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Synthetic Studies on Vancomycin: Synthesis of Seco-Aglucovancomycins

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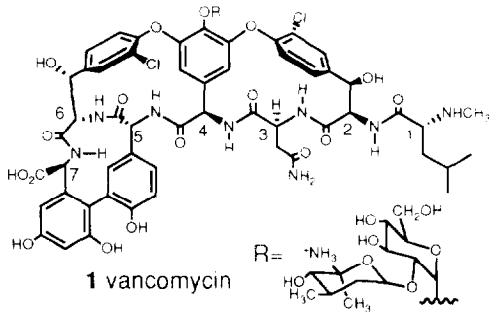
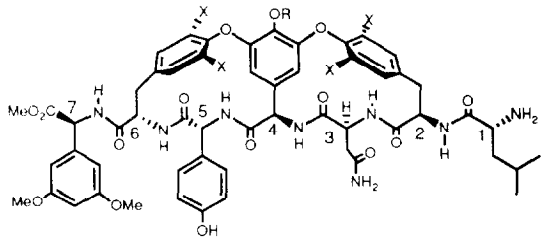
Abstract: Preparation of the vancomycin analogs (SAV-1 and SAV-2) is described. The key step is construction of a bicyclic diaryl ether residue by means of thallium (III) oxidation of the corresponding halogenated phenols.

The glycopeptide antibiotic vancomycin, isolated from *Streptomyces orientalis*, is one of the most challenging molecules for chemists, from the the viewpoint of its characteristic heptapeptide core involving diaryl ethers.[1] The potent bactericidal activities of this antibiotic, particularly against methicillin resistant *Staphylococcus aureus* (MRSA), are considered to be derived from its high affinity to the terminal D-Ala-D-Ala residue of peptidoglycan precursors in bacterial cell wall biosynthesis. However, difficulties of synthesis and derivation of this antibiotic prevent a drug-based analysis of a detailed mechanism of action.[2]



1 vancomycin

2 aglucovancomycin (R= H)



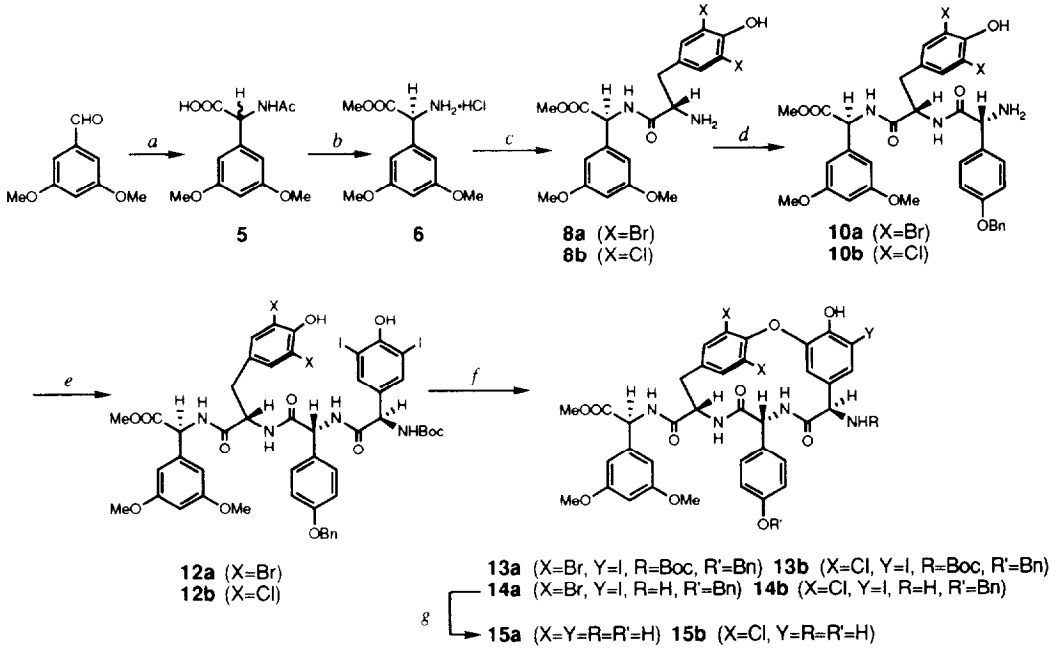
3 SAV-1 (R=X= H)
4 SAV-2 (R= H, X= Cl)

Since our own development of the phenolic oxidation methodology employing thallium (III) salts,[3] natural products possessing a diaryl ether moiety have been extensively synthesized.[3,4] A part of our continuous investigation has been focused on the 12-membered ring of **1**, which consists of the amino acid residue 5-7, bearing one of five points of the plausible hydrogen bonds contributing to complexation with the D-Ala-D-Ala residue.[5] To investigate the role of the ring in the interaction, we have synthesized two seco-aglucovancomycin derivatives [SAV-1 (**3**) and SAV-2 (**4**)]. These compounds are only examples of vancomycin analogs carrying a full peptide chain and a characteristic diaryl ether moiety.[6] The structural similarity to the mother antibiotic will impart a comparable binding property to the bacterial cell wall or its model. Particularly, lack of a rigid biphenyl moiety in the molecule may also promise diverse possibilities of mode of action. We describe herein the synthesis of SAV-1 (**3**) and SAV-2 (**4**).

The synthesis was initiated with Strecker reaction applied to 3,5-dimethoxybenzaldehyde, followed by N-acylation, to give the racemic acetyl amino acid (**5**) in 70% yield (3 steps). Compound **5** was subjected to enzymatic hydrolysis,[7] and protection to afford the optically active phenylglycine derivative (**6**). The

enantiomeric excess (>95% ee) was spectroscopically determined by employing the (+)-MTPA amide of **6**. For the following synthetic process, **6** could be used for the common starting material towards **3** and **4**.

Synthesis of SAV-1 (**3**) was continued by coupling of amine **6** with N-Boc-3,5-dibromotyrosine (**7a**) to furnish the corresponding dipeptide (**8a**). Further peptide chain elongation of **8a** was effected by successive couplings with N-Boc-4-benzyloxyphenylglycine (**9**), and then with N-Boc-3,5-diiodo-4-hydroxyphenylglycine (**11**) to afford the desired tetrapeptide (**12a**) which was a substrate of the following phenolic oxidation.

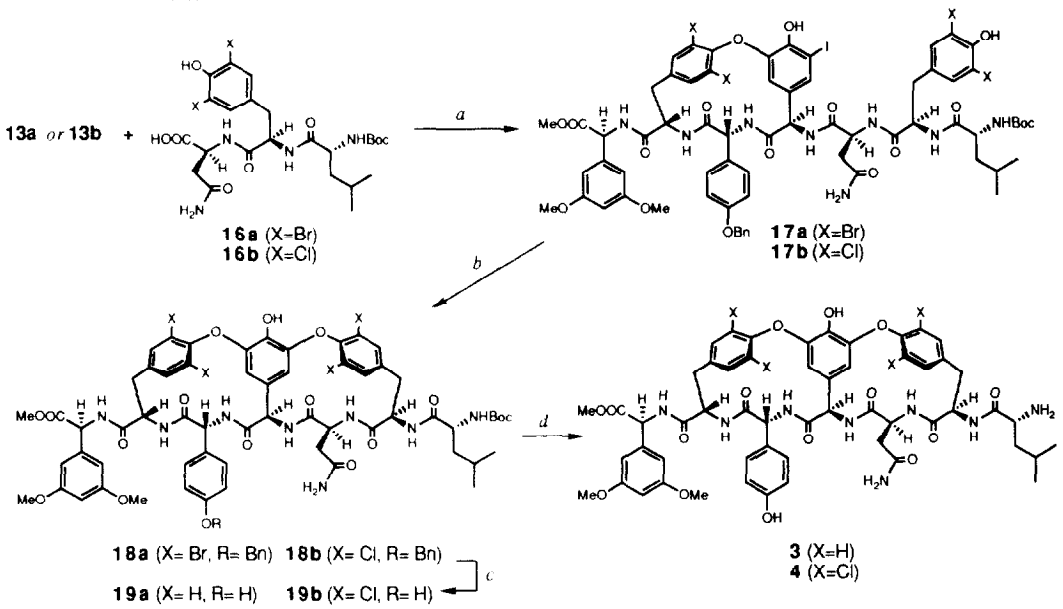


Scheme 1 *Reagents* : *a*. 1) KCN - $Na_2S_2O_5$ / NH_4OH; 2) 6M - HCl; 3) Ac_2O-K_2CO_3*aq*. (70% in 3 steps). *b*. 1) amino acylase ("Amano"); 2) Boc_2O-K_2CO_3*aq*. ; 3) CH_2N_2; 4) TFA, then HCl-MeOH (42% from racemate **5**). *c*. 1) **7a** or **7b**, EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide] - HOBt (1-hydroxybenztriazole), $^iPr_2EtN$; 2) TFA, then $NaHCO_3$ (**8a**: 100%, **8b**: 100% in 2 steps, respectively). *d*. 1) **9**, EDC - HOBt; 2) TFA, then $NaHCO_3$ (**10a**: 73%, **10b**: 82% in 2 steps, respectively). *e*. **11**, EDC - HOBt (**12a**: 91%, **12b**: 78% in 2 steps, respectively). *f*. 1) TTN (2 eq) in THF-MeOH-$CH(OMe)_3$ (8:1:1) (**13a**: 42%, **13b**: 40%); 2) TFA, then $NaHCO_3$ (**14a**: 81%, **14b**: 61%). *g*. H_2-Pd/C AcONa in MeOH (**15a**: 62%, **15b**: *ca*. 50%).

Exposure of **12a** to thallium (III) nitrate (TTN) underwent the desired cyclization to yield **13a** in 42% yield. The reaction mechanism is assumed to be through a synchronized derivation of a thallium phenoxide or through a phenoxy radical intermediate.[3] On addition of the oxidant, the reaction mixture immediately turned to a deep green solution. This observation suggested an electron transfer process, implying the presence of the latter intermediate. The structure of **13a** was confirmed by characterization of **15a** obtained by the usual deprotection and dehalogenation process.[8]

Compound **13a** was deprotected with TFA (81% yield), then subjected to coupling with tripeptide **16a**[9] in the usual manner to yield the corresponding heptapeptide (**17a**) in 59% yield. Final ring closure was undertaken by the same oxidation of **17a** as described in the case of **12a** to provide the expected product (**18a**)

in 35% yield, which was successively submitted to deprotection and dehalogenation to give the target molecule SAV-1 (**3**),[8] as can be seen in Scheme 2.



Scheme 2 *Reagents*: *a*. EDC-HOBt / DMF (**17a**: 59%, **17b**: 53%). *b*. 1) TTN (4 eq) in THF-MeOH-CH(OMe)3 (8:1:1); 2) Zn - AcOH (**18a**: 35%, **18b**: 40% in 2 steps, respectively). *c*. H_2-Pd/C in MeOH (**19a**: *ca*. 40%, **19b**: *ca*. 40%). *d*. TFA (**3**: 61%, **4**: 76%).

The synthesis of the tetrachloro derivative SAV-2 (**4**) was accomplished via a similar protocol starting from **6** (Scheme 1). The first peptide bond formation was performed by coupling with N-Boc-3,5-dichlorotyrosine (**7b**). The peptide elongation afforded the corresponding tetrapeptide (**12b**) in 64% yield (5 steps). The cyclized product (**13b**) was obtained by TTN oxidation in 40% yield. The structural confirmation of **13b** was achieved by characterization of **15b**[8] obtained by the same procedure as that of **15a**.

Compound **13b** underwent a similar sequence to the case of **13a** involving deprotection (61%) and coupling (53%) to provide the heptapeptide (**17b**). Final ring closure of **17b** via the phenolic oxidation procedure afforded the desired product (**18b**), which was further converted to the target molecule SAV-2 (**4**)[8] (Scheme 2).

In conclusion, we successfully synthesized seco-aglucovancomycins SAV-1 (**3**) and SAV-2 (**4**) bearing characteristic bicyclic diaryl ethers and a full peptide chain by means of thallium (III) oxidation methodology as a key step. Conformational analysis of the synthesized compounds and evaluation of their binding manner with the cell wall model will be discussed in the accompanying papers.[11]

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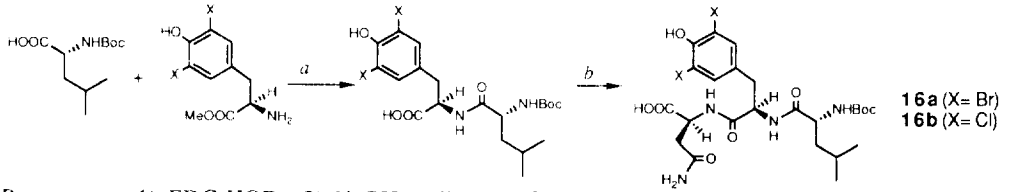
7. According to this method, a large-scale preparation (~20g) of L-arylglycine derivatives can be accomplished. (a) Greenstein, J. P.; Winiz, M. *Chemistry of Amino Acids*, John Wiley & Sons (New York) **1961**. (b) Geenstein, J. P.; Birnbaum, S. M.; Otey, M. C. *J. Am. Chem Soc.* **1953**, *95*, 1994.
8. ^{1}H NMR data of **15a**, **3** and **4** are cited in the accompanying paper (reference 11). **15b**: ^{1}H NMR (CD_3OD) δ: 2.84 (1H, dd, J= 9.5, 13.6 Hz), ~3.3 (1H, complex, overlapped with solvent signal), 3.71 (3H, s), 3.78 (6H, s), 4.61 (1H, dd, J= 5.1, 9.5 Hz) 5.24 (1H, s), 5.34 (1H, s) 6.48 (1H, t, J= 2.2 Hz), 6.51 (2H, d, J=2.2 Hz), 6.55 (1H, d, J= 1.5 Hz), 6.72 (2H, d, J= 8.4 Hz), 6.93 (1H, d, J= 8.0 Hz), 7.02 (1H, dd, J= 8.0, 1.5 Hz), 7.05 (2H, d, J=8.4 Hz), 7.23 (1H, d, J= 1.8 Hz), and 7.51 (1H, d, J= 1.5 Hz).
9. Compounds **16a** and **16b** were synthesized by the following procedure.



Reagents: *a*. 1) EDC-HOBt; 2) NaOH*aq*-dioxane (91% yield for Br derivative, 82% yield for Cl derivative in 2 steps, respectively). *b*. 1) Asn-allyl ester / EDC-HOBt: 2) 0.5 mol% $Pd(PPh_3)_4$ - morpholine (**16a**: 65%, **16b**: 63% in 2 steps, respectively).

10. Although N-methylation could be achieved via the corresponding methylene imine (1. CH_2=O; 2. $NaBH_3CN$ *ca.* 70% in 2 steps), the NH_2 derivatives were used for conformation analysis. See the accompanying papers (reference 11).
11. Nakamura, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* the accompanying papers in this issue.

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