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Total Synthesis of Mannopeptimycins α and β

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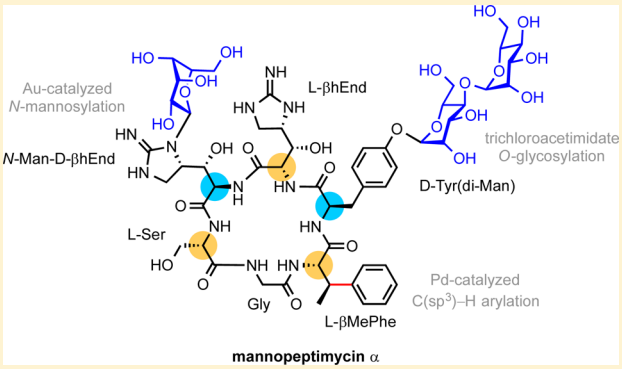
Supporting Information

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 dimannose, 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 *Staphylococcus 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 on the basis of 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] an L-β-methylated Phe (βMePhe), and an *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 that of 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 synthesis of the *O*-linked dimannose residue.[10] The laboratories of Oberthür and Van Nieuwenhze have reported synthesis 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.

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

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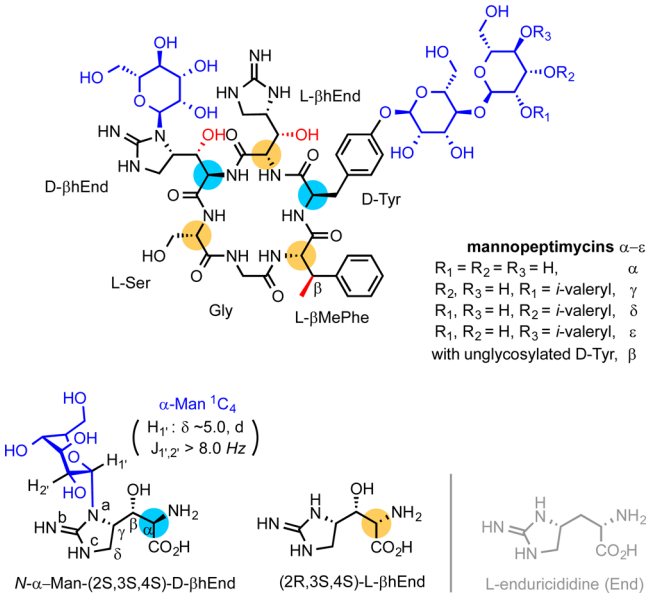
Scheme 1. Structure of Mannopeptimycins



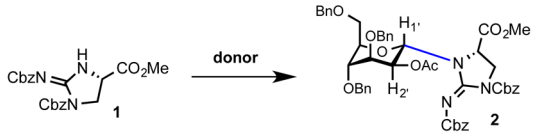
the L-*β*hEnd and *O*-dimannosyl-D-Tyr units, and a convergent assembly of the cyclic peptide backbone followed by a global hydrogenolysis deprotection operation to give the final product.

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-*β*hEnd unit. Compared with the array of established methods for *O*-glycosylation, methods for *N*-glycosylation are much less developed and are 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-*β*hEnd substrate further complicate the synthesis of *N*-*α*-mannosyl-D-*β*hEnd.

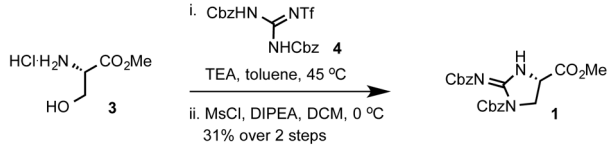
To address this issue, we first investigated the *N*-mannosylation of simpler di-Cbz-protected cyclic guanidine model substrate **1** (Table 1). Compound **1** can be quickly prepared from serine methyl ester **3** via guanylation with Goodman reagent **4**[14] followed by MsCl-mediated C−N cyclization.[15] *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, and 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-*β*hEnd **16** in Scheme 2) with **6** only gave a 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

Table 1. *N*-Mannosylation of Model Cyclic Guanidine 1

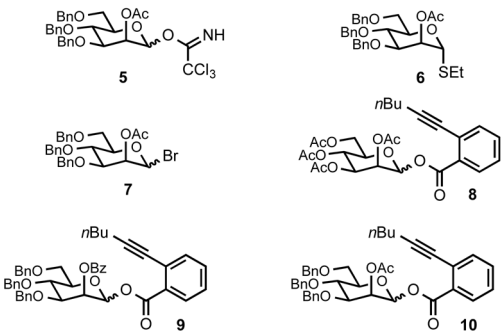


entry	donor (equiv)	reagents (equiv), conditions	yield (%)[a]
1	**7** (3)	Ag_2CO_3 (2), 4A MS, toluene, 80 °C, 12h	12
2	**8** (1.5)	$Ph_3PAuNTf_2$ (0.2), DCM, 4A MS, rt, 18h	15
3	**8** (1.5)	$Ph_3PAuNTf_2$ (0.2), DCM, 4A MS, 45 °C, 24h	54
4	**10** (1.5)	$Ph_3PAuNTf_2$ (0.2), DCM, 4A MS, rt, 18h	85
5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



[a]Isolated yield on a 0.2 mmol scale.

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 *β*hEnd Units. With a gold-catalyzed *N*-mannosylation method in hand, we proceeded to investigate the synthesis of *N*-Man-D-*β*hEnd and L-*β*hEnd units.[11] As shown in Scheme 2A, our initial synthesis route for the *β*hEnd units began from a common precursor **12**, which can be prepared from Garner aldehyde **11** in a large quantity in two 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

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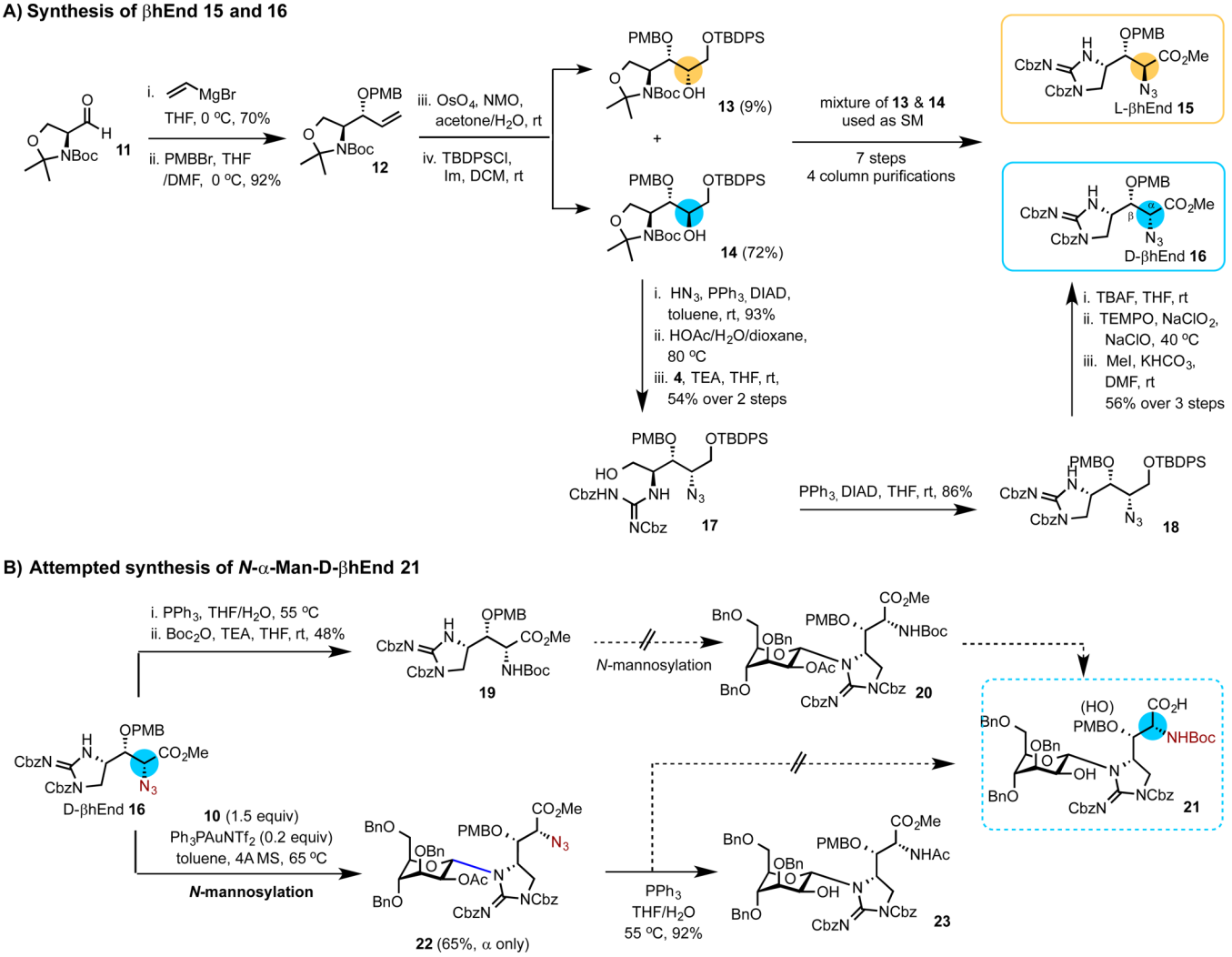
Scheme 2. Our Initial Synthesis Route for L-*β*hEnd and *N*-Man-D-*β*hEnd



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 final azido ester products **15** and **16**, which are easily separable by silica-gel column chromatography. Starting from **11**, both *β*hEnd 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 because of steric hindrance or interference from the Boc-protected NH group.[21] However, *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, 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 because of serious side reactions and decomposition of **22**.[23]

The success of the gold-catalyzed *N*-mannosylation with complex D-*β*hEnd substrate **16** followed by the failed reduction of the azido group to amine prompted us to investigate other *β*hEnd 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-*β*hEnd unit **30** protected by *N*,*O*-acetonide and Boc at the *N* terminus might be useful for the synthesis of *N*-Man-D-*β*hEnd (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-*β*hEnd **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,

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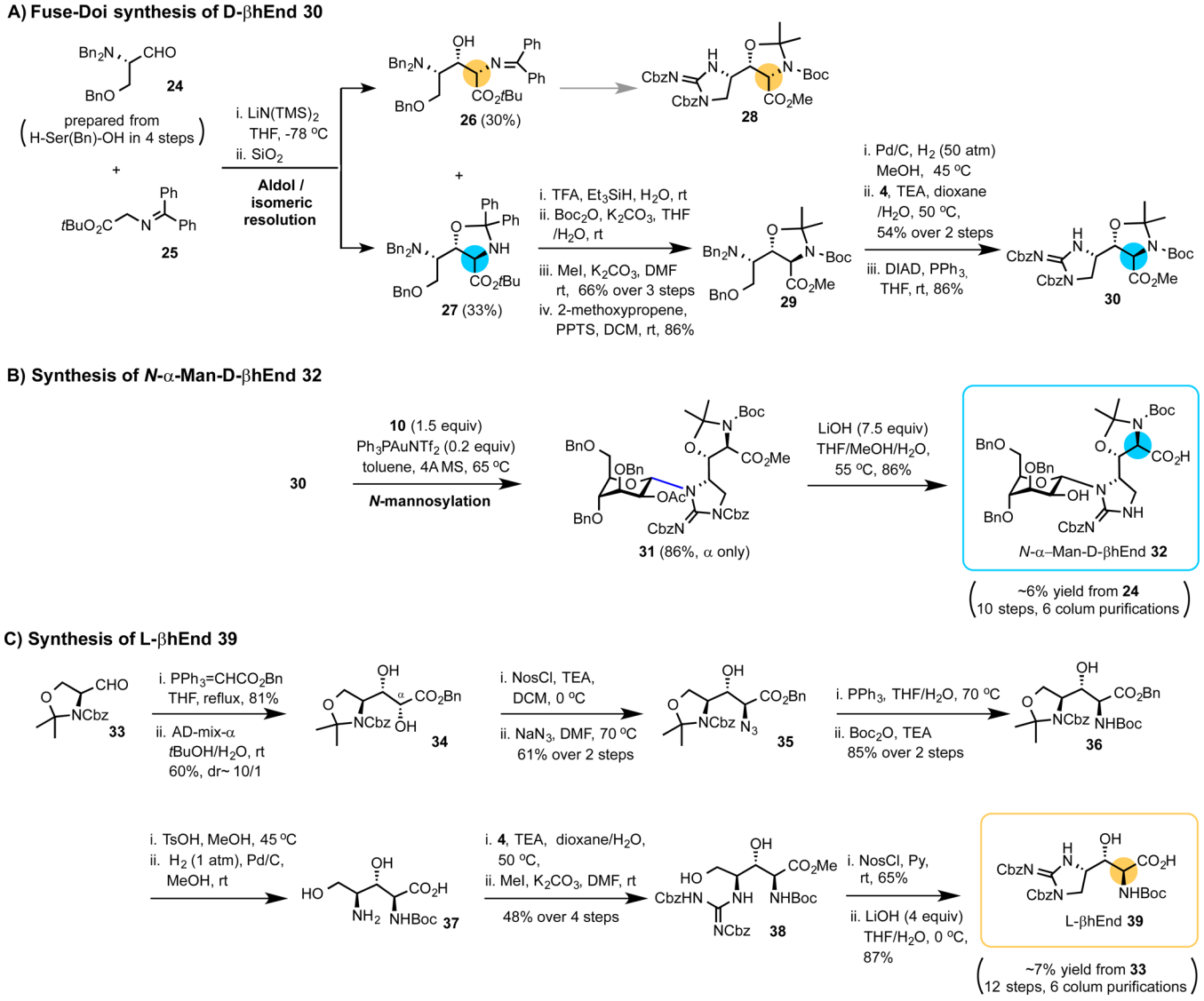
Scheme 3. Synthesis of *N*-Man-D-*β*hEnd 32 and L-*β*hEnd 39



the methyl ester group, and one Cbz group on the cyclic guanidine moiety to give *N*-man-D-*β*hEnd **32** in good yield.

Although intermediate **26** can be converted to L-*β*hEnd **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-*β*hEnd **39** was achieved that was 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 C*α* 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 C*α* ester gave L-*β*hEnd **39**. Starting from **33**, **39** was obtained in 7% yield over 12 steps and 6 column purifications.

Preparation of the Other *α*AA units and the Final Assembly of Mannopeptimycins. With the two *β*hEnd units in hand, we next turned our attention to the preparation of the remaining *α*AA 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 planned to join the two tripeptide fragments at the D-Tyr/L-*β*hEnd 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, (2*S*,3*R*)-*threo*-*β*MePhe 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 five-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-*β*MePhe-OH **43** in good yield and with excellent stereoretention at C*α*.

As shown in Scheme 4B, *O*-dimannosyl-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

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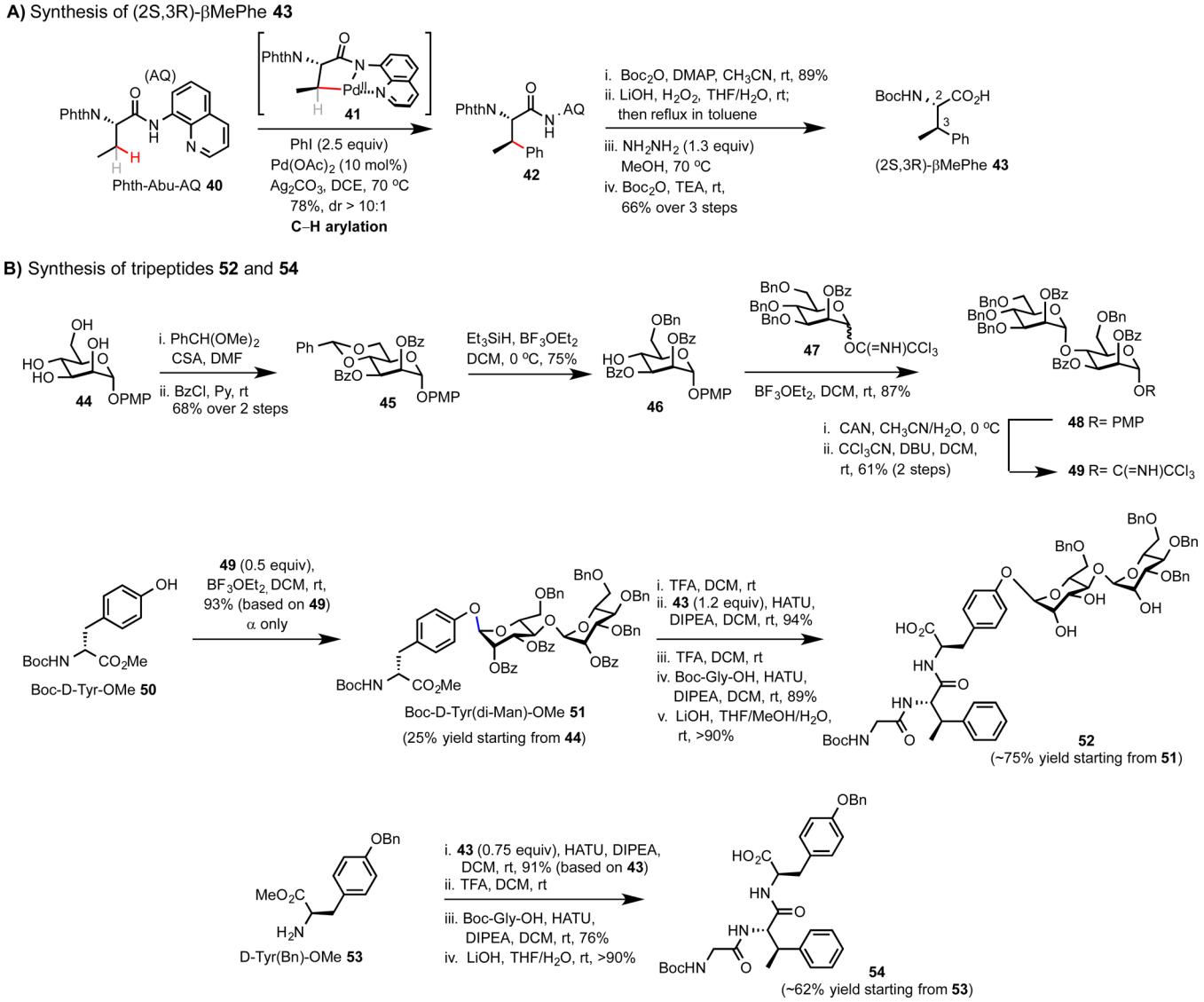
Scheme 4. Synthesis of Tripeptides 52 and 54



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 αAA units **51** and **43** and Boc-Gly-OH followed by saponification with LiOH gave 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 unglycosylated tripeptide **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 ^1H and ^{13}C NMR spectra of both synthetic products were fully consistent with data of isolated samples from the literature. (See Supporting Information for details.)[27]

CONCLUSIONS

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

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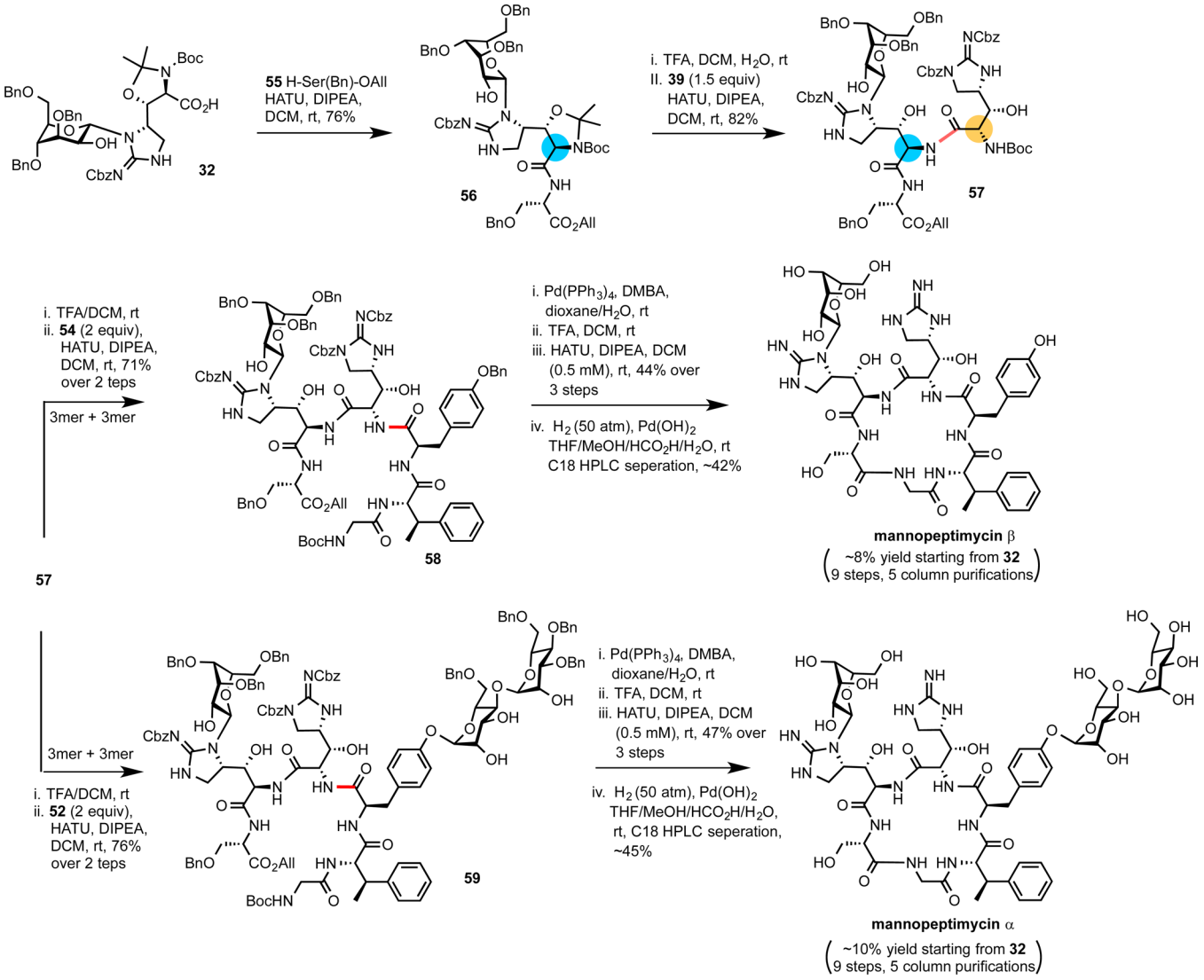
Scheme 5. Total Synthesis of Mannopeptimycins α and β



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 access successfully 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*-Dimannosyl-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 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

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01384.

Additional experimental procedures and spectroscopic data for all new compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) De Voe, S. E.; Kunstmann, M. P. Antibiotic AC98 and production. U.S. Patent 3495004, 1970.
(2) Koehn, F. E. *J. Med. Chem.* **2008**, *51*, 2613.
(3) He, H.; Williamson, R. T.; Shen, B.; Graziani, E. I.; Yang, H. Y.; Sakya, S. M.; Petersen, P. J.; Carter, G. T. *J. Am. Chem. Soc.* **2002**, *124*, 9729.
(4) For isolation of enduracididines, see (a) Horii, S.; Kameda, Y. *J. Antibiot.* **1968**, *21*, 665. (b) Fellows, L. E.; Hider, R. C.; Bell, E. A. *Phytochemistry* **1977**, *16*, 1957.
(5) For biosynthesis study of β-hydroxyenduracididines, see Haltli, B.; Tan, Y.; Magarvey, N. A.; Wagenaar, M.; Yin, X. H.; Greenstein, M.; Hucul, J. A.; Zabriskie, T. M. *Chem. Biol.* **2005**, *12*, 1163.
(6) For references on $^1C_4$ conformation of mannose, see (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205. (b) Onodera, K.; Hirano, S.; Masuda, F.; Kashimura, N. *J. Org. Chem.* **1966**, *31*, 2403.
(7) Breukink, E.; de Kruijff, B. *Nat. Rev. Drug Discovery* **2006**, *5*, 321.
(8) (a) Ruzin, A.; Singh, G.; Severin, A.; Yang, Y.; Dushin, R. G.; Sutherland, A. G.; Minnick, A.; Greenstein, M.; May, M. K.; Shlaes, D. M.; Bradford, P. A. *Antimicrob. Agents Chemother.* **2004**, *48*, 728. (b) Magarvey, N. A.; Haltli, B.; He, M.; Greenstein, M.; Hucul, J. A. *Antimicrob. Agents Chemother.* **2006**, *50*, 2167.
(9) For previous SAR studies based on bio- and semisynthesis, see (a) 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. (b) Dushin, R. J.; 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. (c) Petersen, P. J.; Wang, T. Z.; Dushin, R. G.; Bradford, P. A. *Antimicrob. Agents Chemother.* **2004**, *48*, 739. (d) 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.
(10) For previous syntheses of the *O*-linked dimannose residue, see (a) Babu, R. S.; Guppi, S. R.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1605. (b) Adinolfi, M.; Giacomini, D.; Iadonisi, A.; Quintavalla, A.; Valerio, S. *Eur. J. Org. Chem.* **2008**, *2008*, 2895.
(11) For previous syntheses of unglycosylated βhEnd units, see (a) Schwörer, C. J.; Oberthür, M. *Eur. J. Org. Chem.* **2009**, *2009*, 6129. (b) Olivier, K. S.; Van Nieuwenhze, M. S. *Org. Lett.* **2010**, *12*, 1680. (c) Fischer, S. N.; Schwörer, C. J.; Oberthür, M. *Synthesis* **2014**, *46*, 2234.
(12) (a) Fuse, S.; Koinuma, H.; Kimbara, A.; Izumikawa, M.; Mifune, Y.; He, H.; Shin-ya, K.; Takahashi, T.; Doi, T. *J. Am. Chem. Soc.* **2014**, *136*, 12011. (b) For a solid-phase synthesis of a simplified MPP aglycone substituted with L-,D-Arg and L-Phe residues, see Wang, T.-Z.; Wheless, K. L.; Sutherland, A. G.; Dushin, R. G. *Heterocycles* **2004**, *62*, 131.
(13) For selected syntheses of *N*-glycosides, see (a) Vorbrüggen, H. *Acc. Chem. Res.* **1995**, *28*, 509. (b) Gallant, M.; Link, J. T.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343. (c) Keynes, M. N.; Earle, M. A.; Sudharshan, M.; Hultin, P. G. *Tetrahedron* **1996**, *52*, 8685. (d) Lin, P.; Lee, C. L.; Sim, M. M. *J. Org. Chem.* **2001**, *66*, 8243. (e) Sugimura, H.; Natsui, Y. *Tetrahedron Lett.* **2003**, *44*, 4729. (f) Schnabel, M.; Rompp, B.; Ruckdeschel, D.; Unverzagt, C. *Tetrahedron Lett.* **2004**, *45*, 295. (g) Tanaka, H.; Iwata, Y.; Takahashi, D.; Adachi, M.; Takahashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 1630. (h) Ohno, H.; Terui, T.; Kitawaki, T.; Chida, N. *Tetrahedron Lett.* **2006**, *47*, 5747. (i) Hager, D.; Mayer, P.; Paulitz, C.; Tiebes, J.; Trauner, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 6525.
(14) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432.
(15) The low cyclization yield is caused by the competing elimination reaction. For selected syntheses of cyclic guanidines, see (a) DeMong, D. E.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 8561. (b) Shimokawa, J.; Shirai, K.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1559. (c) Ref 11..
(16) The unique large coupling constant of $H_{1'}$ at the anomeric position of mannose in **2** (δ 5.86 ppm, d, $J_{1',2'}$ = 8.9 Hz, in $CDCl_3$) agrees with the proposed $^1C_4$ conformation of *N*-linked α-mannose in MPPs.
(17) (a) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604. (b) Zhu, Y.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 8329. (c) Tang, Y.; Li, J.; Zhu, Y.; Li, Y.; Yu, B. *J. Am. Chem. Soc.* **2013**, *135*, 18396. (d) Nie, S.; Li, W.; Yu, B. *J. Am. Chem. Soc.* **2014**, *136*, 4157.
(18) (a) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans.* **2001**, 2136. (b) Ojima, I.; Vidal, E. *J. Org. Chem.* **1998**, *63*, 7999. (c) **11** was also used as SM in refs 11b and 11c.
(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 as **22** was also formed in 20% yield. However, its NMR spectra do not fully agree with an ortho ester structure (Supporting Information). 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.
(24) The procedures for converting **29** to **30** have been modified to obtain more reliable yields. See Supporting Information for details.
(25) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135.
(26) Han, Z.; Pinkner, J.; Ford, B.; Obermann, R.; Nolan, W.; Wildman, S.; Hobbs, D.; Ellenberger, T.; Cusumano, C.; Hultgren, S.; Janetka, J. *J. Med. Chem.* **2010**, *53*, 4779.
(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 MPPα 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.

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