Synthesis of an Epimer of a 16-Membered Ring Model for Teicoplanin: Confirmation of Epimerization during Cycloamidation

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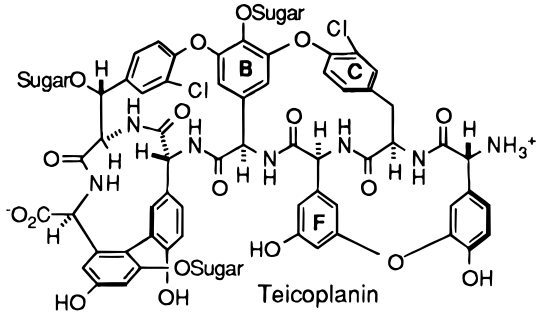
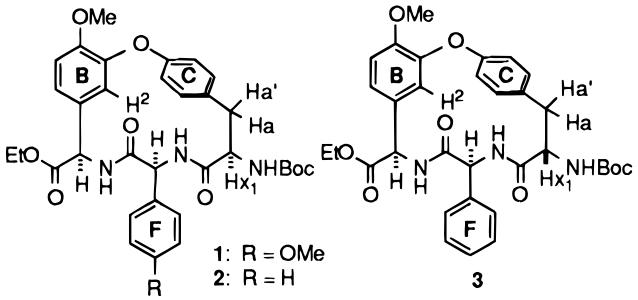
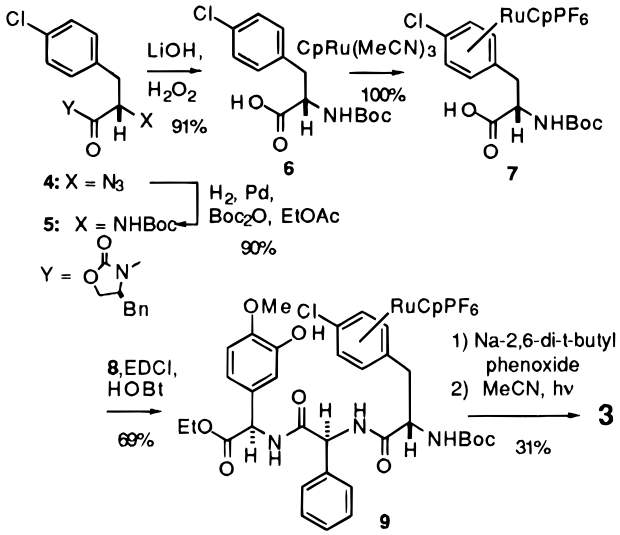
Because of their unique structure and clinical importance, vancomycin and related antibiotics, including teicoplanin and ristocetin, are currently the subject of intensive synthetic studies.[1] One of the difficulties with their total synthesis is the atropisomerism (conformational isomerism) of the biaryl ether linkage and, in the case of chloro-substituted derivatives, the peptido aryl ether rings. In previous studies from our laboratory, areneruthenium chemistry was utilized in the synthesis of two 16-membered cyclic peptides **1** and **2**, which represent models for partial structures of teicoplanin and ristocetin, designed to test the efficacy of our ruthenium-promoted etherification methodology. Compound **1** was obtained by a cycloamidation strategy using different coupling methods, and two cyclized monomers, labeled **1-F1** and **1-F2,** were obtained.[2] We were uncertain whether they were stable conformational isomers or epimers at the phenylalanine residue. Ruthenium-mediated cycloetherification recently reported from our laboratory provided compound **2**.[3] Herein, we report the unambiguous synthesis of compound **3**, which is the epimer of compound **2** in the phenylalanine unit. The result shows that **1-F1** and **1-F2** obtained earlier are epimers and not conformational isomers.



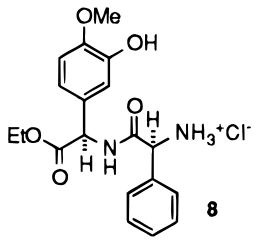


Synthesis of **3** is outlined in Scheme 1, employing cycloetherification procedures analogous to those used for

Scheme 1



the preparation of compound **2**.[3] Thus, the one-step reduction and *in situ* Boc protection of the azidation product **4**[4] gave compound **5**, which was treated with LiOOH to provide *N*-Boc-L-4-chlorophenylalanine (**6**). Complexation of **6** using $(CH_3CN)_3RuCpPF_6$ furnished complex **7**, which was coupled with dipeptide **8** to give



the tripeptide complex **9** in 69% yield. Cycloetherification was effected by treatment with sodium 2,6-di-*tert*-butylphenoxide at −78 °C under high dilution conditions (0.002 M), and photolytic demetalation of the product (Rayonet, 350 nm, CH_3CN) led to compound **3** in 31% unoptimized overall yield. Higher field shift of H^2 (6.12 ppm) in the NMR spectrum indicated the presence of the cyclized product because H^2 in ring B is shielded by ring C. An important structural marker is the benzylic methylene (Ha and Ha′). One of these protons appears as a doublet of doublets at 3.23 ppm with J_{gem} = 12.4 Hz, J_{vic} = 5.1 Hz; the other is a triplet at 2.88 ppm, resulting from large geminal and vicinal couplings (J_{gem} = J_{vic} = 12.4 Hz).

As reported previously, in the NMR spectrum of compound **2**,[3] both benzylic H's showed large geminal and small vicinal coupling constants (J_{gem} = 13.8, J_{vic} = 4.8 Hz and J_{gem} = 13.8, J_{vic} = 3.0 Hz), which is in contrast to that in compound **3**. On the other hand, preparation of compound **1** by cycloamidation using the pentafluorophenyl (PFP) ester method gave a low yield (14%) of two cyclized monomers labeled **1-F1** and **1-F2** in a ratio

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(1) (a) Evans, D. A.; DeVries, K. M. in *Glycopeptide Antibiotics*; Nagarajan, R., Ed.; Marcel Dekker: New York, 1994; p 63. (b) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135.

(2) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1995**, *60*, 7153

(3) Pearson, A. J.; Bignan, G.; Zhang, P.; Chelliah, M. *J. Org. Chem.* **1996**, *61*, 3940. In this work we obtained a 7:1 mixture of epimers in favor of **2**. More recently, we have observed that epimerization apparently occurs during the aqueous quench after peptide coupling; when this is performed carefully at 0 °C, a single isomer is obtained, as described in the preparation of **9** and **3**.

(4) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 225.

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of 7:3.[2] The major component **1-F1** (J_{gem} = 12.2, J_{vic} = 5.2 Hz and $J_{gem} = J_{vic}$ = 12.2 Hz) has a splitting pattern similar to that of **3**, while the minor one **1-F2** (J_{gem} = 14.0, J_{vic} = 5.2 Hz, J_{gem} = 14.0, J_{vic} = 2.9 Hz) was comparable to **2**.

MM2 modeling has been reported for compound **1**.[2] Atropisomers along the biaryl ether bond and epimers at each amino acid residue were considered. In the atropisomer with all the stereochemical features corresponding to that assigned to naturally occurring teicoplanin, the dihedral angles a/X_1 and a′/X_1 were 73° and 43°, respectively, which should give J_{vic}'s consistent with the values found in **1-F2**. The epimer of this atropisomer at chiral center X_1 showed dihedral angles of 61° and 179°. Alternatively, a conformational isomer of the molecule could be produced, which showed dihedral angles of 58° and 175°. It was proposed previously that **1-F1** was the stable conformational isomer because of the large energy difference between the epimeric compounds (10.62 kcal/mol, 15.66 kcal/mol for the epimer). With compounds **2** and **3** in hand, it now appears more likely that **1-F1** is in fact the X_1 epimer.

Because of the favored formation of **1-F1** over **1-F2**, we deduce that, during the cycloamidation reaction using PFP active ester together with Et_3N, the X_1 epimer is kinetically preferred in the cyclization process, considering the dominance of the acyclic epimer is very unlikely under such mild reaction conditions.[5] Similar phenomena have recently been observed in the synthesis of the cycloisodityrosine subunit of deoxybouvardin and RA-VII by Inoue *et al.*[6] and Boger *et al.*[7]

In conclusion, by synthesizing the X_1 epimer of compound **2**, we have demonstrated the formation of the epimer during the cycloamidation reaction. Even though racemization at the phenylalanine chiral center is usually not observed, the favorable orientation of the reactive groups in the acyclic epimer in the transition state for the cycloamidation step is a plausible reason for the dominant formation of the cyclic epimer. Moreover, the present work demonstrates the capability of NMR to easily distinguish these two epimers and helps to confirm the stereochemical assignments that have been made for teicoplanin.[8]

Experimental Section

General methods are as described elsewhere.[4]

(4*S*)-3-[(2*S*)-2-[*N*-[(1,1-Dimethylethoxy)carbonyl]amino]-3-(4-chlorophenyl)-1-oxopropionyl]-4-benzyl-2-oxazolidinone (5). A suspension of 10% Pd/C (~12 mg) in 4 mL of dry EtOAc was stirred vigorously under H_2 atmosphere for 20 min. To the mixture were added compound **4** (100 mg, 0.28 mmol, 1 equiv) and $(Boc)_2O$ (73 mg, 1.2 equiv). After being stirred at rt under H_2 for 3 h, the mixture was filtered through Celite, and the filtrate was evaporated to give 110 mg (90%) of compound **5** as a white solid: mp 150−151 °C; $[\alpha]^{22}_D = +80.1$ (*c* 0.49, $CHCl_3$); R_f 0.25 (hexane/EtOAc, 7/3); IR ($CHCl_3$) 1784, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.18 (m, 9H), 5.72−5.65 (m, 1H), 5.15 (bd, 1H, *J* = 7.0 Hz), 4.62−4.57 (m, 1H), 4.22−4.11 (m, 2H), 3.33 (dd, 1H, *J* = 13.6, 1.3 Hz), 3.14 (dd, 1H, *J* = 12.2, 2.0 Hz), 2.81−2.74 (m, 2H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 155.1, 152.7, 135.0, 134.6, 132.9, 130.8, 129.4, 128.6, 127.4, 80.1, 66.5, 55.5, 54.1, 38.0, 37.5, 28.2; HRMS calcd for $C_{20}H_{18}N_2O_4Cl$ ($M^+ - OBu^t$) 385.0955, found 385.0953.

(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-4-chlorophenylalanine (6). To a solution of compound **5** (110 mg, 0.25 mmol, 1 equiv) in 6 mL of THF/H_2O (3:1) at 0 °C were added 30% H_2O_2 (1.48 mL, 6 equiv) and 1 N LiOH (0.5 mL, 2 equiv). The mixture was stirred for 1 h and quenched with 1.5 M Na_2SO_3 (1.5 mL). The solution was buffered to basic (pH ~9) with saturated $NaHCO_3$. THF was evaporated, and the residue was extracted with CH_2Cl_2 (5 mL × 3), acidified to pH ~2 with 1 N HCl, and extracted with EtOAc (5 mL × 4). The EtOAc layer was dried with $MgSO_4$ and evaporated give compound **6** (65.4 mg, 91%) as a white solid: $[\alpha]^{22}_D = +46.2$ (*c* 0.90, $CHCl_3$); ^1H NMR (DMSO-d_6) δ 7.32 (d, 1H, *J* = 8.5 Hz), 7.25 (d, 1H, *J* = 8.5 Hz), 7.14 (d, 1H, *J* = 8.4 Hz), 4.06 (m, 1H), 2.99 (dd, 1H, *J* = 13.6, 4.4 Hz), 2.78 (dd, 1H, *J* = 13.6, 10.5 Hz); ^{13}C NMR (DMSO-d_6) δ 173.4, 155.4, 137.1, 131.0, 128.0, 78.1, 55.0, 35.7, 28.1; HRMS calcd for $C_{14}H_{18}NO_4Cl$ 299.0924, found 299.0943.

[η^6-[4-Chloro-1-[(2*S*)-2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-hydroxypropyl]benzene]](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (7). A solution of compound **6** (100 mg, 0.33 mmol, 1 equiv) and $(CH_3CN)_3RuCpPF_6$ (189 mg, 1.3 equiv) in 6 mL of 1,2-dichloroethane was purged at rt with Ar for 25 min and then refluxed for 5 h. The cooled solution was filtered through a thin layer of Celite to remove Ru residues and evaporated to give compound **7** (222 mg, 100%) as a brown solid. The complex was used in the next step without further purification: ^1H NMR ($CDCl_3$) δ 6.70−6.20 (m, 4H), 5.83 (br, 1H), 5.54 (s, 5H), 4.47 (m, 1H), 3.15 (dd, 1H, *J* = 13.9, 4.4 Hz), 2.86 (dd, 1H, *J* = 13.9, 9.6 Hz), 1.48 (s, 9H).

[η^6-[4-Chloro-1-[(2*S*)-2-[*N*-[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-3-[[(1*S*)-1-phenyl-2-oxo-2-[[(1*R*)-1-(3-hydroxy-4-methoxyphenyl)-2-ethoxy-2-oxoethyl]amino]-ethyl]amino]propyl]benzene]](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (9). To a stirred solution of the areneruthenium complex **7** (30.5 mg, 0.05 mmol, 1 equiv) and HOBt (10.2 mg, 1.5 equiv) in freshly distilled DMF (1.0 mL) at 0 °C was added EDCI (11.0 mg, 1.1 equiv). In a separate reaction flask, the dipeptide **8** (16.9 mg, 1.0 equiv) and diisopropylethylamine (9.6 μL, 1.1 equiv) in 1.2 mL of DMF were stirred at 0 °C for 25 min. The resulting solution was added dropwise to the solution of **7**, and the mixture was stirred for 4 h at 0 °C and 20 h at rt. The solution was then diluted with 3 mL of H_2O at 0 °C and extracted with CH_3CN/CH_2Cl_2, (1/3, 6 mL × 5). The organic layers were combined and washed with saturated $NaHCO_3$ (4 mL × 2), 1 N $KHSO_4$ (4 mL), and brine (4 mL). The organic layer was then dried over Na_2SO_4, concentrated *in vacuo*, and treated with diethyl ether to precipitate the product. The mixture was then filtered, and the residue was washed with cold diethyl ether and then dried under vacuum to provide the Ru complex **6** (33 mg, 69%) as a pale brown solid foam. Proton NMR showed it to be sufficiently pure for next step: ^1H NMR (CD_3CN) δ 7.76 (bd, 1H, *J* = 7.4 Hz), 7.57 (bd, 1H, *J* = 7.5 Hz), 7.34 (s, 5H), 6.90−6.65 (m, 5H), 6.45−6.35 (m, 2H), 6.09 (m, 2H), 5.34 (s, 5H), 5.45−5.30 (m, 1H), 4.35−4.20 (m, 1H), 4.10 (m, 2H), 3.80 (s, 3H), 2.95−2.60 (m, 2H), 1.35 (s, 9H), 1.15 (t, 3H, *J* = 7.4 Hz).

Cycloetherification Reaction. Synthesis of 3. Sodium hydride (25.0 mg, 60% in oil) was stirred with 128 mg of 2,6-di-*tert*-butylphenol in 10 mL of dry THF for 20 min to give a yellow solution. An aliquot (624 μL, 1.1 equiv) of the resulting solution was diluted with 12 mL of precooled (−78 °C) THF, and a solution of **9** (33 mg, 0.035 mmol) in 5.5 mL freshly distilled THF was added at −78 °C *via* a syringe pump over 4.5 h and the mixture then stirred for an additional 20 h at rt. The solution was concentrated *in vacuo* and was redissolved in 15 mL of freshly distilled CH_3CN, degassed by bubbling with N_2 for 25 min, and then irradiated (Rayonet, 350 nm) for 24 h under N_2. The mixture was cooled to rt, concentrated *in vacuo* to *ca.* 0.5 mL, and treated with excess Et_2O. After filtration, the ethereal filtrate was concentrated under reduced pressure to give a pale yellow residue that was purified first by thin-layer chromatography (SiO_2, EtOAc/hexanes, 1:1) to give compound

(5) It was shown interconversion between **1-F1** and **1-F2** was not successful, which rules out the possibility that **1-F1** was generated from **1-F2** after the cyclization; see ref 2.

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3 (6.5 mg, 31%). Further purification was achieved by HPLC (column: silica gel Whatman Magnum 9; eluant: hexanes/EtOAc, 1:1; flow rate: 3 mL/min; $t_R = 18.9$ min): $[\alpha]^{22}_D = +43.1$ (*c* 0.3, $CHCl_3$); R_f 0.51 (hexane/EtOAc, 1/1); ^1H NMR (CD_3CN) δ 7.50−6.80 (m, 12H), 6.12 (s, 1H), 5.60 (br, 1H), 5.39 (d, 1H, J = 12.9 Hz), 5.31 (d, 1H, J = 10.8 Hz), 4.35 (br, 1H), 4.20 (m, 2H), 3.90 (s, 3H), 3.23 (dd, 1H, J = 12.4, 5.1 Hz), 2.88 (dd, 1H, J = 12.4, 12.4 Hz), 1.40 (s, 9H), 1.25 (t, 3H, J = 7.3 Hz); HRMS calcd for $C_{33}H_{37}N_3O_8$ 603.2581, found 603.2603.

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Supporting Information Available: ^1H, and ^{13}C NMR and MS spectra for the compounds **5**, **6**, **7**, **9**, and **3** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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