Application of Ruthenium-Induced Macrocyclization for the Construction of Macrocyclic Depsipeptides

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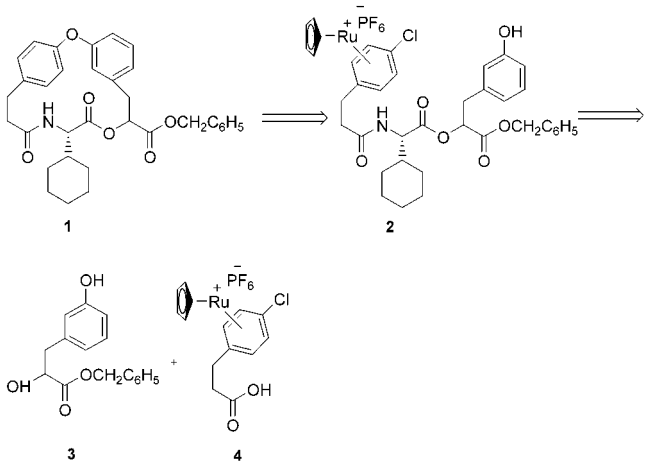
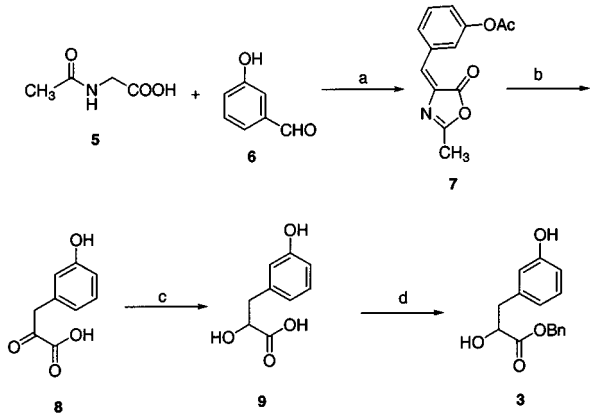
Abstract: The synthesis of a biaryl ether containing macrocyclic depsipeptide **1** was achieved in 6% overall yield. The desired macrocycle was constructed by cyclization of a phenol into η^6-ruthenium complex. The ruthenium metal was subsequently photolytically deprotected to obtain the macrocycle **1**.

Depsipeptides are isosteric replacements of amides that lack the hydrogen bond acceptor, a structural modification avidly incorporated in a wide variety of natural products and pharmaceutical intermediates.[1] The choice of depsipeptides as peptide isosteres generates depeptidized analogues which retain the peptidic exoskeleton and gives rise to inhibitors which are stable to peptidases and have markedly improved pharmacokinetic profile.[1] In the course of depeptidizing our inhibitors we were challenged to develop a synthesis of the depsipeptide biaryl ether macrocycle **1** (Scheme 1). A ruthenium-based strategy was deemed appropriate for the construction of this macrocyclic ether.[2] The use of ruthenium based strategy has been explored for the construction of peptidic macrocycles by the groups of Pearson and Rich.[2] This has been elegantly demonstrated in the approaches to syntheses of vancomycin, ristocetin A, teicoplanin, OF4949III, and K-13. The retrosynthetic analysis of **1** led us to the fragments **3** and **4** used for construction of the macrocyclic precursor **2**.

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) CH_3COONa, $(CH_3CO)_2O$, 90%; (b) aq HCl reflux, 51%; (c) Pd/C, H_2, C_2H_5OH, 100%; (d) $C_6H_5CH_2OH$, PPTS, benzene, 61%.

The synthesis of hydroxy ester **3** was initiated from acetyl glycine and *m*-hydroxybenzaldehyde (Scheme 2).[3] Refluxing a mixture of 3-hydroxybenzaldehyde **6** and acetyl glycine **5** with acetic anhydride and sodium acetate formed the oxazolone **7** in excellent yield, which was subsequently hydrolyzed to the pyruvate **8** by refluxing with aqueous HCl. The pyruvate **8** was further reduced to the hydroxy acid **9** quantitatively using catalytic hydrogenation with Pd/C.[4] Attempts to synthesizes the benzyl ester **3** with K_2CO_3 and BnBr produced a mixture of benzyl ester and benzyl ether in low yields. However refluxing a mixture of acid **9** in benzene with 2 equiv of BnOH and TsOH with azeotropic removal of water resulted in exclusive formation of benzyl ester **3** in 61% yield.[5]

To enable an efficient ester formation of the less reactive alcohol the diol **3** was selectively protected as

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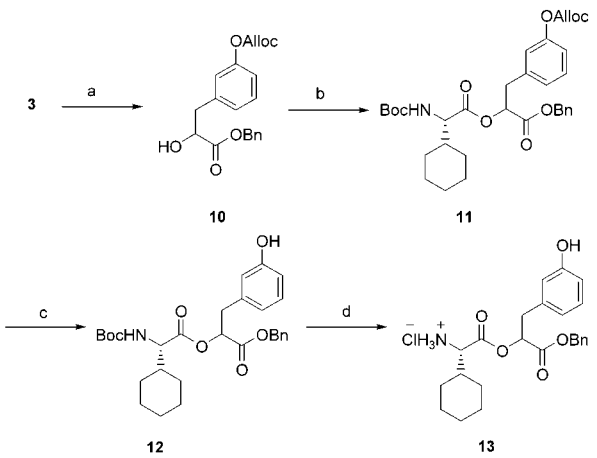
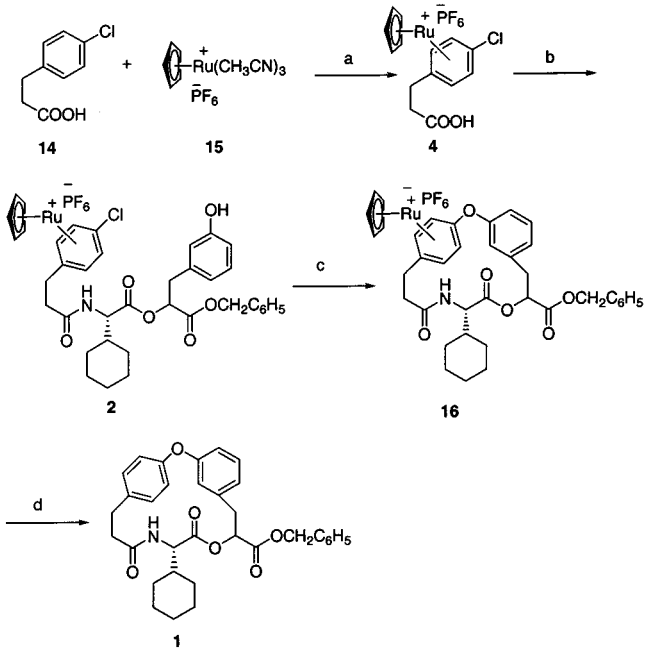
Scheme 3[a]



[a] Reagents and conditions: (a) Alloc-Cl, Et_3N, CH_2Cl_2, −78 °C to rt, 91%; (b) Boc-Chg-OH, DCC, DMAP, $(^iPr)_2EtN$; (c) 5 mol% $Pd(PPh_3)_4$, dimedone, CH_2Cl_2, 78%; (d) 4 M HCl/dioxane.

Scheme 4[a]



[a] Reagents and conditions: (a) $(CH_2Cl)_2$, reflux, 2 h, 73%; (b) **13**, EDCI, HOBt, $(^iPr)_2EtN$, rt, 12 h (c) Cs_2CO_3, DMF, rt, 12 h; (d) CH_3CN, λ = 350 nm, 24 h, 33% over two steps.

the allyl carbamate,[6] which could be efficiently deprotected under neutral conditions (Scheme 3). Reaction of **3** with alloc chloride and Et_3N resulted in the exclusive reaction of the phenol to form the mono protected alcohol **10** in 91% yield. The alcohol **10** was coupled with Boc-protected cyclohexylglycine using DCC and DMAP to form the ester **11**.[7] The allyl carbamate was deprotected using $Pd(PPh_3)_4$ and dimedone to generate phenol **12**.[8] Deprotection of the Boc group with 4 M HCl in dioxane formed hydrochloride salt **13**, which was used for the synthesis of macrocyle.

As outlined in Scheme 4, complex **4** was synthesized by the reaction of 4-chlorophenylpropionic acid **14** with

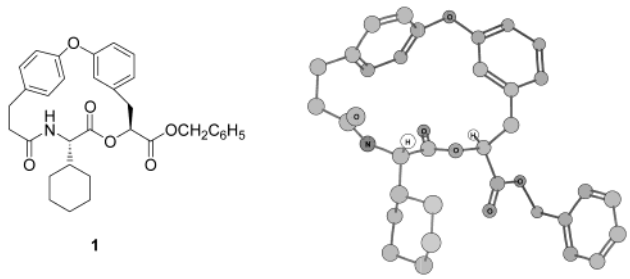


Figure 1. Ball and stick representation of X-ray structure of (*S*)-diastereomer of macrocycle **1**.

$CpRu(CH_3CN)_3$ **15** in refluxing dichloroethane using the procedure of Gill and Mann.[9] The ruthenium complex crystallized from the reaction mixture on cooling to form colorless solid. Complex **4** was coupled with amine **13** using standard EDCI and HOBt[10] conditions to obtain the macrocyclic precursor **2** in excellent yields. The crude mixture was directly cyclized by the treatment with 5 equiv of Cs_2CO_3 to form the macrocyclic depsipeptide **16**. The ruthenium was decomplexed by photolysis of **16** at λ = 350 nm in acetonitrile to form the macrocylic depsipeptide **1** as a mixture of diastereomers.

These isomers were easily separated using flash chromatography, and the relative stereochemisty was determined by single-crystal X-ray structure analysis. As shown in Figure-1, the ball and stick representation of the nonpolar diastereomer (TLC, hexane/CH_2Cl_2/Et_2O: 6:3:1) was determined to be the (*S*)-diastereomer.

In conclusion, an efficient synthesis of the macrocyclic depsipeptide **1** was accomplished by the application of the cationic ruthenium cyclization. The depsipeptide was obtained as mixture of diastereomers that were easily separable**.** The cyclization of the depsipeptide demonstrates the versatility of ruthenium complexes to induce cyclization of even conformationally unrestricted compounds such as depsipeptides.

Experimental Section

General Methods. All glassware were dried in an oven at 150 °C prior to use. Dry solvents were purchased from Aldrich or Acros and used without further purification. Other solvents or reagents were used as acquired except when otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates available from Analtech. Column chromatography was performed using Merck silica gel 60 (particle size 0.040−0.055 mm, 230−400 mesh). Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution, methanolic H_2SO_4, or Vaughn's reagent. NMR spectra were recorded in $CDCl_3$ unless otherwise noted in either 300 or 400 MHz (^{1}H NMR) or 75 or 100 MHz (^{13}C NMR).

Benzyl 2-Hydroxy-3-(3-hydroxyphenyl)propionate (**3**). A solution of acid **9** (4.5 g, 25.0 mmol) in dioxane (30 mL) and benzene (80 mL) was treated with BnOH (8.0 g, 74 mmol, 3.0 equiv) and $TsOH\cdot H_2O$ (713 mg, 3.75 mmol, 15 mol %). The reaction mixture was heated at reflux for 5 h, and the water was separated using a Dean−Stark apparatus. The reaction mixture was concentrated in vacuo, and the residue was purified by chromatography (SiO_2, EtOAc/Hex 3:7) to yield benzyl ester **3** as a colorless oil (4.2 g, 61%); R_f **:** 0.22 (EtOAc/hexanes 3:7); ^{1}H NMR (CD_3OD, 300 MHz) δ, 7.37−7.26 (m, 4 H), 7.05 (t, 1 H,

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J = 7.8 Hz), 6.68−6.61 (m, 3 H), 5.12 (s, 2 H), 4.38 (dd, 1 H, J = 5.4, 2.1 Hz), 3.01−2.82 (m, 2 H); ^{13}C NMR (CH_3OD, 75 MHz,) δ, 175.1, 158.2, 139.7, 137.0, 130.3, 129.5, 129.3, 121.7, 117.4, 114.5, 73.1, 67.6, 41.6; MS (FAB) m/z, relative intensity: 351 ([M + DMSO]$^+$, 70), 273 ([M + 1]$^+$, 100), 255 (20), 227 (30), 181 (40); HRMS calculated for $C_{16}H_{17}O_4$ (M + 1)$^+$: 272.1049; Found: 272.1054.

Benzyl 2-Hydroxy-3-[3-[(allyloxycarbonyl)oxy]phenyl]-propionate (10). A solution of benzyl ester **3** (3.8 g, 12.9 mmol) in CH_2Cl_2 (100 mL) was treated with Et_3N (1.55 g, 15.4 mmol, 2.2 mL) and cooled to −78 °C, and a solution of allyl chloroformate (1.84 g, 15.36 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was allowed to warm to the room temperature and diluted with aq HCl (1 M, 100 mL). The reaction mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with aq HCl (100 mL, 1 M) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo to yield **10** (4.3 g, 93%) which was used in the next step without further purification. R_f: 0.43 (EtOAc/Hex 7:13); ^{1}H NMR (CD_3OD, 300 MHz) δ, 7.35−7.23 (m, 5 H), 7.05 (dd, 1 H, J = 1.2, 6.7 Hz), 7.09−6.98 (m, 2 H), 6.05−5.94 (m, 1H), 5.42−5.26 (m, 2 H), 5.10 (bs, 2 H), 4.69 (m, 1 H), 4.67 (bt, 1 H, J = 15 Hz), 4.39 (dd, 1 H, J = 5.1, 2.1 Hz), 3.10−2.88 (m, 2 H); ^{13}C NMR (CH_3OD, 75 MHz), δ, 174.8, 162.5, 155.0, 152.5, 140.3, 137.1, 132.8, 130.3, 129.6, 129.5, 129.4, 128.4, 123.2, 120.3, 119.4, 72.7, 70.1, 67.8, 41.2, 29.9.

***N*-[(1,1-Dimethylethoxy)carbonyl]cyclohexylglycine 1-[(3-Hydroxyphenyl)methyl]-2-oxo-2-benzyloxyethyl Ester (12).** A solution of Boc-cyclohexylglycine monohydrate (6.02 g, 23.4 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 and dried ($MgSO_4$). The mixture was filtered and concentrated in vacuo. The residue was repeatedly azeotropically dried with toluene three times. The residue was dissolved in CH_2Cl_2 and treated with HOBt (4.73 g, 35.1 mmol, 2.9 equiv), EDCI (6.7 g, 35.1 mmol, 2.9 equiv), and Hünigs base (8.31 g, 64.3 mmol, 11 mL). It was stirred at room temperature for 30 min, and the alloc-protected alcohol **10** (4.3 g, 12.04 mmol) was added. The reaction mixture was stirred at room temperature for 36 h and diluted with aq HCl (1 M, 100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were extracted with aq NaOH (1 M, 100 mL) and brine (100 mL), dried, concentrated in vacuo, and purified by chromatography (SiO_2, EtOAc/Hex 1:4) to yield compound **11** which was charecterized as the deprotected material (7.1 g 100%). R_f: 0.18 (EtOAc/Hex 1:4); Calculated for $C_{28}H_{34}O_7$ (M − Boc)$^+$ 496.2335; Found 496.2333.

A solution of alloc-protected ester **11** (7.8 g, 13.0 mmol) in dry THF (200 mL) was treated with dimedone (3.27 g, 23.4 mmol, 2.0 equiv) and under N_2 was treated with $Pd(Ph_3P)_4$ (780 mg, 0.67 mmol, 5 mol %). The reaction mixture was stirred at room temperature for 1 h, and the disappearance of starting material was followed by TLC (EtOAc/Hex 1:4). The reaction mixture was concentrated in vacuo, and the residue was purified by chromatography (SiO_2, EtOAc/Hexanes 1:4) to yield phenol **12** (5.2 g, 78%) as a colorless solid. R_f: 0.52 (EtOAc/Hex 3:7); ^{1}H NMR (CD_3OD, 300 MHz), δ 7.33−7.19 (m, 4 H), 7.09−7.03 (m, 1 H), 6.73 (bd, 1 H, J = 9.6 Hz), 6.69−6.63 (m, 2 H), 5.27−5.17 (m, 1 H), 5.12 (s, 1 H), 5.07 (d, 1 H, J = 8.4 Hz), 4.10−4.02 (m, 1 H), 3.15−2.93 (m, 2 H), 1.70−1.57 (m, 5 H), 1.40 (m, 9 H), 1.19−0.82 (m, 6 H); ^{13}C NMR (CH_3OD, 75 MHz) δ, 171.7, 169.4, 169.3, 157.2, 156.7, 156.6, 137.2, 136.9, 135.3, 129.2, 128.2, 128.0, 127.9, 120.4, 120.2, 116.1, 116.0, 113.7, 79.3, 73.5, 66.8, 66.7, 60.2, 58.6, 40.0, 36.8, 29.1, 27.7, 27.4, 27.2, 25.6, 19.7, 13.2; MS (ES) m/z, relative intensity: 1023.3 ([2M + 1]$^+$, 20), 512 ([M + 1]$^+$, 20), 412 (100), 202 (40); HRMS Calculated for $C_{24}H_{30}NO_5$ (M − Boc)$^+$ 412.2123; Found: 412.2119.

Cyclohexylglycine 1-[(3-Hydroxyphenyl)methyl]-2-oxo-2-(phenylmethoxy)ethyl Ester Hydrochloride (13). A solution of Boc-protected amine **12** (5.2 g, 10.7 mmol) was stirred with HCl (4 M, dioxane, 200 mL, 800 mmol, 80 equiv) until the starting material **12** disappeared to the baseline as indicated by TLC (EtOAc/Hex 3:7). The reaction mixture was concentrated in vacuo and dried in high vacuum to yield **13** that was directly used in the next step. ^{1}H NMR (CD_3OD, 300 MHz) δ, 7.40−3.23 (m, 5 H), 7.07 (q, 1 H, J = 13 Hz) 6.77−6.6 (m, 3 H), 5.33−5.41 (m, 1 H), 5.3−5.05 (AB, 2 H) 3.99−3.85 (m, 1 H) 3.35−22 (m, 2 H) 2.00−1.5 (m, 5 H), 1.50−0.80 (m, 6 H); MS (FAB) m/z, relative intensity: 412 ([M$^+$, 100); HRMS: Calculated for $C_{24}H_{30}NO_5$ (M − Boc)$^+$ 412.2123: Found 412.2139.

[η^6-3-(4-Chlorophenyl)-1-propionic acid](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (4). A solution of 4-chlorophenylpropionic acid **14** in dichloroethane (200 mL) was treated with $CpRu(CH_3CN)_3PF_6$ **15** (4.7 g, 10.8 mmol, 1.0 equiv) and heated at reflux for 2 h. The reaction mixture was cooled to room temperature, when colorless crystals of the ruthenium complex **4** precipitated out. The crystals were filtered and washed with a mixture of Et_2O/CH_2Cl_2 (1:1 v/v) and dried in vacuo. The colorless crystals (3.3 g, 73%) were analytically pure: ^{1}H NMR (d_6-DMSO, 400 MHz,) δ 6.64 (d, 2 H, J = 6.6 Hz), 6.22 (d, 2 H, J = 6.3 Hz), 5.35 (s, 5 H), 2.49 (t, 2 H, J = 9.6 Hz), 2.74 (dd, 2 H, J = 4.3 Hz); ^{13}C NMR 139.6, 131.6, 129.7, 128.6, 128.5, 100.3, 35.5, 28.9; MS (ES) m/z, relative intensity: 350 [($C_{14}H_{14}ClRu^+$), M$^+$, 100]. Anal. Calculated for $C_{14}H_{14}ClF_6O_2PRu$: C, 33.92; H, 2.85; Cl, 7.15. Found: C, 34.04; H, 3.04; Cl, 7.09.

Cyclo-[[η^6-3-(4-chlorophenyl)-1-propionic acid]-cyclohexylglycine-1-[(3-hydroxyphenyl)methyl]-2-oxo-2-(phenylmethoxy)ethyl ester](η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (16). A solution of [$CpRu(\eta^6$-4-chlorophenylpropionic acid)]PF_6 **4** (2.0 g, 4.03 mmol) in dry DMF (20 mL) were treated with HOBt (835 mg, 6.0 mmol, 1.5 equiv) and Hünigs base (2.06 g, 2.95 mL, 16 mmol, 4.0 equiv). The reaction mixture was cooled to 0 °C and treated with EDCI (1.15 g, 6.0 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 30 min, and the amine hydrochloride **13** (1.8 g, 4.03 mmol, 1.0 equiv) was added in dry DMF (10 mL). The reaction mixture was stirred at room temperature for 12 h, and the DMF was distilled out in vacuo. The residue was diluted with aq HCl (1 M, 100 mL) and extracted into CH_2Cl_2 (3 × 100 mL). The combined organic layers were extracted with aq $NaHCO_3$ (3 × 50 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to yield a brown solid **2** (3.5 g) which was used for cyclization; MS (ES) m/z, relative intensity 743 [(M − PF_6)$^+$, 100], 304 (60); HRMS Calculated for $C_{38}H_{41}NO_6Cl^{102}Ru$ (M − PF_6):$^+$ 744.1666; Found: 744.1694.

A solution of η^6-ruthenium complex **2** (3.5 g, 3.93 mmol) in dry DMF (300 mL) was degassed with dry N_2, treated with Cs_2CO_3 (6.5 g, 19.95 mmol, 5.0 equiv), and stirred at room temperature for 16 h. The reaction mixture was concentrated in vacuo to remove the DMF, and the residue was diluted with H_2O (100 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layers were extracted with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to yield **16** which was directly used for photolytic deprotection; MS (ES) m/z, relative intensity, 708 [(M − PF_6)$^+$, 100]; HRMS Calculated for $C_{38}H_{40}NO_6{}^{102}Ru$ (M − PF_6)$^+$: 708.1892; Found: 708.1918.

Cyclo-[[η^6-3-(4-chlorophenyl)-1-propionic acid]-cyclohexylglycine-1-[(3-hydroxyphenyl)methyl]-2-oxo-2-(phenylmethoxy)ethyl ester] (1). A solution of cyclized ruthenium complex **16** (3.5 g, 3.9 mmol) in CH_3CN (60 mL) was degassed and photolyzed in a quartz tube at λ = 350 nm in two batches for 48 h each. The reaction mixture were pooled together and was purified by chromatography (SiO_2, CH_2Cl_2/Et_2O 9/1) to yield cyclic depsipeptide as a mixture of diastereomers. (700 mg, 33%). The diastereomers were separated by additional chromatography (Hex/CH_2Cl_2/ Et_2O 6:3:1) to yield the two diasteromers of **1** (370 mg, 216 mg) as colorless solid. R_f 0.28 (Hex:EtOAc 3:2); $[\alpha]_D$ = 25 (c 0.15, $CHCl_3$, 20 °C): IR (neat) cm^{-1} 3329 (w), 2960 (m) 2926 (s), 2854 (s), 1745 (s), 1680 (m), 1589 (m), 1506 (m), 1446 (m), 1365 (w), 1259 (s) 1099 (m), 1030 (s), 800 (s), 752 (m), 698 (w) 619 (w): ^{1}H NMR ($CDCl_3$, 300 MHz) δ, 7.40−7.23 (m, 5 H), 7.18−6.99 (m, 4 H), 6.81 (d, 1 H, J = 7.5 Hz), 6.74 (dd, 1 H, J = 2.7, 5.7 Hz), 6.30 (s, 1 H), 5.74 (d, 1 H, J = 7.2 Hz), 5.60 (dd, 1 H, J = 2.4 Hz, 5.4 Hz), 5.18, 5.16 (AB, 2 H, J = 12.3 Hz), 4.23 (dd, 1 H, J = 4.2 Hz, 3.3 Hz), 3.26−3.16 (m, 2 H), 3.10−2.97 (m, 1 H), 2.91−2.86 (m, 1 H), 2.40−2.30 (m,1H) 2.40−2.30 (m, 1H),1.76−1.51 (m, 6 H), 1.51−0.89 (M, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ, 177.3, 171.1, 168.7, 159.8, 155.3, 138.6, 135.4, 134.9, 131.2, 129.7, 129.2, 128.7, 126.6, 126.1, 123.3, 120.8, 120.8, 117.5, 114.2, 71.8, 57.5, 56.9, 41.5, 39.0, 35.7, 32.6, 31.3, 29.0, 27.6, 26.0, 25.9. MS (FAB) m/z, relative intensity 542 [(M + 1)$^+$ 100], 514 (15), 450 (5), 307 (8), 232 (5), 154.1 (17), 136 (14) HRMS: Calcd for $C_{33}H_{36}NO_6$ (M + 1)$^+$ 542.2543, Found: 542.2541.

R_f 0.18 (Hex:EtOAc 3:2) ; $[\alpha]_D = 37.3$ (*c* 0.15, $CHCl_3$, 20 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ, 7.36−7.40 (m, 3 H), 7.28−7.16 (m, 6 H), 7.06 (dd, 1 H, $J = 1.8$, 5.4 Hz), 6.95−6.91 (m, 2 H), 6.69 (d, 1 H, $J = 7.2$ Hz), 6.07 (bt, 1 H), 5.59 (d, 1 H, $J = 9.0$ Hz), 5.16−5.11 (m, 1 Hz), 5.05 (d, 1 H, $J = 8.7$ Hz), 4.45 (dd, 1 H, $J = 6.6$, 2.1 Hz), 3.19−3.09 (m, 3 H), 2.86 (dt, 1 H, $J = 4.2$, 14.1 Hz), 2.68 (dt, 1 H, $J = 5.1$, 4.5 Hz), 2.34−2.25 (m, 1 H), 1.80−1.50 (m, 8H), 1.30−0.85 (m, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ, 171.4, 170.4, 168.4, 165.1, 160.7, 154.1, 137.7, 137.9, 135.1, 131.4, 129.8, 129.4, 128.7, 128.6, 128.3, 122.5, 116.5, 115.1, 74.6, 67.3, 57.5, 42.0, 39.6, 36.7, 31.2, 29.1, 28.5, 26.1, 25.9; MS (FAB) *m*/*z*, relative intensity 542 [$(M + 1)^+$ 100], 514 (15), 466 (5), 344 (8), 232 (5), 154.1 (17), 136 (14). HRMS: Calcd for $C_{33}H_{36}NO_6$ $(M + 1)^+$ 542.2543, Found: 542.2541.

Supporting Information Available: Experimental for the syntheses of compounds **8** and **9**; ^1H and ^{13}C spectra for compounds **3**, **4, 10**, **12**, and **1**; X-ray structure data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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