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Synthesis of aza-analogues of the glycosylated tyrosine portion of Mannopectimycin-E

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Abstract

Two C4' amido disaccharide analogues of mannopectimycin-E were synthesized via an iterative palladium glycosylation sequence. The stereoselective synthesis of the C4' acylated 1,4- 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 hexapeptide with alternating D- and L-amino acids, the mannopectimycins, were isolated as part of this quest. Of the mannopectimycins, mannopectimycin-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 Wyeth³ have synthesized several analogues of mannopectimycin-E. In addition to this isolation/semi-synthetic and synthetic work,⁴ we have been working towards the preparation of mannopectimycin-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 mannopectimycin-E **2**.⁵ In particular, we were interested in the critical role of the C4' isovaleryl group and its specific location played on antibacterial activity.² It has been shown that removal or migration of the C4' isovalerate substitution on the terminal mannose leads to a substantial decrease in antibacterial potency.² Along a 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 C4' acylated 1,4-manno,manno-4' amino disaccharide analogue **3** via the iterative use of highly diastereo- and regioselective palladium-catalyzed allylation reactions.

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 C4' 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** being installed by an azide reduction/acylation and stereoselective bis-dihydroxylation of a 1,4-linked-C4 aminobis 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*).

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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 (TMSN₃, 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 In order 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

The key isovaleryl group was easily installed by treating allylic amine **4** with isovaleric acid and DCC/DMAP in CH₂Cl₂, which provided the C4 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 (OsO₄/NMO, 80%).¹¹ To complete the model system both TBS-ethers were easily 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*-C4'-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 using excess diimide precursor (NBSH) in CH₂Cl₂ affording the 2,3-deoxy-C4'-amido bis-pyranoside **14** in excellent yield (95%).^{5, 12}

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 C4 isovaleramide group. Application of this methodology towards the synthesis of mannopeptimycin-E analogues (**1b**) and their subsequent biological investigation is ongoing.

Experimental Section¹³

(1'S,4'S,5'R,1S,4S,5R)-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-O-4-methyl carbonate (**10**)

To a solution of allylic alcohol **6** (400 mg, 0.50 mmol) in dry CH₂Cl₂ (1.0 mL) at 0 °C, was added pyridine (242 μ L, 3.00 mmol), DMAP (30 mg), and methyl chloroformate (283 mg, 3.00 mmol). After stirring 24 h at room temperature, water (3 mL) was added and then the mixture was extracted with EtOAc (3 $\times$ 10 mL), dried (Na₂SO₄), concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexane (15:85) to give carbonate **10** (402.4 mg, 0.45 mmol, 90%) as viscous oil. *R*_f (30% EtOAc/hexane) = 0.65; [α]_D²⁶ = +50 (*c* = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2928, 2885, 1748, 1441, 1509, 1266, 1090, 981, 865; ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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,1S,4S,5R)-1-[1'-N-carbobenzoyloxy-D-tyrosine methoxycarbonyl -5'-(tert-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(tert-butyl-dimethylsilanyloxymethyl)-4-azido-1,4-dihydro-5H-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 TMSN₃ (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, purified using silica gel flash chromatography eluting with EtOAc/hexane (15:85) to give allylic azide **5** (182 mg, 0.21 mmol, 88%) as viscous oil. R_f (30% EtOAc/hexane) = 0.70;

$[\alpha]_D^{26} = +65$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 2952, 2929, 2856, 2103, 1726, 1510, 1253, 1043, 993, 830; ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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,1S,4S,5R)-1-[1'-N-carbobenzoyloxy-D-tyrosine methoxycarbonyl -5'-(tert-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'H-pyran-4'-yloxy]-5-(tert-butyl-dimethylsilanyloxymethyl)-4-amino-1,4-dihydro-5H-pyran (4)

To a solution of azide **5** (140 mg, 0.16 mmol) in THF/H₂O (9:1, v/v, 0.3 ml) was added (*n*-Bu)₃P (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 using 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); $[\alpha]_D^{26} = +24$ ($c = 1$, MeOH); IR (thin film, cm⁻¹) 3361, 2944, 2833, 1740, 1448, 1374, 1240, 1120, 1040, 981, 847; ¹H NMR (600 MHz, CD₃OD) 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); ¹³C NMR (150 MHz, CD₃OD) 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,1S,4S,5R)-1-[1'- *N*-carbobenzyloxy-D-tyrosine methoxycarbonyl -5'-(*tert*-butyl-dimethylsilanyloxymethyl)-1',4'-dihydro-5'*H*-pyran-4'-yloxy]-5-(*tert*-butyl-dimethylsilanyloxymethyl)-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 CH₂Cl₂ in a round bottom 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 hours and on completion, as monitored by TLC, the reaction mixture was diluted with ether and was quenched with 5 mL of satd. aq. NaHCO₃, extracted (3 × 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with EtOAc/hexanes (30:70) to give amide **11** (94 mg, 0.10 mmol, 85%) as viscous oil. *R*_f (30% EtOAc/hexanes) = 0.70; [α]_D²⁶ = +4 (*c* = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2985, 2927, 1736, 1447, 1372, 1253, 1098, 1043, 938, 846; ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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 [C₄₇H₇₂N₂O₁₁Si₂Na⁺]: 919.4572. Found 919.4543.

1'- *N*-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(*tert*-butyl-dimethylsilanyloxymethyl)-di-1,4-α-D-mannose-*N*-4 isovaleric amide (12)

To a CH₂Cl₂ (1.3 mL) solution of diene amide **11** (120 mg, 0.13 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide / water (0.1 mL). Crystalline OsO₄ (3.4 mg, 10 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (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 viscous oil. *R*_f (90% EtOAc/MeOH) = 0.40; [α]_D²⁶ = +12 (*c* = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 2956, 2928, 1738, 1733, 1510, 1253, 1219, 1123, 986, 835; ¹H NMR (600 MHz, CD₃OD) 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); ¹³C NMR (150 MHz, CD₃OD) 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 [C₄₇H₇₆N₂O₁₅Si₂Na⁺]: 987.4682. Found 987.4680.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(hydroxy methyl)-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 μ L, 0.08 mmol) and the reaction was stirred for 1 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using CH₂Cl₂ (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 viscous oil. R_f (10:50:40 MeOH/EtOAc/hexane) = 0.20; $[\alpha]_D^{26} = +15$ ($c = 0.5$, CH₃OH); IR (thin film, cm⁻¹) 3330, 2960, 2928, 1735, 1621, 1511, 1232, 1092, 983, 829; ¹H NMR (600 MHz, CD₃OD) 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, CD₃OD) 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 [C₃₅H₄₈N₂O₁₅Na⁺]: 759.2947. Found 759.2940.

1'-N-carbobenzyloxy-D-tyrosine methoxycarbonyl -5',5-(*tert*-butyl-dimethylsilanyloxymethyl)-2,3,2',3'-di acetonide-bis-1,4- α -D-mannose-N-4-isovaleric amide (13)

To a CH₂Cl₂ (0.1 mL, 1.0M) 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 was pipetted directly on to a silica gel column using CH₂Cl₂ (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 viscous oil. R_f (50% EtOAc/Hexane) = 0.40; $[\alpha]_D^{26} = +60$ ($c = 1$, CH₂Cl₂); IR (thin film, cm⁻¹) 2951, 2930, 1731, 1498, 1228, 1009, 831; ¹H NMR (600 MHz, CDCl₃) 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, 1H), 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); ¹³C NMR (150 MHz, CDCl₃) 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 [C₅₃H₈₄N₂O₁₅Si₂H⁺]: 1045.5488. Found 1045.5503.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 Supporting Information.

Figure 1.
Structures of mannopeptimycin-E **1** C-4' amido-analogues.

Scheme 1.

Retrosynthetic analysis of mannopeptimycin analogue 3.

Scheme 2.
Synthesis of allylic amine **4**.

Scheme 3.
Synthesis of tyrosine-bis-*manno*-amido disaccharides **3** and **13**.

Scheme 4.
Synthesis of bis-2,3-dideoxy-amido disaccharide analogue **14**.