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Design and Synthesis of Orthogonally Protected D- and L-β-Hydroxyenduracididines from D-*lyxono*-1,4-Lactone

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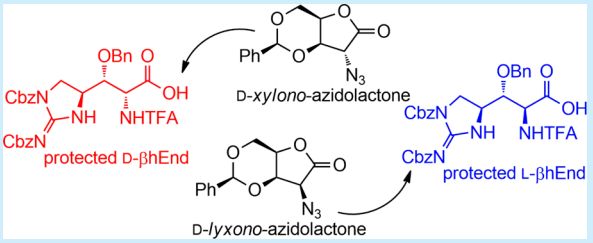
Supporting Information

ABSTRACT: A practical synthesis of the orthogonally protected D- and L-β-hydroxyenduracididines (D- and L-βhEnds), the unique, nonproteinogenic α-amino acids found in mannopeptimycin antibiotics, is described. We appropriately applied D-*lyxono*-1,4-lactone derivatives as a starting template and investigated two transformations: (i) reduction of the lactone in a two-step sequence and (ii) regioselective ring opening of the benzylidene acetal. By careful evaluation of reaction conditions, multigram amounts of both orthogonally protected D- and L-βhEnds were successfully prepared.



Bacterial infections constitute a grave threat to human health, and new molecules, targets, and treatments to combat multidrug resistant bacteria, such as MRSA (methicillin-resistant *Staphylococcus aureus*), VRE (vancomycin-resistant *Enterococcus*), and MDR-TB (multidrug-resistant *tuberculosis*) are urgently sought.[1] Instead of developing molecules that block peptidoglycan-related enzymes' biological functions, recent reports show targeting biosubstrates of peptidoglycan biosynthesis becomes a more attractive and promising approach to develop new antibiotics.[2] For example, vancomycins have been claimed to target the D-Ala-D-Ala moiety of Lipid II, which is an essential membrane-anchored cell-wall precursor, to severely impair peptidoglycan (PGN) biosynthesis. Unfortunately, overuse of the vancomycins has led to the emergence of resistant bacterial *Enterococci* strains since the mid-1980s.[3]

Among current naturally occurring glycopeptide antibiotics,[4] mannopeptimycins **1** (Figure 1), isolated from a strain of *Streptomyces hygroscopicus*, LL-AC98, are a novel class of cyclic glycopeptide antibiotics with potent activity against clinically important Gram-positive pathogens, including MRSA and VRE.[5] Although mannopeptimycins have been proposed to target Lipid II,[6] their detailed interactions with Lipid II or mechanisms of action still are not clear. Such studies would be invaluable for the development of novel mannopeptimycin antiobiotics, but progress is hampered by a paucity of scalable synthetic routes for these complex molecules and their and building blocks, especially protected D- and L-βhEnds.

Structurally, the mannopeptimycin core is based on two unique nonproteinogenic α-amino acids, both the D and L forms of βhEnd, which are derived from arginine by post-translational modification.[7] βhEnd contains three contiguous stereogenic centers at C2, C3, and C4 and a high density of functional groups including an α-amino acid, hydroxyl group, and cyclic guanidine moiety. Because of their structurally unique and interesting but unexplored biological properties, the development of practical methods for their preparation is of paramount importance.

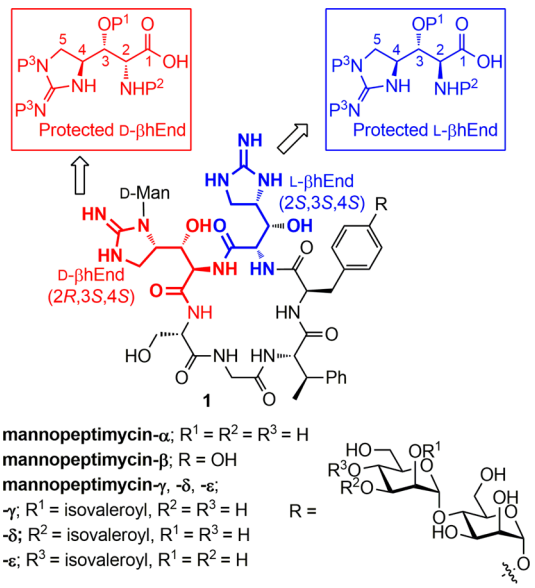


Figure 1. Structure of mannopeptimycins **1** and both protected D- and L-βhEnds.

To date, several methods have been reported by us[8] and others[9] for the preparation of βhEnds. The most common strategy is to use a chiral amino acid or amino acid derivative such as Garner's aldehyde or (*S*)-serinol as the starting material; build out the carbon backbone by conjugation; and then install the hydroxyl, amino, and carboxylic acid group functionality by asymmetric dihydroxylation. Unfortunately, separation of two enoate intermediates and/or side products

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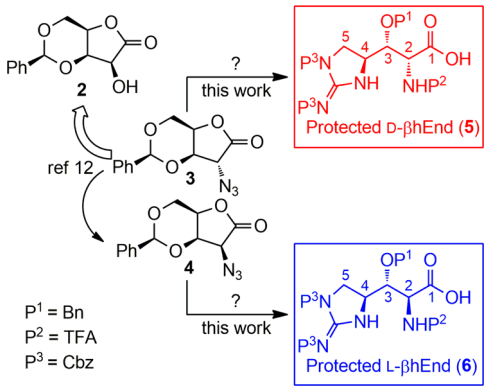
after the asymmetric dihydroxylation step is very tedious, which greatly limits this synthetic approach.

As our research interests include the preparation of glycopeptide antibiotics and bacterial peptidoglycan components including Lipid II, as well as the use of these molecules for biological studies,[10] we realized that development of practical methods for the preparation of both *β*hEnds is a prerequisite for the systematic investigation of mannopeptimycin glycopeptide antibiotics.

To date, use of the chiral sugar pool as starting material for the preparation of the *β*hEnds has not been extensively explored.[11] D-*lyxono*-1,4-Lactone **2** is a versatile building block originally developed by Fleet[12] and was considered by us as a starting material for the asymmetric synthesis of protected D- and L-*β*hEnds (Scheme 1). Lactone **2** already possesses intrinsic

Scheme 1. General Route To Prepare Both D- and L-*β*-*β*hEnds from Azide 3 and 4

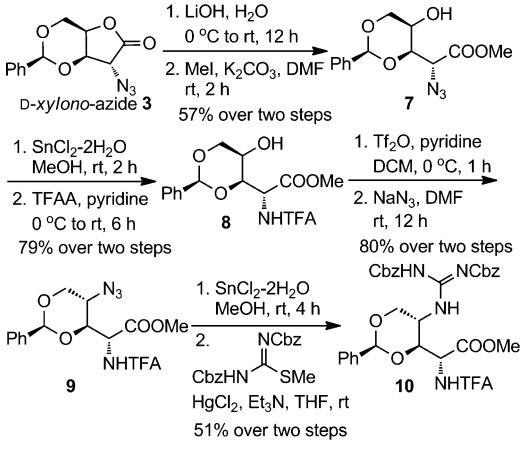


three stereogenic centers, and no extra conjugation with other backbone fragments would be needed. Also, it can be easily converted into D-*xylono*-azide **3** and D-*lyxono*-azide **4**.[13]

Herein, we report our original design in order to develop a straightforward and scalable synthetic approach toward the preparation of orthogonally protected *β*hEnds **5** and **6**, starting from accessible azidolactones **3** and **4**, respectively.

Our synthesis started with the preparation of intermediate **10** (Scheme 2). Enantiopure D-*xylono*-azide **3**, derived from D-*lyxono*-1,4-lactone **2**, was hydrolyzed[14] and methylated[15] with iodomethane under mild conditions to give azido ester **7**. Reduction of the azido group of **7** with tin(II) chloride,

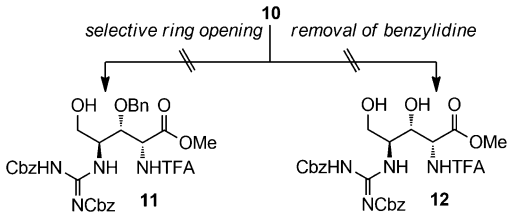
Scheme 2. Synthesis of Guanidine 10



followed by the protection of the amino group with trifluoroacetic anhydride (TFAA), gave *N*-TFA protected **8** (79% over two steps). Subsequent conversion of the hydroxyl group to the azido group at the C4 position with concomitant inversion of the chirality into the desired 4S configuration was performed in two steps (80% yield) to give azide **9**. Reduction of azide **9** with tin(II) chloride followed by guanidinylation with 1,3-bis(benzyloxycarbonyl)-2-methyl-2-thiopseudourea in the presence of mercury(II) chloride gave guanidine **10** (51% over two steps).[16]

As shown in Scheme 3, regioselective reductive ring opening of benzylidine acetal in **10** was carried out under several typical

Scheme 3. Attempts for Selective Ring Opening or Removal of Benzylidine of 10

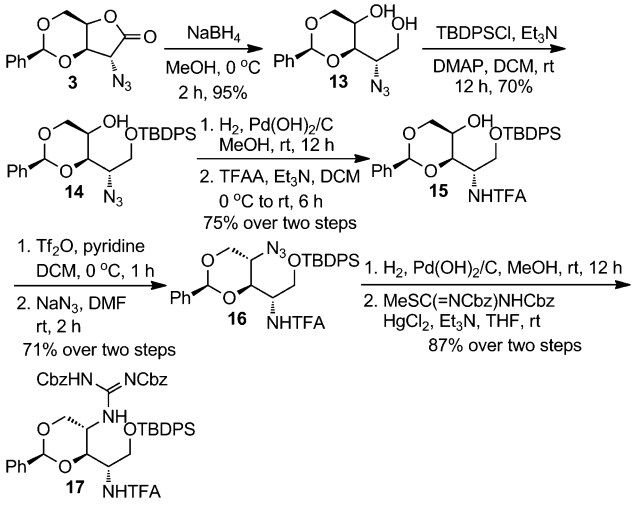


conditions such as $AlCl_3/BH_3$−NMe_3, $AlCl_3/BH_3$−THF, or TMSOTf/BH_3−THF. Unfortunately, no desired compound was observed. Besides, direct removal of benzylidene acetal in **10** under acidic conditions also did not work well. On the basis of the analysis of mass spectra of crude samples, the unfavorable *δ*-lactone or Cbz-deprotected compound was observed.

These disappointing results prompted us to develop a new synthetic route. After our further evaluation and design, it was decided to reduce the ester group in azidolactone **3** to form diol **13** (95%)[17] followed by selective protection of the primary alcohol with a bulky TBDPS group to give **14** (Scheme 4). Expectedly, guanidine **17** was successfully prepared in multigram levels following similar transformations as described in Scheme 2.

With guanidine **17** in hand, regioselective reductive ring opening of benzylidine acetal was tested again (Scheme 5). As shown in Table 1, initial attempts to treat **17** with borane-type reducing agents in the presence of Lewis acids resulted in either

Scheme 4. Synthesis of Guanidine 17



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Scheme 5. Synthesis of Protected D-βhEnd 5 from Intermediate 17

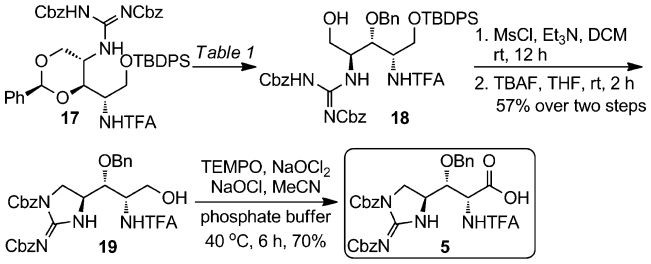
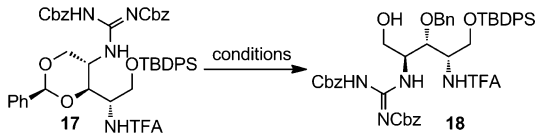


Table 1. Regioselective Reductive Ring Opening of Benzylidene Acetal 17



entry	conditions	yield (%)
1	BH_3–THF, TMSOTf, DCM, 0 °C	
2	BH_3–THF, $Cu(OTf)_2$, DCM, 0 °C	
3	BH_3–NMe_3, $AlCl_3$, DCM, ether, 0 °C	trace
4	$NaBH_3CN$, $TiCl_4$, MeCN, 0 °C	38[a]
5	$NaBH_3CN$, $TiCl_4$ (1M in DCM), MeCN, 0 °C	60[a] (56)[b]

[a]Isolated yield by flash column chromatography. [b]Gram-scale preparation of **18** (5 g).

the decomposition of starting material or no reaction (Table 1, entries 1–3).[18] In contrast, use of sodium cyanoborohydride in the presence of titanium(IV) chloride gave the desired alcohol **18** with excellent regioselectivity (entries 4 and 5).[19] Use of a dilute solution of titanium(IV) chloride (1 M in dichloromethane) was found to result in a higher yield compared with neat titanium(IV) chloride (entries 4 vs 5).

Conversion of **18** to **19** was first performed by conversion of the primary alcohol of **18** to a mesylate group followed by in situ intramolecular nucleophilic substitution (Scheme 5). Mitsunobu conditions were impractical as the desired product was contaminated with DIAD-derived hydrazine and triphenylphosphine, and its purification was found to be laborious. After removal of the silyl protecting group with TBAF in THF, the resulting primary alcohol **19** was oxidized under Anelli's conditions (Zhao's modification, $NaClO_2$, NaOCl, TEMPO) to provide the protected D-βhEnd **5** in 82% yield.[20]

With a feasible route for the preparation of D-βhEnd **5** in hand, we attempted a similar approach for the preparation of the protected L-βhEnd **6**, starting from compound **4**. Unexpectedly, the reduction of D-*lyxono*-azidolactone **4** (**4** to **20**) was found to behave very differently compared with D-*xylono*-azidolactone **3** (**3** to **13**). As summarized in Table 2, no desired diol **20** was obtained when sodium borohydride or lithium borohydride was used (entries 1 and 2). When L-Selectride was applied, only a trace amount of the product was observed (entry 3). In the end, a two-step reduction sequence was successfully developed in which lactone **4** was first reduced to its corresponding lactol with DIBAL and then reduced to the diol **20** with sodium borohydride in reasonable yield (64% over two steps; entry 4).[21]

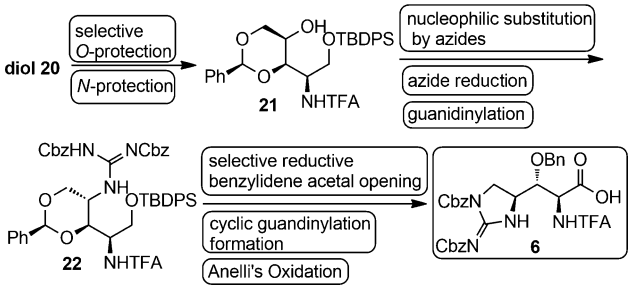
As shown in Scheme 6, several straightforward transformations including *O*- or *N*-protection, installation of the second amino group, guanidinylation, selective benzylidene

Table 2. Conversion of D-*lyxono*-Azidolactone 4 to Diol 20

entry	conditions	yield (%)
1	$NaBH_4$, MeOH, 0 °C, 2 h	
2	$LiBH_4$, THF, 0 °C, 2 h	
3	L-Selectride, THF, −50 °C, 2 h	trace
4	(1) DIBAL, DCM, 0 °C, 1 h	64[a]
	(2) $NaBH_4$, MeOH, 0 °C, 1 h	

[a]Isolated yield by flash column chromatography.

Scheme 6. General Transformations To Prepare Protected L-βhEnd 6 from Diol 20



acetal opening, intramolecular cyclization, and oxidation were performed to successfully generate the orthogonally protected L-βhEnd **6** (20% over 11 steps from **20**), as was done for D-βhEnd **5**.

In conclusion, a straightforward, practical method for the preparation of both orthogonally protected D- and L-βhEnd has been developed. Our method is distinct from those previously reported because it starts from D-*lyxono*-lactone derivatives rather than chiral amino acids and is therefore uniquely advantageous. First, this starting material has a built-in chirality (three stereogenic centers), and therefore, no installation of extra chiral centers is needed. Second, the starting material already possesses an appropriate length of backbone, so no carbon–carbon bond-forming steps are required. To reach our goal, several important transformations, including an amino group installation, cyclic guanidine formation, reduction of the lactone in a two-step sequence, and regioselective ring opening of the benzylidene acetal have been established. Promisingly, this scalable method to prepare these two unique amino acids allows for the systematic study of the mannopeptimycin series of natural products and the development of new antibiotics.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02444.

Experimental procedures and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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