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Synthesis and Evaluation of Ether and Halogenated Derivatives of Mannopeptimycin Glycopeptide Antibiotics

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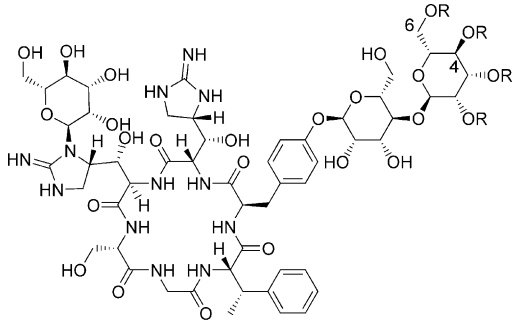
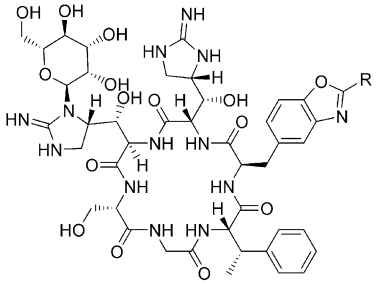
Abstract—A number of 6-*O*-ether and 4-*O*-ether derivatives of mannopeptimycin-α with different steric bulk and lipophilicity were synthesized for structure–activity relationship study. Novel iodo and bromo mannopeptimycin-α were also prepared. These compounds were synthesized via electrophilic aromatic substitution. Many of the new ether derivatives exhibited potent antibacterial activity against Gram-positive resistant strains including VRE, MRSA, and PRSP.

The Mannopeptimycins are a group of novel glycopeptides islolated from *Streptomyces hygroscopicus* about 30 years ago. The chemical structures of these compounds were recently elucidated through extensive NMR spectroscopic and chemical degradation studies.[1,2] Previously, we reported the synthesis and structure–activity of 4-benzyloxyphenyl and 6-methoxy-2-naphthyl ethers attached to the 6, 4, 3 and 2 hydroxyl positions of the terminal mannose of mannopeptimycin-α (**1**) and a series of novel benzoxazole derivatives of mannopeptimycin-β (Fig. 1).[3,4] The in vitro and in vivo data of the ethers indicated that substitutions at the 4- and 6-hydroxyl of the terminal mannose of mannopeptimycin-α (**1**) are important for maintaining the good antibacterial activities.

In continuation of our research to identify compounds with improved activities and pharmacokinetic properties, and to expand the structure–activity relationship study of these compounds, we have synthesized a number of 6-*O*- and 4-*O*-ether derivatives of mannopeptimycin-α (**1**). Compounds with different steric bulk and different lipophilicity were selected for the ether synthesis. Halogenated tyrosine derivatives of mannopeptimycin-α (**1**) were also targeted to probe the electronic and lipophilic factors on the antibacterial activity of the derivatives. With this intent, several electrophilic substitution reactions of mannopeptimycin-α (**1**) were investigated. Herein, we report the synthesis, structure



1 Mannopeptimycin-α R =H
2 Ether of mannopeptimycin-α R = CH_2Ar



3 Benzoxazole of mannopeptimycin-β

Figure 1. Structures of mannopeptimycin-α and -β analogues.

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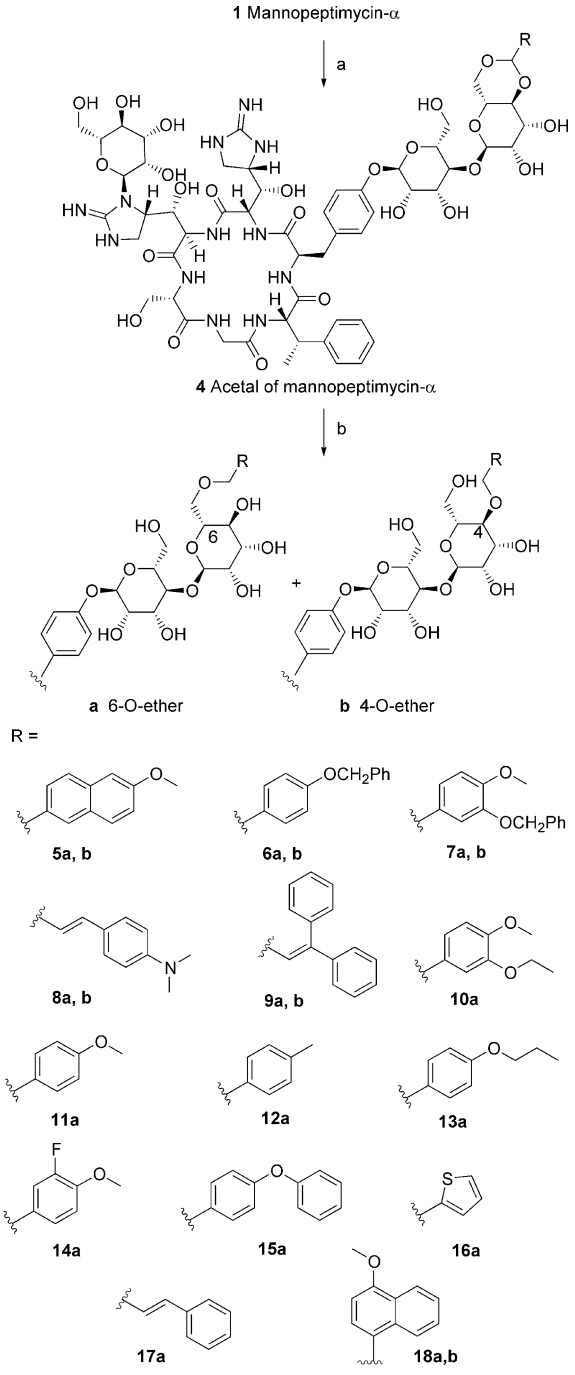
identification and antibacterial activities of these novel mannopeptimycin derivatives.

The syntheses of 6-*O*- and 4-*O*-ether derivatives were carried out using similar method as previously described for 6-methoxy-2-naphthyl analogues.[3] Treatment of mannopeptimycin-α (**1**) with the dimethoxy acetal of appropriate aldehyde in the presence of an acid (1.0 M HCl/ether or *p*-TsOH) as catalyst gave the desired 4-,6-acetal **4** as the major product.[3] Reductive ring cleavage of **4** with $NaCNBH_3$/TFA in DMF gave a mixture of 6-*O*- and 4-*O*-ethers (Scheme 1).



Scheme 1. Synthesis of 6-*O*- and 4-*O*-ether derivatives. Conditions: (a) $RCH(OCH_3)_2/H^+$, 100 °C; (b) $NaCNBH_3$/TFA, DMF, 0 °C to rt.

The ratio of 6-*O*/4-*O*-ethers was 5:2 in the case of 2-thienyl derivative **16**. However, slightly lower selectivity towards the 6-regioisomers (ca. 2:1 to 3:2) was observed with bulkier substrates (e.g., *p*-benzyloxybenzylidene, β-phenylcinnamadehyde acetal, and 6-methoxy-2-naphthaldehyde acetal). The regioselectivity and the ease of reductive ring opening of these 4,6-*O*-benzylidene acetals **4** appeared to be dependent on the electronic nature of the phenyl ring, the steric bulk of the acetal derivatives as well as the reagents and the solvents. Reactions were usually more facile with an electron donating group on the aryl of the benzylidene acetal **4**. In most cases, both the 6-*O* and 4-*O*-ether derivatives were isolated and the biological activity evaluated. In some cases, only the major 6-isomer was isolated for biological activity evaluation. The list of ethers synthesized is shown in Scheme 1.

Regioisomer assignment of the 6-*O*- and 4-*O*-ether derivatives was accomplished by spectral comparison with the parent compound, mannopeptimycin-α (1)[2] along with the results of HMQC, DQF-COSY, ROESY, HSQC and TOCSY experiments recorded in DMSO-d_6. Identification of the 6-*O*-ether is described below using **5a** as representative example (Fig. 2). The main spectral differences between **5a** and **1** occur in the chemical shifts of proton/^{13}C signals for C6 of the terminal mannose; δ 3.54/3.73 ppm; 70.2 ppm in **5a** versus δ 3.44/3.66; 61.3 ppm in **1** (assigned by HSQC)α. Further, by 2D NMR, the benzyl methylene at δ 4.63 ppm was assigned via HSQC data and by ROESY correlation with the *ortho* protons of the naphthyl ring at δ 7.43 and δ 7.80 ppm. The methylene at δ 4.63 also showed a strong ROESY correlation with H6 of the terminal mannose at δ 3.73 ppm. Additionally, a weak ROESY correlation is observed between δ 3.54 ppm (H6 of terminal mannose) and δ 7.80 ppm (H8 of the naphthyl ring). These interactions are shown in Figure 2.

As an example of a 4-*O*-ether derivative, the structure assignment of **18b** was accomplished by NMR experiments (^{1}H, ^{13}C, HMQC, DQF-COSY, ROESY, TOCSY and HMBC). Figure 3 illustrates the chemical shifts for the modified portion of the molecule. The regioisomer assignment of **18b** is made by virtue of a strong HMBC correlation from the proton resonances

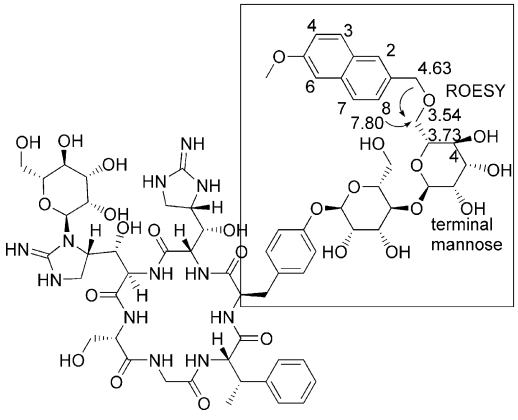


Figure 2. Structure and NMR assignments of **5a**.

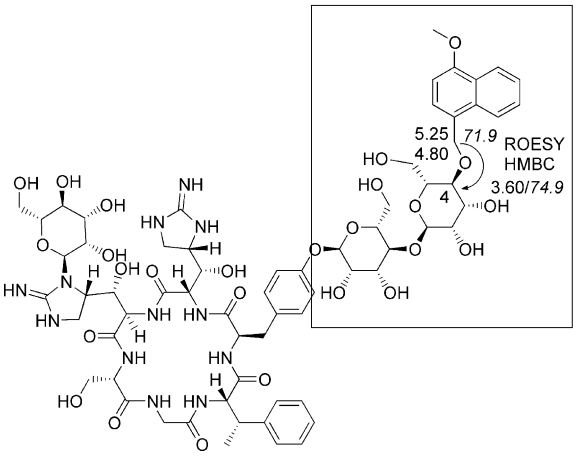
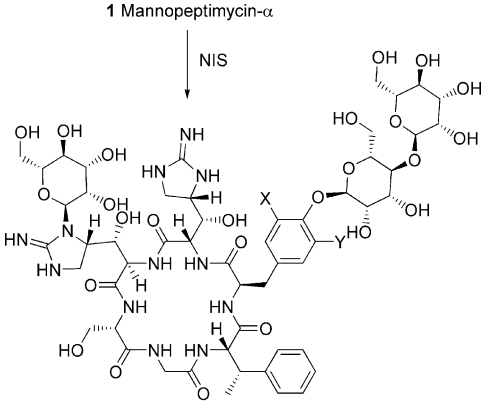


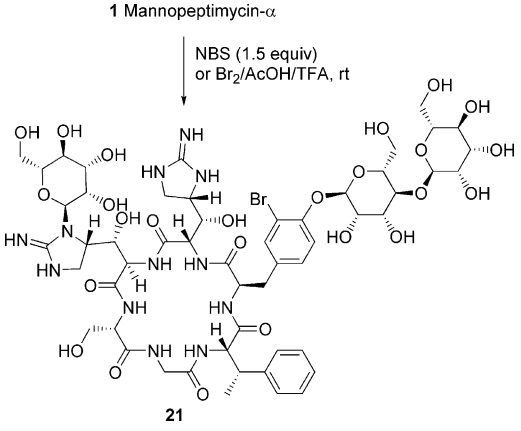
Figure 3. Structure and NMR assignments of **18b**.

of the benzylic methylene at δ 5.25 and 4.80 ppm to the C4 carbon at δ 74.9 ppm (^{1}H: δ 3.60 ppm), along with a ROESY correlation from the methylene protons at δ 5.25 and 4.80 ppm to the C4 methine proton at δ 3.60 ppm.

Mono-iodo analogue of mannopeptimycin-α was synthesized by treating mannopeptimycin-α with 1.25 equivalents of *N*-iodosuccinimide (NIS) in TFA at 0 °C.[5] With 2.5 equivalents of NIS, the reaction gave



Scheme 2. Synthesis of iodo derivatives of mannopeptimycin-α (**1**).



Scheme 3. Synthesis of bromo derivative of mannopeptimycin-α.

diiodide **20** (Scheme 2).[6] The structure of the iodinated compound **19** was identified using analogous NMR experiments as those described above.

Bromo-compound **21** of mannopeptimycin-α was prepared by reacting mannopeptimycin-α (**1**) with either bromine in acetic acid and TFA as solvent or with *N*-bromosuccinimide (NBS) in TFA (Scheme 3).[7]

The in vitro data of the compounds tested are shown in Table 1.[8] In vitro data (MICs) of vancomycin and piperacillin were included for comparison.

Both 6-*O*- and 4-*O*-ether derivatives of mannopeptimycin-α (**1**) demonstrated potent in vitro activity against Gram-positive bacteria. Compounds **5b**, **6a**, **6b**, **7a**, **9a**, **9b**, **12a**, **13a**, and **15a** showed equally good activity against sensitive and resistant strains of staphylococcal, enterococcal and streptococcal isolates (MICs ≤0.06–4 μg/mL). Similar in vitro activity was observed for compounds with bulkier ether substituents, for example **9a** and **9b**. Compound **8a** and **8b**, with a basic dimethylamino group was less active (MICs 1–>64 μg/mL) than **17a** (MICs 0.5–16 μg/mL), suggesting that besides lipophilicity, basicity of the molecule might be important for maintaining good antibacterial activity against gram-positive bacteria. These compounds were also tested against gram-negative bacteria (*Escherichia coli*, three strains, including a permeable mutant strain). Good activities were exhibited against the permeable mutant strain, however, MICs greater than 64 μg/mL were observed for the other two susceptible strains, indicating these compounds are not able to cross the gram-(−) cell wall.

Table 1. In vitro antibacterial activity of selected ether derivatives

Organism; minimum inhibitory concentration (MIC)[a] (μg/mL)			
Compd	*Staphylococcus aureus*	*Streptococcus* spp.	*Enterococcus* spp.
5a	1–2	≤0.06–0.5	2–8
5b	0.25–1	≤0.06	1–2
6a	1–2	≤0.06	1–4
6b	0.5–2	≤0.06	2–4
7a	2–4	≤0.06-0.25	2–4
7b	2–4	≤0.06-2	4–16
8a	32–64	8–32	32–>64
8b	16–32	1–16	16–32
9a	2	≤0.06	2–4
9b	2–4	≤0.06	2–4
10a	1–8	0.5–2	4–32
11a	4	0.5–2	4–32
12a	2	0.12–0.5	2–4
13a	1–2	≤0.06–0.5	2–4
14a	2–8	0.5-2	4–32
15a	2–4	≤0.06–0.12	2–4
16a	1–8	0.5–4	4–64
17a	4–8	0.5–2	8–16
18a	1–4	≤0.12–0.5	2–16
19	>128	>128	>128
Vancomycin	1	0.12-0.5	0.5–>64
Piperacillin	0.5–>64	≤0.06–1	0.25–>64

[a]Range of MICs for *Staph.*, 10 strains, including MRSA (methicillin resistant *S. aureus*); *Strep.* species (six strains, including PRSP (penicillin resistant *S. pneumoniae*); Enterococcus species (11 strains, including VRE (vancomycin resistant *Enterococci*).

In summary, we have synthesized a number of ether derivatives of mannopeptimycin-α (**1**) for structure–activity relationship studies. Iodo and bromo mannopeptimycin-α were also prepared and structures were identified by extensive NMR experiments, MS and HRMS. Most of the ether derivatives showed excellent Gram-positive in vitro activity against sensitive and resistant strains of staphylococcal, enterococcal and streptococcal isolates. The halogenated analogue **19** was tested in vitro, and was less active (MIC >128 μg/mL) than the ether derivatives. Several other halogenated derivatives were also tested in vitro, none showed MIC less than 64 μg/mL. However, the halogenated analogues could serve as important intermediate for further chemical modification.

Acknowledgements

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5. A typical halogenation reaction is as follows: A solution of bis-hydrochloride salt of mannopeptimycin-α (0.152 g) in trifluoroacetic acid (4 mL) was treated with *N*-iodosuccinimide (0.038 g) and the reaction mixture was stirred at ca. 5 °C for 2 h. Solvent was removed in vacuo and the resulting residue triturated with diethyl ether, solid was collected by filtration and washed diethyl ether to give crude mono iodo-derivative **19**. The product was then purified by reverse-phase HPLC. HRMS: calcd M + H, 1421.4246; found M + H, 1421.4268. MS (ES) m/z 711.3 $(M+2H)^{2+}$.
6. Procedure used to synthesize **20** was similar to the one described above except 2.5 equivalents of *N*-iodosuccinimide were used. HRMS, calcd M + H 1546.3212; found 1546.3257. MS (ES) m/z 774.1 $(M+2H)^{2+}$.
7. Procedure used to prepare **21** was similar to the one described in preparing **19**. Mannopeptimycin-α (**1**) was either treated with 1.5 equivalent of *N*-bromosuccinimide at rt in TFA or 1.1 equiv of bromine in acetic acid. HRMS, calcd M + H 1373.4385; found 1373.4370. MS (ES) m/z 687.9 and 688.3 $(M+2H)^{2+}$ in about 1:1 ratio. All the reactions mentioned in this communication were monitored by ES/MS. All final products were purified by reverse-phase HPLC (acetnitrile–water–0.02% trifluoroacetic acid).
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