Asymmetric Synthesis of Orthogonally Protected L-*threo*-β-Hydroxyasparagine

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In the course of efforts on the total synthesis of the novel antimicrobial lipoglycodepsipeptide ramoplanin A2 (**1**, Figure 1), the preparation of the unnatural amino acid L-threo-β-hydroxyasparagine (L-threo-β-OH-Asn) was required as a key subunit.[1] The isomers of β-OH-Asn were originally isolated from human urine and synthesized as a racemic mixture that was separated by resolution.[2] Although there are several reports of the enantioselective synthesis of isomers of β-hydroxyaspartic acid and erythro β-hydroxyasparagine, no descriptions of an asymmetric synthesis of threo β-hydroxyasparagine have been disclosed.[3] Herein, we describe an effective asymmetric synthesis of L-threo-FmocNH-β-OH-Asn(Trt)-OBn (**2**), suitably protected for incorporation into a projected total synthesis of ramoplanin A2, via the Sharpless asymmetric aminohydroxylation (AA) reaction.

The approach to the orthogonally protected L-threo-β-OH-Asn rested on the knowledge that cinnamate esters are excellent substrates for the Sharpless AA reaction, that the trans olefin geometry would fix the desired threo stereochemistry, and that an aromatic group can serve as an effective masking group for a carboxylic acid.[4,5] Thus, the AA reaction on methyl 4-methoxycinnamate (**3**) produced the amino alcohol **4** in 64% yield and over 99% ee (Scheme 1).[6] Sequential protection of the alcohol with *tert*-butyldimethylsilyl triflate (TBDMSOTf), single step *N*-Cbz/Boc exchange, and direct aminolysis of the methyl ester provided **7** in 68% overall yield with no evidence of epimerization. The latent carboxylic acid was unmasked by treating **7** with ruthenium tetraoxide generated in situ and subsequently protected as a benzyl ester to provide **9** in 57% and 84% yields, respectively.[5]

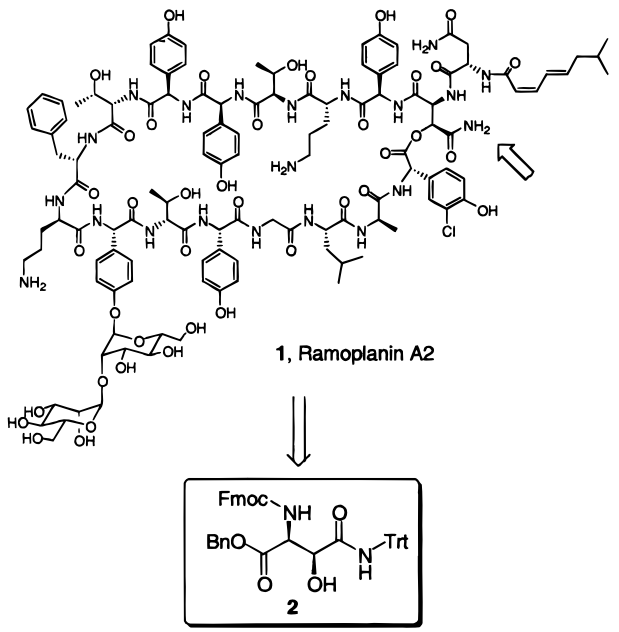
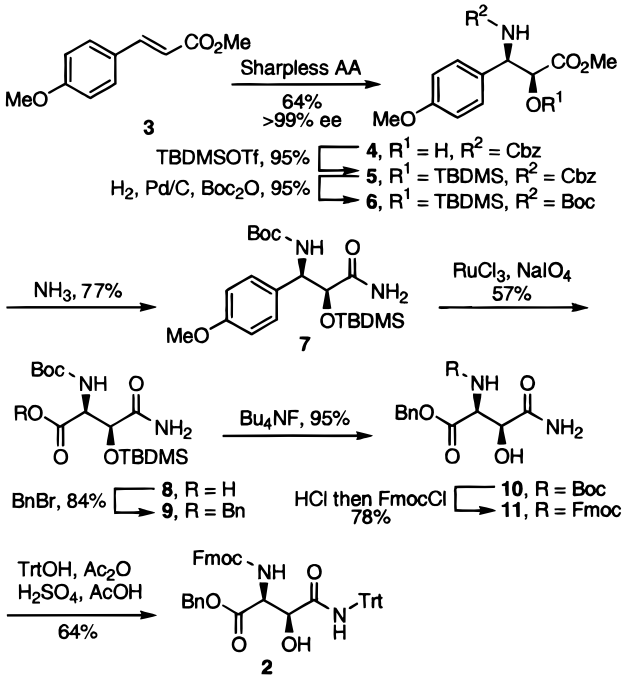


Figure 1.

Scheme 1



The silyl protecting group was then removed with Bu_4NF to provide **10** in 95% yield.

The unprotected carboxamide of an asparagine residue is known to undergo side reactions during peptide coupling, i.e., intramolecular cyclization upon activation of the carboxylic acid leading to a succinimide byproduct, or dehydration to a nitrile. To prevent the formation of such byproducts, additional modifications to **10** were prepared which contain a suitable protecting group such as triphenylmethyl or trityl (Trt). The Boc protecting group was removed quantitatively and the resulting amine salt was reacted with 9-fluorenylmethyl chloro-

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(6) The ee was established by HPLC on a Chiracel OD column (0.46 × 25 cm, 10% *i*-PrOH/hexane, flow rate = 0.6 mL/min): t_R((2*S*,3*R*)-**4**) = 35.7 min, t_R((2*R*,3*S*)-**4**) = 39.5 min.

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formate (FmocCl) to give the Fmoc-protected β-OH-Asn **11** in 78% yield. The acidic conditions developed by Sieber and co-workers to introduce the trityl group were modified to minimize the formation of an acetate byproduct due to the use of acetic anhydride as dehydrating agent.[7] Thus, compound **11** was treated with trityl alcohol and acetic anhydride under acidic conditions to provide trityl-protected residue **2** in 64% yield.

In summary, the asymmetric synthesis of L-threo-FmocNH-β-OH-Asn(Trt)-OBn (**2**) and several related protected asparagine residues (**8**−**11**) was accomplished from methyl 4-methoxycinnamate via the Sharpless asymmetric aminohydroxylation reaction. With three orthogonal protecting groups, asparagine **2** is an attractive building block for further synthetic endeavors. Efforts on the incorporation of **2** into the total synthesis of ramoplanin A2 are in progress and will be disclosed in due course.

Experimental Section

Methyl (2*S*,3*R*)-3-[(Benzyloxycarbonyl)amino]-2-hydroxy-3-(4-methoxyphenyl) propionate (4). Benzyl carbamate (1.88 g, 12.4 mmol) was dissolved in 14 mL of *n*-PrOH. A freshly prepared solution of NaOH (0.488 g, 12.2 mmol) in 22 mL of H_2O was added to this stirred solution, followed by a freshly prepared solution of *tert*-butyl hypochlorite (1.324 g, 12.2 mmol) and a solution of $(DHQD)_2PHAL$ (160 mg, 0.2 mmol) in 8 mL of *n*-PrOH. The reaction vessel was immersed in a room-temperature water bath and stirred for a few minutes. Methyl 4-methoxycinnamate **3** (1.00 g, 5.2 mmol) was added, followed by $K_2OsO_2(OH)_4$ (14.7 mg, 0.04 mmol). The reaction mixture was stirred for 1 h at 0 °C, and the reaction mixture was homogeneous at this point. The homogeneous mixture was stirred at 0 °C for an additional 1 h by which it transformed into a pale yellow slurry. The crystalline precipitate was isolated by filtration. One wash with ice-cold EtOH−H_2O (1:1, 5 mL) yielded 4 as a white solid (1.20 g, 64%, >99% ee):[6] mp 114−115 °C; $[\alpha]^{23}_D$ −5.3 (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.33−7.28 (m, 7H), 6.86 (d, 2H, *J* = 8.8 Hz), 5.58 (d, 1H, *J* = 8.8 Hz), 5.19 (d, 1H, *J* = 8.8 Hz), 5.08 (d, 1H, *J* = 12.5 Hz), 5.04 (d, 1H, *J* = 12.5 Hz), 4.44 (s, 1H), 3.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.3, 136.3, 130.9, 128.5, 128.2, 128.1, 128.0, 114.1, 73.5, 67.0, 56.0, 55.3, 53.1; MALDI−FTMS (DHB) *m*/*z* 382.1269 (M + Na^+, $C_{19}H_{21}NO_6$ requires 382.1267). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.44; H, 5.92; N, 3.85.

Methyl (2*S*,3*R*)-3-[(Benzyloxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)propionate (5). A solution of **4** (1.00 g, 2.78 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with 2,6-lutidine (0.97 mL, 8.35 mmol) followed by TBDMSOTf (0.77 mL, 3.34 mmol). The reaction mixture was stirred at 0 °C for 2.5 h. The reaction mixture was diluted with EtOAc (20 mL) and washed sequentially with 10% aqueous HCl (10 mL), H_2O (15 mL), and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc−hexane) provided **5** as a clear oil (1.25 g, 95%): $[\alpha]^{23}_D$ −0.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (s, 5H), 7.19 (d, 2H, *J* = 8.8 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 5.75 (d, 1H, *J* = 8.8 Hz), 5.16 (d, 1H, *J* = 8.8 Hz), 5.06 (s, 2H), 4.34 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 0.75 (s, 9H), −0.16 (s, 3H), −0.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.7, 159.1, 155.6, 136.4, 131.9, 131.4, 128.5, 128.2, 127.6, 113.8, 75.7, 66.9, 57.1, 55.3, 52.2, 25.5, 18.2, −5.6; MALDI−FTMS (DHB) *m*/*z* 496.2123 (M + Na^+, $C_{25}H_{35}NO_6Si$ requires 496.2131). Anal. Calcd for $C_{25}H_{35}NO_6Si$: C, 63.40; H, 7.45; N, 2.96. Found: C, 63.69; H, 7.71; N, 3.06.

Methyl (2*S*,3*R*)-3-[(*tert*-Butyloxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-3-(4-methoxyphenyl)propionate (6). A solution of **5** (2.50 g, 5.28 mmol) and Boc_2O (1.33 mL, 5.80 mmol) in CH_3OH (100 mL) was treated with 10% Pd−C (50 mg). The resulting black suspension was stirred under H_2 (1 atm) at 25 °C for 6 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. Flash chromatography (SiO_2, 30% EtOAc−hexane) provided **6** as a white solid (2.20 g, 95%): mp 63−64 °C; $[\alpha]^{23}_D$ −1.6 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 5.47 (d, 1H, *J* = 8.8 Hz), 5.10 (d, 1H, *J* = 8.8 Hz), 4.32 (s, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 1.39 (s, 9H), 0.75 (s, 9H), −0.18 (s, 3H), −0.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 159.4, 155.6, 132.2, 128.0, 114.1, 80.0, 76.2, 57.0, 55.7, 52.6, 28.7, 27.8, 25.9, 18.6, −5.2, −5.5; MALDI−FTMS (DHB) *m*/*z* 462.2280 (M + Na^+, $C_{22}H_{37}NO_6Si$ requires 462.2288). Anal. Calcd for $C_{22}H_{37}NO_6Si$: C, 60.11; H, 8.48; N, 3.19. Found: C, 60.10; H, 8.31; N, 3.10.

(1*R*,2*S*)-[2-[(*tert*-Butyldimethylsilyl)oxy]-2-carbamoyl-1-(4-methoxyphenyl)ethyl]carbamic Acid *tert*-Butyl Ester (7). A sample of **6** (2.20 g, 5.0 mmol) was dissolved into CH_3OH (25 mL), and NH_3 was bubbled through the CH_3OH solution at 0 °C until saturation. The tube was sealed and stirred at 25 °C for 7−10 days. The volume of the reaction mixture was reduced to half under reduced pressure and directly subjected to flash chromatography (SiO_2, 25% EtOAc−hexane) which provided **7** as a white solid (1.46 g, 69%; 69−77%): mp 79−80 °C; $[\alpha]^{23}_D$ −9.1 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (d, 2H, *J* = 8.5 Hz), 6.81 (d, 2H, *J* = 8.5 Hz), 6.19 (s, 1H), 6.02 (d, 1H, *J* = 8.8 Hz), 5.43 (s, 1H), 4.93 (dd, 1H, *J* = 9.2, 3.0 Hz), 4.29 (d, 1H, *J* = 3.3 Hz), 3.77 (s, 3H), 1.41 (s, 9H), 0.89 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 159.4, 155.3, 131.0, 128.6, 113.9, 80.0, 76.1, 56.9, 55.7, 28.8, 26.2, 18.5, -4.7, -5.1; MALDI−FTMS (DHB) *m*/*z* 447.2291 (M + Na^+, $C_{21}H_{36}N_2O_5Si$ requires 447.2291). Anal. Calcd for $C_{21}H_{36}N_2O_5Si$: C, 59.40; H, 8.55; N, 6.60. Found: C, 59.24; H, 8.29; N, 6.39.

L-threo-BocNH-β-OTBDMS-Asn (8). A solution of $NaIO_4$ (7.0 g, 33 mmol) in CH_3CN/H_2O (15/24 mL) was treated with a solution of **7** (1.00 g, 2.35 mmol) in CCl_4 (15 mL) followed by $RuCl_3 \cdot 3H_2O$ (10 mg, 0.04 mmol) and $NaHCO_3$ (50 mg). The reaction mixture was stirred vigorously at 25 °C for 24 h. The reaction mixture was extracted into saturated aqueous $NaHCO_3$ and washed with CH_2Cl_2. The aqueous layer was acidified with the addition of 10% aqueous HCl to pH 2−3 in an ice-bath and extracted with EtOAc several times. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to provide **8** as a white solid (485 mg, 57%): mp >250 °C (dec); $[\alpha]^{23}_D$ −142 (*c* 0.65, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 4.60 (d, 1H, *J* = 2.2 Hz), 4.33 (d, 1H, *J* = 2.21), 1.42 (s, 9H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.0, 173.1, 157.8, 81.0, 75.4, 58.3, 28.6, 26.2, 19.1, −5.0, −5.2; IR (film) ν_{max} 2930, 1720, 1502 cm^{-1}; MALDI−FTMS (DHB) *m*/*z* 385.1782 (M + Na^+, $C_{15}H_{30}N_2O_6Si$ requires 385.1765).

L-threo-BocNH-β-OTBDMS-Asn-OBn (9). A solution of **8** (405 mg, 1.15 mmol) in DMF (5.5 mL) at 0 °C was treated with $NaHCO_3$ (190 mg, 2.25 mmol) and benzyl bromide (0.54 mL, 4.5 mmol). The reaction mixture was stirred at 0 °C for 2 h and was allowed to warm to 25 °C and stirred for 24 h before 15 mL of H_2O was added at 0 °C. The mixture was extracted with EtOAc (15 mL) and washed with H_2O (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc−hexane) provided **9** as a white solid (428 mg, 84%): mp 45−47 °C; $[\alpha]^{23}_D$ −5.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.36 (m, 5H), 6.38 (d, 1H, *J* = 9.6 Hz), 5.19 (d, 1H, *J* = 12.5 Hz), 5.13 (d, 1H, *J* = 12.5 Hz), 4.63 (d, 1H, *J* = 2.6 Hz), 4.58 (dd, 1H, *J* = 9.5 Hz, 2.2 Hz), 1.41 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz) δ 175.7, 171.4, 157.8, 136.6, 129.8, 129.6, 129.5, 81.2, 75.0, 68.6, 58.9, 28.6, 26.2, 19.0, −4.9, −5.2; IR (film) ν_{max} 2930, 1698, 1498, 1472 cm^{-1}; MALDI−FTMS (DHB) *m*/*z* 475.2262 (M + Na^+, $C_{22}H_{36}N_2O_6Si$ requires 475.2240). Anal. Calcd for $C_{22}H_{36}N_2O_6Si$: C, 58.38; H, 8.02; N, 6.19. Found: C, 58.59; H, 8.41; N, 5.71.

L-threo-BocNH-β-OH-Asn-OBn (10). A solution of **9** (727 mg, 1.61 mmol) in THF (10 mL) at 0 °C was treated with a premixed solution of 1 M solution of Bu_4NF in THF (4.8 mL, 4.8 mmol) and HOAc (0.276 mL, 4.8 mmol). The reaction mixture was stirred at 0 °C for 30 min, diluted with EtOAc (20 mL), and washed successively with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NH_4Cl (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 75% EtOAc−hexane) provided **10** as a

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white solid (515 mg, 95%): mp 134−135 °C; $[\alpha]^{23}_D$ −17 (*c* 1.5, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.39−7.30 (m, 5H), 5.19 (s, 2H), 4.69 (d, 1H, J = 2.0 Hz), 4.58 (d, 1H, J = 2.0 Hz), 1.40 (s, 9H); ^{13}C NMR (CD_3OD, 125 MHz) δ 178.8, 174.3, 160.4, 139.4, 131.8, 131.5, 131.4, 83.2, 75.0, 70.5, 60.4, 30.9; IR (film) ν_{max} 3346, 2976, 1684, 1561 cm^{-1}; MALDI−FTMS (DHB) *m*/*z* 361.1370 (M + Na^+, $C_{16}H_{22}N_2O_6$ requires 361.1369). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.44; H, 6.20; N, 8.12.

L-threo-FmocNH-*β*-OH-Asn-OBn (11). A solution of **10** (436 mg, 1.29 mmol) in EtOAc (20 mL) was treated with 4 N HCl−EtOAc (6.5 mL). The reaction mixture was stirred for 50 min, and the volatiles were removed. The resulting white residue was dissolved in 1,4-dioxane (20 mL) and H_2O (20 mL), and the solution was treated with $NaHCO_3$ (650 mg, 7.74 mmol) and FmocCl (435 mg, 1.68 mmol). The reaction mixture was stirred for 2 h and partitioned between saturated aqueous $NaHCO_3$ (30 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 75% EtOAc−hexane) provided **11** as a white solid (463 mg, 78%): mp 175−176 °C; $[\alpha]^{23}_D$ −13 (*c* 0.45, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.77 (d, 2H, J = 7.4 Hz), 7.64 (d, 2H, J = 1.8 Hz), 7.38−7.26 (m, 9H), 5.23 (d, 1H, J = 12.5 Hz), 5.19 (d, 1H, J = 12.5 Hz), 4.82 (d, 1H, J = 1.8 Hz), 4.64 (d, 1H, J = 1.8 Hz), 4.35 (dd, 1H, J = 9.9 Hz, 6.6 Hz), 4.22 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 176.4, 171.7, 145.2, 145.1, 142.5, 142.4, 137.0, 129.5, 129.2, 129.1, 128.8, 128.7, 128.2, 128.2, 126.3, 126.2, 120.1, 72.8, 68.4, 68.3, 58.6, 48.2; IR (film) ν_{max} 3331, 1691, 1653, 1539 cm^{-1}; MALDI−FTMS (DHB) *m*/*z* 483.1520 (M + Na^+, $C_{26}H_{24}N_2O_6$ requires 483.1532). Anal. Calcd for $C_{26}H_{24}N_2O_6$: C, 67.82; H, 5.25; N, 6.08. Found: C, 67.64; H, 5.00; N, 6.03.

L-threo-FmocNH-*β*-OH-Asn(Trt)-OBn (2). A solution of **11** (53 mg, 0.115 mmol) and trityl alcohol (300 mg, 1.15 mmol) in HOAc (0.4 mL) at 50 °C was treated successively with concentrated sulfuric acid (4 μL, 0.069 mmol) and acetic anhydride (27 μL, 0.288 mmol). The reaction mixture was stirred at 50 °C for 2.5 h and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was further extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 33% EtOAc−hexane) afforded **2** as a white solid (52 mg, 64%): mp 74−75 °C; $[\alpha]^{23}_D$ −14 (*c* 0.93, $CHCl_3$); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.78 (d, 1H, J = 7.7 Hz), 7.77 (d, 1H, J = 7.7 Hz), 7.66 (d, 1H, J = 7.7 Hz), 7.61 (d, 1H, J = 7.7 Hz), 7.38−7.17 (m, 24H), 5.21 (d, 1H, J = 12.5 Hz), 5.18 (d, 1H, J = 12.5 Hz), 4.80 (d, 1H, J = 2.2 Hz), 4.65 (d, 1H, J = 2.2 Hz), 4.51 (dd, 1H, J = 13.6, 9.9 Hz), 4.17 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 172.2, 171.8, 158.9, 145.7, 145.3, 145.0, 142.6, 142.5, 137.1, 129.9, 129.5, 129.2, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 128.1, 126.5, 126.2, 120.9, 120.8, 73.4, 71.5, 68.6, 68.3, 58.6, 48.2; IR (film) ν_{max} 3366, 3060, 1698, 1668, 1495 cm^{-1}; MALDI−FTMS (DHB) *m*/*z* 752.2621 (M + Na^+, $C_{45}H_{38}N_2O_6$ requires 752.2627). Anal. Calcd for $C_{45}H_{38}N_2O_6$: C, 76.90; H, 5.45; N, 3.99. Found: C, 76.77; H, 5.81; N, 3.68.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **8** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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