Cycloetherification Reactions of Areneruthenium Complexes: Construction of a 16-Membered Cyclic Peptide Model for Teicoplanin

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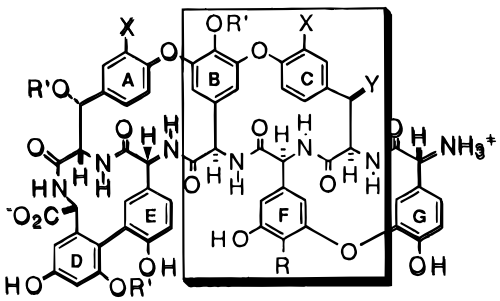
The glycopeptide antibiotic teicoplanin (**1**), related to vancomycin and ristocetin A (**2**),[1] has been recently introduced into clinical use for treatment of infections caused by methicillin resistant *Staphylococcus aureus* (MRSA) and Gram-positive organisms. The mode of action has been extensively studied, and its antibiotic activity results from selective binding with the carboxy-terminal of D-Ala-D-Ala residues, by hydrogen bonds, of a peptido glycan precursor that inhibits bacterial cell wall biosynthesis and leads sometimes to destruction of the bacteria by lysis. But recently, strains which are resistant to vancomycin have been discovered. In effect, resistant bacteria differ in a critical component of their cell wall as they are able to synthesize a depsipeptide, D-Ala-D-lactate, which is incorporated into the PG strands of the cell wall.[2] Consequently, interest in these glycopeptides has increased, especially with regard to the synthesis of analogs.



(1) TEICOPLANIN ; X = Cl ; Y = H ; R = H (R' = sugar unit)
(2) RISTOCETIN A ; X = H ; Y = OH ; R = Me (R' = sugar unit)

These glycopeptides present a challenge to the synthetic organic chemist because of the presence of the arylglycine subunits that are sensitive toward racemization, especially under basic conditions. There exist very few methods for diaryl ether formation by direct coupling of two aryl amino acid derivatives. Some groups have reported elegant solutions by using a methodology including Ullmann and cycloamidation coupling reactions, but no successful total synthesis of vancomycin has been reported.[3] Evans' group accomplished remarkable progress on the construction of vancomycin,[4] and very recently, Yamamura *et al.* have reported the synthesis of vancomycin analogs and their interaction with a bacterial cell wall model.[5]

Chakraborty *et al.* described methodology for the construction of a 14-membered ring model of teicoplanin.[6] We already described an approach to a similar 14-membered ring model for ristocetin A by using arene-manganese chemistry with a cycloamidation reaction for closure of the peptide ring.[7] In the same way, we developed recently a successful synthesis of a 16-membered cyclic peptide model of the B/C/F rings of ristocetin A, by effecting a cycloamidation reaction, in the presence of arylglycine functionality, in low yield.[8] In previous studies, other groups have reported low-yielding cycloamidation or no reaction.[9] Use of chloroareneruthenium complexes is generally efficient when functionalized arylamino acid derivatives have to be linked by aryl ether formation.[7,8]

The recent report from Rich *et al.*[10] on intramolecular etherification applied to the construction of a 17-membered ring prompts us to disclose our own results on the construction of a 16-membered cyclic peptide model (**3**) of the B/C/F ring of ristocetin A and teicoplanin. The present model study shows that cycloetherification occurs in acceptable overall yield with formation of one major diastereoisomer having the conformation found in the natural product.

Our strategy for the construction of the model **3** is illustrated in Scheme 1. We decided to use for the ring F a derivative of phenylglycine in order to study any epimerization during the peptide coupling and the cycloetherification reactions. Protected dipeptide **4**-Cbz was prepared previously in our laboratory,[8b] and complex **5** was synthesized in quantitative yield from the protected 4-chlorophenylalanine, as we already described in a

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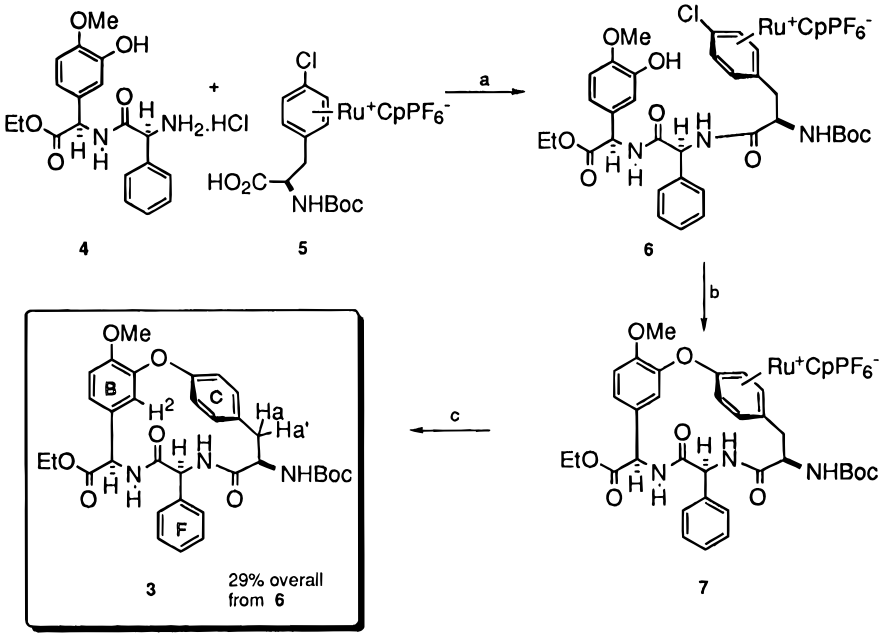
Scheme 1[a]



[a] Reaction conditions, reagents, and yields: (a) iPr_2NEt (1.1 equiv), **5** (1.0 equiv), EDCI (1.1 equiv), HOBT (1.5 equiv in DMF, N_2, 0 °C, 2 h, rt, 24 h, 68%; (b) Na 2,6-di-*tert*-butylphenoxide (1.1 equiv), acetone −30 °C, N_2, 4.5 h, rt, 2 h; (c) sun lamp (275 W), CH_3CN, N_2, 24 h, 29% overall from **6**.

previous paper.[9a] Reaction of the dipeptide **4·HCl** with ruthenium complex **5** was realized by using EDCI and HOBt as coupling reagent in DMF, in the presence of diisopropylethylamine (1.1 equiv) as base, at 0 °C for 2 h, followed by 22 h at rt, and provided the tripeptide π-ruthenium complex **6** in 68% yield. The cycloetherification reaction of **6** was carried out using 2,6-di-*tert*-butyl phenoxide (1.1 equiv) as base, which we have previously found to mediate intermolecular etherification reactions without epimerization of the arylglycine residue. The macrocyclization was accomplished by using high dilution conditions and by slow addition of **6** over 4.5 h at −30 °C to an acetone solution of 2,6-di-*tert*-butyl phenoxide and stirring for an additional 2 h to give the cyclic peptide **7** (final concentration of **6**: 2.5 mg/mL). This derivative was directly submitted to decomplexation by photolysis in CH_3CN (irradiation in acetonitrile, General Electric 275 W Sun Lamp) under nitrogen at 25 °C for 1 day and afforded the cyclic biphenyl ether tripeptide **3** in 29% overall yield (two steps).

The overall yield is better than the macrocycloamidation reaction we already reported.[8] In this reaction, the areneruthenium π-complex is sufficiently electrophilic to allow the construction of the diaryl ether under very mild conditions. The ^1H NMR spectrum of **3** provided evidence for the cycloetherification: as we already observed previously,[8] the aromatic proton BH^2 (Scheme 1) is shifted to higher field (6.21 ppm, broad singlet) as a result of shielding from the neighboring aromatic C-ring, a known feature in this series. But, the most important observation is the formation of one major stereoisomer (ratio 7:1, estimated by integration in the ^1H NMR of the crude product). Our previous macrolactamization studies resulted in the formation of variable ratios of two products, according to the method used, and we assigned these as being stable, separable conformational isomers, based on NMR spectroscopy. There is some uncertainty whether the minor product in the present case is an atropisomer or whether it results from partial epimerization at the phenylalanine residue, as discussed previously.[8] The major product, however, shows NMR characteristics that correspond well with those reported for teicoplanin[1c,d] (cf. Scheme 1 [resonance corresponding to the two methylene protons in the phenylalanine unit]: Ha and Ha′ appeared as a broad doublet of doublets at 3.47 ppm (J_{gem} = 13.8, J_{vic} = 4.8 Hz) and as a doublet of doublets at 2.76 ppm (J_{gem} = 13.8, J_{vic} = 3.0 Hz); teicoplanin pseudoaglycon shows these protons at, respectively, 3.31 ppm and 2.84 ppm, with large geminal and small vicinal couplings (J_{gem} = 13.5 Hz, J_{vic} value not reported)). In contrast, the minor isomer shows the upfield benzylic proton as a doublet of doublets with large vicinal coupling (*ca.* 12 Hz). Future work will be aimed at securing the exact structures of the minor components from these reactions.

The model study described above demonstrates it is possible to synthesize in acceptable yield subunits found in the teicoplanin family, using a cycloetherification. This result shows a promising avenue towards the total synthesis of these glycopeptides. The use of stoichiometric ruthenium in these reactions is not a major problem as we can recover the metal as $[CpRu(CH_3CN)_3]PF_6$, after the decomplexation reaction (though further optimization will be necessary for efficient recycling).

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Supporting Information Available: Description of experimental procedures and copies of spectra are included (9 pages).

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