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Synthetic Studies toward Mannopeptimycin-E: Synthesis of the *O*-Linked Tyrosine 1,4-α,α-*manno,manno*-Pyranosyl Pyranoside

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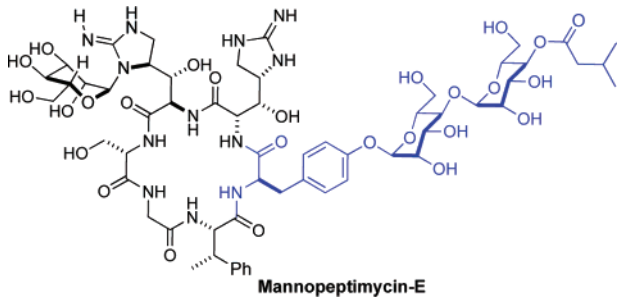
ABSTRACT



The enantioselective synthesis of the *C*-4′ acylated 1,4-α,α-*manno,manno*-disaccharide fragment of mannopeptimycin-E has been achieved in seven steps from D-tyrosine. The route relies upon diastereoselective palladium-catalyzed glycosylation, diastereoselective reduction, and diastereoselective bis-dihydroxylation. The efficiency of the synthesis is demonstrated by the high overall yield (37%) and the preparation of various analogues.

The continuing emergence of bacterial resistance to traditional antibiotics has inspired a never-ending search for new antibiotics.[1] The five mannopeptimycins (**1a**−**e**) were isolated from the fermentation broths of *Streptomyces hygroscopicus* LL-AC98 and related mutant strains.[2] The key structural features of the mannopeptimycins are a cyclic hexapeptide core with alternating D- and L-amino acids, three of which are rare. Two of the amino acids (β-D-hydroxyenuricididine and D-tyrosine) are glycosylated with mannose sugars. The glycosylated amino acids are an *N*-glycosylated β-hydroxyenuricididine with an α-mannose and an *O*-glycosylated tyrosine with a α-(1,4-linked)-bis-*manno*-pyranosyl pyranoside.

The unique structure and unprecedented biological activity have inspired both biological[2,3] and synthetic studies[4] from labs at Wyeth Pharmaceuticals. Among the mannopeptimycins, mannopeptimycin-E (**1e**, Scheme 1) was reported as the most active member against methicillin-resistant staphylococci and vancomycin-resistant enterococci (Table 1).[5]

A particularly interesting aspect of the SAR for the mannopeptimycins is how the specific placement of the isovalerate group on the bis-*manno*-disaccharide correlates with its antibacterial activity. It has been shown that *C*-4 isovalerate substitution on the terminal mannose leads to a

(1) Walsh, C. T. *Nature* **2000**, *406*, 775−781.
(2) He, H.; Williamson, R. T.; Shen, B.; Grazaini, E. I., Yang, H. Y.; Sakya, S. M.; Petersen, P. J.; Carter, G. T. *J. Am. Chem. Soc.* **2002**, *124*, 9729−9736.
(3) (a) Petersen, P. J.; Wang, T. Z.; Dushin, R. G.; Bradford, P. A. *Antimicrob. Agents Chemother.* **2004**, *48*, 739−746. (b) Sum, P. E.; How, D.; Torres, N.; Petersen, P. J.; Lenoy, E. B.; Weiss, W. J.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1151−1155. (c) He, H.; Shen, B.; Petersen, P. J.; Weiss, W. J.; Yang, H. Y.; Wang, T.-Z.; Dushin, R. G.; Koehn, F. E.; Carter, G. T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 279−282.
(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.

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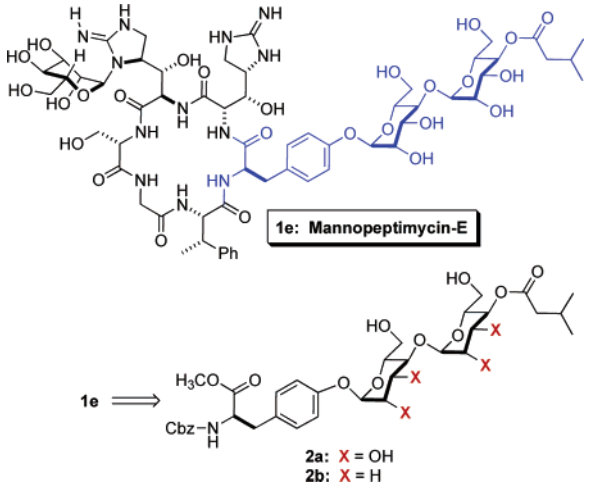
Scheme 1. Structure of Mannopeptimycin-E **1e**

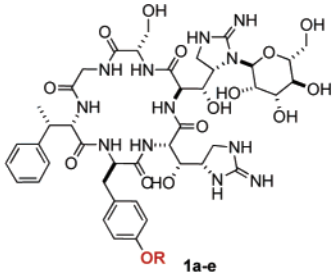


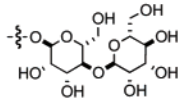
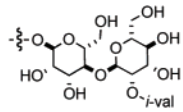
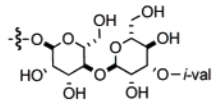
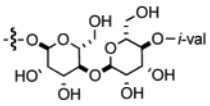
substantial increase in antibacterial potency. For instance, mannopeptimycins-C and -D, which have *C*-2 and *C*-3 isovalerate groups, respectively, have reduced activity, whereas mannopeptimycins-A and -B, which lack isovalerate substitution, have even lower activity (Table 1).[5]

Although the total synthesis of mannopeptimycin has not been reported, Wang et al. have reported a synthesis of cyclic peptides related to mannopeptimycin having a *C*-4/*C*-6 acetal as an isovalerate substitute.[4a] This work also confirmed the importance of the *C*-4 isovaleryl group for antibiotic activity. The critical role isovalerate substitution has on the antibacterial activity of the mannopeptimycin-E inspired us to pursue a synthesis of an appropriate *O*-glycosylated D-tyrosine with *C*-4 isovalerate substitution (e.g., **2a** and **2b**, Scheme 1).[6] In addition to our desire to synthesize and test the mannopeptimycin analogues **2a** and **2b**, we felt that the synthesis of **2a** would serve as part of a model study for our synthesis of the natural product. In addition, the preparation of **3b**, a fully protected bis-glycosylated tyrosine (Scheme 2), would be of use for the synthesis of mannopeptimycin E. Herein, we report the successful implementation of our palladium-catalyzed glycosylation reaction[7,8] for the de novo installation of both a D,D- and an L,L-bis-*manno*-disaccharide fragment on a D-tyrosine. The flexibility of the approach is demonstrated by the syntheses of bis-2,3-dideoxy analogues in their D,D- and an L,L-forms.[9]

Our retrosynthetic analysis of the disaccharide fragment **2a** and its fully protected variant **3b** is outlined in Scheme

Table 1. Activities of the Mannopeptimycins[5]



mannopeptimycin A-E	MIC range (μg/mL) MRSA[a]	MIC range (μg/mL) *Enterococcus faecium*[b]
1a R = 	>128	>128
1b R = **H**	64-128	32->128
1c R = 	8	16-64
1d R = 	8	8-64
1e R = 	4	4-32

[a] Methicillin-resistant *S. aureus*. [b] A range of activities vs four lines of vancomycin resistant. [c] *i*-val = *i*-valerate.

2. We envisioned that the *manno*-stereochemistry in both **2a** and **3b** could be installed by a diastereoselective ketone reduction and a bis-dihydroxylation of a 1,4-linked pyran/pyranone **4**. Similarly, we believed that the pyran/pyranone **4** could be assembled using a diastereoselective palladium-catalyzed glycosylation of tyrosine **5**.[7] Recently, we reported a diastereoselective palladium-catalyzed glycosylation reaction that used alcohols as nucleophiles and pyranones such as **6** as glycosyl donors. Thus, sequential application of our Pd(0)-glycosylation/$NaBH_4$ reduction/Pd(0)-glycosylation sequence to tyrosine **5** and pyranone **6** was expected to allow for the rapid preparation of **4**. Replacing the above-mentioned bis-dihydroxylation with a bis-diimide reduction might also allow for the preparation of the deoxy analogue **2b**. Previously, we have shown that pyranone **6** can be prepared in either enantiomeric form. Thus, this procedure was expected to allow the incorporation of either D- or L-sugars.[10]

Our synthesis studies began with the protected D-tyrosine **5** and pyranone **6** which, when exposed to 1 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 2.5 mol % of PPh_3, underwent a diastereoselective glycosylation with complete α-selectivity to afford the pyranone **8** in 92% yield. A diastereoselective 1,2-

(5) Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Janso, J. E.; Luckman, S. W.; Lenoy, E. B.; Bradford, P. A.; Testa, R. T.; Greenstein, M. *Antimicrob. Agents Chemother.* **2003**, *47*, 62−69.

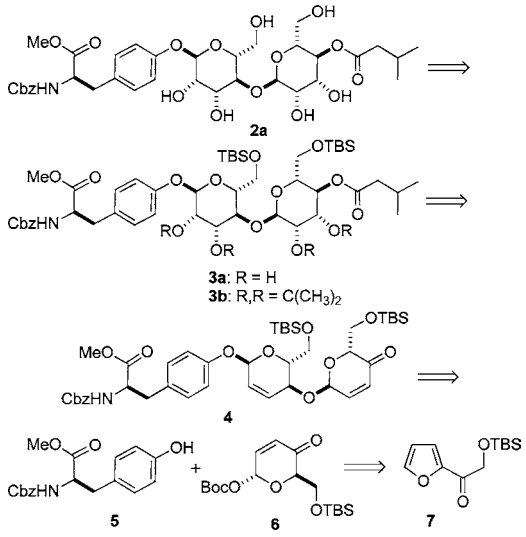
(6) We were mindful of Kahne's discovery of simple disaccharide fragments of vancomycin with significant activity toward vancomycin resistance bacteria, see: Sun, B.; Chen, Z.; Eggert, U. S.; Shaw, S. J.; LaTour, J. V.; Kahne, D. *J. Am. Chem. Soc.* **2001**, *123*, 12722−12723.

(7) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406−12407.

(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) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. VI, p 342.

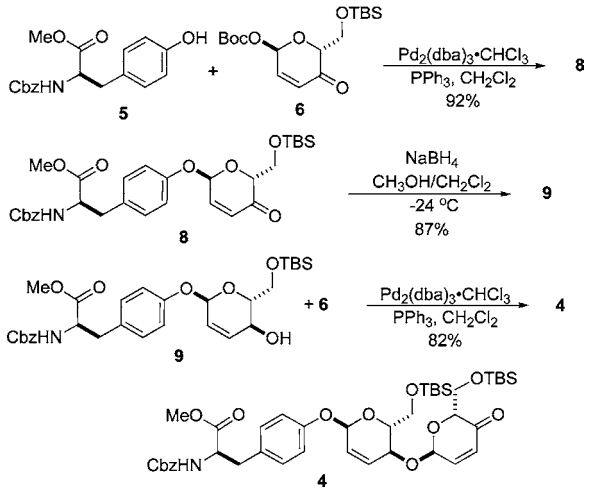
(9) Presumably, the L,L-diastereomer and the bis-2,3-dideoxy analogues of mannopeptimycin-E would have improved bioavailability.

Scheme 2. Retrosynthetic Analysis of Mannopeptimycins



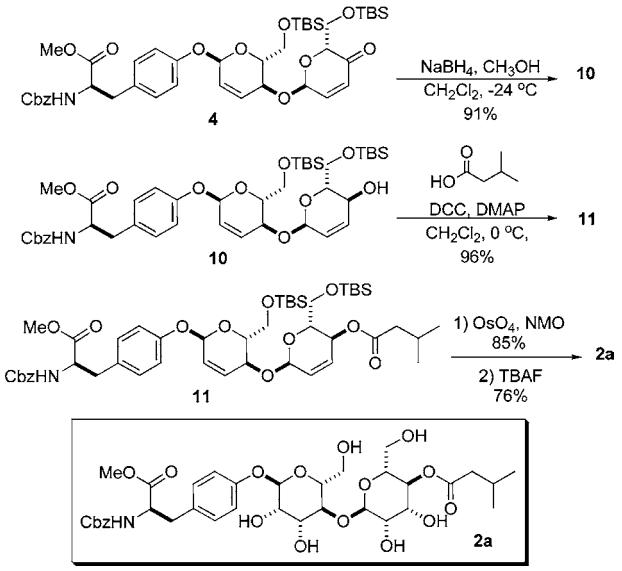
reduction of the enone **8**, when subjected to $NaBH_4$ in CH_2Cl_2/MeOH (1:1) at −24 °C, afforded allylic alcohol **9** as a single diastereomer (dr > 20:1). We next investigated the viability of the *C*-4 alcohol in the Pd-catalyzed glycosylation. Exposing allylic alcohol **9** to a second glycosylation using 1.2 equiv of pyranone **6** and 1 mol % of Pd catalyst (1:2.5, $Pd_2(dba)_3$•$CHCl_3$/PPh_3) afforded the 1,4-linked-α-bis pyranone **4** in good yield (82%) and virtually complete stereocontrol (Scheme 3).

Scheme 3. De Novo Synthesis of Pyran/Pyranone **4**



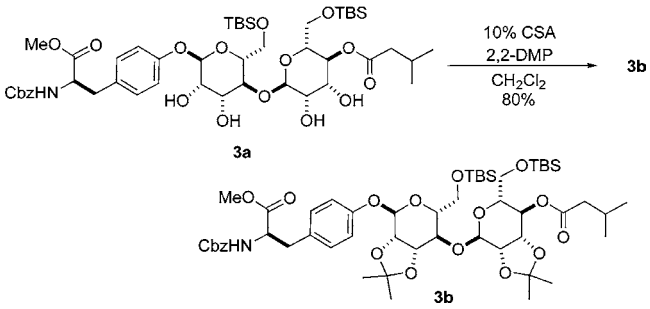
The final post-glycosylation transformation of **4** is shown in Scheme 4. Treatment of 1,4-linked pyran/pyranone **4** under the same reduction conditions as before (**8** to **9**, Scheme 3) gave allylic alcohol **10** in excellent yield (91%) and diastereoselectivity (>20:1). The isovalerate group was installed by treating allylic alcohol **10** with isovaleric acid and DCC/DMAP in CH_2Cl_2, which provided the *C*-4 isovalerate disaccharide precursor **11** in excellent yield (96%). The *manno*-stereochemistry in **3a** was diastereoselectively introduced[11] upon exposure of **11** to the Upjohn conditions (OsO_4/NMO, 85%).[8] Removal of both TBS-ethers was accomplished with TBAF (0 °C in THF) affording the α-1,4-linked-bis-*manno*-disaccharide **2a** in good yield (76%).

Scheme 4. Synthesis of Tyrosine Bis-*manno*-disaccharide

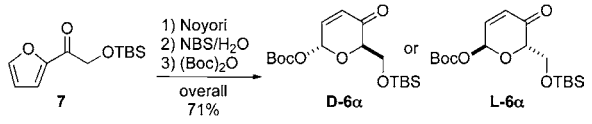


Finally the bis-*manno*-sugar **3a** could also be converted to the fully protected α-1,4-linked-bis-*manno*-disaccharide **3b** without any ester migration (Scheme 5). This was easily accomplished by treating a CH_2Cl_2 solution of tetraol **3a** with 2,2-dimethoxypropane and 10 mol % of CSA, conditions which provided the bis-acetonide **3b** in good yield (80%).

Scheme 5. Synthesis of Fully Protected Bis-*manno*-disaccharide



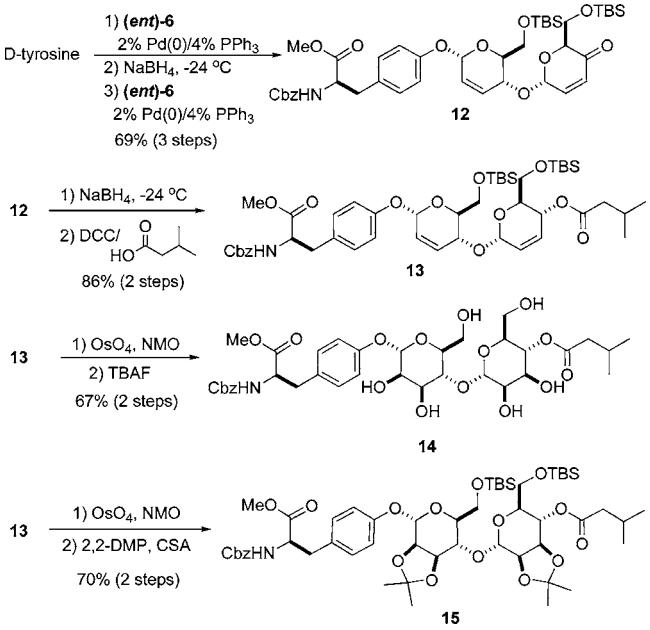
(10) Pyranones such as **6** can be prepared in three steps from achiral acylfurans such as **7** in either enantiomeric form (D/L). The pyranone asymmetry is derived from a Noyori reduction; see ref 7 and: Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005−1009.



(11) The relative stereochemistry of **3a** and **14a** was determined by analysis of various coupling constants from their ^1H NMR spectra; see the Supporting Information.

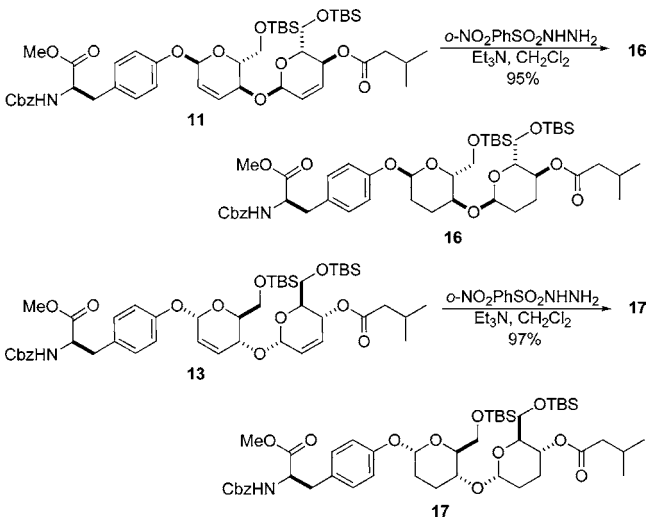
Replacing pyranone **6** with its L-enantiomer **(*ent*)-6** resulted in an equally efficient synthesis of the L,L-bis-*manno*-sugar diastereomer of **2a**, **14** (Scheme 6). Thus, in three analogous steps, D-tyrosine was converted into pyran/pyranone **12** (69% overall yield). The L,L-1,4-linked pyran/pyranone **12** was stereoselectively reduced and acylated to form **13** in good overall yield (86%). Once again, two diastereoselective dihydroxylations occurred upon exposure of **13** to the Upjohn conditions. This bis-dihydroxylation occurred with near perfect stereocontrol, as with the diastereomeric series (cf. Scheme 4).[11] The tetraol product was converted to the unprotected bis-sugar **14** via a TBS group deprotection (TBAF, 78%) or to the fully protected diastereomer **15** by means of an acetonide protection (10 mol % of CSA/2,2-DMP, 81%).

Scheme 6. Synthesis of L,L-Disaccharide Analogues



Having synthesized the key disaccharide fragment of mannopeptimycin E (**2a** and **3b**) along with its L,L-diastereomers (**14** and **15**), we turned our attention to the preparation of deoxy analogues (Scheme 7). The simplest 2,3-deoxy analogue **16** was obtained by an exhaustive diimide reduction.[12] Both double bonds of **11** were reduced using an excess of the diimide precursor in CH_2Cl_2 to afford the 2,3-deoxy-bis-pyranoside **16** in nearly quantitative yield (95%).[13] Under identical conditions, the diasteromeric L,L-1,4-linked bis-pyran **13** reduced to give an excellent yield of the bis-dideoxy analogue **17** (97%).[13]

Scheme 7. Synthesis of Bis-2,3-dideoxydisaccharide Analogues



In conclusion, an enantioselective synthesis of the *manno*-disaccharide fragments of mannopeptimycin-E has been achieved in seven steps and 37% overall yield from D-tyrosine via an iterative palladium-glycosylation strategy. Key to the success of this approach was the ease with which the *C*-4 isovalerate group was introduced, and the high diastereoselectivity of the palladium-catalyzed glycosylation and bis-dihydroxylation reactions. The use of this methodology for the synthesis of mannopeptimycin-E as well as various analogues is ongoing.

Acknowledgment. We thank the NIH (GM63150) and NSF (CHE-0415469) for their generous support of our research program. Funding for a 600 MHz NMR by the NSF-EPSCoR (No. 0314742) is also gratefully acknowledged.

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

OL060254A

(12) We have found *o*-nitrophenylsulfonylhydrazide/triethylamine to be an excellent diimide precursor, ideal for reducing pyrans of this type; see ref 8 and: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771−1774.

(13) To achieve complete conversion, occasionally the crude reaction mixture may need to be resubjected to the diimide conditions.