Pergamon

Tetrahedron Letters 41 (2000) 5991–5996

TETRAHEDRON LETTERS

Synthetic studies on the DEF ring system of ristocetin A via ruthenium-promoted S_NAr reaction: problems and solutions using arylserine–Ru complexes

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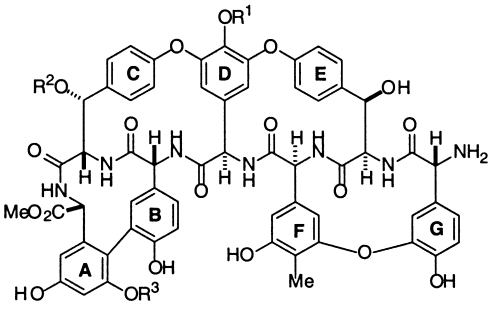
Received 2 May 2000; revised 23 May 2000; accepted 24 May 2000

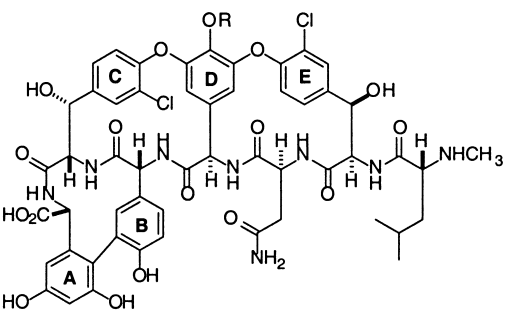
Abstract

Ruthenium-promoted intramolecular S_NAr reaction has allowed the construction of the 16-membered DEF model macrocycle of ristocetin A that incorporates the required arylserine residue as the E ring.

The vancomycin group of antibiotics[1] is of considerable interest because of its clinical importance as well as the complexity of these molecules. Furthermore, the recent upsurge of vancomycin-resistant strains of infectious bacteria[2] provides the impetus for the development of total syntheses[3] of vancomycin analogues. Ristocetin A (**1**) has structural features that are similar to vancomycin (**2**), 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 has posed a considerable challenge due to the presence of base-sensitive amino acid residues, especially arylglycine derivatives.[4] Our group has extensively studied ruthenium-promoted S_NAr reactions for the formation of biaryl ethers.[5] This chemistry allows: (1) complexation with ruthenium under very mild conditions; (2) etherification without appreciable racemization of arylglycines as well as phenylalanine subunits; and (3) demetallation under simple photolytic conditions.



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



R = sugar VANCOMYCIN (**2**)

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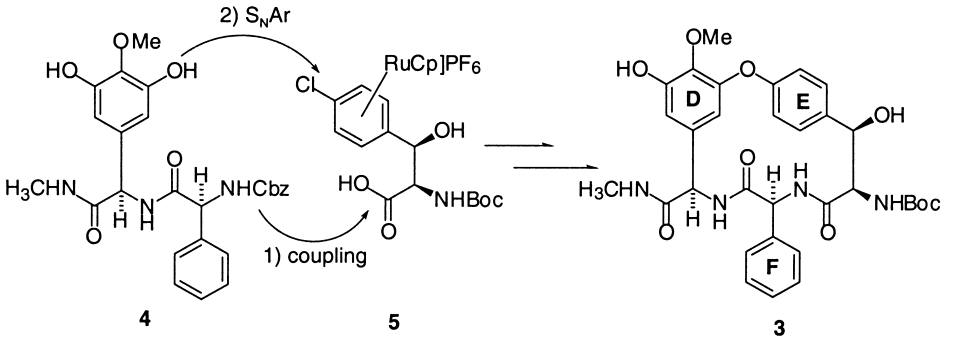
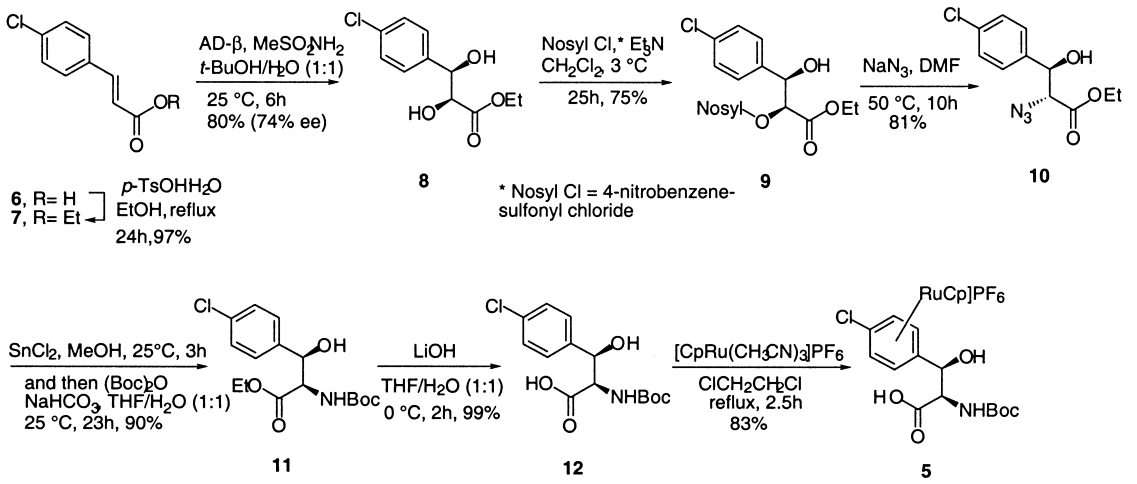
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00855-8

The main objective of the study reported herein was to establish the feasibility of applying ruthenium-promoted S_NAr chemistry to arylserine substrates (**5**). For this purpose we designed target molecule **3** (Scheme 1) in which the C-terminus of the central amino acid **D** would be protected as its *N*-methyl amide to prevent the facile epimerization of this arylglycine,[3a] since previous work has shown that the corresponding methyl ester is easily and totally epimerized under basic conditions.[6]



Scheme 1.

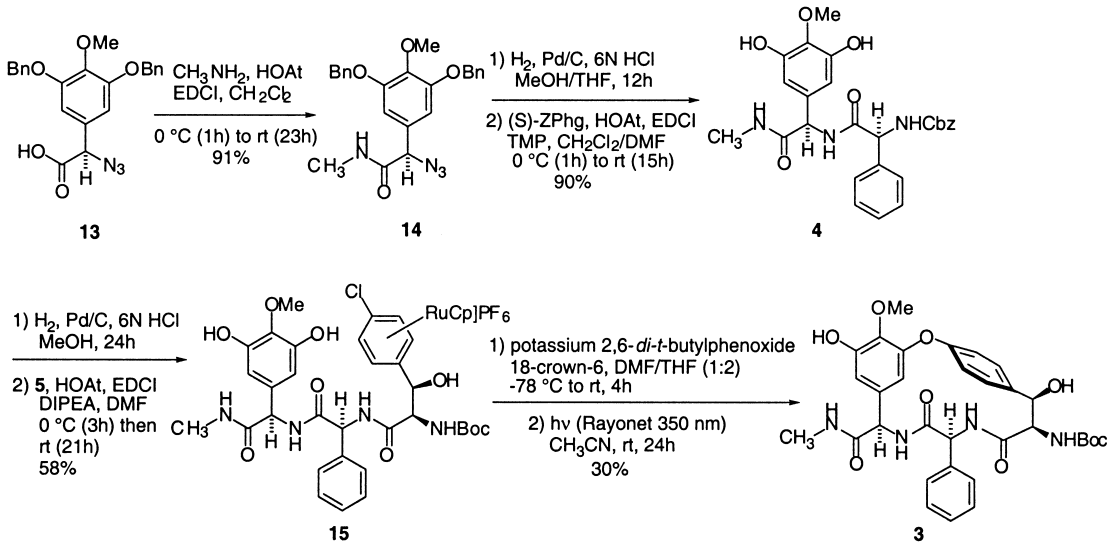
The synthesis of arylserine derivative **12** corresponding to the ruthenium complex **5** was based on the Sharpless asymmetric dihydroxylation reaction[7] (Scheme 2). Ethyl (*E*)-4-chlorocinnamate (**7**), prepared by Fischer esterification of (*E*)-4-chlorocinnamic acid (**6**), was subjected to asymmetric dihydroxylation by treatment with the AD-mix-β (1.4 g/mmol) reagent and $CH_3SO_2NH_2$ (1.0 equiv.) in *t*-BuOH:H_2O (1:1) to provide ethyl (2*S*,3*R*)-3-(4-chlorophenyl)-2,3-dihydroxypropionate (**8**) in good yield (80%, $[\alpha]_D^{25} = -14$ (*c* 1.2, EtOH)) and high ee (74% ee, determined by Mosher ester analysis).[8] One recrystallization from 50% EtOAc–hexanes enriched **8** to >99% ee ($[\alpha]_D^{25} = -19^\circ$ (*c* 1.0, EtOH)).



Scheme 2.

Reaction of **8** with 4-nitrobenzenesulfonyl chloride (nosyl chloride, 1.0 equiv.) and Et_3N (1.5 equiv.) in methylene chloride at 3°C provided α-nosylate **9** (75%) resulting from the acidity difference of the two alcohols.[9] In addition, a small amount (12%) of the α,β-unsaturated ester product, derived from elimination of the disulfonated intermediate, was isolated. Subsequent azide replacement of the sulfonate (NaN_3 (1.5 equiv), DMF, 50°C, 10 h, 81%) gave **10** as a *syn*:*anti* (1:9) mixture, which was separated by chromatography. Subsequent reduction of azide **10** ($SnCl_2$ (2.0 equiv.), MeOH, 25°C, 3 h) and Boc protection ($(Boc)_2O$ (2.0 equiv.), $NaHCO_3$ (4.0 equiv.), THF:H_2O (1:1), 25°C, 23 h, 90% for two steps) provided **11**, which was converted to the arylserine **12** (LiOH (2.0 equiv.), THF:H_2O (1:1), 0°C, 2 h, 99%). Finally, complexation of **12** with $[CpRu(CH_3CN)_3]PF_6$ was accomplished under the conventional reaction conditions ($ClCH_2CH_2Cl$, reflux, 2.5 h) to provide η^6-arene-ruthenium complex **5** in good yield.[10]

With the arene-ruthenium complex **5** in hand, we investigated the ruthenium-promoted S_NAr chemistry as shown in Scheme 3. Our synthesis started with the azido acid **13**, previously reported by our group.[11] The acid was masked as its methylamide (HOAt (1.5 equiv.), EDCI (1.2 equiv.), CH_3NH_2 (3.0 equiv.), 0°C (1 h) to rt (23 h), 91%) to provide **14**. Subsequent azide reduction (H_2, Pd/C, 6N HCl, MeOH/THF, 12 h) and coupling with (*S*)-ZPhg in the presence of HOAt (1.5 equiv.), EDCI (1.2 equiv.), and TMP (2.0 equiv.) provided the dipeptide **4** (90%).

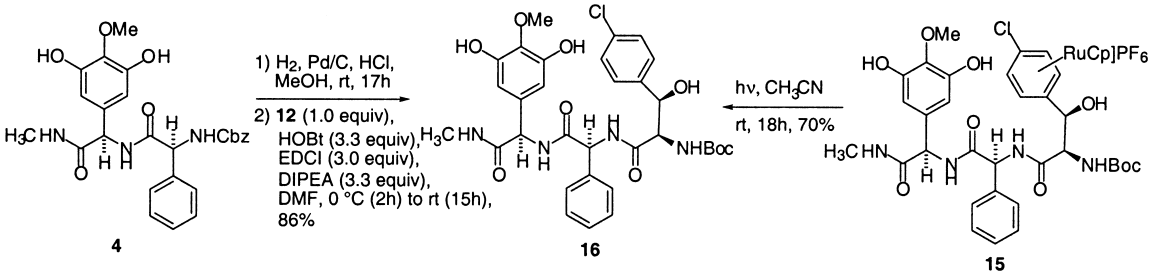


Scheme 3.

Several attempts to prepare the tripeptide-ruthenium complex **15** under standard coupling conditions gave unsatisfactory results (less than 20% yield). In order to examine the coupling reaction in more detail, we carried out the reaction of the dipeptide **4** and the arylserine **12**, not having the attached ruthenium, which gave the tripeptide **16** in excellent yield (Scheme 4). This result indicated that the coupling reaction with the ruthenium complex **5** was likely proceeding efficiently, but the normal work-up procedure by extraction with propionitrile, we thought, could be a problem because of the low solubility of the product. Accordingly, the DMF solvent was removed in vacuo after the coupling reaction (HOAt (3.3 equiv.), EDCI (3.0 equiv.), DIPEA (1.05 equiv.), DMF, 0°C (3 h) to rt (21 h)) and the crude product was isolated by adding pro-

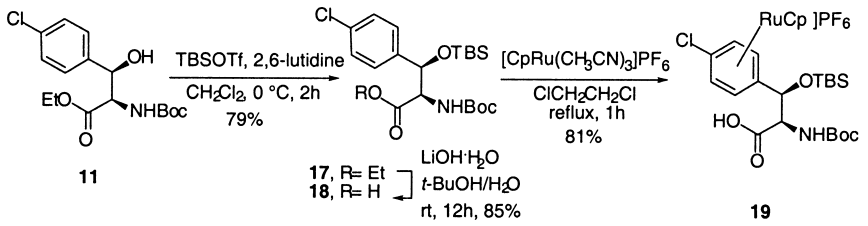
pionitrile. The resulting dark brown solid was filtered, washed (cold H_2O, ethyl ether), and dried to give the desired product (58%). In addition to ^1H NMR and FABHRMS to confirm the structure **15**, demetallation reaction also furnished the same product **16** as synthesized from **4**.

Intramolecular etherification of **15** was achieved under basic conditions (potassium 2,6-di-*t*-butylphenoxide (2.0 equiv.), 18-crown-6 (1.0 equiv.), DMF, –78°C to rt, 4 h) at low concentration (10 mM) to give a cyclized ruthenium intermediate, which was subjected directly to photolysis (350 nm, CH_3CN, 24 h) to provide the cyclized biaryl ether tripeptide **3** in 30% overall yield. The cyclization was easily confirmed by the ^1H NMR (CD_3OD, 300 MHz) spectrum of **3**, which showed that one of the two aromatic protons at the central phenyl D was shifted upfield due to the shielding effect of the neighboring ether linked phenyl group (δ 5.58 ppm).[6] It is especially noteworthy that epimerization among the chiral centers was not observed during this reaction sequence. Nonetheless, the problems caused by low solubility of complexes such as **15** are cause for concern, and we decided to investigate a means of ameliorating this situation.



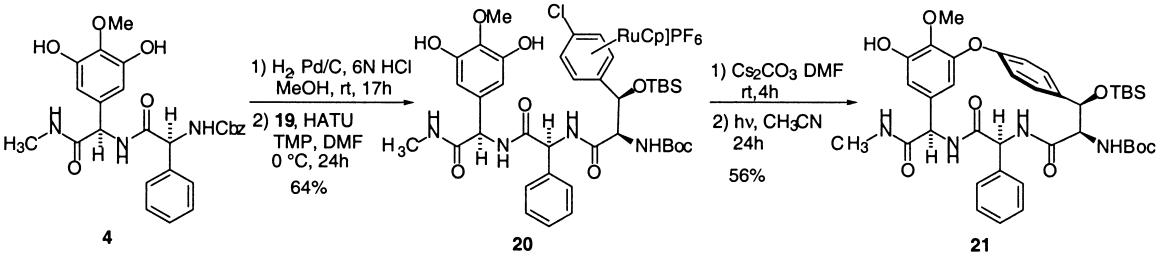
Scheme 4.

In order to improve the solubility of the tripeptide-ruthenium complex **15**, the benzylic hydroxy group was converted to its silyl ether (Scheme 5). Thus, **11** was treated with TBSOTf (1.5 equiv.) and 2,6-lutidine (2.0 equiv.) in CH_2Cl_2 to provide the TBS protected compound **17** in 79% yield. Hydrolysis of ester **17** was carried out by using lithium hydroxide monohydrate (2.0 equiv.) in *t*-buthanol:H_2O (3:1) to obtain the acid **18** in 85% yield ($[\alpha]_D^{25} = -45$ (*c* 0.8, 95% EtOH); after recrystallization from 20% EtOAc–hexanes). Compared to the hydrolysis of hydroxy ester **11**, **17** required a more protic solvent system and increased reaction temperature. The resulting arylserine **18** was complexed with $[CpRu(CH_3CN)_3]PF_6$ by using the same conditions as previous to give the arene-ruthenium complex **19** in good yield. Prolonged reaction time (> 2 h) led to the formation of the desilylated side product **5**.



Scheme 5.

Coupling of the dipeptide **4** with the arene-ruthenium complex **19** provided tripeptide-ruthenium complex **20** in good yield, and without epimerization, with significant improvement of its solubility (Scheme 6). Now, the tripeptide ruthenium complex can be conveniently used in less polar organic solvents such as THF and CH_2Cl_2. Treatment of **20** with Cs_2CO_3 (5 equiv.) in DMF (5–10 mM), followed by photolysis (Rayonet 350nm, 24 h) in CH_3CN, effected its smooth conversion to macrocycle **21** ($[\alpha]_D^{25} = -13.2^\circ$ (*c* 0.6, MeOH)) in good yield without epimerization.



Scheme 6.

At this point we were concerned about the possibility of the complete inversion of configuration at the central amino acid **D**, as we had earlier noted in the case of the corresponding methyl ester under the same basic conditions.[6] Since this epimerization is thermodynamically driven to completion, it would go unnoticed during the cycloetherification. Therefore, we carried out the same macrocyclization starting from racemic azido amide **14**. Through all the coupling steps the tripeptide ruthenium complex maintained its diastereomeric ratio (1:1). Cyclization under standard conditions provided two macrocyclic products in 1:1 ratio arising from the original amide-terminal mixture. These results establish that the *N*-methyl amide derivative is effective for suppressing this epimerization, as a result of the lower acidity of the benzylic proton.

Conclusions: A 16-membered DEF model of ristocetin A was prepared by using ruthenium-promoted intramolecular S_NAr reaction under conditions that were mild enough to avoid epimerization, when the C-terminal of the central amino acid **D** was protected as the *N*-methyl amide linkage. Application of ruthenium-arylserine complex was successful for the construction of the biaryl ether linkage. The efforts developed here can be extended to the total synthesis of ristocetin and related molecules.

Acknowledgements

We are grateful to the National Institutes of Health for financial support of this research (GM-36925), and to Mariappan Chelliah for preliminary work leading to this study.

References

1. (a) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364–369. (b) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172–1193.
2. Walsh, C. T.; Fisher, S. L.; Park, I.-S.; Parhalad, M.; Wu, Z. *Chem. Biol.* 1996, *3*, 21.

3. (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700–2704. (b) Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2704–2707. (c) Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N.; Takayanagi, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2707–2714. (d) Nicolaou, K. C.; Jain, N. F.; Natarajan, S.; Hughes, R.; Solomon, M. E.; Li, H.; Ramanjulu, J. M.; Takayanagi, M.; Koumbis, A. E.; Bando, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 2714–2716. (e) Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2716–2719. (f) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004–10011.
4. For reviews, see: (a) Evans, D. A.; DeVries, K. M. In *Glycopeptide Antibiotics*; Nagarajan, R., Ed.; Marcel Dekker: New York, 1994; pp. 63–104. (b) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135–2167. (c) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096–2152.
5. (a) Pearson, A. J.; Zhang, P.; Lee, K. *J. Org. Chem.* **1996**, *61*, 6581–6586. (b) Pearson, A. J.; Bignan, G. *Tetrahedron Lett.* **1996**, *37*, 735–738. (c) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1995**, *60*, 7153–7160. (d) Pearson, A. J.; Belmont, P. O. *Tetrahedron Lett.* **2000**, *41*, 1671–1675.
6. Pearson, A. J.; Chelliah, M. V. *J. Org. Chem.* **1998**, *63*, 3087–3098.
7. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. (c) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544–8556.
8. Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147.
9. Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869–2875.
10. Pearson, A. J.; Park, G. W. *J. Org. Chem.* **1992**, *57*, 1744–1752.
11. Pearson, A. J.; Chelliah, M. V.; Bignan, G. C. *Synthesis* **1997**, 536–540.