Articles

Practical Synthesis of a Highly Enantioselective Receptor for Peptides

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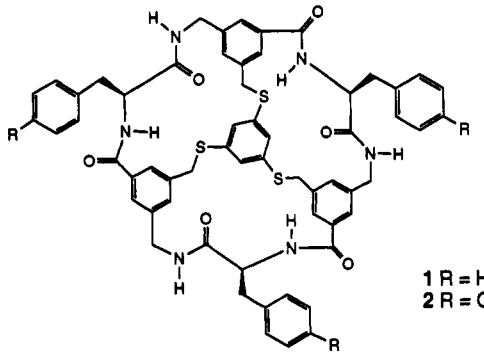
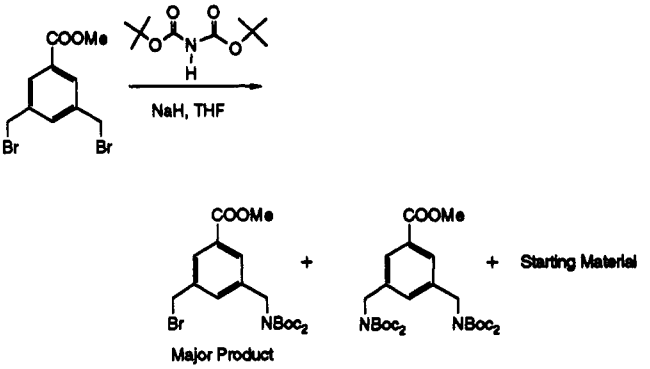
A practical synthesis of a highly enantioselective, C_3-symmetric host molecule (2) has been developed. The basic strategy is a significant improvement over the relatively lengthy previous synthesis and involves direct addition of a Boc-tyrosine amide anion derivative 4 to methyl 3,5-bis(bromomethyl)-benzoate to give an advanced intermediate (5). The final step, a triple macrolactamization, closes three 19-membered rings simultaneously to produce the bridged macrotricyclic receptor in 70–80% yield.

We recently described the preparation and properties of a novel, C_3-symmetric receptor (1).[1] This molecule is one of the most enantioselective synthetic receptors yet reported and binds *N*-Boc-*N'*-methylamide derivatives of simple amino acids with enantioselectivity ranging from 2 to 3 kcal/mol (90–99% ee).[2] Because such highly enantioselective receptors could have practical applications as resolving agents, we have worked to develop derivatives of 1 which could be covalently bound to a solid support. We report here the practical synthesis of one such material, the *O*-allyl tyrosyl receptor 2.



1 R = H
2 R = $OCH_2CH{=}CH_2$

While our original synthesis provided 1 in hundred-milligram quantities, it had several problems which made it unsuitable for preparation of 1 or 2 on large scale. First, the unsymmetrical trisubstituted aromatic spacers were prepared by the desymmetrization reaction shown below. Although the reaction proceeded in reasonable yield (60–70%), it required use of the relatively expensive di-*tert*-butyl iminodicarboxylate amine anion equivalent and a tedious chromatography of products having similar mobilities on silica gel:



Second, the 8-step procedure starting from methyl 3,5-bis(bromomethyl)benzoate provided 1 in only 9% overall yield.

For a derivative of 1 which could be bound to a solid support, we chose the *O*-allyl derivative 2. Such otherwise stable ethers can be deprotected[3] with transition metals to free phenols or attached[4] directly to a support using free radical chemistry. In our new synthesis, we decided to avoid the problematic di-*tert*-butyl iminodicarboxylate anion coupling and not to add nitrogen and amino acid in separate steps. Instead, we planned a more convergent route in which an N-anionic amino acid fragment would be added to bis(bromomethyl)benzoate in a single step. As summarized in the following diagram, our plan was to use a Boc-stabilized amide ion made from *N*-Boc-*O*-allyltyrosine amide using methodology developed by Grieco and co-workers.[5] In the event, however, the desired *N*-Boc amide turned out to be more reactive to acylation than was the primary amide. Thus, the major product with 1 equiv of Boc_2O and catalytic 4-(dimethylamino)-pyridine (DMAP) was a tri-Boc amino acid amide. With excess Boc_2O/DMAP, the tri-Boc material could be isolated in 95% yield.

As shown in Scheme I, the desired Boc-stabilized amide anion could nevertheless be obtained and the planned

(1) Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111.

(2) Other enantioselective hosts for neutral molecules: Canceill, J.; Lacombe, L.; Collet, A. *J. Am. Chem. Soc.* **1985**, *107*, 6993. Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 5975. Sanderson, P. E. J.; Kilburn, J. D.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 8314. Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5834. Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Org. Chem.* **1990**, *55*, 5184. Jeong, K.-S.; Muehldorf, A. V.; Rebek, J. *J. Am. Chem. Soc.* **1990**, *112*, 6144. Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554.

(3) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 436.

(4) Tambute, A.; Begos, A.; Lienne, M.; Macaudiere, P.; Caude, M.; Rosset, R. *New J. Chem.* **1989**, *13*, 625.

(5) Flynn, D. A.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

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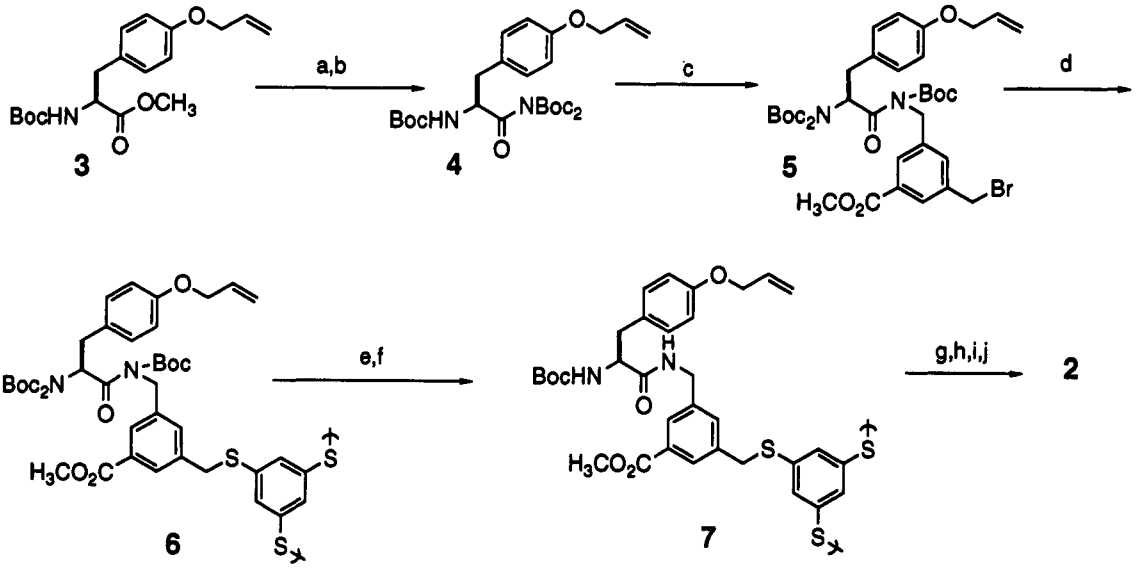
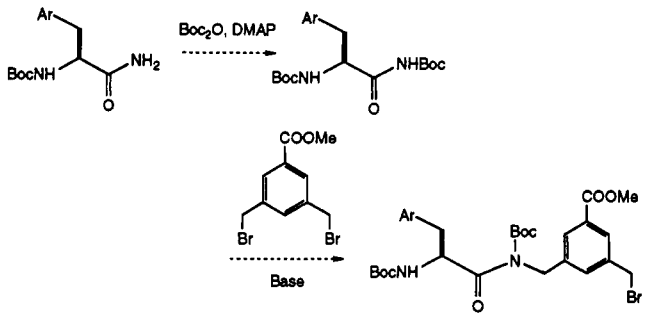
Scheme I[a]

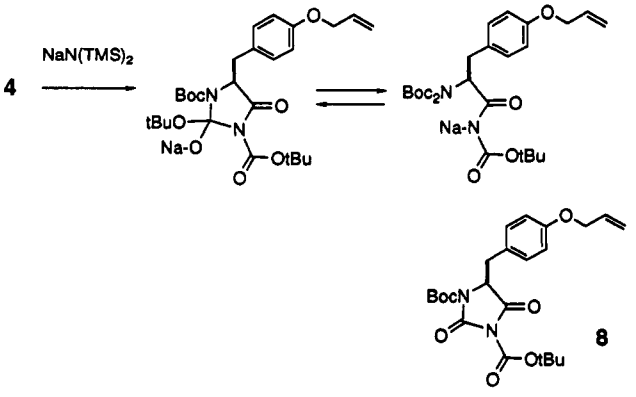


[a] (a) Methanol/ammonia 4:1, rt, 2 days, 97%; (b) Boc_2O, *i*-Pr_2NEt, 4-DMAP (10 mol %), CH_2Cl_2, 1 h, 90%; (c) $NaN(TMS)_2$, THF, −78 °C, 3 min; add tetra-*n*-butylammonium iodide and methyl 3,5-bis(bromomethyl)benzoate; warm to 10 °C, 2 h, 82%; (d) benzene-1,3,5-trithiol, *i*-Pr_2NEt, THF, 8 h, 78%; (e) TFA, anisole, CH_2Cl_2, rt, 16 h, quant; (f) Boc_2O, *i*-Pr_2NEt, K_2CO_3, CH_2Cl_2, rt, 24 h, 86%; (g) THF, EtOH, H_2O, LiOH, 6 h, quant; (h) F_5-phenol, EDC, THF, rt, 4 h, 68%; (i) TFA, anisole, CH_2Cl_2, rt, 4 h, quant; (j) TFA salt in DMA dropwise to *i*-Pr_2NEt, THF, rt, 40 h, 78%.



coupling achieved. Thus starting with commercially available *O*-allyl-*N*-Boc-tyrosine methyl ester (**3**), we used NH_3 to prepare the corresponding primary amide and then formed the tri-Boc derivative **4** as described above.

On treatment of **4** with sodium hexamethyldisilylazide in THF at −78 °C, a rapid deprotonation and Boc-migration occurred, leading to the Boc-stabilized amide anion shown below. While this anion was stable enough to be alkylated with benzylic bromides at low temperature, warming it to 15 °C caused elimination of *tert*-butoxide leading to **8**. For preparation of **2**, we used 1.2 equiv of 3,5-bis(bromomethyl)benzoate with Bu_4NI catalysis and obtained **5** in 82% yield.



Although the alkylation proceeded smoothly, we were concerned that **5** might be acidic enough to have racemized under the basic conditions of the alkylation. To test for such racemization, we treated a sample of **5** with K_2CO_3 in methanol and then with HCl in methanol. The first treatment converted[5] the C-terminal Boc-amide to methyl ester while the second removed the two N-terminal Boc groups, yielding *O*-allyltyrosine methyl ester. This material was then coupled using DCC to (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) to provide the corresponding amide. ^1H and ^{13}C NMR comparison of this material with corresponding amides from authentic D- and L-*O*-allyltyrosine methyl ester showed that very little (<5%) racemization had occurred. Under the conditions of our ^1H NMR experiment, as little as 2% of the epimerized D-tyrosine derivative could have been detected.

The benzylic bromide **5** was then used to triply alkylate *sym*-trimercaptobenzene[6] using Hunig's base (*i*-Pr_2NEt) providing C_3-symmetric **6** in 78% yield. The remainder of the synthesis involved a triple macrolactamization via an activated benzoic acid ester which proved a little more difficult to prepare than we had anticipated. The problem was that the Boc-substituted amide was quite labile toward acid and base, and we were unable to convert the methyl ester to acid in its presence. Furthermore, we could not remove the problematic Boc from the C-terminal amide without simultaneously deprotecting the tyrosyl amine. An effective, though less than ideal, solution to the problem was to remove all Boc protecting groups with TFA and then restore Boc protection of the free amines with Boc_2O to obtain **7** in 86% yield over both steps.

Having solved the problem of the labile amide, we hydrolyzed the three methyl esters of **7** using aqueous lithium hydroxide and then esterified the resulting acids to pentafluorophenol using 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide in THF. Flash chromatography[7]

(6) Bellavita, V. *Gazz. Chim. Ital.* **1932**, *62*, 655.
(7) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

provided the activated tris(pentafluorophenyl ester) in 68% yield. After removing the remaining Boc protecting groups using trifluoroacetic acid, we added the crude trifluoroacetate salt in *N,N*-dimethylacetamide via syringe pump to a large volume of dry THF containing excess Hunig's base. The addition was carried out at room temperature over 36 h using a syringe pump and the final concentration of reactant was ~0.5 mM. This triple macrolactamization was a particular good one for reactions of this type and provided **2** in 78% yield after silica gel chromatography.

In summary, we have developed a practical synthesis of the C_3-symmetric receptor **2** which proceeds in an overall yield of 27% and requires no high resolution chromatographic separations. Solution-phase binding experiments in $CDCl_3$ showed that **2** bound *N*-Boc-*N'*-methylamides of amino acids with the same high enantioselectivities we previously found with **1**. We are now using **2** in a solid-phase resolution system for protected amino acids and the results will be reported in due course.[8]

Experimental Section

All reported compounds were homogeneous by TLC and are ≥90% pure by ^1H (400 MHz) and ^{13}C (75 MHz) NMR. Solvents used were reagent grade and purified by distillation prior to use. Nonaqueous reactions were carried out under argon using oven-dried glassware. All aqueous (aq) solutions were saturated with the specified salt unless otherwise indicated. Organic solutions were dried over $MgSO_4$ (or Na_2SO_4 in the case of amine products) after workup and solvents were removed by evaporation at reduced pressure. Flash chromatography[7] was carried out using 40–63 μm silica gel. Thin layer chromatography was carried out using glass-backed silica gel 60 plates (E. Merck 5715) with the eluting solvents indicated. Melting points are uncorrected.

***N*-Boc-*O*-allyl-L-tyrosine Amide (3).** Di-*tert*-butyl dicarbonate (13.0 g, 59.6 mmol) was added to a solution of L-tyrosine methyl ester hydrochloride (10.0 g, 43.2 mmol) and *i*-Pr_2NEt (6.6 mL, 38.0 mmol) in DMF (100 mL). The reaction mixture was poured into 1 M aq $KHSO_4$ after 8 h and extracted with ethyl acetate (3X). The combined extracts were washed with aq $NaHCO_3$ and brine. Drying and evaporation afforded a yellow oil which was dissolved in DMF (100 mL). Potassium carbonate (12.0 g, 86 mmol), allyl bromide (4.5 mL, 51.8 mmol), and *n*-Bu_4NI (1.5 g, 4.3 mmol) were added. The reaction mixture was stirred for 16 h, poured into 1 M aq $KHSO_4$, and extracted with ethyl acetate (3X). The combined organic layers were washed with aq $NaHCO_3$ and brine. Drying and solvent removal afforded *N*-Boc-*O*-allyl-L-tyrosine methyl ester as a yellow oil.

Ammonia (20 mL) was condensed into a solution of *N*-Boc-*O*-allyl-L-tyrosine methyl ester in CH_3OH (60 mL) at −78 °C in a high pressure glass reaction vessel. The vessel was sealed and slowly warmed to rt. After 2 days, the vessel was cooled to −78 °C and opened. Argon was bubbled through the solution while it was allowed to warm slowly to rt. After 1 h, the solution was transferred to a round-bottom flask and all volatiles were removed. The light brown solid residue was washed with hexane/ethyl acetate (2:1) to yield the *N*-Boc-*O*-allyl-L-tyrosine amide (**3**) (13.0 g, 94%) as a white solid: mp 145 °C; R_f 0.28 (diethyl ether); ^1H NMR ($CDCl_3$) δ 1.40 (9 H, s), 2.97 (1 H, dd, *J* = 7.2, 13.6 Hz), 3.05 (1 H, dd, *J* = 6.4, 13.6 Hz), 4.30 (1 H, m), 4.51 (d, *J* = 5.2 Hz), 5.06 (1 H, m), 5.29 (1 H, dd, *J* = 1.4, 10.8 Hz), 5.38 (1 H, dd, *J* = 1.2, 19.2 Hz), 5.40 (1 H, bs), 5.78 (1 H, bs), 6.04 (1 H, m), 6.86 (2 H, d, *J* = 8.4 Hz), 7.13 (2 H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 27.9, 37.3, 55.2, 68.5, 77.2, 114.6, 117.3, 128.4, 130.0, 132.9, 148.8, 157.3, 173.7; IR (KBr) 3677, 3390, 3195, 1678, 1661, 1515, 1248, 1168 cm^{-1}; HRMS calcd for $C_{17}H_{24}N_2O_4$ 320.1736; found 320.1741.

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***N*-Boc-*O*-allyl-L-tyrosine *N,N*-Di-Boc-amide (4).** To a solution of **3** (3.0 g, 9.38 mmol) in CH_2Cl_2 at rt was added *i*-Pr_2NEt (6.52 mL, 37.5 mmol), DMAP (192 mg, 1.56 mmol), and di-*tert*-butyl dicarbonate (5.12 g, 23.5 mmol). After 2 h the reaction mixture was washed with 1 M aq $KHSO_4$ and 1 M aq $NaHCO_3$. Drying, concentration, filtration through a pad (10 g) of silica gel with 30% ether in pentane and evaporation afforded crude **4** (4.39 g, 90%) as a pale yellow oil. Trituration with hexane gave **4** as a white amorphous solid: mp 87 °C; R_f 0.55 (50% ether/hexane); ^1H NMR ($CDCl_3$) δ 1.36 (9 H, s), 1.53 (18 H, s), 2.76 (1 H, dd, *J* = 6.8, 14.0 Hz), 3.13 (1 H, dd, *J* = 4.8, 14.0 Hz), 4.51 (d, *J* = 5.2 Hz), 5.05 (1 H, d, *J* = 9.6 Hz), 5.26 (1 H, dd, *J* = 1.6, 10.0 Hz), 5.41 (1 H, dd, *J* = 1.6, 18.0 Hz), 5.57 (1 H, dd, *J* = 4.8, 6.8 Hz), 6.05 (1 H, m), 6.84 (2 H, d, *J* = 8.4 Hz), 7.12 (2 H, d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 27.6, 28.3, 38.3, 54.8, 68.8, 79.6, 85.2, 114.6, 117.5, 128.1, 130.7, 133.4, 149.2, 155.0, 157.8, 174.7; IR (KBr) 2979, 2361, 1788, 1728, 1609, 1511, 1458, 1368, 1316, 1224, 1144, 1011 cm^{-1}; HRMS (M + 1) calcd for $C_{27}H_{43}N_2O_8$ 521.2863, found 521.2854. Anal. Calcd for $C_{27}H_{42}N_2O_8$: C, 62.05; H, 8.10; N, 5.36. Found: C, 62.29; H, 7.70; N, 5.38.

Boc-amidomethyl Methyl (Bromomethyl)benzoate 5. $NaN(TMS)_2$ (1 M THF; 4.75 mL, 4.75 mmol) was added dropwise to a solution of **4** (2.50 g, 4.81 mmol) in THF (40 mL) at −78 °C. Methyl 3,5-bis(bromomethyl)benzoate (1.86 g, 5.77 mmol) and *n*-Bu_4NI (431 mg, 1.17 mmol) were added after 5 min, and the reaction mixture was warmed to 10–15 °C. After 45 min the reaction mixture was diluted with ether (40 mL) and washed with aq NH_4Cl. The aqueous phase was extracted with ether (2X) and the extracts were washed with brine. Drying, concentration, and flash chromatography (10–20% ethyl acetate/hexane) afforded **5** (2.96 g, 82%) as a white foam; R_f 0.45 (50% ether/hexane); ^1H NMR ($CDCl_3$) δ 1.33 (9 H, s), 1.42 (18 H, s), 3.09 (1 H, dd, *J* = 8.4, 14.0 Hz), 3.44 (1 H, dd, *J* = 6.4, 14.0 Hz), 3.89 (3 H, s), 4.45 (2 H, s), 4.51 (d, *J* = 5.2 Hz), 4.56 (1 H, d, *J* = 15.2 Hz), 4.95 (1 H, dd, *J* = 15.2 Hz), 5.29 (1 H, d, *J* = 10.8 Hz), 5.41 (1 H, d, *J* = 17.6 Hz), 5.72 (1 H, dd, *J* = 6.0, 8.4 Hz), 6.05 (1 H, m), 6.81 (2 H, d, *J* = 8.4 Hz), 7.18 (2 H, d, *J* = 8.4 Hz), 7.50 (1 H, s), 7.90 (1 H, s), 7.92 (1 H, s); ^{13}C NMR (d_6-DMSO) δ 27.2, 27.3, 33.2, 35.0, 48.0, 52.2, 61.5, 68.1, 82.0, 83.1, 114.3, 117.1, 120.9, 128.0, 128.7, 130.1, 130.5, 133.8, 133.8, 139.0, 139.3, 151.9, 151.9, 156.8, 165.6, 173.6; IR (film) 3286, 2979, 2933, 1787, 1752, 1710, 1611, 1511, 1481, 1458, 1368, 1302, 1238, 1142, 1027, 999, 923 cm^{-1}; HRMS (M + 1) calcd for $C_{37}H_{50}O_{10}N_2Br$ 763.2637, found 763.2755.

Nona-Boc Trisulfide 6. **5** (2.0 g, 2.63 mmol) was added to a suspension of benzene-1,3,5-trithiol[6] (140 mg, 0.80 mmol) and *i*-Pr_2NEt (610 μL, 35.1 mmol) in THF (20 mL) at rt. The reaction mixture was quenched with aq NH_4Cl after 16 h and extracted with ether (2X). After a brine wash and concentration, flash chromatography (5–3:1:1 pentane:benzene:diethyl ether) gave **6** (1.38 g, 78%) as a solid white foam: mp 80 °C; R_f 0.35 (33% hexane/diethyl ether); ^1H NMR ($CDCl_3$) δ 1.31 (27 H, s), 1.40 (54 H, s), 3.13 (3 H, dd, *J* = 8.4, 13.2 Hz), 3.44 (3 H, dd, *J* = 6.0, 13.2 Hz), 3.86 (9 H, s), 4.08 (6 H, s), 4.50 (6 H, d, *J* = 5.2 Hz), 4.54 (3 H, d, *J* = 15.2), 4.98 (3 H, *J* = 15.2 Hz), 5.27 (3 H, *J* = 9.6 Hz), 5.40 (3 H, d, *J* = 15.2 Hz), 5.71 (3 H, dd, *J* = 6.0, 8.4 Hz), 6.03 (3 H, m), 6.82 (6 H, d, *J* = 8.4 Hz), 7.02 (3 H, s), 7.19 (6 H, d, *J* = 8.4 Hz), 7.51 (3 H, s), 7.86 (6 H, s); ^{13}C NMR (d_6-DMSO) δ 27.2, 27.3, 35.0, 35.7, 48.0, 52.0, 61.4, 81.9, 83.0, 114.3, 117.1, 120.9, 124.2, 127.1, 128.5, 129.8, 130.5, 132.6, 133.8, 137.6, 138.0, 138.9, 151.3, 151.8, 156.8, 165.6, 173.6; IR (film) 3420, 2979, 1791, 1733, 1653, 1636, 1609, 1558, 1511, 1474, 1457, 1436, 1368, 1314, 1219, 1145, 1011, 960, 926, 850, 772 cm^{-1}. Anal. Calcd for $C_{117}H_{150}N_6O_{30}S_3$: C, 63.40; H, 6.82; N, 3.79. Found: C, 62.87; H, 6.80; N, 3.68.

Tri-Boc Trisulfide 7. Trifluoroacetic acid (75 mL) and anisole (19 mL) were added via syringe to a solution of **6** (11.4 g, 5.15 mmol) in CH_2Cl_2 (150 mL) at rt. After 18 h, concentration gave a light pink residue which was triturated with ether to yield a white powder (low resolution mass spectrophotometric data; *m/z* = 1316). That material was dissolved in DMF (80 mL) containing K_2CO_3 (3.78 g, 31 mmol), *i*-Pr_2NEt (5.4 mL, 31 mmol), and di-*tert*-butyl dicarbonate (5.61 g, 25.75 mmol). After 17 h, the reaction mixture was poured into ethyl acetate (1000 mL) and washed with 1 M aq $KHSO_4$, $NaHCO_3$, and brine. Drying, concentration, and trituration with ether afforded **7** (7.07 g, 85%)

as a white powder: mp 138 °C; R_f 0.39 (10% acetone/CH_2Cl_2); ^{1}H NMR (d_6-DMSO) δ 1.29 (27 H, s), 2.67 (3 H, dd, J = 10.4, 14.0 Hz), 2.86 (3 H, dd, J = 4.4, 14.0 Hz), 3.76 (9 H, s), 4.10 (3 H, m), 4.27 (12 H, m), 4.45 (6 H, d, J = 5.2 Hz), 5.20 (3 H, d, J = 10.4 Hz), 5.33 (3 H, J = 17.6 Hz), 6.04 (3 H, m), 6.77 (6 H, d, J = 8.4 Hz), 7.10 (3 H, s), 7.11 (6 H, d, J = 8.4 Hz), 7.51 (3 H, s), 7.73 (3 H, s), 7.81 (3 H, s), 8.50 (3 H, m); ^{13}C NMR (d_6-DMSO) δ 27.2, 30.8, 35.8, 36.6, 41.7, 52.1, 56.2, 68.0, 78.0, 114.2, 117.2, 123.7, 127.0, 128.1, 129.8, 130.1, 132.6, 133.8, 137.7, 140.6, 155.3, 156.6, 162.3, 165.9, 172.0; IR (KBr) 3310, 2926, 1720, 1511, 1437, 1367, 1310, 1242, 1167, 1024 cm^{-1}. Anal. Calcd for $C_{87}H_{102}N_6O_{18}S_3$: C, 64.66; H, 6.36; N, 5.20. Found: C, 64.07; H, 6.50; N, 5.02.

Pentafluorophenyl Ester of 7. A solution of 1 M aq LiOH (15 mL, 15 mmol) was added to 7 (500 mg, 0.309 mmol) in THF/EtOH/H_2O (6:3:2, 100 mL). The reaction mixture was poured into 1 M aq $KHSO_4$ after 8 h and extracted with ethyl acetate (3X). After the extracts were washed with brine and dried, solvent removal afforded the crude acid as a light brown powder which was washed with ether.

Pentafluorophenol (600 mg, 3.26 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (320 mg, 1.69 mmol) were added to a stirred solution of the crude acid (470 mg) in THF (7.0 mL). After 4 h of stirring, concentration gave a brown residue from which the tris(pentafluorophenyl ester) (435 mg, 68%) was isolated by flash chromatography (0–10% acetone/CH_2Cl_2) as an amorphous white solid: mp 158 °C; R_f 0.24 (5% acetone/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.35 (27 H, s), 2.98 (6 H, d, J = 7.2 Hz), 4.02 (6 H, s), 4.35 (6 H, d, J = 4.4 Hz), 4.44 (6 H, ddd, J = 1.6, 1.8, 5.6 Hz), 5.25 (3 H, dd, J = 1.6, 10.4 Hz), 5.36 (3 H, dd, J = 1.6, 17.2 Hz), 5.99 (3 H, dddd, J = 1.6, 1.8, 10.4, 17.2 Hz), 6.76 (6 H, d, J = 8.4 Hz), 6.98 (3 H, s), 7.05 (6 H, d, J = 8.4 Hz), 7.34 (3 H, s), 7.90 (3 H, s), 7.99 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 29.5, 32.3, 39.0, 39.3, 44.1, 57.5, 70.1, 81.7, 116.1, 119.0, 128.9, 129.8, 129.9, 130.1, 131.4, 131.6, 134.5, 135.7, 138.7, 140.0, 140.9, 141.0, 157.0, 158.9, 163.3, 173.5; IR (KBr) 3371, 2979, 1686, 1615, 1517, 1444, 1368, 1224, 1166 cm^{-1}. Anal. Calcd for $C_{102}H_{93}F_{15}O_{18}S_3$: C, 59.13; H, 4.52; N, 4.06. Found: C, 58.53; H, 4.52; N, 4.06.

Tyrosine Macrocycle 2. Anisole (12 mL) and trifluoroacetic acid (60 mL) were added via syringe to a stirring solution of the above tris(pentafluorophenyl ester) (3.16 g, 1.52 mmol) in CH_2Cl_2 (125 mL). After 6 h, the reaction mixture was concentrated. The resulting pink oil was triturated with ether to yield the tris-TFA amine salt as a white powder (3.20 g).

A solution of the above tris-TFA amine salt (1.50 g, 0.710 mmol) in N,N-dimethylacetamide (25 mL) was added dropwise over 36 h to a rapidly stirred solution of i-Pr_2NEt (30 mL, 172 mmol) in THF (1200 mL) at rt. After the solution was stirred for an additional 12 h, 800 mL of THF was removed and the remaining solution was diluted with ethyl acetate (400 mL). The solution was then washed with 0.5 M aq HCl (2X), aq $NaHCO_3$ (2X), and brine. Drying, concentration, and flash chromatography (10–50% acetone in CH_2Cl_2) afforded **2** as an amorphous white solid (680 mg, 78%): mp 200 °C; R_f 0.38 (20% acetone/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.09 (3 H, dd, J = 7.2, 14.0 Hz), 3.24 (3 H, dd, J = 7.2, 14.0 Hz), 3.78 (3 H, d, J = 15.2 Hz), 4.03 (3 H, dd, J = 4.2, 14.2 Hz), 4.11 (3 H, d, J = 15.2 Hz), 4.38 (3 H, dd, J = 6.8, 14.2 Hz), 4.53 (6 H, d, J = 5.2 Hz), 4.80 (3 H, dd, J = 7.2, 15.6 Hz), 5.28 (3 H, dd, J = 1.2, 9.6 Hz), 5.41 (3 H, dd, J = 1.2, 17.2 Hz), 6.04 (3 H, m), 6.65 (3 H, d, J = 8.0 Hz), 6.68 (3 H, s), 6.83 (3 H, bs), 6.92 (6 H, d, J = 8.4 Hz), 7.08 (3 H, s), 7.21 (6 H, d, J = 8.4 Hz), 7.44 (3 H, s), 7.55 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 32.3, 35.8, 37.6, 45.0, 56.1, 70.2, 116.3, 119.1, 127.3, 129.7, 130.3, 131.5, 131.6, 131.8, 134.2, 134.5, 134.7, 137.9, 140.0, 141.0, 158.9, 168.6, 172.4; IR (KBr) 3310, 2926, 1654, 1510, 1457, 1242, 1178, 1113, 1019, 926, 824 cm^{-1}; HRMS calcd for $C_{69}H_{66}N_6O_9S_3$ 1219.4130, found 1219.4093.

Determination of Optical Purity of 5. K_2CO_3 (20 mg, 0.145 mmol) was added to a stirred solution of **3** (100 mg, 0.131 mmol) in CH_3OH (2 mL). After 30 min, the reaction mixture was filtered, diluted with ether (10 mL), and washed with aq NH_4Cl and brine. Concentration followed by flash chromatography (20% diethyl ether/pentane) afforded N-Boc-O-allyltyrosine methyl ester (40.0 mg, 92%).

The above methyl ester was dissolved in CH_3OH (5.0 mL) and acetyl chloride (1.0 mL, 13.5 mmol) was carefully added by pipette. After 3 h, all volatiles were removed and the resulting white solid was taken up in diethyl ether which was washed with 0.5 M aq LiOH and brine. Drying and solvent removal afforded O-allyltyrosine methyl ester as a waxy solid (26.8 mg, 95%).

O-Allyltyrosine methyl ester (20 mg, 0.084 mmol) was added to a stirred solution of (*S*)-(−)-methoxy(trifluoromethyl)phenylacetic acid (28.0 mg, 0.120 mmol) and DCC (40 mg, 0.20 mmol) in CH_2Cl_2 (0.50 mL). After 3 h the reaction mixture was diluted with CH_2Cl_2 (10.0 mL), filtered, and washed with 0.5 M aq NaOH. Drying and solvent removal afforded the crude (*S*)-(−)-methoxy(trifluoromethyl)phenylacetamide as a waxy oil containing DCC and N,N-dicyclohexylurea: R_f 0.55 (50% ether/hexane); ^{1}H NMR ($CDCl_3$) δ 3.05 (1 H, dd, J = 6.4, 14.4 Hz), 3.13 (1 H, dd, J = 5.4, 14.4 Hz), 3.24 (3 H, s), 3.74 (3 H, s), 4.52 (2 H, d, J = 5.2 Hz), 4.87 (1 H, ddd, J = 5.4, 6.0, 6.4 Hz), 5.29 (1 H, d, J = 10.4 Hz), 5.41 (1 H, d, J = 17.6 Hz), 6.06 (1 H, m), 6.83 (2 H, d, J = 8.4 Hz), 7.05 (2 H, d, J = 8.4 Hz), 7.28 (1 H, d, J = 6.0 Hz), 7.39 (3 H, m), 7.52 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 28.9, 37.0, 52.5, 53.4, 53.7, 55.0, 69.0, 77.9, 115.2, 117.8, 127.8, 128.1, 128.7, 129.8, 130.4, 133.4, 158.0, 166.2, 171.9; IR (film) 3411, 3140, 2953, 2851, 1745, 1696, 1511, 1244, 1233, 1224, 1178 cm^{-1}; HRMS (M + 1) calcd for $C_{23}H_{25}F_3NO_5$ 452.1685, found 452.1685.

O-Allyltyrosine methyl ester (20 mg, 0.084 mmol) was added to a stirring solution of (*RS*)-(±)-methoxy(trifluoromethyl)-phenylacetic acid (28.0 mg, 0.120 mmol) and DCC as described in the preceding paragraph to yield an authentic mixture of diastereomeric MTPA amides: R_f 0.55 and 0.57 (50% ether/hexane); ^{1}H NMR ($CDCl_3$) δ 2.95–3.15 (2 H, m), 3.24/3.46 (3 H, s), 3.74/3.76 (3 H, s), 4.50 (2 H, m), 4.80–5.0 (1 H, m), 5.26 (1 H, d, J = 10.4 Hz), 5.38 (1 H, d, J = 17.4 Hz), 6.03 (1 H, m), 6.71/6.83 (2 H, d, J = 8.4 Hz), 6.77/7.05 (2 H, d, J = 8.4 Hz), 7.28 (1 H, m), 7.39 (3 H, m), 7.50 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 28.9, 36.62, 37.0, 52.2, 52.5, 53.4, 53.7, 54.6, 69.0, 77.9, 114.6, 114.7, 117.4, 117.5, 127.1, 127.7, 128.2, 128.3, 129.1, 129.3, 129.9, 130.0, 133.0, 158.0, 166.2, 171.9; IR (film) 3411, 3140, 2953, 2851, 1745, 1696, 1511, 1244, 1233, 1224, 1178 cm^{-1}; HRMS (M + 1) calcd for $C_{23}H_{25}F_3NO_5$ 452.1685, found 452.1695.