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Approaches to the Fully Functionalized DEF Ring System of Ristocetin A via Highly Selective Ruthenium-Promoted S_NAr Reaction

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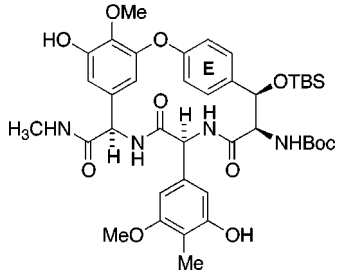
ABSTRACT



Ruthenium-promoted intramolecular S_NAr reaction has allowed the construction of the fully functionalized 16-membered DEF macrocycle 4 of ristocetin A that incorporates the required arylglycine and arylserine residues as the F and E ring, respectively.

Ristocetin A (**1**), a glycopeptide related to vancomycin (**2**), is an antibiotic[1] produced by the microorganism *Nocardia lurida* (Figure 1). Vancomycin is currently in clinical use and is well-known as the "antibiotic of last resort" in hospitals. Ristocetin A was also clinically employed to treat bacterial infections in the late 1950s, but undesirable side effects led to its discontinuation. Teicoplanin (**3**) is a potentially useful experimental drug. Recently, the increasing incidence of vancomycin-resistant strains of infectious bacteria,[2] as well as the challenging molecular architecture of these antibiotics, has evoked considerable interest in the total synthesis of these compounds.

Molecules of this group generally have a heptapeptide backbone structure with embedded biaryl ether and biphenyl linkages.[3] Both ristocetin A and teicoplanin have structural features that are similar to vancomycin, but they incorporate an additional 14-membered ring with biaryl ether connection between amino acid residues F and G. Only recently have total syntheses of vancomycin and its aglycon been accomplished.[4−6] Our own efforts have focused on construc-

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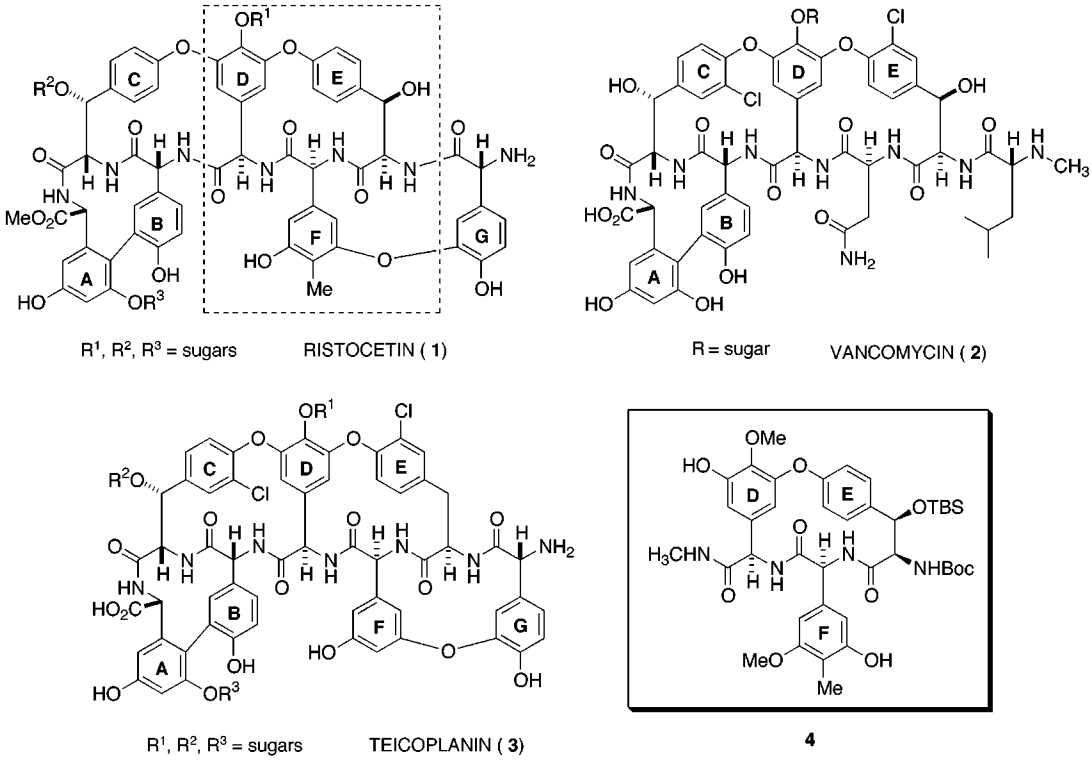

Figure 1.

tion of the ristocetin and teicoplanin structures using ruthenium-promoted S_NAr reactions.[7] Although we have published Ru-based technology using a chloroarylserine−RuCp complex as a key element for approaches to Ristocetin synthesis,[8] the work described herein represents a fairly significant advance in this chemistry, allowing it to be used successfully with a molecule that has competing functionality. In the present work it is demonstrated that the DEF ring system can be constructed using a fully functionlized F-ring residue and without orthogonal protection steps, which sets the stage for the final building of the entire ristocetin molecule by using the "end-game" methodology that we have reported. Herein we describe an efficient approach to the fully functionalized DEF ring system (**4**) of ristocetin A that will be useful for building on the final DEFG ring of ristocetin and teicoplanin.[9]

First, the requisite differentially protected F ring amino acid was prepared by a Sharpless asymmetric aminohydroxylation reaction[10] (Scheme 1). Starting from 3,5-dihydroxy-4-methylbenzoic acid (**5**), prepared by the literature procedure,[11] methyl ester **6** was obtained by Fischer esterification [MeOH, *p*-TsOH·H_2O (0.2 equiv), reflux, 24 h, 80%]. Methylation of **6** [Me_2SO_4 (1.2 equiv), K_2CO_3 (2.0 equiv), *n*-Bu_4NI (0.2 equiv), reflux, acetone, 24 h] afforded the monomethyl ether **7** (42%) along with the corresponding bismethyl ether (33%). Subsequent benzylation of **7** [BnBr (1.05 equiv), NaH (1.1 equiv), *n*-Bu_4NI (0.1 equiv), THF, room temperature, 2 h, 96%] provided **8**, which was subjected to reduction [$LiAlH_4$ (1.5 equiv), THF, reflux, 2.5 h] and oxidation [PCC (3.0 equiv), CH_2Cl_2, room temperature, 3 h] to give aldehyde **9** in 96% yield for two steps. Methylenation of **9** via Wittig reaction [$Ph_3P{=}CH_2$ (2.0 equiv), THF, −78 °C to room temperature, 2 h, 95%] afforded styrene **10**, required for the Sharpless asymmetric aminohydroxylation.

The terminal olefin **10** was converted to the corresponding benzyloxyamino alcohol with a good regioselectivity (1° alcohol **11**:2° alcohol = 4/1) and enantioselectivity (≥90% ee) under the typical reaction conditions [$BnOCONH_2$ (3.1 equiv), *t*-BuOCl (3.05 equiv), NaOH (3.1 equiv), $(DHQ)_2$-PHAL (5 mol %), $K_2OsO_2(OH)_4$ (4 mol %), *n*-PrOH/H_2O/Et_2O (3:2:1), room temperatrue, 1 h, 80%]. In this reaction the use of diethyl ether as cosolvent was necessary to improve the solubility of styrene **10**. The enantiomeric purity of amino alcohol **11**, separated by chromatography, was determined by Mosher ester analysis.[12] As a final step, oxidation of **11** [TEMPO (1.05 equiv), NaOCl (2.0 equiv),

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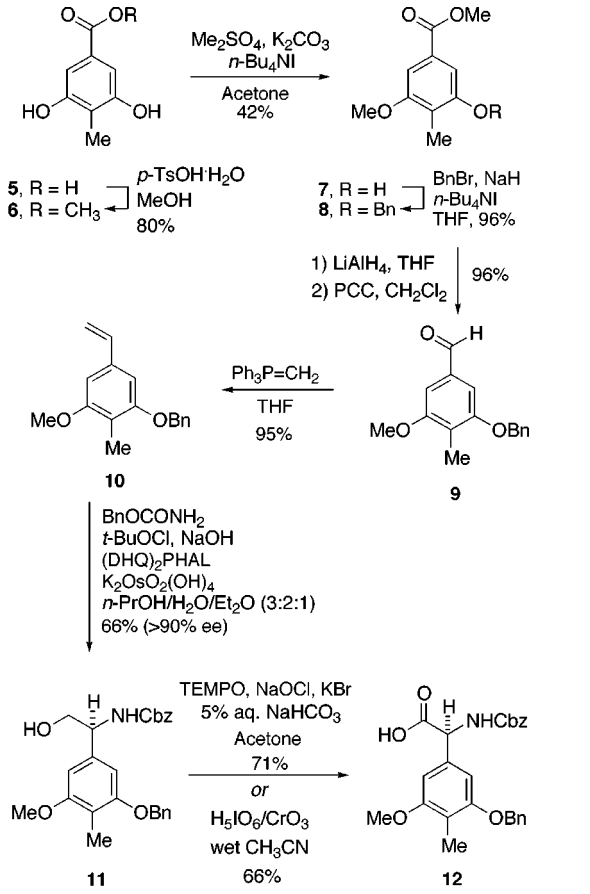
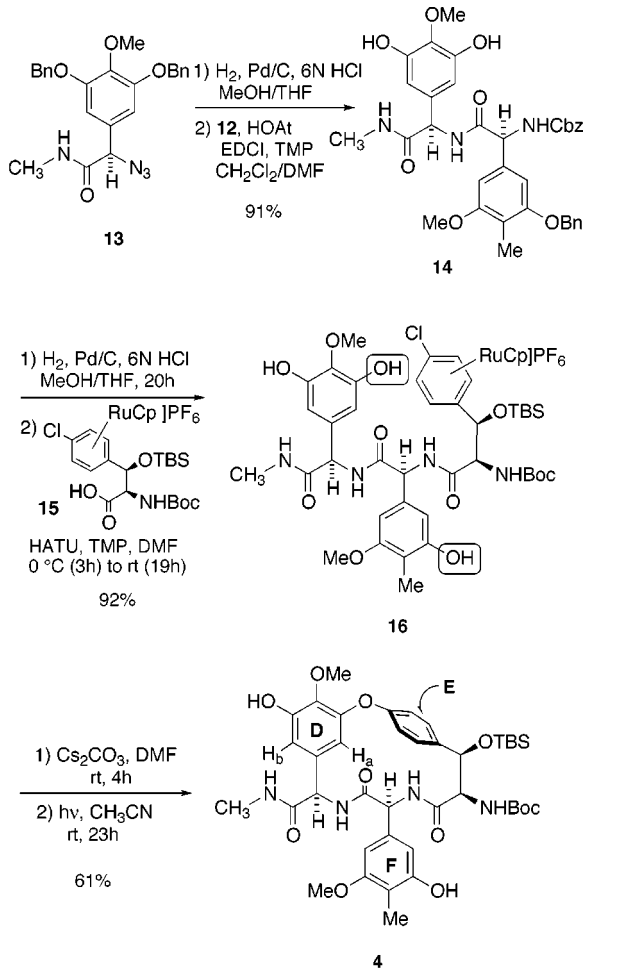
Scheme 1



Scheme 2



KBr (0.14 equiv), 5% $NaHCO_3$, acetone, 0 °C, 2.5 h] led to carboxylic acid **12** in good yield ($[\alpha]^{25}_D = +94$, *c* 1.0, EtOH, after recrystallization from Et_2O). An alternative approach for the oxidation of **12** was also successful using H_5IO_6/CrO_3 (66% yield).[13]

With arylglycine **12** in hand, we have investigated the synthesis of the fully functionalized DEF ring system as shown in Scheme 2. Our synthesis started with azido amide **13**, derived from the carboxylic acid previously reported by our group.[8,14] Simultaneous azide reduction and benzyl ether deprotection of **13** (H_2, Pd/C, 6 N HCl, MeOH/THF), followed by coupling of the resulting amine salt with (*S*)-arylglycine **12** [HOAt (1.5 equiv), EDCI (1.5 equiv), TMP (2.0 equiv)][15] provided the dipeptide **14** in 91% yield. After deprotection of both the benzyl carbamate and benzyl ether of the dipeptide **14** (H_2, Pd/C, 6 N HCl, MeOH/THF), coupling with the arylserine−ruthenium complex **15**[8] proceeded smoothly [HATU (2.0 equiv), TMP (2.2 equiv), DMF] to provide the tripeptide−ruthenium complex **16** in 92% yield. It is noteworthy that little or no epimerization was observed during the coupling reaction, according to the ^1H NMR spectrum of **16**.

The macrocyclization using ruthenium-promoted S_NAr reaction on **16** could in principle lead to 16-membered and 13-membered diaryl ether rings by reaction of hydroxy moieties on the D ring and on the F ring, respectively. Before this step, of course, an orthogonally protected amino acid corresponding to the F ring could be used to mask the free hydroxy group. However, intramolecular cyclization was expected to provide exclusively the 16-membered ring as a result of the large ring strain of the 13-membered ring. Computational studies[16] predict a steric energy difference of ∼18 kcal/mol favoring the 16-membered ring **4** (−26.775 kcal/mol) over 13-membered ring **17** (−8.508 kcal/mol).

Exposure of tripeptide−ruthenium complex **16** to Cs_2CO_3 (5.0 equiv) in DMF (5 mM), followed by photolytic

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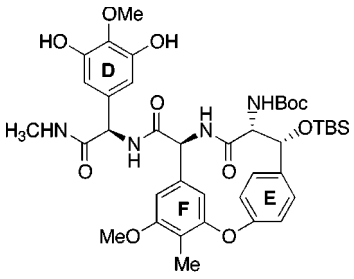
(15) HOAt, 1-hydroxy-7-azabenzotriazole; EDCI, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; TMP, 2,4,6-trimethylpyridine; HATU, *O*-(7-azabenzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexaflourophosphate.

(16) Molecular mechanics calculations were performed by using MM2 force field molecular modeling software, *Chem3D*.

(17) After this manuscript was submitted, a total synthesis of the teicoplanin aglycon was disclosed by Boger et al.: Boger, D. L.; Kim, S. H.; Mizayaki, S.; Strittmatter, H.; Weng, J.-H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 7416−7417.



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demetalation (Rayonet 350 nm, CH_3CN) provided a single compound, macrocycle **4** ($[\alpha]^{25}_D = -19.1$ (*c* 0.47, MeOH)), in 61% yield. ^{1}H NMR showed the characteristic chemical shift difference between the two *ortho*-protons on the D ring corresponding to the 16-membered macrocycle, because H_a is located within the shielding zone of the neighboring E ring: δ 6.65 (d, 1H, $J = 1.5$ Hz, H_b), 5.75 (d, 1H, $J = 1.5$ Hz, H_a).[7d,8] Another clear indication for formation of the 16-membered ring is that the D-ring methoxy singlet is shifted downfield approximately 0.2 ppm after cyclization, while the F-ring methyl singlet remains unaffected (groups ortho to the hydroxyl are expected to show significant changes upon etherification). One of the advantages of this selectivity is that additional hydroxyl protection and deprotection steps are not necessary, which will ultimately allow for construction of the DEFG ring system by intermolecular etherification and intramolecular macroamidation as described by our group.[9,17]

In summary, we have developed a convenient synthesis of the fully functionalized DEF ring system of ristocetin A using ruthenium-promoted S_NAr chemistry. Indeed, the regiospecific macrocyclization in favor of the 16-membered ring promises an efficient approach to the final DEFG ring system of ristocetin A and teicoplanin.

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Supporting Information Available: Detailed experimental procedures and spectral data for compounds **11, 12, 14, 16,** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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