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Ruthenium-promoted diaryl ether synthesis in the construction of the F-O-G ring system of a teicoplanin model

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Abstract

An end-game approach is described for the synthesis of glycopeptide antibiotics related to teicoplanin, using ruthenium-promoted diaryl ether formation, followed by cycloamidation.

Considerable attention has been focused recently on synthesis of the vancomycin group of antibiotics, as a result of their molecular complexity, which poses a significant challenge to the synthetic chemist, as well as the emergence of vancomycin resistant strains of infectious bacteria.[1] The development of successful approaches to the total synthesis of these compounds can be expected to pave the way for the design of analogs that might overcome bacterial resistance, and in this regard the recent syntheses of vancomycin and its aglycone represent milestones toward such a goal.[2] Our own efforts have focused on methodology for the construction of the ristocetin (**2**) and teicoplanin (**3**) structures, which are somewhat more complex than vancomycin owing to the presence of an extra aryl ether ring (F-O-G) as well as two extra arylglycine residues. These particular amino acids are prone to base catalyzed racemization under quite mild conditions, therefore placing extra demands on the methods for making the diaryl ether units. We have recently described a 'left-to-right' strategy, indicated on structure **4**, that is dictated by a proclivity of the ring D residue to thermodynamically driven epimerization when this is present as a carboxyl ester terminus.[3] Such tendencies prohibit an alternate 'right-to-left' synthesis, and this has also been recognized by Boger[2c] and Nicolaou.[2b] However, the 'left-to-right' approach requires an efficient method for introducing the final F-O-G ring system onto an advanced intermediate of general structure **4**. Prior to embarking on the total synthesis of ristocetin A or teicoplanin, we considered it essential to determine the feasibility of this undertaking. While we have previously shown that arene-manganese chemistry can be used for the construction of similar F-O-G ring structures,[4] this approach is not applicable as an end-game of the type required. Alternate approaches to the synthesis of related structures have been described by Chakraborty[5] and Beugelmans[6] but those methods have not been utilized with the intact arylglycine subunits that are needed in the final product. This letter describes a

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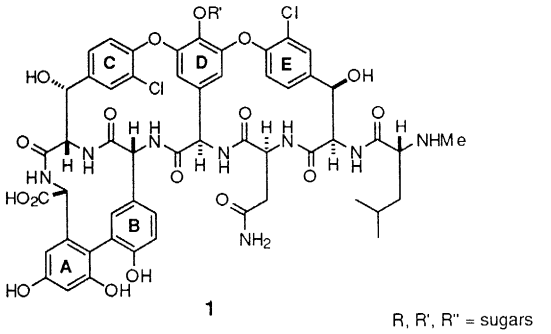
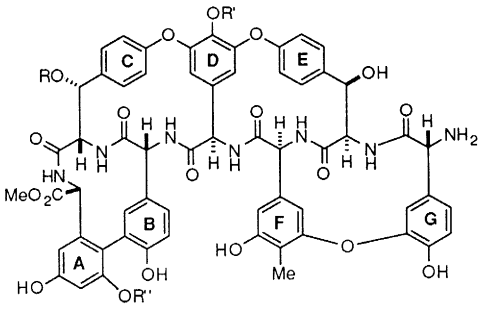
successful and efficient approach that we expect will be useful for building on the final peptido aryl ether ring of teicoplanin, though the methodology is also appropriate for ristocetin.

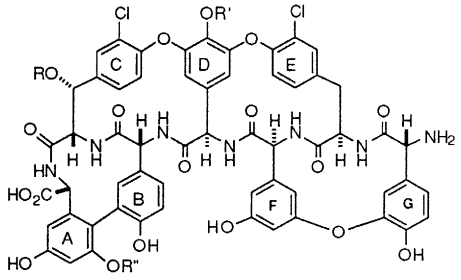


1

R, R', R'' = sugars

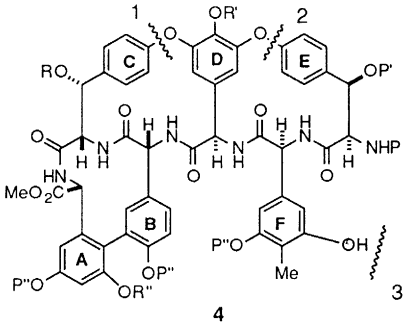


2



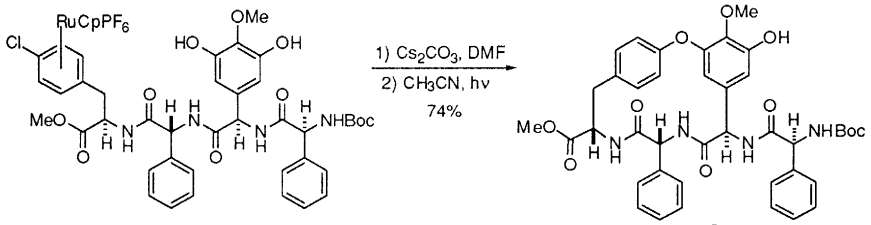
3

Sequence of aryl ether bond construction



4

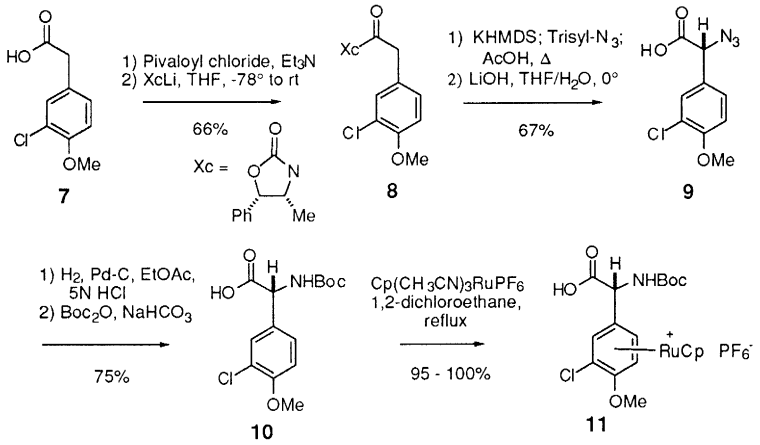
In our previous studies on the construction of molecules that represent the C-O-D-O-E aryl ether rings of ristocetin and teicoplanin, we showed that peptide coupling followed by intramolecular ether formation, promoted by complexation of the chlorophenylalanine residue with cyclopentadienylruthenium(+), provided an efficient approach to the synthesis.[3,7] This strategy has also been employed for the total synthesis of similar cyclic peptido aryl ethers by Rich and co-workers, and by Krämer.[8] Cycloetherification leads to formation of the 16-membered ring **6** in good yield, whereas the alternative ring closure by cycloamidation is highly problematic.[7,9] On the other hand, construction of the 14-membered ring system corresponding to the F-O-G linkage has been achieved by using either cycloamidation techniques,[4,5] or by cycloetherification.[6] Therefore, we decided to study both of these strategies for the construction of the F-O-G system in a manner that would be appropriate for its addition onto an advanced intermediate of type **4**.



5 6

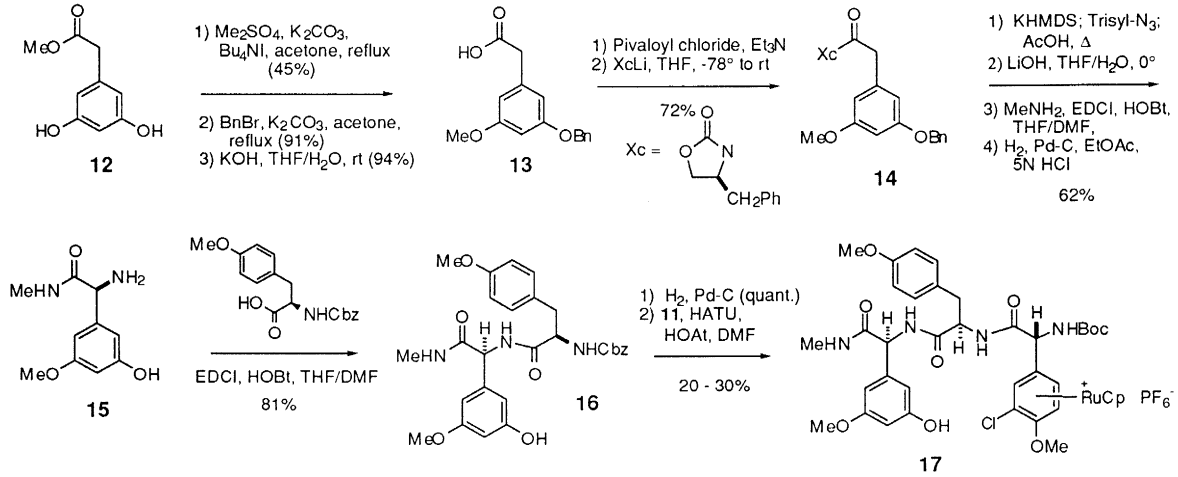
The key building block for addition of the final F-O-G ring of teicoplanin or ristocetin, using ruthenium-promoted aryl etherification, is the complex **11** (Scheme 1). This compound was readily prepared in essentially quantitative yield from the protected amino acid **10**, which itself was made (>98%

e.e.) by using standard Evans asymmetric azidation technology.[10] It should be noted that complex **11** is quite stable and can be stored indefinitely in the refrigerator.



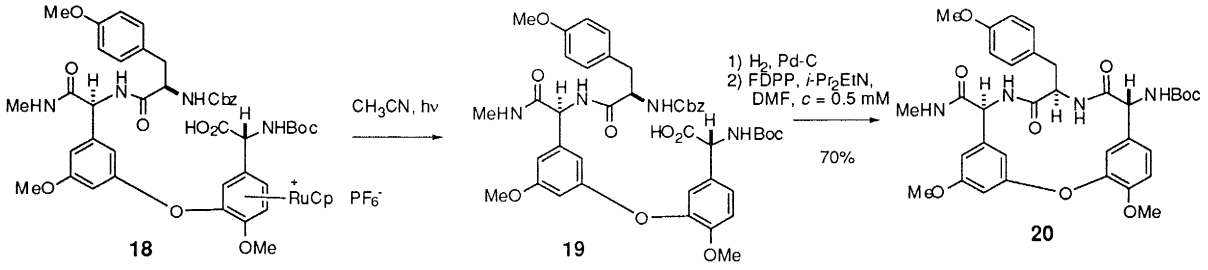
Scheme 1.

We first studied the use of **11** in a cycloetherification approach to the requisite F-O-G model system (Scheme 2). The protected dipeptide **16** was prepared according to standard methodology, and was obtained in stereochemically homogeneous form after chromatographic purification. Deprotection of **16** followed by peptide coupling with complex **11** afforded **17** but in low yields. The use of different coupling reagents (EDCI, DCC, etc.) did not improve the situation, which we ascribe to increased steric hindrance at the activated ester due to the neighboring arene-ruthenium system. Indeed, the same coupling between deprotected **16** and the uncomplexed derivative **10** afforded the corresponding tripeptide in high yield (ca. 80%), supporting this hypothesis. Attempted cycloetherification of **17**, under a variety of conditions that we have previously shown to effect cyclization of complexes such as **5**, failed to produce the desired material, instead giving multiple unidentified products. This situation was not unexpected, as the benzylic proton on the arene-Ru system is now quite acidic, being flanked by an amide carbonyl and the electron deficient arene-RuCp cation. On this basis we surmised that the source of the problem lay in competing deprotonation of the G-ring residue in complex **17**, and proceeded to investigate the alternative etherification/cycloamidation approach in an effort to solve the problem.



Scheme 2.

Reaction of **16** with **11**, using potassium di-*t*-butylphenoxide (2.2 equiv.) as base in the presence of 18-crown-6 (THF solvent), afforded complex **18**, which was directly demetallated under photochemical conditions to afford **19** in 60% yield for two steps. The acidity of the benzylic proton on complex **11** is not a problem for this coupling reaction, because its p*K*a is raised by the carboxylate anion that is formed coincidentally. Removal of the Cbz protecting group, followed by cycloamidation using pentafluorophenyl diphenylphosphinate (FDPP) as coupling reagent, to generate the active pentafluorophenyl ester in situ,[11] afforded the cyclized product **20** in 70% yield (Scheme 3).



Scheme 3.

Conclusions: We have shown in this paper that a convenient building block approach can be used for the construction of the F-O-G peptido aryl ether ring system of ristocetin or teicoplanin molecules. The final subunit for a 'left-to-right' strategy, complex **11**, is readily prepared on a multigram scale, and is easily stored and used when needed. While the amidation/cycloetherification approach, that has been used for building the 16-membered rings such as **6**, is problematic, the successful alternative is in fact even more attractive from the standpoint of ruthenium chemistry, because the stoichiometric RuCp system is retained for only one coupling step, and the ruthenium may be more efficiently recovered, as $Cp(CH_3CN)_3RuPF_6$, and recycled.

Acknowledgements

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