Novel Dipeptide Macrocycles from 4-Oxo, -Thio, and -Amino-Substituted Proline Derivatives

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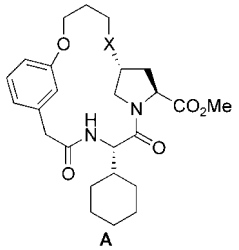
Abstract: Dipeptide macrocycles of type **A** have been constructed in a versatile manner from the corresponding 4-heteroatom-substituted proline derivatives using an intramolecular Mitsunobu strategy.

While peptides are used extensively to probe the binding pocket of enzymes or receptors, their use as drug candidate is severely limited. This is due to the fact that peptides are prone to rapid degradation by proteolytic enzymes and, therefore, lack acceptable pharmaceutical properties.[1] An effective solution to this problem involves cyclization of the linear peptides resulting in macrocyclic molecules.[2] The aforementioned strategy leads to conformationally constrained structures devoid of peptide-like properties. In general, macrocycles are resistant toward proteolytic enzymes and often exhibit improved binding affinity and acceptable pharmacokinetic profile.[2] Several groups have successfully demonstrated this approach in the design and synthesis of biologically important molecules.[3]

A common structural motif that emerges in the macrocyclization strategy is the aryl−*O*-alkyl linkage, which has been well exploited in the HIV protease inhibitor field.[4] During the course of our studies leading to novel peptidomimetics, we designed macrocyclic structures of type **A** that incorporated the aryl−alkyl ether linkage. Furthermore, introduction of the 4-heteroatom substitution on the core proline moiety was required to provide macrocycles of suitable size and conformation. These types of macrocycles arising from 4-heteroatom-substituted proline derivative are rare.[5] Herein we describe the synthesis of these macrocyclic molecules starting from commercially available *trans*- or *cis*-4-hydroxyproline derivatives. The key step in our synthesis was macrocyclization via an intramolecular Mitsunobu protocol.[6]



A
(X = O, S, N-SO_2Ph)

Our efforts started with the construction of the 16-membered macrocycle with a 4-ether linkage as depicted in Scheme 1. Commercially available *trans*-4-hydroxyproline derivative **1** was alkylated with 3-benzyloxy-1-bromopropane to install the "top" three-carbon linker. Esterification of the crude residue with trimethylsilyldiazomethane afforded compound **2** in 44% isolated yield for two steps. Attempted alkylation of the methyl ester of **1** (structure not shown) using cesium carbonate or sodium hydride resulted in no reaction or low yields of **2** with concomitant loss of stereochemical integrity at the α-center next to the ester functionality. Deprotection of the *N*-Boc residue of **2** (4 M HCl in dioxane) and subsequent coupling with *N*-Boc-L-cyclohexylglycine using EDCI and HOOBt under cold (−20 to −10 °C) conditions provided the dipeptide **3**. The "bottom" amide linker was introduced via a similar protocol involving deprotection followed by coupling with commercially available 3-hydroxyphenylacetic acid to afford compound **4**. Cleavage of the benzyl-protecting group under catalytic hydrogenation unraveled the free alcohol **5**, setting the stage for the key macrocyclization step. The final cyclization was carried out by intramolecular Mitsunobu strategy. The reaction was performed in dichloromethane using triphenylphosphine and 1,1′-(azodicarbonyl)dipip-

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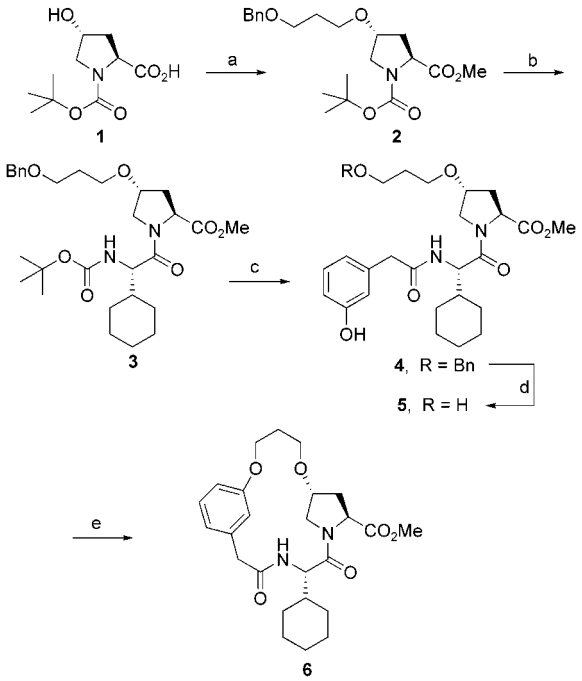
Scheme 1[a]



[a] Reagents and conditions: (a) (i) 3-benzyloxy-1-bromopropane, NaH, NaI; (ii) $TMSCHN_2$ (44%); (b) (i) 4 M HCl/dioxane; (ii) *N*-Boc-Chg-OH, EDCl, HOOBt, NMM (84%); (c) (i) 4 M HCl/dioxane; (ii) 3-hydroxyphenylacetic acid, EDCl, HOOBt, NMM (90%); (d) H_2, 10% Pd/C (87%); (e) PPh_3, ADDP (35%).

eridine (ADDP) to provide the constrained dipeptide macrocycle **6** in 35% isolated yield. It was found necessary to bubble argon gas into the reaction mixture before addition of triphenylphosphine to obtain reasonable yields of the cyclized product.

Preparation of the 4-thioether-linked macrocycle was initiated with commercially available 4-*cis*-hydroxyproline derivative **7** (Scheme 2). The hydroxyl group was activated as the brosylate (Bs) via treatment with brosyl chloride and triethylamine in the presence of catalytic amounts of DMAP. Displacement of the brosylate **8** with the monosodium salt of mercaptopropanol resulted in the incorporation of the 4-thioether moiety along with the "top" linker in high yields (78%) to provide compound **9**. It should be noted that use of the corresponding 4-mesylate (structure not shown) derived from **7** did not afford the required product **9**. Processing of compound **9** as outlined above (from **2** to **3**) gave the dipeptide **10**. The amide-linked macrocycle precursor (step d, Scheme 2) was obtained by deprotection of the *N*-Boc functionality of **10** and coupling with 3-hydroxyphenylacetic acid. The intramolecular Mitsunobu cyclization for the construction of macrocycle **11** took place in dichloromethane with triphenylphosphine and ADDP in 22% isolated yield.

Synthetic studies on the 4-nitrogen-linked macrocycle (Scheme 3) started with the 4-aminoproline derivative **12** that was obtained from **1** using previously reported chemistry.[7] Treatment of **12** with benzenesulfonyl chloride furnished the phenylsulfonamido derivative **13**. Deprotection followed by peptide coupling with *N*-Boc-L-cyclohexylglycine using standard conditions (EDCI,

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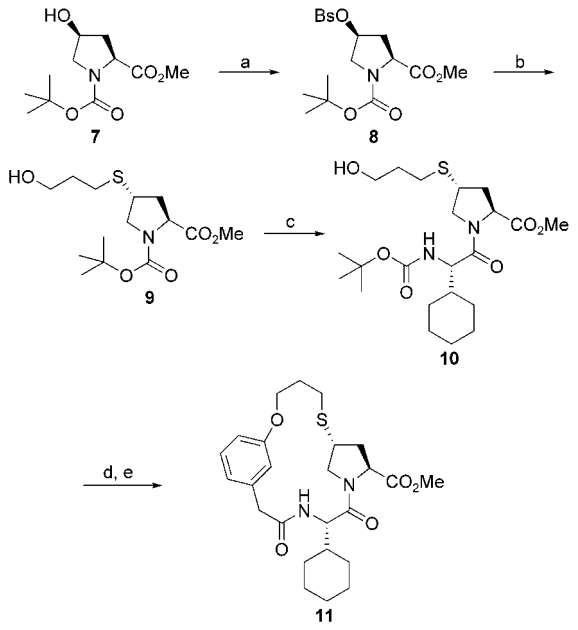
Scheme 2[a]



[a] Reagents and conditions: (a) BsCl, Et_3N, DMAP (97%); (b) 3-mercaptopropanol, NaH (78%); (c) (i) 4M HCl/Dioxane; (ii) *N*-Boc-Chg-OH, EDCl, HOOBt, NMM (80%); (d) (i) 4 M HCl/Dioxane; (ii) 3-hydroxyphenylacetic acid, EDCl, HOOBt, NMM (40%); (e) PPh_3, ADDP (22%).

HOOBt, NMM) resulted in the dipeptide **14**. In this case, attachment of the "top" three-carbon linker followed an intermolecular Mitsunobu protocol under neutral conditions with 3-benzyloxypropanol to afford compound **15**. Subsequent steps for the building of **16**, i.e., installation of the "bottom" amide linker, release of the alcohol, and final cyclization proceeded as described previously in Scheme 1. After purification, the N-linked proline-derived macrocycle **16** was isolated in 20% yield over two steps. No attempts were made to optimize the yields of the final cyclization step in the above schemes.

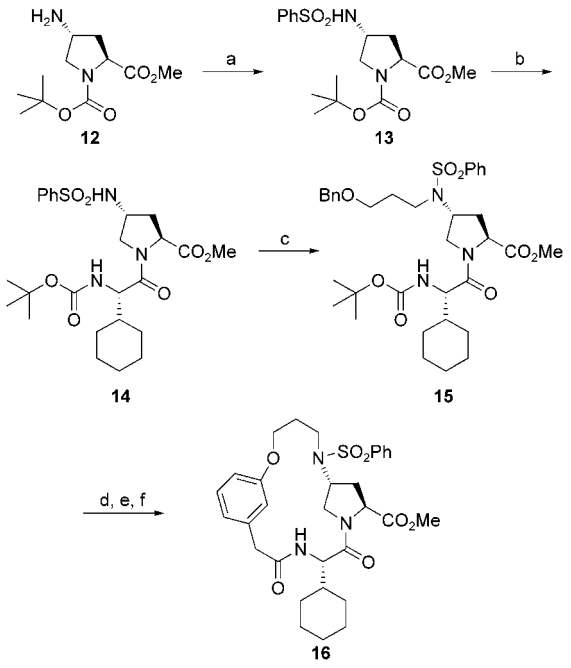
In summary, we have developed a versatile synthetic route for the construction of novel conformationally restrained 16 membered macrocyclic structures containing 4-oxo-, 4-thio-, and 4-aminoproline moiety via intramolecular Mitsunobu protocol. These macrocycles are currently being evaluated as appropriate peptidomimetics.

Experimental Section

All reagents/solvents were purchased from commercial sources and used without further purification. When required, reactions were performed under N_2 or Ar atmosphere. Flash chromatography was carried out using Selecto silica gel (230−400 mesh). NMR spectra (300 or 400 MHz for ^1H and 75 or 100 MHz for ^{13}C) were obtained in $CDCl_3$ unless otherwise specified.

4(*R*)-[3-(Phenylmethoxy)propoxy]-1,2(*S*)-pyrrolidinedicarboxylic Acid, 1-(1,1-Dimethylethyl) 2-Methyl Ester (2). To a solution of *N*-Boc-Hyp-OH **1** (7.0 g, 30.3 mmol) and benzyl 3-bromopropyl ether (7.8 g, 34.0 mmol) in anhydrous DMF (400 mL) at room temperature were added sodium hydride (3.5 g, 60% dispersion in mineral oil, 87.5 mmol) and sodium iodide (0.5 g, 3.34 mmol). The resulting suspension was vigorously stirred at room temperature overnight (18 h). The reaction mixture was cooled to 0 °C and was quenched carefully with slow addition of water (50 mL) followed by 6 N HCl solution (20 mL). After addition of ethyl acetate (800 mL), brine (150 mL), and more water (150 mL), the two layers were separated, and the organic solution was washed with 5% H_3PO_4 (3 × 200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an

Scheme 3[a]



[a] Reagents and conditions: (a) $PhSO_2Cl$, Et_3N, DMAP (59%); (b) (i) 4 M HCl/dioxane; (ii) *N*-Boc-Chg-OH, EDCl, HOOBt, NMM (60%); (c) 3-benzyloxypropanol, PPh_3, ADDP (34%); (d) (i) 4 M HCl/Dioxane; (ii) 3-hydroxyphenylacetic acid, EDCl, HOOBt, NMM (99%); (e) H_2, 10% Pd/C; (f) PPh_3, ADDP (20%).

oil. To this oil in benzene (25 mL) and methanol (28 mL) at ambient temperature was added a solution of trimethylsilyldiazomethane (27 mL, 2.0 M in hexane) with caution. After being stirred at room temperature for 1 h, the mixture was concentrated and the product purified by flash chromatography (8−20% EtOAc−CH_2Cl_2) to afford **2** (5.15 g, 44%) as an oil: HRMS *m*/*z* 394.2228 (calcd for $C_{21}H_{32}NO_6$, 394.2230).

Methyl 1-[2(*S*)-Cyclohexyl-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxoethyl]-4(*R*)-[3-(phenylmethoxy)propoxy]-2(*S*)-pyrrolidinecarboxylate (3). Compound **2** (5.83 g, 14.8 mmol) was dissolved in 4 M HCl/dioxane (80 mL, 320 mmol), and the resulting solution was stirred at ambient temperature. The progress of the reaction was monitored by TLC. After 5 h, the solution was concentrated in vacuo, and the residue was kept under vacuum overnight to yield a white solid. To this solid in anhydrous DMF (150 mL) and CH_2Cl_2 (150 mL) at −20 °C were added *N*-Boc-cyclohexylglycine (4.10 g, 14.9 mmol), HOOBt (2.60 g, 15.9 mmol), EDCI (3.41 g, 17.8 mmol), and NMM (6.50 mL, 59.1 mmol). After this temperature was maintained for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then allowed to warm to room temperature over 1 h. EtOAc (450 mL), brine (100 mL), and 5% H_3PO_4 (100 mL) were added. After the two layers were separated, the organic solution was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 × 150 mL), water (150 mL), and brine (150 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash chromatography (10 to 20% EtOAc−CH_2Cl_2) afforded **3** (6.60 g, 84% two steps) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36−7.25 (m, 5 H), 6.87 (d, J = 8.9 Hz, 1 H), 4.46−4.40 (m, 2 H), 4.25 (t, J = 8.3 Hz, 1 H), 4.11 (s, 1 H), 4.05−4.04 (m, 1 H), 4.03−3.94 (m, 1 H), 3.60 (s, 3 H), 3.50−3.41 (m, 4 H), 2.25−2.20 (m, 1 H), 1.95−1.88 (m, 1 H), 1.77−1.55 (m, 9 H), 1.35 (s, 9 H), 1.19−0.90 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 170.7, 155.6, 138.8, 128.2, 127.4, 127.3, 78.0, 77.1, 71.9, 66.6, 65.1, 57.4, 56.3, 51.8, 34.5, 29.6, 28.6, 28.2, 25.9, 25.6, 25.5; HRMS *m*/*z* 533.3232 (calcd for $C_{29}H_{45}N_2O_7$, 533.3227).

Methyl 1-[(2*S*)-2-cyclohexyl-2-[[(3-hydroxyphenyl)acetyl]amino]-1-oxoethyl]-4(*R*)-[3-(phenylmethoxy)propoxy]-2(*S*)-pyrrolidinecarboxylate (4). The *N*-Boc-amino methyl ester **3** (6.53 g, 12.3 mmol) was dissolved in 4 M HCl/dioxane (60 mL, 240 mmol), and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 4 h, the solution was concentrated in vacuo and the residue was kept under vacuum overnight to give a white solid that was used in the next coupling reaction without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36−7.27 (m, 5 H), 4.43 (s, 2 H), 4.35−4.31 (m, 1H), 3.88 (d, J = 11.7 Hz, 1 H), 3.62 (s, 3 H), 3.62−3.57 (m, 2 H), 3.53−3.41 (m, 3 H), 2.32−2.27 (m, 1 H), 1.97−1.91 (m, 1 H), 1.79−1.60 (m, 8 H), 1.17−1.07 (m, 5 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 167.4, 138.6, 133.3, 129.1, 128.8, 128.2, 127.4, 77.1, 71.9, 66.5, 65.3, 57.8, 54.9, 52.4, 52.0, 34.0, 29.6, 27.7, 27.0, 25.6, 25.5, 25.48; HRMS *m*/*z* 433.2702 (calcd for $C_{24}H_{36}N_2O_5$, 433.2702). To the amine·HCl from above in anhydrous DMF (250 mL) and CH_2Cl_2 (100 mL) at −20 °C were added 3-hydroxyphenylacetic acid (1.90 g, 12.5 mmol), HOOBt (2.10 g, 12.9 mmol), EDCI (2.85 g, 14.9 mmol), and NMM (4.20 mL, 38.2 mmol). After 30 min at this temperature, the reaction mixture was kept in a freezer overnight (18 h). It was then allowed to warm to room temperature over 1 h. EtOAc (500 mL), brine (100 mL), and 5% H_3PO_4 (100 mL) were added. The separated organic solution was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 × 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (10−20% EtOAc−CH_2Cl_2) afforded **4** (6.30 g, 11.1 mmol, 90% (two steps)) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1 H), 8.19 (d, J = 8.5 Hz, 1 H), 7.36−7.25 (m, 5 H), 7.05−7.01 (m, 1 H), 6.66−6.64 (m, 1 H), 6.60−6.57 (m, 1 H), 4.46−4.39 (m, 2 H), 4.34 (t, J = 8.3 Hz, 1 H), 4.29−4.25 (m, 1 H), 4.09−4.08 (m, 1 H), 3.91 (d, J = 11.0 Hz, 1 H), 3.66−3.58 (m, 1 H), 3.61 (s, 3 H), 3.50−3.39 (m, 5 H), 3.30 (d, J = 13.7 Hz, 1 H), 2.24−2.18 (m, 1 H), 1.95−1.89 (m, 1 H), 1.74−1.57 (m, 8 H), 1.18−0.89 (m, 5 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 170.3, 170.0, 157.1, 138.6, 137.6, 128.9, 128.2, 127.4, 127.3, 119.6, 116.1, 113.2, 76.9, 71.8, 66.6, 65.2, 57.4, 54.7, 51.9, 51.8, 41.8, 34.4, 29.6, 28.5, 28.0, 25.5, 25.5; HRMS *m*/*z* 567.3073 (calcd for $C_{32}H_{42}N_2O_7$, 567.3070).

Methyl 1-[(2*S*)-2-Cyclohexyl-2-[[(3-hydroxyphenyl)acetyl]-amino]-1-oxoethyl]-4(*R*)-(3-hydroxypropoxy)-2(*S*)-pyrrolidinecarboxylate (5). To a solution of **4** (6.23 g, 11.0 mmol) in ethanol (200 mL) under nitrogen at room temperature was added 10% Pd−C (1.5 g) cautiously. The resulting suspension was vigorously stirred at room temperature under hydrogen atmosphere for 23 h. After filtration through Celite, the solution was concentrated in vacuo. Flash chromatography (2−5% MeOH−CH_2Cl_2) afforded **5** (4.54 g, 9.52 mmol, 87%) as a solid: mp 49−51 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1 H), 8.22 (d, J = 8.6 Hz, 1 H), 7.06−7.02 (m, 1 H), 6.66−6.58 (m, 3 H), 4.42−4.40 (m, 1 H), 4.35−4.31 (s, 1 H), 4.27 (t, J = 8.3 Hz, 1 H), 4.10−4.09 (m, 1 H), 3.92 (d, J = 11.2 Hz, 1 H), 3.64 (dd, J = 11.2, 4.3 Hz, 1 H), 3.61 (s, 3 H), 3.59−3.43 (m, 5 H), 3.40−3.38 (m, 1 H), 2.26−2.21 (m, 1 H), 1.97−1.90 (m, 1 H), 1.74−1.55 (m, 8 H), 1.18−0.89 (m, 5 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 170.3, 170.1, 157.1, 137.6, 129.0, 119.6, 116.0, 113.3, 76.9, 65.2, 57.6, 57.4, 54.8, 51.9, 51.8, 41.7, 34.4, 32.6, 28.5, 28.0, 25.9, 25.52, 25.49; HRMS *m*/*z* 477.2606 (calcd for $C_{25}H_{36}N_2O_7$, 477.2601).

Methyl (7*R*,9*S*)-12(*S*)-Cyclohexyl-11,14-dioxo-2,6-dioxa-10,13-diazatricyclo[14.3.1.1^{7,10}]heneicosa-1(20),16,18-triene-9-carboxylate (6). Argon gas was bubbled into a solution of **5** (4.50 g, 9.43 mmol) and ADDP (6.60 g, 26.2 mmol) in anhydrous CH_2Cl_2 for 20 min while the reaction mixture was cooled to 0 °C. To this solution was added triphenylphosphine (4.10 g, 16.3 mmol). After the solution was stirred at 0 °C for 20 min, a second portion of triphenylphosphine (3.40 g, 13.5 mmol) was added. The solution was then warmed to room temperature and stirred overnight (24 h) under nitrogen atmosphere until TLC indicated complete consumption of the starting material. After removal of solvent in vacuo, the residue was purified by flash chromatography (1−2% MeOH in CH_2Cl_2) to afford the macrocycle **6** (1.51 g, 35%) as an off-white solid: mp 77−79 °C; $[\alpha]^{20}_D$ = −54.85° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 9.7 Hz, 1 H), 7.17−7.13 (m, 1 H), 6.79 (s, 1 H), 6.73 (d, J = 1.8 Hz, 1 H), 6.71 (d, J = 1.8 Hz, 1 H), 4.50−4.45 (m, 1 H), 4.24 (dd, J = 10.3, 7.6 Hz, 1 H), 4.17−4.06 (m, 4 H), 3.68 (d, J = 15.1 Hz, 1 H), 3.63 (s, 3 H), 3.60−3.51 (m, 2 H), 3.37 (d, J = 15.1 Hz, 1 H), 3.35−3.27 (m, 1 H), 2.51−2.43 (m, 1 H), 1.85−1.47 (m, 9 H), 1.22−1.12 (m, 3 H), 0.97−0.88 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 170.0, 169.8, 158.4, 138.1, 129.1,

121.8, 115.4, 112.2, 77.0, 64.9, 63.6, 57.0, 54.3, 53.4, 51.8, 41.3, 33.2, 28.9, 28.5, 28.2, 26.0, 25.2; HRMS *m*/*z* 459.2495 (calcd for $C_{25}H_{34}N_2O_6$, 459.2495).

4(*R*)-[(3-Hydroxypropyl)thio]-1,2(*S*)-pyrrolidinedicarboxylic Acid, 1-(1,1-Dimethylethyl) 2-Methyl Ester (9). To a suspension of sodium hydride (60% dispersion in mineral oil, 187 mg, 4.68 mmol) in DMF at 0 °C was added 3-mercaptopropanol (0.42 mL, 4.85 mmol) under argon atmosphere. The mixture was stirred for 30 min while the temperature was maintained. A solution of brosylate **8** (1.5 g, 3.23 mmol) in DMF (total volume = 10 mL) was added slowly, and the mixture was warmed to ambient temperature over 2 h. The reaction was quenched by pouring into cold 10% citric acid solution. The aqueous layer was extracted with ethyl acetate, and the organic layer was dried (Na_2SO_4) and concentrated. The crude material was purified by flash column chromatography using 85/15 dichloromethane/ethyl acetate to provide 800 mg (78% yield) of the sulfide **9** as an oil: ^{1}H NMR (mixture of rotamers, $CDCl_3$) δ 1.41 and 1.47 (2s, 9H), 1.83−1.89 (m, 2H), 2.13−2.34 (m, 2H), 2.69 (t, 2H), 3.23−3.49 (m, 2H), 3.73−3.78 (m, 5H), 3.86−3.95 (m, 1H), 4.33−4.37 and 4.42−4.46 (2dd, 1H); ^{13}C NMR (mixture of rotamers, $CDCl_3$) δ 28.21, 28.30, 32.15, 32.23, 36.65, 37.27, 40.45, 40.89, 52.16, 52.35, 52.50, 52.84, 58.32, 58.55, 61.22, 61.41, 80.35, 153.49, 153.99, 173.05, 173.23; HRMS (FAB) calcd for $C_{14}H_{26}NO_5S$ 320.1532 $(M + H)^+$, found 320.1528.

Methyl 1-[(2*S*)-2-Cyclohexyl-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxoethyl]-4(*R*)-[(3-hydroxypropyl)thio]-2(*S*)-pyrrolidinecarboxylate (10). The desired compound was prepared by the protocol described for compound **3**. Reaction conditions: Boc deprotection, 0 °C, 1 h; coupling reaction, −8 °C, 2 days. After workup, the product **10** was sufficiently pure by TLC and was obtained in 80% yield: HRMS (FAB) calcd for $C_{22}H_{39}N_2O_6S$ 459.2529 $(M + H)^+$, found 459.2523.

Methyl (7*R*,9*S*)-12(*S*)-Cyclohexyl-11,14-dioxo-2-oxa-6-thia-10,13-diazatricyclo[14.3.1.1^{7,10}]heneicosa-1(20),16,18-triene-9-carboxylate (11). Deprotection of the Boc functionality and subsequent coupling with 3-hydroxyphenylacetic acid was carried out as described for **4**. The crude product was purified by flash column chromatography using 98/2 of dichloromethane/methanol to provide the macrocyclization precursor in 40% yield as a white solid: ^{1}H NMR (mixture of rotamers, $CDCl_3$) δ 0.90−1.26 (m), 1.66−1.88 (m), 2.22−2.31 (m, 2H), 2.73 (t, 2H), 3.47 (s), 3.5−3.55 (m), 3.65−3.75 (m), 3.88−3.94 (dd, 1H), 4.07−4.12 (dd, 1H), 4.53 (t, 1H), 4.62 (t, 1H), 6.73−6.80 (m, 4H), 7.17 (t, 1H); ^{13}C NMR (mixture of rotamers, $CDCl_3$) δ 25.80, 25.89, 26.14, 27.71, 28.55, 29.22, 31.88, 35.46, 40.58, 42.44, 43.16, 52.32, 52.90, 55.49, 58.46, 60.30, 114.59, 116.27, 121.01, 130.02, 135.90, 156.73, 171.25, 171.87, 171.96; HRMS (FAB) calcd for $C_{25}H_{37}N_2O_6S$ 493.2372 $(M + H)^+$, found 493.2364. This material was subjected to macrocyclization conditions as described for **6**. After completion of the reaction, the crude product was suspended in 80/20 ethyl acetate/hexane and the solid material was filtered off. The filtrate was concentrated and purified by flash column chromatography using 80/20 hexane/acetone to yield 22% of **11** as a solid: mp 123−125 °C; $[\alpha]^{20}_D = -33.07°$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.98−1.30 (m), 1.64−1.90 (m), 2.06−2.14 (m, 1H), 2.16−2.21 (dd, 2H), 2.62−2.70 (m, 2H), 3.38−3.46 (m, 2H), 3.60−3.66 (m, 3H), 3.71 (s, 3H), 3.88−3.94 (dd, 1H), 4.07−4.15 (m, 1H), 4.22−4.29 (m, 1H), 4.48 (t, 1H), 4.60 (t, 1H), 5.97 (br t, 1H), 6.76−6.81 (m, 2H), 6.99 (br s, 1H), 7.20 (dd, 1H); ^{13}C NMR (DMSO-d_6) δ 25.31, 25.36, 26.00, 26.47, 28.12, 28.65, 29.22, 34.71, 38.87, 41.47, 42.22, 51.89, 53.11, 54.63, 57.94, 66.86, 114.91, 115.25, 122.26, 129.20, 137.80, 157.88, 169.31, 170.32, 171.55; HRMS (FAB) calcd for $C_{25}H_{35}N_2O_5S$ 475.2267 $(M + H)^+$, found 475.2260.

Methyl 1-[(2*S*)-2-Cyclohexyl-2- [[(1,1-dimethylethoxy)carbonyl]amino]-1-oxoethyl]-4(*R*)-[(phenylsulfonyl)amino]-2(*S*)-pyrrolidinecarboxylate (14). The expected product was obtained by the method described for preparation of **3**. Purification of the residue by column chromatography using 99/1 dichloromethane/MeOH provided a 60% yield of **14**: mp 75−77 °C; ^{1}H NMR ($CDCl_3$) δ 0.85−1.02 (m, 2H), 1.10−1.25 (m, 3H), 1.46 (s, 9H), 1.61−2.00 (m, 7H), 2.45−2.55 (m, 1H), 3.45−3.55 (m, 1H), 3.72 (s, 3H), 3.80−3.95 (m, 2H), 4.04 (app. d, 1H), 4.64 (app. t, 1H), 5.04 (d, 1H), 6.10 (d, 1H), 7.50−7.64 (m, 3H), 7.86−7.93 (m, 2H); HRMS (FAB) calcd for $C_{25}H_{38}N_3O_7S$ 524.2430 $(M + H)^+$, found 524.2425.

Methyl 1-[(2*S*)-2-Cyclohexyl-2-[[(1,1-dimethylethoxy)carbonyl]amino]-1-oxoethyl]-4(*R*)-[[3-(phenylmethoxy)propyl](phenylsulfonyl)amino]-2(*S*)-pyrrolidinecarboxylate (15). Argon gas was bubbled into a cold (0 °C) solution of **14** (1.72 g, 3.28 mmol) in dichloromethane (40 mL) for 20−30 min. ADDP (2.5 g, 9.84 mmol) was added followed by triphenylphosphine (2.6 g, 9.84 mmol) and 3-benzyloxypropanol (0.57 mL, 3.61 mmol). The reaction was warmed to ambient temperature and allowed to stand for 2 days. The reaction mixture was concentrated, and Et_2O (50 mL) was added to the residue. The precipitated solid material was filtered off. This operation was repeated twice to remove most of the side products. The filtrate was concentrated and purified by flash chromatography using 90/10 to 85/15 dichloromethane/EtOAc to provide 330 mg of **15**. The recovered starting material, along with some triphenylphosphine oxide, was resubjected to the above conditions to provide additional 420 mg of **15**: combined yield = 34%; ^{1}H NMR ($CDCl_3$) δ 0.85−1.25 (m), 1.39 (s, 9H), 1.50−1.84 (m), 1.90−2.06 (m, 3H), 2.12−2.24 (m, 1H), 3.02−3.35 (m, 3H), 3.44−3.57 (m, 3H), 3.72 (s, 3H), 3.99 (dd, 1H), 4.44−4.66 (m, 4H), 5.09 (br. d, 1H), 7.27−7.35 (m, 5H), 7.53−7.64 (m, 3H), 7.79−7.85 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.90, 26.23, 27.82, 28.30, 29.54, 31.32, 31.96, 40.83, 41.78, 47.05, 52.48, 55.40, 56.21, 56.39, 66.92, 67.02, 73.00, 79.53, 127.05, 127.68, 127.74, 128.43, 129.34, 132.99, 138.12, 139.72, 155.62, 171.15, 171.44; HRMS (FAB) calcd for $C_{35}H_{50}N_3O_8S$ 672.3319 $(M + H)^+$, found 672.3330.

Methyl (7*R*,9*S*)-12(*S*)-Cyclohexyl-11,14-dioxo-6-(phenylsulfonyl)-2-oxa-6,10,13-triazatricyclo[14.3.1.1^{7,10}]heneicosa-1(20),16,18-triene-9-carboxylate (16). Deprotection of the Boc functionality of **15** and subsequent coupling with 3-hydroxyphenylacetic acid was carried out as described for **4**. Purification by flash chromatography with 60/40 to 50/50 dichloromethane/EtOAc provided the coupled product in almost quantitative (99%) yield: ^{1}H NMR ($CDCl_3$) δ 0.80−0.96 (m, 2H), 1.00−1.26 (m, 3H), 1.55−1.74 (m, 6H), 1.90−2.04 (m, 3H), 2.10−2.18 (m, 1H), 3.10−3.18 (m, 1H), 3.24−3.53 (m, 7H), 3.68 (s, 3H), 4.25 (app. t, 1H), 4.43−4.50 (m, 3H), 4.54−4.64 (m, 1H), 6.39 (d, 1H), 6.62 (app. t, 1H), 6.69−6.71 (m, 2H), 7.11 (app. t, 1H), 7.25−7.34 (m, 6H), 7.48−7.53 (m, 2H), 7.57−7.61 (m, 1H), 7.79−7.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.76, 25.95, 26.08, 28.14, 29.38, 31.19, 31.43, 31.86, 36.48, 40.41, 41.73, 43.31, 47.13, 52.46, 55.12, 55.28, 56.50, 67.07, 72.95, 114.49, 116.17, 120.78, 127.02, 127.68, 127.79, 128.41, 129.34, 129.96, 133.02, 136.00, 138.05, 139.90, 157.00, 162.54, 171.10, 171.25, 171.32; HRMS (FAB) calcd for $C_{38}H_{48}N_3O_8S$ 706.3162 $(M + H)^+$, found 706.3157. Removal of the benzyl-protecting group was carried out in MeOH as described for **5**. The final macrocyclization reaction was performed as described for **6**. After completion of reaction, the solvent was evaporated. Et_2O (50 mL) was added, and the solids were filtered off. The filtrate was concentrated and Et_2O/EtOAc (50 mL/50 mL) was added. The precipitated solids were filtered off, and the filtrate was concentrated. The residue was purified by flash chromatography using 85/15 to 80/20 dichloromethane/EtOAc to afford **16** in 20% yield (for two steps) as a white solid: mp 98−100 °C; ^{1}H NMR ($CDCl_3$) δ 0.91−1.10 (m, 1H), 1.16−1.30 (m, 3H), 1.62−1.84 (m, 9H), 1.98−2.09 (m, 1H), 2.18−2.32 (m, 1H), 2.90−3.08 (m, 2H), 3.20−3.30 (m, 1H), 3.33 (app. d, 1H), 3.57 (app. d, 1H), 3.67 (s, 3H), 3.79 (dd, 1H), 4.20−4.34 (m, 3H), 4.45 (t, 1H), 4.55 (t, 1H), 5.82 (d, 1H), 6.74−6.80 (m, 2H), 6.89 (s, 1H), 7.19 (app. t, 1H), 7.52−7.65 (m, 3H), 7.77−7.80 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.59, 26.26, 28.44, 29.61, 30.74, 30.87, 39.35, 40.75, 44.16, 48.64, 52.54, 55.02, 55.41, 56.68, 65.28, 111.91, 116.80, 121.76, 126.89, 129.44, 130.37, 133.05, 137.09, 139.35, 157.91, 170.54, 171.17, 214.91; HRMS (FAB) calcd for $C_{31}H_{40}N_3O_7S$ 598.2587 $(M + H)^+$, found 598.2581.

Supporting Information Available: ^{1}H spectra for compounds **9**, **13**, and **14**; ^{1}H and ^{13}C spectra for compounds **3**, **4**, **6**, **11**, **15**, and **16**. Experimental conditions for the preparation of compounds **8** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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