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Studies toward the total synthesis of ristocetin A aglycone using arene–ruthenium complexes as S_NAr substrates: construction of an advanced tricyclic intermediate

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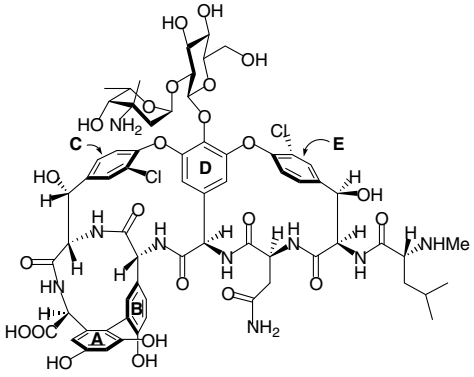
Abstract

Ruthenium-mediated S_NAr reactions are used to construct the diaryl ether linkages in two key intermediates for a projected total synthesis of the aglycone of ristocetin A.

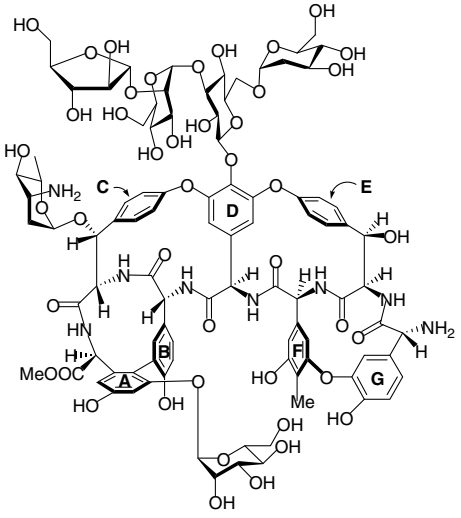
1. Introduction

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 recent emergence of vancomycin resistant strains of infectious bacteria.[2] Recent increased activity in searching for new antibacterials is expected to lead to solutions to this problem.[3]

Ristocetin A (**2**) is structurally related to vancomycin, but possesses different glycoside units, as well as different



Vancomycin (1)



Ristocetin A (2)

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F and G amino acid residues and an additional ring that is formed by aryl ether bridging between them. Ristocetin, teicoplanin (not shown, but structurally related to ristocetin), and vancomycin are the three most important members of this class of antibiotics, and therefore prime targets for total synthesis efforts. Several total syntheses of vancomycin aglycone have been reported,[4] and Nicolaou has completed the synthesis of vancomycin itself.[5] Two independent total syntheses of the teicoplanin aglycone have been reported,[6] and Boger has completed a total synthesis of ristocetin A aglycone.[7] While ristocetin A exhibits antibiotic activity similar to vancomycin, its clinical use was discontinued owing to fatalities[8] that were likely the result of platelet aggregation caused by the antibiotic.[9] The aglycone of ristocetin has been shown to be a useful lead compound for development of new antibiotics that exhibit activity against vancomycin resistant bacteria.[10]

Our approach to the total synthesis of these compounds rests on the ability of a transition metal, coordinated η^6 to an aromatic ring, to induce nucleophilic attack on the arene. When the aromatic ligand is a halobenzene derivative, most commonly a chloroarene (and therefore readily prepared), the result is nucleophilic substitution. Ruthenium is especially useful for such applications, 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 be removed in a reusable form by non-invasive photochemical methods. This overall process is illustrated schematically in Figure 1.

2. Results and discussion

Following successful model studies,[11] we have focused on developing a total synthesis of ristocetin aglycone (**3**, Scheme 1) that illustrates the compatibility of arene–ruthenium chemistry with complex molecular synthesis. Our strategy was to construct the left hand portion first, as intermediate **4**, which would then be coupled to the E–F–*O*–G intermediate **5**, or a similar building block. The coupling product would then be subjected to S_NAr cyclization, demetallation, and further conversion to the target molecule. A previous report has detailed our synthesis of intermediate **4**, which also used arene–ruthenium chemistry to construct the aryl ether macrocycle connecting rings C and D.[12]

Scheme 2 summarizes our approach to the F–*O*–G building block **13**, which has now been further optimized.[13] Amine protection, as Teoc on the F-ring residue, was to be utilized for intermediate **9** to ensure orthogonality with the remaining units. While we have successfully carried out Sharpless aminohydroxylation of the styrene derivative **6** using $TeocNH_2$ as the carbamate partner, which directly affords the *N*-Teoc protected amino alcohol,[14] this approach was actually less satisfactory in terms of yield, enantiomeric purity, and ease of purification of the product, than the indirect method shown in Scheme 2. Removal of the Boc protecting group (**7**), followed by Teoc re-protection and chromatographic purification afforded the required material **8** with high ee (99%). Hydrogenolysis of the benzyl ethers to give **9**, followed by intermolecular etherification using complex **12**, then methylation of the remaining phenolic OH afforded the F–*O*–G building block **13**.

The S_NAr reaction between **9** and **12** was rather capricious, so we investigated the alternate approach outlined in Scheme 3.[14] The known[7] benzyloxycarbonyl derivative **17** (95% ee, prepared as shown) was converted to **18** by hydrogenolysis followed by Teoc protection of the amine. Reaction of **18** with **12** also proved somewhat troublesome, which we tentatively attribute to the sterically congested

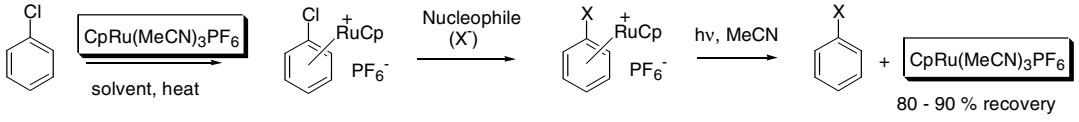
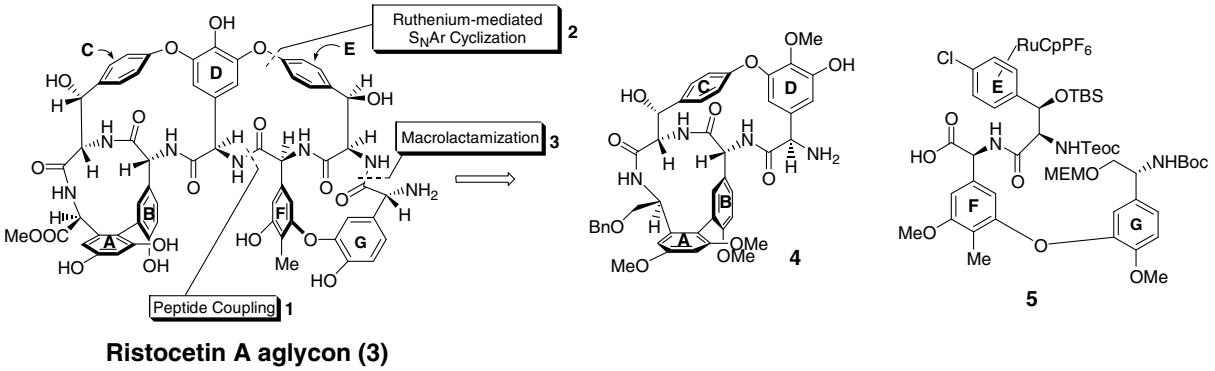
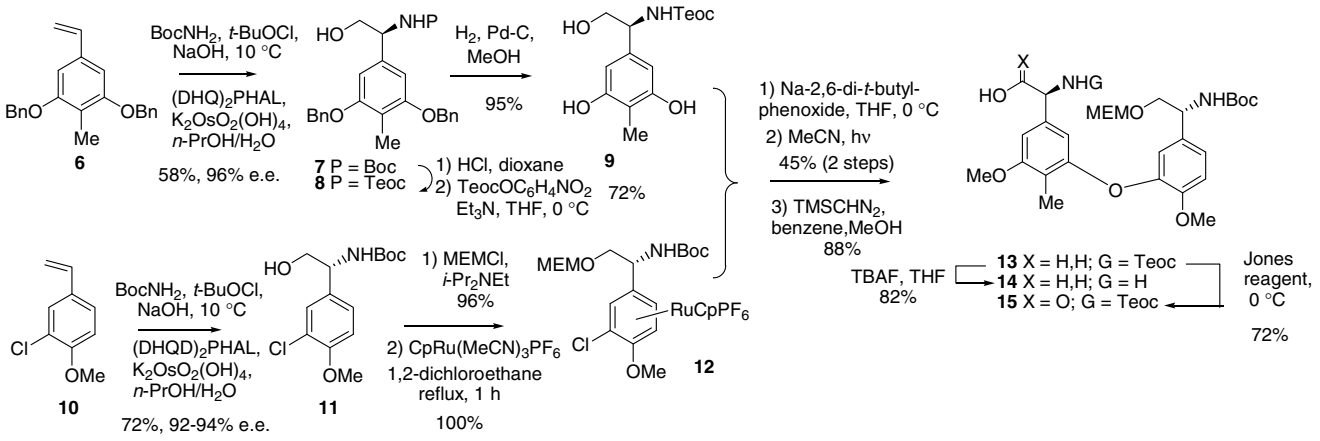


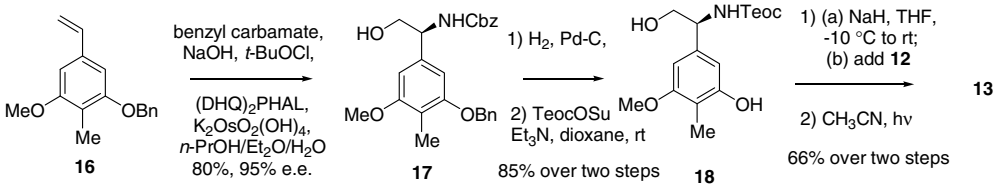
Fig. 1. Schematic representation of ruthenium-mediated S_NAr chemistry.



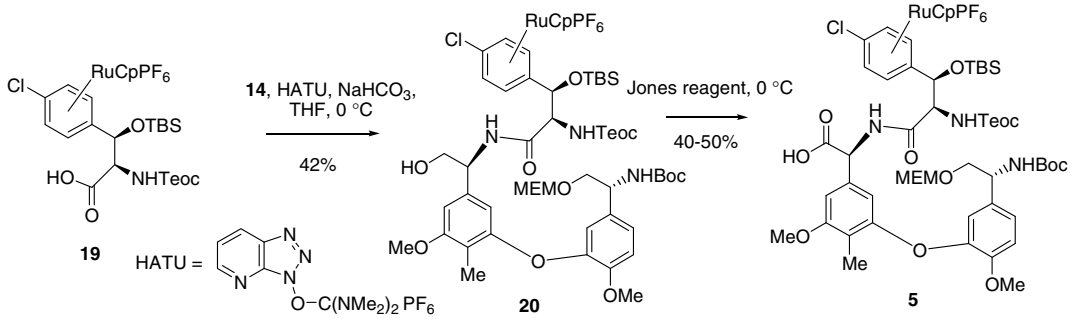
Scheme 1.



Scheme 2.



Scheme 3.



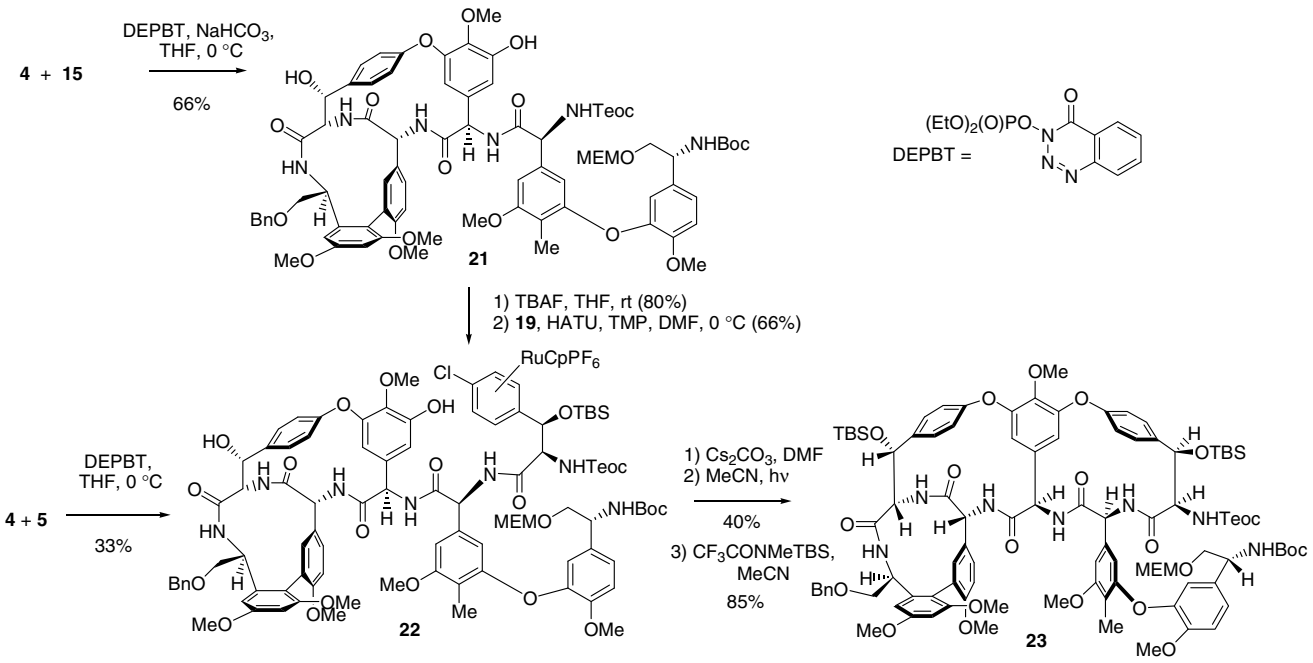
Scheme 4.

nature of the chloroareneRuCp complex. After some experimentation, it was found that the treatment of **18** with NaH in THF, followed by the addition of complex **12** in small portions, then photolytic demetallation, reproducibly afforded **13** in 66% yield over two steps.

Building block **13** was used in two approaches to the target molecule (Scheme 5[15]), of which the more convergent required coupling of **14**, from Teoc deprotection of **13**, with complex **19**, prepared as described previously.[11a] This coupling afforded **20** in 42% yield (Scheme 4). Jones oxidation of **20** was somewhat problematic, affording carboxylic acid **5** in variable yield. Direct coupling between **4** and **5** afforded intermediate **22** in 33% yield.

The alternate approach involved coupling of **4** with **15** to afford **21**, which was then deprotected and coupled with complex **19** to afford intermediate **22**. Given the problematic steps in the construction of **5** and the low yield for its coupling with **4**, the less convergent route to **22** via **21** is the preferred one. Cycloetherification of **22**, followed by demetallation and TBS protection of the C-ring secondary alcohol afforded the advanced intermediate **23**.

In conclusion, we have demonstrated that chloroarene–ruthenium complexes are versatile intermediates for the construction of aryl ether linkages in complex molecular environments. They are easy to prepare, have excellent shelf life, and the organometallic moiety is stable to numerous organic reaction conditions and can be attached to and disengaged from the arene substrate without detriment to sensitive functionality. Further transformations of **23** are required to afford the aglycone of ristocetin A, and these will be the subject of future work in our laboratory.



Scheme 5.

Acknowledgments

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Supplementary data

Experimental procedures and spectroscopic data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.094.

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