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Synthetic studies on the BCDF ring system of ristocetin A via ruthenium-promoted S_NAr reaction

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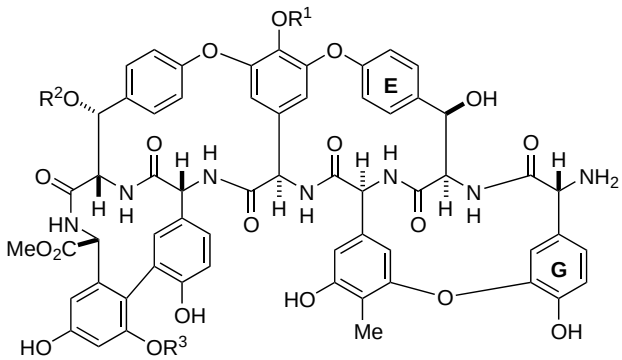
Abstract—Ruthenium-promoted intramolecular S_NAr reaction has allowed the construction of the 16-membered BCD model macrocycle of ristocetin A that incorporates the required arylserine residue as the C ring, and includes a fully functionalized F ring.

The vancomycin group of antibiotics[1] is of contemporary interest to synthetic chemists because of the clinical importance as well as the structural complexity of these molecules. Moreover, the recent occurrence of vancomycin-resistant strains of infectious bacteria[2] provides the impetus for the development of total syntheses[3] of vancomycin. Ristocetin A (**1**) has structural features that are similar to vancomycin, but incorporates an additional 14-membered biaryl ether connection between amino acid residues F and G. The construction of the biaryl ether linkage in these structures poses a significant challenge due to the presence of base-sensitive amino acid residues, especially arylglycine derivatives.[4] Studies toward the total synthesis of ristocetin A in our group have focussed on the use of ruthenium-promoted S_NAr reactions to incorporate the diaryl ethers.[5] Complexation of the aromatic subunits with ruthenium is accomplished under very mild conditions, etherification can be effected without appreciable racemization of arylglycines as well as phenylalanine subunits, and demetallation under simple photolytic conditions allows release of the desired organic structure as well as recycling of the ruthenium complex precursor.

The present study focuses on the use of ruthenium complexes of chloroarylserine derivatives that represent the C ring of the ristocetin structure, to determine whether there are likely to be any problems associated with this subunit, and if so, their solution. We have previously reported studies that utilize arylserine–ruthenium systems that represent the E ring, which is diastereomeric with the C ring.[6]



R^1, R^2, R^3 = sugars RISTOCETIN (**1**)

Our synthesis began with the chlorocinnamic esters **2** (a and b), which were subjected to the Sharpless asymmetric aminohydroxylation[7] protocol to afford directly the *N*-Boc-protected arylserines **3** (Scheme 1). It should be noted that the *N*-Cbz analogue of **3** has previously been reported,[7] but the use of the benzyloxycarbonyl protecting group is precluded for preparation of arene ruthenium complexes because of the competition between two aromatic rings. The absolute stereochemistry of **3a** was confirmed by conversion to the known Cbz derivative (CF_3CO_2H, CH_2Cl_2, 0°C; CbzCl, Na_2CO_3) and comparison of the optical rotation with this compound. The enantiomeric excess was determined by conversion to the Mosher amide[8] (CF_3CO_2H, CH_2Cl_2, 0°C; MTPA-Cl, TMP, CH_2Cl_2, 0°C), followed by NMR analysis. Complexation of **3a** under the conditions previously reported[5] afforded complex **4** (R = Me) in excellent yield.

At this stage we examined the stability of complex **4** to the conditions that are required for intramolecular

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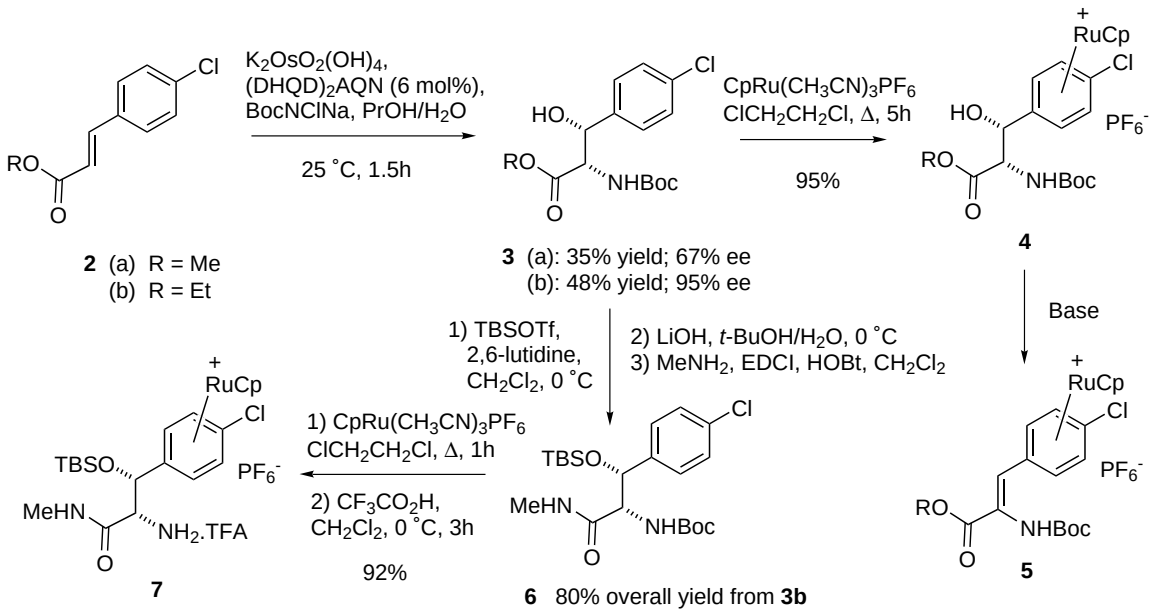
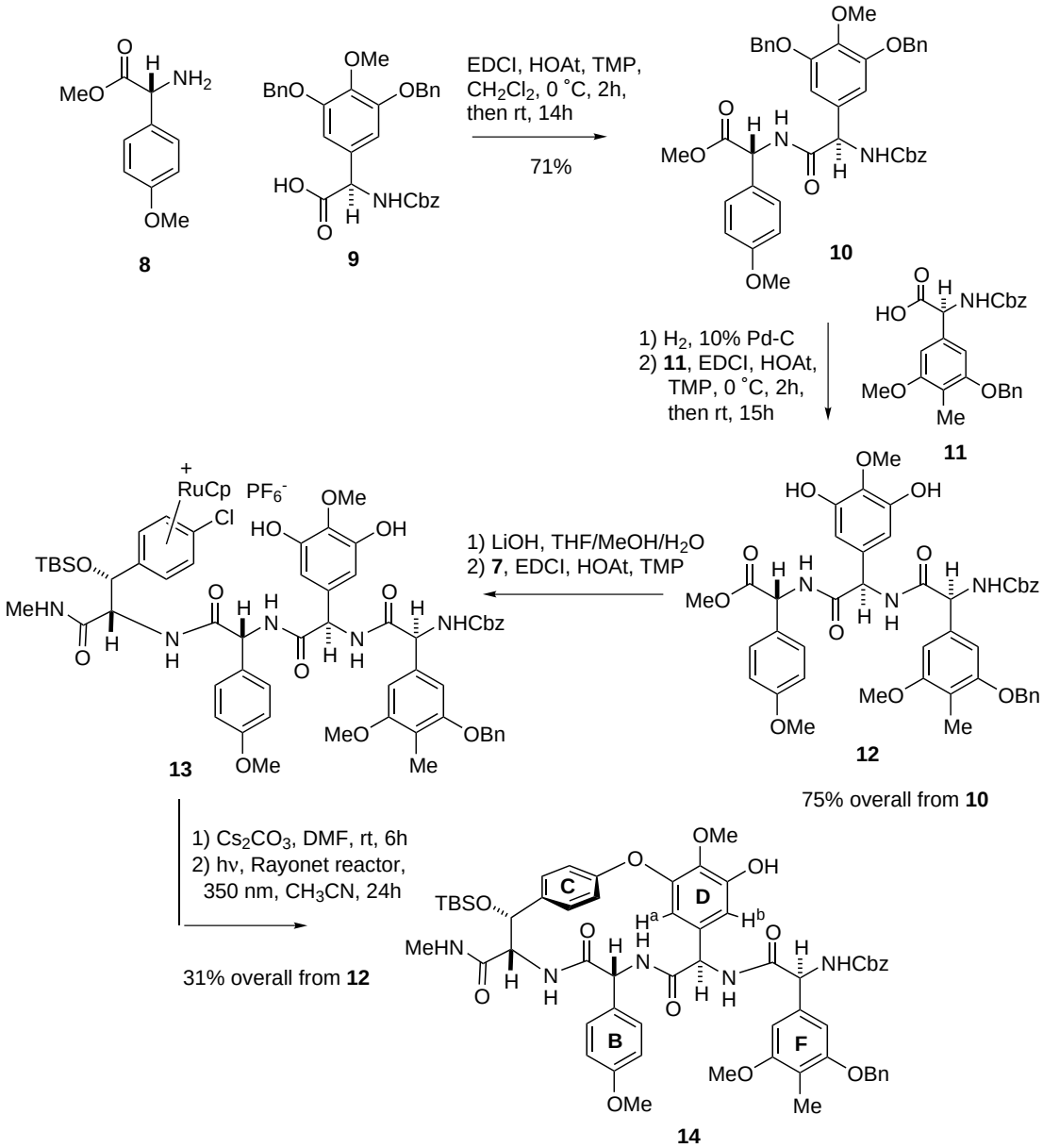


Scheme 1.

S_NAr reaction that would be used later in the sequence. Treatment of the complex with mild base (Cs_2CO_3 or sodium 2,6-di-*t*-butylphenoxide) resulted in dehydra- tion to afford **5**. This result indicates that steps must be taken to prevent this elimination reaction if the arene–ruthenium system is to be used for construction of the ristocetin BCD ring structure. It may be noted that similar dehydration does not occur with the ruthenium complex of the ring E chloroarylserine.[6] Logically, one would expect that lowering the acidity of the proton alpha to the carbonyl group, and/or tempering the leaving group capability of the benzylic oxygen, would ameliorate the situation. This indeed proved to be the case: use of either the *N*-methylamide derivative, *or* the silyl ether of **4** produced a system that was quite stable to base. In order to be assured that a synthesis of the BCD ring structure of the target molecule could be completed, we chose to use the silyl ether/*N*-methylamide **7**, for two reasons: the dehydration is prevented by both measures, and the silyl ether (TBS) renders the compound soluble in organic solvents that are used for subsequent coupling reactions. Evans' group have reported an efficient procedure for conversion of *N*-methylamide to carboxylic acid that is compatible with the vancomycin system, so one is assured that this will not present difficulties later in the synthesis.[9] (In fact, we did survey the use of the free hydroxyl derivative corresponding to **7**, as well as the TBS ether of **4** in the later reactions. In the first case, solubility problems arose, while in the second we were unable to secure good yields in the cycloetherification step that is used for the diaryl ether construction.) Conversion of the ethyl ester derivative **3b** to the fully protected methylamide **6** proceeded uneventfully, and complexation followed by *N*-deprotection afforded **7** in good yield. The stereochemical homogeneity of **6** was confirmed by NMR spectroscopy.

In considering the approach that we would ultimately use for the total synthesis of the aglycone of ristocetin A, we focussed on developing a strategy that would be most efficient in its use of ruthenium. Accordingly, our preference would be to use as few steps as possible after the preparation of complex **7**, which requires that we couple this compound with a building block representing the ABDF sequence of arylamino acids. For the present study, which was to establish the feasibility of this approach, we decided to forego the use of the AB biaryl structure and instead use a tripeptide corresponding approximately to the BDF sequence. Since methodology for construction of the biaryl is already known,[3] we felt that this approach would lay the necessary groundwork for a final assault on the actual total synthesis of ristocetin.

Scheme 2 summarizes the successful construction of an advanced intermediate that represents the BCDF ring structure of ristocetin. Coupling of the 4-methoxyphenylglycine methyl ester **8** with the known D ring precursor **9**,[10] using standard conditions, afforded good yield of the dipeptide derivative **10** after chromatographic purification to remove minor amounts of epimerized material. Simultaneous removal of the benzyl ether and Cbz protecting groups, by standard hydrogenolysis, followed by coupling with the F ring building block **11**, previously reported by us,[6] produced the protected tripeptide **12**, again in good yield. Hydrolysis of the methyl ester of **12** afforded the corresponding carboxylic acid in 73% yield, with no detectable epimerization of any of the arylglycine residues (by NMR). The carboxylic acid was coupled with ruthenium complex **7** under standard conditions to yield **13**, though difficulties with



Scheme 2.

rigorous purification of this compound, without material loss, prompted us to use the crude product in the subsequent etherification/demetallation, which proceeded smoothly to afford the cyclic compound **14** in good overall yield (45% from the carboxylic acid; 31% from **12**). We did not observe any evidence for epimerization or elimination from NMR spectroscopy of the crude product from this sequence of reactions.

Successful formation of the 16-membered ring of **14** is evidenced by the expected[3,5,6] upfield NMR shift of one of the ring-D protons, as a result of the shielding effect of the neighboring C ring, underneath which this proton is situated (see H^a versus H^b in structure **14**). In the present case the observed chemical shifts (600 MHz) are δ 5.88 (H^a) and 6.53 (H^b), which may be compared with the chemical shifts for the same protons in the cyclization precursors (e.g. both at δ 6.37 for **12**).

Conclusions

A 16-membered BCD model of ristocetin A was prepared by using ruthenium-promoted intramolecular S_NAr reaction under conditions that are sufficiently mild to avoid epimerization. Application of ruthenium–arylserine complex **7** was successful for the construction of the biaryl ether linkage. The chemistry developed in this study is currently being extended to the total synthesis of the aglycone of ristocetin A.

Acknowledgements

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