JOC Notes

Synthesis of Aza-Analogues of the Glycosylated Tyrosine Portion of Mannopeptimycin-E

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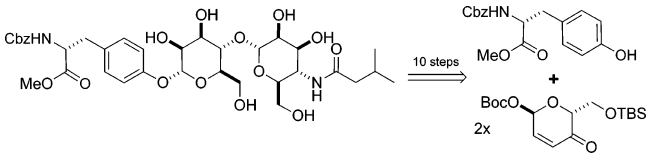
Received February 23, 2007



Two *C*4′ amido disaccharide analogues of mannopeptimycin-E were synthesized via an iterative palladium glycosylation sequence. The stereoselective synthesis of the *C*4′ acylated 1,4-α,α-*manno*,*manno*-amido disaccharide has been achieved in ten steps from a protected D-tyrosine. The path relies upon a regio- and diastereoselective palladium-catalyzed azide substitution reaction. The competence of the synthesis is demonstrated by the good overall yield (21%) from protected tyrosine.

The problem associated with the ability of organisms to develop resistance mechanisms to antibiotics has fueled the perpetual search for new antibacterial agents.[1] A tris-*manno*-glycosylated class of cyclic hexapeptides with alternating D- and L-amino acids, the mannopeptimycins, were isolated as part of this quest. Of the mannopeptimycins, mannopeptimycin-E (**1a**) (Figure 1) is the most active member, displaying activity against methicillin-resistant staphylococci and vancomycin-resistant enterococci.[2] In an effort to identify compounds with improved activity and SAR studies, chemists at Wyeth[3] have synthesized several analogues of mannopeptimycin-E. In addition to this isolation/semisynthetic and synthetic work,[4] we have been working toward the preparation of mannopeptimycin-E analogues (e.g., **1b**, **3**, and **14**), with particular emphasis on the glycosylated tyrosine peptide portion of the macrocycle. To these ends, we recently synthesized several *O*-linked tyrosine 1,4-α,α-*manno*,*manno*-pyranosyl pyranoside fragment of the mannopeptimycin-E **2**.[5] In particular, we were interested in the critical role of the *C*4′ isovaleryl group and its specific location played on antibacterial activity.[2] It has been shown that removal or migration of the *C*4′ isovalerate substitution on the terminal mannose leads to a substantial decrease in antibacterial potency.[2] Along this vein, we became interested in an aza-analogue **3** that should be resistant to both hydrolysis and migration (Figure 1). Herein, we describe the enantioselective synthesis of the *C*4′ acylated 1,4-*manno*,*manno*-4′amino disaccharide analogue **3** via the iterative use of highly diastereo- and regioselective palladium-catalyzed allylation reactions.

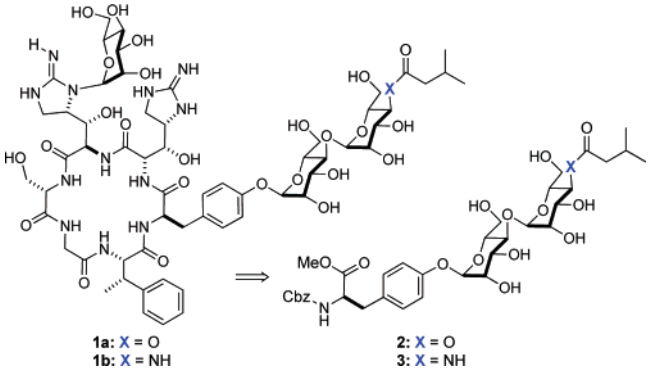


FIGURE 1. Structures of mannopeptimycin-E **1** *C*-4′ amido analogues.

Our retrosynthetic analysis of the aza-disaccharide fragment **3** is outlined in Scheme 1. This route begins with allylic alcohol **6**, which we have previously prepared enroute to the disaccharide **2**, via the sequential application of our Pd(0)-glycosylation/post-glycosylation transformations upon a protected tyrosine **7**.[5,6] Key to this new approach to the *C*4′ amido analogue **3** is the regio- and stereoselective conversion of the allylic alcohol **6** to the allylic azide **5** by a palladium-catalyzed allylic substitution.[7] Finally, we envisioned the *manno*,*manno*-stereochemistry in **3**

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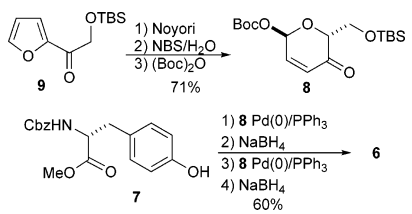
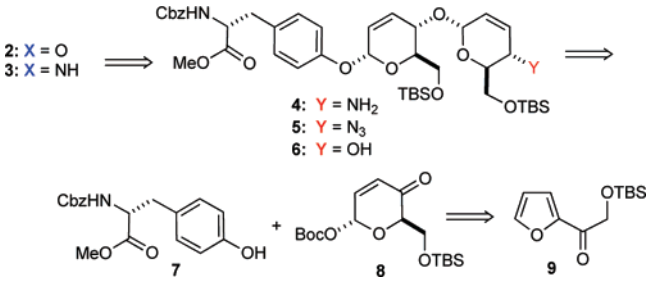
(4) (a) Wang, T.-Z.; Wheless, K. L.; Sutherland, A. G.; Dushin, R. G. *Heterocycles* **2004**, *62*, 131−135. (b) Dushin, R. G.; Wang, T.-Z.; Sum, P. E.; He, H.; Sutherland, A. G.; Ashcroft, J. S.; Graziani, E. I.; Koehn, F. E.; Bradford, P. A.; Petersen, P. J.; Wheless, K. L.; How, D.; Torres, N.; Lenoy, E. B.; Weiss, W. J.; Lang, S. A.; Projan, S. J.; Shlaes, D. M.; Mansour, T. S. *J. Med. Chem.* **2004**, *47*, 3487−3490.
(5) Babu, R. S.; Guppi, S. R.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1605−1608.
(6) We have shown that pyranones like **8** can be prepared in either enantiomeric form from achiral furans like **9** and with highly diastereoselective Pd π-allylation/ketone reduction dimerized to form **6**.



(7) This sort of regio- and stereoselective transformation has been demonstrated in our swainsonine synthesis, see: Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609−1612.

10.1021/jo070326r CCC: $37.00
Published on Web 05/26/2007

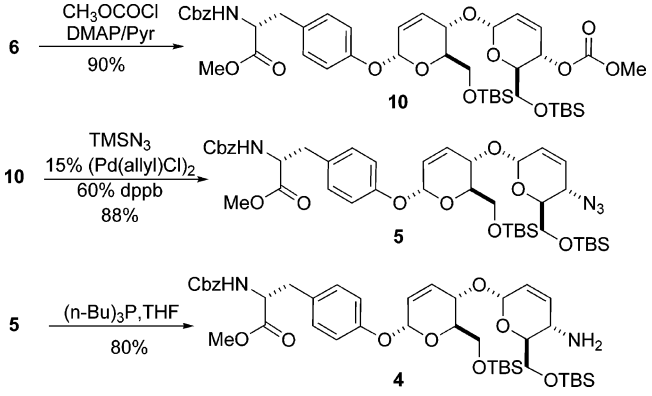
SCHEME 1. Retrosynthetic Analysis of Mannopeptimycin Analogue 3



being installed by an azide reduction/acylation and stereoselective bis-dihydroxylation of a 1,4-linked-*C*4′ amino-bis-pyran **4**.[8] Simply substituting a bis-diimide reduction for the above-mentioned bis-dihydroxylation will also allow for the preparation of a deoxy-analogue (vide infra).

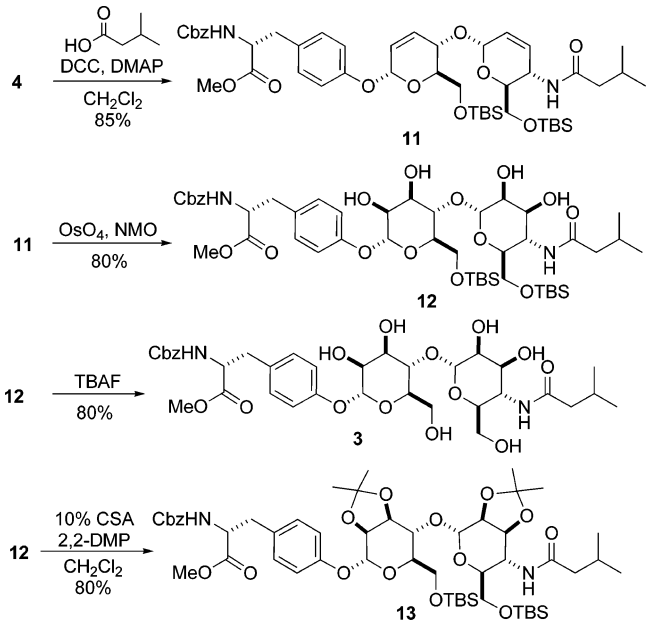
Our divergent approach to the aza-analogue **3** began with the known bis-pyran **6** with the conversion of the allylic alcohol portion into a π-allyl palladium leaving group (Scheme 2). We chose to use the methyl carbonate group as in **10**, which was readily prepared by treating **6** with methyl chloroformate in excellent yield (90%). Exposing carbonate **10** to the conditions developed by Sinou ($TMSN_3$, $(Pd(allyl)Cl)_2$/1,4-bis(diphenylphosphino)butane) at room temperature afforded a single regio- and stereoisomeric allylic azide **5** in good yield (88%).[9] To avoid problems with allylic rearrangements, the allylic azide **5** was immediately reduced with P(*n*-Bu)$_3$/THF to give allylic amine **4** (80%).[10]

SCHEME 2. Synthesis of Allylic Amine 4



The key isovaleryl group was easily installed by treating allylic amine **4** with isovaleric acid and DCC/DMAP in CH_2Cl_2, which provided the *C*4 isovaleryl amide disaccharide precursor **11** in excellent yield (85%) (Scheme 3). The *manno*-stereochemistry in **12** was diastereoselectively introduced upon exposure of **12** to the Upjohn conditions (OsO_4/NMO, 80%).[11] To complete the model system both TBS-ethers were easily

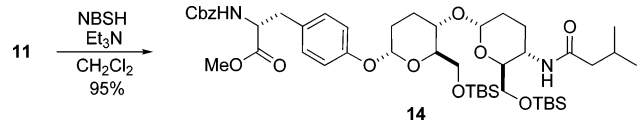
SCHEME 3. Synthesis of Tyrosine-bis-*manno*-amido Disaccharides 3 and 13



removed with TBAF (0 °C in THF) affording the 1,4-linked-bis-*manno*-4′-amido-disaccharide **3** in good yield (80%). In addition, the fully protected disaccharide **13** was also prepared for macrocyclic peptide assembly. This was easily accomplished by converting the bis-*manno*-*C*4′-amido disaccharide **12** to the bis-acetonide **13** (10 mol % CSA/2,2-DMP, 80%).

Finally, the 2,3-deoxy analogue **14** was readily prepared by an exhaustive diimide reduction (Scheme 4). Both double bonds of **11** were reduced with excess diimide precursor (NBSH) in CH_2Cl_2 affording the 2,3-deoxy-*C*4′-amido bis-pyranoside **14** in excellent yield (95%).[5,12]

SCHEME 4. Synthesis of Bis-2,3-dideoxyamido Disaccharide Analogue 14



In summary, two 1,4-linked-bis-*manno*-4′-amido-disaccharide analogues of mannopeptimycin-E have been synthesized in 10 steps with 21% overall yield from D-tyrosine via an iterative palladium-catalyzed glycosylation strategy. Key to the success of this approach was the use of a palladium-catalyzed azide allylation reaction for the stereoselective installation of the *C*4 isovaleramide group. Application of this methodology toward the synthesis of mannopeptimycin-E analogues (**1b**) and their subsequent biological investigation is ongoing.

Experimental Section[13]

(1′*S*,4′*S*,5′*R*,1*S*,4*S*,5*R*)-1-[1′-*N*-Carbobenzyloxy-D-tyrosine methoxycarbonyl-5′-(*tert*-butyldimethylsilanyloxymethyl)-1′,4′-dihydro-5′*H*-pyran-4′-yloxy]-5-(*tert*-butyldimethylsilanyloxymethyl)-

(8) (a) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428−3429. (b) Babu, R. S.; O'Doherty, G. A. *J. Carbohydr. Chem.* **2005**, *24*, 169−177. (c) Guppi, S. R.; Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 293−296.

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(13) Presented in the Experimental Section, for space considerations, is a partial list of the procedures and spectral data. Complete experimental procedures and spectral data for all new compounds are presented in the Supporting Information.

1,4-dihydro-5*H*-pyran-*O*-4-methyl Carbonate (10). To a solution of allylic alcohol **6** (400 mg, 0.50 mmol) in dry CH_2Cl_2 (1.0 mL) at 0 °C was added pyridine (242 μL, 3.00 mmol), DMAP (30 mg), and methyl chloroformate (283 mg, 3.00 mmol). After the solution was stirred for 24 h at room temperature, water (3 mL) was added and then the mixture was extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified by using silica gel flash chromatography eluting with EtOAc/hexane (15:85) to give carbonate **10 (**402.4 mg, 0.45 mmol, 90%) as a viscous oil. R_f (30% EtOAc/hexane) =0.65; $[\alpha]^{26}_D$ +50 (c = 1, CH_2Cl_2); IR (thin film, cm^{-1}) 2928, 2885, 1748, 1441, 1509, 1266, 1090, 981, 865; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 7.00 (m, 4H), 6.18 (d, J = 10.2 Hz, 1H), 6.01 (d, J = 10.2 Hz, 1H), 5.94 (dd, J = 2.4, 1.8 Hz, 1H), 5.92 (ddd, J = 10.8, 2.4, 1.8 Hz, 1H), 5.77 (ddd, J = 10.2, 3.0, 1.8 Hz, 1H), 5.59 (d, J = 1.8 Hz, 1H), 5.31 (dd, J = 3.0, 1.8 Hz, 1H), 5.29 (dd, J = 3.0, 2.4 Hz, 1H), 5.11 (d, J = 12.6 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.61 (ddd, J = 8.4, 6.0, 5.4 Hz, 1H), 4.43 (d, J = 9.6 Hz, 1H), 3.88 (dd, J = 5.4, 2.4 Hz, 1H), 3.86 (dd, J = 6.0, 2.4 Hz, 1H), 3.84 (dd, J = 4.8, 1.8 Hz, 1H), 3.83 (dd, J = 4.8, 2.4 Hz, 1H), 3.81 (dd, J = 4.8, 1.8 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 1H), 3.71 (s, 3H), 3.07 (ddd, J = 8.4, 5.4, 5.4 Hz, 1H), 3.05 (ddd, J = 7.8, 6.0, 5.4 Hz, 1H), 0.89 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 156.6, 155.6, 155.0, 136.2, 130.3, 130.1 (2C), 129.4, 129.0, 128.5 (2C), 128.1, 128.0, 127.6, 126.2, 117.2, 117.0, 109.9, 92.9, 91.0, 71.4, 69.3, 68.4, 66.9, 66.4, 62.7, 62.0, 54.9, 54.8, 52.2, 37.4, 25.93 (3C), 25.91 (3C), 18.43, 18.42, −5.0, −5.2, −5.4 (2C); CIHRMS calcd for $[C_{44}H_{65}NO_{13}Si_2Na^+]$ 894.3892, found 894.3890.

(1′*S*,4′*S*,5′*R*,1*S*,4*S*,5*R*)-1-[1′-*N*-Carbobenzyloxy-D-tyrosine methoxycarbonyl-5′-(*tert*-butyldimethylsilanyloxymethyl)-1′,4′-dihydro-5′*H*-pyran-4′-yloxy]-5-(*tert*-butyldimethylsilanyloxymethyl)-4-azido-1,4-dihydro-5*H*-pyran (5). To a mixture of carbonate **10** (210 mg, 0.24 mmol), allylpalladium chloride dimer (13.2 mg, 0.03 mmol), and 1,4-bis(diphenylphosphino)butane (61.6 mg, 0.13 mmol) in anhydrous THF (0.25 mL) was added $TMSN_3$ (277 mg, 1.20 mmol) under argon atmosphere. The solution was stirred at room temperature for 3 h. Then the mixture was evaporated under reduced pressure and purified with silica gel flash chromatography eluting with EtOAc/hexane (15:85) to give allylic azide **5** (182 mg, 0.21 mmol, 88%) as a viscous oil. R_f (30% EtOAc/hexane) 0.70; $[\alpha]^{26}_D$ +65 (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 2952, 2929, 2856, 2103, 1726, 1510, 1253, 1043, 993, 830; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.99 (m, 4H), 6.18 (d, J = 10.2 Hz, 1H), 6.00 (d, J = 10.2 Hz, 1H), 5.94 (ddd, J = 10.8, 2.4, 1.8 Hz, 1H), 5.83 (ddd, J = 10.2, 3.0, 2.4 Hz, 1H), 5.59 (d, J = 2.4 Hz, 1H), 5.26 (d, J = 1.8 Hz, 1H), 5.11 (d, J = 12.6 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.62 (ddd, J = 7.8, 6.0, 5.4 Hz, 1H), 4.42 (d, J = 9.0 Hz, 1H), 4.14 (dd, J = 3.8, 1.8 Hz, 1H), 4.12 (dd, J = 10.2, 1.8 Hz, 1H), 3.92 (d, J = 3.0 Hz, 1H), 3.90 (d, J = 3.0 Hz, 1H), 3.88 (ddd, J = 4.2, 3.6, 3.0 Hz, 1H), 3.86 (d, J = 1.8 Hz, 1H), 3.80 (dd, J = 4.2, 2.4 Hz, 1H), 3.71 (s, 3H), 3.65 (ddd, J = 9.0, 3.0, 1.8 Hz, 1H), 3.08 (ddd, J = 8.4, 6.0, 5.4 Hz, 1H), 3.04 (ddd, J = 8.4, 6.0, 5.4 Hz, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.099 (s, 3H), 0.094 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 156.6, 155.6, 136.2, 130.3, 130.1 (2C), 129.0 (2C), 128.5 (2C), 128.1, 128.0 (2C), 126.2, 117.2 (2C), 109.9, 92.9, 90.8, 71.3, 70.5, 66.9, 66.2, 62.6, 62.4, 54.8, 53.4, 52.2, 37.3, 25.9 (6C), 18.4 (2C), −5.0, −5.2 (2C), −5.3; CIHRMS calcd for $[C_{42}H_{62}N_4O_{10}Si_2Na^+]$ 861.3902, found 861.3910.

(1′*S*,4′*S*,5′*R*,1*S*,4*S*,5*R*)-1-[1′-*N*-Carbobenzyloxy-D-tyrosine methoxycarbonyl-5′-(*tert*-butyldimethylsilanyloxymethyl)-1′,4′-dihydro-5′*H*-pyran-4′-yloxy]-5-(*tert*-butyldimethylsilanyloxymethyl)-4-amino-1,4-dihydro-5*H*-pyran-(4). To a solution of azide **5** (140 mg, 0.16 mmol) in THF/H_2O (9:1, v/v, 0.3 mL) was added (n-Bu)$_3$P (84 mg, 0.41 mmol), then the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated with a little silica gel under reduced pressure and the crude product was purified with silica gel flash chromatography eluting with MeOH/EtOAc/hexane (10:40:50) to give allylic amine **4** (104 mg, 0.13 mmol, 80%) as a colorless oil. R_f 0.50 (10:40:50 MeOH/EtOAc/hexane); $[\alpha]^{26}_D$ +24 (c 1, MeOH); IR (thin film, cm^{-1}) 3361, 2944, 2833, 1740, 1448, 1374, 1240, 1120, 1040, 981, 847; ^{1}H NMR (600 MHz, CD_3OD) δ 7.27 (m, 5H), 6.99 (m, 4H), 6.21 (d, J = 9.6 Hz, 1H), 5.91 (d, J = 10.2 Hz, 1H), 5.84 (ddd, J = 10.2, 10.2, 8.4 Hz, 1H), 5.69 (ddd, J = 11.4, 10.2, 10.2 Hz, 1H), 5.59 (d, J = 2.4 Hz, 1H), 5.22 (br s, 1H), 5.02 (d, J = 12.6 Hz, 1H), 4.95 (d, J = 12.6 Hz, 1H), 4.36 (m, 1H), 4.27 (d, J = 9.0 Hz, 1H), 3.91 (dd, J = 10.8, 4.2 Hz, 1H), 3.86 (m, 1H), 3.83 (dd, J = 6.0, 3.0 Hz, 1H), 3.80 (dd, J = 10.2, 4.2 Hz, 1H), 3.75 (dd, J = 10.8, 6.0 Hz, 1H), 3.65 (s, 3H), 3.50 (ddd, J = 9.6, 4.2, 3.6 Hz, 1H), 3.46 (ddd, J = 9.0, 4.8, 4.2 Hz, 1H), 3.36 (dd, J = 11.4, 9.6 Hz, 1H), 3.03 (ddd, J = 8.4, 6.0, 5.4 Hz, 1H), 2.85 (ddd, J = 8.4, 6.0, 5.4 Hz, 1H), 2.11 (s, 2H), 0.89 (d, J = 4.2 Hz, 9H), 0.79 (d, J = 5.4 Hz, 9H), 0.77 (d, J = 4.2 Hz, 6H), −0.004 (s, 3H), −0.02 (d, J = 2.4 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 174.1, 158.5, 158.0, 138.3, 132.0, 131.7, 131.3, 129.5 (2C), 129.0, 128.7, 127.5, 118.5, 118.1, 94.5, 92.6, 74.8, 73.1, 68.3, 67.7, 65.0, 64.4, 57.2, 52.8, 37.9, 33.2, 30.8, 30.5, 30.0, 26.67 (3C), 26.61 (3C), 23.8, 19.4, 14.5, −4.3, −4.6, −4.7, −4.9; CIHRMS calcd for $[C_{42}H_{64}N_2O_{10}Si_2H^+]$ 813.4177, found 813.4177.

(1′*S*,4′*S*,5′*R*,1*S*,4*S*,5*R*)-1-[1′-*N*-Carbobenzyloxy-D-tyrosine methoxycarbonyl-5′-(*tert*-butyldimethylsilanyloxymethyl)-1′,4′-dihydro-5′*H*-pyran-4′-yloxy]-5-(*tert*-butyldimethylsilanyloxymethyl)-1,4-dihydro-5*H*-pyran-*N*-4-isovaleric Amide (11). The amine compound **4** (100 mg, 0.12 mmol), isovaleric acid (15 mg, 0.15 mmol), and DCC (30 mg, 0.14 mmol) were dissolved in 0.3 mL of CH_2Cl_2 in a round-bottomed flask and cooled to 0 °C then DMAP (2 mg, 0.01 mmol) was added and the reaction mixture was stirred at 0 °C for 6 h and on completion, as monitored by TLC, the reaction mixture was diluted with ether and quenched with 5 mL of satd aq $NaHCO_3$, extracted (3 × 5 mL) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified with silica gel flash chromatography eluting with EtOAc/hexanes (30:70) to give amide **11** (94 mg, 0.10 mmol, 85%) as a viscous oil. R_f (30% EtOAc/hexanes) 0.70; $[\alpha]^{26}_D$ +4 (c 1, CH_2Cl_2); IR (thin film, cm^{-1}) 2985, 2927, 1736, 1447, 1372, 1253, 1098, 1043, 938, 846; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.00 (m, 4H), 6.20 (d, J = 10.8 Hz, 1H), 5.92 (ddd, J = 10.2, 3.0, 1.8 Hz, 1H), 5.81 (d, J = 10.2 Hz, 1H), 5.71 (ddd, J = 10.2, 3.0, 2.4 Hz, 1H), 5.56 (d, J = 2.4 Hz, 1H), 5.21 (m, 1H), 5.07 (br s, 2H), 4.58 (dd, J = 10.2, 5.4 Hz, 1H), 4.52 (d, J = 8.4 Hz, 1H), 4.32 (d, J = 9.0 Hz, 1H), 3.90 (m, 1H), 3.86 (d, J = 11.4 Hz, 1H), 3.82 (m, 2H), 3.76 (ddd, J = 11.4, 5.4, 4.8 Hz, 1H), 3.72 (dd, J = 11.4, 3.0 Hz, 1H), 3.69 (s, 3H), 3.66 (dd, J = 3.0, 2.4 Hz, 1H), 3.64 (dd, J = 4.2, 2.4 Hz, 1H), 3.03 (m, 2H), 2.11 (m, 1H), 2.00 (d, J = 7.8 Hz, 2H), 0.93 (d, J = 6.6 Hz, 6H), 0.87 (s, 9H), 0.80 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 156.6, 155.6, 136.2, 133.1, 130.5, 130.1, 129.0, 128.4 (2C), 128.1 (2C), 128.0 (2C), 126.1, 125.4 (2C), 117.2 (2C), 92.8, 91.1, 71.4, 70.0, 66.9 (2C), 66.8, 66.7, 65.3 (2C), 62.6, 54.8, 52.2, 37.3, 27.3, 25.9 (3C), 25.8 (3C), 24.0, 18.3, 18.2, −5.0, −5.1, −5.4, −5.6; CIHRMS calcd for $[C_{47}H_{72}N_2O_{11}Si_2Na^+]$ 919.4572, found 919.4543.

1′-*N*-carbobenzyloxy-D-tyrosine Methoxycarbonyl-5′,5-(*tert*-butyldimethylsilanyloxymethyl)-di-1,4-α-D-mannose-*N*-4-isovaleric Amide (12). To a CH_2Cl_2 (1.3 mL) solution of diene amide **11** (120 mg, 0.13 mmol) at 0 °C was added a solution of (50% w/v) *N*-methyl morpholine *N*-oxide/water (0.1 mL). Crystalline OsO_4 (3.4 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and pipetted directly onto a silica gel column with CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexanes (10:40:50). Pure fractions were combined and concentrated to afford bis-*manno*-amido-tetrol **12** (128 mg, 0.13 mmol, 80%) as a viscous oil. R_f (90% EtOAc/MeOH)

0.40; $[\alpha]^{26}_D$ +12 (*c* 1, CH_2Cl_2); IR (thin film, cm^{-1}) 2956, 2928, 1738, 1733, 1510, 1253, 1219, 1123, 986, 835; ^1H NMR (600 MHz, CD_3OD) δ 7.30 (m, 5H), 6.98 (m, 4H), 5.45 (d, J = 1.2 Hz, 1H), 5.34 (d, J = 1.8 Hz, 1H), 5.22 (d, J = 1.8 Hz, 1H), 5.01 (d, J = 12.6 Hz, 1H), 5.00 (d, J = 12.6 Hz, 1H), 4.50 (br s, 1H), 4.37 (dd, J = 8.4, 5.4 Hz, 1H), 4.34 (dd, J = 9.0, 4.8 Hz, 1H), 4.06 (dd, J = 14.4, 7.2 Hz, 1H), 4.02 (dd, J = 6.6, 6.6 Hz, 1H), 3.99 (dd, J = 9.0, 4.2 Hz, 1H), 3.93 (dd, J = 6.0, 4.2 Hz, 1H), 3.91 (m, 1H), 3.85 (d, J = 11.4 Hz, 1H), 3.82 (dd, J = 6.0, 5.4 Hz, 1H), 3.81 (dd, J = 9.6, 5.4 Hz, 1H), 3.73 (dd, J = 6.6, 3.0 Hz, 1H), 3.72 (d, J = 3.0 Hz, 1H), 3.70 (dd, J = 3.0, 1.8 Hz, 1H), 3.68 (dd, J = 6.0, 1.8 Hz, 1H), 3.65 (s, 3H), 3.60 (m, 1H), 3.03 (dd, J = 9.6, 4.8 Hz, 1H), 3.02 (dd, J = 9.0, 4.8 Hz, 1H), 2.86 (dd, J = 9.0, 4.2 Hz, 1H), 2.84 (dd, J = 9.6, 4.2 Hz, 1H), 2.15 (m, 1H), 2.04 (dd, J = 5.4, 1.8 Hz, 1H), 2.02 (dd, J = 4.8, 1.2 Hz, 1H), 0.87 (d, J = 6.0 Hz, 6H), 0.81 (s, 9H), 0.80 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 173.0, 172.9, 157.3, 155.9, 137.1, 131.1, 130.3 (2C), 128.4 (2C), 127.9, 127.6 (2C), 116.9 (2C), 101.1, 99.0, 73.7, 73.5, 72.5, 72.1, 71.3 (2C), 69.7, 69.4, 66.5, 64.1, 63.3, 56.0, 51.6, 43.5, 36.81, 30.9, 28.8, 25.8 (3C), 25.5 (3C), 21.8, 18.3, 18.2, −5.7, −5.9, −6.1, −6.3; CIHRMS calcd for $[C_{47}H_{76}N_2O_{15}Si_2Na^+]$ 987.4682, found 987.4680.

1′-*N*-Carbobenzyloxy-D-tyrosine Methoxycarbonyl-5′,5-(hydroxymethyl)-di-1,4-α-D-mannose-*N*-4-isovaleric Amide (3). To a THF (0.4 mL, 0.1 M) solution of D-*manno*-tetrol **12** (40 mg, 0.04 mmol) at 0 °C was added a solution of TBAF in THF (85 μL, 0.08 mmol) and the reaction was stirred for 1 h. The reaction mixture was concentrated and pipetted directly onto a silica gel column with CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/EtOAc/hexane (20:40:40). Pure fractions were combined and concentrated to afford hexol **3** (31 mg, 0.04 mmol, 80%) as a viscous oil. R_f (10:50:40 MeOH/EtOAc/hexane) 0.20; $[\alpha]^{26}_D$ +15 (*c* 0.5, CH_3OH); IR (thin film, cm^{-1}) 3330, 2960, 2928, 1735, 1621, 1511, 1232, 1092, 983, 829; ^1H NMR (600 MHz, CD_3OD) δ 7.30 (m, 5H), 6.99 (m, 4H), 5.39 (d, J = 1.2 Hz, 1H), 5.33 (d, J = 1.8 Hz, 1H), 5.23 (d, J = 1.8 Hz, 1H), 5.00 (m, 2H), 4.37 (dd, J = 5.4, 4.8 Hz, 1H), 4.35 (dd, J = 5.4, 4.2 Hz, 1H), 4.16 (dd, J = 11.4, 6.6 Hz, 1H), 4.01 (dd, J = 9.0, 3.6 Hz, 1H), 3.96 (dd, J = 9.6, 6.6 Hz, 1H), 3.91 (dd, J = 3.6, 1.8 Hz, 1H), 3.80 (dd, J = 9.6, 3.0 Hz, 1H), 3.74 (dd, J = 8.4, 4.8 Hz, 1H), 3.71 (dd, J = 8.4, 4.2 Hz, 1H), 3.67 (d, J = 3.0 Hz, 1H), 3.65 (m, 3H), 3.60 (dd, J = 9.0, 4.2 Hz, 1H), 3.58 (dd, J = 9.6, 4.2 Hz, 1H), 3.53 (dd, J = 5.4, 3.0 Hz, 1H), 3.15 (dd, J = 5.4, 2.4 Hz, 1H), 3.05 (dd, J = 9.0, 4.8 Hz, 1H), 3.04 (dd, J = 9.6, 4.8 Hz, 1H), 2.84 (m, 2H), 2.22 (dd, J = 4.8, 1.8 Hz, 1H), 2.19 (dd, J = 5.4, 1.8 Hz, 1H), 2.04 (m, 1H), 0.92 (d, J = 6.6 Hz, 6H); NMR (150 MHz, CD_3OD) δ 174.5, 174.0, 158.4, 156.8, 138.2, 132.2, 131.4 (2C), 129.5 (2C), 129.0, 128.7 (2C), 117.8 (2C), 102.8, 100.1, 75.7, 74.9, 74.0, 73.8, 73.6, 73.0, 72.5, 70.6, 67.6, 65.2, 62.8, 62.4, 57.1, 52.8, 44.4, 37.9, 26.8, 22.9; CIHRMS calcd for $[C_{35}H_{48}N_2O_{15}Na^+]$ 759.2947, found 759.2940.

1′-*N*-Carbobenzyloxy-D-tyrosine Methoxycarbonyl-5′,5-(*tert*-butyldimethylsilanyloxymethyl)-2,3,2′,3′-diacetonide-bis-1,4-α-D-mannose-*N*-4-isovaleric Amide (13). To a CH_2Cl_2 (0.1 mL, 1.0 M) solution of D-*manno*-amido-tetrol **12** (10 mg, 0.01 mmol) and 2,2-dimethoxypropane (2.4 mg, 0.02 mmol) at 0 °C was added CSA (0.23 mg, 10 mol %) and the reaction was stirred for 3 h. The reaction mixture was concentrated and pipetted directly onto a silica gel column with CH_2Cl_2 (1 mL) in three portions. Impurities were eluted with ether and the product was eluted with EtOAc/hexane (50:50). Pure fractions were combined and concentrated to afford di-acetonide **13** (9 mg, 0.01 mmol, 80%) as a viscous oil. R_f (50% EtOAc/hexane) 0.40; $[\alpha]^{26}_D$ +60 (*c* 1, CH_2Cl_2); IR (thin film, cm^{-1}) 2951, 2930, 1731, 1498, 1228, 1009, 831; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.98 (m, 4H), 5.77 (d, J = 10.8 Hz, 1H), 5.39 (d, J = 8.4 Hz, 1H), 5.20 (d, J = 7.8 Hz, 1H), 5.09 (br s, 2H), 4.62 (dd, J = 7.2, 4.8 Hz, 1H), 4.44 (dd, J = 6.0, 1.2 Hz, 1H), 4.32 (d, J = 5.4 Hz, 1H), 4.16 (d, J = 5.4 Hz, 1H), 4.09 (d, J = 4.8 Hz, 1H), 4.08 (dd, J = 10.2, 4.8 Hz, 1H), 3.95 (m, H), 3.72 (s, 3H), 3.69 (m, 2H), 3.69 (m, 1H), 3.62 (d, J = 3.6 Hz, 1H), 3.55 (dd, J = 10.2, 3.0 Hz, 1H), 3.09 (dd, J = 13.2, 6.0 Hz, 1H), 3.03 (dd, J = 12.8, 6.0 Hz, 1H), 2.16 (s, 1H), 2.15 (m, 1H), 2.12 (dd, J = 4.8, 1.2 Hz, 1H), 2.09 (m, 1H), 2.05 (d, J = 3.6 Hz, 1H), 1.65 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 0.95 (d, J = 6.6 Hz, 6H), 0.87 (s, 9H), 0.84 (s, 9H), 0.42 (s, 3H), 0.03 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 156.6, 155.6, 143.8, 136.2, 133.3, 130.2, 130.1 (2C), 129.1 (2C), 128.6 (2C), 128.5, 128.1, 128.0 (2C), 128.8, 126.6, 117.0 (2C), 92.9 (2C), 89.8 (2C), 76.7 (2C), 71.2 (2C), 66.9, 66.5, 62.9 (2C), 62.5, 54.8 (2C), 52.2, 37.3 (2C), 25.85 (3C), 25.83 (3C), 25.7 (2C), 18.35, 18.32, −5.1, −5.3 (2C), −5.4; CIHRMS calcd for $[C_{53}H_{84}N_2O_{15}Si_2H^+]$ 1045.5488, found 1045.5503.

Acknowledgment. We would like to thank Dr. Novruz G. Akhmedov for his helpful discussions. We are grateful to WVU-ARTS program, NIH (GM63150), and NSF (CHE-0415469) for the support of our research program and NSF-EPSCoR (0314742) for a 600 MHz NMR spectrometer at WVU.

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070326R