H, arom), 7.03−6.80 (m, 7H, arom), 5.51 (d, J = 1.8 Hz, 1H), 4.99 (d, 9.6 Hz, 1H), 4.94(br s, 2H), 4.74 (overlapping signals, 4H), 4.05 (overlapping signals, 3H), 3.80 (s 3H), 3.38 (m, 2H), 2.27 (m, 2H), 2.10 (s, 3H), 1.99−1.41 (m, 6H), 1.39 (d, J = 6.0 Hz, 3H), 1.09 (d, J = 6.0 Hz, 3H), 1.06 (d, J = 6.6 Hz, 3H), 0.99 (t, J = 7.5 Hz, 9H), 0.66 (q, J = 7.5 Hz, 6H).

Alcohol 24. To a solution of trisaccharide **23** (260.0 mg, 0.33 mmol) in 4 mL of THF at 0 °C was added TBAF (0.7 mL of 1 M solution in THF, 0.70 mmol). After 5 min, the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1.5:1 hexanes−ethyl acetate) to furnish 193 mg (86%) of **24** as an amorphous solid: $[\alpha]^{25}_D$ −72.4° (*c* 0.89, $CHCl_3$); IR (CHCl3) 2976, 1737, 1378, 1240, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 2H, arom), 6.96−6.91 (overlapping signals, 7H, arom), 5.02 (dd, J = 9.6, 1.5 Hz, 1H), 4.96 (br s, 1H), 4.91 (br s, 1H), 4.75 (app t, J = 9.3 Hz, 1H), 4.71 (s, 2H), 4.54 (d, J = 10.5 Hz, 1H), 4.52 (br s, 1H), 3.97 (q, J = 6.9 Hz, 1H), 3.84 (m, 1H), 3.76 (s, 3H), 3.70 (m, 1H), 3.55 (dq, J = 9.6, 6.0 Hz, 1H), 3.45 (dq, J = 9.3, 6.3 Hz, 1H), 3.06 (app t, J = 8.7 Hz, 1H), 2.22 (m, 2H), 2.07 (s, 3H), 2.00−1.42 (m, 6H), 1.32 (d, J = 6.0 Hz, 3H), 1.26 (d, J = 6.0 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 168.6, 157.5, 154.8, 150.9, 129.4, 121.6, 117.7, 114.4, 114.3, 100.6, 98.2, 92.5, 88.3, 74.2, 70.7, 70.4, 70.3, 69.2, 65.0, 64.8, 55.4, 37.9, 35.5, 23.7, 22.6, 20.8, 17.7, 17.3, 16.8; HRMS (FAB) *m*/*z* 697.2841 [(M + Na)$^+$, calcd for $C_{35}H_{46}NaO_{13}$ 697.2836]. $[\alpha]^{25}_D$ −53.5° (*c* 0.74, $CHCl_3$); IR (CHCl3) 2931, 1741, 1509, 1219, 1046; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.22 (m, 2H, arom), 7.05−6.84 (complex m, 7H, arom), 5.06 (m, 1H), 5.02 (dd, J = 9.3, 1.8 Hz, 1H), 4.94 (br s, 1H), 4.93 (br s, 1H), 4.71 (s, 2H), 4.68 (app t, J = 9.3 Hz, 1H), 4.52 (dd, J = 9.9, 1.5 Hz, 1H), 3.97 (q, J = 6.6 Hz, 1H), 3.79 (m, 1H), 3.77 (s, 3H), 3.49 (m, 1H), 3.39 (overlapping signals, 2H), 2.45−2.25 (m, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 2.00−1.40 (complex m, 6H), 1.34 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8, 168.7, 157.7, 155.1, 150.9, 129.5, 121.8, 118.1, 114.5, 114.4, 99.9, 98.1, 92.5, 81.5, 74.9, 71.2, 71.1, 70.4, 70.3, 70.1, 65.1, 64.9, 55.6, 36.5, 35.8, 23.8, 22.7, 21.3, 21.0, 18.1, 17.8, 17.0; HRMS (FAB) *m*/*z* 697.2841 [(M + Na)$^+$, calcd for $C_{37}H_{48}NaO_{14}$ 697.2836].

Diacetate 25. To a solution of trisaccharide **24** (215 mg, 0.41 mmol) in 2.8 mL of dichloromethane and 0.7 mL of pyridine was added acetic anhydride (150 μL, 1.60 mmol) followed by a catalytic amount (ca. 5 mg) of 4-(dimethylamino)pyridine. The resulting mixture was stirred at room temperature for 5 h, diluted with dichloromethane (50 mL), and sequentially washed with 20% aqueous $CuSO_4$ solution (2 × 15 mL), water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (4:1 hexanes−ethyl acetate) to afford 214 mg (92%) of **25** as an amorphous solid: $[\alpha]^{25}_D$ −53.5° (*c* 0.74, $CHCl_3$); IR (CHCl3) 2931, 1741, 1509, 1219, 1046; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.22 (m, 2H, arom), 7.05−6.84 (complex m, 7H, arom), 5.06 (m, 1H), 5.02 (dd, J = 9.3, 1.8 Hz, 1H), 4.94 (br s, 1H), 4.93 (br s, 1H), 4.71 (s, 2H), 4.68 (app t, J = 9.3 Hz, 1H), 4.52 (dd, J = 9.9, 1.5 Hz, 1H), 3.97 (q, J = 6.6 Hz, 1H), 3.79 (m, 1H), 3.77 (s, 3H), 3.49 (m, 1H), 3.39 (overlapping signals, 2H), 2.45−2.25 (m, 2H), 2.07 (s, 3H), 2.06

(s, 3H), 2.00−1.40 (complex m, 6H), 1.34 (d, J = 6.3 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H), 1.09 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.8, 168.7, 157.7, 155.1, 150.9, 129.5, 121.8, 118.1, 114.5, 114.4, 99.9, 98.1, 92.5, 81.5, 74.9, 71.2, 71.1, 70.4, 70.3, 70.1, 65.1, 64.9, 55.6, 36.5, 35.8, 23.8, 22.7, 21.3, 21.0, 18.1, 17.8, 17.0; HRMS (FAB) m/z 739.2956 [(M + Na)$^+$, calcd for $C_{37}H_{48}NaO_{14}$ 739.2942].

Alcohol 5. To trisaccharide **25** (44.0 mg, 0.06 mmol) was added a methanol solution of anhydrous hydrazine (0.35 mL of a 0.29 M solution in methanol, 0.10 mmol). The reaction mixture was stirred at 0 °C for 4 h and concentrated. The residue was purified by flash chromatography (1:1 hexanes−ethyl acetate) to afford 26 mg (72%) of alcohol **5** as an amorphous solid: $[\alpha]^{25}_D$ −69.7° (*c* 1.29, $CHCl_3$); IR (CHCl3) 1742, 1505, 1216, 1051 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 5.07 (m, 1H), 5.02 (dd, J = 9.6, 2.1 Hz, 1H), 4.92 (br s, 1H), 4.69 (app t, J = 9.3 Hz, 1H), 4.53 (dd, J = 9.6, 1.8 Hz, 1H), 3.88 (q, J = 6.6 Hz, 1H), 3.84−3.75 (m, 1H), 3.77 (s, 3H), 3.55 (br s, 1H, −OH), 3.52 (m, 1H), 3.40 (superimposed m, 2H), 2.36 (m, 2H), 2.07 (s, 3H), 2.06 (s, 3H), 1.42−1.95 (m, 6H), 1.35 (d, J = 6.3 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H), 1.19 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 169.9, 155.1, 150.9, 118.1, 114.4, 99.9, 98.1, 92.8, 81.5, 74.9, 71.2, 71.0, 70.3, 70.1, 67.2, 66.3, 55.6, 36.5, 35.8, 25.5, 23.3, 21.3, 20.9, 18.1, 17.8, 17.1; HRMS(FAB) m/z 605.2582 [(M + Na)$^+$, calcd for $C_{29}H_{42}NaO_{12}$: 605.2574].

Hexasaccharide 3. Glycosyl phosphite **27** (18 mg, 0.027 mmol) and glycosyl acceptor **5** (19 mg, 0.032 mmol) were concentrated from benzene (3 × 4 mL). Anhydrous toluene (0.8 mL) was introduced, and the resultant solution cooled to −94 °C. TMSOTf (2 μL of 0.5 M solution in dichloromethane, 0.001 mmol) was added to the solution, and the mixture was stirred for 5 min and quenched with triethylamine (0.5 mL). The resulting mixture was allowed to warm to 0 °C, passed through a plug of silica gel, and flushed with EtOAc (40 mL), and the filtrate was concentrated. The residue was purified by HPLC (65:35 hexanes−ethyl acetate, 5 mL/min) to afford 6.2 mg (21%) of hexasaccharide **3** and 6.7 mg (23%) of the corresponding α isomer, both amorphous solids. Hexasaccharide **3** exhibited the following characteristics: $[\alpha]^{25}_D$ −71.0° (*c* 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, J = 9.2 Hz, 2H, arom), 6.81 (d, J = 9.2 Hz, 2H, arom), 5.04 (m, 1H, 3a), 5.00 (dd, J = 12.0, 2.4 Hz, 1H, 1a), 4.95 (br s superimposed m, 2H, 1f, 3d), 4.91 (br s, 1H, 4f), 4.78 (br s, 1H, 1c), 4.67 (overlapping app t, J = 9.6, J = 9.6 Hz, 2H, 4b, 4e), 4.49 (overlapping signals, 3H, 1b, 1d, 1e), 3.95 (q, J = 6.0 Hz, 1H, 5f), 3.79 (s superimposed m, 6 H, −OMe, 3b, 5c, 3e), 3.49 (m, 1H, 5a), 3.42 (br s, 1H, 4c), 3.40−3.24 (complex m, 5H, 5b, 5d, 5e, 4a, 4d), 2.42 (ddd, J = 12.0, 5.1, 2.0 Hz, 1H), 2.22 (overlapping signals, 2H), 2.12 (s, 3H, −OAc), 2.06 (s, 3H, −OAc), 2.06 (s, 3H, −OAc), 2.05 (s, 3H, −OAc), 2.05 (s, 3H, −OAc), 1.95−1.42 (complex m, 13H), 1.33 (d, J = 6.0 Hz, 3H, −Me), 1.27 (d, J = 7.2 Hz, 3H, −Me), 1.21 (d, J = 6.4 Hz, 3H, −Me), 1.20 (d, J = 6.4 Hz, 3H, −Me), 1.13 (d, J = 6.4 Hz, 3H, −Me), 1.11 (d, J = 6.4 Hz, 3H, −Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.3, 170.1, 170.0, 169.8, 155.1, 150.9, 118.1, 114.5, 101.1, 100.0, 98.2, 92.9, 92.6, 81.7, 81.5, 78.4, 77.2, 75.1, 75.0, 71.3, 71.0, 70.7, 70.4, 70.1, 69.2, 66.1, 65.1, 60.4, 55.6, 36.7, 36.5, 35.8, 29.7, 24.5, 24.1, 24.0, 22.7, 21.3, 21.1, 21.0, 20.9, 18.1, 18.0, 17.8, 17.1, 17.0; HRMS(FAB) m/z 1105.4851, [(M + Na)$^+$, calcd for $C_{53}H_{78}NaO_{23}$: 1105.4830].

Characterization data for hexasaccharide α-3: $[\alpha]^{25}_D$ −55.3° (*c* 0.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 9.3 Hz, 2H, arom), 6.81 (d, J = 9.0 Hz, 2H, arom), 5.30 (m, 1H), 5.05 (m, 1H), 5.02 (dd, J = 9.3, 1.8 Hz, 1H), 4.96 (br s, 2H), 4.91 (br s, 1H), 4.68 (app t, J = 9.3 Hz, 1H), 4.67 (app t, J = 9.3 Hz, 1H), 4.53 (d, J = 8.1 Hz, 1H), 4.51 (d, J = 8.1 Hz, 1H), 4.00−3.75 (overlapping signals, 9H), 3.52−3.25 (complex m, 7H), 2.45−2.25 (complex m, 4H), 2.12 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.95−1.45 (complex m, 12H), 1.35 (d, J = 6.0 Hz, 3H), 1.25−1.20 (overlapping signals, 12H), 1.11 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.1, 170.0, 169.9, 169.8, 155.2, 151.0, 118.2, 114.5, 100.0, 99.8, 98.1, 92.8, 92.6, 82.4, 81.5, 77.2, 75.1, 75.0, 71.3, 71.1, 71.0, 70.4, 70.1, 69.6, 69.2, 68.8, 67.2, 66.4, 65.1, 55.6, 36.5, 36.0, 35.8, 35.5, 24.0, 23.6, 22.7, 21.4, 21.3, 21.1, 21.0, 20.9, 20.1, 18.1, 17.8, 17.6, 17.0; HRMS(FAB) m/z 1105.4869, [(M + Na)$^+$, calcd for $C_{53}H_{78}NaO_{23}$: 1105.4830].

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Supporting Information Available: Experimental procedure and characterization data for compounds **6**, **13**, **17**−**21**, and **22** (9 pages). See any current masthead page for ordering and Web access instructions.

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