Syntheses of Novel 4-*tert*-Alkyl Ether Proline-Based 16- and 17-Membered Macrocyclic Compounds

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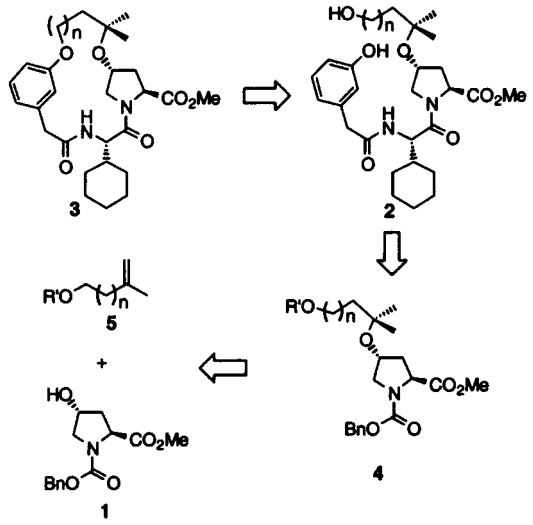
Abstract: Starting from *N*-Cbz-4-hydroxyproline methyl ester **1**, a boron trifluoride−diethyl etherate-catalyzed reaction provided 4-*tert*-alkyl ether proline **4**. Two deprotections and amide bond formations furnished the phenol alcohol **2**. The macrocyclization of **2** was accomplished through a Mitsunobu reaction using triphenylphosphine and 1,1′-(azodicarbonyl)dipiperidine (ADDP), to afford novel 16- and 17-membered proline-based macrocyclic compounds of type **3**.

In recent years, a large number of inhibitors for various proteases have been developed.[1] Many of these inhibitors are peptidic in nature, whose design is based on the structure of native substrates. Many of these compounds are easily cleaved by peptidases and thus suffer from low bioavailability and poor pharmacological profiles.[2] Currently, major efforts have been undertaken in designing peptidomimetics with minimum peptide characters. One such approach that is showing considerable promise is macrocyclization.[3] Many biologically active macrocyclic molecules have been discovered in nature. Important examples include the glycopeptide vancomycin family of antibiotics[4] and the chloropeptins.[5] Recently, a number of potent and selective macrocyclic inhibitors with novel structures have been designed for HIV protease, ACE, renin, matrix metalloproteases (MMP), and TACE.[3,6] Macrocycles offer some potential advantages over acyclic peptides as drug candidates in terms of enhanced stability, membrane permeability and bioavailability.[7]

As a key intermediate in an ongoing project, the novel proline-based macrocyclic structures of type **3** were designed as a conformationally constrained dipeptide moiety. The retrosynthetic plan is outlined in Scheme 1. We envisioned that formation of the *tert*-alkyl ether, one of the key reactions, could be achieved through an acid-catalyzed reaction between alkene **5** and 4-hydroxyproline **1**. After removing the Cbz protecting group from **4**, the amine could be coupled to an appropriate amino acid. The subsequent deprotection and another amide formation with 3-hydroxyphenylacetic acid would afford compound **2**. Finally, macrocyclization of **2** could be accomplished through a Mitsunobu[8] reaction to give the desired macrocycles.

Scheme 1



The preparation of a 16-membered ring macrocycle is outlined in Schemes 2 and 3. The construction of functionalized *tert*-alkyl ether on 4-hydroxyproline is a challenge. There have been no literature reports of such reactions on functionalized substrates. The reaction between *N*-Cbz-*trans*-4-hydroxyproline methyl ester **1** and 4-benzyloxy-2- methyl-1-butene **7** (Scheme 2), which was prepared from 2-methyl-1-buten-4-ol (**6**),[9] was not successful under the conditions of Wright et al. (H_2SO_4, $MgSO_4$, CH_2Cl_2).[10] The starting material **1** was recovered along with large amount of polymeric material, which was a result of an acid-catalyzed polymerization of alkene **7**. However, when treated with catalytic amount of boron trifluoride−diethyl etherate ($BF_3{\cdot}Et_2O$, 0.15−0.20 equiv),[11] the desired product **9** was obtained in moderate to good yield (41−69%) when excess amount (2.5−5.8 equiv) of alkene **7** was used. On the other hand, in an effort to differentiate the protecting groups on proline nitrogen and on primary alcohol, the reaction between acetate **8** and **1** was attempted in the presence of $BF_3{\cdot}Et_2O$. Not surprisingly, no expected product **10** was obtained. The acetate group did not survive the reaction condition.

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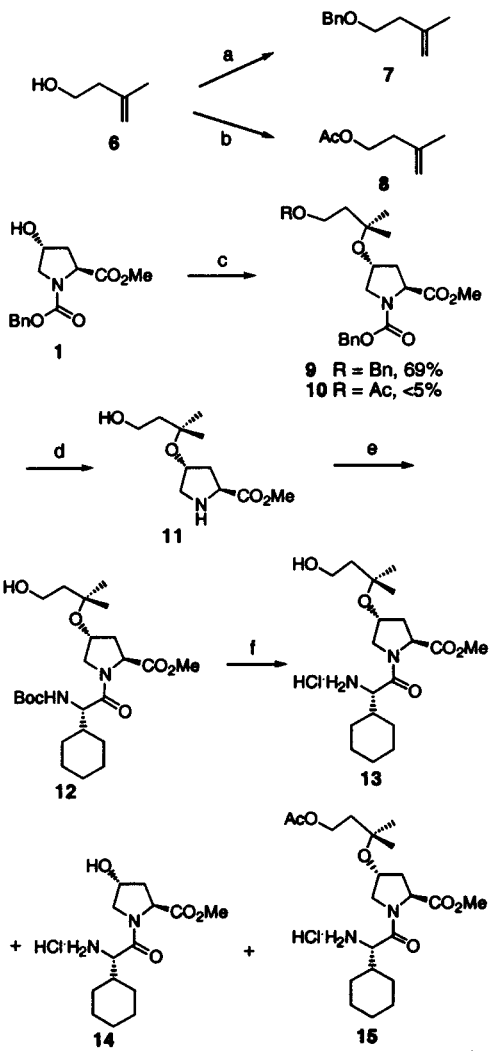
Scheme 2[a]

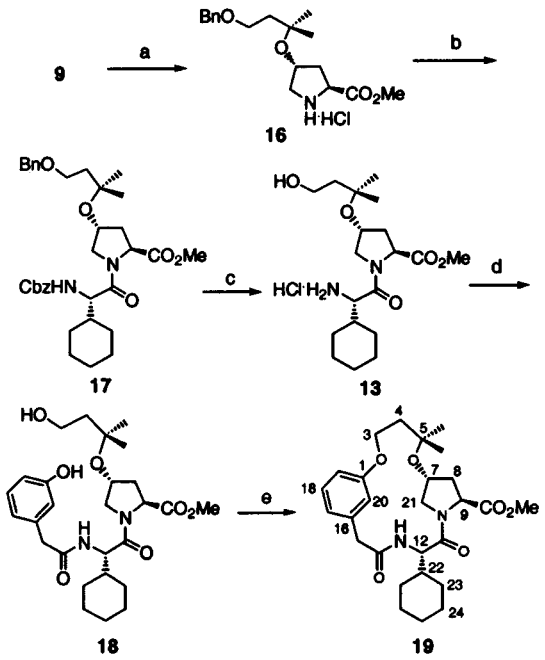


[a] Reagents and conditions: (a) NaH, BnBr, *n*-$Bu_4N^+I^-$, THF, rt, 89%; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; (c) **7**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 41−69%; (d) H_2, 10% Pd−C, EtOH; (e) *N*-Boc-cyclohexylglycine, HOOBt, EDCI, 4-methylmorpholine, DMF/CH_2Cl_2 (1:1), −20 °C, 61%; (f) 2 N HCl, 1,4-dioxane/EtOAc (1:1), rt.

The *N*-Cbz-protected proline benzyl ether **9** was then hydrogenated in the presence of a palladium catalyst to give amino alcohol **11**. Addition of hydrochloric acid seemed to facilitate the cleavage of the benzyl ether in larger scale hydrogenolysis. The catalytic activity of palladium catalyst appeared to be affected by free amines. Next, the proline methyl ester **11** was coupled to *N*-Boc-cyclohexylglycine under standard coupling conditions using 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (HOOBt), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) hydrochloride, and 4-methylmorpholine (NMM) to provide dipeptide **12**. Selective deprotection of the Boc group in the presence of a *tert*-alkyl ether was not anticipated to be difficult. However, when **12** was treated with 2 N HCl, three amino products were obtained, i.e., the desired amino alcohol **13**, the undesired amino alcohol **14**, and the amino acetate **15**. Presumably, hydroxyproline **14** was derived from the cleavage of the *tert*-alkyl ether, and acetate **15** was a result of transesterification from the solvent ethyl acetate. Both reactions were acid catalyzed.

Because of the difficulties encountered in the removal of the protecting groups in compounds **9** and **12**, a revised synthetic route was designed (Scheme 3). Thus, compound **9** was converted to **16** via a catalytic hydrogenation. Amine **16** was then couple to *N*-Cbz-cyclohexylglycine to afford dipeptide **17** under standard conditions. Both Cbz and benzyl protecting groups were removed smoothly by a palladium-catalyzed hydrogenation in the presence of hydrochloric acid. The product **13** was then reacted with 3-hydroxyphenylacetic acid using HOOBt, EDCI, and NMM to give phenol alcohol **18**, which was the precursor for the desired 16-membered macrocycle. The key step, i.e., macrocyclization, of the whole synthesis was accomplished through a Mitsunobu reaction[8] to furnish the desired macrocyclic ester **19** in 40% yield by using triphenylphosphine and 1,1′-(azodicarbonyl)dipiperidine (ADDP). Bubbling of the reaction solution with argon gas seemed to be necessary for higher yield.

Scheme 3[a]



[a] Reagents and conditions: (a) H_2, 10% Pd−C, EtOH, rt; then 1 N HCl in 1,4-dioxane (1.2 equiv), quant; (b) *N*-Cbz-cyclohexylglycine, HOOBt, EDCI, 4-methylmorpholine, DMF/CH_2Cl_2 (1:1), −20 °C, 89%; (c) H_2, 10% Pd−C, HCl (2.0 equiv), EtOH, 0 °C; (d) 3-hydoxyphenylacetic acid, HOOBt, EDCI, 4-methylmorpholine, DMF/CH_2Cl_2 (1:1), rt, 61% (two steps); (e) Ph_3P, ADDP, CH_2Cl_2, rt, 40%.

To determine the preferred conformations of the macrocycle, conformational analysis of **19** was performed by NMR spectroscopy. Proton and carbon NMR resonance of **19** ($CDCl_3$, 25 °C) were assigned by using combination of two-dimensional homonuclear DQF−COSY, NOESY, and heteronuclear HSQC, HMBC experiments. Random conformational search carried out by molecular mechanics approach (PCMODEL V 7.5, MMX force field) implied possible multiple rotamers of cyclohexane with regard to the macrocycle, and conformational diversity in *tert*-alkyl linker of the macrocycle. Presence of two large vicinal *J*-coupling in O(2)−CH_2−CH_2−C(5) fragment (9.7 and 10.2 Hz) suggested that it has the predominant *anti*-orientation between O(2) and C(5) atoms. Also, large *J*-coupling (9.3 Hz) between protons on C(12) and C(22) indicated a higher population of *anti*-orientation for these protons and consequently a coplanar orientation of the macrocycle and the cyclohexane ring.

More quantitative analysis of the *J*-couplings in the *tert*-alkyl fragment was carried out on the bases of four

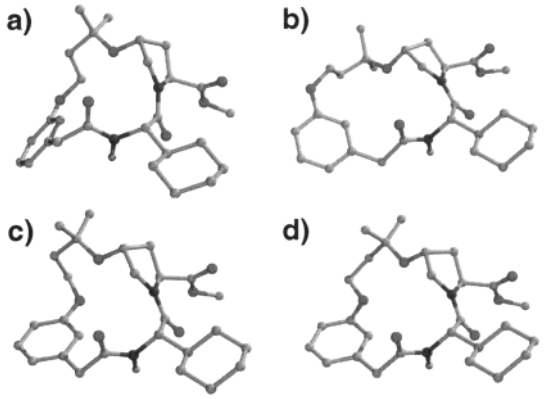
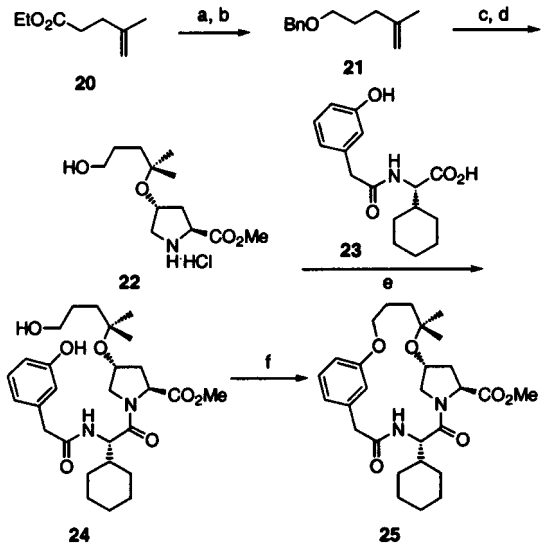


Figure 1. Four representative conformations obtained by PCMODEL V 7.5: (**a**) *anti1*, (**b**) *anti2*, (**c**) *gauche1*, and (**d**) *gauche2*. The relative population of **a**:**b**:**c**:**d** determined by NMR study is 49:35:16:0.

Scheme 4[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, rt, quant; (b) NaH, BnBr, *n*-$Bu_4{}^+I^-$,THF, rt, 67%; (c) **1**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 34%; (d) H_2, 10% Pd−C, HCl (1.5 equiv), 86%; (e) **23**, HOOBt, EDCI, 4-methylmorpholine, DMF/CH_2Cl_2 (1:1), −20 °C, 65%; (f) Ph_3P, ADDP, CH_2Cl_2, 10%.

representative theoretical conformations, *anti1*, *anti2*, *gauche1*, *gauche2* (Figure 1). The *anti* and *gauche* are orientations of atom O(2) with respect to atom C(5). The least squares minimization algorithm was used to fit theoretical *J*-couplings to experimental ones by varying the populations of the four conformations (Microsoft, Excel). The best fit obtained for relative populations of **a**:**b**:**c**:**d** was 49:35:16:0. The predominance of conformation **a** for **19** was also confirmed by the fact that the set of six proton−proton *J*-couplings of the hydroxyproline ring associated with this conformation was the one which most closely resembled the experimentally observed values (see Supporting Information). Qualitative assessment of NOE enhancements observed between aromatic proton at C(20) and protons at C(3) and C(4) also indicated relative predominance of *anti*-type conformations in this fragment.

During the course of our study, the 17-membered macrocycle **25** was also of interest to us. It was prepared following a slightly different synthetic sequence (Scheme 4). Alkene **21** was readily available through a reduction of the ester **20** by $LiAlH_4$, and a subsequent benzylation of the resulting alcohol. When treated with $BF_3{\cdot}Et_2O$, alkene **21** and hydroxyproline **1** formed the desired *tert*-alkyl ether in moderate yield. Removal of both benzyl and Cbz groups via catalytic hydrogenation as previously discussed furnished amino alcohol **22**. The other coupling partner, acid **23**, was obtained through an amide formation between 3-hydroxylphenylacetic acid and cyclohexylglycine methyl ester (HOOBt, EDCI and NMM), followed by hydrolysis of the methyl ester product. The coupling of **22** and **23** was realized without any epimerization under standard coupling conditions. With the macrocyclization precursor **24** in hand, a similar Mitsunobu protocol as described above was used for the 17-membered macrocycle formation. The desired product **25** was obtained in 10% yield. No effort has been made to optimize the yield by varying reaction conditions.

In conclusion, a concise and efficient synthesis of 16- and 17-membered macrocycles has been accomplished. The novel functionalized *tert*-alkyl ether of 4-hydroxyproline was constructed by a $BF_3{\cdot}Et_2O$-catalyzed ether formation. The key macrocyclization of the phenol alcohols **18** and **24** was achieved through Mitsunobu protocol using Ph_3P and ADDP. Future studies on the biological activity of the compounds incorporating these macrocycles should provide invaluable information about their conformational characteristics and pharmacokinetic profiles.

Experimental Section

General. All reagents and solvents were purchased from commercial sources and used without further purification. All reactions were performed under a nitrogen or argon atmosphere. Flash chromatography was carried out using 230−400 mesh silica gel. NMR spectra were recorded at 300, 400, or 500 MHz for ^1H and at 75, 100, or 125 MHz for ^{13}C in $CDCl_3$ or d_6-DMSO. NMR conformational analyses were performed on a 600 MHz spectrometer.

Methyl *N*-Benzyloxycarbonyl-4(*R*)-(1-benzyloxy-3,3-dimethylpropoxy)-L-prolinecarboxylate (9). A solution of **1** (7.0 g, 25.1 mmol) and **7** (25.6 g, 145 mmol) in anhydrous CH_2Cl_2 (250 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.65 mL, 5.13 mmol). The resulting mixture was stirred at room temperature for 2 days. Saturated $NaHCO_3$ solution (150 mL), brine (150 mL), and EtOAc (600 mL) were added, and the two layers were separated. The aqueous solution was extracted with EtOAc (2 × 300 mL), and the combined organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. Flash chromatography (5 to 20% EtOAc/CH_2Cl_2) afforded **9** (7.92 g, 69%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ (two rotamers observed) 7.37−7.27 (m, 10 H), 5.30−5.01 (m, 2 H), 4.53−4.26 (m, 4 H), 3.79−3.51 (m, 6 H), 3.39−3.24 (m, 1 H), 2.17−2.03 (m, 2 H), 1.84−1.78 (m, 2 H), 1.18−1.16 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9, 165.1, 128.4, 128.0, 127.8, 127.6, 127.5, 127.4, 73.0, 68.9, 68.2, 67.1, 66.5, 57.8, 57.6, 53.8, 53.1, 52.3, 40.7, 38.5, 37.5, 29.3, 26.6, 26.4; HRMS *m*/*z* (M^+) Calcd for $C_{26}H_{33}NO_6$: 456.2386. Found: 456.2393.

Methyl *N*-*tert*-Butoxycarbonyl-L-cyclohexylglycine-4(*R*)-(1-hydroxy-3,3-dimethylpropoxyl)-L-prolinecarboxylate (12). The solution of **9** (2.0 g, 4.39 mmol) and 10% palladium on carbon (0.5 g) in ethanol (50 mL) and EtOAc (50 mL) at room temperature was opened to vacuum and refilled three times with hydrogen gas through a balloon. After being stirred at room temperature for 24 h, the reaction was complete as indicated by TLC. The solution was filtered through a Celite pad, and the Celite pad was washed with EtOAc (3 × 20 mL). The solution was concentrated in vacuo to give compound **11** as an oil (1.14 g, quant). To a solution of **11** (1.10 g, 4.40 mmol), *N*-Boc-cyclohexylglycine (1.18 g, 4.59 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (HOOBt) (0.79 g, 4.84 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) hydrochloride (1.06 g, 5.53 mmol) in anhydrous DMF (50 mL) and CH_2Cl_2 (50 mL) at −20 °C was added 4-methylmorpholine (1.20 mL, 10.9 mmol). After being stirred at this temperature for 30 min, the reaction

mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1 h. EtOAc (150 mL), brine (50 mL) and 5% H_3PO_4 (50 mL) were added. The separated organic solution was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 × 100 mL), water (100 mL), and brine (100 mL), dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (10 to 20% EtOAc−CH_2Cl_2) afforded **12** (1.25 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18−5.14 (m, 1 H), 4.62−4.57 (m, 1 H), 4.41−4.34 (m, 1 H), 4.27−4.21 (m, 1H), 3.82−3.68 (m, 6 H), 2.63 (br s, 1H), 2.23−2.05 (m, 2H), 1.83−1.62 (m, 10 H), 1.43 (s, 9 H), 1.29−1.01 (m, 11 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.4, 171.3, 155.8, 85.7, 79.6, 69.6, 59.0, 57.5, 56.3, 54.1, 52.3, 43.2, 41.1, 37.0, 29.4, 28.3, 28.1, 26.2, 26.1, 25.9; HRMS *m*/*z* (M^+) Calcd for $C_{24}H_{42}N_2O_7$: 471.3070. Found: 471.3061.

Methyl *N*-Benzyloxycarbonyl-L-cyclohexylglycine-4(*R*)-(1-hydroxy-3,3-dimethylpropoxyl)-L-prolinecarboxylate (17). Amino ester **16** was prepared from **9** following the procedures described for the preparation of compound **11**, except that after the hydrogenation was complete, 1 N HCl (1.2 equiv) in dioxane was added. The solution was then concentrated in vacuo to give an oil. The coupling of **16** and *N*-Cbz-cyclohexylglycine followed the procedure described for **12** to give product **17** as a white solid (3.5 g, 89%, two steps) after flash chromatography (1% MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.28 (m, 10 H), 5.44 (br d, J = 9.08 Hz, 1H), 5.08 (AB q, J = 12.2 Hz, 2 H), 4.58 (dd, J = 8.5, 6.3 Hz, 1 H), 4.49 (AB q, J = 11.7 Hz, 2 H), 4.36−4.30 (m, 2H), 3.79 (dd, J = 10.1, 5.7 Hz, 1 H), 3.73 (s, 3 H), 3.60−3.52 (m, 3 H), 2.15−2.02 (m, 1 H), 2.07−2.02 (m, 1 H), 1.83−1.65 (m, 7 H), 1.28−1.00 (m, 11 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 171.1, 156.5, 136.6, 128.7, 128.6, 128.3, 128.2, 127.9, 127.8, 75.7, 73.3, 69.5, 66.9, 66.8, 57.9, 57.1, 54.4, 52.5, 41.4, 41.0, 37.2, 29.7, 28.1, 26.8, 26.6, 26.4, 26.3, 26.2; HRMS *m*/*z* (M^+) Calcd for $C_{34}H_{46}N_2O_7$: 595.3383. Found: 595.3375.

Methyl *N*-(3-Hydroxyphenyl)acetyl-L-cyclohexylglycine-4(*R*)-(1-hydroxy-3,3-dimethylpropoxyl)-L-prolinecarboxylate (18). To the mixture of **17** (3.5 g, 5.89 mmol) and 10% palladium on carbon (1.1 g) in absolute ethanol (110 mL) at 0 °C was added a 4 N HCl solution in 1,4-dioxane (3.0 mL, 12 mmol). The reaction flask was opened to vacuum and refilled three times with hydrogen gas through a balloon. After being stirred at 0 °C for 1 h, the reaction was complete as indicated by TLC. The solution was filtered through a Celite pad, and the Celite pad was washed with EtOAc (3 × 50 mL). The solution was concentrated in vacuo to give **13** as a yellow solid. This product was coupled to 3-hydroxyphenylacetic acid following the procedure described for **12** to give phenol alcohol **18** as an off-white solid (1.6 g, 61% from **17**) after flash chromatography (2.5−5% MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 714−7.11 (m, 1 H), 6.72−6.63 (m, 3 H), 6.29 (br d, 1 H), 4.56−4.53 (m, 1 H), 4.50−4.46 (m, 1 H), 4.35−4.34 (m, 1 H), 3.92 (d, J = 11.1 Hz, 1 H), 3.78−3.65 (m, 3 H), 3.68 (s, 3 H), 3.50 (AB q, J = 15.4 Hz, 2 H), 2.23−2.19 (m, 1 H), 2.04−1.99 (m, 1 H), 1.79−1.60 (m, 7 H), 1.50−0.93 (m, 11 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.3, 157.5, 136.1, 130.3, 121.6, 121.1, 115.4, 115.1, 78.8, 70.3, 59.6, 58.0, 55.5, 55.4, 52.5, 44.0, 43.4, 40.9, 37.7, 29.4, 28.9, 26.5, 26.4, 26.2, 26.1, 26.0, 25.7; HRMS *m*/*z* (M^+) Calcd for $C_{27}H_{40}N_2O_7$: 505.2914 Found: 505.2910.

Methyl 7(*R*)-12(*S*)-Cyclohexyl-5,5-dimethyl-11,14-dioxo-2,6-dioxa-10,13-diazatricyclo[14.3.1.1(7,10)]heneicosa-1(20),16,18-triene-9(*S*)-carboxylate (19). A solution of the phenol alcohol **18** (1.60 g, 3.16 mmol) and 1,1′-(azodicarbonyl)-dipiperidine (ADDP) (2.40 g, 9.51 mmol) in anhydrous CH_2Cl_2 (400 mL) was bubbled with argon gas through a frit glass bubbler for 20 min. To this solution at 0 °C was added triphenylphosphine (2.50 g, 9.53 mmol). After 20 min at 0 °C, the solution was allowed to warm to room temperature and stirred overnight (24 h) under a nitrogen atmosphere. TLC indicated the complete consumption of the starting material. After removal of solvent in vacuo, the residue was purified by flash chromatography (1−3% MeOH/CH_2Cl_2) to afford the macrocycle **19** (0.62 g, 40%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.16−7.14 (m, 1H), 6.74−6.69 (m, 3 H), 6.24 (br d, J = 9.2 Hz, 1 H), 4.74−4.70 (m, 1 H), 4.57 (dd, J = 10.6, 7.5 Hz, 1 H), 4.33−4.32 (m, 1 H), 4.25−4.18 (m, 1 H), 4.12−4.07 (m, 1 H), 4.00−3.97 (m, 1 H), 3.75 (s, 3 H), 3.70−3.66 (m, 2 H), 3.49−3.47 (m, 1 H), 2.32−2.28 (m, 1 H), 2.03−1.93 (m, 2 H), 1.87−1.66 (m, 7 H), 1.31−1.02 (m, 11 H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 170.6, 168.8, 157.3, 134.7, 127.7, 119.6, 114.5, 109.0, 107.5, 74.0, 67.1, 56.8, 55.4, 54.4, 51.2, 42.1, 40.4, 37.7, 36.8, 29.3, 28.0, 25.5, 25.3, 24.8, 24.1, 22.7, 22.0; HRMS *m*/*z* (M^+) Calcd for $C_{27}H_{38}N_2O_6$: 487.2808. Found: 487.2799.

Methyl *N*-(3-Hydroxyphenyl)acetyl-L-cyclohexylglycine-4(*R*)−(1-hydroxy-4,4-dimethylbutoxyl)-L-prolinecarboxylate (24). (i) Preparation of 5-Benzyloxy-2-methyl-1-pentene (**21**): To the solution of ethyl 4-methylpent-4-enoate (**20**) (10.0 g, 70.3 mmol) in anhydrous tetrahydrofuran (200 mL) at 0 °C under a nitrogen atmosphere was added cautiously a lithium aluminum hydride solution in THF (91.0 mL, 1.0 M, 91.0 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. It was cooled to 0 °C, and aqueous saturated potassium hydrogen sulfate solution was added cautiously until no further gas evolution. Diethyl ether (400 mL), water (100 mL), and brine (150 mL) were added, and the layers were separated. The aqueous solution was extracted with ether (2 × 200 mL). The organic solutions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a clear and colorless oil. The benzylation of this alcohol product followed the procedure described for **7** to afford the benzyl ether **21** (8.25 g, 67% two steps). (ii) Preparation of *N*-(3-Hydroxyphenyl)acetylcyclohexylglycine (**23**): The corresponding methyl ester of **23** (4.9 g, 60%) was prepared from 3-hydroxyphenylacetic acid (6.15 g, 40.4 mmol) and methyl cyclohexylglycine carboxylate hydrochloride (5.6 g, 27.0 mmol) following the procedure described for **12**. The solution of this methyl ester (4.9 g, 16.2 mmol) and lithium hydroxide (0.78 g, 32.4 mmol) in THF/MeOH/water (40 mL, 1:1:1) was stirred at −10 °C for 4 h before it was concentrated in vacuo to one-third of its original volume. Ethyl acetate (100 mL) and brine (50 mL) were added, and layers were separated. The aqueous solution was extracted with EtOAc (2 × 80 mL). The organic solutions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a brown solid, which was used without further purification. ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.5 (br s, 1 H), 9.27 (br s, 1 H), 8.16 (d, J = 8.6 Hz, 1 H), 7.07−7.03 (m, 1H), 6.68−6.58 (m, 3 H), 4.13−4.11 (m, 1 H), 3.45−3.35 (m, 2 H), 1.72−1.55 (m, 6 H), 1.23−0.95 (m, 5 H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 172.0, 169.3, 156.1, 136.7, 128.0, 118.1, 115.0, 112.2, 85.0, 68.4, 55.8, 40.8, 28.2, 27.0, 24.7, 24.6; LRMS *m*/*z* (M^+) Calcd for $C_{16}H_{21}NO_4$: 292.3. Found: 292.1. (iii) Compound **24** was prepared as a white solid from the coupling between **22** (2.97 g, 10.5 mmol) and **23** (3.70 g, 12.7 mmol) following the procedure described for **12** (3.56 g, 65% two steps) after flash chromatography (3−5% MeOH/CH_2Cl_2). ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.25 (br s, 1 H), 8.12 (d, J = 8.4 Hz, 1 H), 7.05−7.00 (m, 1H), 6.65−6.55 (m, 3 H), 5.16 (br s, 1 H), 4.37−4.23 (m, 3 H), 3.71−3.44 (m, 5 H), 3.39−3.14 (m, 8 H), 2.11−2.03 (m, 1 H), 1.91−1.82 (m, 1 H), 1.72−0.87 (m, 14 H); ^{13}C NMR (75.5 MHz, d_6-DMSO) δ 172.2, 170.3, 169.9, 157.7, 137.7, 129.0, 119.7, 119.6, 116.1, 113.2, 68.8, 57.5, 55.2, 54.9, 54.6, 51.7, 41.8, 37.1, 28.6, 28.1, 27.9, 26.6, 25.8, 25.5; HRMS *m*/*z* (M^+) Calcd for $C_{28}H_{43}N_2O_7$: 519.3070. Found: 519.3080.

Methyl 8(*R*)-13(*S*)-Cyclohexyl-6,6-dimethyl-12,15-dioxo-2,7-dioxa-11,14-diazatricyclo[15.3.1.1(8,11)]docosa-1(21),17,19-triene-10(*S*)-carboxylate (25). Compound **25** was prepared from the phenol **24** (3.55 g, 6.84 mmol) following the procedure described for **19** to give **25** as a white solid (0.35 g, 10%) after flash chromatography (1% MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17−7.14 (m, 1 H), 6.77−6.70 (m, 3 H), 6.16 (br d, J = 8.5 Hz, 1 H), 4.61−4.57 (m, 1 H), 4.42−4.39 (m, 1 H), 4.27−4.25 (m, 1 H), 4.02−3.99 (m, 2 H), 3.77−3.75 (m, 1 H), 3.69 (s, 3 H), 3.68−3.65 (m, 1 H), 3.58 (d, J = 14.6 Hz, 1 H), 3.47 (d, J = 14.6 Hz, 1 H), 2.24−2.19 (m, 1 H), 1.93−1.59 (m, 10 H), 1.52−1.42 (m, 1 H), 1.29−0.96 (m, 11 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 171.1, 171.0, 158.6, 136.4, 129.8, 121.5, 116.8, 112.0, 75.7, 69.7, 68.3, 57.9, 56.0, 55.3, 52.1, 43.6, 41.3, 39.7, 37.8, 29.0, 28.8, 26.9, 26.3, 25.8, 25.7, 24.1, 23.0; HRMS *m*/*z* (M^+) Calcd for $C_{28}H_{41}N_2O_6$: 501.2965. Found: 501.2959.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for key compounds, and NMR conformational analysis of **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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