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Total Synthesis of Mannopeptimycins α and β

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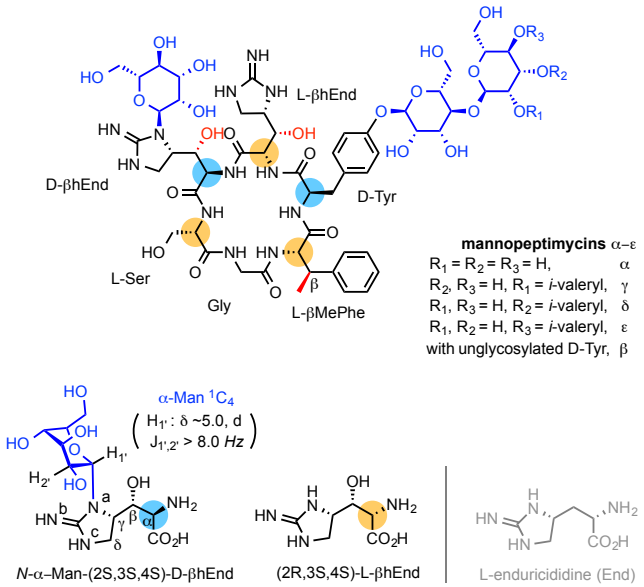
ABSTRACT: The mannopeptimycins are a class of glycopeptide natural products with unusual structures and potent antibiotic activity against a range of Gram-positive multidrug-resistant bacteria. Their cyclic hexapeptide core features a pair of unprecedented β-hydroxyenduracididines (L- and D-βhEnd), an *O*-glycosylated D-Tyr carrying an α-linked di-mannose, and a β-methylated Phe residue. The D-βhEnd unit also carries an α-linked mannopyranose at the most hindered *N* of its cyclic guanidine ring. Herein, we report the first total synthesis of mannopeptimycin α and β with fully elaborated *N*- and *O*-linked sugars. Critically, a gold-catalyzed *N*-glycosylation of a D-βhEnd substrate with a mannosyl *ortho*-alkynylbenzoate donor enabled the synthesis of the most challenging *N*-Man-D-βhEnd unit with excellent efficiency and stereoselectivity. The L-βMePhe unit was prepared using a Pd-catalyzed C–H arylation method. The L-βhEnd, D-Tyr(di-Man) and L-βMePhe units were prepared in gram quantities. A convergent assembly of the cyclic peptide scaffold and a single global hydrogenolysis deprotection operation provided mannopeptimycin α and β.

INTRODUCTION

The mannopeptimycins (MPP) are a class of glycopeptide natural products produced by *Streptomyces hygroscopicus* LL-AC98.[1] They have shown potent antibiotic activity against a range of Gram-positive multidrug-resistant pathogens including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE) and have demonstrated compelling potential as clinically useful antibacterials.[2] The MPPs were originally isolated in 1950s, but their structures were first elucidated in 2002 by researchers at Wyeth Pharmaceuticals based on NMR and chemical degradation studies.[3] The MPPs contain a cyclic hexapeptide core comprised of alternating L- and D-α-amino acids (αAAs). Among the αAA units are a pair of unprecedented β-hydroxyenduracididine (L- and D-βhEnd)[4,5], a L-β-methylated Phe (βMePhe), and a *O*-glycosylated D-Tyr carrying an α-(1,4-linked)-bis-manno-pyranosyl pyranoside (Scheme 1). More strikingly, it was proposed that the D-βhEnd unit bears a α-mannopyranose in $^1C_4$ conformation[6] at the most hindered *N* atom on the cyclic guanidine ring. An *N*-glycosylated guanidine motif has not been found in any other natural product. Biological studies have indicated that the MPPs interfere with the late stages of bacterial cell wall synthesis by binding cell wall precursor lipid II[7] in a manner unlike other lipid II binders such as ramoplanin and vancomycin.[8] Bio- and semisynthetic studies of MPPs suggest that both *N*- and *O*-linked sugars are necessary for antibiotic activity.[9]

The highly unusual structures, novel mode of action, and promising antibiotic activity of the MPPs have generated great interest in their chemical synthesis and structural modification over the past decade.[9-12] Modifications on the *O*-linked sugar residues and βMePhe unit have provided significantly improved lead compounds for preclinical trials.[9c] The laboratories of O'Doherty and Iadonisi have reported syntheses of the *O*-linked di-mannose residue.[10] The laboratories of Oberthür and Van Nieuwenhze have reported syntheses of unglycosylated L- and D-βhEnd units.[11] In 2014, Fuse and Doi reported the first total synthesis of mannopeptimycin aglycone and revised the Cβ stereochemistry of the L-βMePhe unit.[12a] However, the synthesis of *N*-man-D-βhEnd remains elusive, posing a formidable obstacle to the total synthesis of the mannopeptimycins.



Scheme 1. Structure of mannopeptimycins

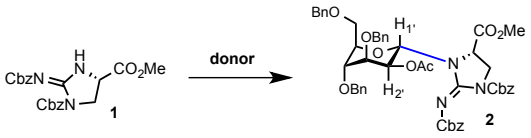
Herein, we report the first total synthesis of mannopeptimycin α and β with fully elaborated *N*- and *O*-linked sugars. Key features include a highly efficient gold-catalyzed *N*-mannosylation for the

synthesis of the *N*-man-D-βhEnd unit, a stereoselective synthesis of the L-βMePhe unit via Pd-catalyzed directed C–H arylation, a gram-scale preparation of the L-βhEnd and *O*-di-mannosyl-D-Tyr units, and a convergent assembly of the cyclic peptide backbone followed by a global hydrogenolysis deprotection operation to give the final product.

RESULTS AND DISCUSSION

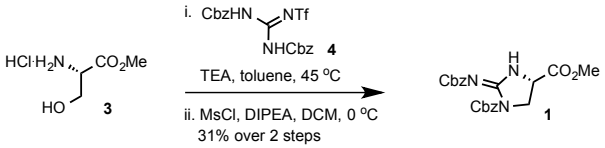
N-mannosylation of a model cyclic guanidine

Intrigued by the extraordinary structure and highly promising antibiotic activity of the MPPs, we began our attempt at the total synthesis of this class of glycopeptide natural products seven years ago. The most difficult challenge in the synthesis of MPP is the preparation of a suitable *N*-α-mannosyl-D-βhEnd unit. Compared with the array of established methods for *O*-glycosylation, methods for *N*-glycosylation are much less developed, and primarily limited to the synthesis of *N*-glycosides of nucleotides and heteroarenes.[13] Moreover, poor compatibility with Lewis acid-promoted conditions, steric hindrance about the *N*-glycosylation site on the cyclic guanidine ring, and the delicate structure of the D-βhEnd substrate further complicate of the synthesis of *N*-α-mannosyl-D-βhEnd.



entry	donor (equiv)	reagents (equiv), conditions	yield (%)[a]
1	**7** (3)	Ag_2CO_3 (2), 4A MS, toluene, 80 °C, 12h	12
2	**8** (1.5)	$Ph_3PAuNTf_2$ (0.2), DCM, 4A MS, rt, 18h	15
3	**8** (1.5)	$Ph_3PAuNTf_2$ (0.2), DCM, 4A MS, 45 °C, 24h	54
4	**10** (1.5)	$Ph_3PAuNTf_2$ (0.2), DCM, 4A MS, rt, 18h	85
5	**10** (1.5)	$Ph_3PAuNTf_2$ (0.2), toluene, 4A MS, rt, 18h	87
6	**10** (1.5)	$Ph_3PAuNTf_2$ (0.2), toluene, 4A MS, 65 °C, 4h	83
7	**10** (1.5)	$Ph_3PAuNTf_2$ (0.1), toluene, 4A MS, 65 °C, 18h	55
8	**9** (1.5)	$Ph_3PAuNTf_2$ (0.2), toluene, 4A MS, 65 °C, 4h	80

Preparation of 1



donors:

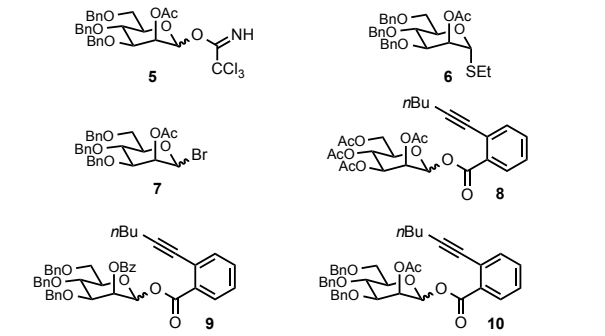


Table 1. *N*-mannosylation of model cyclic guanidine **1**. a) isolated yield on a 0.2 mmol scale.

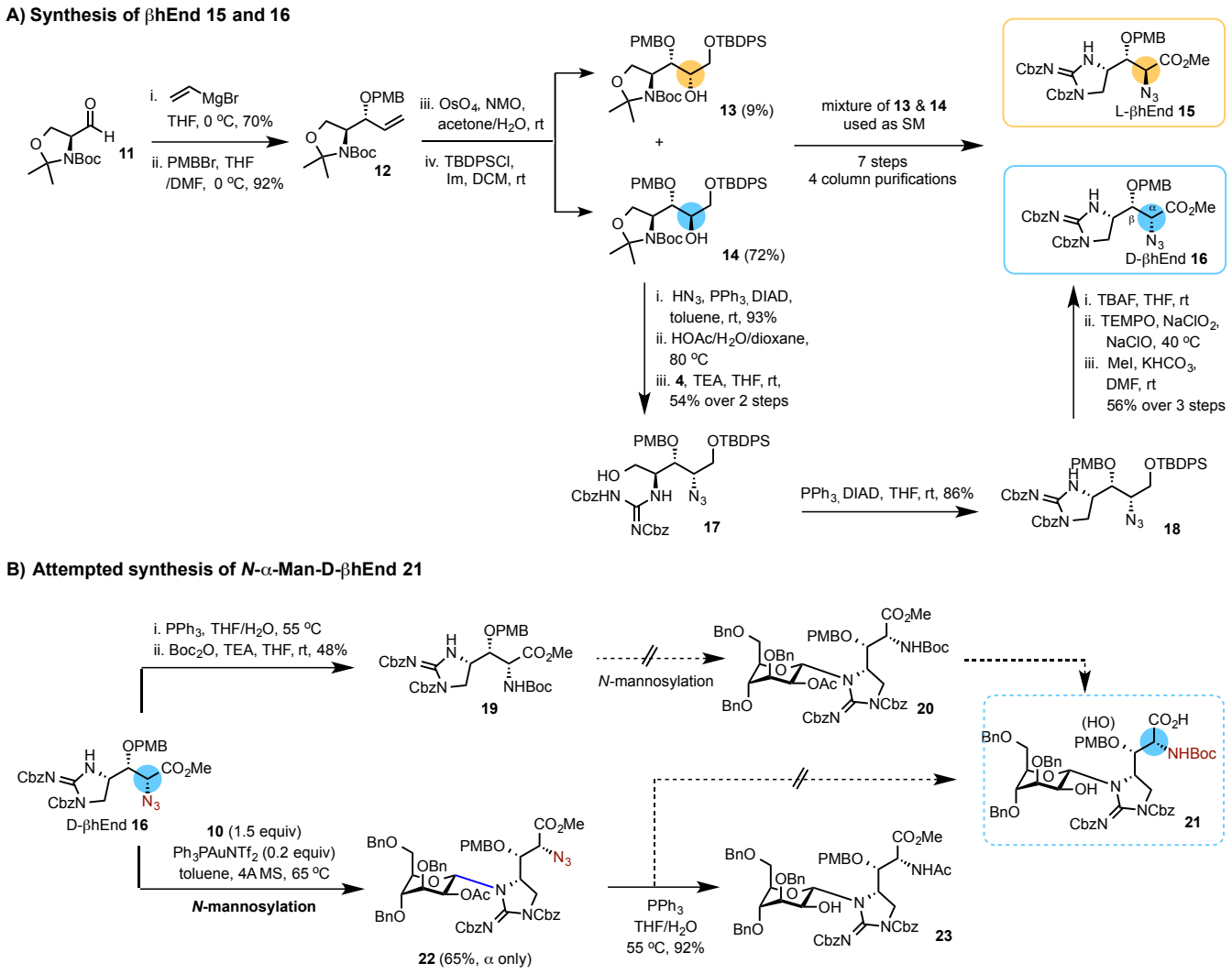
To address this issue, we first investigated the *N*-mannosylation of simpler di-Cbz-protected cyclic guanidine model substrate **1** (Table 1). Compound **1** can be quickly prepared from serine methyl ester **3** via guanylation with Goodman reagent **4**[14] followed by MsCl-mediated C–N cyclization.[15] *N*-mannosylation of **1** with mannosyl trichloroacetimidate donor **5** and ethyl sulfide donor **6** under various Lewis acid-promoted conditions (e.g. with TMSOTf, BF_3OEt_2, NIS) failed to give any *N*-mannosylated product. *N*-mannosylation of **1** with bromide donor **7** promoted by weakly basic Ag_2CO_3[13e] in toluene at 80 °C gave product **2**[16] in 12% yield. However, the Koenigs-Knorr-type *N*-mannosylation of more complex substrates (e.g. D-βhEnd **16** in Scheme 2) with **6** only gave trace amount of product (<5%). The failure of these conventional glycosylation methods prompted us to test a gold(I)-catalyzed glycosylation method, recently reported by Yu, using *ortho*-alkynylbenzoate donors.[17] Encouraged by a successful application in nucleoside synthesis,[17b] we expected that the unique π-acid activation mode of Yu's method, orthogonal to the Lewis basic guanidine *NH*, might provide an efficient *N*-mannosylation method for cyclic guanidines. To our delight, the $Ph_3PAuNTf_2$-catalyzed *N*-mannosylation of **1** with mannosyl *ortho*-alkynylbenzoate **10** proceeded in excellent yield and with exclusive α-stereoselectivity at room temperature (entries 4 and 5). The reaction time can be shortened at elevated temperature (entry 6). As in donor **7**, the 2-*O*Ac group of **10** is required to control the α stereoselectivity via neighboring group participation. Donor **9** carrying a 2-*O*Bz group gave slightly lower yield (entry 8). Disarmed tetra-OAc substituted donor **8** gave considerably lower mannosylation yield under the same reaction conditions (entries 2 and 3, see Supporting Information for preparation of **8**-**10**).

Preparation of the βhEnd units

With a gold-catalyzed *N*-mannosylation method in hand, we proceeded to investigate the synthesis of *N*-Man-D-βhEnd and L-βhEnd units.[11] As shown in Scheme 2A, our initial synthetic route for the βhEnd units began from a common precursor **12**, which can be prepared from Garner aldehyde **11** in large quantity in 2 steps.[18,19] OsO_4-catalyzed dihydroxylation of **12** and TBDPS protection of the terminal OH group gave a separable diastereomeric mixture of **13** and **14** with 1:8 selectivity.[20] Mitsunobu reaction of **14** gave an azido compound. The removal of *N,O*-acetonide and Boc groups, followed by guanylation with Goodman reagent **4**, and PPh_3/DIAD-mediated C–N cyclization provided **18**. Removal of the TBDPS group of **18** with TBAF, TEMPO oxidation, and esterification with MeI gave α-azido methyl ester **16**. A diastereomeric mixture of **13** and **14** can be subjected to the same reaction sequence (from **14** to **16**) without separating the diastereomeric intermediates until the final azido ester products **15** and **16**, which are easily separable by silica gel column chromatography. Starting from **11**, both βhEnd compounds **15** and **16** were obtained in 14% combined yield via a single sequence of 11 steps and 7 column purifications.

As shown in Scheme 2B, azido ester **16** can be converted to **19** via reduction with PPh_3 followed by Boc protection. Disappointingly, *N*-mannosylation of **19** using various methods failed to give any of the desired product **20** possibly due to steric hindrance or interference from the Boc-protected NH group.[21] On the other hand, *N*-mannosylation of azido ester **16** with **10** proceeded successfully under the gold-catalyzed conditions at 65 °C to give product **22** in 65% yield and complete α-stereoselectivity.[22] However,

Scheme 2. Our initial synthetic route for L-βhEnd and *N*-Man-D-βhEnd

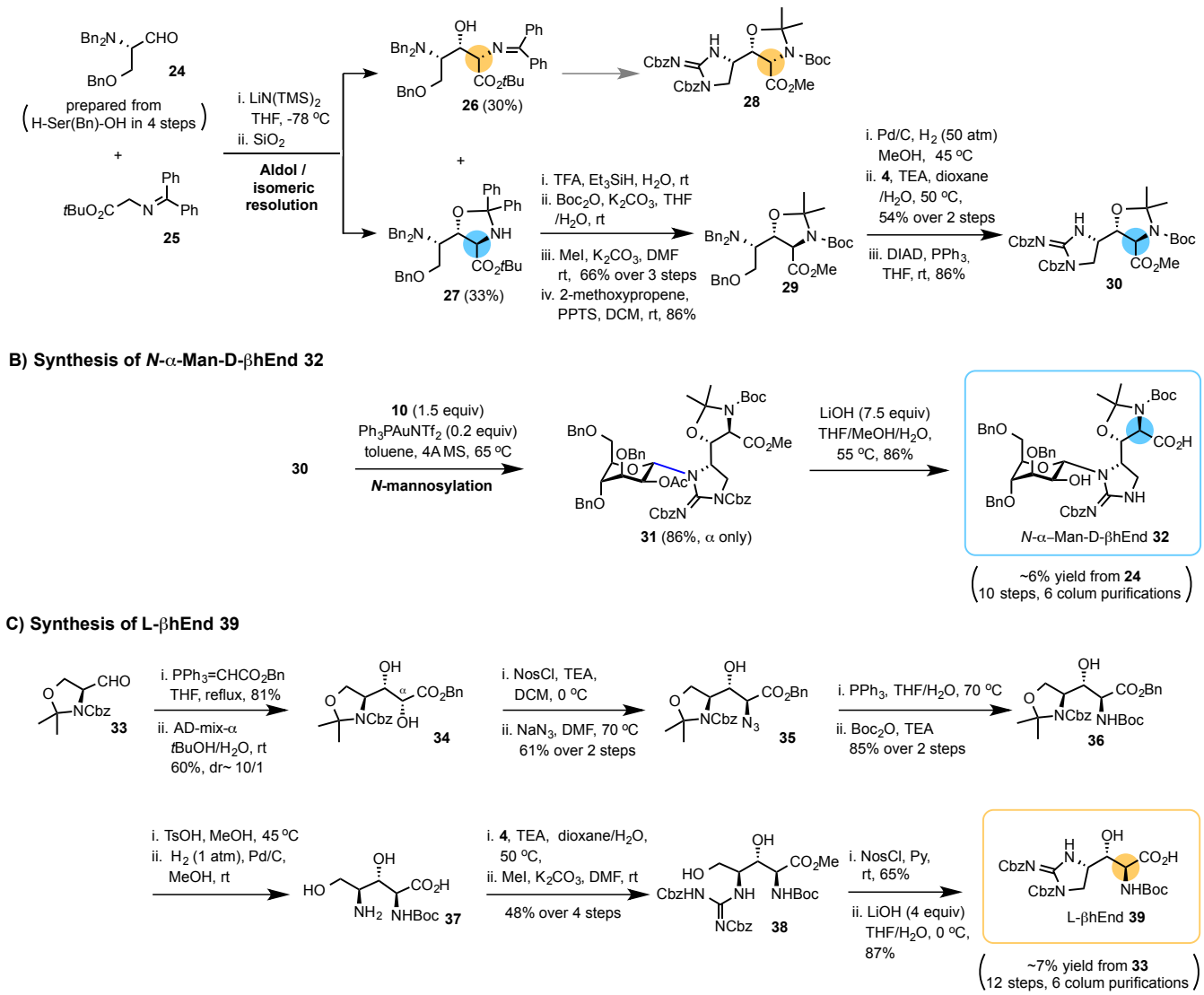


attempted reduction of the azido group of **22** under various conditions failed to give the desired amine product, predominately forming acetamide byproduct **23** through an intramolecular *O* to *N* acyl transfer process. The attempted removal of the OAc group of **22** under acidic or basic conditions failed due to serious side reactions and decomposition of **22**.[23]

The success of the gold-catalyzed *N*-mannosylation with the complex D-βhEnd substrate **16** followed by the failed reduction of the azido group to amine prompted us to investigate other βhEnd substrates bearing a more properly protected *N*-terminus. Encouraged by the report of MPP aglycone synthesis by Fuse and Doi,[12a] we wondered whether their D-βhEnd unit **30** protected by *N,O*-acetonide and Boc at *N*-terminus might be useful for the synthesis of *N*-man-D-βhEnd (Scheme 3A). Following the reported procedure, a separable mixture of **26** and **27** was obtained via a tandem aldol/cyclization reaction between tribenzyl protected 2-aminopropanol **24** and *N*-(diphenylmethylene) glycine *t*-butyl ester **25**. Compound **27** was then converted to compound **30** in 7 steps.[24] To our delight, the gold-catalyzed *N*-mannosylation of D-βhEnd **30** with *ortho*-alkynylbenzoate donor **10** in toluene at 65 °C proceeded very cleanly to give desired product **31** in 86% isolated yield and with complete α-stereoselectivity on a gram scale (Scheme 3B). Compared to the *N*-mannosylation reaction of substrate **16**, little undesired side product was formed, possibly because the guanidine *NH* group of the acetonide protected substrate is less hindered. Finally, treatment of **31** with LiOH successfully removed the 2-OAc group on mannose, the methyl ester group, and one Cbz group on the cyclic guanidine moiety to give *N*-man-D-βhEnd **32** in good yield.

Although intermediate **26** can be converted to L-βhEnd **28** via a similar sequence in Fuse and Doi's report, the overall yield of this route was very low in our hands. As shown in Scheme 3C, a more scalable synthesis of L-βhEnd **39** was achieved based on modification of a method recently reported by Oberthür.[11c] The synthesis of **39** began with Wittig reaction of compound **33** and $Ph_3P{=}CHCO_2Bn$ followed by diastereoselective dihydroxylation to form **34**. The Cα OH group was then converted to BocNH. The acetonide, Bn and Cbz groups of **36** were then removed to give **37**. The use of the free carboxylic acid form of **37** was necessary to avoid a competing intramolecular γ-lactamization observed when ester derivatives of **37** were subjected to basic conditions. Formation of the cyclic guanidine group followed by saponification of the Cα ester gave L-βhEnd **39**. Starting from **33**, **39** was obtained in 7% yield over 12 steps and 6 column purifications.

Scheme 3. Synthesis of *N*-Man-D-βhEnd **32** and L-βhEnd **39**

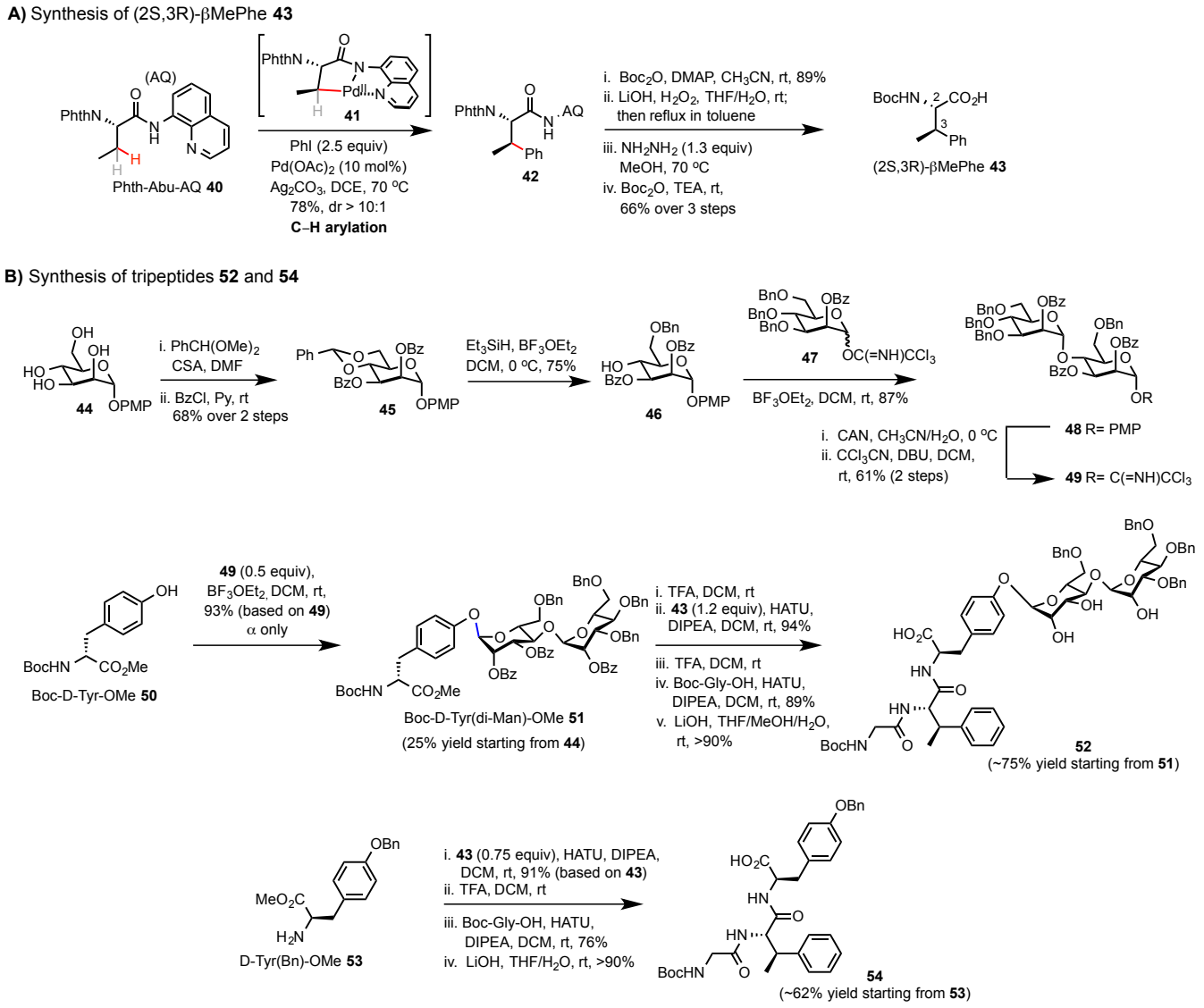


Preparation of the other αAA units and the final assembly of mannopeptimycins

With the two βhEnd units in hand, we next turned our attention to the preparation of the remaining αAA units and the final assembly of the cyclic hexapeptide. Following Fuse and Doi's peptide coupling strategy in the synthesis of MPP aglycone,[12a] we planed to join the two tripeptide fragments at the D-Tyr/L-βhEnd site and then cyclize at the Ser/Gly site.[12b] To simplify the final deprotection operation, Bn was used as the protecting group for Ser and D-Tyr units. As shown in Scheme 4A, the (2*S*,3*R*)-*threo*-βMePhe unit **43** was prepared using our previously developed Pd-catalyzed aminoquinoline (AQ)-directed C–H arylation chemistry.[25] Pd-catalyzed β-C(sp^3)–H arylation of phthaloyl-L-2-aminobutyramide **40** with PhI gave **42** in excellent yield and diastereoselectivity. The stereochemistry of C–H arylation was controlled by the α,β-trans-configuration of 5-membered palladacycle intermediate **41**. The AQ auxiliary was cleaved with LiO_2H following Boc activation. The Phth group was then replaced with Boc to give Boc-βMePhe-OH **43** in good yield and with excellent stereoretention at Cα.

As shown in Scheme 4B, *O*-di-mannosyl-D-Tyr unit **51** was prepared via glycosylation of Boc-D-Tyr-OMe **50** with dimannosyl trichloroacetimidate donor **49**.[10] Mannose **44** with a PMP group[26] at the anomeric position was first protected as a 4,6-*O*-benzylidene intermediate, and then treated with BzCl to give **45**. The benzylidene group of **45** was selectively opened via treatment with Et_3SiH and BF_3OEt_2 to give **46**. BF_3OEt-promoted glycosylation of **46** with 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-D-mannsoyl trichloroacetimidate **47** gave 1,4-linked dimannose **48** in excellent yield and α-selectivity. Treatment of **48** with cerium ammonium nitrate (CAN) removed the anomeric PMP group and reaction with CCl_3CN and DBU gave corresponding trichloroacetimidate donor **49**. The BF_3OEt_2-promoted *O*-glycosylation of **50** with **49** gave Boc-D-Tyr(di-Man)-OMe **51** in excellent yield and α-selectivity. Boc deprotection and HATU-mediated amide couplings of the αAA units **51**, **43** and Boc-Gly-OH followed by saponification with LiOH gave the tripeptide Boc-Gly-βMePhe-D-Tyr(di-Man)-OH **52**. Similarly, peptide coupling of Boc-D-Tyr(Bn)-OMe **53**, Boc-βMePhe-OH **43** and Boc-Gly-OH gave the un-glycosylated tripeptide **54**.

Scheme 4. Synthesis of tripeptides **52** and **54**

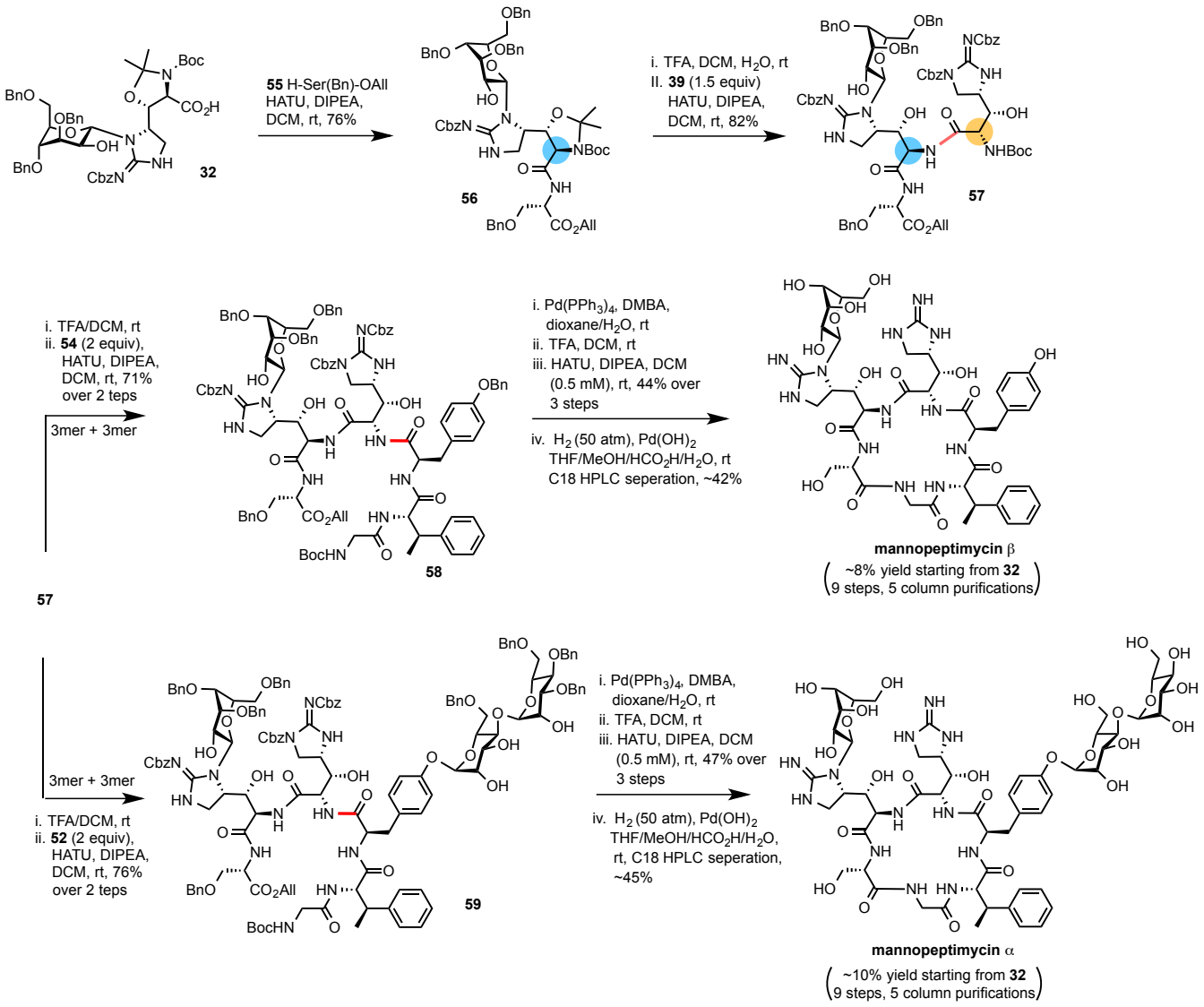


As shown in Scheme 5, the HATU-mediated amide coupling of *N*-man-D-βhEnd **32** with H-Ser(Bn)-OAll **55** gave **56** in good yield. To our delight, the *N*-linked mannose residue of **56** remained intact during the deprotection of acetonide and Boc groups under acidic conditions. HATU-mediated amide coupling between the two sterically hindered βhEnd sites also proceeded smoothly to give tripeptide **57** in excellent yield. The Boc group of **57** was removed and HATU-mediated amide coupling with tripeptide **54** gave linear hexapeptide **58**. Removal of the *C*-terminus allyl group, removal of the *N*-terminus Boc group, and HATU-mediated macrolactamization provided the cyclized hexapeptide in ~44% yield over 3 steps. Finally, a global deprotection of the Cbz and Bn groups provided mannopeptimycin β, following reverse phase HPLC purification. Following the same sequence, the tripeptide fragments **57** and **52** were coupled, cyclized and deprotected to give mannopeptimycin α in similar yield. The ^{1}H and ^{13}C NMR spectra of both synthetic products was fully consistent with data of isolated samples from the literature (see SI for details).[27]

Conclusion

The unique peptide scaffold and unprecedented glycosylation pattern of the mannopeptimycins has until now prevented their total synthesis. The structural complexity of the MPPs requires judicious choices at the level of individual αAA building block synthesis as well as peptide assembly. Our early studies revealed that Yu's gold-catalyzed *N*-glycosylation with a mannosyl *ortho*-alkynylbenzoate donor offered a uniquely powerful means to install *N*-linked mannose moiety on cyclic guanidine substrates with high efficiency and stereoselectivity. Our subsequent investigation revealed that the choice of protecting groups for the *N*-terminus and β-OH group of the D-βhEnd substrate is critical to successfully access the *N*-Man-D-βhEnd building block. Building upon the earlier reports by Fuse-Doi and Oberthür, we developed efficient and scalable syntheses for both *N*-Man-D-βhEnd and L-βhEnd units. Boc-βMePhe-OH was prepared via Pd-catalyzed C–H arylation chemistry. *O*-di-mannosyl-D-tyrosine was prepared via glycosylation of Boc-D-Tyr-OMe with a dimannosyl trichloroacetimidate donor. Each of these αAA building blocks can be prepared in gram quantities. Finally, a convergent assembly of the cyclic peptide backbone and a single global hydrogenolysis deprotection

Scheme 5. Total synthesis of mannopeptimycins α and β



operation provided mannopeptimycins α and β. Our synthesis provides conclusive evidence for the structural determination of these highly complex glycopeptide natural products. We hope that this work will enable exploration of previously inaccessible mannopeptimycin derivatives, provide mechanistic understanding of their mode of action, and promote the development of new analogues with enhanced antibacterial activity.

ASSOCIATED CONTENT

Additional experimental procedures and spectroscopic data for all new compounds are supplied. This material is available free of charge via the Internet at http://pubs.acs.org.

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19. The corresponding Bn-protected analogues of **16**, **19**, and **22** (Scheme 2B) were also prepared using the same strategy for precursor **12**. However, we found that a Bn protecting group at Cβ OH of these analogues cannot be cleanly removed under catalytic hydrogenolysis conditions.
20. A 1.1:1 ratio of **13** and **14** was obtained in 91% combined yield when the AD-mix-β catalyst was used in the dihydroxylation step.
21. Protection of NH_2 with Phth gave very low yield (<15%).
22. An unidentified side product with the same molecular weight of **22** was also formed in 20% yield. However, its NMR spectra do not fully agree with an ortho ester structure (see SI). Gold-catalyzed *N*-mannosylation of compound **18** with **10** also worked well. However, the attempted conversion of the resulting *N*-mannosylated intermediate to **21** was unsuccessful.
23. The conformation of **22** might affect the accessibility of the OAc group.
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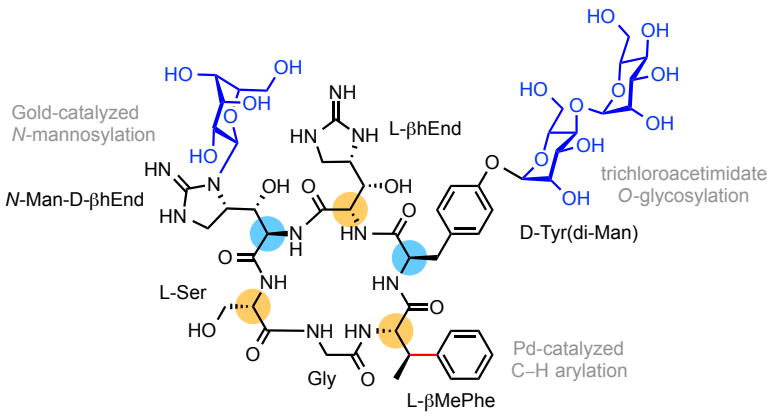
27. No NMR spectra of isolated MPPs were provided in the original structural determination paper (ref 3). Our ^1H and ^{13}C-NMR spectra of both MPP α and β fully agree with the listed NMR data within an error of 0.1 ppm for ^1H-NMR and 0.2 ppm for ^{13}C-NMR.



mannopeptimycin α