**HETEROCYCLES, Vol. 62, 2004, pp. 131 - 135**
**Received, 15th July, 2003, Accepted, 25th August, 2003, Published online, 14th October, 2003**

# SOLID-PHASE SYNTHESIS OF CYCLIC GLYCOPEPTIDES RELATED TO MANNOPEPTIMYCIN DERIVATIVES

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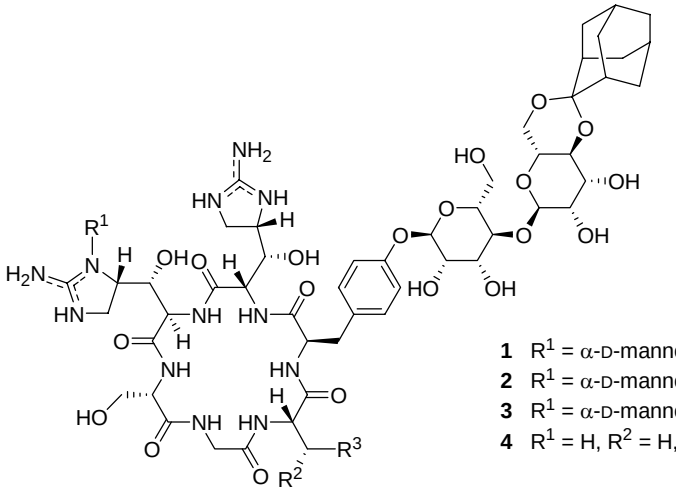
**Abstract** – The mannopeptimycins comprise a novel series of glycopeptide antibiotics that display activity against susceptible and resistant forms of gram-positive bacteria. Low isolated yields of these products from fermentation make the synthesis of easily accessible analogs attractive. A simplified hexapeptide is synthesized using a combination of solid-phase and solution-phase techniques.

Naturally occurring and semisynthetic mannopeptimycins comprise a novel class of glycopeptide antibiotics that display activities against both susceptible and resistant forms of gram-positive bacteria.[1~3] The key structural feature is a cyclic hexapeptide core that contains alternating D- and L-amino acids and includes an epimeric pair of a previously unknown amino acid, β-hydroxyenduricididine. One of these



**1** $R^1$ = α-D-mannose, $R^2$ = Me, $R^3$ = Ph
**2** $R^1$ = α-D-mannose, $R^2$ = H, $R^3$ = Ph
**3** $R^1$ = α-D-mannose, $R^2$ = H, $R^3$ = cyclohexyl
**4** $R^1$ = H, $R^2$ = H, $R^3$ = cyclohexyl

Figure 1

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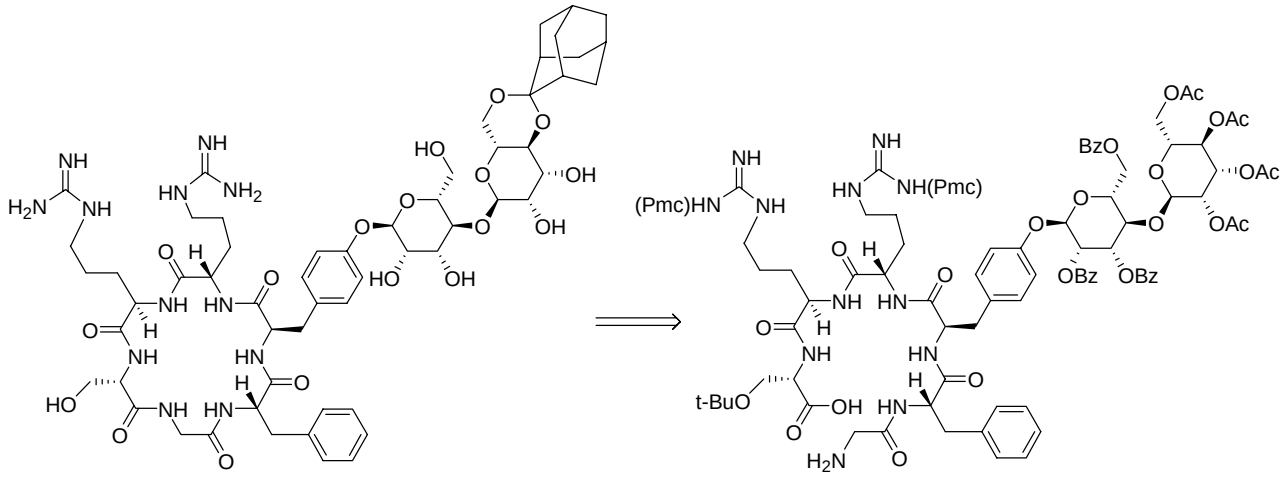
Dedicated with best wishes to Professor Leo A. Paquette on the occasion of his 70th birthday

novel residues contains a mannopyranose moiety in the α-configuration while a D-tyrosine residue contains an α-linked mannose disaccharide. In the natural series, isovalerate substitution occurs on the terminal mannose of this disaccharide, and this substitution conveys substantial increases in antibacterial potency over the non-derivatized parent molecule.[2] Similarly, those semisynthetic variants that display potent antibacterial activities are derivatized on the same terminal mannose.[3] Notably, replacements of the β-methylphenylalanine residue with phenylalanine or cyclohexylalanine are tolerated, and derivatives lacking the *N*-linked mannose or the hydroxyl substituents on the β-hydroxyenduricididine side chains also retain good levels of antibacterial activities. Among the more potent and most easily accessed semisynthetic derivatives are adamantyl ketals (**1-4**) (Figure 1).[3] The apparent tolerability of structural variation on these three residues provided impetus to prepare simplified derivatives in which the β-hydroxyenduricididine residues are replaced with arginines. Herein we report results on the total synthesis of a representative compound.

Retrosynthetically, we envisioned that target compound (**5**) could be derived from an appropriately protected linear glycopeptide (**6**) which could be assembled using solid-phase techniques (Figure 2). We anticipated that cyclization to provide the hexapeptide core would be most readily accomplished with amide bond formation between the L-serine and unhindered glycine residues. Five of the six requisite amino acids are commercially available, while the D-tyrosine containing a mannose disaccharide would be prepared synthetically.

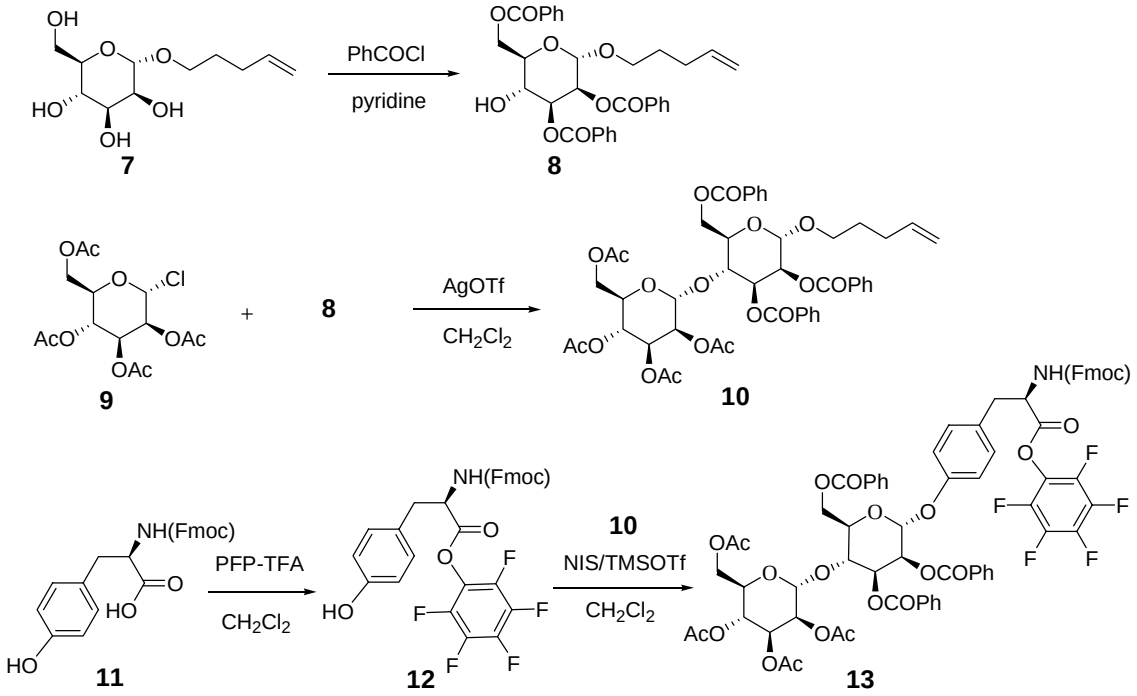


**5** **6**

Figure 2

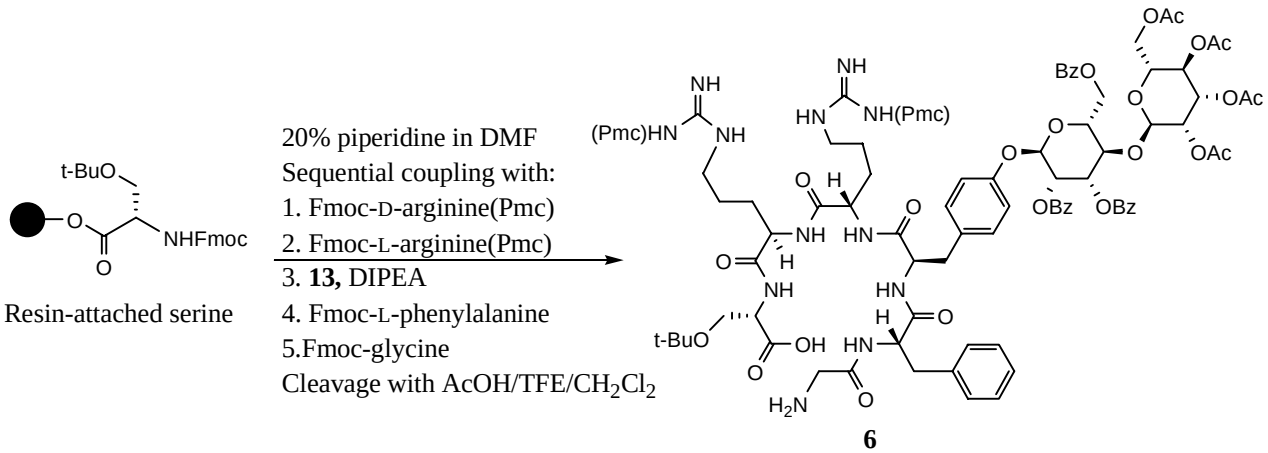
Synthesis of the disaccharide started with the known pentenyl-α-D-mannopyranoside (**7**)[4] which was selectively protected with benzoyl chloride to give pentenyl-2,3,6-tri-*O*-benzoyl-α-D-mannopyranoside (**8**) retaining a hydroxy substituent on the 4-position open for glycosylation[5] (Scheme 1). Dimannoside (**10**) was obtained in modest yield by silver(I) triflate-promoted coupling of **8** with 1-α-chlorotetraacetylmannose (**9**).[6] Prior to glycosylation, the commercially available *N*-Fmoc-tyrosine

(**11**) was reacted with pentafluorophenyl trifluoroacetate (PFPTFA) to give pentafluorophenyl ester (**12**) which is suitably protected for glycosylation and activated for amide bond formation during peptide synthesis.[7] Coupling of the dimannoside (**10**) with **12** was mediated by *N*-iodosuccinimide/trimethylsilyl triflate and gave the glycosylated tyrosine derivative (**13**) required for peptide synthesis.[4] The stereochemistry of both α-anomeric centers was assigned based on literature precedents[4,6] and was confirmed by $^{1}H$ and $^{13}C$ NMR spectroscopy.[8]



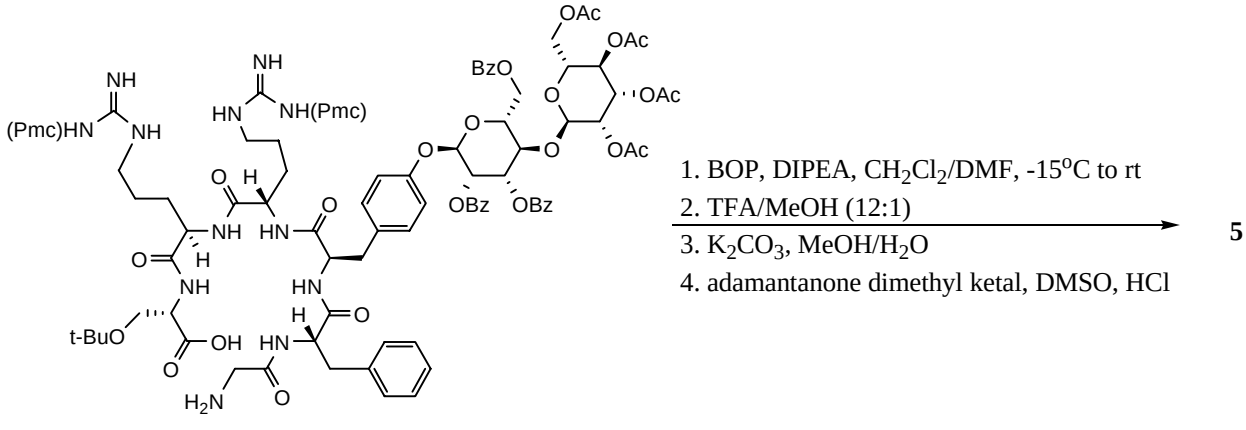

Scheme 1

For solid-phase synthesis, we employed a 2-chlorotrityl chloride resin with HBTU/HOBt coupling protocols and Fmoc protection. The synthesis commenced with attachment of *O-tert*-butyl-*N*-Fmoc-serine to the resin. The loading of the resin was determined to be in the range of ~0.5 mmol/g by UV quantification of the Fmoc-piperidine adduct.[9] The linear peptide chain was then assembled on the resin




Scheme 2

in a sequential fashion using standard procedures **(**Scheme 2**)**. Peptide coupling reactions were monitored for completion by negative Kaiser ninhydrin test. Once peptide elongation was accomplished, the protected linear hexapeptide (**6**) was released from the resin by cleavage with a mixture of acetic acid, trifluoroethanol and dichloromethane (1:1:8). The cyclization of **6** was effected by using BOP/DIPEA as the dehydrating reagent in a mixed solvent system of DMF/$CH_2Cl_2$ (1:1). The cyclic peptide was thereby obtained cleanly with almost complete suppression of dimerization when the concentration of the substrate was held at $<10^{-2}$ M. Deprotection was accomplished sequentially by treatment with TFA/MeOH to remove the *tert*-butyl and the 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) groups, and then with $K_2CO_3$/MeOH for hydrolysis of the acetates and benzoates. The fully deprotected glycopeptide was converted to the final target (**5**) by transketalization with admantanone dimethyl ketal (Scheme 3). The selectivity at 4,6-position of the terminal mannose is in accordance to those observed for natural mannopeptimycins with the formation of only a small amount of the corresponding 2,3-ketal isomer. To our surprise, the synthetic glycopeptide (**5**) was found to have very poor activity against a diverse panel of bacteria. The disparity of activities between this fully synthetic analog and the semisynthetic derivatives (**1-4**) demonstrates that the cyclic guanidines on the β-hydroxyenduricidine residues play a very important role in conveying antibacterial activities of the mannopeptimycin derivatives.




Scheme 3


## ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support of Magid Abou-Gharbia, Tarek Mansour, and Janis Upeslacis. Xidong Feng, Kaiko Tabei, Murthy Damarla, Rachel Garlish, Mark Tischler and Joseph Ashcroft are acknowledged for providing separations and analytical support.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