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단 신

아렌-류테늄 화학을 이용한 Ristocetin A의 BCF-고리를 닮은 환형 펩티드 전구물질의 효율적인 합성

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An Efficient Synthesis of a Cyclic Peptide Precursor Mimicking BCF-Ring of Ristocetin A Using Arene-Ruthenium Chemistry

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INTRODUCTION

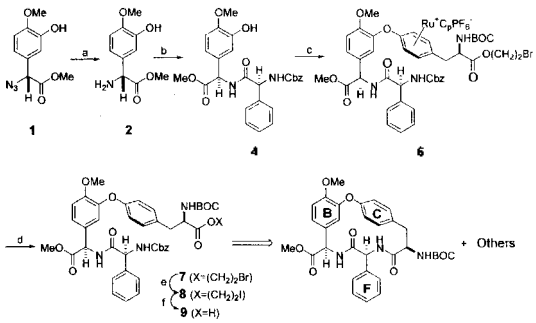
Ristocetin A and teicoplanin, structually related to vancomycin, are representative members of a large and growing family of glycopeptide antibiotics and the structural features are the sugars on the aryl rings and the presence of a heptapeptide backbone cross-linked by diaryl ether and biphenyl linkages.[1] The structural complexity as well as their therapeutic activities against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive bacteria as the drug of last-resort have made them attractive and challenging targets for synthetic chemists more than three decades,[2] and very recently the successful total syntheses of vancomycin and orienticin C (bis-dechlorovancomycin) aglycons *via* multistep sequences have been reported.[3]

The 16-membered peptide ring constitutes a very important parent skeleton of the northern bicyclic framework of glycopeptide aglycon and its synthesis has been an active research area.[4] During our study of BCF-peptide ring cyclization problem using *p*-methoxyphenylglycine as a F-component,[5] we obtained an unexpected product, which was initially thought to be an atropisomer but later confirmed to be an epimer of the phenylalanine residue by the result of cycloetherification approach.[6] Considering that phenylglycine is far more racemization-prone than phenylalanine by 30 times and *p*-methoxy substituent of the phenylglycine suppress epimerization at its chiral center,[7] it is highly desirable to make a thorough investigation whether simple phenylglycine for a F-component will be epimerized and/or will affect the epimerization at the chiral center of phenylalanine (C-component) during the cycloamidation step. Thus, in this paper, a new BCF-ring model precursor **9** with simple phenylglycine devoid of any electron-donating group on the aryl moiety, was synthesized (*Scheme* 1) for the model studies of the above-mentioned cycloamidation.

RESULTS AND DISCUSSION

The synthetic pathway to a new peptide ring precursor **9** began with α-azidophenylacetic acid methyl ester **1**, which was prepared in accordance with our previous result (*Scheme* 1).[8]

Reduction of azide to amine and simultaneous cleavage of the benzyl group of **1** using Pd-C/H_2 (1 atm) in methanol provided free phenoxy amine **2** in excellent yield. This free amine **2** was then coupled with Cbz-phenylglycine **3** in the presence of EDC and HOBT at 0 °C to furnish diastereomerically pure dipeptide **4** in 77% yield. The key coupling reaction was done as usual: Dipeptide **4** was treated first with sterically hindered base (sodium 2,6-di-*t*-butylphenoxide) and the resulting phenoxide anion was transferred into a precooled (−78 °C)



Scheme 1. (a) Pd-C (10%), H_2 (1atm), (MeOH/THF, 1/1), 24 h, rt, 79% (b) *N*-Cbz-Phenylglycine (**3**), EDC, HOBT, 0 °C, 77% (c) Sodium 2,6-di-*t*-butylphenoxide (1.0eq), THF, 0 °C (15min), Ru-complexed, *p*-chlorophenylalanine derivative (**5**), −78 °C (15min), rt (1.5h), N_2, 84% (d) Sunlamp (275W), CH_3CN, 24h, 3 times, N_2, 56% (e) NaI (5.0eq), acetone, reflux, 5h, N_2, 86% (f) SmI_2 (7.0eq), DMPU (42.0eq), THF, rt, 2.5h, N_2, 81%.

solution of Ru-complexed, *p*-chlorophenylalanine derivative **5**[5] in THF.[4e] The coupling reaction was easily confirmed by ^{1}H-NMR, showing the upfield-shift of aryloxylated, Ru-complexed aromatic proton peaks to *ca.* 6 ppm owing to aryl-ether oxygen and the presence of two amide rotamers with equal ratio. This amide rotamerism, attributed to the restricted rotation about a C-N bond and well-documented in the literatures,[9] has been consistently observed throughout free acid **9** as our related studies.[5,8] Ligand exchange reaction of **6** under photolytic conditions (CH_3CN, 275W, Quartz cell, 24 h, 3 times)[10] gave the demetallated, diaryl ether **7** in *ca.* 56% combined yield. In order to obtain the free carboxylic acid for cyclolamidation reaction, bromoethyl ester **7** was treated with NaI in dry acetone to give iodoethyl ester **8**, which was then reacted with SmI_2/DMPU to afford the desired free acid **9** in excellent yield. In conclusion, a new BCF-ring precursor **9** has been successfully prepared by utilizing our well-established protocols, and the cycloamidation study using various coupling reagents is in progress and will be reported in due course.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are not corrected. IR-spectra were recorded on a Nicolet Impact 400 using $CHCl_3$ or CH_2Cl_2 as a solvent. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded in $CDCl_3$, DMSO-d_6 on a Varian Gemini-300 spectrometer using TMS or $CHCl_3$ (77.0 ppm) as an internal standard. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. EI, HR- and LR-FAB mass spectra were recorded on a Kratos MS-25A instrument. Flash column chromatography was carried out on E. Merck 320-400 mesh silica gel and solvents are reported as V/V precent mixtures. THF was distilled from sodium benzophenone ketyl; CH_2Cl_2, Et_3N and CH_3CN were distilled from calcium hydride. *n*-Butyllithium in hexane was obtained from Aldrich Co., and standardized according to the reported method.[11] All other commercial reagents were purchased from commercial sources and were used as received unless otherwise noted. The synthetic procedures for compound **6**, **7**, **8**, **9** were analogous to those described elsewhere.[5]

(2*R*)-2-Amino-2-(3-hydroxy-4-methoxy)phenylacetic acid Methyl Ester (2). (2*R*)-2-Azido-2-(3-benzyloxy-4-methoxy)phenylacetic acid methyl ester **1**[8] (394.8 mg, 1.21 mmol) was added to a stirred slurry of Pd-C (40 mg) in 40 mL of organic solvent (MeOH/THF, 1/1) and the resulting mixture was stirred for 1 h under H_2 (1 atm), filtered through a celite pad (1×2 cm) and the filtered cake was washed with MeOH. The combined organic layers were concentrated *in vacuo* to afford a pale-brown solid, which was purified by flash column chromatography on silica gel (EtOAc then EtOAc/MeOH, 95/5). Yield : 202.2 mg (79%); mp 151.5-153.5 °C; $[\alpha]^{24}_D$ -106.6° (c 0.56, $CHCl_3$); R_f 0.27 (hexanes/EtOAc, 5/5); IR ($CHCl_3$) 3697, 3542, 3029, 2963, 1736, 1598, 1515, 1223 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.94 (d, 1H, *J*=1.8 Hz, *aromatic*-H^2), 6.86 (dd, 1H, *J*=7.8, 1.8 Hz, *aromatic*-H^6), 6.82 (d, 1H, *J*=7.8 Hz, *aromatic*-H^5), 4.52 (s, 1H, ArC*H*CO_2), 3.88 (s, 3H, -OCH_3), 3.70 (s, 3H, -OCH_3); ^{13}C-NMR ($CDCl_3$) δ174.5, 146.4, 145.8, 133.5, 118.4, 113.1, 110.7, 58.2, 55.9, 52.3; HRMS calcd for $C_{10}H_{13}NO_4$ 211.0845, found 211.0849.

***N*-(Phenylmethoxy)carbonyl-L-phenylglycine (3).** L-Phenylglycine (0.75 g, 4.96 mmol) was added to an aqueous solution of Na_2CO_3 (1.31 g, 12.4 mmol) in 38 mL of H_2O in one portion and the resulting slurry was stirred vigorously until the acid was completely dissolved, and the solution was cooled to 0 °C with an ice bath. To this was added benzyloxycarbonylchloride (0.90 mL,

1.27 equiv) by syringe and the resulting mixture was stirred vigorously for 2 h at 0 °C, then for 22 h at rt. The solution was washed with Et_2O (10 mL×3) and the aqueous layer was acidified to pH 2 with 10% HCl. The white solid formed was filtered, washed well with cold H_2O, and then dissolved in 50 mL of EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. Purification of the crude product from flash column chromatography on silica gel (hexanes/EtOAc, 5/5) furnished a white powder. Yield: 1.16 g (82%); mp 130.5-132.5 °C; $[\alpha]^{23}_D$ +120.7° (c, 0.65, EtOAc); R_f 0.21 (EtOAc/MeOH, 9/1); IR ($CHCl_3$) 3436, 3026, 1725, 1667, 1497 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.87 (bs, 1H, -CO_2H), 8.12 (d, 1H, *J*=8.1 Hz, -N*H*Cbz), 7.42-7.29 (m, 10H, *aromatic* Hs), 5.18 (d, 1H, *J*=8.1 Hz, -C*H*CO_2H), 5.05 (s, 2H, -OCH_2Ph); ^{13}C NMR ($CDCl_3$) δ 172.1, 155.9, 137.1, 136.9, 128.4, 128.3, 127.9, 127.7, 65.6, 58.1; HRMS calcd for $C_{16}H_{15}NO_4$ 285.1001, found 285.1001.

***N*-[*N*-(Phenylmethoxy)carbonyl-L-phenylglycinyl]-D-(3-hydroxy-4-methoxy)phenylglycine Methyl Ester (4).** A mixture of crude α-aminoacid methyl ester **2** (186.0 mg, 0.88 mmol), *N*-Cbz-phenylglycine **3** (276.3 mg, 1.1 equiv) and HOBT (142.9 mg, 1.2 equiv) was dissolved in 10 mL of mixed solvent (THF/DMF, 1/1) and the resulting solution was cooled to 0 °C under N_2. To this solution was added EDC (185.8 mg, 1.10 equiv) in one portion and the resulting mixture was stirred for 2 h at 0 °C, then 20 h at rt under N_2. The solvent was evaporated *in vacuo* and the residue was extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were washed with $NaHSO_3$ (10 mL, 1N), brine, dried over $MgSO_4$, and concentrated. Flash column chromatography of the crude product on silica gel (hexanes/EtOAc, 5/5) and subseqent recrystallization from hexanes/THF (6/4) afforded 325.1 mg (77%) of diastereomerically pure product **4** as a white powder. mp 187.5-189.5 °C; $[\alpha]^{23}_D$ -7.1 (c 0.42, $CHCl_3$); R_f 0.41 (hexanes/EtOAc, 4/6); IR ($CHCl_3$) 3545, 3415, 3033, 2970, 1738, 1689, 1684, 1512, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33-7.22 (m, 10H, *aromatic* Hs of C_6H_5CHNH- and Cbz), 6.71-6.58 (m, 4H, *aromatic* Hs of Ar^{OMe} overlapped with -N*H*Cbz), 6.00 (bs, 1H, Ar^{OMe}CHN*H*-), 5.58 (s, 1H, *Phenolic*-H), 5.40 (d, 1H, *J*=6.8 Hz, -C*H*NHCbz), 5.29 (bs, 1H, Ar^{OMe}C*H*NH-), 5.10 (d, 1H, *J*=12.3 Hz, -OC*H*HPh), 5.02 (d, 1H, *J*=12.3 Hz, -OCH*H*Ph), 3.84 (s, 3H, -OCH_3), 3.70 (s, 3H, -OCH_3); ^{13}C NMR ($CDCl_3$) δ 170.9, 168.9, 155.6, 146.8, 145.9, 137.7, 136.1, 129.1, 128.6, 128.5, 128.1, 127.4, 118.8, 113.0, 110.6, 67.0, 58.7, 56.2, 55.9, 52.9; HRMS calcd for $C_{25}H_{26}N_2O_7$ 478.1740, found 478.1751.

[η⁶-(2R,2'R)-4-[2-Methoxy-5-[1-[*N*-(phenylmethoxy)carbonyl-L-phenylglycinyl]amino]-2-methoxy-2-oxoethyl]phenoxy]-1-[3-(2-bromoethoxy)-2-[(1,1-dimethylethoxy)carbonyl]amino-3-oxopropyl]-benzene] (η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (6). Dipeptide **4** was coupled with chloroarene-Ru complex **5**[5] as usual to afford aryloxylated, arene-Ru complex **6** as a pale-brown solid foam. Mixture of two amide rotamers. Yield: 87%; IR ($CHCl_3$) 3684, 3421, 3019, 2987, 1741, 1707, 1602, 1511, 1500, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ7.42-6.80 (m, 14H, *aromatic* Hs of Ar^{OMe}, Ar, Cbz, overlapped with -N*H*Cbz), 6.46-5.82 (m, 5H, *aromatic* Hs Ar^{Ru+} overlapped with Ar^{OMe}CHN*H*-), 5.54-5.00 (m, 9H, Ar^{OMe}C*H*NH-, -C*H*NHCbz, Cp, -OCH_2Ph, -N*H*BOC), 4.53-4.41 (m, 3H, -CH_2CH$_2$Br overlapped with -C*H*NHBOC), 3.84 (s, 3/2H, -OCH_3), 3.82 (s, 3/2H, -OCH_3), 3.77 (s, 3/2H, -OCH_3), 3.70 (s, 3/2H, -OCH_3), 3.11-2.80 (m, 2H, Ar^{Ru+}CH_2-), 1.42 (s, 9H, -*BOC*).

(2*R*)-3-[4-[3-(2-Bromoethoxy)-2-[(1,1-dimethylethoxy)carbonyl]-amino-3-oxopropyl]phenoxy]-4-methoxy-*N*-[*N*-(phenylmethoxy)-carbonyl-L-phenylglycinyl]-D-phenylglycine Methyl Ester (7). Aryloxylated, arene-Ru-complex **6** was demetallated three times (24 h×3) as usual to give the pale-brown residue, which was purified by flash column chloromatography (SiO_2, hexanes/EtOAc, 6/4) to provide **7** as an off-white solid. Mixture of two amide rotamers. Total yield: 56%; $[\alpha]^{23}_D$ +34.9 (c, 0.45, $CHCl_3$); R_f 0.30 (hexanes/EtOAc, 5/5); IR ($CHCl_3$) 3440(br), 3020, 2986, 1774, 1710, 1693, 1512, 1223, 1177 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34-6.72 (m, 18H, *aromatic* Hs overlapped with -N*H*Cbz), 6.09 (bs, 1H, Ar^{OMe}CHN*H*-), 5.46-5.32 (m, 2H, two doublets (21/2H) of -C*H*NHCbz overlapped with Ar^{OMe}C*H*-: 5.44 (d, 1/2H, *J*=6.8 Hz, -C*H*NHCbz), 5.39 (d, 1/2H, *J*=6.8 Hz, -C*H*NHCbz)), 5.15-4.99 (m, 3H, two doublets (21H) of -OCH_2Ph overlapped with -N*H*BOC: 5.07 (d, 1H, *J*=12.2 Hz, -OC*H*HPh), 5.01 (d, 1H, *J*=12.2 Hz, -OCH*H*Ph)), 4.60-4.56 (m, 1H, -C*H*NHBOC), 4.43-4.36 (m, 2H, -CH_2CH$_2$Br), 3.79 (s, 3/2H, -OCH_3), 3.76 (d, 3/

2H, -OCH_3), 3.68 (s, 3/2H, -OCH_3), 3.62 (s, 3/2H, -OCH_3), 3.46-3.41 (m, 2H, -CH_2CH_2Br), 3.07 (bs, 2H, -CH_2CHNHBOC), 1.41 (s, 9H, -*BOC*); ^{1}H NMR (DMSO-d_6) δ 9.08 (d, 1/2H, *J*=7.7 Hz), 9.01 (d, 1/2H, *J*=7.7 Hz), 7.96 (d, 1H, *J*=8.8 Hz), 7.43-6.95 (m, 16H), 6.73 (d, 1H, *J*=8.4 Hz), 6.68 (d, 1H, *J*=8.4 Hz), 5.46 (d, 1/2H, *J*=9.2 Hz), 5.42 (d, 1/2H, *J*=9.1 Hz), 5.35 (d, 1/2H, *J*=3.4 Hz), 5.33 (d, 1/2H, *J*=3.2 Hz), 5.02 (s, 2/2H, -OCH_2Ph), 5.01 (s, 2/2H, -OCH_2Ph), 4.41-4.29 (m, 2H, -CH_2CH$_2$Br), 4.18-4.11 (m, 1H, -C*H*NHBOC), 3.72 (s, 3/2H, -OCH_3), 3.70 (s, 3/2H, -OCH_3), 3.61 (s, 3H, -OCH_3), 3.52 (m, 2H, -CH$_2$CH_2Br), 2.97 (dd, 1H, *J*=14.0, 4.7 Hz, -C*H*HCHNHBOC), 2.83 (dd, 1H *J*=14.0, 10.0 Hz, -CH*H*CHNHBOC), 1.32 (s, 9H, -*BOC*); HRMS FAB (*m*-NBA) calcd for (MH)$^+$ (Br^{79}, Br^{81}) 848.2394, 850.2373, found (MH$^+$) (Br^{79}, Br^{81}) 848.2349, 850.2358; Anal. calcd for $C_{32}H_{46}BrN_3O_{11}$:C, 59.44; H, 5.46; N, 4.95. Found:C, 59.80; H, 5.70;N, 4.80.

(2*R*)-[3-[4-[2-[(1,1-Dimethylethoxy)carbonyl]amino-3-oxo-3-(2-iodoethoxy)propyl]phenoxy]-*N*-[*N*-(phenylmethoxy)carbonyl-L-phenylglycinyl]]-D-phenylglycine Methyl Ester (8). Halide exchange reaction of bromoethyl ester **7** as usual afforded iodoethyl ester **8** as an off-white solid form after flash column chromatography (SiO_2, hexanes/EtOAc, 5/5). Mixture of two amide rotamers. Yield: 86%; $[\alpha]^{26}_D$ +34.3° (c 0.65, $CHCl_3$); R_f 0.35 (hexanes/EtOAc, 5/5); IR ($CHCl_3$) 3431(br), 3018, 2989, 1744, 1716, 1507, 1218, 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35-6.72 (m, 18H, *aromatic* Hs overlapped with -N*H*Cbz), 6.15 (bs, 1H, Ar^{OMe}CHN*H*-), 5.49-5.39 (m, 2H, Two doublets (2×1/2H) of -C*H*NHCbz overlapped with Ar^{OMe}C*H*-: (5.45 (d, 1/2H, *J*=7.0 Hz, -C*H*NHCbz), 5.40 (d, 1/2H, *J*=6.9 Hz, -C*H*NHCbz)), 5.14-4.97 (m, 3H, Two doublets (2×1H) of -CO$_2$CH_2Ph overlapped with -C*H*NHBOC: (5.08 (d, 1H, *J*=4.7 Hz, -OC*H*HPh), 5.02 (d, 1H, *J*=4.7 Hz, -OCH*H*Ph)), 4.57 (m, 1H, -C*H*NHBOC), 4.35-4.30 (m, 2H, -CH_2CH$_2$I), 3.77 (s, 3/2H, -OCH_3), 3.75 (s, 3/2H, -OCH_3), 3.67 (s, 3/2H, -OCH_3), 3.61 (s, 3/2H, -OCH_3), 3.23-3.21 (m, 2H, -CH$_2$CH_2I), 3.19-3.06 (m, 2H, -CH_2CHNHBOC), 1.41 (s, 9H, -*BOC*); HRMS FAB (*m*-NBA) cacld for (MH)$^+$ 896.2257, found 896.2291; Anal. cacld for $C_{42}H_{46}N_3O_{11}I$: C, 56.32; H, 5.18; N, 4.69. Found:C, 56.61; H, 5.36; N, 4.56.

(*R*)-4-[2-Methoxy-5-[[1-[*N*-(phenylmethoxy)carbonyl-L-phenyl-glycinyl]amino]-2-methoxy-2-oxoethyl]phenoxy]-*N*-(1,1-dimethyl-ethoxy)cabonyl-D-phenylalanine (9). Deprotection of 2-iodoethyl ester **8** into carboxylic acid **9** was accomplished by using SmI_2 and DMPU as usual. Purification of the crude product by flash column chromatography on SiO_2 (hexanes/EtOAc/AcOH, 35/65/1% then CH_2Cl_2/EtOAc,70/30/1%) provided 58.4mg (81%) of pure acid **9** as a white solid powder. Mixture of two amide rotamers. Yield: 81%; R_f 0.42 (hexanes/EtOAc/AcOH, 20/80/1%); $[\alpha]^{22}_D$ +24.1° (c 0.53, $CHCl_3$); IR ($CHCl_3$) 3683, 3627, 3428(br), 3020, 2981, 1737, 1704(br), 1686, 1509, 1429, 1222, 1048, 929 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38-6.69 (m, 18H, *aromatic* Hs overlapped with -N*H*Cbz), 6.36 (d, 1H, *J*=2.5 Hz, Ar^{OMe}CHN*H*-), 5.41 (bs, 1H, Ar^{OMe}C*H*NH-), 5.36 (d, 1H, *J*=7.3 Hz, -C*H*NHCbz), 5.33 (d, 1H, *J*=7.3 Hz, -N*H*BOC), 5.05 (s, 2H, -OCH_2Ph), 4.33-4.28 (m, 1H, -C*H*NHBOC), 3.77 (s, 3/2H, -OCH_3), 3.74 (s, 3/2H, -OCH_3), 3.66 (s, 3/2H, -OCH_3), 3.59 (s, 3/2H, -OCH_3), 3.08 (dd, 1H, *J*=13.7, 5.0 Hz, ArC*H*HCHCO$_2$H), 2.92-2.83 (m, 1H, ArCH*H*CH-), 1.36 (s, 9H, -*BOC*); HRMS FAB (*m*-NBA) calcd for $C_{40}H_{44}N_3O_{11}$ (MH)$^+$ 742.2976, found 742.3000; Anal. calcd for $C_{40}H_{43}N_3O_{11}$: C, 64.77; H, 5.84; N, 5.66. Found C, 64.66; H, 6.26; N, 5.51.

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