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Ruthenium mediated S_NAr reactions in synthetic approaches to ristocetin A aglycon: preparation of an ABCD ring intermediate

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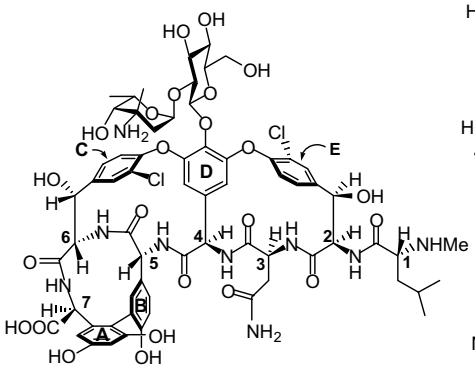
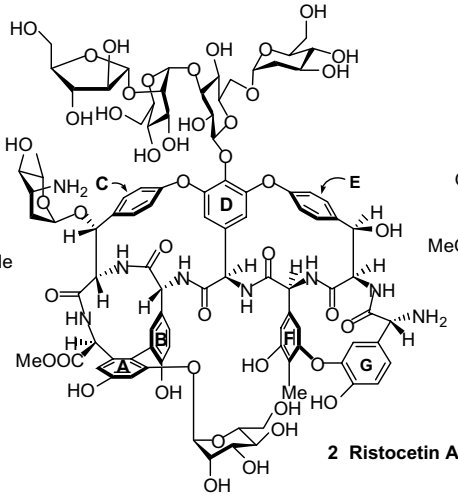
Abstract—A synthesis of an intermediate representing the ABCD ring system of ristocetin A aglycon is described, in which ruthenium-mediated intramolecular etherification is used as a key bond-forming step.

Vancomycin (**1**)[1] has captured the interest of synthetic chemists for a number of years, as a result of its molecular complexity and, perhaps more importantly, the emergence of vancomycin resistant strains of infectious bacteria.[2] Such resistance has triggered alarm because this compound has been in use for some time as the antibiotic of last resort for treatment of methicillin-resistant infections. Several total syntheses of vancomycin aglycon have been reported,[3] and Nicolaou et al. have completed the synthesis of vancomycin itself.[4]

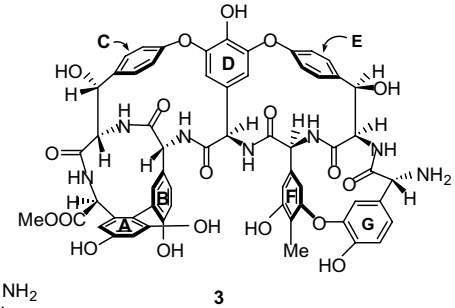
Ristocetin A (**2**) is structurally related to vancomycin, but possesses very different F and G residues, as well as an additional ring that is formed by aryl ether bridging between them. In fact, ristocetin is more closely related to the structure of teicoplanin (structure not shown here), another important member of this class. While ristocetin A exhibits antibiotic activity similar to vancomycin, its clinical use was discontinued owing to fatalities.[5] This is likely the result of platelet aggregation caused by the antibiotic,[6] and it has been shown that such activity is eliminated when rhamnose is cleaved from the tetrasaccharide moiety. The aglycone of ristocetin is a useful lead compound for development of new antibiotics that exhibit activity against vancomycin resistant bacteria.[7] At present, the main use of ristocetin



1 Vancomycin



2 Ristocetin A



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A is in clinical diagnosis of von Willebrand's disease, a genetic hemorrhagic disorder. Two independent total syntheses of the teicoplanin aglycon have been reported,[8] and more recently, while our own work was in progress, Boger et al. have completed a total synthesis of ristocetin A aglycon (**3**).[9]

Our approach to the total synthesis of **3** rests on the ability of a transition metal, that is η^6 coordinated to an aromatic ring, to induce nucleophilic attack on the arene. When the aromatic ligand is a halobenzene derivative, most commonly a chloroarene, the result is nucleophilic substitution. The RuCp moiety is well suited for this particular application, since it is strongly activating, can be attached to the aromatic moiety without detriment to a wide range of functional side chains (in the present case amino acids), is stable to numerous chemical transformations, and can generally be removed in a reusable form by non-invasive photochemical methods. This overall process is illustrated schematically in Figure 1.

We have described a number of model studies designed to demonstrate that arene–ruthenium chemistry can be used for the purposes of ristocetin construction.[10] This letter describes the preparation of an actual intermediate representing the ABCD ring system of **3**.[11] The synthesis demonstrates the viability of using ruthenium promoted intramolecular S_NAr reactions in a very complex molecular environment.[12]

Ruthenium complex **4** was required for this effort, and we examined two approaches for its construction from the previously prepared[10c] chlorophenylserine derivative **5** (Scheme 1). One can either remove the Boc protecting group before, or after conversion to the arene–RuCp complex. In the event, while deprotection can indeed be carried out without detriment to the organometallic moiety (see **7** → **4**), the overall yield is higher when free amine **6** is used in the complexation step.

We next required intermediate **11** (Scheme 2) for coupling with **4** in an effort to secure an advanced intermediate **12** that could be subjected to cycloetherification. The biaryl **8** was prepared using a known synthesis[3a] and was coupled with the D-ring N-protected amino acid **9**[13] to afford methyl ester **10**, which was hydrolyzed to **11** under standard conditions. It should be noted that

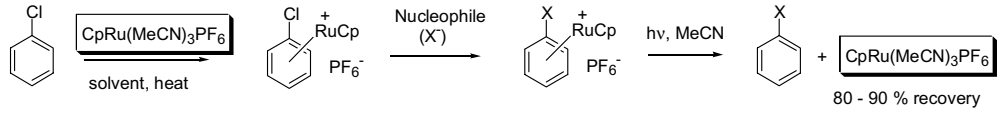
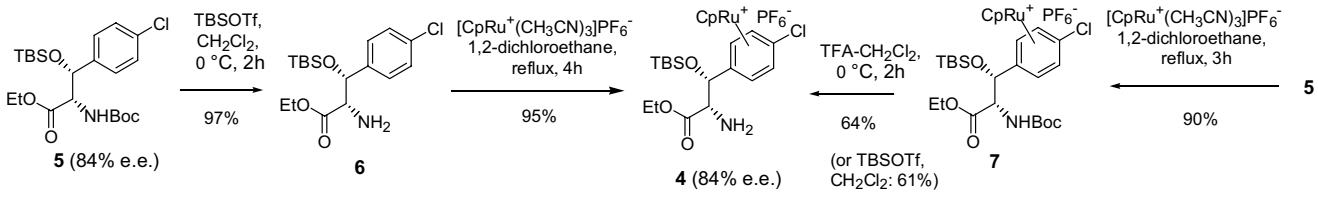
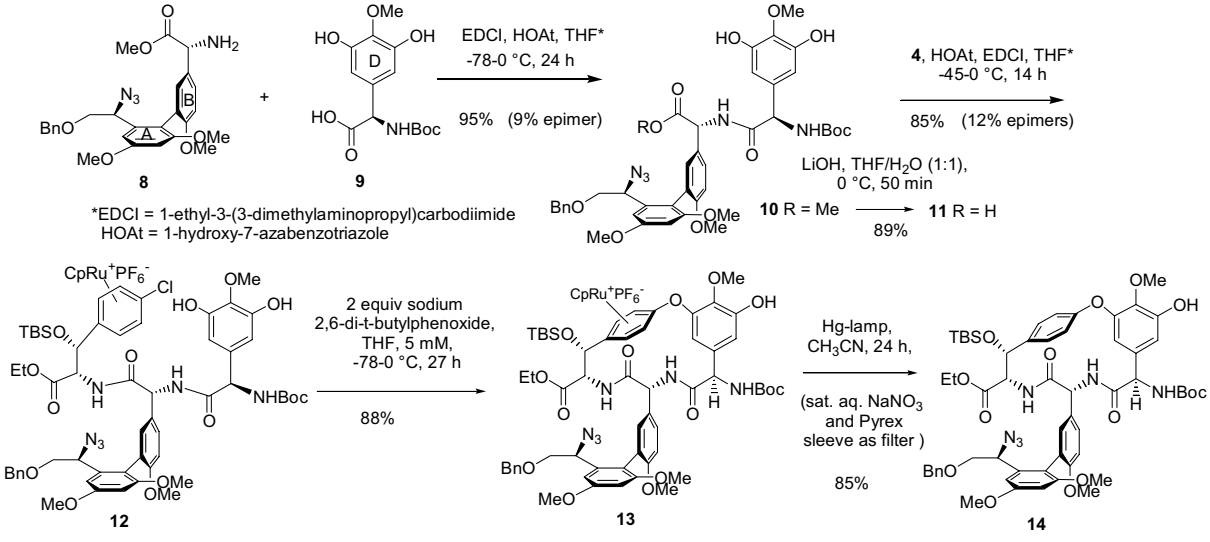


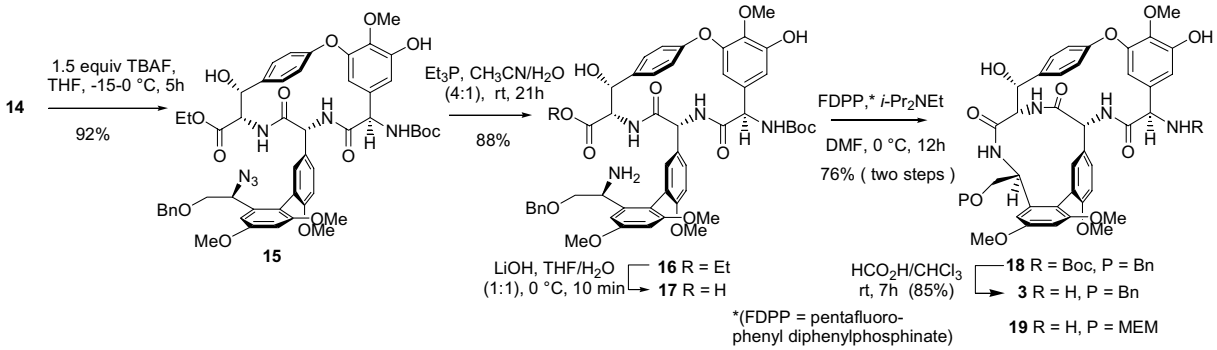
Figure 1. Schematic representation of ruthenium-mediated S_NAr chemistry.



Scheme 1.



Scheme 2.



Scheme 3.

minor epimerization (ca 9%) occurs during the peptide coupling, but **10** was not subjected to rigorous purification to minimize loss of material. Coupling **11** with **4**, using HOAt/EDCI at low temperature afforded the desired ruthenium complex **12** in 85% yield. Several minor epimeric compounds (12% total) were observed in the ^{1}H NMR spectrum of this material, as expected because the subunits are not optically pure, but these were not removed at this stage. Cycloetherification of **12** was carried out by treatment with the weak non-nucleophilic base, sodium 2,6-di-*t*-butylphenoxide, to afford **13** in excellent yield. The reactivity of the chloroarene–ruthenium complexes is sufficiently great that this weak base can be used, which minimizes the risk of epimerization of sensitive residues. Removal of the ruthenium from **13** followed the photochemical method used in our earlier work, but with slight modification to control the UV wavelength (Hanovia reactor using $NaNO_3$ solution as filter). Also, the $[CpRu(CH_3CN)_3]PF_6$ that is generated in this process caused side reactions on the product **14** during its isolation.[14] Accordingly, this complex was destroyed immediately after photolysis, by treating the reaction mixture with aq ammonia, and intermediate **14** was isolated in 85% yield, after purification by flash chromatography. It should be noted that minor epimeric impurities generated during the earlier coupling steps were removed during this purification.

Conversion of **14** to the desired ABCD intermediate followed tactics similar to those used by Nicolaou et al. in their synthesis of the vancomycin aglycone (Scheme 3).[3a] It is necessary to deprotect the secondary alcohol of the arylserine C ring residue to ensure high yield in the subsequent ester hydrolysis step. Treatment of **14** with excess TBAF at low temperature effects this transformation without side reactions—at higher temperatures significant dehydration and retroaldol-type reaction of the arylserine C-ring residue occurs. The A-ring azide was reduced to amine using triethylphosphine, and the ester was hydrolyzed using LiOH in THF to afford the amino acid derivative **17**, which was used directly in the cycloamidation step to afford **18**. Removal of the Boc protecting group from **18** afforded **3**, which differs from Boger's ABCD intermediate (**19**) only in the nature of the primary alcohol protecting group.

In conclusion, this work demonstrates that arene–ruthenium chemistry can be used in the context of complex molecular synthesis. The RuCp moiety is extremely versatile in its ability to withstand numerous chemical transformations elsewhere in the molecule, and its attachment to highly functionalized amino acid derivatives.

Acknowledgements

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Supplementary data

Spectroscopic data for all new compounds reported herein. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.108.

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14. During isolation of **14** it was found that RuCp becomes attached to the D-ring arene system, most likely a result of the electron rich character of this residue. Destruction of the released $[CpRu(CH_3CN)_3]PF_6$ by immediate treatment with aqueous ammonia prevents this.