# Total Synthesis and Stereochemistry Revision of Mannopeptimycin Aglycone

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# Total Synthesis and Stereochemistry Revision of Mannopeptimycin Aglycone

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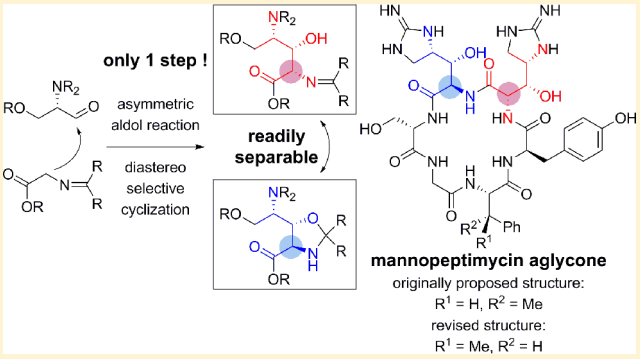
Supporting Information

**ABSTRACT:** Development of efficient methods for preparation of bioactive nonribosomal peptides, containing densely functionalized nonproteinogenic amino acids, is an important task in organic synthesis. We have employed a concise synthesis for such amino acids by asymmetric aldol addition coupled with an isomeric resolution via diastereoselective cyclization. This approach is successfully applied to the first total synthesis of the cyclic hexapeptide aglycone of the mannopeptimycins, a group of glycopeptides known for potent activity against drug-resistant bacteria. The facile preparation of the key amino acids and the synthesis of the aglycone pave the way for further studies on this class of antibiotics and the development of new lead compounds with therapeutic potential. In addition, our studies have led to the revision of the stereochemistry of the β-methylphenylalanine residue in the mannopeptimycin aglycone.




## INTRODUCTION

Many natural products that contain densely functionalized nonproteinogenic amino acids possess noteworthy biological activity and some are used in clinic or considered as promising leads for drug discovery.[1] Often the availability of such nonproteinogenic amino acids is the key to the synthesis of the parent compounds and novel analogs with therapeutic potential.[2,3]

Mannopeptimycins represent a novel class of glycopeptides originally discovered as an antibiotic complex from culture broth of *Streptomyces hygroscopicus* LL-AC98 in the 1950s.[4] The full structural characterization of mannopeptimycins α−ε, as purified from the complex, was revealed in 2002 (Figure 1).[5] Mannopeptimycins are cyclic hexapeptides containing a pair of diastereomeric α-amino-β-[4′-(2′-iminoimidazolidinyl)]-β-hydroxypropionic acid residues (Aiha-A and -B). These new amino acids are also referred to as β-hydroxyenduracididines.[6,7] In both *in vitro* and *in vivo* experiments, mannopeptimycins are effective against Gram-positive bacteria, including drug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).[8] Mechanistic studies have indicated that these antibiotics inhibit the late stages of bacterial cell wall biosynthesis[9] and target transglycosylation by interaction with lipid II, a substrate of transglycosidase, at a location different from the vancomycin binding site.[9] Mannopeptimycins, with their unprecedented structures, potent antibiotic activity, and distinct mode of action, have attracted broad interest in the past decade.[5,8−28] The recent work on this class of compounds has been carried out owing to the urgent need for novel antibiotics, with unique chemical structures and mode of action, to effectively combat drug-resistant bacterial pathogens.[29−31]

A series of semisynthetic derivatives with modified disaccharide side-chains attached to the D-tyrosine (Tyr) were prepared, and these compounds exhibited greater potency against susceptible and resistant Gram-positive bacteria than the natural mannopeptimycins.[10−16] In particular, a cyclic ketal-containing compound, AC98−6446, demonstrated exceptionally potent *in vitro* activity (MICs: 0.015−0.06 μg/mL against MRSA, 0.06−0.12 μg/mL against VRE, and ≤0.008 μg/mL against penicillin-resistant *Streptococcus pneumoniae*) and *in vivo* efficacy ($ED_{50}$ = 0.08 mg/kg against *S. aureus*, Smith strain and 0.39 mg/kg against VRE).[13,15] However, an analog of AC98−

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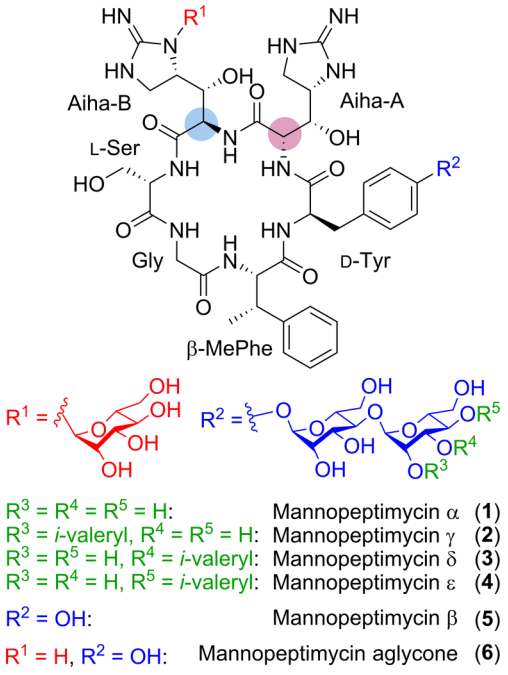



**Figure 1.** Originally proposed structure of mannopeptimycin $\alpha$–$\varepsilon$ (**1**–**5**) and mannopeptimycin aglycone (**6**).

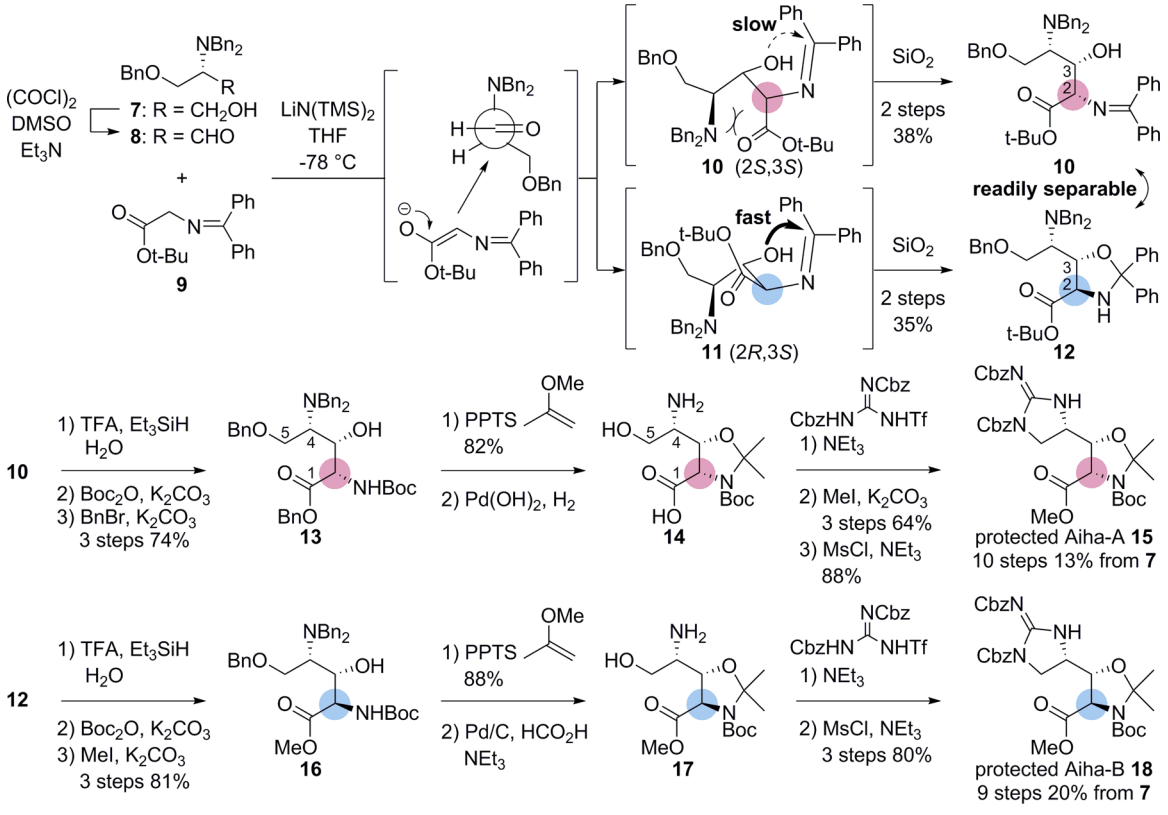
6446 with a simplified aglycone, comprising L- and D-arginine to, respectively, replace Aiha-A and -B, showed very weak antimicrobial activity.[17] The sharp contrast in antibacterial potency between these two compounds demonstrated the critical role Aiha-A and -B play in determining the biological activity of the mannopeptimycins. The structures of these compounds indicated that the biggest challenge for synthesizing mannopeptimycins and generating new antibiotic derivatives was the access to Aiha-A and -B, two cyclic guanidine-containing amino acids featuring three adjacent chiral centers. Though recently two research groups have prepared these complex amino acids, the reported synthetic routes were relatively lengthy.[25,26] Obviously, simple and convenient synthesis of Aiha-A and -B remains pivotal to the preparation of the mannopeptimycins and their derivatives.

In previous reports, we described the syntheses of naturally occurring cyclic depsipeptides and their analogs, containing nonproteinogenic amino acids.[32−38] Based on these results we further developed a one-step synthesis of highly functionalized amino acids, using a sequence of asymmetric aldol addition and then isomeric resolution via diastereoselective cyclization. This approach was successfully utilized in the synthesis of Aiha-A and -B, which ultimately enabled us to achieve the total synthesis of the aglycone. During the course of our work, we found that the absolute configuration of the $\beta$-methylphenylalanine ($\beta$-MePhe) residue was incorrectly assigned as originally reported.[5] Herein, we wish to report the first total synthesis of mannopeptimycin aglycone and a revision of its stereochemistry.

## RESULTS AND DISCUSSION

The synthesis of the mannopeptimycin aglycone started with the preparation of the amino acid building blocks. The strategy was to synthesize selectively protected Aiha-A **15** and Aiha-B **18**, in which the cyclic guanidino structure could be introduced using the 4-amino and 5-hydroxy groups in **14** and **17** (Scheme 1). Since the latter two compounds could be synthesized from **10** and **12**, respectively, using conventional procedures, the

**Scheme 1. Synthesis of Protected Aiha-A 15 and -B 18**





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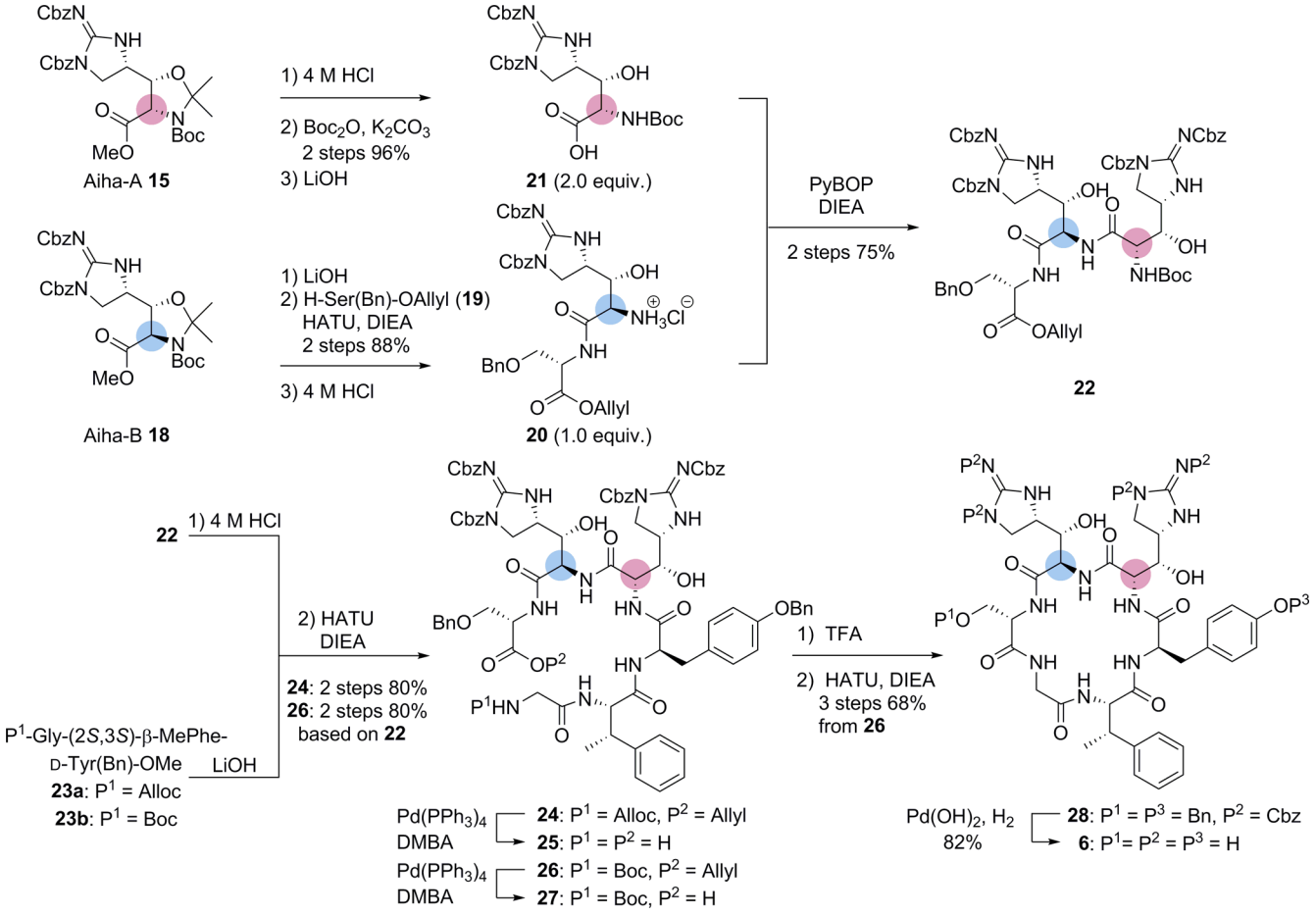
**Scheme 2. Synthesis of the Proposed Structure of Mannopeptimycin Aglycone (6)**




critical step for the designed synthesis was, therefore, the efficient construction of the intermediates **10** and **12**.

For the synthesis of **10** and **12**, a one-step sequential reaction of asymmetric aldol addition followed by isomeric resolution via stereoselective cyclization was employed. The (*S*)-3-(benzyloxy)-2-(dibenzylamino)propanal (**8**) was obtained from oxidation of **7**, which was readily prepared from commercially available H-Ser(Bn)-OH (3 steps 93% yield), where Bn is benzyl.[39] The critical asymmetric aldol addition between **8** and **9** was carried out,[40,41] and the stereochemistry of the products was examined by converting **10** and **12** to the reported, protected Aiha-A and -B as described hereinafter. Based on the Felkin-Anh model, the formation of a mixture of diastereomeric (2*S*,3*S*,4*S*)-aldol **10** and (2*R*,3*S*,4*S*)-aldol **11** was anticipated. Separation of a mixture of diastereomers could be a difficult task, but we expected that **11** would smoothly cyclize to afford the corresponding oxazolidine **12**, whereas **10** be kept acyclic due to an unfavorable stereo orientation derived from the steric repulsion between $NBn_2$ and $CO_2t$-Bu groups (*t*-Bu is *tert*-butyl) as shown in Scheme 1. The experimental results were consistent with this analysis, and the aldols **10** and **12** were found to be the major products, easily separated by silica-gel chromatography. Previously Corey,[40] Molinski,[41] and co-workers reported syntheses of *β*-hydroxy-*α*-amino acids using asymmetric aldol reactions between achiral aldehydes and *N*-(diphenylmethylene)glycine *tert*-butyl ester (**9**) or its silyl ether in the presence of a chiral amine or ammonium salt as catalyst. In their reports, the stereochemistry of the products at the *α*-position was mediated by the chiral amines. In our approach to synthesize Aiha-A and -B however, a chiral aldehyde **8** was employed, and the asymmetric aldol addition between **8** and **9** was carried out without using a chiral catalyst. The stereochemistry of the products at the *β*-position was controlled by the chirality of **8** to simultaneously construct desired stereocenters at C2 and C3 in **10** and **12**. It is noteworthy that variants of **10** and **12** were found in many biologically active natural products, and their properly protected forms prepared by this method potentially can be used in synthesis of their parent compounds.[42−49]

The synthesis of protected Aiha-A **15** from (2*S*,3*S*,4*S*)-aldol **10** is outlined in Scheme 1. A five-step manipulation of the protecting groups afforded the amino alcohol **14** in good yield. A guanidino moiety was introduced to **14** using Goodman's reagent.[50] The carboxylic acid was converted to the corresponding methyl ester and the primary alcohol to a mesylate, which induced the formation of a cyclic guanidine to afford the protected Aiha-A **15** (10 steps 13% yield from **7**). In a similar manner, the protected Aiha-B **18** was synthesized from oxazolidine **12** (9 steps 20% yield from **7**). Structures of **15** and **18** were confirmed by converting them to the reported analog of Aiha-A **S4** and Aiha-B **S5**, respectively (synthetic details for **S4** and **S5**, see Supporting Information). The asymmetric aldol addition coupled with an isomer resolution via diastereoselective cyclization enabled us to establish a concise and scalable synthesis for Aiha-A and -B, that was significantly more efficient than the previously reported methods.[25,26]

The amino acids **15** and **18** were then utilized in the assembly of the cyclic peptide aglycone **6**. The peptide chain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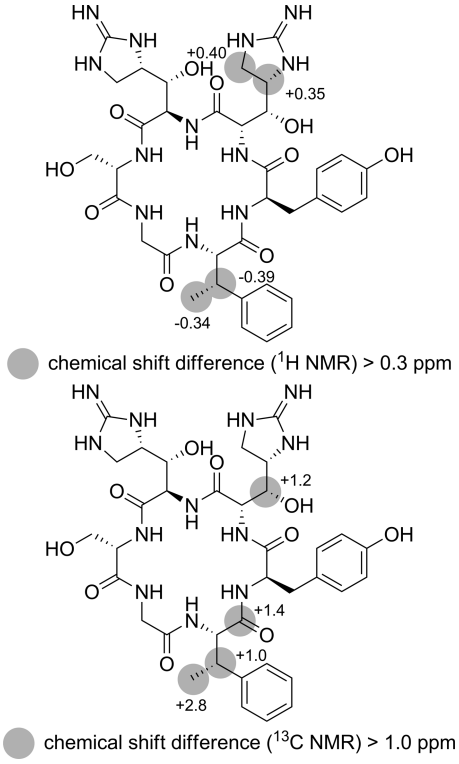
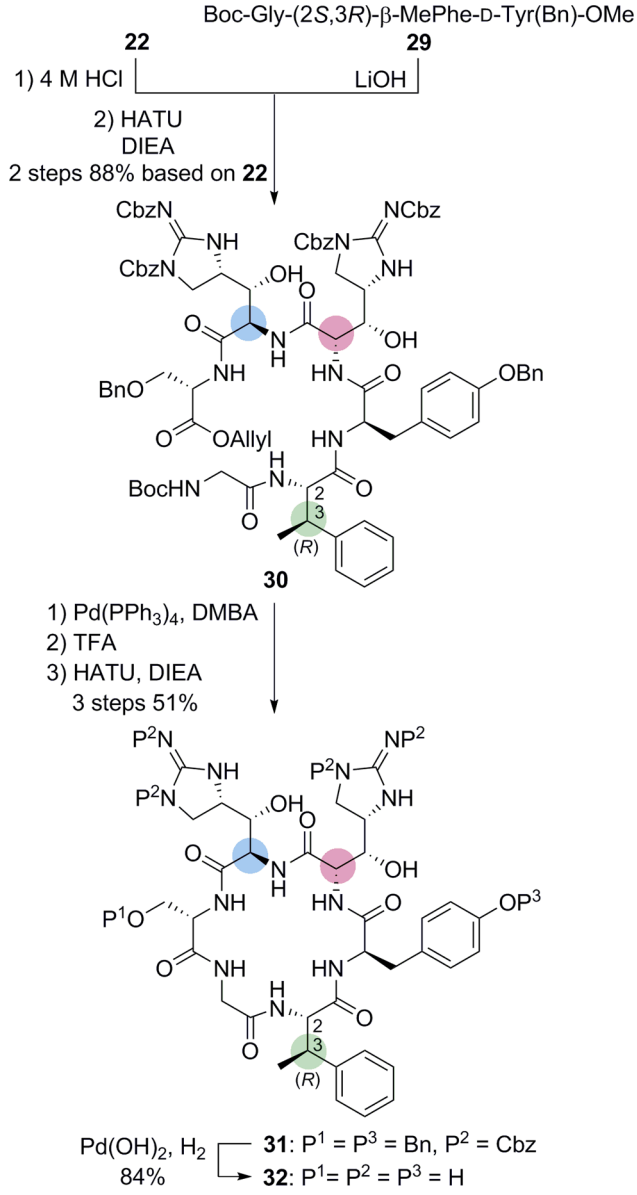



**Figure 2.** Graphically depicted $^1$H and $^{13}$C NMR chemical shift differences between the observed spectra of the synthesized aglycone **6** and the reported spectra of the aglycone. The protons emphasized are those with $^1$H NMR chemical shifts that differed from the reported ones by more than 0.3 ppm (top). Concentration- and pH-sensitive N−H or O−H protons were precluded. The carbons emphasized are those with $^{13}$C NMR chemical shifts that differed from the reported ones by more than 1.0 ppm (bottom).

was elongated based on a convergent approach as shown in Scheme 2. H-Ser(Bn)-OAllyl (**19**) was coupled with **18**, and then the *tert*-butyloxycarbonyl (Boc) group was removed and oxazolidine opened by 4 M HCl to afford **20**. The hydrolysis of the methyl ester **15** turned out to be difficult, likely due to the steric hindrance. Therefore, the Boc group and the oxazolidine ring were hydrolyzed using HCl, which yielded a product easily saponified to the carboxylic acid **21**. The subsequent coupling reaction between **20** and **21** was optimized by testing various combinations of coupling agents (benzotriazole-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (PyBOP), *O*-(7-azabenzotriazole-1-yl)- *N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, bromotripyrrolidinophosphonium hexafluorophosphate, and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide), additives (1-hydroxy-7-azabenzotriazole and 1-hydroxybenzotriazole), and solvents ($CH_2Cl_2$ and *N*,*N*-dimethylformamide (DMF)). As a result, the desired coupling product **22** was obtained in high yield using PyBOP in DMF.

The coupling between **22** and **23a** (synthetic details for **23a**, see Supporting Information) was also studied using several coupling conditions, and the desired hexapeptide **24** was obtained when HATU was used (2 steps 80% yield). The allyloxycarbonyl (Alloc) and Allyl groups in **24** were removed in the presence of $Pd(PPh_3)_4$ and 1,3-dimethylbarbituric acid. However, the resulting product **25** containing both amino and carboxyl groups was poorly soluble in the common solvents

**Scheme 3. Synthesis of Aglycone 32 with (2*S*,3*R*)-*β*-MePhe**




and difficult to purify. Because the macrolactamization using the crude **25** did not afford the expected compound, we decided to change the protecting group for the amine. The hexapeptide **26** with a Boc group replacing the Alloc group in **24**, was prepared from a coupling between **22** and **23b** (synthetic details for **23b**, see Supporting Information). Upon deprotection of the allyl group, **27** was obtained by silica-gel chromatography. The Boc group in **27** was cleaved under acidic condition to obtain the precursor for the critical macrolactamization, and the reaction was proceeded using HATU to afford the protected mannopeptimycin aglycone **28** in good yield. Finally, the global deprotection of all the Bn and benzyloxycarbonyl groups, using $Pd(OH)_2$ in MeOH/THF/$H_2O$/$HCO_2H$, afforded the expected product **6**. We confirmed that no epimerization of (2*S*,3*S*)-*β*-MePhe, D-Tyr, and L-Ser residues had occurred by Marfey's analysis for **23b**, **26**, and **6** (details for Marfey's analysis, see Supporting Information). In addition, we also confirmed that no epimerization of Aiha-A and -B residues had occurred by preparing epimers **S17** and **S18** and by comparing their HPLC retention times to those of


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**Table 1. Comparisons between the Observed and Reported NMR Spectra of Mannopeptimycin Aglycone Trifluoroacetic Acid Salt in DMSO-$d_6$ Solvent[a]**

| amino acid[b] | $^1$H 400 MHz reported | $^1$H 600 MHz observed | $^{13}$C 75 MHz reported | $^{13}$C 150 MHz observed |
|---|---|---|---|---|
| | | Aiha-A | | |
| C=O (1) | | | 170.4 | 170.6 |
| α (2) | 4.39 (dd, 8.6, 8.6) | 4.37 (dd, 8.4, 8.4) | 53.6 | 53.8 |
| α-NH | 8.12 (d, 8.6) | 8.12 (d, 8.4) | | |
| β (3) | 3.62 (m) | 3.61−3.65 (m) | 69.5 | 70.0 |
| β-OH | 5.40 (d, 5.6) | 5.39 (brs) | | |
| 1′ | 7.76 (m) | 7.60−7.82 (m) | | |
| 2′ | | | 159.2 | 159.3 |
| 3′ | 8.04 (brs) | 8.01 (brs) | | |
| 4′ | 3.42 (ddd, 2.2, 5.1, 9.7) | 3.37−3.44 (m) | 55.8 | 56.0 |
| 5′ | 3.55 (m) | 3.52−3.56 (m) | 42.2 | 42.4 |
| | 3.22 (dd, 5.1, 13.0) | 3.18−3.23 (m) | | |
| 6′ | 7.63 (brs) | 7.60−7.82 (m) | | |
| | | Aiha-B | | |
| C=O (1) | | | 169.1 | 169.3 |
| α (2) | 4.22 (dd, 2.5, 7.3) | 4.24 (brs) | 55.7 | 55.9 |
| α-NH | 8.46 (d, 7.3) | 8.43 (d, 6.6) | | |
| β (3) | 3.95 (brdd, 6.3, 7.1) | 3.94 (brs) | 70.5 | 70.7 |
| β-OH | 5.64 (d, 6.3) | 5.62 (d, 5.4) | | |
| 1′ | 8.00 (brs) | 7.97 (brs) | | |
| 2′ | | | 159.2 | 159.3 |
| 3′ | 7.79 (m) | 7.60−7.82 (m) | | |
| 4′ | 3.84 (ddd, 7.1, 7.1, 9.0) | 3.84 (m) | 56.5 | 56.8 |
| 5′ | 3.58 (m) | 3.54−3.59 (m) | 43.9 | 44.2 |
| 6′ | 7.77 (m) | 7.60−7.82 (m) | | |
| | | L-Ser | | |
| C=O (1) | | | 169.8 | 170.1 |
| α (2) | 4.31 (m) | 4.30 (m) | 54.0 | 54.2 |
| α-NH | 7.93 (d, 7.5) | 7.93 (brs) | | |
| β (3) | 3.62 (m) | 3.56−3.63 (m) | 61.0 | 61.2 |
| | 3.72 (m) | 3.67−3.74 (m) | | |
| β-OH | 5.15 (t, 5.1) | 5.13 (brs) | | |
| | | Gly | | |
| C=O (1) | | | 168.4 | 168.7 |
| α-NH | 8.21 (t, 6.0) | 8.18 (brs) | | |
| α (2) | 3.66 (m) | 3.62−3.67 (m) | 42.8 | 43.0 |
| | | β-MePhe | | |
| C=O (1) | | | 169.5 | 169.8 |
| α (2) | 4.49 (dd, 6.5, 8.7) | 4.48 (dd, 7.2, 7.8) | 57.4 | 57.6 |
| α-NH | 7.77 (m) | 7.60−7.82 (m) | | |
| β (3) | 3.19 (m) | 3.15−3.19 (m) | 40.0 | 40.2 |
| β-Me | 1.06 (d, 7.1) | 1.07 (d, 7.2) | 16.3 | 16.6 |
| 1′ | | | 143.0 | 143.2 |
| 2′, 6′ | 7.14 (d, 7.1) | 7.19 (d, 6.6) | 127.5 | 127.8 |
| 3′, 5′ | 7.21 (dd, 7.1, 7.5) | 7.22 (m) | 127.9 | 128.2 |
| 4′ | 7.15 (t, 7.1) | 7.13−7.18 (m) | 126.2 | 126.5 |
| | | D-Tyr | | |
| C=O (1) | | | 170.1 | 170.4 |
| α (2) | 4.30 (m) | 4.30 (m) | 54.3 | 54.6 |
| α-NH | 7.80 (d, 8.8) | 7.77−7.80 (m) | | |
| β (3) | 2.65 (dd, 7.6, 13.5) | 2.64 (m) | 36.1 | 36.3 |
| | 2.41 (dd, 6.3, 13.5) | 2.41 (m) | | |
| 1′ | | | 127.3 | 127.5 |
| 2′, 6′ | 6.83 (d, 8.3) | 6.82 (d, 7.8) | 129.9 | 130.2 |
| 3′, 5′ | 6.58 (d, 8.3) | 6.58 (d, 7.8) | 114.7 | 114.9 |
| 4′ | | | 155.9 | 156.1 |
| 4′-OH | 9.20 (brs) | 9.18 (brs) | | |

[a]Notation for position followed the ref 5. [b]Chemical shifts were shown in units of parts per million (ppm). Multiplicities and coupling constants in Hertz (Hz) were shown in the parentheses.

**S16** and **22** (details of these experiments, see Supporting Information).

Although the $^1$H and $^{13}$C NMR spectral data of **6** were consistent with a cyclic hexapeptide, they were not identical to those reported earlier for the mannopeptimycin aglycone.[5] As shown in Figure 2, the observed $^1$H and $^{13}$C NMR chemical shifts in the Aiha-A and β-MePhe regions, particularly for the methyl group, were significantly different from the reported data. We considered two possible explanations for these discrepancies: (1) The assignment of the Aiha-A and -B residues in the proposed aglycone was reversed. (2) The reported absolute stereochemistry for β-MePhe was incorrect. To investigate these scenarios, an isomer of **6**, with the reversed order of Aiha-A and -B, was synthesized using the above synthetic route without much difficulty. Although it showed the robustness of the procedure, the $^1$H NMR spectral data of this product were again inconsistent with the reported mannopeptimycin aglycone.

We then focused our attention on the stereochemistry of the β-MePhe residue. The $^1$H NMR chemical shifts and coupling constants, along with the optical rotation of (2*S*,3*R*)-β-MePhe prepared in accordance with the reported procedure,[51] were measured and shown to be consistent with the β-MePhe prepared from the mannopeptimycin aglycone.[5] These observations led us believe that the correct configuration of the β-MePhe was most likely (2*S*,3*R*). Therefore, the cyclic hexapeptide aglycone **32**, that contained a (2*S*,3*R*)-β-MePhe residue, was synthesized according to Scheme 3. The structure of **32** was confirmed by a detailed spectroscopic analysis, and the $^1$H and $^{13}$C NMR data of its trifluoroacetic acid salt, as


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listed in Table 1, were identical to those recorded for the mannopeptimycin aglycone. These conclusive results allowed us to confidently revise the stereochemistry of the β-MePhe residue from the proposed (2*S*,3*S*) to the correct (2*S*,3*R*).[52]

A disk-diffusion assay was carried out to evaluate the antimicrobial activity against *S. aureus* for **S8**, **S12**, **S15**, **6**, and **32**. As a result, these compounds did not show antimicrobial activity. In a previous report, the antibacterial potency was only associated with the mannopeptimycin class when the peptide aglycone, the mannose mono- and disaccharide, and a small hydrophobic substituent were properly positioned.[10−12,14,15] Clearly, the future work for this project will be the installation of the saccharide moieties, along with a hydrophobic group, on the aglycone.

## CONCLUSION

In summary, we successfully synthesized densely functionalized amino acids **10** and **12** with three adjacent chiral centers by a one-step synthesis from readily available compounds **8** and **9**. This procedure involved an asymmetric aldol addition coupled with an isomeric resolution via diastereoselective cyclization, to simultaneously construct two stereo centers in each amino acid **10** and **12** from the chiral center of **8**. The resulting (2*R*,3*S*,4*S*)-aldol **11** was readily cyclized to afford the corresponding oxazolidine **12**, whereas (2*S*,3*S*,4*S*)-aldol **10** remained acyclic due to its stereo orientation. The two products **10** and **12** were easily separated and further modified to afford **15** and **18**, respectively. These building blocks were then utilized in the assembly of the correct mannopeptimycin aglycone **32** and two of its stereoisomers. A spectroscopic analysis of these compounds required a revision of the absolute configuration of the β-MePhe residue in the aglycone from the reported (2*S*,3*S*) to the corrected (2*S*,3*R*). The revision of the stereochemistry obviously should be extended to all natural mannopeptimycins and their semisynthetic analogs.[5,10−12,14,15] The efficient preparation of the key amino acid residues, Aiha-A and -B, and the synthesis of the aglycone established a basis for further SAR studies that could yield useful new antibiotics of the mannopeptimycin class.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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