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Synthesis of the Antigenic Tetrasaccharide Side Chain from the Major Glycoprotein of *Bacillus anthracis* Exosporium

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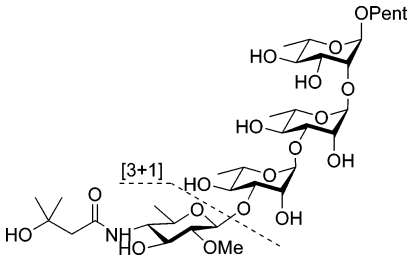

A synthesis of the pentenyl glycoside of the tetrasaccharide side chain from the major glycoprotein of *Bacillus anthracis* by a [3 + 1] approach is described. The construction of the 1,2-*trans*-glycosidic linkage in the terminal anthrose moiety was achieved through the application of known α-nitrilium ion-mediated *β*-selective glycosylation methodology. An iterative glycosylation strategy was used for the assembly of the trirhamnan building block. A new route to the anthrose saccharide was developed from D-galactose.

Introduction

Because of the recent uses of *Bacillus anthracis*, a Gram positive bacteria and the etiological agent of anthrax,[1,2] as a biological weapon, inexpensive, effective methods of detection and vaccination against this organism are highly desired. The similarity of the *B. anthracis* spore-cell-surface antigens with those of the opportunistic human pathogen *B. cereus* and other bacteria of this group complicates the design of reliable selective antibody-based detection systems. The spores of *Bacillus anthracis* are enclosed by a prominent loose fitting layer called the exosporium, which is the primary barrier of the spore and the source of the spore antigens,[3,4] and which interacts with the environment, detection devices, and spore-binding cells in the mammalian host and host defenses. The exosporium therefore plays an important role in the spore survival and/or pathogenesis. A highly immunogenic glycoprotein BclA, an important constituent of the exosporium, was found to be substituted with multiple copies of an O-linked oligosaccharide **1**,[5] which contains the previously unknown terminal substituent, 2-*O*-methyl-4-(3-hydroxy-3-methylbutylamino)-4,6-dideoxy-D-glucose. This sugar, which is also referred to as anthrose, appears to be specific for the spores of this bacteria, as it was not found in spores of either *Bacillus cereus* or *Bacillus thuringiensis*, the most phylogenetically similar species.[5] Thus, tetrasacchride **1** is a very attractive tool for the development of species-specific biomarkers, as well as of novel vaccines which target anthrax spores. In view of the fact that pure cell surface oligosaccharides are often difficult to obtain by isolation, effective synthetic approaches to the tetrasaccharide and its analogues are highly desirable.

Since its isolation in 2004,[5] the preparation of several synthetic tri-[6] and tetrasaccharide[7−10,11] analogues of **1** has been

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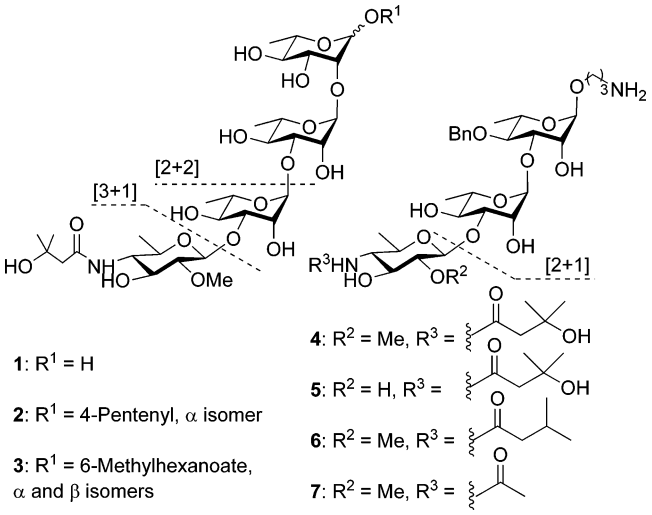
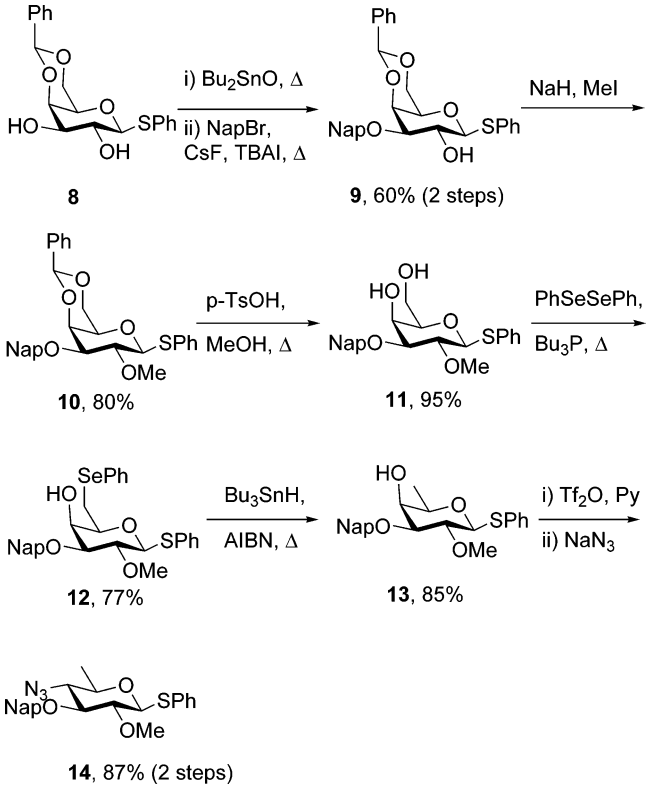


FIGURE 1. Literature approaches to the target.

reported in the literature (Figure 1). The first total synthesis described, that of the tetrasaccharide analogue **2**,[7] featured a terminal pentenyl group, which served as a convenient point of attachment to a carrier protein in vaccine development. In this first synthesis a convergent approach was utilized to facilitate access to analogues and shorter sequences, and assembly of the terminal anthrose was accomplished in a short, straightforward way starting from D-fucose. A different [3 + 1] tack was taken in the synthesis of **3**;[8−10] both a stepwise approach proceeding from the downstream toward the upstream end of the oligosaccharide[9,10,12] as well as sequential glycosylation with different types of glycosyl donors[8] were explored in the construction of the trirhamnan. In this second approach the terminal anthrose building block was synthesized by a more lengthy strategy from a 4-azido-4,6-dideoxy-D-mannose derivative.[13−16] A similar, [2 + 1] approach was taken for the synthesis of trisaccharide analogues **4**−**7**,[6] but in this case an azido deoxy galactose derivative[17] was used as precursor of the terminal anthrose unit.

Despite the different overall strategies, these syntheses have many points in common. First, glycosylation with neighboring group (bromoacetyl or levulinoyl) participation was used in the construction of the β-linkage to the terminal anthrose unit,[7−10] thereby necessitating subsequent removal of the protecting group at 2-position and then methylation.[18] Second, α-selectivity in the rhamnosylation reactions was achieved in all but one case by anchimeric assistance.[6,7] In all cases the synthesis of the anthrose building block required extensive protective group manipulations,[13−16] or an expensive starting material.[7] In planning our synthesis of **2** in a [3 + 1] manner, we wanted to address these problems through (a) application of known

SCHEME 1. Synthesis of the Anthrose Donor



α-nitrilium-mediated β-selective glycosylation[19,20] methodology for the construction of the 1,2-*trans* glycosidic linkage in the terminal anthrose moiety; (b) the straightforward assembly of the rhamnan building block through the recently developed iterative glycosylation strategy[21] using thiorhamnoside donors, known to give good α-selectivity without neighboring group participation; and (c) developing a new, shorter route to the anthrose saccharide, utilizing inexpensive D-galactose as a precursor.

Results and Discussion

We began our synthesis of the anthrose monosaccharide building block with the galactose derivative **8**, which is readily available from D-galactose in four steps (Scheme 1).[22] Regioselective installation of a 2-naphthylmethyl (Nap)[23−25] group at the 3-position through the intermediacy of a tin acetal,[26,27] followed by methylation, gave **10**. Deprotection in acidic media, followed by regioselective substitution of the primary 6-OH in

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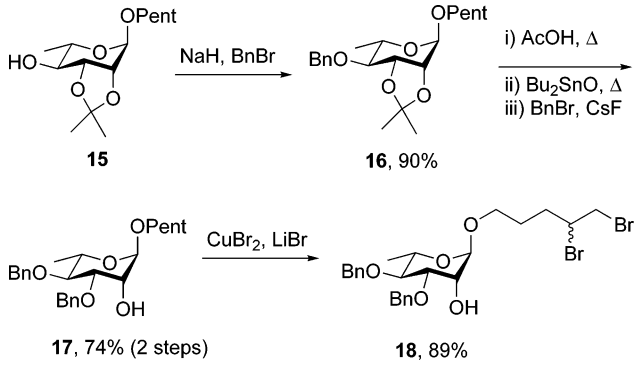
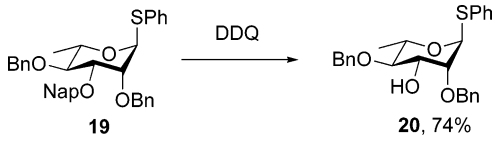
SCHEME 2. Synthesis of Monosaccharide 18



SCHEME 3. Synthesis of Monosaccharide 19



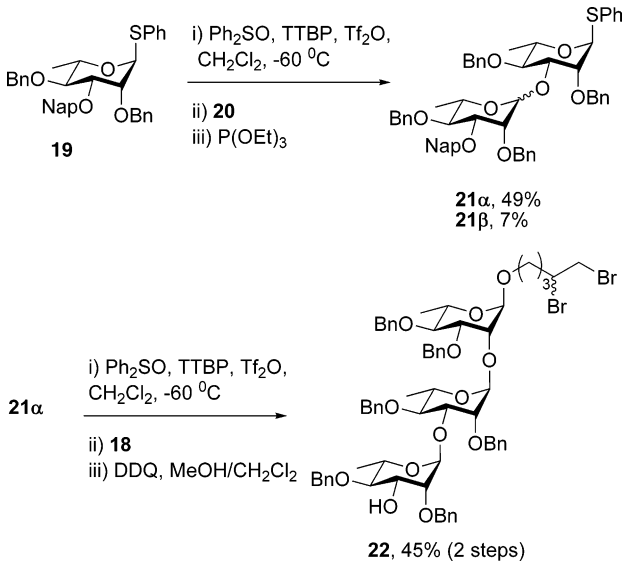
the presence of the secondary 4-OH with a phenylseleno group,[28] gave **12**. Reduction with tributyltin hydride[29,30] gave the 6-deoxygalactose derivative **13**. Displacement of the 4-*O*-triflate, introduced by the reaction of **13** with triflic anhydride, with azide gave desired donor **14**.

With **14** in hand, we proceeded to the synthesis of the trirhamnan building blocks. Benzylation of known n-pentenyl rhamnoside **15**,[31] readily available through Fischer glycosylation of l-rhamnose and further acetonide protection,[31] gave **16** (Scheme 2). Cleavage of the 2,3-*O*-isopropylidene group in acidic media, followed by stannyl-activated regioselective benzylation, gave **17**,[7] which was converted, using a known procedure,[32] to the desired dibromide acceptor **18**. Building block **19**[33] was synthesized using a known procedure[33] and then converted to the acceptor **20**,[33] following the protocol outlined in Scheme 3. A higher yield of **20** was achieved by utilizing a mixture of methanol and dichloromethane as a solvent than in the pure dichloromethane used previously.

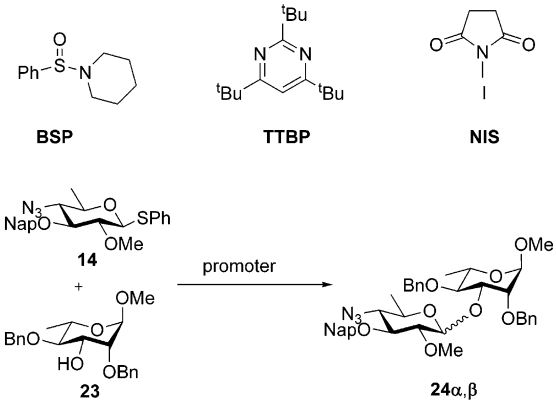
The assembly of the trirhamnan moiety **22** started with preactivation of donor **19**, followed by the addition of acceptor **20**. Subsequent quenching of the reaction mixture with triethyl phosphite[34,35] provided disaccharide **21**, predominantly as the α-anomer. In a similar manner, but omitting the quenching step, **21**α was allowed to react with **18**, to give the crude trisaccharide, which was further deprotected under oxidative conditions to give the desired trisaccharide building block **22** (Scheme 4).

In order to find an optimal promoter/solvent combination for the synthesis of the tetrasaccharide, the glycosylation of donor

SCHEME 4. Trisaccharide Synthesis



SCHEME 5. Exploratory Couplings to the Anthrose Donor



promoter	solvent	α/β ratio, (yield)
BSP/TTBP/Tf_2O	CH_2Cl_2	7.3/1 (82%)
BSP/TTBP/Tf_2O	C_2H_5CN	~ 1/1 (70%)
NIS/TfOH	C_2H_5CN	1/3.3 (93%)

14 was investigated using model acceptor **23**[36] and the activation systems outlined in Scheme 5. In the case of preactivation of **14** with 1-benzenesulfinylpiperidine (BSP)/Tf_2O[37] in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) and subsequent addition of acceptor **23**, a considerable improvement in the β-selectivity was observed, as expected, when the solvent was changed from dichloromethane to propionitrile.[19,20] Use of analogous promoters (Ph_2SO,[35] 1 or 2 equiv) did not improve the selectivity. However, activation of the donor **14** in the presence of acceptor **23** by the NIS/TfOH system[38−40] resulted

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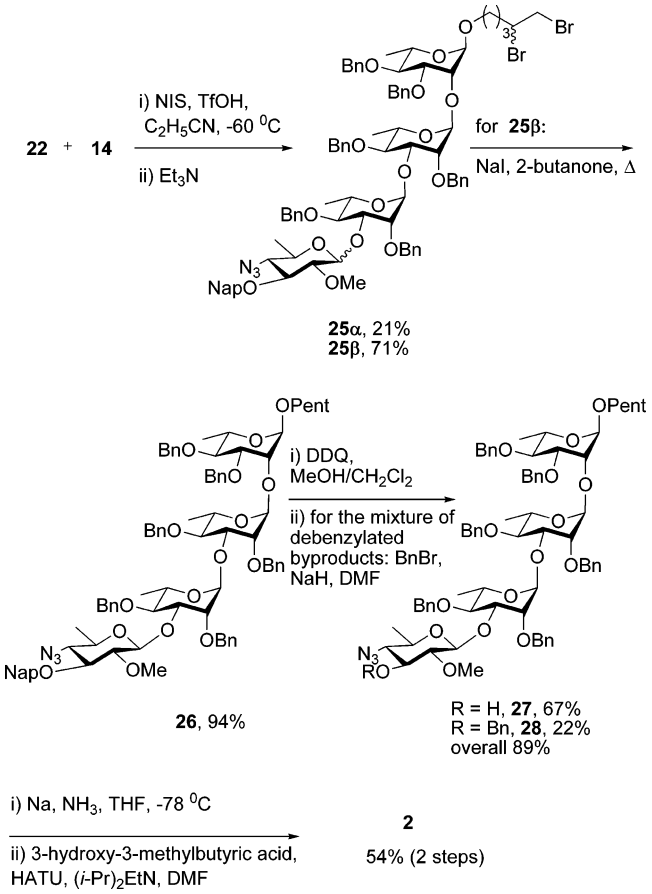
SCHEME 6. Completion of the Synthesis



in a significant enhancement of the steroselectivity, as well as in the overall yield of the reaction.

To complete the synthesis, the anthrose unit **14** was coupled to trisaccharide **22** using the optimal NIS/TfOH/propionitrile conditions to afford **25** as an approximately 3:1 β:α-mixture of anomers in 92% overall yield. Thus, the increased efficiency of the direct introduction of the anthrose moiety in this manner is achieved at the expense of some loss of selectivity. Debromination[32] of **25**β gave **26** from which oxidative cleavage of the 2-naphthylmethyl group afforded tetrasaccharide **27**, suitable for further modifications in the terminal anthrose moiety, such as were found to be essential for the constitution of the highly specific antigenic determinant.[41] The moderate yield of **27** is attributable to the previously reported problem of the competing debenzylation reactions in the course of the DDQ-promoted cleavage of 2-naphthylmethyl/*p*-methoxyphenyl ethers.[33] To overcome this difficulty the mixture of debenzylated byproducts from the 2-naphthylmethyl deprotection reaction was benzylated under standard conditions to give **28**, suitable for further transformations to the target molecule through the same routes as **27**. Final removal of the benzyl protecting groups and transformation of azide moiety to the amine was achieved by application of sodium in liquid ammonia to the mixture of **27** and **28**. Subsequent coupling to the 3-hydroxy-3-methylbutyric acid under peptide-coupling conditions[42] led to the tetrasaccharide **2**, whose spectroscopic data was identical to that previously reported (Scheme 6).[7]

In conclusion, a synthesis of an antigenic tetrasaccharide from *Bacillus anthracis* has been accomplished in a [3 + 1] manner. A straightforward route to the anthrose building block from D-galactose was developed in which no extensive protective group manipulations or expensive starting materials were necessary. The assembly of the trirhamnan building block via an iterative glycosylation strategy, and the construction of the 1,2-*trans*-glycosidic linkage to the terminal anthrose moiety through the α-nitrilium ion-mediated β-selective glycosylation methodology, enables the use of a minimal protecting group strategy and increases the efficiency of the overall synthesis.

Experimental Section

General. Unless otherwise noted, reactions were conducted under an inert atmosphere of argon or nitrogen. All ^{1}H and ^{13}C spectra were recorded in $CDCl_3$, except for **2**, where CD_3OD was used as a solvent.

***S*-Phenyl 4,6-*O*-Benzylidene-3-*O*-(2-naphthylmethyl)-β-D-thiogalactopyranoside (9).** A suspension of **8**[22] (490 mg, 1.36 mmol) and dibutyltin oxide (610 mg, 2.45 mmol) in toluene (7 mL) was heated to reflux in a Dean−Stark apparatus for 4 h, after which most of the solvent was distilled off. The reaction mixture was cooled to room temperature, and the residual solvent was evaporated under reduced pressure. CsF (414 mg, 2.72 mmol), 2-(bromomethyl)naphthalene (602 mg, 2.72 mmol), tetrabutylammonium iodide (1.00 g, 2.72 mmol), and DMF (6 mL) were then added. The reaction mixture was heated to reflux overnight, diluted with ethyl acetate, washed (sat. aq $NaHCO_3$, brine), dried (Na_2SO_4), and concentrated. Purification by column chromatography (SiO_2, 1/9 to 1/3 ethyl acetate/hexanes) gave **9** (490 mg, 60%) as a white solid. Mp 175−176 °C. $[\alpha]^{21}_D$ +32.4 (*c* 0.38, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 7.73−7.85 (m, 4H), 7.66−7.72 (m, 2H), 7.44−7.52 (m, 3H), 7.34−7.44 (m, 5H), 7.22−7.32 (m, 3H), 5.42 (s, 1H), 4.90 (s, 2H), 4.51 (d, J = 9.5 Hz, 1H), 4.34 (dd, J = 12.3, 1.6 Hz, 1H), 4.15 (dd, J = 3.4, 0.7 Hz, 1H), 3.92−4.02 (m, 2H), 3.56 (dd, J = 9.3, 3.3 Hz, 1H), 3.41−3.43 (m, 1H), 2.52 (d, J = 1.9 Hz, 1H); ^{13}C NMR (101 MHz) δ: 137.8, 135.5, 133.8, 133.2, 133.1, 130.6, 129.1 128.9, 128.3, 128.2, 127.9, 127.7, 126.8, 126.6, 126.2, 126.1, 125.8, 101.2, 87.1, 80.2, 73.4, 71.9, 70.1, 69.4, 67.3; ESIHRMS Calcd for $C_{30}H_{28}NaO_5S$ $[M + Na]^+$: 523.1555. Found 523.1562.

***S*-Phenyl 4,6-*O*-Benzylidene-2-*O*-methyl-3-*O*-(2-naphthylmethyl)-β-D-thiogalactopyranoside (10).** A solution of **9** (9.34 g, 18.7 mmol) in DMF (300 mL) was cooled to −15 °C, NaH (60% in mineral oil, 1.12 g, 28.0 mmol) was added slowly, and the reaction mixture was allowed to stir for 30 min at this temperature. Methyl iodide (1.98 mL, 31.7 mmol) was then added slowly, and the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was quenched with MeOH, diluted with $CHCl_3$, washed (water, brine), dried (Na_2SO_4), and concentrated. Purification by column chromatography (SiO_2, 1/4 ethyl acetate/hexanes) gave **10** (7.7 g, 80%) as a white solid. Mp 174−176 °C. $[\alpha]^{21}_D$ +28.4 (*c* 0.40, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 7.76−7.87 (m, 4H), 7.68−7.73 (m, 2H), 7.45−7.55 (m, 5H), 7.36−7.43 (m, 3H), 7.19−7.27 (m, 3H), 5.46 (s, 1H), 4.93 (d, J = 12.7 Hz, 1H), 4.86 (d, J = 12.6 Hz, 1H), 4.49 (d, J = 9.4 Hz, 1H), 4.33 (dd, J = 12.3, 1.5 Hz, 1H), 4.12 (dd, J = 3.4, 0.7 Hz, 1H), 3.94 (dd, J = 12.4, 1.6 Hz, 1H), 3.64 (t, J = 9.2 Hz, 1H), 3.59 (s, 3H), 3.57 (dd, J = 9.2, 3.4 Hz, 1H), 3.35−3.37 (m, 1H); ^{13}C NMR (101 MHz) δ: 137.9, 135.7, 133.2, 133.0, 132.9, 132.6,

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129.1, 128.8, 128.2, 127.9, 127.7, 127.5, 126.7, 126.6, 126.2, 126.0, 125.8, 101.4, 86.4, 81.1, 76.9, 74.0, 72.1, 69.8, 69.4, 61.1; ESIHRMS Calcd for $C_{31}H_{30}NaO_5S$ $[M + Na]^+$: 537.1712. Found 537.1696.

***S*-Phenyl 2-*O*-Methyl-3-*O*-(2-naphthylmethyl)-β-D-thiogalactopyranoside (11).** A mixture of **10** (510 mg, 1.0 mmol), *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol) and MeOH (10 mL) was heated to reflux for 45 min, cooled to room temperature, diluted with ethyl acetate, washed (sat. aq $NaHCO_3$, brine), dried (Na_2SO_4), and concentrated. Purification by column chromatography (SiO_2, 2/3 to 1/1 ethyl acetate/hexanes) gave **11** (401 mg, 95%) as a white solid. Mp 144−145 °C. $[\alpha]^{21}D$ −11.7 (*c* 0.62, $CHCl_3$). ^1H NMR (400 MHz) δ: 7.78−7.87 (m, 4H), 7.46−7.57 (m, 5H), 7.22−7.32 (m, 3H), 4.88 (s, 2H), 4.54 (d, J = 9.2 Hz, 1H), 4.02−4.05 (m, 1H), 3.90−3.98 (m, 1H), 3.73−3.81 (m, 1H), 3.65 (s, 3H), 3.42−3.55 (m, 3H), 2.74 (br s, 1H), 2.28−2.34 (m, 1H); ^{13}C NMR (101 MHz) δ: 135.1, 133.6, 133.2, 133.1, 131.7, 129.0, 128.5, 127.9, 127.8, 127.5, 126.8, 126.4, 126.2, 125.7, 87.4, 82.1, 78.8, 78.0, 72.4, 67.6, 62.7, 61.4; ESIHRMS Calcd for $C_{24}H_{26}NaO_5S$ $[M + Na]^+$: 449.1399. Found 449.1391.

***S*-Phenyl 2-*O*-Methyl-3-*O*-(2-naphthylmethyl)-6-deoxy-6-phenylseleno-β-D-thiogalactopyranoside (12).** A mixture of **11** (1.06 g, 2.49 mmol), diphenyl diselenide (3.89 g, 12.47 mmol), tributylphosphine (4.3 mL, 17.43 mmol), and toluene (20 mL) was heated to reflux for 24 h. Concentration of the reaction mixture, followed by purification by column chromatography (SiO_2, hexanes to 2/3 ethyl acetate/ hexanes), gave **12** (1.09 g, 77%) as a white solid. Mp 128−132 °C. $[\alpha]^{21}D$ +16.4 (*c* 1.01, $CHCl_3$). ^1H NMR (500 MHz) δ: 7.78−7.88 (m, 4H), 7.58−7.63 (m, 2H), 7.43−7.54 (m, 5H), 7.18−7.34 (m, 6H), 4.87 (s, 2H), 4.48 (d, J = 9.5 Hz, 1H), 4.12 (t, J = 2.5 Hz, 1H), 3.65 (s, 3H), 3.41−3.52 (m, 3H), 3.30 (dd, J = 12.8, 6.7 Hz, 1H), 3.18 (dd, J = 12.7, 7.2 Hz, 1H), 2.36 (d, J = 1.8 Hz, 1H); ^{13}C NMR (126 MHz) δ: 135.1, 133.7, 133.2, 133.1, 132.6, 132.1, 129.7, 129.2, 128.9, 128.5, 127.9, 127.8, 127.5, 127.1, 126.8, 126.3, 126.2, 125.8, 87.7, 82.4, 78.7, 77.6, 72.5, 67.5, 61.3, 27.5; ESIHRMS Calcd for $C_{30}H_{30}NaO_4SSe$ $[M + Na]^+$: 589.0928. Found 589.0900.

***S*-Phenyl 2-*O*-Methyl-3-*O*-(2-naphthylmethyl)-β-D-thiofucopyranoside (13).** A solution of **12** (820 mg, 1.45 mmol), AIBN (98 mg, 0.58 mmol), and Bu_3SnH (576 μL, 2.17 mmol) in benzene (145 mL) was heated to reflux for 3 h. The solvent was evaporated, and the residual syrup was dissolved in acetonitrile, washed twice with hexanes, and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, 1/19 to 1/4 ethyl acetate/hexanes) gave **13** (504 mg, 85%) as a white solid. Mp 108−111 °C. $[\alpha]^{20}D$ −11.2 (*c* 0.33, $CHCl_3$). ^1H NMR (501 MHz) δ: 7.79−7.87 (m, 4H), 7.55−7.59 (m, 2H), 7.46−7.53 (m, 3H), 7.22−7.33 (m, 3H), 4.89 (s, 2H), 4.50 (d, J = 9.7 Hz, 1H), 3.80 (d, J = 2.8 Hz, 1H), 3.65 (s, 3H), 3.51−3.55 (m, 2H), 3.43 (t, J = 9.4 Hz, 1H), 2.33 (br s, 1H), 1.35 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz) δ: 135.3, 133.9, 133.2, 133.1, 132.0, 128.9, 128.5, 128.0, 127.8, 127.4, 126.8, 126.3, 126.2, 125.8, 87.4, 82.6, 78.7, 74.2, 72.3, 69.7, 61.4, 16.8; ESIHRMS Calcd for $C_{24}H_{26}NaO_4S$ $[M + Na]^+$: 433.1450. Found 433.1445.

***S*-Phenyl 4-Azido-4-deoxy-2-*O*-methyl-3-*O*-(2-naphthylmethyl)-β-D-thioquinovopyranoside (14).** To a solution of **13** (313 mg, 0.76 mmol) and pyridine (185 μL, 2.29 mmol) in CH_2Cl_2 (7 mL) was added Tf_2O (256 μL, 1.52 mmol) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature, diluted with CH_2Cl_2, washed (sat. aq $NaHCO_3$, brine), dried (Na_2SO_4), and concentrated. The residue was dissolved in DMF (3 mL), and NaN_3 (64 mg, 0.98 mmol) was added. The reaction mixture was allowed to stir for 2.5 h, diluted with ethyl acetate, washed (brine), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 1/ 19 ethyl acetate/ hexanes) gave **14** (288 mg, 87%) as a white solid. Mp 85−86 °C. $[\alpha]^{23}D$ +32.3 (*c* 0.25, $CHCl_3$). ^1H NMR (501 MHz) d: 7.81−7.90 (m, 4H), 7.46−7.59 (m, 5H), 7.26−7.35 (m, 3H), 5.07 (d, J = 10.8 Hz, 1H), 5.02 (d, J = 10.8 Hz, 1H), 4.53 (d, J = 9.9 Hz, 1H), 3.67 (s, 3H), 3.51 (t, J = 9.1 Hz, 1H), 3.20−3.28 (m, 2H), 3.18 (t, J = 9.6 Hz, 1H), 1.38 (d, J = 6.1 Hz, 3H); ^{13}C NMR (126 MHz) δ: 135.2, 133.42, 133.35, 133.1, 132.1, 129.0, 128.3, 128.1, 127.8, 127.7, 127.2, 126.3, 126.2, 126.1, 87.4, 84.7, 83.0, 75.7, 74.8, 67.6, 61.2, 18.8; ESIHRMS Calcd for $C_{24}H_{25}NaN_3O_3S$ $[M + Na]^+$: 458.1514. Found 458.1505.

***n*-Pentenyl 4-*O*-Benzyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (16).** To a solution of **15**[31] (1.46 g, 5.36 mmol) in DMF (8 mL) was slowly added NaH (60% in mineral oil, 321 mg, 8.04 mmol) at 0 °C, followed by benzyl bromide (961 μL, 8.04 mmol), and the reaction mixture was allowed to stir for 3 h at room temperature. The reaction mixture was diluted with ethyl acetate, washed (sat. aq NH_4Cl, brine), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 1/19 ethyl acetate/hexanes) gave **16** (1.74 g, 90%) as a white solid. Mp 38−39 °C. $[\alpha]^{19}D$ −46.4 (*c* 0.71, $CHCl_3$). ^1H NMR (500 MHz) δ: 7.26−7.40 (m, 5H), 5.77−5.86 (m, 1H), 5.04 (ddd, J = 17.1, 3.1, 1.5 Hz, 1H), 4.99 (dq, J = 10.2, 1.5 Hz, 1H), 4.96 (s, 1H), 4.92 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.27−4.31 (m, 1H), 4.15 (d, J = 5.7 Hz, 1H), 3.66−3.74 (m, 2H), 3.43 (dt, J = 9.6, 6.4 Hz, 1H), 3.23 (dd, J = 9.8, 7.1 Hz, 1H), 2.09−2.17 (m, 2H), 1.64−1.74 (m, 2H), 1.53 (s, 3H), 1.39 (s, 3H), 1.29 (d, J = 6.2 Hz, 3H); ^{13}C NMR (126 MHz) δ: 138.4, 138.0, 128.3, 128.0, 127.6, 115.0, 109.1, 97.0, 81.2, 78.7, 76.2, 73.0, 66.8, 64.5, 30.3, 28.6, 28.1, 26.4, 17.9; ESIHRMS Calcd for $C_{21}H_{30}NaO_5$ $[M + Na]^+$: 385.1991. Found 385.1980.

***n*-Pentenyl 2,4-Di-*O*-benzyl-α-L-rhamnopyranoside (17).** A mixture of **16** (1.25 g, 3.45 mmol) and acetic acid (80% in water, 10 mL) was heated for 4 h at 90 °C. Solvents were then evaporated, and residual syrup was dried by addition of toluene, followed by evaporation (two times). Bu_2SnO (1.03 g, 4.14 mmol) was then added to this syrup, followed by benzene (25 mL), and the mixture was heated to reflux in a Dean−Stark apparatus for 3 h, after which most of the solvent was distilled off. The reaction mixture was cooled to room temperature, and the residual solvent was evaporated under reduced pressure. CsF (1.05 g, 6.90 mmol), benzyl bromide (536 μL, 4.49 mmol), and DMF (20 mL) were then added. The reaction mixture was allowed to stir overnight, diluted with ethyl acetate, washed (water, brine), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 3/17 ethyl acetate/hexanes) gave **17** (1.06 g, 74%). Spectral data matched that reported in literature.[7]

4,5-Dibromopentyl 2,4-Di-*O*-benzyl-α-L-rhamnopyranoside (18). A solution of **17** (300 mg, 0.73 mmol) in THF/acetonitrile (3 mL/ 6 mL) was added to a mixture of $CuBr_2$ (812 mg, 3.64 mmol) and LiBr (632 mg, 7.28 mmol) in THF/ acetonitrile (6 mL/ 12 mL). The reaction mixture was stirred overnight in the dark at room temperature, then diluted with ethyl acetate, washed (water, two times), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 1/4 ethyl acetate/hexanes) gave **18** as a mixture of two diastereomers in the dibromopentyl chain (370 mg, 89%). ^1H NMR (500 MHz) δ: 7.28−7.41 (m, 10H), 4.91 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 1.5 Hz, 1H), 4.72 (s, 2H), 4.66 (d, J = 10.8 Hz, 1H), 4.15−4.22 (m, 1H), 4.01−4.04 (m, 1H), 3.84−3.89 (m, 2H), 3.69−3.77 (m, 2H), 3.63 (t, J = 10.1 Hz, 1H), 3.48 (t, J = 9.4 Hz, 1H), 3.42−3.47 (m, 1H), 2.60 (s, 1H), 2.20−2.30 (m, 1H), 1.79−1.93 (m, 2H), 1.67−1.76 (m, 1H), 1.34 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz) δ: 138.4, 137.9, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 99.1, 99.0, 80.0, 75.5, 72.1, 68.6, 67.5, 66.54, 66.51, 52.6, 52.5, 36.2, 33.01, 32.95, 26.9, 18.0; ESIHRMS Calcd for $C_{25}H_{32}NaBr_2O_5$ $[M + Na]^+$: 593.0514. Found 593.0519.

***S*-Phenyl 2,4-Di-*O*-benzyl-α-L-thiorhamnopyranoside (20).** To a solution of **19**[33] (1.83 g, 3.17 mmol) in MeOH/CH_2Cl_2 (10 mL/

30 mL) was added DDQ (2.16 g, 9.51 mmol) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and stirred for a further 5 h before it was diluted with CH_2Cl_2 and quenched with sat. aq Na_2CO_3. The organic phase was separated, washed (sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 1/9 ethyl acetate/hexanes) gave **20** (1.03 g, 74%), whose spectral data matched that reported in literature.[33]

S*-Phenyl 2,4-Di-*O*-benzyl-3-*O*-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-thiorhamnopyranoside (21α) and *S*-Phenyl 2,4-Di-*O*-benzyl-3-*O*-(2-naphthylmethyl)-*β*-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-thiorhamnopyranoside (21*β*).** To a solution of **19** (304 mg, 0.53 mmol), TTBP (262 mg, 1.05 mmol), Ph_2SO (107 mg, 0.53 mmol), and activated 3 Å powdered molecular sieves in CH_2Cl_2 (10 mL) was added Tf_2O (98 μL, 0.58 mmol) at −60 °C. The reaction mixture was stirred for 1 h at this temperature, and a solution of **20** (391 mg, 0.90 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The reaction mixture was stirred for an additional 30 min at −60 °C and then quenched by the addition of $P(OEt)_3$ (184 μL, 1.05 mmol). The reaction mixture was warmed to room temperature, filtered, diluted with CH_2Cl_2, washed (sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 1/9 ethyl acetate/hexanes), followed by the HPLC (SiO_2, hexanes to 1/9 ethyl acetate/ hexanes), gave **21**α (235 mg, 49%), **21β* (34 mg, 7%), and **20** (70 mg, 18%) was recovered. **21**α. $[\alpha]^{24}_D$ −61.2 (*c* 0.20, $CHCl_3$). ^{1}H NMR (501 MHz) *δ*: 7.66−7.83 (m, 4H), 7.41−7.49 (m, 5H), 7.35−7.40 (m, 6H), 7.18−7.35 (m, 17H), 5.52 (s, 1H), 5.18 (s, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.78 (d, *J* = 12.1 Hz, 1H), 4.67−4.74 (m, 3H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.45−4.55 (m, 4H), 4.12−4.20 (m, 1H), 4.07 (dd, *J* = 9.5, 2.9 Hz, 1H), 4.01−4.04 (m, 1H), 3.99 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.81−3.88 (m, 1H), 3.73−3.76 (m, 1H), 3.70 (t, *J* = 9.4 Hz, 1H), 3.58 (t, *J* = 9.4 Hz, 1H), 1.35 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz) *δ*: 139.0, 138.4, 137.8, 136.0, 134.6, 133.3, 133.0, 131.5, 129.1, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.84, 127.81, 127.71, 127.66, 127.6, 127.5, 127.4, 127.0, 126.5, 126.1, 125.9, 99.9 ($^1J_{CH}$ = 168.7 Hz), 85.5 ($^1J_{CH}$ = 164.9 Hz), 80.8, 80.5, 79.9, 79.6, 76.0, 75.2, 74.7, 72.6, 72.5, 72.2, 69.5, 68.9, 18.2, 17.9; ESIHRMS Calcd for $C_{57}H_{58}NaO_8S$ [M + Na]$^+$: 925.3750. Found 925.3741. **21***β*. $[\alpha]^{22}_D$ +7.4 (*c* 0.50, $CHCl_3$). ^{1}H NMR (501 MHz) *δ*: 7.69−7.86 (m, 4H), 7.37−7.51 (m, 9H), 7.26−7.37 (m, 13H), 7.18−7.25 (m, 6H), 5.54 (d, *J* = 2.9 Hz, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 5.00 (d, *J* = 12.5 Hz, 1H), 4.92 (d, *J* = 12.5 Hz, 1H), 4.66−4.75 (m, 2H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.55 (d, *J* = 10.6 Hz, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 4.29 (s, 1H), 4.18 (dd, *J* = 7. 9, 3.1 Hz, 1H), 4.11−4.17 (m, 1H), 3.91 (t, *J* = 3.0 Hz, 1H), 3.82 (d, *J* = 2.9 Hz, 1H), 3.63−3.70 (m, 2H), 3.40 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.22−3.29 (m, 1H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (126 MHz) *δ*: 138.9, 138.7, 138.6, 137.7, 135.9, 134.8, 133.3, 133.0, 131.6, 129.1, 128.5, 128.44, 128.37, 128.24, 128.18, 128.14, 128.10, 128.0, 127.9, 127.8, 127.6, 127.4, 127.3, 126.2, 125.9, 125.6, 99.0 ($^1J_{CH}$ = 154.9 Hz), 85.4 ($^1J_{CH}$ = 166.2 Hz), 82.2, 80.3, 80.2, 76.5, 76.3, 75.5, 74.7, 74.3, 74.1, 72.12, 72.09, 71.6, 69.0, 18.4, 18.2; ESIHRMS Calcd for $C_{57}H_{58}NaO_8S$ [M + Na]$^+$: 925.3750. Found 925.3744.

4,5-Dibromopentyl 2,4-Di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (22). To a solution of **21**α (677 mg, 0.75 mmol), TTBP (373 mg, 1.50 mmol), Ph_2SO (151 mg, 0.75 mmol), and activated 3 Å powdered molecular sieves in CH_2Cl_2 (22 mL) was added Tf_2O (139 μL, 0.82 mmol) at −60 °C. The reaction mixture was stirred for 1 h at this temperature, and a solution of **18** (644 mg, 1.13 mmol) in CH_2Cl_2 (7 mL) was added dropwise. After being stirred for 30 min at −60 °C, the reaction mixture was warmed to room temperature, filtered, diluted with CH_2Cl_2, washed (sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. The crude reaction mixture was filtered through a pad of silica gel (with ethyl acetate as an eluent) and purified by radial chromatography (SiO_2, hexanes to 1/9 ethyl acetate/hexanes). Fractions containing product were combined and concentrated to give a clear oil. To a solution of this oil in CH_2Cl_2/MeOH (18 mL/6 mL) was added DDQ (400 mg, 1.76 mmol) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and further stirred for 9 h before it was diluted with CH_2Cl_2 and quenched with sat. aq Na_2CO_3. The organic phase was separated, washed (sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 3/17 ethyl acetate/hexanes) gave **22** as a mixture of two diastereomers in the dibromopentyl chain (413 mg, 45%, two steps). ^{1}H NMR (501 MHz) *δ*: 7.14−7.40 (m, 30H), 5.23 (s, 1H), 5.13 (d, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 4.89 (d, *J* = 10.9 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.70−4.75 (m, 2H), 4.57−4.69 (m, 4H), 4.48−4.55 (m, 2H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.20 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.16−4.22 (m, 1H), 4.12 (d, *J* = 11.7 Hz, 1H), 4.01−4.05 (m, 1H), 3.97 (td, *J* = 9.0, 3.5 Hz, 1H), 3.79−3.89 (m, 4H), 3.60−3.77 (m, 6H), 3.42−3.47 (m, 1H), 3.42 (t, *J* = 9.5 Hz, 1H), 3.31 (t, *J* = 9.3 Hz, 1H), 2.29 (d, *J* = 9.5 Hz, 1H), 2.20−2.30 (m, 1H), 1.79−1.92 (m, 2H), 1.67−1.77 (m, 1H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.30 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (126 MHz) *δ*: 138.8, 138.6, 138.5, 138.3, 138.1, 137.8, 128.50, 128.47, 128.4, 128.1, 127.84, 127.78, 127.6, 126.9, 99.2 ($^1J_{CH}$ = 170.0 Hz), 99.1($^1J_{CH}$ = 168.7 Hz), 99.0 ($^1J_{CH}$ = 170.0 Hz), 98.5 ($^1J_{CH}$ = 170.0 Hz), 82.2, 81.1, 80.6, 79.9, 79.2, 77.9, 76.8, 75.5, 74.9, 74.7, 74.6, 72.6, 72.5, 72.4, 71.7, 68.9, 68.2, 67.7, 66.4, 52.6, 52.5, 36.1, 33.03, 33.00, 26.9, 18.2, 18.1, 18.0; ESIHRMS Calcd for $C_{65}H_{76}Br_2NaO_{13}$ [M + Na]$^+$: 1245.3550. Found 1245.3521.

Methyl 2,4-Di-*O*-benzyl-3-*O*-(2-naphthylmethyl)-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (24α) and Methyl 2,4-Di-*O*-benzyl-3-*O*-(2-naphthylmethyl)-*β*-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranoside (24*β*).

Method A. To a solution of **14** (17 mg, 0.039 mmol), TTBP (19 mg, 0.078 mmol), BSP (8 mg, 0.039 mmol), and activated 3 Å powdered molecular sieves in CH_2Cl_2 (1.5 mL) was added Tf_2O (7.2 μL, 0.043 mmol) at −60 °C. The reaction mixture was stirred for 5 min at this temperature, and solution of **23** (17 mg, 0.048 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise. The reaction mixture was stirred for an additional 2 min at −60 °C, slowly warmed to room temperature, filtered, washed (sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by means of radial chromatography (SiO_2, hexanes to 3/17 ethyl acetate/hexanes) gave **24**α (19 mg, 72%) and **24***β* (3 mg, 10%). **24**α. $[\alpha]^{23}_D$ +252.3 (*c* 0.13, $CHCl_3$). ^{1}H NMR (500 MHz) *δ*: 7.79−7.87 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.41−7.48 (m, 4H), 7.28−7.40 (m, 8H), 5.10 (d, *J* = 3.3 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 4.82−4.87 (m, 2H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.69 (s, 1H), 4.59 (d, *J* = 10.6 Hz, 1H), 4.04 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.92 (t, *J* = 9.5 Hz, 1H), 3.81−3.88 (m, 2H), 3.62−3.71 (m, 2H), 3.55 (s, 3H), 3.39 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.31 (s, 3H), 3.13 (t, *J* = 9.8 Hz, 1H), 1.35 (d, *J* = 5.5 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (126 MHz) *δ*: 138.4, 138.0, 135.6, 133.3, 133.0, 128.4, 128.1, 128.0, 127.8, 127.73, 127.71, 127.67, 127.0, 126.2, 126.0, 125.9, 98.8 ($^1J_{CH}$ = 168.7 Hz), 93.5 ($^1J_{CH}$ = 167.4 Hz), 82.6, 79.8, 75.64, 75.56, 75.4, 74.3, 72.8, 68.3, 68.0, 66.4, 59.5, 54.7, 18.5, 18.1; FABHRMS Calcd for $C_{39}H_{45}N_3NaO_8$ [M + Na]$^+$:706.3104. Found 706.3097. **24***β*. $[\alpha]^{23}_D$ +12.2 (*c* 0.18, $CHCl_3$). ^{1}H NMR (400 MHz) *δ*: 7.81−7.89 (m, 4H), 7.56 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.44−7.51 (m, 2H), 7.39−7.43 (m, 4H), 7.27−7.37 (m, 6H), 5.1 (d, *J* = 11.0 Hz, 1H), 4.96−5.02 (m, 2H), 4.84 (d, *J* = 12.3 Hz, 1H), 4.74 (d, *J* = 12.3

Hz, 1H), 4.55−4.65 (m, 3H), 4.03 (dd, J = 8.9, 3.2 Hz, 1H), 3.82 (dd, J = 3.1, 1.8 Hz, 1H), 3.69 (s, 3H), 3.59−3.68 (m, 2H), 3.45 (t, J = 9.0 Hz, 1H), 3.29 (s, 3H), 3.11−3.22 (m, 3 H), 1.36 (d, J = 5.9 Hz, 3H), 1.29 (d, J = 5.4 Hz, 3H); ^{13}C NMR (101 MHz) δ: 138.8, 138.5, 135.5, 133.3, 133.1, 128.4, 128.24, 128.18, 128.0, 127.9, 127.8, 127.7, 127.5, 127.1, 126.3, 126.1, 126.0, 103.7 ($^1J_{CH}$ = 160.9 Hz), 99.7 ($^1J_{CH}$ = 168.3 Hz), 84.9, 82.8, 80.8, 79.1, 78.4, 75.5, 74.8, 73.5, 70.3, 67.9, 67.7, 60.8, 54.5, 18.6, 18.0; FABHRMS Calcd for $C_{39}H_{45}N_3NaO_8$ [M + Na]$^+$: 706.3104. Found 706.3080.

Method B. To a solution of **14** (18 mg, 0.042 mmol), TTBP (21 mg, 0.085 mmol), BSP (9 mg, 0.042 mmol), and activated 3 Å powdered molecular sieves in propionitrile (1.5 mL) Tf_2O (7.9 μL, 0.047 mmol) was added at −60 °C. The reaction mixture was stirred for 5 min at this temperature, and solution of **23** (19 mg, 0.052 mmol) in propionitrile (0.6 mL) was added dropwise. The reaction mixture was stirred for an additional 2 min at −60 °C, warmed to room temperature, filtered, diluted with CH_2Cl_2, washed (sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 3/17 ethyl acetate/ hexanes) gave **24**α (10.3 mg, 36%) and **24**β (9.7 mg, 34%).

Method C. A solution of **14** (27 mg, 0.062 mmol), **23** (18 mg, 0.050 mmol), and activated 3 Å powdered molecular sieves in propionitrile (1 mL) was stirred for 10 min at room temperature and then cooled to −60 °C, and *N*-iodosuccinimide (14 mg, 0.062 mmol), followed by TfOH (1.1 μL, 0.012 mmol), was added. The reaction mixture was stirred for 8 h at −60 to −65 °C, quenched with Et_3N (9 μL, 0.062 mmol), filtered, diluted with CH_2Cl_2, washed (sat. aq $Na_2S_2O_3$, sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 3/17 ethyl acetate/hexanes) gave **24**α (8 mg, 23%) and **24**β (25 mg, 70%).

4,5-Dibromopentyl 4-Azido-4-deoxy-2-*O*-methyl-3-*O*-(2-naphthylmethyl)-α-D-quinovopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L -rhamnopyranoside (25α) and 4,5-Dibromopentyl4-Azido-4-deoxy-2-*O*-methyl-3-*O*-(2-naphthylmethyl)-*β*-D-quinovopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (25*β*). A solution of **22** (118 mg, 0.096 mmol), **14** (50 mg, 0.115 mmol), and activated 3 Å powdered molecular sieves in propionitrile (2.4 mL) was stirred for 10 min at room temperature and then cooled to −60 °C, and *N*-iodosuccinimide (26 mg, 0.116 mmol), followed by TfOH (1.7 μL, 0.019 mmol), was added. The reaction mixture was stirred for 9 h at −60 to −65 °C, quenched with Et_3N (16 μL, 0.115 mmol), filtered, diluted with CH_2Cl_2, washed (sat. aq $Na_2S_2O_3$, sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 3/17 ethyl acetate/hexanes) gave **25**α as a mixture of two diastereomers in the dibromopentyl chain (32 mg, 21%) and **25**β as a mixture of two diastereomers in the dibromopentyl chain (105 mg, 71%). **25**α. ^{1}H NMR (500 MHz): 7.74−7.87 (m, 4H), 7.51 (dd, J = 8.4, 1.7 Hz, 1H), 7.42−7.47 (m, 2H), 7.12−7.35 (m, 30H), 5.21 (s, 1H), 5.10 (d, J = 1.5 Hz, 1H), 5.00−5.04 (m, 2H), 4.91 (d, J = 11.0 Hz, 1H), 4.85 (d, J = 10.8 Hz, 1H), 4.82 (d, J = 10.8 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.70 (d, J = 1.5 Hz, 1H), 4.62−4.67 (m, 2H), 4.55−4.61 (m, 3H), 4.51−4.55 (m, 2H), 4.49 (s, 1H), 4.40 (d, J = 11.6 Hz, 1H), 4.11−4.21 (m, 3H), 3.99−4.01 (m, 1H), 3.76−3.90 (m, 8H), 3.55−3.71 (m, 5H), 3.37−3.46 (m, 5H), 3.34 (dd, J = 9.4, 3.5 Hz, 1H), 3.10 (t, J = 9.8 Hz, 1H), 2.18−2.27 (m, 1H), 1.77−1.89 (m, 2H), 1.63−1.74 (m, 1H), 1.282 (d, J = 6.2 Hz, 3H), 1.278 (d, J = 6.1 Hz, 3H), 1.24 (d, J = 6.2 Hz, 3H), 1.06 (d, J = 6.2 Hz, 3H); ^{13}C NMR (126 MHz) δ: 138.6, 138.4, 138.3, 138.0, 135.6, 133.3, 133.0, 128.47, 128.42, 128.34, 128.26. 128.12, 128.09, 128.0, 127.8, 127.68, 127.65, 127.60, 127.56, 127.5, 127.0, 126.2, 126.0, 125.9, 99.5 ($^1J_{CH}$ = 169.9 Hz), 99.1 ($^1J_{CH}$ = 169.2 Hz), 99.0 ($^1J_{CH}$ = 169.2 Hz), 98.9 ($^1J_{CH}$ = 168.5 Hz), 93.1 ($^1J_{CH}$ = 165.3 Hz), 82.6, 80.8, 80.5, 79.9, 79.7, 77.6, 75.52, 75.49, 75.4, 75.2, 74.7, 74.5, 72.6, 72.4, 72.3, 68.8, 68.2, 68.1, 66.3, 59.1, 52.6, 52.5, 36.1, 33.01, 32.97, 26.8, 18.5, 18.10, 18.05; ESIHRMS Calcd for $C_{83}H_{95}N_3NaO_{16}Br_2$ [M + Na]$^+$: 1570.4977. Found 1570.4920. **25**β. ^{1}H NMR (501 MHz) δ: 7.82−7.87 (m, 4H), 7.53 − 7.57 (m, 1H), 7.44−7.50 (m, 2H), 7.38−7.42 (m, 2H), 7.16−7.37 (m, 28H), 5.12 (s, 1H), 5.09 (s, 1H), 5.06 (d, J = 10.8 Hz, 1H), 4.95−5.00 (m, 2H), 4.87 (d, J = 10.8 Hz, 1H), 4.66−4.72 (m, 2H), 4.54−4.66 (m, 7H), 4.44−4.50 (m, 3H), 4.10−4.21 (m, 3H), 3.99−4.01 (m, 1H), 3.88−3.91 (m, 1H), 3.81−3.87 (m, 4H), 3.75−3.80 (m, 1H), 3.66−3.69 (m, 4H), 3.59−3.71 (m, 3H), 3.55 (t, J = 9.1 Hz, 1H), 3.35−3.45 (m, 3H), 3.16 (t, J = 8.4 Hz, 1H), 3.08 (t, J = 9.4 Hz, 1H), 3.00−3.08 (m, 1H), 2.17−2.28 (m, 1H), 1.77−1.89 (m, 2H), 1.64−1.74 (m, 1H), 1.283 (d, J = 6.1 Hz, 3H), 1.279 (d, J = 6.1 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 5.5 Hz, 3H); ^{13}C NMR (126 MHz) δ: 138.8, 138.5, 138.3, 138.2, 135.5, 133.4, 133.1, 128.5, 128.33, 128.28, 128.2, 128.13, 128.07, 128.0, 127.73, 127.69, 127.66, 127.60, 127.58, 127.42, 127.39, 127.1, 126.3, 126.1, 126.0, 103.6 ($^1J_{CH}$ = 161.2 Hz), 100.3 ($^1J_{CH}$ = 168.7 Hz), 99.0 ($^1J_{CH}$ = 170.0 Hz), 98.9 ($^1J_{CH}$ = 169.2 Hz), 84.9, 82.8, 81.0, 80.61, 80.55, 80.0, 79.4, 78.6, 78.1, 75.49, 75.46, 74.84, 74.76, 74.7, 73.4, 72.5, 72.2, 70.3, 68.7, 68.4, 68.1, 67.8, 66.3, 60.8, 52.6, 52.5, 36.1, 33.02, 32.99, 26.8, 18.5, 18.1, 18.0; ESIHRMS Calcd for $C_{83}H_{95}N_3NaO_{16}Br_2$ [M + Na]$^+$: 1570.4977. Found 1570.4930.

***n*-Pentenyl 4-Azido-4-deoxy-2-*O*-methyl-3-*O*-(2-naphthylmethyl)-*β*-D-quinovopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (26).** A mixture of **25**β (98 mg, 0.063 mmol), NaI (190 mg, 1.268 mmol), and 2-butanone (6 mL) was heated to reflux for 5 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, washed (sat. aq $Na_2S_2O_3$,), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 1/9 ethyl acetate/hexanes) gave **26** (82 mg, 94%). $[\alpha]^{15}_D$ +10.0 (*c* 0.23, $CHCl_3$). ^{1}H NMR (501 MHz) δ: 7.83−7.91 (m, 4H), 7.56 (dd, J = 8.5, 1.4 Hz, 1H), 7.45−7.51 (m, 2H), 7.15−7.43 (m, 30H), 5.76−5.85 (m, 1H), 5.13 (br s, 1H), 5.11 (d, J = 1.5 Hz, 1H), 5.08 (d, J = 11.0 Hz, 1H), 5.01−5.06 (m, 1H), 4.97−5.01 (m, 3H), 4.88 (d, J = 10.8 Hz, 1H), 4.59−4.73 (m, 8H), 4.57 (d, J = 11.2 Hz, 1H), 4.44−4.51 (m, 3H), 4.11−4.17 (m, 2H), 4.02−4.04 (m, 1H), 3.90 (dd, J = 2.6, 1.7 Hz, 1H), 3.82−3.87 (m, 3H), 3.77−3.82 (m, 1H), 3.62−3.71 (m, 6H), 3.56 (t, J = 9.4 Hz, 1H), 3.35−3.45 (m, 3H), 3.17 (dd, J = 8.9, 8.0 Hz, 1H), 3.09 (t, J = 9.5 Hz, 1H), 3.01−3.09 (m, 1H), 2.06−2.14 (m, 2H), 1.62−1.69 (m, 2H), 1.30 (d, J = 6.2 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 5.9 Hz, 3H); ^{13}C NMR (126 MHz) δ: 138.7, 138.4, 138.33, 138.31, 138.2, 138.0, 135.5, 133.3, 133.1, 128.4, 128.3, 128.2, 128.14, 128.09, 128.05, 128.03, 127.98, 127.7, 127.64, 127.57, 127.53, 127.50, 127.4, 127.1, 126.2, 126.1, 125.9, 114.9, 103.5 ($^1J_{CH}$ = 161.2 Hz), 100.3 ($^1J_{CH}$ = 168.7 Hz), 98.9 ($^1J_{CH}$ = 168.7 Hz), 84.8, 82.7, 80.9, 80.58, 80.55, 80.1, 79.3, 78.5, 78.0, 75.5, 75.4, 74.7, 74.6, 73.3, 72.4, 72.1, 70.2, 68.6, 68.4, 67.9, 67.7, 66.7, 60.8, 30.3, 28.6, 18.4, 18.02, 17.98, 17.95; ESIHRMS Calcd for $C_{83}H_{95}N_3NaO_{16}$ [M + Na]$^+$: 1412.6610. Found 1412.6560.

***n*-Pentenyl 4-Azido-4-deoxy-2-*O*-methyl-*β*-D-quinovopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-l-rhamnopyranoside (27) and *n*-Pentenyl 4-Azido-3-*O*-benzyl-4-deoxy-2-*O*-methyl-*β*-D-quinovopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→3)-2,4-di-*O*-benzyl-α-L-rhamnopyranosyl-(1→2)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (28).** To a solution of **26** (122 mg, 0.088 mmol) in MeOH/CH_2Cl_2 (0.7 mL/ 2.1 mL) was added DDQ (60 mg, 0.26 mmol) at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and further

stirred for 5 h before it was diluted with CH_2Cl_2 and quenched with sat. aq Na_2CO_3. The organic phase was separated, washed (sat. aq Na_2CO_3), dried (Na_2SO_4), and concentrated. Filtration of the crude reaction mixture through a pad of silica gel (with ethyl acetate as an eluent) and purification by radial chromatography (SiO_2, hexanes to 1/9 ethyl acetate/hexanes) gave **27** (74 mg, 67%). $[\alpha]^{15}_D$ −11.6 (*c* 0.76, $CHCl_3$). ^{1}H NMR (501 MHz) δ: 7.13−7.39 (m, 30H), 5.74−5.85 (m, 1H), 5.11 (br s, 1H), 5.10 (d, J = 1.7 Hz, 1H), 5.02 (dq, J = 17.2, 1.5 Hz, 1H), 4.95−4.99 (m, 1H), 4.88 (t, J = 10.5 Hz, 2H), 4.70 (d, J = 11.4 Hz, 1H), 4.65−4.69 (m, 2H), 4.54−4.63 (m, 6H), 4.48 (d, J = 11.9 Hz, 1H), 4.39−4.44 (m, 2H), 4.12 (ddd, J = 12.2, 9.4, 3.0 Hz, 1H), 4.00−4.02 (m, 1H), 3.87 (dd, J = 2.8, 1.7 Hz, 1H), 3.81−3.86 (m, 3H), 3.76−3.82 (m, 1H), 3.60−3.69 (m, 6H), 3.54 (t, J = 9.0 Hz, 1H), 3.47 (td, J = 9.1, 2.1 Hz, 1H), 3.41 (t, J = 9.5 Hz, 1H), 3.34−3.39 (m, 1H), 3.01−3.09 (m, 1H), 3.01 (t, J = 9.5 Hz, 1H), 2.97 (dd, J = 9.2, 7. 9 Hz, 1H), 2.66 (d, J = 2.6 Hz, 1H), 2.06−2.13 (m, 2H), 1.60−1.69 (m, 2H), 1.27−1.29 (m, 6H), 1.26 (d, J = 6.4 Hz, 3H), 1.11 (d, J = 5.7 Hz, 3H); ^{13}C NMR (126 MHz) δ: 138.7, 138.54, 138.47, 138.4, 138.2, 138.1, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.74, 127.68, 127.62, 127.56, 127.41, 127.38, 115.0, 103.4 ($^1J_{CH}$ = 161.2 Hz), 100.2 ($^1J_{CH}$ = 166.2 Hz), 99.0 ($^1J_{CH}$ = 168.7 Hz), 84.0, 81.1, 80.62, 80.59, 80.1, 79.4, 78.2, 78.1, 75.5, 75.2, 74.8, 74.7, 73.4, 72.5, 72.1, 70.5, 68.6, 68.4, 67.9, 67.4, 66.8, 61.0, 30.3, 28.7, 18.3, 18.1, 18.02, 17.99; ESIHRMS Calcd for $C_{72}H_{87}N_3NaO_{16}$ [M + Na]$^+$: 1272.5984. Found 1272.5943. Further elution of with ethyl acetate gave a mixture of the debenzylated byproducts, which was dissolved in DMF (2 mL). Benzyl bromide (60 μL, 0.50 mmol) was then added, followed by NaH (60% in mineral oil, 20 mg, 0.50 mmol), and the reaction mixture was stirred overnight, diluted with ethyl acetate, washed (brine, water), dried (Na_2SO_4), and concentrated. Purification by radial chromatography (SiO_2, hexanes to 3/17 ethyl acetate/hexanes) gave **28** (26 mg, 22%, two steps). $[\alpha]^{14}_D$ +2.4 (*c* 1.08, $CHCl_3$). ^{1}H NMR (501 MHz): 7.12−7.45 (m, 35H), 5.75−5.85 (m, 1H), 5.08−5.14 (m, 2H), 5.02 (dq, J = 17.2, 1.7 Hz, 1H), 4.96−4.99 (m, 2H), 4.90 (d, J = 10.7 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 10.6 Hz, 1H), 4.65−4.72 (m, 3H), 4.54−4.64 (m, 6H), 4.44−4.50 (m, 3H), 4.13 (td, J = 9.5, 3.0 Hz, 2H), 4.01−4.02 (m, 1H), 3.89 (dd, J = 2.8, 1.7 Hz, 1H), 3.76−3.86 (m, 4H), 3.61−3.70 (m, 6H), 3.55 (t, J = 9.5 Hz, 1H), 3.42 (t, J = 9.5 Hz, 1H), 3.31−3.39 (m, 2H), 3.13 (dd, J = 9.1, 8.0 Hz, 1H), 2.95−3.07 (m, 2H), 2.06−2.13 (m, 2H), 1.61−1.69 (m, 2H), 1.284 (d, J = 6.2 Hz, 3H), 1.279 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 5.7 Hz, 3H); ^{13}C NMR (126 MHz) δ: 138.80, 138.78, 138.5, 138.40, 138.38, 138.2, 138.1, 138.0, 128.44, 128.40, 128.32, 128.26, 128.12, 128.08, 127.9, 127.71, 127.68, 127.60, 127.56, 127.5, 127.40, 127.37, 114.9, 103.6 ($^1J_{CH}$ = 161.2 Hz), 100.3 ($^1J_{CH}$ = 173.7 Hz), 99.1 ($^1J_{CH}$ = 167.4 Hz), 99.0 ($^1J_{CH}$ = 167.4 Hz), 84.8, 82.7, 81.0, 80.64, 80.63, 80.1, 79.4, 78.6, 78.1, 75.49, 75.45, 74.8, 74.6, 73.4, 72.5, 72.2, 70.3, 68.7, 68.4, 68.0, 67.7, 66.8, 60.8, 30.3, 28.7, 18.5, 18.1, 18.02, 17.99; ESIHRMS Calcd for $C_{79}H_{93}N_3NaO_{16}$ [M + Na]$^+$: 1362.6454. Found 1362.6404.

***n*-Pentenyl 4-Deoxy-4-(3-hydroxy-3-methylbutanamido)-2-*O*-methyl-*β*-D-quinovopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranoside (2).** Ammonia was condensed at −78 °C in a reaction vessel, containing a solution of **27** (26 mg, 0.021 mmol) and **28** (9 mg, 0.007 mmol) in THF (6 mL), until a total volume of about 20 mL was reached. Sodium (45 mg, 1.96 mmol) was then added in small pieces, affording a solution of dark blue color. The reaction mixture was stirred for 1 h at this temperature and then quenched by the addition of the methanol. The reaction mixture was warmed to room temperature in order to evaporate the ammonia, and then concentrated. Purification by column chromatography (eluting first with $CHCl_3$ to remove most of the byproducts and then with 1/4 MeOH/$CHCl_3$ and finally MeOH) gave a crude product, which was dissolved in (i-Pr)$_2$EtN and concentrated (two times). DMF (2 mL) was then added, followed by 3-hydroxy-3-methylbutyric acid (5 mg, 0.042 mmol), HATU (16 mg, 0.042 mmol), and (i-Pr)$_2$EtN (28 μL, 0.16 mmol). The reaction mixture was stirred overnight and then concentrated. Purification by column chromatography (SiO_2, $CHCl_3$ to 9/31 MeOH/$CHCl_3$), followed by purification by preparative TLC (9/31 MeOH/$CHCl_3$) and further column chromatography (SiO_2, $CHCl_3$ to 9/31 MeOH/ $CHCl_3$), gave **2** (12 mg, 54%, 2 steps), whose spectral data matched that reported in the literature.[7] $[\alpha]^{20}_D$ −63.5 (*c* 0.2, MeOH); Lit.[7] $[\alpha]_D$ −7.9 (*c* 0.18, $CHCl_3$).[43] IR (thin film): 3377, 2972, 2931, 2879, 1658, 1649, 1641, 1381, 1122, 1061 cm^{-1}.

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Supporting Information Available: Full experimental details for substrate preparation and copies of spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) The literature specific rotation appears to be an error, as the compound is not soluble in the recorded solvent.