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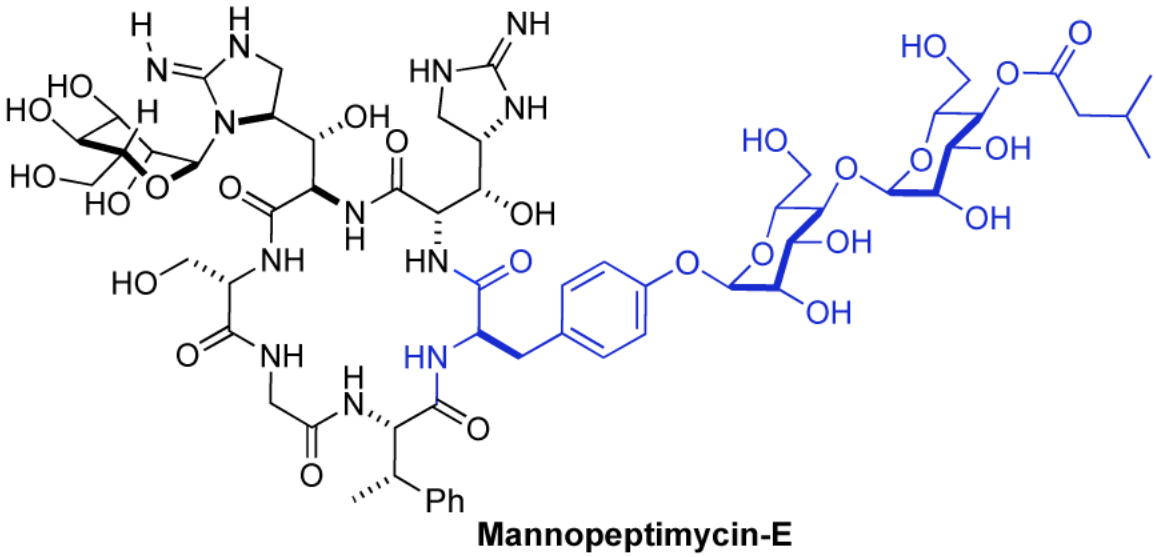
# Synthetic Studies Towards Mannopeptimycin-E:

## Synthesis of the *O*-Linked Tyrosine 1,4-α,α-*Manno,Manno*-Pyranosyl-Pyranoside

**Ravula Satheesh Babu**, **Sanjeeva R. Guppi**, and **George A. O'Doherty**
*Department of Chemistry, West Virginia University, Morgantown, WV 26506*

## Abstract




The enantioselective synthesis of the *C*-4′ acylated 1,4-α,α-*manno,manno*-disaccharide fragment of mannopeptimycin-E has been achieved in 7 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,

George.ODoherty@mail.wvu.edu.

**Supporting Information Available:** Complete experimental procedures and spectral data for all new compounds can be found in the Supporting Information (59 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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 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 mannnopeptimycins-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 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 like **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-analog **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, exposed to 1 mol% $Pd_2(dba)_3$•$CHCl_3$ and 2.5 mol% $PPh_3$, underwent a diastereoselective glycosylation with complete α-selectivity to afford the pyranone **8** in 92% yield. A diastereoselective 1,2-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% 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.

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%).

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% CSA; conditions which provided the bis-acetonide **3b** in good yield (80%).

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 (c.f. 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% CSA/2,2-DMP, 81%).

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 excess of the diimide precursor in $CH_2Cl_2$ affording 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 analog **17** (97%).[13]

In conclusion, an enantioselective synthesis of the *manno*-disaccharide fragments of mannopeptimycin-E has been achieved in 7 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

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B, Petersen PJ, Weiss WJ, Yang HY, Wang T-Z, Dushin RG, Koehn FE, Carter GT. Bioorg. Med. Chem. Lett 2004;14:279–282. [PubMed: 14684343]

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(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 US, Shaw SJ, LaTour JV, Kahne D. J. Am. Chem. Soc 2001;123:12722–12723. [PubMed: 11741455]

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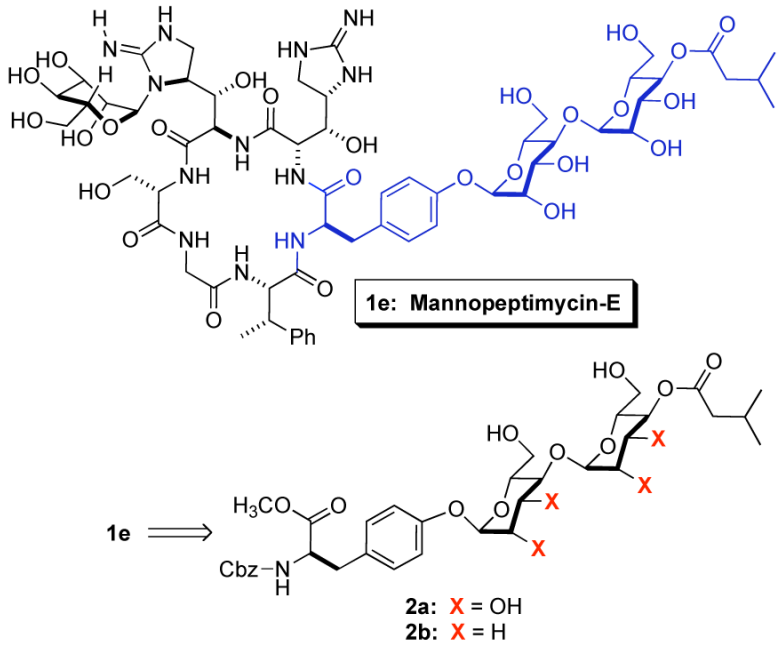
(9). Presumably, the L,L-diastereomer and the bis-2,3-dideoxy analogues of mannopeptimycin-E would have improved bioavailability.

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

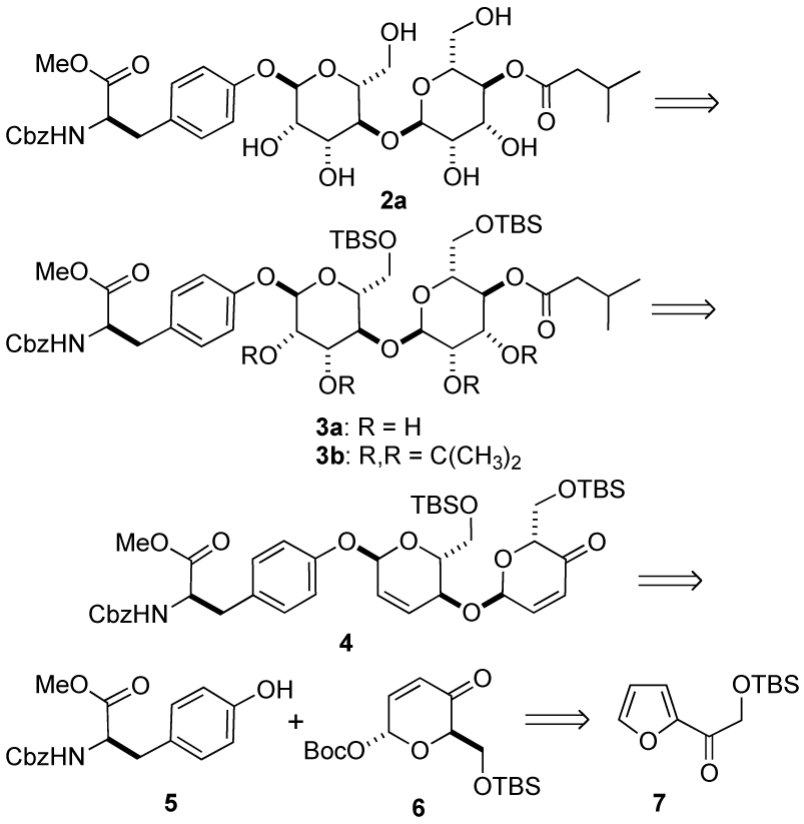
(11). The relative stereochemistry of **3a** and **14a** was determined by analysis of various coupling constants from their $^{1}$H NMR spectra, see supporting information.

(12). We have found that *o*-nitrophenylsulfonylhydrazide/triethylamine to be an excellent diimide precursor, ideal for reducing pyrans of this type, see: ref. 8 and Haukaas MH, O'Doherty GA. Org. Lett 2002;4:1771–1774. [PubMed: 12000295]

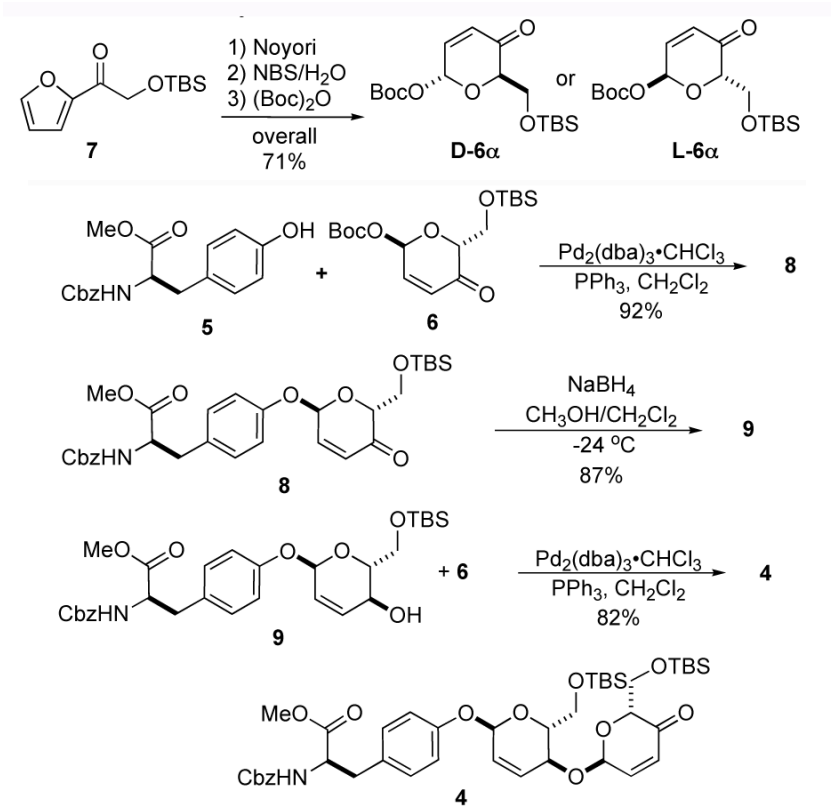
(13). To achieve complete conversion, occasionally the crude reaction mixture may need to be re-subjected to the diimide conditions.



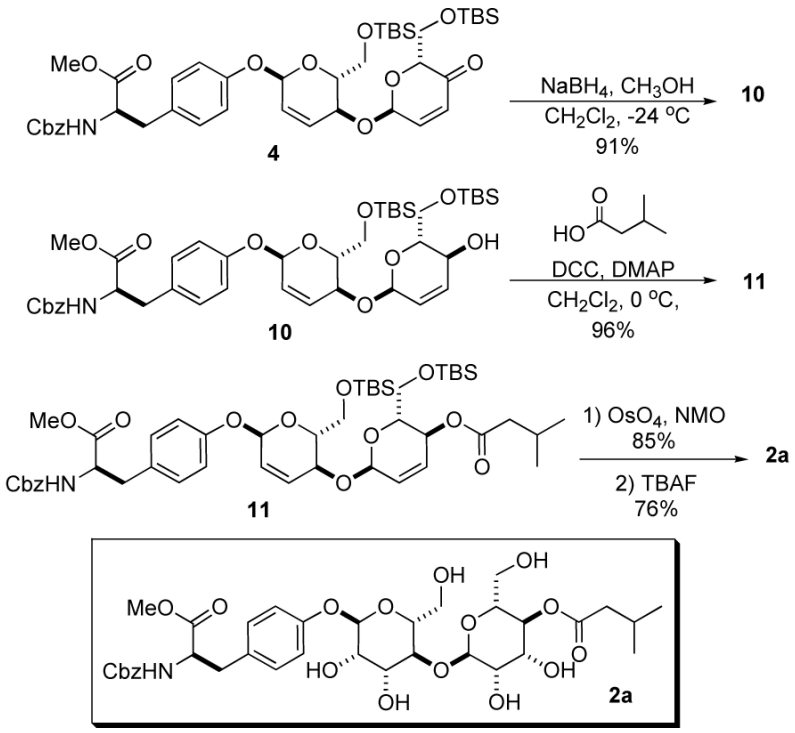

**Scheme 1.**
Structure of mannopeptimycin E **1e**



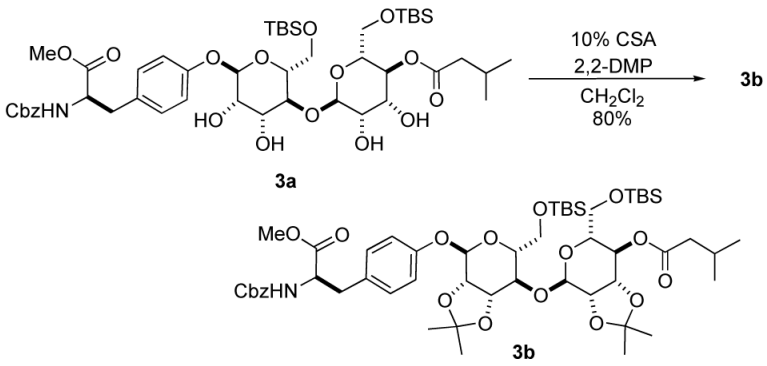

**Scheme 2.**
Retrosynthetic analysis of mannopeptimycins



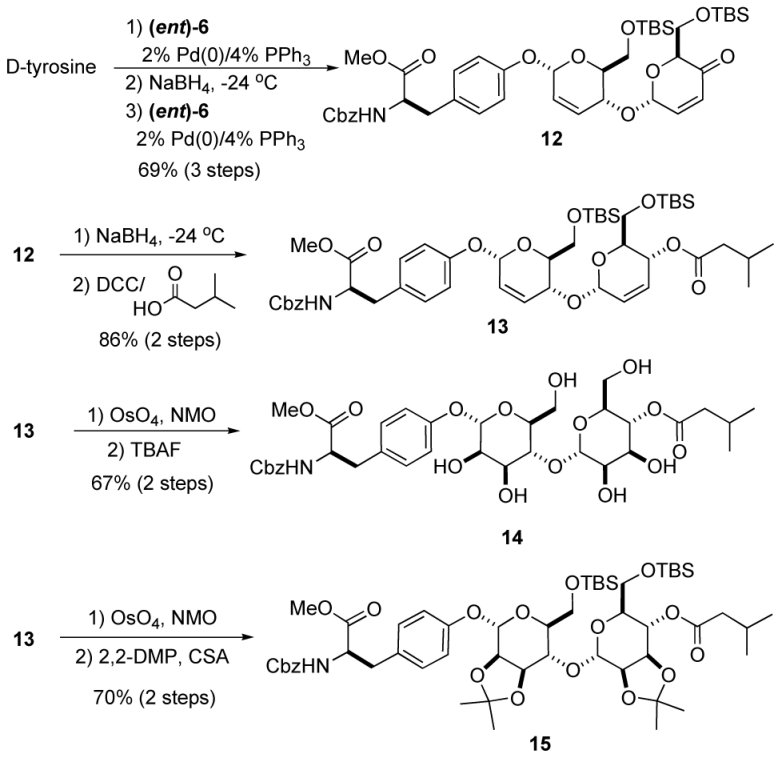

**Scheme 3.**
De novo synthesis of pyran/pyranone **4**



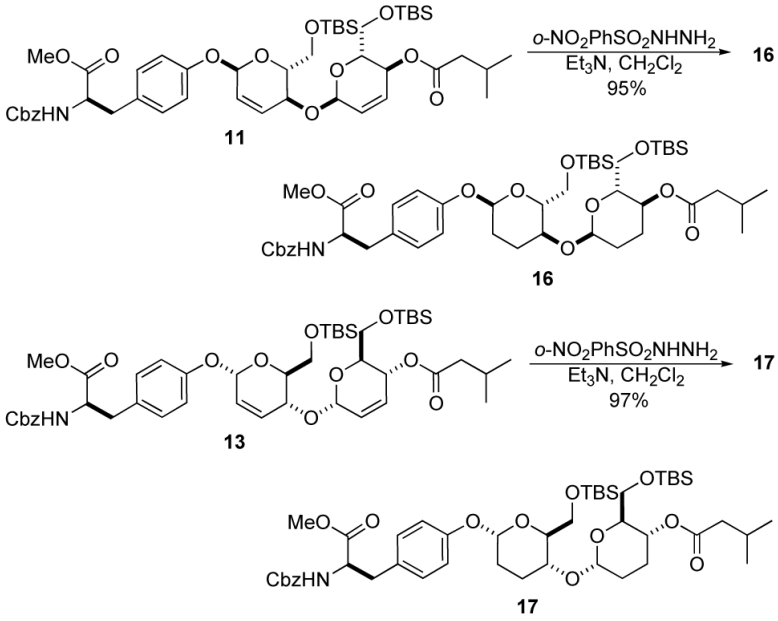

**Scheme 4.**
Synthesis of tyrosine-bis-*manno*-disaccharide




**Scheme 5.**
Synthesis of fully protected bis-*manno*-disaccharide



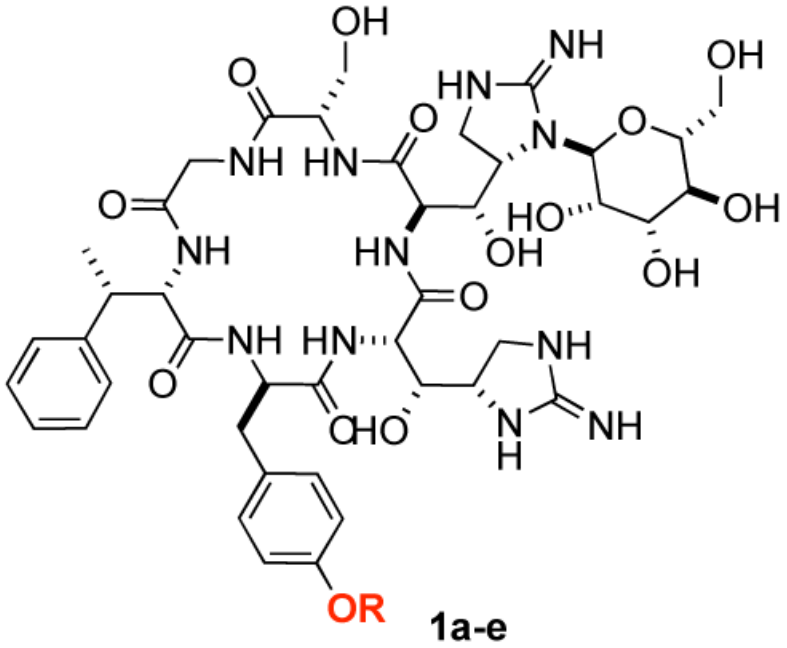

**Scheme 6.**
Synthesis of L,L-disaccharide analogs



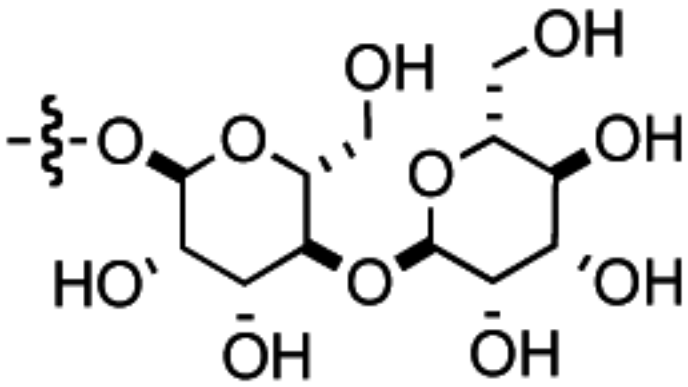

**Scheme 7.**
Synthesis of bis-2,3-dideoxy-disaccharide analogues

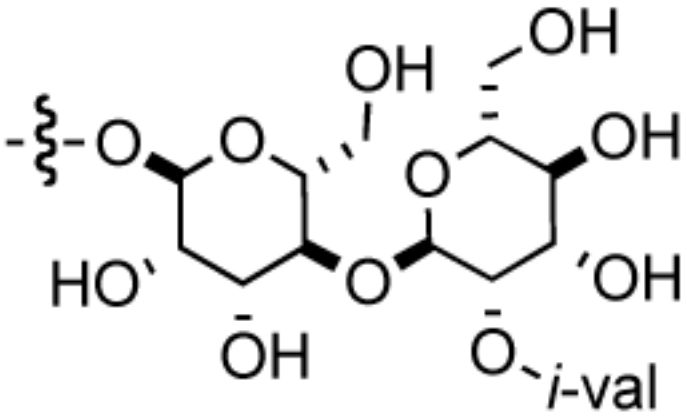
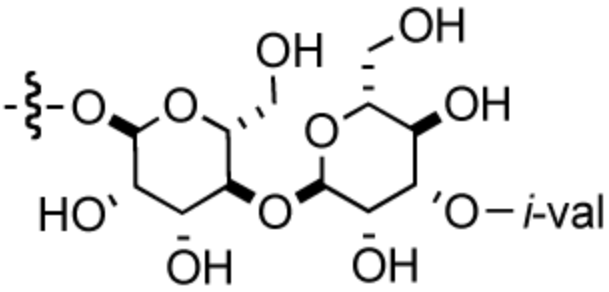
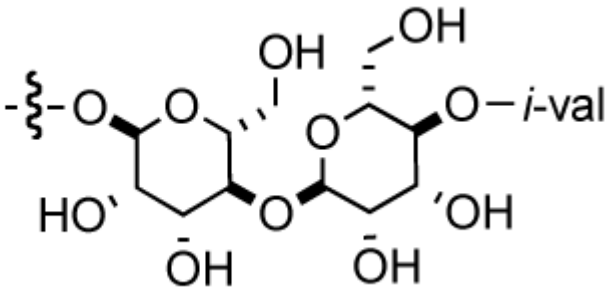
**Table 1**

Activities of the mannopeptimycins[5]




**1a-e**

| mannopeptimycin A-E | MIC range (μg/mL) | |
|---|---|---|
| | MRSA[a] | Enterococus faecium[b] |
| **1a R =**  | >128 | >128 |
| 1b R= **H** | 64-128 | 32->128 |

| mannopeptimycin A-E | MIC range (μg/mL) | |
|---|---|---|
| | MRSA[a] | Enterococcus faecium[b] |
| 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 4 lines of vancomycin-resistant.

[c] *i*-val = *i*-valerate