classes of indices showed no unusual trends. All calculations were performed on a VAX computer using SDP/VAX.[19]

X-ray Analysis of 4. Crystal Data. Compound 4: $C_{20}H_{22}N_2O_4$, M_r = 354.41; monoclinic; a = 11.853 (3), b = 10.235 (1), and c = 15.144 (4) Å, β = 108.34 (1)°, V = 1743 (1) Å^3, Z = 4, ρ_{calcd} = 1.350 g/cm^3, F_{000} = 752.0, μ = 0.88 cm^{-1}, space group $P2_1/c$ from systematic absences.

Data Collection. A pale yellow chunk of compound 4 having approximate dimensions of 0.31 × 0.19 × 0.10 mm was mounted on a glass fiber in a random orientation. The data collection was performed with Mo Kα radiation (λ = 0.710 73 Å) on an Enraf-Nonius CAD4 computer controlled κ axis diffractometer equipped with a graphite crystal, incident beam monochromator.[16] Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range of $9 < 2\theta < 17°$, measured by the computer controlled diagonal slit method of centering. The data were collected at a temperature of 20 ± 1° using the $\omega - 2\theta$ scan technique. The scan rate varied from 1 to 20°/min (in ω). Data were collected to a maximum 2θ of 45.0°. A total of 2434 unique reflections were collected. Lorentz and polarization corrections were applied to the data. The linear absorption coefficients is 0.9 cm^{-1} for Mo Kα radiation. No absorption correction was necessary.

(19) Frenz, B. A. The Enraf-Nonius CAD 4 SDP—A Real-time System for Concurrent X-ray Data Collection and Crystal Structure Determination. In *Computing and Crystallography*; Schenk, H., Olthof-Hazelkamp, R., vanKonigsveld, H., Bassi, G. C., Eds., Delft University Press: Delft, Holland, 1978; pp 64-71.

Structure Analysis. The structure was solved by direct methods using MULTAN. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and added to the structure factor calculations but their positions were not refined. Because of the small size of the crystal, only 966 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 175 variable parameters and converged with unweighted and weighted agreement factors of 0.051 and 0.056 respectively.[17] The highest peak in the final difference Fourier had a height of 0.18 e/Å^3 with an estimated error based on δF of 0.05.[18] Plots of $E_w(F_o - F_c)^2$ versus Fo, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. All calculations were performed on a VAX computer using SDP/VAX.[19]

Acknowledgment. This investigation was supported by Grant AI25712, awarded by the National Institute of Allergy and Infectious Diseases, DHHS. We are grateful to Phillip E. Fanwick for his assistance in the X-ray studies, to John F. Kozlowski and Dhanapalan Nagarathnam for recording the 500-MHz NMR spectra, and to Joseph G. Stowell for his helpful comments.

Registry No. 1, 549-21-3; 2, 128902-99-8; 3, 128903-00-4; (±)-4, 128903-01-5; (±)-5, 128903-02-6; (±)-6, 128903-03-7; (±)-7, 128903-04-8.

Supplementary Material Available: X-ray data for 3 and 4 (25 pages). Ordering information is given on any current masthead page.

Total Synthesis of L,L-Isodityrosine and Isodityrosine-Derived Agents: K-13, OF4949-III, and OF4949-IV

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Full details of the development of reaction conditions for implementation of an activated Ullmann condensation reaction that may be conducted without amino acid racemization and that have proven suitable for incorporation of the selectively protected catechol of functionalized L-Dopa derivatives are described. The application of this procedure in the total synthesis of L,L-isodityrosine (**15**), K-13 (**1**), and OF4949-III/OF4949-IV (**4**/**5**) is detailed. Full details of a study of the macrocyclization reaction required for formation of the 17-membered tripeptides incorporating a diaryl ether linked meta- and paracyclophane structural subunit are provided and illustrate that the cyclization in route to K-13/OF4949-I - OF4949-IV is optimally conducted on substrates bearing a carbamate derivative of the C-15/C-9 amine and a C-4 free phenol with C^{11}-N^{10}/C^{10}-N^{11} amide bond closure.

Introduction

K-13 (**1**), an isodityrosine-derived cyclic tripeptide isolated from *Micromonospora halophytica* ssp. *exilisia K-13* and identified by spectroscopic and chemical degradative studies,[2] has been shown to be a potent, noncompetitive inhibitor of angiotensin I converting enzyme (I_{50} = 0.17 μg/mL, K_i = 0.35 μM) and weak inhibitor of aminopeptidase B.[3] Consequently K-13[4-6] represents the newest addition to a class of isodityrosine-derived[7,8] cyclic peptides now including OF4949-I - OF4949-IV (**2**-**5**),[9-13] potent inhibitors of aminopeptidase B with confirmed immunopotentiating and antitumor properties isolated from *Penicillium rugulosum*, piperazinomycin (**6**),[14-17] and the bi-

(1) Purdue University Cancer Center Graduate Fellow (1988-89).

(2) K-13 structure determination: Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455.

(3) K-13 fermentation, isolation, and biological properties: Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450.

(4) K-13 total synthesis: Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379.

(5) K-13 and OF4949-III total synthesis: Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063.

(6) K-13 total synthesis: Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498.

(7) Isodityrosine: Fry, S. C. *Biochem. J.* **1982**, *204*, 449. Cooper, J. B.; Varner, J. E. *Biochem. Biophys. Res. Commun.* **1983**, *112*, 161.

(8) (a) Isodityrosine synthesis: Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 2053. (b) Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Tetrahedron Lett.* **1989**, *30*, 4211.

(9) OF4949-I - OF4949-IV structure elucidation: Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685. OF4949-I-OF4949-IV fermentation, isolation, and characterization: Sano, S.; Ikai, K.; Kuroda, H.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1674. Biosynthesis: Sano, S.; Ueno, M.; Katayama, K.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1986**, *39*, 1697.

(10) Sano, S.; Ikai, K.; Yoshikawa, Y.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1987**, *40*, 512. Sano, S.; Kuroda, H.; Ueno, M.; Yoshikawa, Y.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1987**, *40*, 519.

(11) OF4949-II total synthesis: Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559.

(12) OF4949-III total synthesis: Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227.

(13) OF4949-III and OF4949-IV total syntheses: Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 5061.

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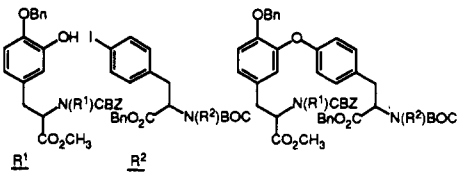
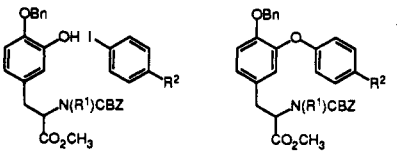
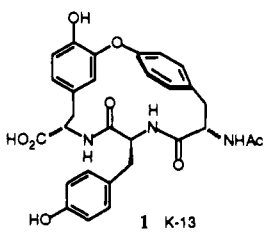
cyclic hexapeptide antitumor antibiotics including bouvardin (7),[18] deoxybouvardin (8),[18,19] and RA-I – RA-VII (8–14).[20–31] Since the OF4949 agents *lack* cytotoxic activity but possess confirmed antitumor activity, the agents constitute a new class of potentially useful antitumor agents that act as immunopotentiators and that may not display host antigenicity or toxicity.[10] In the instances tested, the isodityrosine-derived structural subunit of the agents has proven to be of fundamental importance to their properties[20,28,29] and in many of the instances examined[17,28,30] have been characterized by the failure of synthetic efforts to effect direct diaryl ether formation on a fully assembled peptide precursor. Nonetheless, an indirect thallium trinitrate promoted two-step method for achieving the intramolecular phenol coupling has been introduced by Yamamura and subsequently applied in total syntheses of K-13 (two steps, 15% yield),[4] OF4949-III (two steps, 18% yield),[11] piperazinomycin (two steps, 19% yield),[16] deoxybouvardin and RA-VII (two steps, 2.2%, 5% yield).[19,20] Alternatives to such an approach have included Evans' de novo amino acid synthesis on a functionalized diaryl ether,[5] Schmidt's direct implementation of an intermolecular Ullmann diaryl ether condensation reaction comparable to our own efforts,[12] Jung's indirect use of an intermolecular Ullmann condensation reaction,[8b] a recent modification of the Yamamura thallium trinitrate cyclization,[32] and the development of phenoxide nucleophilic additions to arene–manganese carbonyl complexes or aryl iodonium salts.[33]

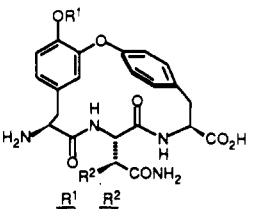
Table I[a,b]

entry	phenol	iodide	diaryl ether	time, h	yield, % (L:D ratio)
1a[c]	 R¹ = CH_3 22	R² = CH_3 16	18	12	0
1b[c]	R¹ = H 23	R² = H 17	19	12	0
2a	 R¹ = CH_3 22	R² = $CO_2{}^tBu$ 20	24	pyridine 8	36 (55:45)
2b			24	chlorobenzene 8	22
2c			24	diglyme 8	trace
2d			24	xylene 8	trace
2e			24	DMF 8	22
2f			24	DMSO 8	33 (62:38)
2g[d]			24	nitrobenzene 8	45 (94:6)
2h[d]	H 23	$CO_2{}^tBu$ 20	25	nitrobenzene 8	46 (94:6)
2i[d]	H 23	CO_2Na 21	25	nitrobenzene 8	51 (94:6)

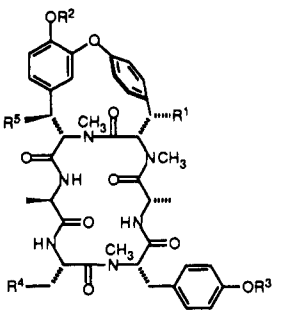
[a] Abbreviations: Bn, benzyl; BOC, *tert*-butyloxycarbonyl; CBZ, carbobenzyloxy. [b] Reaction conditions: 1.2 equiv of NaH, 1.2 equiv of CuBr, pyridine, 125 °C (bath temperature). [c] Attempts employing the modified Ullmann conditions (NaH, $CuBr{\cdot}SMe_2$, $C_6H_5NO_2$, 130 °C, 8 h) afforded no isolable diaryl ether products. [d] CuBr was employed as its dimethyl sulfide complex.

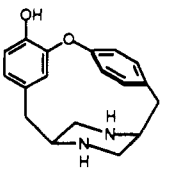


1 K-13



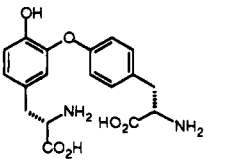
	R¹	R²	
2	CH_3	OH	OF4949-I
3	H	OH	OF4949-II
4	CH_3	H	OF4949-III
5	H	H	OF4949-IV





6 piperazinomycin

	R¹	R²	R³	R⁴	R⁵	
7	OH	H	CH_3	H	H	bouvardin
8	H	H	CH_3	H	H	deoxybouvardin, (RA-V)
9	H	H	CH_3	OH	H	RA-I
10	H	CH_3	H	H	H	RA-II
11	H	CH_3	CH_3	OH	H	RA-III
12	H	CH_3	CH_3	H	OH	RA-IV
13	OH	CH_3	CH_3	H	H	O-methyl bouvardin, (RA-VI)
14	H	CH_3	CH_3	H	H	O-methyl deoxybouvardin, (RA-VII)



15 isodityrosine

Herein we provide full details of the synthesis of L,L-

(14) Piperazinomycin fermentation, isolation, characterization, biological properties: Tamai, S.; Kaneda, M.; Nakamura, S. *J. Antibiot.* **1982**, *35*, 1130.

(15) Piperazinomycin X-ray structure determination: Kaneda, M.; Tamai, S.; Nakamura, S.; Hirata, T.; Kushi, Y.; Suga, T. *J. Antibiot.* **1982**, *35*, 1137.

(16) Piperazinomycin total synthesis: Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481.

(17) Piperazinomycin synthetic studies: Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909.

(18) Bouvardin isolation and structure determination: Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040.

(19) Deoxybouvardin total synthesis: Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Iitokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957.

(20) RA-VII total synthesis: Itokawa, H.; Inoue, T.; Umezawa, I.; Yuasa, M.; Inaba, T. Japan Patent 63 05,0098; *Chem. Abstr.* **1989**, *110*, 213344s.

(21) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762.

(22) Itokawa, H.; Takeya, K.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424.

(23) Itokawa, H.; Takeya, K.; Mori, N.; Kidohoro, S.; Yamamoto, H. *Planta Med.* **1984**, *51*, 313.

(24) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Serisawa, N.; Hamanaka, T.; Mihashi, S. *Chem. Pharm. Bull.* **1984**, *32*, 3216.

(25) Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann* **1984**, *75*, 929.

(26) Itokawa, H.; Takeya, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Mihara, K. *Chem. Pharm. Bull.* **1984**, *32*, 284.

(27) Microbial conversion of bouvardin to *O*-desmethylbouvardin and bouvardin catechol: Petroski, R. J.; Bates, R. B.; Linz, G. S.; Rosazza, J. P. *J. Pharm. Sci.* **1983**, *72*, 1291.

(28) Bates, R. B.; Gin, S. L.; Hassen, M. A.; Hruby, V. J.; Janda, K. D.; Kreik, G. R.; Michaud, J.-P.; Vine, D. B. *Heterocycles* **1984**, *22*, 785.

(29) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487.

(30) Inoue, T.; Naitoh, K.; Kosemura, S.; Umezawa, I.; Sonobe, T.; Serizawa, N.; Mori, N. *Heterocycles* **1983**, *20*, 397.

(31) Synthesis of thioether analogue of K-13: Hobbs, D. W.; Still, W. C. *Tetrahedron Lett.* **1989**, *30*, 5405.

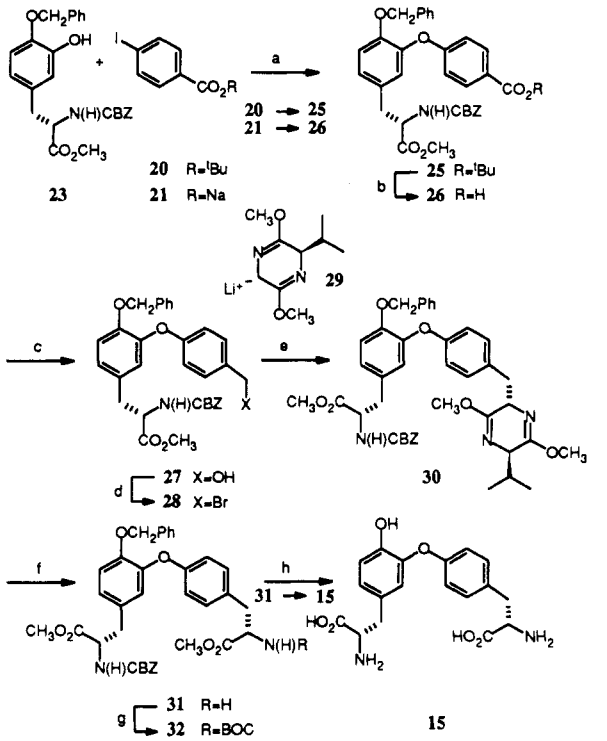
(32) Evans, D. A.; Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912.

(33) Pearson, A. J.; Bruhn, P. R.; Gouzoules, F.; Lee, S.-H. *J. Chem. Soc., Chem. Commun.* **1989**, 659. Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017, 2021.

isodityrosine (15) based on the development of reaction conditions for implementation of an activated Ullmann diaryl ether condensation reaction that proceeds without amino acid racemization and that has proven suitable for incorporation of the selectively protected catechol of functionalized L-Dopa derivatives.[8a] The incorporation of the L,L-isodityrosine precursor **31** into the total synthesis of the cyclic tripeptide K-13 (**1**) is detailed,[6] and the extension of this work to the total synthesis of OF4949-III and OF4949-IV[13] is described. A full study of the macrocyclization reaction required for 17-membered ring formation with incorporation of the diaryl-linked meta- and paracyclophane structural subunit is detailed and highlight unusual effects remote substituents may have on the relative rate of macrocyclization. From these studies, it was found that the K-13/OF4949 macrocyclization is optimally conducted on substrates bearing a carbamate derivative of the C-15/C-9 amine and a free C-4 phenol with C^{11}–N^{10}/C^{10}–N^{11} amide bond closure.

Studies on the Ullmann Diaryl Ether Coupling Reaction. Although the availability of L-3-iodotyrosine initially directed our and related efforts[9,17,30] toward studies of the Ullmann condensation[34,35] of suitably protected derivatives of this amino acid with a protected L-tyrosine derivative, the results of such studies have proven unsuccessful.[8] As illustrated with the representative examples summarized in earlier work,[8a] the Ullmann condensation of electron-rich aryl iodides with unactivated phenols has proven successful for simple substrates[35] and modestly successful for simple electron-rich aryl iodides bearing an ortho alkoxy substituent and for reactions of a single functionalized tyrosine derivative, but has not proven successful when applied to the coupling of two functionalized tyrosine derivatives. Presumably this may be attributed to the steric and electronic deceleration of the Ullmann condensation due to the aryl iodide ortho electron-donating substituent,[35] the sensitivity of a protected amino acid to standard Ullmann reaction conditions, and competitive coupling reactions.[36-39] The alternative combination of promoting an Ullmann condensation of a selectively protected catechol including the L-Dopa derivative **23** did prove successful. Although the direct Ullmann condensation of **23** with protected *p*-iodophenylalanine derivatives (Table I, entry 1) proved unsuccessful and its condensation with unactivated aryl iodides proved only modestly successful, the Ullmann condensation of **23** with activated aryl iodides proved viable. A study of the Ullmann condensation of **23** with **20** revealed suitably mild reaction conditions (130 °C, nitrobenzene) that permitted the coupling to proceed without amino acid racemization[6,41] and that this Ullmann condensation could be extended to the productive use of sodium *p*-iodobenzoate (**21**). Representative results of the optimization of the chemical conversion for the Ullmann condensation of **23** with **20–21** with minimization of the extent of racemization are detailed in Table I.

Scheme I[a]

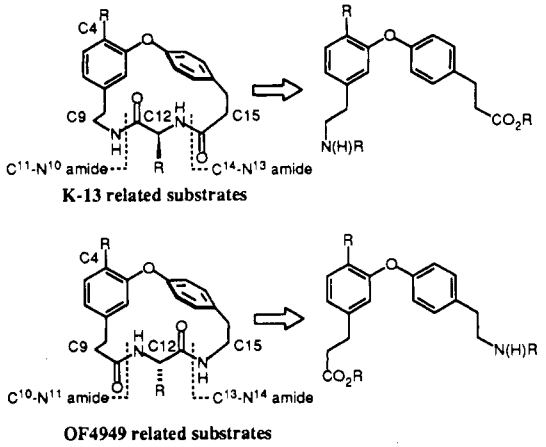


[a] (a) 1.0 equiv of NaH, 1.4 equiv of CuBr, $C_6H_5NO_2$, 130 °C, 8 h, 46% for **25**, 51% for **26**; (b) 3.0 M HCl/EtOAc, 25 °C, 1.5 h, 95%; (c) 1.0 equiv of 1.0 M BH_3·THF, THF, 0 °C, 3 h, 89%; (d) 2.0 equiv of CBr_4, 2.0 equiv of Ph_3P, Et_2O, 25 °C, 72%; (e) 1.0 equiv of NaH, THF, 0 °C, 5 min; 1.2 equiv of **29**, THF, −78 °C, 14 h; (f) 0.5 N HCl(aq)/THF, 25 °C, 57% from **28**; (g) 1.0 equiv of $(BOC)_2O$, K_2CO_3, THF, 25 °C; (h) 6.0 N HCl, 65 °C, 6 h.

Synthesis of L,L-Isodityrosine (15). The synthesis of L,L-isodityrosine (**15**) was initiated with the incorporation of the selectively protected L-Dopa derivative **23**[40] (chiral phase HPLC L:D ratio 95:5) in the Ullmann condensation with *tert*-butyl 4-iodobenzoate (**20**, NaH, CuBr·SMe_2, $C_6H_5NO_2$, 130 °C, 8 h, 46%)[41] to afford **25** (chiral phase HPLC L:D ratio 94:6) (Scheme I). Conversion of the *tert*-butyl ester **25** to the carboxylic acid **26** (3.0 M HCl/EtOAc, 25 °C, 1.5 h, 95%) and subsequent reduction (BH_3·THF, THF, 0 °C, 3 h, 89%) provided alcohol **27** which was converted to bromide **28** (CBr_4, Ph_3P, Et_2O). Alternatively, the carboxylic acid **26** could be obtained directly from the Ullmann condensation reaction of **23** with sodium *p*-iodobenzoate (**21**, NaH, CuBr·SMe_2, $C_6H_5NO_2$, 130 °C, 8 h, 51%). Treatment of **28** with Schöllkopf's reagent[42] **29** (NaH, THF, 0 °C, 5 min; **29**, THF, −78 °C, 14 h) and subsequent acid-catalyzed hydrolysis of the cyclic imidate **30** (0.5 N aqueous HCl/THF, 25 °C, 15 h, 57–60% from **28**) provided **31**. HPLC analysis of *tert*-butyloxycarbonyl derivative **32** revealed a 90:4.5:4.5:<1 ratio of diastereomers indicating that the alkylation proceeded with 95% de. In studies of the hydrolysis of **30** to **31** we noted that the conversion was diminished if extended hydrolysis reaction times were employed, and presumably is the result of competitive Fisher deesterification of the methyl ester. Exhaustive removal of protecting groups (6.0 N HCl, 65 °C, 6 h, 100%) of **31** afforded L,L-isodityrosine

(34) Whitesides, G. M.; Sadowski, J. S.; Liburn, J. *J. Am. Chem. Soc.* **1974**, *96*, 2829.
(35) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679.
(36) Fitton, P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 6. Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287. A variety of reaction conditions were examined to promote the Ullmann condensation through generation of an arylpalladium(II) intermediate and proved unsuccessful (Table II, supplementary material).
(37) Cava, M. P.; Afzali, A. *J. Org. Chem.* **1975**, *40*, 1553.
(38) Cairncross, A.; Sheppard, W. A.; Wonchoba, E. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 875.
(39) Afzali, A.; Firouzabadi, H.; Khalafi-nejad, A. *Synth. Commun.* **1983**, *13*, 335.
(40) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1987**, *52*, 5283.
(41) In contrast to the independent and related efforts of Schmidt,[12] we have observed substantial racemization of **23** and **25–26** if the Ullmann condensation is conducted under standard reaction conditions (pyridine, 130 °C, 8–18 h, ca. 90% racemization). The apparent difference in the observations may be due to the diminished acidity of a *tert*-butyl ester relative to a methyl ester.
(42) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798.

Scheme II

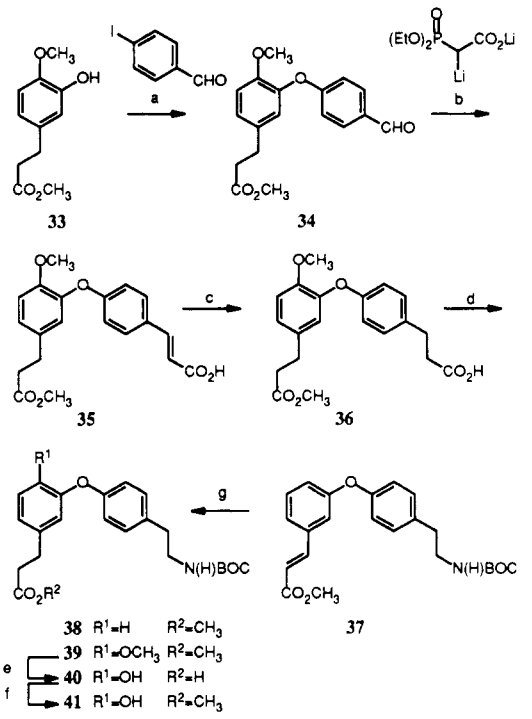


15 as the bishydrochloride salt [15·2HCl, $[\alpha]^{22}_D$ −28.2° (*c* 1.0, MeOH)], completing a five-step synthesis of optically active 15.

Macrocyclization Studies: Formation of 17-Membered Cyclic Tripeptides Bearing a Diaryl Ether Linked Meta- and Paracyclophane. In efforts to determine the optimal site and method for macrocyclization suited for use in the total synthesis of K-13/OF4949 and structurally related agents and with the intent of providing access to simplified subunits that could be incorporated into key partial structures of the natural agents, acyclic substrates with both the K-13 (**52–63**) and OF4949 (**64–69**) amino- and carboxy-termini arrangement were prepared (Scheme II). The simplified OF4949 related diaryl ethers **38–41** containing the pertinent skeletal amino acid of isodityrosine were prepared as detailed in Scheme III. Ullmann condensation of methyl 3-iodocinnamate[43] with *N*-(*tert*-butyloxycarbonyl)tyramine[29] (NaH, CuBr·SMe_2, pyridine, 115 °C, 12 h, 63% **37**) followed by hydrogenation of **37** (2 atm of H_2, 10% Pd–C, MeOH, 25 °C, 8 h) provided **38**. Derivatives **39** and **41** were prepared through Ullmann reaction of **33**[44] with *p*-iodobenzaldehyde (NaH, CuBr·SMe_2, pyridine, 115 °C, 8 h, 78%) to afford the aldehyde **34**. Condensation of **34** with the dianion derived from (diethylphosphono)acetic acid[45] (THF, −78 °C, 4 h, 86%) followed by reduction of **35** (3 atm of H_2, 10% Pd–C, MeOH, 25 °C, 12 h, 99%) provided **36**. Curtius rearrangement of **36** (Et_3N, DPPA, *t*-BuOH, 85 °C, 10 h, 81%)[46] afforded **39**. The phenol **41** was obtained through exhaustive demethylation of **39** (EtSNa, DMF, 155 °C, 3 h, 78%)[47] followed by Fisher esterification (MeOH, cat. H_2SO_4).

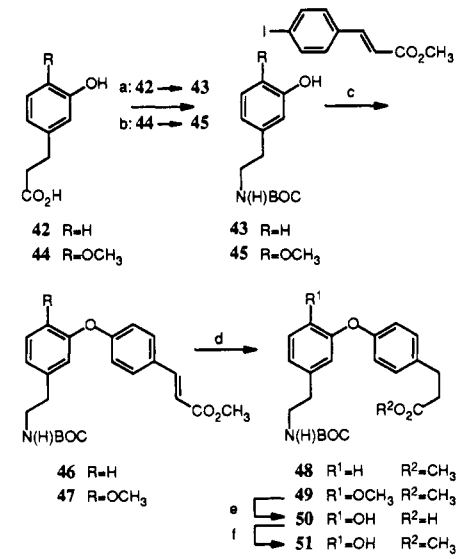
Benzylation of commercially available **42** (1 equiv of $C_6H_5CH_2Br$, 2 equiv of NaH, 0.1 equiv of *n*-Bu_4NI, DMF, 25 °C, 3 h) followed by Curtius rearrangement[46] (Et_3N, DPPA, *t*-BuOH, 85 °C, 8 h) and catalytic hydrogenolysis (3 atm of H_2, 10% Pd–C, THF, 25 °C, 6 h, 87% overall) provided **43** (Scheme IV). Similarly, Curtius rearrangement of 3-hydroxy-4-(methoxyphenyl)propanoic acid (**44**,[44] Et_3N, DPPA, *t*-BuOH, 80 °C, 10 h, 63%) afforded **45**. Ullmann condensation of the phenols **43** and **45** with methyl *p*-iodocinnamate[48] (NaH, CuBr·SMe_2, pyridine, 115 °C, 12 h) provided the diaryl ethers **46** and **47** in 51% and 77% yield, respectively. Reduction of the olefins (H_2, 10% Pd–C, MeOH, 25 °C) afforded **48** (97%) and **49** (100%) suitable for incorporation into the preparation of K-13 macrocyclization substrates. Demethylation[47] of **49** (4.0

Scheme III[a]



[a] (a) 1.0 equiv of NaH, 1.0 equiv of CuBr·SMe_2, 2.0 equiv of *p*-iodobenzaldehyde, pyridine, 115 °C, 8 h, 78%; (b) THF, −78 °C, 4 h, 86%; (c) 0.1 wt equiv of 10% Pd–C, MeOH, 25 °C, 12 h, 99%; (d) 1.0 equiv of Et_3N, 1.5 equiv of DPPA, *t*-BuOH, 85 °C, 10 h, 81% **39**; (e) 4.0 equiv of EtSNa, DMF, 155 °C, 3 h, 78%; (f) 0.05 equiv of H_2SO_4, MeOH, 65 °C, 8 h, 100%; (g) 0.1 wt equiv of 10% Pd–C, 2 atm of H_2, MeOH, 25 °C, 8 h, 100% **38**.

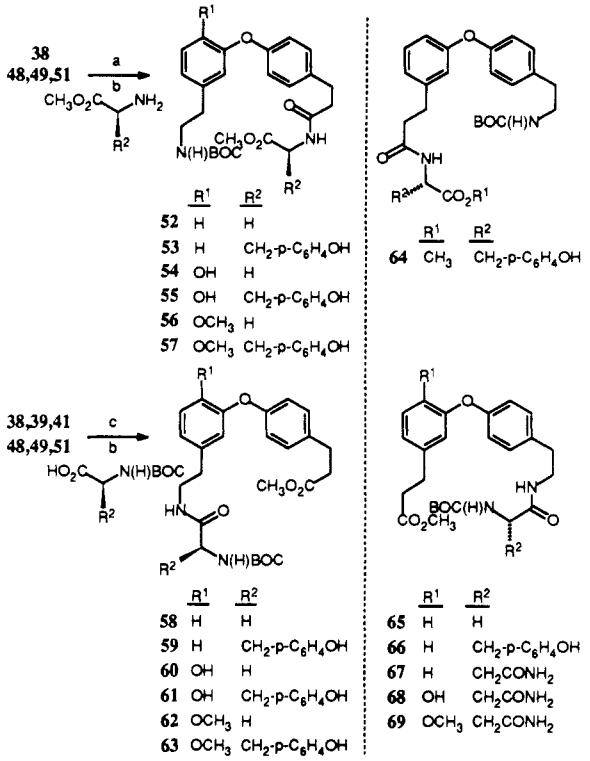
Scheme IV[a]



[a] (a) 1.0 equiv of benzyl bromide, 2.0 equiv of NaH, 0.1 equiv of *n*-Bu_4NI, DMF, 25 °C, 10 h, 100%; 1.0 equiv of Et_3N, 1.2 equiv of DPPA, *t*-BuOH, 85 °C, 8 h; 0.3 wt equiv of 10% Pd–C, 3 atm of H_2, THF, 25 °C, 6 h, 87% from **42**; (b) 1.0 equiv of Et_3N, 1.5 equiv of DPPA, *t*-BuOH, 80 °C, 10 h, 63%; (c) 1.0 equiv of NaH, 1.0 equiv of CuBr·SMe_2, 2.0 equiv of methyl *p*-iodocinnamate, pyridine, 115 °C, 12 h, 77% for **46**; 51% for **47**; (d) 0.1 wt equiv of 10% Pd–C, 3 atm of H_2, MeOH, 25 °C, 3 h, 97% for **48**, 100% for **49**; (e) 4.0 equiv of EtSNa, DMF, 155 °C, 3 h, 74%; (f) 0.05 equiv of H_2SO_4, MeOH, 70 °C, 9 h, 100%.

(43) Happer, A. R.; Steenson, B. E. *Aust. J. Chem.* **1985**, *38*, 337.
(44) McCorkindale, N. J.; McCulloh, A. W.; Magrill, D. S. *Tetrahedron* **1969**, *25*, 5475.
(45) Coutrot, P.; Snoussi, M.; Savignac, P. *Synthesis* **1978**, 133.
(46) Yamada, S.; Ninoyama, K.; Shioiri, T. *Tetrahedron* **1974**, *30*, 2151.
(47) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, *16*, 1719.
(48) Dombrovskii, V. A.; Gavril'chuk, V. M.; Dombrovskii, A. V. *Izv. Vyssh. Ucheb. Azved., Khim. Khim. Technol.* **1971**, *14*, 895.

Scheme V[a]



[a] (a) LiOH, THF/MeOH/H_2O; (b) EDCI, DMF, 25 °C; (c) 3.0 M HCl/EtOAc, 25 °C.

equiv, EtSNa, DMF, 155 °C, 3 h, 74%) and reesterification of **50** (MeOH, cat. H_2SO_4, 70 °C) provided the phenol derivative **51**.

The diphenyl ethers **38**, **39**, **41** and **48**, **49**, **51** were coupled on the amino termini with the *N*-*tert*-butyloxycarbonyl derivatives of glycine, L-tyrosine, and L-asparagine and on the carboxy termini with the methyl esters of glycine and L-tyrosine employing carbodiimide-promoted peptide bond formation procedures (Scheme V). The resultant agents **52–69** were subjected to hydrolysis of the methyl esters (LiOH, THF/MeOH/H_2O, 25 °C) to generate the corresponding carboxylic acids which were converted directly to the amino acid hydrochlorides (3.0 M HCl/EtOAc) or to the corresponding pentafluorophenyl esters (C_6F_5OH, EDCI, CH_2Cl_2, 25 °C) which in turn were converted to the active-ester amine hydrochlorides (3.0 M HCl/EtOAc).

With a full range of substrates available for examination, comparative studies on the method, site, and substrate structural features affecting the 17-membered macrocyclization were conducted. A range of macrocyclization techniques were examined,[49-51] and without exception, the diphenyl phosphorazidate promoted ring closure of the substrate amino acid hydrochloride conducted at low temperature (0 °C) at moderate concentrations (0.008 M) under the recently modified conditions (1.5 equiv of DPPA,

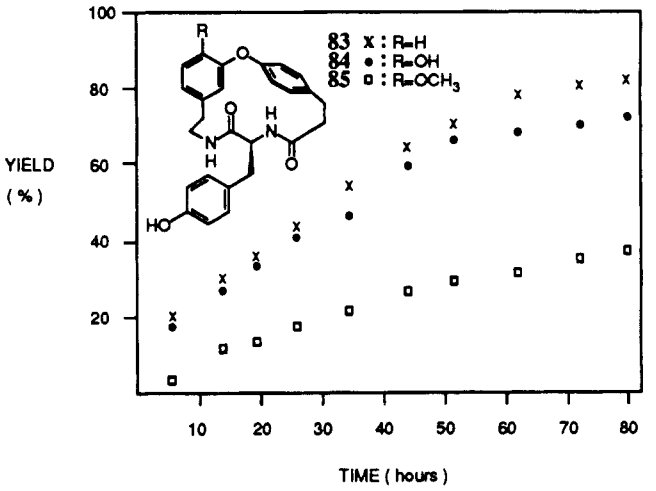


Figure 1. Plot of percent yield (HPLC separation, UV detection) of the products (**83**, **84**, **85**) of cyclization of a 1:1:1 mixture of **86**:**87**:**88** versus time (1.5 equiv of DPPA, 5.0 equiv of $NaHCO_3$, DMF, 0.008 M, 0 °C), illustrating the comparable rates of macrocyclization of **86** and **87** and the substantially slower rate of cyclization of **88**. k_{rel}: **83** (1.0), **84** (0.94), **85** (0.40).

5.0 equiv of $NaHCO_3$, DMF, 0 °C, 72 h)[49] proved technically most convenient and provided the cyclic peptides in excellent yields (Table II). In the course of the initial studies to promote the 17-membered macrocyclization reaction of the K-13 related substrates (Table II, entries 1–5), two apparently unrelated substrate structural features proved to be key elements to the establishment of a successful ring closure reaction. The first, and anticipated, structural requirement was highlighted by unsuccessful efforts to promote the ring closure of acetamides **90–91** with formation of the C^{14}–N^{13} amide bond (Table II, entry 4). Presumably, intramolecular active ester closure to a 5-membered oxazolidinone proved competitive with the 17-membered ring closure reaction thus precluding C^{14}–N^{13} amide bond formation. This was apparently confirmed with the quantitative recovery of the free carboxylic acid **90** from the attempted cyclization of active ester **91** (Table II, entry 4c). However, initial attempts to promote the macrocyclization of acetamides **92–93** under comparable reaction conditions failed to provide cyclic tripeptide and do not suffer from an available competitive oxazolidinone ring closure reaction pathway (Table II, entry 5a–b). Thus, although the origin of the failure or rate deceleration of the macrocyclization of acetamides **92–93** is not obvious it does suggest that a carbamate derivative of the C-15 amine would be preferred or required for observation of the 17-membered macrocyclization (Table II, entry 5c–d). More unusual was the effect that a remote C-4 aryl substituent had on the 17-membered ring closure. In *three* separate series, simple substrates lacking an aryl C-4 substituent and those bearing a C-4 free phenol were found to undergo macrocyclization without event while the identical substrates bearing a C-4 methyl ether often failed to close productively to the 17-membered ring.[52] This proved most pronounced in the high dilution,

(49) Brady, S. F.; Freidinger, R. M.; Paleveda, W. J.; Colton, C. D.; Homnick, C. F.; Whitter, W. L.; Curley, P.; Nutt, R. F.; Veber, D. F. *J. Org. Chem.* **1987**, *52*, 764. Brady, S. F.; Varga, S. L.; Freidinger, R. M.; Schwenk, D. A.; Mendlowski, M.; Holly, F. W.; Veber, D. F. *J. Org. Chem.* **1979**, *44*, 3101.

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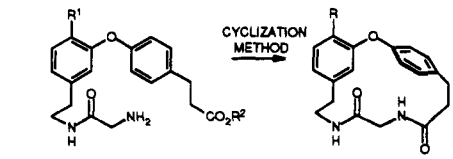
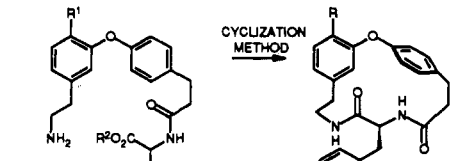
(52) This failure to observe cyclization is due to competitive hydrolysis of the pentafluorophenyl esters attributable to the presence of adventitious water. This competitive hydrolysis was observed *only* with the slower cyclization reactions and can be avoided by employing rigorously dried solvents. Under such conditions, high yields of cyclization products may be obtained from the cyclization of the pentafluorophenyl esters. We thank Professor D. A. Evans for bringing this to our attention and sharing unpublished observations. There is, nonetheless, a modest to substantial rate deceleration (Figures 1–2) of the cyclization of substrates **72–73**, **81–82**, and **88–89** that may be attributed to the presence of the C-4 methoxy substituent.

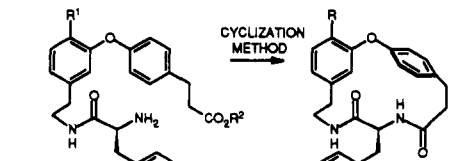
Table II[a,b]



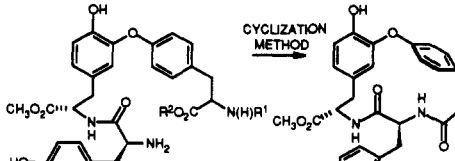
Entry		R¹	R²				R	
1a	70	H	H	A	71%	74	H	
b	71	OH	H	A	68%	75	OH	
c	72	OCH_3	H	A	66%	76	OCH_3	
d	73	OCH_3	C_6F_5	C	0%	76	OCH_3	(88% 72)
e	73	OCH_3	C_6F_5	D	61%	76	OCH_3	



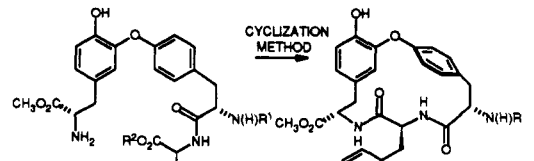
		R¹	R²				R	
2a	77	H	H	A	62%	83	H	
b	77	H	H	B	69%	83	H	
c	78	H	C_6F_5	C	49%	83	H	
d	79	OH	H	A	59%	84	OH	
e	79	OH	H	B	62%	84	OH	
f	80	OH	C_6F_5	C	57%	84	OH	
g	81	OCH_3	H	A	71%	85	OCH_3	
h	82	OCH_3	C_6F_5	C[c]	0%	85	OCH_3	(88% 81)



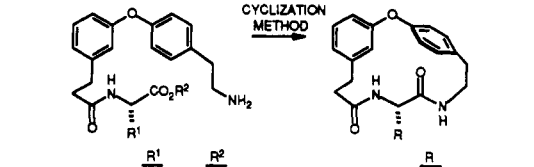
		R¹	R²				R	
3a	86	H	H	A	68%	83	H	
b	87	OH	H	A	66%	84	OH	
c	88	OCH_3	H	A	12-25%	85	OCH_3	(88-70% 88)
d	88	OCH_3	H	A[d]	0%	85	OCH_3	(100% 88)
e	89	OCH_3	C_6F_5	C	0%	85	OCH_3	(96% 88)
f	89	OCH_3	C_6F_5	C[e]	53%	85	OCH_3	(36% 88)
g	89	OCH_3	C_6F_5	D	58%	85	OCH_3	
h	89	OCH_3	C_6F_5	E	68%	85	OCH_3	



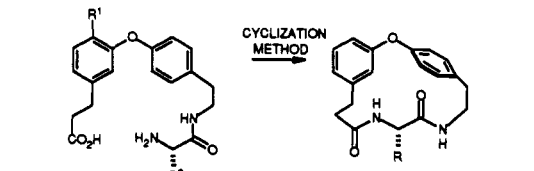
		R¹	R²			R	
4a	90	$COCH_3$	H	A	cyclic or linear oligomer		
b	90	$COCH_3$	H	B	cyclic or linear oligomer		
c	91	$COCH_3$	C_6F_5	C	0%	114	$COCH_3$ (95% 90)



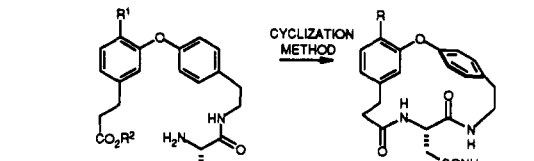
		R¹	R²				R	
5a	92	$COCH_3$	H	A	0%	114	$COCH_3$	(100% 92)
b	93	$COCH_3$	C_6F_5	C	0%	114	$COCH_3$	(62% 92)
c	112	$CO_2{}^tBu$	H	A	61%	114	$CO_2{}^tBu$	
d	113	$CO_2{}^tBu$	C_6F_5	C	51%	114	$CO_2{}^tBu$	



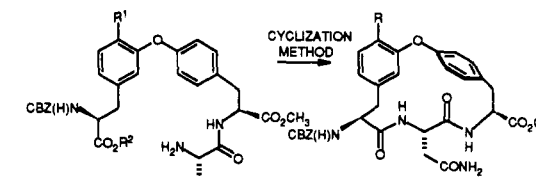
		R¹	R²				R	
6	94	$CH_2C_6H_4OH$	C_6F_5	C	61%	95	$CH_2C_6H_4OH$	



		R¹	R²				R	
7a	96	H	$CH_2C_6H_4OH$	A	62%	95	$CH_2C_6H_4OH$	
b	97	H	H	A	53%	98	H	



		R¹	R²				R	
8a	99	H	H	A	72%	102	H	
b	100	OH	H	A	70%	103	OH	
c	101	OCH_3	H	A	39%	104	OCH_3	



		R¹	R²				R	
9a	126	OH	H	A	65%	128	OH	
b	127	OCH_2Ph	H	A	36%	130	OCH_2Ph	

[a] All cyclization substrates were employed as their hydrochloride salts. [b] Standard reaction conditions used for each cyclization method are as follows. Method A: diphenylphosphorazidate (1.5 equiv), $NaHCO_3$ (5.0 equiv), DMF (0.008 M), 0 °C, 72 h, ref 49. Method B: *n*-Bu_4NOH (1.0 equiv), $C_6H_5CH_3$; mesitylenesulfonyl chloride (3.0 equiv), $(iPr)_2EtN$ (3.0 equiv), C_6H_6, 35 °C, 48 h, ref 50. Method C: DMF (18 h addition, 0.0003 M final concentration), $NaHCO_3$ (5.0 equiv), DMF, 90 °C, additional 1 h, ref 51. Method D: (cyclization substrate employed as *N*-carbobenzyloxy derivative) dioxane (8 h addition, 0.001 M final concentration), H_2 (1 atm), Pd(0) (0.1 wt equiv), *N*-methylmorpholine (1.0 equiv), dioxane (1% absolute EtOH), ref 5. Method E: dioxane (12 h addition, 0.0004 M final concentration), dioxane–pyridine, 90 °C, additional 1 h, ref 5. [c] Higher (120 °C) reaction temperatures afforded the same result. [d] 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) was employed as a catalyst (0.1 equiv). [e] Rigorously dried pyridine was used as the reaction solvent with no additional $NaHCO_3$.

thermal cyclization of the pentafluorophenyl esters (Table II, entries 1c–e, 2g–h, 3c–h, and 3e). On substrates comparable to those required for the total synthesis of K-13, this rate deceleration of the macrocyclization reaction proved substantial and most pronounced in efforts to close the C^{14}–N^{13} versus C^{11}–N^{10} amide bond (Table II, entries

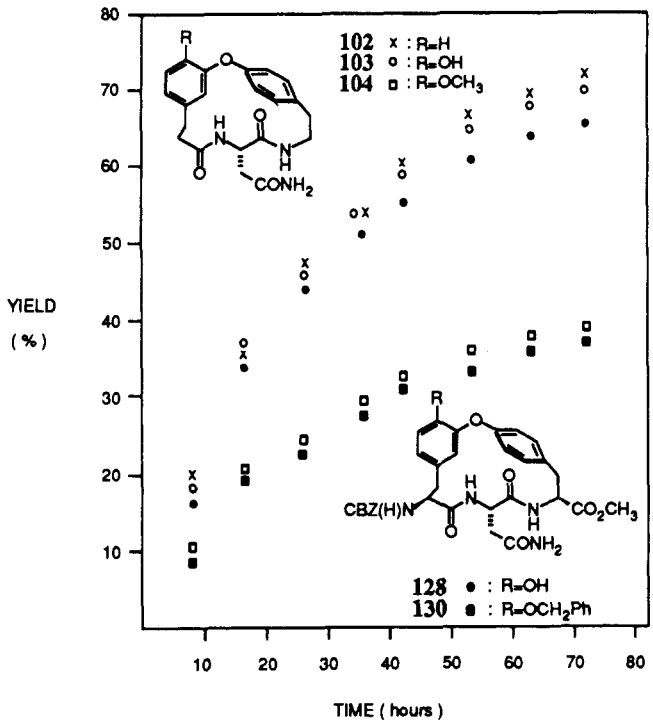


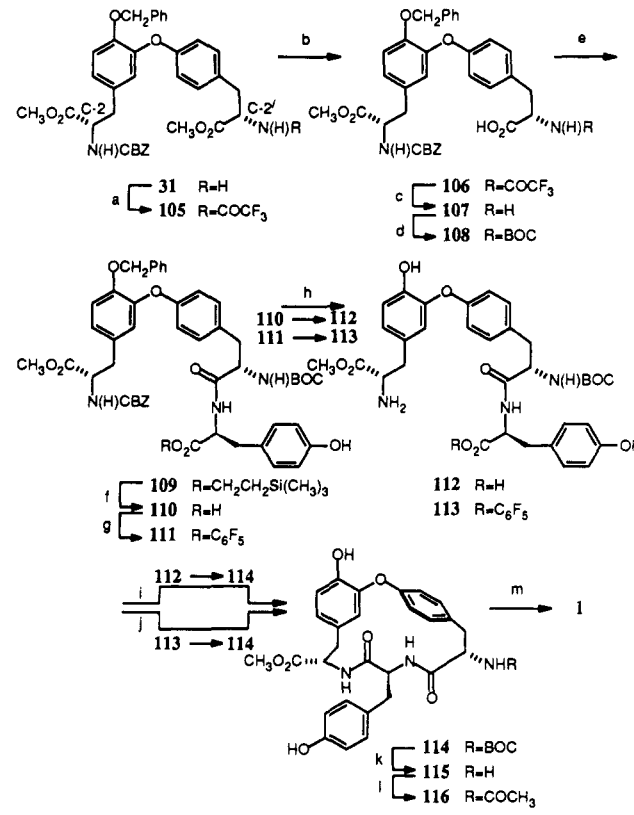
Figure 2. Plot of percent yield (HPLC separation, UV detection) of the products (**102, 103, 104, 128, 130**) of cyclization of **99:100:101** and of **126, 127** versus time (1.5 equiv of DPPA, 5.0 equiv of $NaHCO_3$, DMF, 0.008 M, 0 °C), illustrating the effects of remote substitution on the OF4949 macrocyclization. k_{rel}: **102** (1.0), **103** (0.98), **128** (0.92), **104** (0.54), **130** (0.51).

3 versus 2) but could be overcome employing rigorously dried solvents in the pentafluorophenyl ester macrocyclization reaction (Table II, entry 3e versus 3f–h and 1d versus 1e).[52] A direct comparison of the relative rates of ring closure to **83–85** revealed that this effect arises from a *rate deceleration* that may be attributed uniquely to the presence of the aryl C-4 methoxy substituent (Figure 1), k_{rel}: **83** (1.0), **84** (0.94), **85** (0.40). Thus, the experimental observations illustrate that the macrocyclization reaction enroute to the preparation of K-13 is optimally conducted on substrates bearing a carbamate derivative of the C-15 amine and a free C-4 phenol with C^{11}–N^{10} amide bond closure. With such substrates, the macrocyclization reaction may be conducted uneventfully under established macrocyclization reaction conditions including the high dilution, thermal cyclization of an active pentafluorophenyl ester (Table II, entries 5c–d).[52]

Similarly, C^{13}–N^{14} macrocyclization of the OF4949 related substrates was confirmed with **94** (Table II, entry 6), however, the potential OF4949 C^{13}–N^{14} macrocyclization route was not further pursued due to anticipated competitive, succinimide formation with incorporation of the OF4949 asparagine side chain.[53] As a consequence of the unanticipated effect an aryl C-4 alkoxy substituent had on the rate of the K-13 macrocyclization,[6] the comparative macrocyclization reactions of the series of OF4949-related substrates **99–101** were studied in detail. The relative rates of macrocyclization of **99–101** and **125–126** were directly compared with the intent of defining the C^{10}–N^{11} macrocyclization rate effects due to the presence and nature of

(53) Schmidt and co-workers[12] have successfully employed the C^{14}–N^{13} amide bond macrocyclization of OF4949-III using the aspartic acid methyl ester which avoids the competitive reactions associated with the use of asparagine carboxamide.

Scheme VI[a]



[a] (a) 1.05 equiv of $(CF_3CO)_2O$, THF, 25 °C, 1 h, 97%; (b) 1.0 equiv of NaH, THF, 0 °C → 25 °C, 1 h, 68%; (c) 10% K_2CO_3/MeOH–H_2O (5:2), 25 °C, 6 h, 86%; (d) 1.05 equiv of $(t\text{-}BuO_2C)_2O$, 2.0 equiv of K_2CO_3, THF, 25 °C, 2 h, 91%; (e) 1.0 equiv of (2-(trimethylsilyl)ethyl)-L-tyrosine, 1.0 equiv of EDCI, CH_2Cl_2, 25 °C, 9 h, 85%; (f) 1.0 equiv of *n*-Bu_4NF, DMF, 25 °C, 4 h, 92%; (g) 1.0 equiv of EDCI, 2.0 equiv of C_6F_5OH, CH_2Cl_2, 25 °C, 2 h, 85%; (h) 10 wt equiv of 10% Pd–C, 1 atm of H_2, 2.0 equiv of 10% HCl(aq), THF, 25 °C, 4 h; (i) 1.5 equiv of DPPA, DMF, 0.008 M, pH 7 ($NaHCO_3$), 0 °C, 72 h, 61%; (j) DMF addition (18 h) to DMF containing 5 equiv of $NaHCO_3$, 0.0003 M final concentration; 90 °C, additional 2 h, 51%; (k) 3.0 M HCl/EtOAc, 25 °C, 2 h; (l) 1.05 equiv of $(CH_3CO)_2O$, 3.0 equiv of $NaHCO_3$, THF, 25 °C, 2 h, 89%; (m) 2.5 equiv of LiOH·H_2O, THF–MeOH–H_2O (3:1:1), 25 °C, 4 h, 93%.

the aryl C-4 substituent, the C-9 substituent, and the C-15 substituent (Table II, entries 8–9). Consistent with the prior observations, the presence of a C-4 free phenol as well as the nature and presence of a C-9 and C-15 substituent had *no* substantial effect on the rate of the macrocyclization reaction with C^{10}–N^{11} amide bond closure [k_{rel}: **102** (1.0), **103** (0.98), **128** (0.92), Figure 2]. In addition and as anticipated, the presence of a C-4 alkoxy substituent in substrates lacking (**101**) or possessing (**127**) both a C-9 and C-15 substituent exhibited a substantial rate deceleration of the macrocyclization reaction that may be attributed exclusively to the presence of the aryl C-4 alkoxy substituent [k_{rel}: **104** (0.54), **130** (0.51), Figure 2].

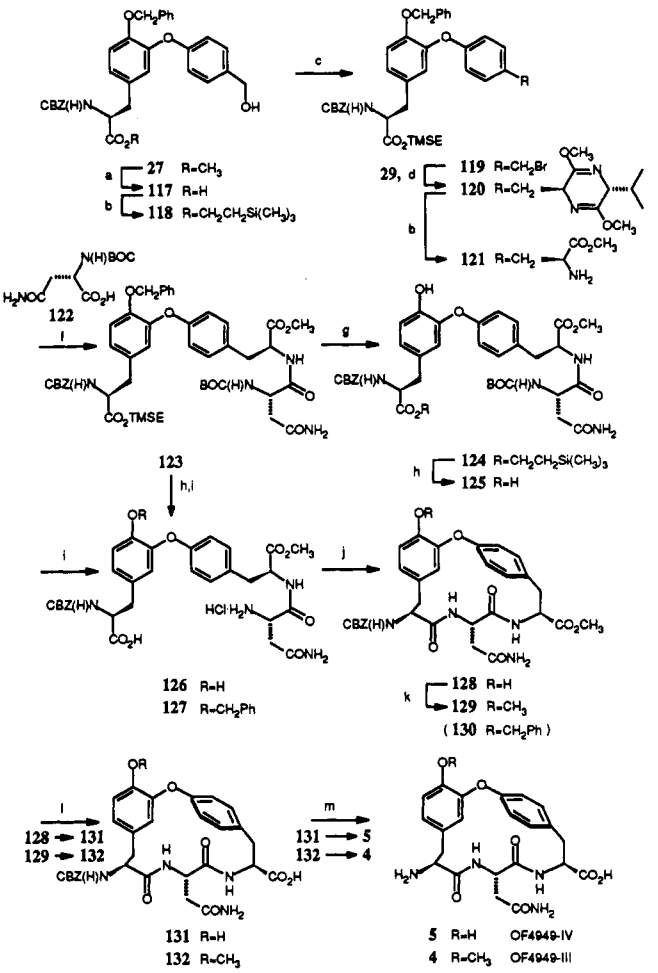
Total Synthesis of K-13. Amino ester **31**, which served as the immediate precursor to L,L-isodityrosine, was viewed as a potential candidate for conversion to K-13 provided the C-2/C-2′ methyl esters could be effectively differentiated. Directed hydrolysis of the C-2′ methyl ester was accomplished through conversion of the free amine **31** to the trifluoroacetamide **105** (97%) (Scheme VI). Intramolecular, base-catalyzed closure of **105** (NaH, THF, 0–25 °C, 68%) to the corresponding unstable oxazolidinone provided the carboxylic acid **106** upon aqueous workup.

Reconversion of **106** to the methyl ester **105** (CH_2N_2, Et_2O, 25 °C) and normal-phase HPLC analysis revealed a single peak with an identical retention time to **105** obtained from trifluoroacetamide formation (**31** → **105**). Thus, this directed intramolecular hydrolysis of the C-2′ methyl ester proved sufficiently mild to proceed without racemization of the C-2′ center. Preliminary efforts to employ the corresponding acetamide derivative directly in a comparable conversion failed to close cleanly and rapidly to the intermediate oxazolidinone and suffered competitive racemization. Removal of the trifluoroacetamide (K_2CO_3, CH_3OH-H_2O) followed by *tert*-butyloxycarbonyl carbamate formation provided **108**, which was coupled directly with (2-(trimethylsilyl)ethyl)-L-tyrosine to provide **109**. 2-(Trimethylsilyl)ethyl ester removal (*n*-Bu_4NF, DMF, 25 °C, 4 h, 92%) afforded **110**, catalytic hydrogenolysis removal of the C-4 phenol benzyloxy and C-9 amine benzyloxycarbonyl protecting groups followed by diphenyl phosphorazidate promoted cyclization of the free amine employing the recently improved reaction conditions[49] (1.5 equiv of DPPA, $NaHCO_3$, DMF, 0.008 M, pH = 7, 0 °C, 72 h, 61%) provided cyclic tripeptide **114**. Alternatively, the carboxylic acid **110** was converted to the pentafluorophenyl ester **111** (C_6F_5OH, EDCI, CH_2Cl_2, 25 °C, 2 h, 85%) and the corresponding C-4 free phenol, C-9 free amine **113** (H_2, 10% Pd–C, 2.0 equiv of aqueous HCl) was subjected to high-dilution macrocyclization reaction conditions (18 h addition to DMF solution containing 5 equiv of $NaHCO_3$, 0.003 M final concentration, 90 °C, 51%) and provided the cyclic peptide **114** in comparable yield. Exchange of the *tert*-butyloxycarbonyl carbamate of **114** for the acetamide followed by hydrolysis of the C-9 methyl ester provided K-13 ($[\alpha]^{22}_D$ −5.6° (*c* 0.53, CH_3OH),[6] natural[2] K-13 $[\alpha]_D$ −3.4° (*c* 0.6, CH_3OH), synthetic K-13 $[\alpha]_D$ −6.5° (*c* 0.46, CH_3OH),[5] −7.4° (*c* 0.65, CH_3OH)[4]) identical in all other comparable respects to naturally occurring material.[54]

Total Syntheses of OF4949-III and OF4949-IV. Ester exchange of alcohol **27** (LiOH, 92%; EDCI, HOBt, $Me_3SiCH_2CH_2OH$, CH_2Cl_2, 25 °C, 12 h, 86%) followed by treatment of the primary alcohol **118** with Appel's reagent[55] provided **119** (CBr_4, Ph_3P, Et_2O) (Scheme VII). Treatment of **119** with Schöllkopf's reagent **29**[42] (NaH, THF, 0 °C, 20 min; 1.0 equiv of **29**, THF, −78 °C, 12 h) and subsequent acid-catalyzed hydrolysis of the cyclic imidate **120** (0.5 N aqueous HCl–THF, 1:1, 25 °C, 14 h, 59% from **119**) provided **121**. Normal-phase HPLC analysis of the *N-tert*-butyloxycarbonyl derivative of **121** revealed a 89:5:5<1 ratio of diastereomers indicating that the alkylation proceeded with 94% de.

As previously described,[13] OF4949 macrocyclization with closure at the C^{11}–N^{10} amide bond could be expected to productively provide the 17-membered cyclic tripeptides and closure at the C^{14}–N^{13} amide bond was anticipated to suffer competitive succinimide or iminosuccinic anhydride formation. Consequently, acylation of **121** with *N*-BOC-L-asparagine (**122**, EDCI, HOBt, DMF, 25 °C, 12 h, 88%) provided **123**. As anticipated from our prior studies, the OF4949 macrocyclization reaction was expected and shown to be optimally conducted on substrates bearing a C-9 carbamate derivative and the *free C-4 phenol* with C^{10}–N^{11} amide bond closure. O-Debenzylation of **123** (H_2, 10% Pd–C, THF, 25 °C, 3 h; $ClCO_2CH_2Ph$, $NaHCO_3$, THF, 25 °C, 86%) followed by sequential deprotection of the C-15 carboxylic acid (*n*-Bu_4NF, DMF, 25 °C, 4 h, 90%) and the C-9 terminal amine (3.0 M HCl/EtOAc, 25 °C, 0.5 h) provided **126**. Diphenyl phosphoroazidate promoted cyclization of the liberated free amine employing the recently improved reaction conditions (1.5 equiv of DPPA, $NaHCO_3$, DMF, 0.008 M, pH 7, 0 °C, 72 h, 58%)[49] provided the cyclic tripeptide **128**. Hydrolysis of the C-15 methyl ester followed by C-9 amine deprotection (H_2, 10% Pd–C) provided OF4949-IV (**5**) identical in all comparable respects with natural[9] material ($[\alpha]^{25}_D$ −43.2° (*c* 1.1, 0.1 N HCl)). Similarly, O-methylation of **128** (CH_2N_2, Et_2O, 0 °C) followed by C-15 methyl ester hydrolysis (LiOH, THF–H_2O–MeOH, 25 °C, 92%) and C-9 amine deprotection (H_2, 10% Pd–C, THF, 25 °C, 95%) provided OF4949-III (**4**) identical in all comparable respects to natural[9] and synthetic[5,11] material ($[\alpha]^{25}_D$ −34° (*c* 1.0, 0.1 N HCl); literature $[\alpha]^{30}_D$ −35° (*c* 1.14, 1 N HCl),[5] $[\alpha]^{27}_D$ −38.2° (*c* 1.06, 0.1 N HCl)[11]).[56]

Scheme VII[a]



[a] (a) 3.0 equiv of LiOH, THF/H_2O/MeOH, 92%; (b) 3.0 equiv of $(CH_3)_3SiCH_2CH_2OH$, 1.0 equiv of EDCI, 86%; (c) 2.0 equiv of Ph_3P, 2.0 equiv of CBr_4, Et_2O, 25 °C, 12 h, 70%; (d) 1.1 equiv of NaH, THF; 1.0 equiv of **29**, THF, −78 °C, 12 h; (e) 0.5 N HCl/THF, 25 °C, 11 h, 59% from **119**; (f) 2.0 equiv of EDCI, 2.0 equiv of HOBt, 2.0 equiv of *N*-BOC-L-asparagine, DMF, 25 °C, 12 h, 88%; (g) 1 atm of H_2, 10%, Pd–C, THF, 25 °C, 3 h; 1.0 equiv of $ClCO_2CH_2Ph$, 3.0 equiv of $NaHCO_3$, THF, 25 °C, 3 h, 86%; (h) 2.0 equiv of *n*-Bu_4NF, THF, 25 °C, 4 h, 90%; (i) 3.0 M HCl/EtOAc, 25 °C, 0.5 h; (j) 1.5 equiv of DPPA, 5.0 equiv of $NaHCO_3$, DMF, 0.008 M, 0 °C, 72 h, 58%; (k) CH_2N_2, Et_2O, 25 °C, 100%; (l) 3.0 equiv of LiOH, THF/H_2O/MeOH, 25 °C, 88% for **131**, 92% for **132**; (m) 1 atm H_2, 10% Pd–C, 93% for **4**, 95% for **5**.

(54) A comparison sample of natural K-13 was not available. The spectra of synthetic (mp 264–268 °C) K-13 and the spectra of natural (mp 265–270 °C) K-13 proved indistinguishable by ^1H NMR (CD_3OD and DMSO-d_6, 300 MHz), IR (KBr), and FABMS (glycerol–0.1 N HCl).

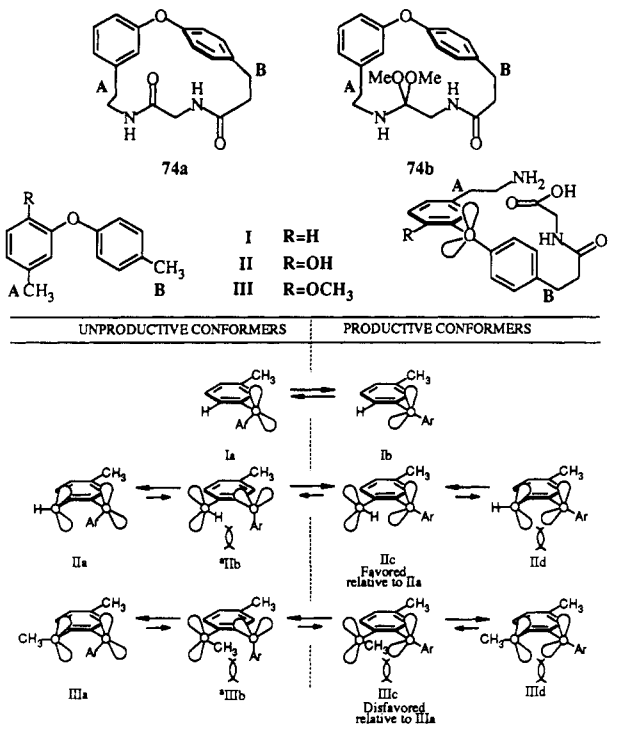
(55) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.

Table III

	MM2			AM1			
conf.	rel energy, kcal/mol	A–B dist, Å	rel pop., % (0 °C)	prod. conf pop., %	rel energy, kcal/mol	A–B dist, Å	rel pop., % (0 °C)	prod. conf pop., %
Ib	0.0	8.16	50	50	0.00	8.06	50	50
Ia	0.0	10.17	50		0.03	10.07	50	
IIc	0.0	8.18	48		0.00	8.13	47	47
IId	0.9	8.17	9	57	3.67	8.16	<1	
IIa	1.1	9.98	6		3.57	9.14	<1	
IIb	0.7	9.61	13		0.70	9.21	13	
IIe	0.4	8.83	23		0.09	8.61	40	
IIIc	1.2	8.25	4		0.68	8.12	7	
IIId	0.0	8.19	36	36–40	0.60	8.28	8	23
IIIa	0.0	9.99	36		0.00	9.14	25	
IIIb	≥1.6	8.81	2		≥4.00	9.17	<1	
IIIe[a]	0.4	9.16	17		0.02	9.02	24	
IIIf[a]	1.6	10.03	2		0.33	8.58	13	
IIIg[a]	1.6	8.28	2		0.57	8.08	9	
IIIh	2.3	8.83	1		0.65	8.02	7	
					0.65	8.37	7	

[a] Out of plane (OCH_3) conformation.

Origin of the Macrocyclization Effects. The unexpected rate deceleration exhibited by the C-4 methoxy substituted diaryl ethers resulted in an investigation of the origin of this effect. Simplified diaryl ethers possessing the appropriate aryl C-4 substituent (I–III, R = H, OH, OCH_3) and a methyl group at the site of attachment of the amino acid side chains were constructed in MacroModel[57] and a full set of low-energy conformations for each of the three representative diaryl ethers were generated.[57b] Each of the low-energy conformations was additionally optimized with AM1,[58] and the results are summarized in Table III. The significance of the conformations available to the models was found to be distinguished by the diaryl ether Me–Me distances (A–B distances) and their relationship to the A–B distances available to accessible conformations of **79a** and **79b**. A full search[57c] of conformations available to **79a** was conducted in which all torsional angles were varied except those originating within the benzene rings, and all structures lying within 3 kcal/mol of the lowest energy structure were evaluated. An equivalent analysis was conducted on **79b** representing a model of a tetrahedral intermediate for the K-13 macrocyclization reaction.[57c] The searches established a value of 8.2 Å (MM2, AM1)[58b]



(a) perpendicular aryl conformation.

Figure 3.

as the maximum A–B distance that may be achieved within the accessible conformations of **79a–b**. Using the value of 8.2 Å as the A–B distance beyond which macrocyclization cannot occur, the available conformations of I–III may be considered productive (A–B ≤ 8.2 Å) or unproductive (A–B > 8.2 Å). Calculation of a Boltzmann distribution (0 °C) based on the relative energies of the available conformations of each of the diaryl ethers was found to indicate that productive conformations for macrocyclization of I and II were relatively more populated than the productive conformations of III. This corresponds nicely to the observed rate differences for macrocyclization (0 °C) of **86–88** where **86–87** undergo cyclization approximately 2 times faster than **88** (k_{rel} **86** (1.0), **87** (0.94), **88** (0.40)). The origin of the results may be rationalized as follows. For I (R = H), two low-energy (gauche) confor-

(56) Synthetic (mp 217–222 °C dec) and natural (mp 217–225 °C dec) OF4949-III proved indistinguishable in direct comparisons by ^1H NMR (D_2O, 300 MHz), IR (KBr), and thin-layer chromatography (R_f 0.40 in 30% NH_4OH/*n*-propanol, R_f 0.37 in EtOAc/HOAc/H_2O/*n*-butanol, 1:1:1:1). A comparison sample of natural OF4949-IV was not available. The spectra of synthetic OF4949-IV compared with the reported spectra of natural OF4949-IV (^1H NMR (DMSO-d_6) and IR (KBr)).[9]

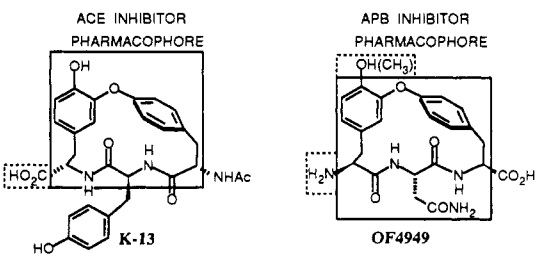
(57) (a) Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T. *MacroModel V2.0*; Department of Chemistry, Columbia University, New York. (b) The available conformations were generated in MacroModel Multiconformer (number of rotations = 3 (R = OCH_3, R = OH), 2 (R = H); number of rings closed = 0; number of distance checks = 0; nonbonded distance cutoff = 1.5 Å; heavy atom 1.5 cutoff = 3.0 Å; torsional resolution = 60°; bond angle resolution = 10°) and minimized (MM2) to provide the available low energy conformations of I–III. (c) The conformational searches were performed employing both the AMBER/OPLS and MM2 force fields (OPLSA and MM2 MacroModel, Version 2.5). Global minima and close, low-lying minima (≤ 5 kcal) were located by used directed Monte Carlo sampling of the starting conformations (MCMM = 10000, MCSS = 2) generated by random variations (0–180 °C) in two to five of the available torsional angles excluding those originating in benzene rings until the global minima were repeatedly (≥11 times for **79a**, ≥8 times for **79b**) found. See: Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(58) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) The pertinent MM2 structures were subsequently optimized with AM1.

mations were found (Ib = Ia) and one conformation proved productive. Five potential low-energy conformations for II (R = OH) were located, and the major four are the in-plane hydroxy and gauche/perpendicular phenoxy conformations represented in Figure 3. The major and a productive conformation proved to be IIc (IIc > IIa) and intuitively would be expected to derive its preferential stabilization from intramolecular hydrogen bonding. Conformation IId suffers additional destabilization relative to IIc derived from the well-recognized lone pair–lone pair repulsion.[59] Nonetheless, conformation IId proved comparable to IIa and conformation IIb which suffers from anticipated destabilizing steric interactions relative to IIIc and which exists preferentially in the perpendicular phenoxy conformation. The net result is that the macrocyclization productive and unproductive conformations of I and II are nearly equally populated. By contrast, the unproductive conformations of III are preferentially populated. With III, a number of out-of-plane methoxy conformations are energetically comparable to the in-plane conformations, and their relative contributions to productive and unproductive conformations were necessarily assessed. However, the major distinction between III and I–II is manifested in the relative destabilization of conformation IIIc versus IIIa (vs IIa/IIc or Ia/Ib) and the net result of an increased population of the unproductive versus productive conformations of III. As such, the results highlight that subtle changes in remote substituents may have substantial, conformationally derived effects on the rate of macrocyclization reactions. In the case of **86–88**, even the seemingly productive introduction of a C-4 phenol protecting group decelerates rather than facilitates macrocyclization and does so by preferentially populating the unproductive macrocyclization conformations of **88**.[60]

(59) For recent descriptions of the conformational behavior of 1,2-dialkoxybenzenes and alkenes, see: (a) Breen, P. J.; Berstein, E. R.; Secor, H. V.; Seeman, J. I. *J. Am. Chem. Soc.* **1989**, *111*, 1958. (b) Dodziuk, H.; von Voithenberg, H.; Allinger, N. L. *Tetrahedron* **1982**, *38*, 2811. (c) Eliel, E. L.; Juaristi, E. *J. Am. Chem. Soc.* **1978**, *100*, 6114. (d) Zefirov, N. S.; Gurovich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211. (e) Kirby, A. J. The Anomeric Effect and Related Stereoelectronic Effects at Oxygen. In *Reactivity and Structure Concepts in Organic Chemistry*, *15*; Hafner, K., Lehn, J.-M., Rees, C. W., Schleyer, P. v. R., Trost, B. M., Zahradnik, R., Eds.; Springer-Verlag: Berlin, 1982; references cited therein.

(60) Selected acyclic precursors and cyclic agents constituting the key substructures of isodityrosine, K-13, and OF4949-III and -IV were subjected to comparative evaluation for in vitro cytotoxic activity and comparative enzyme inhibitory activity in two enzyme assays: angiotensin I converting enzyme (ACE) assay[61] and rat liver aminopeptidase B (APB) assay.[62]. The results summarized in supplementary material provided the agent pharmacophore identification illustrated below.



(61) The antiotensin I converting enzyme (ACE) assay was conducted at the Squibb Institute for Medical Research by Dr. M. M. Asaad using ACE obtained from rabbit lung employing the method of Cushman and Cheung (supplementary material): Cushman, D. W.; Cheung, H. S. *Biochem. Pharmacol.* **1971**, *20*, 1673. For reviews, see: Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science (Washington, D.C.)* **1977**, *196*, 441. Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *16*, 5484. *Angiotensin Converting Enzyme Inhibitors*; Ferguson, R. K., Vlasses, P. H., Eds.; Futura: New York, 1987.

Experimental Section[63]

***N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-3-[4-[(1,1-dimethylethoxy)carbonyl]phenoxy]-L-tyrosine Methyl Ester (25).** A solution of **23**[40] (5.00 g, 11.5 mmol) in 20 mL of nitrobenzene was added dropwise to a suspension of sodium hydride (60% oil dispersion, 0.459 g, 11.5 mmol, 1.0 equiv) in 25 mL of nitrobenzene at 0 °C. The reaction mixture was stirred at 0 °C (5 min), and cuprous bromide–dimethyl sulfide complex (3.29 g, 16.1 mmol, 1.4 equiv) was added. The reaction mixture was stirred at 23 °C (0.5 h), treated with *tert*-butyl 4-iodobenzoate (**20**, 6.98 g, 22.9 mmol, 2.0 equiv), and warmed at 130 °C (8 h). The cooled reaction solution was poured onto saturated aqueous ammonium chloride (100 mL), and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with 10% aqueous HCl (3 × 100 mL) and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 5 × 20 cm, 25% EtOAc–hexane eluant) afforded **25** (3.23 g, 7.02 g theoretical, 46%) as a clear yellow oil: $[\alpha]^{22}_D$ −4.2° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.92 (d, 2 H, *J* = 8.8 Hz, C3′-H and C5′-H), 7.32 (br s, 10 H, two Ph), 7.24 (d, 1 H, *J* = 2.4 Hz, C2-H), 7.12 (dd, 1 H, *J* = 8.4, 2.4 Hz, C6-H), 6.93 (d, 1 H, *J* = 8.4 Hz, C5-H), 6.87 (d, 2 H, *J* = 8.8 Hz, C2′-H and C6′-H), 5.24 (d, 1 H, *J* = 8 Hz, NH), 5.08 (s, 2 H, $PhCH_2O$), 5.01 (s, 2 H, $PhCH_2O_2C$), 4.63 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 3.67 (s, 3 H, OCH_3), 3.07 and 3.02 (2 dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH), 1.58 (s, 9 H, $C(CH_3)_3$); APT ^{13}C NMR ($CDCl_3$, 75 MHz, ppm), 173.2 (e, CO_2CH_3), 165.4 (e, $CO_2{}^tBu$), 161.9 (e, C-1′), 156.0 (e, OCON), 149.7 (e, C4), 144.0 (e, C3), 136.4 (e, 2 C, $OCH_2(C)C{=}C$), 131.2 (o, aryl CH), 129.3 (e, C-1′), 128.5 (o, five aryl CH), 126.9 (e, C4′), 115.1 (o, 2 C, aryl CH), 80.6 (e, $C(CH_3)_3$), 70.7 (e, OCH_2Ph), 66.9 (e, $OCOCH_2Ph$), 54.7 (o, $NCHCO_2Me$), 52.3 (o, OCH_3), 37.4 (e, $OC(NH)CHCH_2Ar$), 28.2 (o, 3 C, $C(CH_3)_3$); IR (neat) ν_{max} 3855, 3753, 3651, 3353, 3034, 2976, 1730, 1717, 1708, 1698, 1602, 1583, 1504, 1455, 1368, 1291, 1272, 1222, 1179, 1155, 1117, 1058, 1025, 851, 771, 737 cm^{-1}; EIMS *m/e* (relative intensity) 611 (M^+, 1), 334 (12), 333 (57), 243 (8), 232 (11), 231 (14), 91 (base); CIMS (isobutane) *m/e* (relative intensity) 612 (M^+ + H, 1), 611 (3), 556 (10), 538 (11), 513 (29), 512 (base); EIHRMS *m/e* 611.6909 ($C_{36}H_{37}NO_8$ requires 611.6902). Chiral-phase HPLC analysis revealed a 94:6 ratio of L:D **25**; t_R = 21 min/23 min, 2.0 mL/min, 10% 2-propanol–hexane from reaction of a 95:5 ratio of L:D **23**; t_R = 18 min/28 min, 2.0 mL/min, 10% 2-propanol–hexane.

Ullmann Reaction in Pyridine. A solution of **23** (0.224 g, 0.49 mmol) in 0.5 mL of dry pyridine was added dropwise to a suspension of sodium hydride (60% oil dispersion, 0.020 g, 0.49 mmol, 1.0 equiv of 1 mL of pyridine) at 0 °C. The reaction mixture was stirred at 0 °C (10 min) before the addition of cuprous bromide–dimethyl sulfide complex (0.142 g, 0.686 mmol, 1.4 equiv). The reaction mixture was stirred at 25 °C (0.5 h), treated with *tert*-butyl 4-iodobenzoate (**20**, 0.304 g, 0.980 mmol, 2.0 equiv), and warmed at reflux (135 °C bath temperature, 8 h). The cooled reaction solution was poured onto saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with 10% aqueous HCl (1 × 10 mL) and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, 30% EtOAc–hexane eluant) afforded **25** (0.134 g, 0.306 g theoretical, 44%) as a clear yellow oil identical in spectral characteristics with the product obtained from the Ullmann reaction conducted in nitrobenzene. Chiral-phase HPLC analysis under the conditions detailed above revealed a 55:45 ratio of L:D **25**.

***N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-3-(4-carboxyphenoxy)-L-tyrosine Methyl Ester (26).** A solution of **25** (2.8 g, 4.58 mmol) in 10 mL of 3.0 M HCl/EtOAc at 25 °C was stirred for 1.5 h (25 °C). The volatiles were removed in vacuo

(62) The aminopeptidase B (APB) assay was conducted using APB obtained from male Sprague–Dawley rat livers employing the method of Harbeson and Rich (supplementary material): Harbeson, S. L.; Rich, D. H. *Biochemistry* **1988**, *27*, 7301. For recent studies, see: Harbeson, S. L.; Rich, D. H. *J. Med. Chem.* **1989**, *32*, 1378. Ocain, T. D.; Rich, D. H. *J. Med. Chem.* **1988**, *31*, 2193.

(63) General experimental details are provided in supplementary material.

to afford a yellow oil. Short column chromatography (SiO_2, 3 × 5 cm, Et_2O) afforded **26** (2.44 g, 2.54 g theoretical, 96%) as a clear viscous oil: $[\alpha]^{22}_D$ −7.2° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 8.03 (d, 2 H, *J* = 8.7 Hz, C3′-H and C5′-H), 7.32 (br s, 10 H, two Ph), 7.24 (d, 1 H, *J* = 2.3 Hz, C2-H), 7.10 (dd, 1 H, *J* = 8.5, 2.6 Hz, C6-H), 6.93 (d, 1 H, *J* = 8.5 Hz, C5-H), 6.90 (d, 2 H, *J* = 8.7 Hz, C2′-H and C6′-H), 5.26 (d, 1 H, *J* = 8 Hz, NH), 5.09 (s, 2 H, $PhCH_2O$), 5.01 (s, 2 H, $PhCH_2O_2C$), 4.66 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 3.68 (s, 3 H, OCH_3), 3.09 and 3.04 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCHNH$ and $CHHCHNH$); IR (neat) ν_{max} 3347, 3065, 3034, 2953, 1718, 1603, 1587, 1508, 1455, 1438, 1381, 1347, 1272, 1219, 1178, 1162, 1126, 1060, 1024, 912, 852, 773, 739 cm^{-1}; EIMS *m/e* (relative intensity) 555 (M^+, 3), 333 (5), 91 (base); CIMS (isobutane) *m/e* (relative intensity) 556 (M^+ + H, 8), 513 (21), 448 (8), 91 (base); EIHRMS *m/e* 555.5835 ($C_{32}H_{29}NO_8$ requires 555.5830).

Alternatively, a solution of the phenol **23** (2.97 g, 6.83 mmol) in 10 mL of nitrobenzene was added dropwise to a suspension of sodium hydride (60% oil dispersion, 252 mg, 8.19 mmol, 1.2 equiv) in 10 mL nitrobenzene at 0 °C. The reaction mixture was stirred 5 min before the addition of cuprous bromide–dimethyl sulfide complex (1.68 g, 8.19 mmol, 1.2 equiv). The reaction mixture was stirred at 25 °C (0.5 h), treated with sodium 4-iodobenzoate (**21**, 3.70 g, 13.66 mmol, 2.0 equiv), and warmed at 130 °C (bath temperature) for 8 h. The cooled reaction mixture was poured onto saturated aqueous ammonium chloride (50 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with 10% aqueous HCl (3 × 40 mL) and saturated aqueous NaCl, dried ($MgSO_4$), and concenrated in vacuo. Flash chromatography (SiO_2, 3 × 5 cm, Et_2O) afforded **26** (1.93 g, 3.79 g theoretical, 51%) as a clear oil identical in all respects with **26** obtained from acid-catalyzed deprotection of **25**.

***N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-3-[4-(hydroxymethyl)phenoxy]-L-tyrosine Methyl Ester (27).** A 1.0 M solution of BH_3·THF (0.918 mL, 0.918 mmol, 1.0 equiv) was added dropwise to a solution of **26** (0.551 g, 0.918 mmol) in 5 mL of tetrahydrofuran at 0 °C. The reaction mixture was stirred at 0 °C (1 h) and was allowed to warm to 25 °C (2 h). Unreacted borane was quenched with the dropwise addition of 2 mL of tetrahydrofuran/water (1:1), and the resulting reaction mixture was poured over water (10 mL) and extracted with ether (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 15 cm, 50% Et_2O–pentane eluant) afforded **27** (441 mg, 496 mg theoretical, 89%) as a yellow oil: $[\alpha]^{22}_D$ −19.2° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.32 (br s, 10 H, two Ph), 7.22 (d, 1 H, *J* = 2.4 Hz, C2-H), 7.12 (dd, 1 H, *J* = 8.4, 2.5 Hz, C6-H), 6.98 (d, 1 H, *J* = 8.4 Hz, C5-H), 6.95 (d, 2 H, *J* = 5 Hz, C3′-H and C5′-H), 6.91 (d, 2 H, *J* = 5 Hz, C2′-H and C6′-H), 5.20 (d, 1 H, *J* = 8 Hz, NH), 5.09 (s, 2 H, $PhCH_2O$), 5.01 (s, 2 H, $PhCH_2O_2C$), 4.64 (s, 2 H, OCH_2OH), 4.56 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 3.63 (s, 3 H, OCH_3), 3.02 and 2.93 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCHNH$ and $CHHCHNH$); IR (neat) ν_{max} 3854, 3838, 3821, 3802, 3745, 3676, 3650, 3629, 3339, 2924, 1718, 1700, 1653, 1636, 1577, 1559, 1539, 1507, 1456, 1437, 1270, 1215, 1125, 1025, 833, 738 cm^{-1}; EIMS *m/e* (relative intensity) 541 (M^+, 1), 319 (5), 289 (3), 211 (14), 108 (14), 91 (base); EIHRMS *m/e* 541.5990 ($C_{32}H_{31}NO_7$ requires 541.5994).

***N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-3-[4-(bromomethyl)phenoxy]-L-tyrosine Methyl Ester (28).** A solution of **27** (0.343 g, 0.638 mmol) in 2 mL of ether at 25 °C was treated with carbon tetrabromide (422 mg, 1.28 mmol, 2.0 equiv) and triphenylphosphine (0.366 g, 1.28 mmol, 2.0 equiv), and the reaction mixture was stirred at 25 °C (6 h). The reaction mixture was filtered through Celite (Et_2O wash), and the filtrate was washed with water (3 × 3 mL) and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 10 cm, 25% EtOAc–hexane eluant) afforded **28** (273 mg, 380 mg theoretical, 72%) as a clear yellow oil: $[\alpha]^{22}_D$ −29.3° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm), 7.33 (br s, 5 H, Ph), 7.30 (br s, 5 H, Ph), 7.16 (d, 1 H, *J* = 8 Hz, C5-H), 7.14 (d, 1 H, *J* = 2.3 Hz, C2-H), 6.92 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.85 (dd, 1 H, *J* = 8, 2 Hz, C6-H), 6.84 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.22 (d, 1 H, *J* = 8 Hz, NH), 5.08 (s, 2 H, $PhCH_2O_2C$), 4.61 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 4.49 (s, 2 H, CH_2Br), 3.65 (s, 3 H, OCH_3), 3.04 and 3.02 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCHNH$ and $CHHCHNH$); IR (neat) ν_{max} 3855, 3752, 3677, 3650, 3354, 3033, 2952, 1720, 1654, 1607, 1586, 1507, 1455, 1437, 1380, 1349, 1271, 1221, 1169, 1126, 1058, 1024, 911, 834, 738 cm^{-1}; EIMS *m/e* (relative intensity) 605/603 (M^+, 1/1), 524 (M^+ − Br, 1), 91 (base); CIMS (isobutane) *m/e* (relative intensity) 606/604 (M^+ + H, 1/1), 524 (M^+ + H − HBr, 34), 107 (base).

Table IV. Hydrolysis Reaction

time, h	yield, %	time, h	yield, %
20	49	11	60
18	55	10	60
14	59		

***(S)*-*O*-[5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)ethyl]-2-(phenylmethoxy)phenyl]-L-tyrosine Methyl Ester (31).** Freshly titrated *n*-butyllithium (2.1 M in hexane, 0.347 mL, 0.730 mmol, 1.20 equiv) was added dropwise to a −78 °C solution of (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[42] (0.135 g, 0.730 mmol, 1.20 equiv) in 2 mL of tetrahydrofuran under argon, and the reaction mixture was stirred for 10 min (−78 °C). In a separate vessel, sodium hydride (0.030 g, 0.73 mmol, 1.2 equiv) was added to a 0 °C solution of **28** (0.343 g, 0.612 mmol) in 2 mL of tetrahydrofuran, and the mixture was stirred for 10 min (0 °C) before this solution was transferred by cannula to the −78 °C solution of **29** (dropwise addition). After the addition was complete, the reaction mixture was stirred at −78 °C (14 h) and then quenched with the addition of tetrahydrofuran/water (1:1; 1 mL). The reaction mixture was poured onto water (5 mL) and extracted with ethyl acetate (3 × 6 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Short column chromatography (SiO_2, 2 × 5 cm, 30% EtOAc–hexane eluant) afforded the intermediate dihydropyrazine adduct (0.282 g, 0.433 g theoretical, 65%) as a colorless oil which was used directly in the following reaction. For **30**: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.32 (br s, 10 H, two Ph), 7.35–7.20 (m, 2 H, aromatic H's), 7.06 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.78 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.28 (d, 1 H, *J* = 8 Hz, NH), 5.08 (s, 2 H, $PhCH_2O$), 5.04 (s, 2 H, $PhCH_2O_2C$), 4.64 (q, 1 H, J = 8 Hz, CH_2CHN), 4.32 (br s, 1 H, $CH_2CHN{=}C$), 3.70 (s, 3 H, CO_2CH_3), 3.65 (br s, 6 H, two $N{=}COCH_3$), 3.20 and 3.11 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCHNH$ and $CHHCHNH$), 3.04 and 2.96 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCHN{=}C$ and $CHHCHN{=}C$), 0.95 (d, 3 H, *J* = 7 Hz, $CHCH_3$), 0.62 (d, 3 H, *J* = 7 Hz, $CHCH_3$); IR (neat) ν_{max} 3678, 3321, 2959, 2871, 2346, 1722, 1697, 1608, 1506, 1456, 1438, 1382, 1271, 1241, 1169, 1126, 1015, 831, 737 cm^{-1}.

A solution of **30** (0.282 g, 0.399 mmol) in 0.5 N aqueous HCl/THF (2 mL) was stirred at 25 °C (15 h). The reaction mixture was poured over saturated aqueous Na_2CO_3 (5 mL) and extracted with ether (5 × 3 mL). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 12 cm, 90% Et_2O–hexane eluant) afforded **31** (0.213 g, 0.374 g theoretical, 57% from **28**) as an off-white solid: mp 139–141 °C (MeOH, white needles); $[\alpha]^{22}_D$ −93.8° (*c* 0.21, MeOH); ^1H NMR (Me_2SO-d_6, 300 MHz, ppm) 7.30 (br s, 10 H, two Ph), 7.20 (d, 1 H, *J* = 2 Hz, C2-H), 7.10 (dd, 1 H, *J* = 8, 2 Hz, C6-H), 7.01 (d, 1 H, *J* = 8 Hz, C5-H), 7.00 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.75 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.04 (s, 2 H, $PhCH_2O$), 4.96 (s, 2 H, $PhCH_2O_2C$), 3.66 (br s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 2.98 and 2.92 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCH$ and $CHHCH$), 2.8 and 2.74 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCH$ and $CHHCH$); IR (KBr) ν_{max} 3854, 3745, 3676, 3650, 2951, 1735, 1717, 1701, 1654, 1607, 1559, 1507, 1456, 1388, 1270, 1218, 1172, 1127, 1024, 737 cm^{-1}; CIMS (isobutane) *m/e* (relative intensity), 613 (M^+ + H, 1); CIHRMS *m/e* 613.6784 ($C_{35}H_{36}N_2O_8$ requires 613.6780).

Anal. Calcd for $C_{35}H_{36}N_2O_8$: C, 68.63; H, 5.88; N, 4.57. Found: C, 68.66; H, 5.57; N, 4.52.

A summary of the effect of reaction time on the hydrolysis reaction of the intermediate dihydropyrazine adduct is provided in Table IV.

Diastereomeric Analysis of 32. A solution of **31** (5 mg, 0.008 mmol) in 0.1 mL of THF at 25 °C was treated with di-*tert*-butyl dicarbonate (2 μL, 0.009 mmol, 1.1 equiv) and stirred at 25 °C (12 h). The solution was diluted in ethyl acetate (1 mL) and

washed with water (3 × 1 mL), dried ($MgSO_4$), and concentrated in vacuo. Short column chromatography (SiO_2, 1 × 0.5 cm, Et_2O) afforded **32** (5 mg, 6 mg theoretical, 87%) as an oil. Normal-phase HPLC analysis of **32** employing an Alltech Econosil silica column (10 μ) revealed a 90:4.5:4.5<1 ratio of diastereomers; t_R = 15 min/17 min/18 min/20 min, 1.5 mL/min, 15% 2-propanol–hexane.

L,L-Isodityrosine (15). Aqueous 6 N HCl (1 mL) was added to a vessel containing amine **31** (36 mg, 0.659 mmol), and the mixture was warmed at 65 °C for 6 h. The reaction mixture was extracted with ethyl acetate (2 × 2 mL), and the aqueous phase was concentrated in vacuo. Recrystallization ($MeOH/H_2O$, 1:2) afforded the bishydrochloride salt of **15** (23 mg, 23.7 mg theoretical, 97%) as a white solid: mp >300 °C dec; $[\alpha]^{22}_D$ −28.2° (*c* 1.0, MeOH); ^1H NMR (D_2O, 200 MHz, ppm) 7.18 (d, 2 H, *J* = 8.7 Hz, C2′, C6′-H), 7.07 (br s, 2 H, Ar-H), 6.89 (d, 2 H, *J* = 8.7 Hz, C3′, C5′-H), 6.82 (br s, 1 H, Ar-H), 4.14 (dd, 1 H, *J* = 7.3 Hz, 4.9 Hz, CH_2CHNH), 4.11 (dd, 1 H, *J* = 7.0, 5.5 Hz, CH_2CHNH), 3.35–3.02 (m, 4 H, two CH_2CHN); IR (KBr) ν_{max} 3400, 3100, 1740, 1580, 1408, 1318, 1290, 1170, 1060 cm^{-1}; EIMS *m/e* (relative intensity) 360 (M^+, 3), 316 (12), 300 (10), 272 (base); EIHRMS *m/e* 360.3656 ($C_{18}H_{20}N_2O_6$ requires 360.3658).

Anal. Calcd for $C_{18}H_{20}N_2O_6$ (free amino acid): C, 60.00; H, 5.56; N, 7.78. Found: C, 60.01; H, 5.49; N, 7.68.

General Procedure for Macrocyclization Reactions, Method A: (*S*)-12-(2-Amino-2-oxoethyl)-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene (102). A solution of hydrochloride **99** (0.087 g, 0.210 mmol) in dry *N,N*-dimethylformamide (26 mL) was cooled to 0 °C and treated with sodium bicarbonate (0.088 g, 1.05 mmol, 5.0 equiv) and diphenyl phosphorazidate (DPPA, 0.068 mL, 0.088 g, 0.310 mmol, 1.5 equiv), and the reaction mixture was stirred for 72 h (0 °C). The reaction mixture was poured onto water (30 mL) and extracted with ethyl acetate (2 × 15 mL). The combined ethyl acetate extracts were washed with 10% aqueous HCl (1 × 15 mL), water (3 × 15 mL), and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 15 cm, 5–25% THF–EtOAc gradient eluant) afforded **102** (0.055 g, 0.077 g theoretical, 71%) as a glassy, tan solid: mp 178–181 °C (MeOH, tan flakes); $[\alpha]^{22}_D$ −19° (*c* 1.3, MeOH); ^1H NMR (methanol-d_4, 300 MHz, ppm) 7.34–6.83 (m, 8 H, Ar-H), 5.80 (s, 1 H, C22-H), 4.59 (dd, 1 H, *J* = 4, 10 Hz, $NHCHCH_2CONH_2$), 3.72 (dd, 2 H, *J* = 6, 8 Hz, CH_2NH), 3.09 (t, 2 H, *J* = 6 Hz, CH_2CH_2NH), 2.71 (t, 2 H, *J* = 6 Hz, CH_2CH_2CO), 2.64 (t, 2 H, *J* = 6 Hz, CH_2CH_2CO), 2.41–2.34 (m, 2 H, CH_2CONH_2); IR (KBr) ν_{max} 2958, 2904, 1688, 1646, 1590, 1561, 1417, 1254, 1168, 1031, 902, 850, 727 cm^{-1}; EIMS *m/e* (relative intensity) 381 (M^+, base), 338 (10), 324 (41), 307 (33), 267 (18), 222 (17); CIMS (isobutane) *m/e* (relative intensity) 382 (M^+ + H, base); EIHRMS *m/e* 381.4038 ($C_{21}H_{23}N_3O_4$ requires 381.4304).

Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.14; H, 6.04; N, 11.02. Found: C, 66.37; H, 6.44; N, 11.21.

General Procedure for Macrocyclization Reactions, Method B: (*S*)-4-Hydroxy-12-[(4-hydroxyphenyl)methyl]-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene (84). A suspension of **79** (0.040 g, 0.080 mmol) was dissolved in a 1.0 M solution of tetra-*n*-butylammonium hydroxide in methanol (0.08 mL), the solution was azeotroped with toluene, and the residue was dried under vacuum. A solution of this salt in 6 mL of dry benzene was added (18 h) to a solution of mesitylenesulfonyl chloride (0.052 g, 0.24 mmol, 3.0 equiv) and diisopropylethylamine (0.017 mL, 0.24 mmol, 3.0 equiv) in 10 mL of dry benzene at 35 °C. The reaction mixture was stirred for an additional 1 h (35 °C) after completion of addition. The cooled reaction solution was concentrated in vacuo and partitioned between ethyl acetate (10 mL) and water (10 mL). The organic phase was washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 10 cm, 85% EtOAc–hexane eluant) afforded **84** (0.022 g, 0.036 g theoretical, 62%) as a white solid: mp 201–203 °C ($MeOH–CH_2Cl_2$, white needles); $[\alpha]^{22}_D$ −22° (*c* 1.0, MeOH); ^1H NMR (methanol-d_4, 300 MHz, ppm) 7.28 (dd, 1 H, *J* = 8, 2 Hz, C_{18}-H), 7.10 (dd, 1 H, *J* = 8, 2 Hz, C_{19}-H), 7.05 (d, 2 H, *J* = 8 Hz, C_5^{Tyr}-H_2), 7.00 (dd, 1 H, *J* = 8, 2 Hz, C_{21}-H), 6.92 (d, 1 H, *J* = 8 Hz, C_{20}-H), 6.76 (d, 2 H, *J* = 8 Hz, C_6^{Tyr}-H_2), 6.73 (dd, 1 H, *J* = 8, 2 Hz, C_5-H), 6.68 (dd, 1 H, *J* = 8, 2 Hz, C_6-H), 6.31 (d, 1 H, *J* = 2 Hz, C_{22}-H), 4.22 (dd, 1 H, *J* = 10, 6 Hz, C_{12}-H), 3.75 (m, 2 H, CH_2CH_2NH), 3.11 (t, 2 H, *J* = 6 Hz, NCH_2CH_2Ar), 3.00 and 2.96 (2 dd, 1 H each, *J* = 12, 5 Hz, $CHHCH$ and $CHHCH$), 2.73 (t, 2 H, *J* = 6 Hz, OCH_2CH_2Ar), 2.63 (t, 2 H, *J* = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 3324, 2940, 2284, 1681, 1658, 1586, 1508, 1488, 1446, 1367, 1250, 1218, 1171, 1014, 830, 739 cm^{-1}; EIMS *m/e* (relative intensity) 446 (M^+, base), 389 (28), 355 (41), 344 (21); CIMS (isobutane) *m/e* (relative intensity) 447 (M^+ + H, base); EIHRMS *m/e* 446.5021 ($C_{26}H_{26}N_2O_5$ requires 446.5018).

General Procedure for Macrocyclization Reactions, Method C: 10,13-Dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene (98). A solution of the carboxylic acid corresponding to **65** (0.093 g, 0.21 mmol) in 1 mL of methylene chloride was treated with pentafluorophenol (0.042 g, 0.23 mmol, 1.10 equiv) and EDCI (0.042 g, 0.21 mmol, 1.0 equiv) at 25 °C under nitrogen, and the mixture was stirred at 25 °C (4 h). The reaction mixture was poured over 5% aqueous HCl (5 mL) and extracted with ethyl acetate (3 × 2 mL). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, 50% EtOAc–hexane) afforded *N*-BOC-**97** (124 mg, 128 mg theoretical, 97%) as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.30–6.85 (m, 8 H, Ar-H), 6.14 (br s, 1 H, $NHCOCH_2$), 5.05 (br s, 1 H, $NHCO_2{}^tBu$), 3.76 (d, 2 H, *J* = 6 Hz, $CH_2NHCO_2{}^tBu$), 3.53 (q, 2 H, *J* = 8, 6 Hz, CH_2CH_2NH), 3.05 (t, 2 H, *J* = 6 Hz, $CH_2CH_2CO_2C_6F_5$), 2.99 (t, 2 H, *J* = 6 Hz, $CH_2CH_2CO_2C_6F_5$), 2.81 (t, 2 H, *J* = 6 Hz, CH_2CH_2NH), 1.44 (s, 9 H, $C(CH_3)_3$); IR (neat) ν_{max} 3854, 3315, 3034, 2980, 2935, 2668, 2462, 1789, 1701, 1663, 1606, 1586, 1522, 1487, 1449, 1418, 1393, 1368, 1252, 1218, 1169, 1102, 1044, 996, 948, 908, 861, 786 cm^{-1}; CIMS (isobutane) *m/e* (relative intensity) 609 (M^+ + H, 12), 553 (base).

A solution of the active ester *N*-BOC-**97** (0.116 g, 0.19 mmol) in 1 mL of 3.0 M HCl/EtOAc at 25 °C was stirred for 1 h (25 °C). The volatiles were removed in vacuo to afford the hydrochloride salt as a white solid (mp 181–182.5 °C, EtOH), which was used directly in the following reaction. A solution of amine hydrochloride **97**·HCl (0.104 g, 0.192 mmol) in 50 mL of dry *N,N*-dimethylformamide was added dropwise to a suspension of potassium carbonate (0.262 g, 1.92 mmol) in 500 mL of *N,N*-dimethylformamide prewarmed to 90 °C. After the addition was complete (18 h), the reaction mixture was stirred an additional 1 h. The cooled reaction mixture was concentrated in vacuo to a volume of 20 mL and poured over water (20 mL). The aqueous solution was extracted with ethyl acetate (3 × 15 mL), and the combined organic extracts were washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 15 cm, 5–15% THF–EtOAc eluant) afforded **98** (0.037 g, 0.062 g theoretical, 61%) as a tan solid: mp 168–169 °C ($MeOH–CH_2Cl_2$); ^1H NMR (pyridine-d_5, 300 MHz, ppm) 8.55 (br d, 1 H, NH), 8.44 (br d, 1 H, NH), 7.34–6.85 (m, 8 H, Ar-H), 5.77 (s, 1 H, C22-H), 4.22 (d, 2 H, *J* = 6 Hz, $COCH_2NH$), 3.72 (dd, 2 H, *J* = 6, 8 Hz, CH_2NH), 3.06 (t, 2 H, *J* = 6 Hz, CH_2CH_2NH), 2.72 (t, 2 H, *J* = 6 Hz, CH_2CH_2CO), 2.62 (t, 2 H, *J* = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 3293, 3097, 2949, 1686, 1645, 1513, 1464, 1377, 1252, 1156, 1109, 978, 901, 848, 738 cm^{-1}; EIMS *m/e* (relative intensity) 324 (M^+, base), 307 (42), 267 (18), 222 (58), 210 (41); CIMS (isobutane) *m/e* (relative intensity) 325 (M^+ + H, base); EIHRMS *m/e* 324.0024 ($C_{19}H_{20}N_2O_3$ requires 324.0026).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 8.64. Found: C, 70.43; H, 5.88; N, 8.40.

General Procedure for Macrocyclization Reactions, Method D: 4-Hydroxy-11,14-dioxo-2-oxa-10,13-diazatricyclo-[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene (76). A solution of active ester **73**·HCl (0.072 g, 0.108 mmol) in 5 mL of dry dioxane was added dropwise (8 h) to a prewarmed (90 °C) suspension of palladium black (115 mg), *N*-methylmorpholine (12 μL, 0.011 g, 0.108 mmol, 1.0 equiv), and absolute ethanol (2 mL) in freshly distilled dioxane (100 mL). Hydrogen was bubbled through the reaction solution continuously throughout addition of the active ester and for 1 h after the completion of the addition. The cooled reaction mixture was filtered through Celite, and the Celite was washed with CH_2Cl_2–MeOH (1:1, 3 × 30 mL). The combined filtrate was concentrated in vacuo to give a brown solid. Flash chromatography (SiO_2, 2 × 15 cm, 2–10% THF–Et_2O gradient elution) afforded **76** (0.022 g, 0.037 g theoretical, 61%) as a glassy

solid: mp 165–168 °C (MeOH–benzene, tan flakes); ^{1}H NMR (methanol-d_4, 300 MHz, ppm), 7.31–6.77 (m, 7 H, aryl CH), 6.41 (d, 1 H, J = 2 Hz, C_{22}-H), 4.20 (d, 2 H, J = 6 Hz, OCH_2NH), 3.82 (s, 3 H, OCH_3), 3.73 (m, 2 H, CH_2CH_2NH), 3.08 (t, 2 H, J = 6 Hz, NCH_2CH_2Ar), 2.71 (t, 2 H, J = 6 Hz, OCH_2CH_2Ar), 2.63 (t, 2 H, J = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 3410, 2932, 1681, 1654, 1616, 1586, 1558, 1540, 1506, 1488, 1448, 1366, 1250, 1168, 1104, 1018, 830, 737 cm^{-1}; EIMS m/e (relative intensity) 354 (M^+, base), 338 (21), 297 (32), 252 (44); CIMS (isobutane) m/e (relative intensity) 355 (M^+ + H, base); EIHRMS m/e 354.4047 ($C_{20}H_{22}N_2O_4$ requires 354.4048).

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.79; H, 6.21; N, 7.91. Found: C, 67.66; H, 5.92; N, 8.10.

General Procedure for Macrocyclization Reactions, Method E: (*S*)-4-Methoxy-12-[(4-hydroxyphenyl)methyl]-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-3,5,7-(22),17,19,20-hexaene (85). A solution of **89**·HCl (0.069 g, 0.101 mmol) in 10 mL of dry dioxane was added dropwise (12 h) to a prewarmed (90 °C) mixture of dioxane–pyridine (5:1, 250 mL). The reaction mixture was stirred for an additional 1 h after completion of addition. The cooled reaction solution was concentrated in vacuo. Flash chromatography (SiO_2, 2 × 10 cm, 1–6% THF–Et_2O gradient elution) afforded **85** (0.032 g, 0.046 g theoretical, 68%) as a glassy, tan solid: mp 187–189 °C (MeOH, glassy flakes); $[\alpha]^{22}_D$ −13° (c 1.2, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.30 (dd, 1 H, J = 8, 2 Hz, C_{18}-H), 7.08 (dd, 1 H, J = 8, 2 Hz, C_{19}-H), 7.06 (d, 2 H, J = 8 Hz, C_5^{Tyr}-H_2), 6.99 (dd, 1 H, J = 8, 2 Hz, C_{21}-H), 6.93 (d, 1 H, J = 8 Hz, C_{20}-H), 6.76 (d, 2 H, J = 8 Hz, C_6^{Tyr}-H_2), 6.74 (dd, 1 H, J = 8, 2 Hz, C_5-H), 6.69 (dd, 1 H, J = 8, 2 Hz, C_6-H), 6.35 (d, 1 H, J = 1.7 Hz, C_{22}-H), 4.25 (dd, 1 H, J = 11, 6 Hz, C_{12}-H), 3.82 (s, 3 H, OCH_3), 3.75 (m, 2 H, CH_2CH_2NH), 3.11 (t, 2 H, J = 6 Hz, NCH_2CH_2Ar), 3.01 and 2.97 (2 dd, 1 H each, J = 12, 5 Hz, CHHCH and CHHCH), 2.73 (t, 2 H, J = 6 Hz, OCH_2CH_2Ar), 2.65 (t, 2 H, J = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 3350, 2899, 2283, 1682, 1656, 1588, 1510, 1469, 1445, 1250, 1180, 1014, 828, 737 cm^{-1}; EIMS m/e (relative intensity) 460 (M^+, base), 403 (13), 369 (19), 358 (46), 346 (28); CIMS (isobutane) m/e (relative intensity) 461 (M^+ + H, base); EIHRMS m/e 460.5283 ($C_{27}H_{28}N_2O_5$ requires 460.5286).

Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.28; H, 6.09; N, 6.07. Found C, 70.39; H, 5.92; N, 5.86.

11,14-Dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene (74): mp 172–174 °C (MeOH, white plates); ^{1}H NMR (pyridine-d_5, 300 MHz, ppm) 8.54 (d, 1 H, J = 8 Hz, NH), 8.44 (d, 1 H, J = 8 Hz, NH), 7.30–6.75 (m, 7 H, aryl CH), 6.40 (d, 1 H, J = 2 Hz, C_{22}-H), 4.22 (d, 2 H, 6 Hz, OCH_2NH), 3.73 (m, 2 H, CH_2CH_2NH), 3.06 (t, 2 H, J = 6 Hz, NCH_2CH_2Ar), 2.72 (t, 2 H, J = 6 Hz, OCH_2CH_2Ar), 2.63 (t, 2 H, J = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 3292, 3097, 2968, 2922, 2866, 1686, 1646, 1590, 1508, 1499, 1443, 1418, 1376, 1252, 1214, 1109, 1032, 901, 885, 783 cm^{-1}; EIMS m/e (relative intensity) 324 (M^+, base), 307 (15), 267 (22), 222 (52), 210 (38); CIMS (isobutane) m/e (relative intensity) 325 (M^+ + H, base); EIHRMS m/e 324.3784 ($C_{19}H_{20}N_2O_3$ requires 324.3786).

4-Methoxy-11,14-dioxo-2-oxa-10,13-diazatricyclo-[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene (75): mp 192–193 °C (MeOH–hexane, tan flakes); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.28–6.72 (m, 7 H, aryl CH), 6.36 (d, 1 H, J = 2 Hz, C_{22}-H), 4.26 (d, 2 H, J = 6 Hz, OCH_2NH), 3.76 (m, 2 H, CH_2CH_2NH), 3.09 (t, 2 H, J = 6 Hz, NCH_2CH_2Ar), 2.75 (t, 2 H, J = 6 Hz, OCH_2CH_2Ar), 2.63 (t, 2 H, J = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 3321, 3095, 2972, 2931, 1686, 1646, 1588, 1506, 1442, 1379, 1252, 1214, 1210, 1111, 1031, 908, 782, 745 cm^{-1}; EIMS m/e (relative intensity) 340 (M^+, base), 282 (40), 237 (28), 225 (29); CIMS (isobutane) m/e (relative intensity) 341 (M^+ + H, base); EIHRMS m/e 340.3776 ($C_{19}H_{20}N_2O_4$ requires 340.3780).

(*S*)-12-[(4-Hydroxyphenyl)methyl]-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene (83): mp 159–163 °C (MeOH–CH_2Cl_2, fine tan needles); $[\alpha]_D^{22}$ −11° (c 0.8, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.32–6.74 (m, 7 H, aryl CH), 6.36 (d, 1 H, J = 1.5 Hz, C_{22}-H), 4.20 (dd, 1 H, J = 11, 6 Hz, C_{12}-H), 3.72 (m, 2 H, CH_2CH_2NH), 3.10 (t, 2 H, J = 6 Hz, NCH_2CH_2Ar), 3.01 and 2.98 (2 dd, 1 H each, J = 12, 6 Hz, CHHCH and CHHCH), 2.73 (t, 2 H, J = 6 Hz, OCH_2CH_2Ar), 2.65 (t, 2 H, J = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 3320, 2286, 1680, 1659, 1586, 1510, 1451, 1248, 1170, 1019, 843, 729 cm^{-1}; EIMS m/e (relative intensity) 430 (M^+, base), 373 (16), 339 (18), 328 (44); CIMS (isobutane) m/e (relative intensity) 431 (M^+ + H, base); EIHRMS m/e 430.5024 ($C_{26}H_{26}N_2O_4$ requires 430.5024).

Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.56; H, 6.05; N, 6.51. Found: C, 72.56; H, 5.92; N, 6.42.

(*S*)-12-[(4-Hydroxyphenyl)methyl]-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene (95): mp 143–146 °C (MeOH, tan plates); $[\alpha]_D^{22}$ −15° (c 0.68, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.34–6.68 (m, 12 H, Ar-H), 5.81 (s, 1 H, C22-H), 4.19 (dd, 1 H, J = 4, 10 Hz, $NHCHCH_2Ph$), 3.72 (dd, 2 H, J = 6, 8 Hz, CH_2NH), 3.10 (t, 2 H, J = 6 Hz, CH_2CH_2NH), 3.00 and 2.96 (2 dd, 1 H each, J = 11, 6 Hz, CHCHHAr and CHCHHAr), 2.70 (t, 2 H, J = 6 Hz, CH_2CH_2CO), 2.63 (t, 2 H, J = 6 Hz, CH_2CH_2CO); IR (KBr) ν_{max} 2958, 2904, 1670, 1646, 1590, 1563, 1264, 1168, 1131, 1033, 910, 725 cm^{-1}; EIMS m/e (relative intensity) 430 (M^+, base), 373 (11), 339 (21), 328 (23), 323 (7); CIMS (isobutane) m/e (relative intensity) 431 (M^+ + H, base); EIHRMS m/e 430.5019 ($C_{26}H_{26}N_2O_4$ requires 430.5024).

Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.56; H, 6.05; N, 6.51. Found: C, 72.48; H, 5.92; N, 6.18.

(*S*)-4-Hydroxy-12-(2-amino-2-oxoethyl)-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene (103): mp 196–199 °C (MeOH, white plates); $[\alpha]_D^{22}$ −41° (c 0.53, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.35–6.70 (m, 7 H, Ar-H), 5.79 (s, 1 H, C22-H), 4.60 (dd, 1 H, J = 4, 10 Hz, $NHCHCH_2CONH_2$), 3.72 (dd, 2 H, J = 6, 8 Hz, CH_2NH), 3.10 (t, 2 H, J = 6 Hz, CH_2CH_2NH), 2.71 (t, 2 H, J = 6 Hz, CH_2CH_2CO), 2.65 (t, 2 H, J = 6 Hz, CH_2CH_2CO), 2.40–2.35 (m, 2 H, CH_2CONH_2); IR (KBr) ν_{max} 3250, 2960, 1689, 1645, 1590, 1559, 1254, 1166, 1030, 848, 728 cm^{-1}; EIMS m/e (relative intensity) 397 (M^+, base), 354 (19), 340 (33), 307 (33), 267 (22), 222 (10); CIMS (isobutane) m/e (relative intensity) 398 (M^+ + H, base); EIHRMS m/e 397.4292 ($C_{21}H_{23}N_3O_5$ requires 397.4298).

Anal. Calcd for $C_{21}H_{23}N_3O_5$: C, 63.47; H, 5.79; N, 10.58. Found: C, 63.09; H, 6.01; N, 10.23.

(*S*)-4-Methoxy-12-(2-amino-2-oxoethyl)-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene (104): mp 150–155 °C (MeOH, colorless plates); $[\alpha]_D^{22}$ −23° (c 0.98, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.34–6.75 (m, 7 H, Ar-H), 5.76 (s, 1 H, C22-H), 4.58 (dd, 1 H, J = 4, 10 Hz, $NHCHCH_2CONH_2$), 3.84 (s, 3 H, OCH_3), 3.71 (dd, 2 H, J = 6, 8 Hz, CH_2NH), 3.10 (t, 2 H, J = 6 Hz, CH_2CH_2NH), 2.71 (t, 2 H, J = 6 Hz, CH_2CH_2CO), 2.63 (t, 2 H, J = 6 Hz, CH_2CH_2CO), 2.42–2.36 (m, 2 H, CH_2CONH_2); IR (KBr) ν_{max} 2959, 1688, 1645, 1563, 1254, 1170, 1033, 900, 727 cm^{-1}; EIMS m/e (relative intensity) 411 (M^+, base), 396 (12), 369 (22), 355 (29), 340 (14), 324 (17), 307 (9), 298 (13), 267 (10), 222 (8); CIMS (isobutane) m/e (relative intensity) 412 (M^+ + H, base); EIHRMS m/e 411.4560 ($C_{22}H_{25}N_3O_5$ requires 411.4566).

Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 61.31; H, 6.08; N, 10.22. Found: C, 60.98; H, 6.07; N, 10.08.

(*S*)-*N*-(2,2,2-Trifluoroacetyl)-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)ethyl]-2-(phenylmethoxy)phenyl]-L-tyrosine Methyl Ester (105). Trifluoroacetic anhydride (84 μL, 0.595 mmol, 1.05 equiv) was added dropwise to a solution of **31** (345 mg, 0.566 mmol) in 5 mL of tetrahydrofuran at 25 °C, and the reaction mixture was stirred for 1 h (25 °C). The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL), dried ($NaHCO_3$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, 40% Et_2O–hexane eluant) provided **105** (388 mg, 401 mg theoretical, 97%) as a clear oil: $[\alpha]_D^{22}$ −128.2° (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.28 (br s, 10 H, two Ph), 7.18 (d, 1 H, J = 2 Hz, C2-H), 7.09 (dd, 1 H, J = 8, 2 Hz, C6-H), 7.00 (d, 1 H, J = 8 Hz, C5-H), 6.98 (d, 2 H, J = 8 Hz, C3′-H and C5′-H), 6.73 (d, 2 H, J = 8 Hz, C2′-H and C6′-H), 6.68 (d, 1 H, J = 8 Hz, $NHCOCF_3$), 5.10 (d, 1 H, J = 7 Hz, $NHCO_2$), 5.08 (s, 2 H, $PhCH_2O$), 5.01 (s, 2 H, $PhCH_2O_2C$), 4.90 (t, 1 H, J = 7 Hz, $CHNHCOCF_3$), 4.47 (t, 1 H, J = 7 Hz, $CHNHCO_2Bn$), 3.65 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 2.99 and 2.90 (2 dd, 1 H each, J = 16, 8 Hz, CHHCHNH and CHHNH), 2.84 and 2.74 (2 dd, 1 H each, J = 16, 8 Hz, $CHNHCO_2$ and $CHHNHCO_2$); IR (neat) ν_{max} 3800, 3751, 3690, 3649, 2954, 2899,

1735, 1722, 1704, 1658, 1610, 1563, 1456, 1392, 1226, 1181, 1030, 730 cm^{-1}; CIMS (isobutane) m/e (relative intensity) 709 (M^+ + H, 6); CIHRMS m/e 708.6863 ($C_{37}H_{35}F_3N_2O_4$ requires 708.6867).

(*S*)-*N*-(2,2,2-Trifluoroacetyl)-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)ethyl]-2-(phenylmethoxy)phenyl]-L-tyrosine (106). A suspension of sodium hydride (10% oil dispersion, 0.020 g, 0.49 mmol, 1.0 equiv) in 10 mL of tetrahydrofuran at 0 °C was treated dropwise with **105** (0.350 g, 0.49 mmol) in 5 mL of tetrahydrofuran (10 min addition). The reaction mixture was allowed to warm slowly to ambient temperature (25 °C) after the addition of **105** was complete. After 2 h, the reaction solution was poured onto 20 mL of 10% aqueous HCl and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, 80% Et_2O–hexane eluant) provided **106** (233 mg, 342 mg theoretical, 68%) as a white solid: mp 156.5–157.5 °C (MeOH, white flakes); $[\alpha]_D^{22}$ 98° (*c* 1.2, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.25 (br s, 10 H, two Ph), 7.19 (d, 1 H, *J* = 2 Hz, C2-H), 7.09 (dd, 1 H, *J* = 8, 2 Hz, C6-H), 7.00 (d, 1 H, *J* = 8 Hz, C5-H), 6.97 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.72 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 6.66 (d, 1 H, *J* = 8 Hz, NHCOCF$_3$), 5.09 (d, 1 H, *J* = 7 Hz, NHCO$_2$Bn), 5.06 (s, 2 H, PhCH$_2$O), 5.00 (s, 2 H, PhCH$_2$O$_2$C), 4.88 (t, 1 H, *J* = 7 Hz, C*H*NHCOCF$_3$), 4.46 (t, 1 H, *J* = 7 Hz, C*H*NHCO$_2$Bn), 3.64 (s, 3 H, OCH$_3$), 2.98 and 2.89 (2 dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH), 2.76 and 2.68 (2 dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH); IR (KBr) ν_{max} 3710–2350, 1738, 1718, 1701, 1698, 1588, 1501, 1456, 1447, 1389, 1347, 1288, 1219, 1103, 1023, 913, 851, 772, 738 cm^{-1}; EIMS m/e (relative intensity) 694 (M^+, 2), 612 (12), 604 (19), 561 (41), 91 (base); CIMS (isobutane) m/e (relative intensity) 695 (M^+ + H, 11); EIHRMS m/e 694.6598 ($C_{36}H_{33}F_3N_2O_9$ requires 694.6599).

Anal. Calcd for $C_{36}H_{33}F_3N_2O_9$: C, 62.24; H, 4.75; N, 4.03. Found: C, 62.36; H, 4.59; N, 4.00.

Diastereomeric Analysis of 106. An ether solution of diazomethane was prepared by the addition of *N*-nitrosomethyl urea (0.2 g) to a two-phase mixture of 40% aqueous potassium hydroxide–ether (10 mL; 10 mL) at 0 °C. After 10 min, 5 mL of the upper layer of this mixture was added to a 25 °C solution of **106** (0.010 g, 0.015 mmol) in 2 mL of ether, and the reaction solution was stirred (25 °C) until the yellow color of excess diazomethane was absent (ca. 4 h). The volatiles were removed in vacuo to afford **105** (0.011 g). HPLC analysis (4.6 mm × 25 cm Alltech 10 μ SiO_2 column, 25% EtOAc–hexane, 258 nm, 2 mL/min) revealed a single peak with an identical retention time (t_R = 15.2 min) to the product of the previous experimental (**105**, t_R = 15.2 min).

(*S*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)ethyl]-2-(phenylmethoxy)phenyl]-L-tyrosine (108). The trifluoroacetamide **106** (0.210 g, 0.304 mmol) was dissolved in 5 mL of a solution of 10% potassium carbonate in methanol–water (5:2) at 25 °C, and the reaction mixture was stirred for 6 h (25 °C). The reaction mixture was extracted with ether (1 × 3 mL) and was then adjusted to pH 7 by the careful, dropwise addition of 10% aqueous HCl. The reaction mixture was extracted with methylene chloride (6 × 5 mL), and the combined extracts were dried (Na_2SO_4), and concentrated in vacuo to afford crude **107** (0.156 g, 0.181 g theoretical, 86%) as an amorphous white solid which was used directly in the following reaction. For **107**: ^1H NMR (methanol-d_4, 300 MHz, ppm), 7.31 (br s, 10 H, two Ph), 7.23 (d, 1 H, *J* = 2 Hz, C2-H), 7.13 (dd, 1 H, *J* = 8, 2 Hz, C6-H), 7.05 (d, 1 H, *J* = 8 Hz, C5-H), 6.98 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.73 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.14 (d, 1 H, *J* = 8 Hz, NHCO$_2$Bn), 5.10 (s, 2 H, PhCH$_2$O), 5.00 (s, 2 H, PhC*H*$_2$O$_2$CN), 4.51 (t, 1 H, *J* = 7 Hz, CH$_2$C*H*NHCO$_2$Bn), 4.02 (m, 1 H, CH$_2$C*H*NH$_2$), 3.65 (s, 3 H, OCH$_3$), 2.98 and 2.89 (2 dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH), 2.78 (m, 2 H, C*H*$_2$CHNH$_2$); IR (KBr) ν_{max} 3408–2250 (b), 1760, 1718, 1700, 1661, 1602, 1550, 1449, 1395, 1366, 1272, 1172, 1103, 1029, 998, 736 cm^{-1}.

A solution of **107** (0.156 g, 0.256 mmol) in 3 mL of tetrahydrofuran/water (4:1) at 25 °C was treated with potassium carbonate (0.071 g, 0.519 mmol, 2.0 equiv) and di-*tert*-butyl dicarbonate (0.059 g, 0.286 mmol, 1.05 equiv) and was stirred 2 h (25 °C). The reaction mixture was poured over 10 mL of 10% aqueous HCl and extracted with ethyl acetate (5 × 5 mL). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, Et_2O eluant) afforded **108** (0.162 g, 0.178 g theoretical, 91%) as a yellow oil: $[\alpha]_D^{22}$ −102° (*c* 0.8, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.24 (br s, 10 H, two Ph), 7.19 (d, 1 H, *J* = 2 Hz, C2-H), 7.10 (dd, 1 H, *J* = 8, 2 Hz, C6-H), 6.99 (d, 1 H, *J* = 8 Hz, C5-H), 6.96 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.71 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.12 (d, 1 H, *J* = 8 Hz, NHCO$_2$), 5.08 (d, 1 H, *J* = 8 Hz, NHCO$_2$), 5.05 (s, 2 H, PhCH$_2$O), 5.00 (s, 2 H, PhCH$_2$O$_2$CN), 4.51 (t, 1 H, *J* = 8 Hz, C*H*NH), 4.43 (t, 1 H, *J* = 8 Hz, C*H*NHCO$_2$Bn), 3.65 (s, 3 H, OCH$_3$), 2.99 and 2.92 (2 dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH), 2.76 and 2.68 (2 dd, 1 H each, *J* = 16, 8 Hz, C*H*HCHNH and CH*H*CHNH), 1.41 (s, 9 H, C(C*H*$_3$)); IR (neat) ν_{max} 3740–2380, 1738, 1700, 1696, 1591, 1581, 1510, 1456, 1442, 1437, 1400, 1388, 1351, 1289, 1251, 1220, 1100, 1015, 912, 850, 736 cm^{-1}; CIMS (isobutane) m/e (relative intensity) 699 (M^+ + H, 19), 655 (M^+ + H − CO_2, base); CIHRMS m/e 698.7682 ($C_{39}H_{42}N_2O_{10}$ requires 698.7682).

(*S*)-*N*-[*N*-[(1,1-Dimethylethoxy)carbonyl]-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)ethyl]-2-(phenylmethoxy)phenyl]-L-tyrosyl]-L-tyrosine 2-(Trimethylsilyl)ethyl Ester (109). A solution of **108** (0.150 g, 0.215 mmol) in 3 mL of methylene chloride at 25 °C was treated with L-tyrosine 2-(trimethylsilyl)ethyl ester (0.060 g, 0.215 mmol, 1.0 equiv), EDCI (0.041 g, 0.215 mmol, 1.0 equiv), and hydroxybenzotriazole hydrate (5 mg, 0.021 mmol, 0.1 equiv) and was stirred for 9 h (25 °C). The reaction mixture was poured over 10 mL of 10% aqueous HCl and extracted with ethyl acetate (5 × 10 mL). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 15 cm, 10% THF–EtOAc eluant) afforded **109** (0.176 g, 0.206 g theoretical, 85%) as a white, amorphous, hygroscopic solid: $[\alpha]_D^{22}$ +115° (*c* 0.9, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.35–7.18 (m, 4 H, ArH), 7.34 (br s, 10 H, two Ph), 7.18–6.73 (m, 11 H, ArH), 6.61 (d, 1 H, *J* = 8 Hz, CHN*H*COC), 5.12 (d, 1 H, *J* = 8 Hz, NHCO$_2$), 5.08 (d, 1 H, *J* = 8 Hz, NHCO$_2$), 5.05 (s, 2 H, PhCH$_2$OAr), 4.99 (s, 2 H, PhCH$_2$O$_2$CN), 4.60 (m, 1 H, CH$_2$C*H*NH), 4.40–4.22 (m, 2 H, two CH$_2$C*H*NH), 4.33 (t, 2 H, *J* = 9 Hz, OC*H*$_2$CH$_2$Si), 3.69 (s, 3 H, OCH$_3$), 3.10–2.68 (m, 6 H, three ArC*H*$_2$CH), 1.40 (s, 9 H, C(C*H*$_3$)$_3$), 1.02 (t, 2 H, *J* = 9 Hz, OCH$_2$C*H*$_2$Si), 0.03 (s, 9 H, Si(CH$_3$)$_3$); IR (KBr) ν_{max} 3417, 3309, 3130–2850, 1739, 1722, 1688, 1621, 1612, 1579, 1521, 1455, 1441, 1402, 1378, 1352, 1293, 1218, 1013, 913, 740 cm^{-1}.

Anal. Calcd for $C_{54}H_{63}N_3O_{12}Si$: C, 65.36; H, 6.47; N, 4.32. Found: 65.13; H, 6.80; N, 4.71.

(*S*)-*N*-[*N*-[(1,1-Dimethylethoxy)carbonyl]-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)ethyl]-2-(phenylmethoxy)phenyl]-L-tyrosyl]-L-tyrosine (110). A solution of **109** (0.098 g, 0.102 mmol) in 3 mL of *N*,*N*-dimethylformamide under argon at 25 °C was treated with tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 103 μL, 1.0 equiv) and was stirred 4 h (25 °C). The reaction solution was poured over 5 mL of 5% aqueous HCl and extracted with ethyl acetate (5 × 3 mL). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Short column chromatography (SiO_2, 2 × 5 cm, 15% THF–EtOAc eluant) afforded **110** (0.081 g, 0.088 g theoretical, 92%) as a white foam: $[\alpha]_D^{22}$ +48.8° (*c* 0.92, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.35–7.17 (m, 4 H, Ar-H), 7.34 (br s, 10 H, two Ph), 7.18–6.73 (m, 11 H, Ar-H), 6.60 (d, 1 H, *J* = 8 Hz, CHN*H*COC), 5.13 (d, 1 H, *J* = 8 Hz, NHCO$_2$), 5.05 (s, 2 H, PhCH$_2$OAr), 4.99 (s, 2 H, PhC*H*$_2$O$_2$CN), 4.60 (m, 1 H, CH$_2$C*H*NH), 4.41–4.24 (m, 2 H, two CH$_2$C*H*NH), 3.69 (s, 3 H, OCH$_3$), 3.10–2.69 (m, 6 H, three ArCH$_2$CH), 1.41 (s, 9 H, C(CH$_3$)$_3$); IR (KBr) ν_{max} 3685, 3412, 3160, 3100–2830, 1740, 1717, 1682, 1650, 1612, 1580, 1510, 1452, 1442, 1400, 1370, 1220, 920, 738 cm^{-1}.

Anal. Calcd for $C_{49}H_{51}N_3O_{12}$: C, 65.98; H, 7.22; N, 4.81. Found: C, 65.59; H, 7.02; N, 5.18.

Methyl (9*S*,12*S*,15*S*)-15-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-hydroxy-12-[(4-hydroxyphenyl)methyl]-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene-9-carboxylate (114). Method A. A solution of **110** (0.083 g, 0.096 mmol) in 2 mL of tetra-

hydrofuran at 25 °C was treated with 10% palladium on carbon (0.010 g, 0.12 wt equiv) and aqueous 10% HCl (0.160 mL, 0.192 mmol, 2.0 equiv) and was stirred at 25 °C (4 h) under an atmosphere of hydrogen. The reaction mixture was filtered through Celite (THF) and concentrated in vacuo. Benzene (5 mL) was added, the volatiles were removed in vacuo, and the residue was dried under vacuum. The crude amine salt **112**·HCl was dissolved in *N*,*N*-dimethylformamide (12 mL) and cooled to 0 °C before the addition of sodium bicarbonate (0.040 g, 0.48 mmol) and diphenyl phosphorazidate (DPPA, 32 μL, 0.144 mmol, 1.5 equiv). The reaction mixture was stirred for 72 h (0 °C) and poured onto 20 mL of water and extracted with ethyl acetate (6 × 5 mL). The combined extracts were washed with water (2 × 10 mL) and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 8 cm, 60–80% EtOAc–hexane gradient elution) afforded **114** (0.036 g, 0.059 g theoretical, 61%) as a light tan, glassy solid. A sample (0.030 g) of the solid was further purified by preparative HPLC (10 mm × 25 cm Alltech 10 μ SiO_2 column, 20% CH_3OH/CH_2Cl_2, 258 nm, 2 mL/min, t_R = 7.65 min): mp 214–216 °C (MeOH, tan flakes); $[\alpha]^{22}_D$ +187° (*c* 1.2, MeOH); ^1H NMR (methanol-d_4, 300 MHz, ppm) 7.30 (dd, 1 H, *J* = 8, 2 Hz, $C_{5b}{}^1$-H), 7.06 (dd, 1 H, *J* = 8, 2 Hz, $C_{6b}{}^2$-H), 6.98 (dd, 1 H, *J* = 8, 2 Hz, $C_{5a}{}^1$-H), 6.95 (d, 2 H, *J* = 8 Hz, $C_5{}^2$-H), 6.75 (d, 1 H, *J* = 8 Hz, $C_{6b}{}^3$-H), 6.72 (dd, 1 H, *J* = 8, 2 Hz, $C_{5b}{}^2$-H), 6.68 (dd, 1 H, *J* = 8, 2 Hz, $C_{6a}{}^1$-H), 6.59 (d, 1 H, *J* = 8 Hz, $C_6{}^2$-H), 6.33 (d, 1 H, *J* = 1.5 Hz, $C_{5a}{}^3$), 4.34 (m, 1 H, CH_2CHNH), 4.16 (m, 1 H, CH_2CHNH), 3.91 (m, 1 H, CH_2CHNH), 3.69 (s, 3 H, OCH_3), 3.29–2.72 (m, 6 H, three CH_2CH), 1.47 (br s, 9 H, $C(CH_3)_3$); ^{13}C NMR (methanol-d_4, 75 MHz, ppm) 172.6, 171.7, 170.4, 158.2, 156.9, 149.3, 148.1, 132.3, 131.4, 130.6, 128.2, 124.0, 120.5, 119.3, 117.2, 114.1, 80.0, 55.0, 53.2, 52.3, 39.1, 35.0, 28.6; IR (KBr) ν_{max} 3410, 3317, 3301, 3290, 2833, 1739, 1664, 1635, 1588, 1522, 1509, 1277, 1233, 1217, 1127, 1020, 987, 868, 737 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m*/*e* 642 (M^+ + Na), 620 (M^+ + H); FABHRMS *m*/*e* 620.6778 ($C_{33}H_{37}N_3O_9$ requires 620.6779).

Method B. A solution of **110** (0.022 g, 0.025 mmol) in 1 mL of methylene chloride at 25 °C was treated with pentafluorophenol (0.010 g, 0.051 mmol, 2.0 equiv) and EDCI (0.006 g, 0.025 mmol, 1.0 equiv) and was stirred for 2 h (25 °C). The reaction mixture was poured over water (2 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo to afford crude **111** (0.022 g, 0.026 g theoretical, 85%) [IR (neat) ν_{max} 1780 cm^{-1}] which was used immediately in the following reaction. A solution of **111** (0.022 g, 0.021 mmol) in 2 mL of tetrahydrofuran was treated with 10% palladium on carbon (0.003 g, 0.14 wt equiv) and aqueous 10% HCl (36 μL, 0.044 mmol, 2.0 equiv) and was stirred at 25 °C (4 h) under an atmosphere of hydrogen. The reaction mixture was filtered through Celite (THF) and concentrated in vacuo, and the residue was dried thoroughly under vacuum. The crude amine hydrochloride (**111**·HCl) was dissolved in *N*,*N*-dimethylformamide (3 mL) and slowly added over 18 h (syringe pump) to a prewarmed (90 °C) suspension of $NaHCO_3$ (0.011 g, 0.125 mmol, 5.0 equiv) in *N*,*N*-dimethylformamide (70 mL). The reaction mixture was stirred for an additional hour at 90 °C. The reaction mixture was concentrated in vacuo to a volume of 5 mL, filtered through Celite (DMF), and further concentrated in vacuo. Flash chromatography (SiO_2, 1 × 8 cm, 70% EtOAc–hexane eluant) afforded **114** (0.007 g, 0.013 g theoretical, 51%), identical in all respects with the product of the DPPA cyclization.

Methyl (9*S*,12*S*,15*S*)-15-(Acetylamino)-4-hydroxy-12-[(4-hydroxyphenyl)methyl]-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene-9-carboxylate (116). A solution of **114** (0.032 g, 0.052 mmol) in 1 mL of 3.0 M HCl/EtOAc was stirred at 25 °C (2 h). The volatiles were removed in vacuo, and the solid residue was dried under vacuum. The crude amine hydrochloride salt (**115**·HCl) dissolved in tetrahydrofuran (1 mL) was treated with $NaHCO_3$ (0.014 g, 0.155 mmol, 3.0 equiv) and acetic anhydride (5 μL, 0.055 mmol, 1.05 equiv), and the mixture was stirred for 2 h (25 °C). The reaction mixture was filtered through Celite (THF) and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 6 cm, 5–10% MeOH–CH_2Cl_2 gradient elution) afforded **116** (0.026 g, 0.029 g theoretical, 89%) as a white solid: mp 241–242 °C (MeOH, fine needles): $[\alpha]^{22}_D$ –33° (*c* 1.3, MeOH); ^1H NMR (methanol-d_4, 300 MHz, ppm) 7.30 (dd, 1 H, *J* = 8, 2 Hz, $C_{5b}{}^1$-H), 7.07 (dd, 1 H, *J* = 8, 2 Hz, $C_{6b}{}^1$-H), 6.98 (dd, 1 H, *J* = 8, 2 Hz, $C_{5a}{}^1$-H), 6.84 (d, 2 H, *J* = 8 Hz, $C_5{}^2$-H_2), 6.75 (d, 1 H, *J* = 8 Hz, $C_{6b}{}^3$-H), 6.72 (dd, 1 H, *J* = 8, 1.5 Hz, $C_{5b}{}^3$-H), 6.67 (dd, 1 H, *J* = 8, 2 Hz, $C_{6a}{}^1$-H), 6.59 (d, 2 H, *J* = 8 Hz, $C_6{}^2$-H_2), 6.33 (d, 1 H, *J* = 1.5 Hz, $C_{5a}{}^3$-H), 4.60 (dd, 1 H, *J* = 12, 5 Hz, $C_2{}^3$-H), 4.43 (dd, 1 H, *J* = 8, 3 Hz, $C_2{}^1$-H), 4.15 (t, 1 H, *J* = 5 Hz, $C_2{}^2$-H), 3.76 (s, 3 H, OCH_3), 3.05 and 2.90 (2 dd, 1 H each, *J* = 15, 3 Hz, $C_3{}^3HHCH$ and $C_3{}^3HHCH$), 2.90 and 2.73 (2 dd, 1 H each, *J* = 12, 3 Hz, $C_3{}^2HHCH$ and $C_3{}^2HHCH$), 2.90 and 2.69 (2 dd, 1 H each, *J* = 11, 10 Hz, $C_3{}^1HHCH$ and $C_3{}^1HHCH$), 2.01 (s, 3 H, $COCH_3$); IR (KBr) ν_{max} 3400, 3341, 3300, 3109, 2860, 2836, 1740, 1666, 1634, 1523, 1508, 1477, 1400, 1355, 1250, 1230, 1215, 1136, 1025, 937, 848, 738 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m*/*e* 584 (M^+ + Na), 562 (M^+ + H); FABHRMS *m*/*e* 562.5978 ($C_{30}H_{31}N_3O_8$ requires 562.5981).

(9*S*,12*S*,15*S*)-15-(Acetylamino)-9-carboxy-4-hydroxy-12-[(4-hydroxyphenyl)methyl]-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-3,5,7(22),17,19,20-hexaene (1, K-13). A solution of **116** (0.009 g, 0.016 mmol) in 1 mL of THF–MeOH–H_2O (3:1:1) at 25 °C was treated with lithium hydroxide monohydrate ($LiOH·H_2O$, 0.002 g, 0.040 mmol, 2.5 equiv) and was stirred for 4 h (25 °C). The reaction mixture was adjusted to pH 4 ($KHSO_4$), filtered through Celite (THF–MeOH), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, 10–20% MeOH/CH_2Cl_2 gradient elution) provided K-13 (1, 0.008 g, 0.0087 g theoretical, 93%) as a white solid: mp 264–268 °C (MeOH, powder) [natural K-13[2] mp 265–270 °C dec, synthetic K-13[5] mp 260–270 °C dec]; $[\alpha]^{22}_D$ –5.6° (*c* 0.53, MeOH) [natural K-13[2] $[\alpha]^{22}_D$ –3.4° (*c* 0.6, CH_3OH), synthetic K-13[5] $[\alpha]^{22}_D$ –6.5° (*c* 0.46, CH_3OH)]; ^1H NMR (methanol-d_4, 300 MHz, ppm) 7.29 (dd, 1 H, *J* = 8, 2 Hz, $C_{5b}{}^1$-H), 7.06 (dd, 1 H, *J* = 8, 2 Hz, $C_{6b}{}^1$-H), 6.99 (dd, 1 H, *J* = 8, 2 Hz, $C_{5a}{}^1$-H), 6.95 (d, 2 H, *J* = 8 Hz, $C_5{}^2$-H), 6.75 (d, 1 H, *J* = 8 Hz, $C_{6b}{}^3$-H), 6.71 (dd, 1 H, *J* = 8, 2 Hz, $C_{5b}{}^3$-H), 6.68 (dd, 1 H, *J* = 8, 2.5 Hz, $C_{6a}{}^1$-H), 6.59 (d, 2 H, *J* = 8 Hz, $C_6{}^2$-H), 6.33 (d, 1 H, *J* = 1.4, $C_{5a}{}^3$-H), 4.42 (dd, 1 H, *J* = 12, 5 Hz, $C_2{}^1$-H), 4.22 (dd, 1 H, *J* = 8, 3 Hz, $C_2{}^3$-H), 4.11 (dd, 1 H, *J* = 6, 4 Hz, $C_2{}^2$-H), 3.15 and 2.90 (2 dd, 1 H, each, *J* = 15, 5 Hz, $C_3{}^3HHCH$ and $C_3{}^3HHCH$), 3.00 and 2.80 (2 dd, 1 H each, *J* = 12, 7 Hz, $C_3{}^1HHCH$ and $C_3{}^1HHCH$), 2.91 (t, 2 H, *J* = 12 Hz, $C_3{}^2$-H_2); IR (KBr) ν_{max} 3855, 3822, 3802–2950, 2924, 2852, 1647, 1515, 1443, 1224, 1170, 1114, 925, 807 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m*/*e* 570 (M^+ + Na), 548 (M^+ + H); FABHRMS *m*/*e* 548.5712 ($C_{29}H_{29}N_3O_8$ requires 548.5713).

***N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-3-[4-(hydroxymethyl)phenoxy]-L-tyrosine (117).** A solution of **27** (0.910 g, 1.73 mmol) in 10 mL of THF/MeOH/H_2O (3:1:1) at 25 °C was treated with lithium hydroxide monohydrate (3.0 equiv, 5.16 mmol, 0.217 g) and was stirred at 25 °C (0.5 h). The reaction mixture was poured onto 10% aqueous HCl (25 mL) and extracted with ethyl acetate (4 × 10 mL). The combined extracts were washed with 10% aqueous HCl, water, saturated aqueous NaCl, dried ($Na2SO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 20 cm, Et_2O eluant) afforded **117** (0.815 g, 0.885 g theoretical, 92%) as a cream-colored solid: mp 179 °C sharp (MeOH); $[\alpha]^{22}_D$ –48.2° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.32 (br s, 10 H, two Ph), 7.24 (d, 1 H, *J* = 2.3 Hz, C2-H), 7.12 (dd, 1 H, *J* = 8.4, 2.3 Hz, C6-H), 6.99 (d, 1 H, *J* = 8.4 Hz, C5-H), 6.96 (d, 2 H, *J* = 5 Hz, C3′-H and C5′-H), 6.91 (d, 2 H, *J* = 5.1 Hz, C2′-H and C6′-H), 5.22 (d, 1 H, *J* = 8 Hz, NH), 5.09 (s, 2 H, $PhCH_2O$), 5.02 (s, 2 H, $PhCH_2O_2C$), 4.62 (s, 2 H, CH_2OH), 4.38 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 3.06 and 2.97 (2 dd, 1 H each, *J* = 16, 8 Hz, $CHHCHNH$ and $CHHCHNH$); IR (KBr) ν_{max} 3550–2520 (b), 1725, 1715, 1700, 1660, 1638, 1610, 1575, 1558, 1509, 1454, 1438, 1272, 823, 736 cm^{-1}; EIMS *m*/*e* (relative intensity) 527 (M^+, 1), 305 (7), 275 (8), 197 (5), 108 (5), 91 (base); EIHRMS *m*/*e* 527.5720 ($C_{31}H_{29}NO_7$ requires 527.5726).

Anal. Calcd for $C_{31}H_{39}NO_7$: C, 62.05; H, 5.50; N, 2.66. Found: C, 61.90; H, 5.61; N, 2.69.

***N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-3-[4-(hydroxymethyl)phenoxy]-L-tyrosine 2-(Trimethylsilyl)ethyl Ester (118).** 2-(Trimethylsilyl)ethanol (0.317 g, 2.68 mmol, 3.0 equiv) was added to a solution of **117** (0.461 g, 0.895 mmol) in 5 mL of methylene chloride, and the solution was cooled to 0 °C. EDCI (0.170 g, 0.895 mmol, 1.0 equiv) was added, and the reaction mixture was stirred at 25 °C (12 h). The reaction mixture was

poured onto 10 mL of water and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 15 cm, 30–40% EtOAc–hexane eluant) afforded **118** (0.473 g, 0.550 g theoretical, 86%) as a clear oil: $[\alpha]^{22}_D$ −29.3° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.32 (br s, 10 H, two Ph), 7.22 (d, 1 H, *J* = 2.4 Hz, C2-H), 7.12 (dd, 1 H, *J* = 8.4, 2.5 Hz, C6-H), 6.98 (d, 1 H, *J* = 8.4 Hz, C5-H), 6.95 (d, 2 H, *J* = 5 Hz, C3′-H and C5′-H), 6.91 (d, 2 H, *J* = 5 Hz, C2′-H and C6′-H), 5.20 (d, 1 H, *J* = 8 Hz, NH), 5.09 (s, 2 H, $PhCH_2O$), 5.01 (s, 2 H, $PhCH_2O_2C$), 4.64 (s, 2 H, CH_2OH), 4.56 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 4.34 (m, 2 H, $CO_2CH_2CH_2$), 3.02 and 2.93 (2 dd, 1 H, *J* = 16, 8 Hz, *CH*HCHNH and CH*H*CHNH), 1.0 (t, 2 H, *J* = 6 Hz, CH_2Si), 0.06 (s, 9 H, $Si(CH_3)_3$); IR (neat) ν_{max} 3836, 3825, 3800, 3741, 3650, 3639, 3339, 1720, 1701, 1650, 1636, 1569, 1559, 1539, 1509, 1410, 1437, 1275, 1215, 1125, 1025, 840, 765 cm^{-1}; EIMS *m/e* (relative intensity) 627 (M^+, 3), 305 (7), 275 (8), 197 (5), 108 (5), 91 (base); CIMS (isobutane) *m/e* (relative intensity) 628 (M^+ + H, base); EIHRMS *m/e* 627.8071 ($C_{36}H_{41}NO_7$ requires 627.8079).

***N*-[(Phenylmethoxy)carbonyl]-*O*-(phenylmethyl)-3-[4-(bromomethyl)phenoxy]-L-tyrosine 2-(Trimethylsilyl)ethyl Ester (119).** A solution of **118** (0.250 g, 0.406 mmol) in 3 mL of ether at 25 °C was treated with triphenylphosphine (0.213 g, 0.813 mmol, 2.0 equiv) and carbon tetrabromide (0.270 g, 0.813 mmol, 2.0 equiv), and the reaction mixture was stirred at 25 °C (12 h). The reaction mixture was diluted with methylene chloride (3 mL) and filtered through Celite (Et_2O), and the filtrate was concentrated in vacuo. Short column chromatography (SiO_2, 4 × 10 cm, 50% Et_2O–hexane) afforded **119** (0.193 g, 0.275 g theoretical, 70%) as a yellow oil: $[\alpha]^{22}_D$ −62° (*c* 1.3, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm), 7.34 (br s, 5 H, Ph), 7.30 (br s, 5 H, Ph), 7.18 (d, 1 H, *J* = 8 Hz, C5-H), 7.14 (d, 1 H, *J* = 2.3 Hz, C2-H), 6.97 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.89 (dd, 1 H, *J* = 8, 2 Hz, C6-H), 6.84 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.22 (d, 1 H, *J* = 8 Hz, NH), 5.08 (s, 2 H, $PhCH_2O_2C$), 4.61 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 4.49 (s, 2 H, CH_2Br), 4.34 (m, 2 H, $CO_2CH_2CH_2$), 3.04 and 3.02 (2 dd, 1 H each, *J* = 16, 8 Hz, *CH*HCHNH and CH*H*CHNH), 1.0 (t, 2 H, *J* = 6 Hz, CH_2Si), 0.05 (s, 9 H, $Si(CH_3)_3$); IR (neat) ν_{max} 3782, 3652, 3354, 2957, 1722, 1654, 1609, 1586, 1455, 1437, 1380, 1350, 1271, 1169, 1126, 1058, 911, 831, 740 cm^{-1}; EIMS *m/e* (relative intensity) 678/680 (M^+, 1/1), 598 (M^+ − Br, 3), 91 (base); CIMS (isobutane) *m/e* (relative intensity) 679/681 (M^+ + H, 1/1), 598 (M^+ + H − HBr, 26), 107 (base).

Anal. Calcd for $C_{36}H_{40}BrNO_6Si$: C, 63.90; H, 5.92; N, 2.07. Found: C, 63.72; H, 5.95; N, 2.26.

(*S*)-*O*-[5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-[[2-(trimethylsilyl)ethoxy]carbonyl]ethyl]-2-(phenylmethoxy)phenyl]-L-tyrosine Methyl Ester (121). A solution of **119** (0.190 g, 0.28 mmol) in 0.5 mL of tetrahydrofuran was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.012 g, 0.31 mmol, 1.1 equiv) in 0.5 mL of tetrahydrofuran at 0 °C. The resulting solution was stirred for 5–10 min at 25 °C before dropwise addition by cannula to a −78 °C solution of **29** prepared by dropwise addition of *n*-butyllithium (2.3 M in hexane, 0.13 mL, 0.31 mmol, 1.1 equiv) to a solution of (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine[42] (0.184 g, 0.28 mmol, 1.0 equiv) in 0.5 mL of tetrahydrofuran at −78 °C. The reaction mixture was stirred at −78 °C (12 h) and was quenched with the addition of tetrahydrofuran/water (1:1, 1 mL) before warming to room temperature. The reaction mixture was poured onto water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Short column chromatography (SiO_2, 1 × 5 cm, 25% EtOAc-hexane eluant) afforded **120** (0.149 g, 0.219 g theoretical, 68%) as a clear yellow oil which was used directly in the following reaction. For **120**: ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.33 (br s, 10 H, two Ph), 7.36–7.22 (m, 2 H, aromatic H), 7.08 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.80 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.26 (d, 1 H, *J* = 8 Hz, NH), 5.10 (s, 2 H, $PhCH_2O$), 5.04 (s, 2 H, $PhCH_2O_2C$), 4.64 (q, 1 H, *J* = 8 Hz, CH_2CHNH), 4.38 (m, 2 H, $CO_2CH_2CH_2$), 4.32 (br s, 1 H, $CH_2CHN{=}C$), 3.66 (s, 6 H, two $N{=}COCH_3$), 3.20 and 3.11 (2 dd, 1 H, each, *J* = 16, 8 Hz, *CH*HCHNH and CH*H*CHNH), 3.04 and 2.96 (2 dd, 1 H each, *J* = 16, 8 Hz, *CH*HCHN=C and CH*H*CHN=C), 1.04 (t, 2 H, *J* = 6 Hz, CH_2Si), 0.95 (d, 3 H, *J* = 7 Hz, $CHCH_3$), 0.62 (d, 3 H, *J* = 7 Hz, $CHCH_3$), 0.05 (s, 9 H, $Si(CH_3)_3$); IR (neat) ν_{max} 3682, 3320, 2963, 2869, 2346, 1726, 1696, 1608, 1506, 1450, 1382, 1271, 1168, 1124, 1015, 831, 738 cm^{-1}.

Anal. Calcd for $C_{35}H_{36}N_2O_8$: C, 68.62; H, 5.88; N, 4.58. Found: C, 69.02; H, 5.90; N, 4.11.

A solution of **120** (0.149 g, 0.191 mmol) in 0.5 N HCl/THF (2 mL) at 25 °C was stirred 11 h (25 °C). The reaction mixture was poured over saturated aqueous $NaHCO_3$ (3 mL), and the aqueous mixture was extracted with ether/tetrahydrofuran (4:1, 3 × 3 mL). The organic extracts were washed with aqueous saturated NaCl, dried (Na_2SO_4), and concentrated in vacuo. Short column chromatography (SiO_2, 1 × 5 cm, 90% Et_2O–hexane eluant) afforded **121** (0.115 g, 0.196 g theoretical, 59% from **119**) as a viscous oil: $[\alpha]^{22}_D$ −93.8° (*c* 0.4, MeOH); ^1H NMR (Me_2SO-d_6, 300 MHz, ppm) 7.32 (br s, 10 H, two Ph), 7.21 (d, 1 H, *J* = 2 Hz, C2-H), 7.10 (dd, 1 H, *J* = 8, 2 Hz, C6-H), 7.02 (d, 1 H, *J* = 8 Hz, C5-H), 6.99 (d, 2 H, *J* = 8 Hz, C3′-H and C5′-H), 6.75 (d, 2 H, *J* = 8 Hz, C2′-H and C6′-H), 5.04 (s, 2 H, $PhCH_2O$), 4.99 (s, 2 H, $PhCH_2O_2C$), 4.65 (q, 1 H, *J* = 6 Hz, CH_2CH_2Si), 4.35 (m, 2 H, $CO_2CH_2CH_2$), 3.64 (s, 3 H, OCH_3), 2.98 and 2.92 (2 dd, 1 H each, *J* = 16, 8 Hz, *CH*HCH and CH*H*CH), 2.8 and 2.74 (2 dd, 1 H each, *J* = 16, 8 Hz, *CH*HCH and CH*H*CH), 1.01 (t, 2 H, *J* = 6 Hz, CH_2Si), 0.06 (s, 9 H, $Si(CH_3)_3$); IR (KBr) ν_{max} 3745, 3680, 2652, 2951, 1734, 1717, 1700, 1654, 1607, 1559, 1507, 1456, 1391, 1274, 1219, 1172, 1024, 849, 737 cm^{-1}; CIMS (isobutane) *m/e* (relative intensity), 613 (M^+, 1); CIHRMS *m/e* 613.6784 ($C_{35}H_{36}N_2O_8$ requires 613.6780).

Diastereomeric Analysis of 121. A solution of **121** (10 mg, 0.016 mmol) in 0.5 mL of tetrahydrofuran at 25 °C was treated with di-*tert*-butyl dicarbonate (4 μL, 0.016 mmol, 1.0 equiv) and was stirred at 25 °C (7 h). The reaction mixture was poured over water (1.0 mL) and extracted with ethyl acetate (3 × 0.5 mL). The combined extracts were washed with 10% aqueous HCl (0.5 mL), 5% aqueous sodium bicarbonate, and saturated aqueous NaCl. Flash chromatography (SiO_2, 1 × 3 cm, 50% Et_2O–hexane) provided the *N*-BOC derivative of **121** (11 mg). HPLC analysis (4.6 mm × 25 cm Alltech 10 μ SiO_2 column, 25% EtOAc–hexane, 258 nm, 2 mL/min) revealed an 89:5:5:<1 ratio of diastereomers, t_R = 13 min/15 min/15.5 min/17 min, indicating the alkylation proceeded with 94% de.

(*S*)-*O*-[5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-[[2-(trimethylsilyl)ethoxy]carbonyl]ethyl]-2-(phenylmethoxy)phenyl]-*N*-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-asparaginyl]-L-tyrosine Methyl Ester (123). A solution of **121** (0.068 g, 0.097 mmol), *N*-BOC-L-asparagine (0.044 g, 0.194 mmol, 2.0 equiv), and hydroxylbenzotriazole ($HOBt{\cdot}H_2O$, 0.026 g, 0.194 mmol, 2.0 equiv) in 3 mL of dry *N*,*N*-dimethylformamide was cooled to 0 °C before the addition of EDCI (0.037 g, 0.194 mmol, 2.0 equiv). The reaction mixture was allowed to stir for 12 h (25 °C) before it was poured over water (10 mL) and was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with 10% $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 10 cm, 10% THF–EtOAc eluant) afforded **123** (0.078 g, 0.088 g theoretical, 88%) as an off-white solid: mp 159–163 °C (EtOAc); $[\alpha]^{22}_D$ −103° (*c* 0.63, MeOH); ^1H NMR ($CDCl_3$, 300 MHz, ppm) 7.35–7.20 (m, 4 H, ArH), 7.34 (br s, 10 H, two Ph), 7.17–6.73 (m, 11 H, ArH), 6.63 (d, 1 H, *J* = 8 Hz, CHN*H*COC), 5.12 (d, 1 H, *J* = 8 Hz, $NHCO_2$), 5.07 (d, 1 H, *J* = 8 Hz, $NHCO_2$), 5.05 (s, 2 H, $PhCH_2OAr$), 5.00 (s, 2 H, $PhCH_2O_2CN$), 4.60 (m, 1 H, CH_2CHNH), 4.40–4.22 (m, 2 H, two CH_2CHNH), 4.34 (t, 2 H, *J* = 9 Hz, $CO_2CH_2CH_2$), 3.69 (s, 3 H, OCH_3), 3.10–2.68 (m, 4 H, two $ArCH_2CH$), 2.58–2.54 (m, 2 H, CH_2CON), 1.40 (s, 9 H, $C(CH_3)_3$), 1.02 (t, 2 H, *J* = 9 Hz, CH_2Si), 0.03 (s, 9 H, $Si(CH_3)_3$); IR (KBr) ν_{max} 3428, 3133–2852, 1740, 1722, 1689, 1621, 1582, 1521, 1455, 1402, 1355, 1293, 1218, 1013, 915, 740 cm^{-1}.

Anal. Calcd for $C_{52}H_{60}N_4O_{12}Si$: C, 65.00; H, 6.25; N, 5.83. Found: C, 64.62; H, 6.33; N, 6.15.

(*S*)-*O*-[5-[2-[(Phenylmethoxy)carbonyl]-2-[[2-(trimethylsilyl)ethoxy]carbonyl]ethyl]-2-hydroxyphenyl]-*N*-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-asparaginyl]-L-tyrosine Methyl Ester (124). A solution of **123** (0.066 g, 0.073 mmol) in 1.0 mL of dry tetrahydrofuran at 25 °C was treated with 10% palladium on carbon (7 mg, 0.12 weight equiv) and was stirred at 25 °C (3 h) under an atmosphere of hydrogen. The reaction mixture was diluted with 2–3 mL of tetrahydrofuran and filtered

through Celite. The filtrate was concentrated in vacuo, and the residue was dried under vacuum to afford a yellow oil. A solution of this oil in 1.5 mL of dry tetrahydrofuran was treated at 25 °C with sodium bicarbonate (0.018 g, 0.219 mmol, 3.0 equiv) and benzyl chloroformate (0.012 g, 10 μL, 1.0 equiv), and the resulting mixture was stirred at 25 °C (3 h). The reaction mixture was poured onto 5 mL of 5% aqueous HCl and extracted with ethyl acetate (3 × 3 mL). The combined extracts were washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 10 cm, 10% THF–EtOAc eluant) afforded **124** (0.051 g, 0.060 g theoretical, 86%) as a white, flaky solid: mp 181–183 °C (EtOAc, small cubes); $[\alpha]^{25}_D$ −89° (*c* 0.3, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.35–7.18 (m, 4 H, ArH), 7.34 (br s, 10 H, two Ph), 7.18–6.73 (m, 11 H, ArH), 6.61 (d, 1 H, *J* = 8 Hz, CHN*H*COC), 5.12 (d, 1 H, *J* = 8 Hz, $NHCO_2$), 5.08 (d, 1 H, *J* = 8 Hz, $NHCO_2$), 5.01 (s, 2 H, $PhCH_2O_2CN$), 4.60 (m, 1 H, CH_2CHNH), 4.40–4.22 (m, 2 H, two CH_2CHNH), 4.33 (t, 2 H, *J* = 9 Hz, $CO_2CH_2CH_2$), 3.69 (s, 3 H, OCH_3), 3.12–2.70 (m, 4 H, two $ArCH_2CH$), 2.57–2.52 (m, 2 H, CH_2CON), 1.40 (s, 9 H, $C(CH_3)_3$), 1.02 (t, 2 H, *J* = 9 Hz, CH_2Si), 0.04 (s, 9 H, $Si(CH_3)_3$); IR (KBr) ν_{max} 3417, 3309, 3130–2850, 1739, 1722, 1688, 1621, 1612, 1579, 1521, 1455, 1441, 1402, 1378, 1352, 1293, 1218, 1013, 913, 740 cm^{-1}.

Anal. Calcd for $C_{43}H_{54}N_4O_{12}Si$: C, 60.99; H, 6.38; N, 6.62. Found: C, 60.68; H, 6.42; N, 6.33.

(*S*)-*O*-[5-[2-[[(Phenylmethoxy)carbonyl]amino]-2-carboxyethyl]-2-hydroxyphenyl]-*N*-[*N*-[(1,1-dimethylethoxy)carbonyl]-L-asparaginyl]-L-tyrosine Methyl Ester (125). A solution of **124** (0.082 g, 0.100 mmol) in 1.5 mL of dry tetrahydrofuran at 25 °C was treated with tetra-*n*-butylammonium fluoride (1 M solution in THF, 200 μL, 0.200 mmol, 2.0 equiv), and the reaction mixture was stirred at 25 °C (4 h). The reaction solution was poured over water (5 mL) and extracted with tetrahydrofuran/ether (3:1, 3 × 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Short column chromatography (SiO_2, 1 × 10 cm, 10–25% THF/Et_2O eluant) afforded **125** (0.065 g, 0.072 g theoretical, 90%) as an off-white solid: mp 146–148 °C (THF); $[\alpha]^{22}_D$ −82° (*c* 0.34, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.35–6.98 (m, 9 H, Ar-H), 6.88 (d, 1 H, *J* = 1.8 Hz, $C_{5a}{}^2$-H), 6.70 (d, 1 H, *J* = 8 Hz, $C_3{}^2$-H), 5.05 (s, 2 H, $PhCH_2O_2CN$), 4.66 (t, 1 H, *J* = 7 Hz, CH_2CHNH), 4.41 (t, 1 H, *J* = 6 Hz, CH_2CHNH), 4.02 (dd, 1 H, *J* = 9, 5 Hz, CH_2CHNH), 3.72 (s, 3 H, OCH_3), 3.10–2.85 (m, 4 H, two $ArCH_2CH$), 2.53 (m, 2 H, $CHCH_2CON$), 1.41 (s, 9 H, $C(CH_3)_3$); IR (KBr) ν_{max} 3680–2100, 1732, 1710, 1682, 1650, 1612, 1580, 1510, 1452, 1401, 1372, 1220, 920, 738 cm^{-1}.

Anal. Calcd for $C_{40}H_{42}N_4O_{12}$: C, 62.34; H, 5.45; N, 7.27. Found: C, 62.65; H, 5.74; N, 7.36.

Methyl (9*S*,12*S*,15*S*)-12-(2-Amino-2-oxoethyl)-9-[[(phenylmethoxy)carbonyl]amino]-4-hydroxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene-15-carboxylate (128). A solution of **125** (0.065 g, 0.090 mmol) in 1 mL of 3.0 M HCl/EtOAc at 25 °C was stirred for 0.5 h. The volatiles were removed in vacuo, and the resulting solid was triturated with tetrahydrofuran/ether (1:1) to remove unreacted starting material. The amine salt **126** was used directly for the following reaction without further purification. A solution of **126** (0.058 g, 0.088 mmol) in 11 mL of dry *N*,*N*-dimethylformamide was cooled to 0 °C before the addition of sodium bicarbonate (0.036 g, 0.440 mmol, 5.0 equiv) and diphenyl phosphorazidate (DPPA, 0.028 mL, 0.036 g, 0.130 mmol, 1.5 equiv). The reaction mixture was allowed to stir at 0 °C (72 h). The reaction solution was concentrated in vacuo to a volume of 1 mL, poured over water (2 mL), and extracted with ethyl acetate (3 × 2 mL). The combined extracts were washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 20 cm, 6–10% MeOH/CH_2Cl_2 eluant) afforded **128** (0.031 g, 0.053 g theoretical, 58%) as a white solid: mp 259–262 °C dec (CH_3CN–H_2O; very fine white needles); $[\alpha]^{22}_D$ −32° (*c* 0.5, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.34–7.21 (m, 7 H, Ar-H), 7.09 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.86 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.78 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.69 (d, 1 H, *J* = 8 Hz, Ar-H), 5.80 (s, 1 H, $C_{5a}{}^2$-H), 4.73–4.30 (m, 3 H, $C_2{}^{Asn,1,2}$-H), 3.66 (s, 3 H, OCH_3), 3.40 (dd, 1 H, *J* = 3, 12 Hz, C3′-*H*H), 2.96 (d, 1 H, *J* = 14 Hz, $C_3{}^2$-*H*H), 2.90 (dd, 1 H, *J* = 5, 14 Hz, $C_3{}^2$-H*H*), 2.84 (dd, 1 H, *J* = 3.5, 15 Hz, $C_3{}^{Asn}$-H), 2.70 (t, 1 H, *J* = 12 Hz, $C_3{}^1$-H*H*); IR (KBr) ν_{max} 3550–3450 (b), 3400, 1670, 1587, 1514, 1270, 1234, 1204, 1129, 1121, 820 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m*/*e* 627 (M^+ + Na), 605 (M^+ + H); FABHRMS 604.6153 ($C_{31}H_{32}N_4O_9$ requires 604.6152).

(9*S*,12*S*,15*S*)-12-(2-Amino-2-oxoethyl)-9-[[(phenylmethoxy)carbonyl]amino]-4-hydroxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene-15-carboxylate (131). A solution of **128** (0.025 g, 0.041 mmol) in THF/MeOH/H_2O (1 mL; 3:1:1) at 25 °C was treated with lithium hydroxide monohydrate (6 mg, 0.124 mmol, 3.0 equiv), and the reaction mixture was stirred at 25 °C (6 h). The reaction mixture was diluted with 10% aqueous HCl (2 mL) and extracted with chloroform/2-propanol (5:1:7 × 2 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Recrystallization from $CHCl_3$/MeOH/H_2O (2:1:2) afforded **131** (0.021 g, 0.024 g theoretical, 88%) as white flakes: mp 271–278 °C dec; $[\alpha]^{22}_D$ −51° (*c* 1.2, MeOH–H_2O); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.34 (br s, 6 H, Ar-H), 7.21 (dd, 1 H, *J* = 1.5, 8 Hz, Ar-H), 7.10 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.91 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.79 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.69 (d, 1 H, *J* = 8 Hz, Ar-H), 5.84 (s, 1 H, $C_{5a}{}^5$-H), 4.7–4.3 (m, 3 H, $C_2{}^{Asn,1,2}$-H), 3.40 (dd, 1 H, *J* = 3, 12 Hz, $C_3{}^1$-*H*H), 2.96 (d, 1 H, *J* = 14 Hz, $C_3{}^2$-*H*H), 2.90 (dd, 1 H, *J* = 5, 14 Hz, $C_3{}^2$-H*H*), 2.83 (dd, 1 H, *J* = 3.5, 15 Hz, $C_3{}^{Asn}$-H), 2.70 (t, 1 H, *J* = 12 Hz, $C_3{}^1$-H*H*); IR (KBr) ν_{max} 3488–2500, 3396, 1725, 1709, 1670, 1588, 1512, 1503, 1401, 1233, 1128, 1121, 820 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m*/*e* 613 (M^+ + Na), 591 (M^+ + H); FABHRMS 590.5879 ($C_{30}H_{30}N_4O_9$ requires 590.5884).

Anal. Calcd for $C_{30}H_{30}N_4O_9$: C, 61.02; H, 5.08; N, 9.49. Found: C, 59.06; H, 5.19; N, 9.56.

(9*S*,12*S*,15*S*)-12-(2-Amino-2-oxoethyl)-9-amino-4-hydroxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene-15-carboxylic Acid (5, OF4949-IV). A solution of **131** (0.018 g, 0.031 mmol) in 2 mL of methanol at 25 °C was treated with 10% palladium on carbon (2 mg, 0.10 wt equiv) and was stirred under an atmosphere of hydrogen (3 h). The reaction mixture was filtered through glass wool and concentrated in vacuo. The resulting solid was triturated with chloroform to remove unreacted **131**, and the solid was dried under vacuum to afford OF4949-IV (0.013 g, 0.014 g theoretical, 93%) as a white amorphous solid (powder): mp 209–212 °C dec (MeOH); $[\alpha]^{22}_D$ −43° (*c* 1.1, 0.1 N HCl); ^{1}H NMR (D_2O, 300 MHz, ppm) 7.34 (dd, 1 H, *J* = 1.5, 8 Hz, aryl C-H), 7.21 (dd, 1 H, *J* = 1.5, 8 Hz, aryl C-H), 7.09 (dd, 1 H, *J* = 1, 8 Hz, aryl C-H), 6.86 (dd, 1 H, *J* = 1, 8 Hz, aryl C-H), 6.78 (dd, 1 H, *J* = 1, 8 Hz, aryl C-H), 6.69 (d, 1 H, *J* = 8 Hz, aryl, C-H), 5.80 (s, 1 H, $C_{5a}{}^5$-H), 4.73–4.30 (m, 3 H, $C_2{}^{Asn,1,2}$-H), 3.40 (dd, 1 H, *J* = 3, 12 Hz, $C_3{}^1$-*H*H), 2.96 (d, 1 H, *J* = 14 Hz, $C_3{}^2$-*H*H), 2.90 (dd, 1 H, *J* = 5, 14 Hz, $C_3{}^2$-H*H*), 2.84 (dd, 1 H, *J* = 3.5, 15 Hz, $C_3{}^{Asn}$-H), 2.70 (t, 1 H, *J* = 12 Hz, $C_3{}^1$-H*H*); IR (KBr) ν_{max} 3577–2500, 3396, 1671, 1587, 1512, 1503, 1401, 1270, 1233, 1204, 1128, 1110, 922, 820 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m*/*e* 479 (M^+ + Na), 457 (M^+ + H); FABHRMS 456.4545 ($C_{22}H_{24}N_4O_7$ requires 456.4542).

Methyl (9*S*,12*S*,15*S*)-12-(2-Amino-2-oxoethyl)-9-[[(phenylmethoxy)carbonyl]amino]-4-methoxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene-15-carboxylate (129). A solution of **128** (0.020 g, 0.033 mmol) in ether/tetrahydrofuran (2:1, 2 mL) at 0 °C was treated with an ether solution of diazomethane (5 mL), and the reaction mixture was stirred at 0 °C (12 h). Removal of the volatiles afforded **129** (0.020 g, 0.020 g theoretical, 100%) as a tan solid: mp 178–182 °C (MeOH); $[\alpha]^{22}_D$ −74° (*c* 0.1, MeOH); ^{1}H NMR (methanol-d_4, 300 MHz, ppm) 7.40–7.20 (m, 7 H, Ar-H), 6.98 (dd, 1 H, *J* = 2, 8 Hz, Ar-H), 6.93 (dd, 1 H, *J* = 2, 8 Hz, Ar-H), 6.82 (dd, 1 H, *J* = 2, 8 Hz, Ar-H), 6.69 (dd, 1 H, *J* = 2, 8 Hz, Ar-H), 5.88 (s, 1 H, $C_{5a}{}^5$-H), 5.08 (s, 2 H, NCO_2CH_2Ph), 4.80 (m, 1 H, CH_2CHNH), 4.61 (m, 1 H, CH_2CHNH), 4.50 (m, 1 H, CH_2CHNH), 3.82 (s, 3 H, $ArOCH_3$), 3.66 (s, 3 H, CO_2CH_3), 3.31 (dd, 1 H, *J* = 13, 4 Hz, CHC*H*HAr), 3.10 and 2.84 (2 dd, 1 H, each, *J* = 13, 6 Hz, $CHCH_2Ar$), 2.83 (dd, 1 H, *J* = 13, 5 Hz, CHCH*H*CON); IR (KBr) ν_{max} 3580–2500, 3399, 1740, 1732, 1728, 1722, 1670, 1589, 1507, 1500, 1405, 1268, 1233, 1201, 1130, 1112, 925, 805 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m*/*e* 641 (M^+ + Na), 619 (M^+ + H); FABHRMS 618.6416 ($C_{32}H_{34}N_4O_9$ requires 618.6420).

(9*S*,12*S*,15*S*)-12-(2-Amino-2-oxoethyl)-9-[[(phenylmethoxy)carbonyl]amino]-4-methoxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene-15-

carboxylic Acid (132). A solution of **129** (0.019 g, 0.031 mmol) in THF/MeOH/H_2O (1 mL; 3:1:1) at 25 °C was treated with lithium hydroxide monohydride (4 mg, 0.092 mmol, 3.0 equiv) and was stirred at 25 °C (3 h). The reaction mixture was diluted was 10% aqueous HCl (1 mL) and extracted exhaustively with chloroform–2-propanol (5:1; 10 × 1 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Trituration of the resulting solid with tetrahydrofuran/ether (1:1) to remove unreacted **129** and drying the solid under vacuum afforded **132** (0.017 g, 0.018 g theoretical. 92%) as white flakes: mp 234–238 °C (MeOH); $[\alpha]^{22}_D$ −87° (*c* 0.27, MeOH); ^1H NMR (methanol-D_4, 300 MHz, ppm) 7.40 (dd, 1 H, *J* = 1.4, 8 Hz, Ar-H), 7.33 (br s, 5 H, PhH), 7.22 (dd, 1 H, *J* = 1.4, 8 Hz, Ar-H), 7.11 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.90 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.80 (dd, 1 H, *J* = 1, 8 Hz, aryl CH), 6.71 (d, 1 H, *J* = 8 Hz, aryl CH), 5.81 (s, 1 H, $C_{5a}{}^2$-H), 5.07 (s, 2 H, NCO_2CH_2Ph), 4.7–4.3 (m, 3 H, $C_2{}^{Asn,1,2}$-H), 3.81 (s, 3 H, OCH_3), 3.40 (dd, 1 H, *J* = 3, 12 Hz, $C_3{}^1$-*H*H), 2.98 (d, 1 H, *J* = 14 Hz, $C_3{}^2$-*H*H), 2.90 (dd, 1 H, *J* = 5, 14 Hz, $C_3{}^2$-H*H*), 2.85 (dd, 1 H, *J* = 3.5, 15 Hz, $C_3{}^{Asn}$-H), 2.70 (t, 1 H, *J* = 12 Hz, $C_3{}^1$-H*H*); IR (KBr) ν_{max} 3550–2500, 3398, 1725, 1709, 1670, 1590, 1510, 1500, 1405, 1266, 1233, 1201, 1130 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m/e* 627 (M^+ + Na), 6.05 (M^+ + H); FABHRMS 604.6154 ($C_{31}H_{32}N_4O_9$ requires 604.6152).

(9*S*,12*S*,15*S*)-12-(2-Amino-2-oxoethyl)-9-amino-4-methoxy-10,13-dioxo-2-oxa-11,14-diazatricyclo[15.2.2.1]docosa-3,5,7(22),17,19,20-hexaene-15-carboxylic Acid (4, OF4949-III). A solution of **132** (0.010 g, 0.016 mmol) in 2 mL of methanol was treated with 10% palladium on carbon (1 mg, 0.1 wt equiv) and was stirred under an atmosphere of hydrogen (3 h). The reaction mixture was filtered through glass wool and concentrated in vacuo. The resulting solid was triturated with cold tetrahydrofuran, and the solid was dried under vacuum to afford OF4949-III (7.6 mg, 8.0 mg theoretical, 95%) as a cream-colored amorphous solid: mp 217–222 °C (MeOH) (literature mp 219–225 °C dec);[5] $[\alpha]^{22}_D$ −34° (*c* 1.0, 0.1 N HCl); literature $[\alpha]^{22}_D$ −35° (*c* 1.14, 0.1 N HCl)[5] and $[\alpha]^{22}_D$ −38.2° (*c* 1.06, 0.1 N HCl);[11] ^1H NMR (D_2O, 300 MHz, ppm) 7.40 (dd, 1 H, *J* = 1.4, 8 Hz, Ar-H), 7.22 (dd, 1 H, *J* = 1.4, 8 Hz, Ar-H), 7.10 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.90 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.79 (dd, 1 H, *J* = 1, 8 Hz, Ar-H), 6.72 (d, 1 H, *J* = 8 Hz, Ar-H), 5.81 (s, 1 H, $C_{5a}{}^2$-H), 4.7–4.3 (m, 3 H, $C_2{}^{Asn,1,2}$-H), 3.81 (s, 3 H, OCH_3), 3.40 (dd, 1 H, *J* = 3, 12 Hz, $C_3{}^1$-*H*H), 2.98 (d, 1 H, *J* = 14 Hz, $C_3{}^2$-*H*H), 2.90 (dd, 1 H, *J* = 5, 14 Hz, $C_3{}^2$-H*H*), 2.85 (dd, 1 H, *J* = 3.5, 15 Hz, $C_3{}^{Asn}$-H), 2.70 (t, 1 H, *J* = 12 Hz, $C_3{}^1$-H*H*); IR (KBr) ν_{max} 3580–2500, 3398, 1670, 1589, 1507, 1500, 1405, 1266, 1233, 1201, 1130, 1112, 925, 805 cm^{-1}; FABMS (glycerol–0.1 M HCl) *m/e* 493 (M^+ + Na), 471 (M^+ + H); FABHRMS 470.4812 ($C_{23}H_{26}N_4O_7$ requires 470.4810).

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Registry No. 1, 108890-90-0; 1 (methyl ester), 129285-38-7; 4, 107140-32-9; 4 (methyl ester), 129151-12-8; **5**, 107140-31-8; **15** (free base), 113351-28-3; **15**·2HCl, 125873-94-1; **16**, 129150-57-8; **17**, 129150-58-9; **20**, 120363-13-5; **21**, 1005-30-7; **22**, 110774-06-6; **23**, 105229-41-2; L-**24**, 125786-85-8; D-**24**, 129150-59-0; **25**, 120363-14-6; **26**, 129150-60-3; **27**, 120385-11-7; **28**, 120363-16-8; **30**, 120363-17-9; **31**, 120363-18-0; **32**, 125786-86-9; **33**, 129150-61-4; **34**, 129150-62-5; **35**, 129150-63-6; **36**, 129150-64-7; **37**, 125786-87-0; **38**, 112196-72-2; **39**, 129150-65-8; **40**, 129150-66-9; **41**, 129150-67-0; **42**, 621-54-5; **43**, 129150-68-1; **44**, 1135-15-5; **45**, 31493-49-9; **46**, 129150-69-2; **47**, 129150-70-5; **48**, 129150-71-6; **49**, 129150-72-7; **50**, 129150-73-8; **51**, 129150-74-9; **52**, 129150-75-0; **53**, 129150-76-1; **54**, 129150-77-2; **55**, 129150-78-3; **56**, 129150-79-4; **57**, 129150-80-7; **58**, 129150-81-8; **59**, 129150-82-9; **60**, 129150-83-0; **61**, 129150-84-1; **62**, 129150-85-2; **63**, 129150-86-3; **64**, 129150-87-4; **65**, 129150-88-5; **66**, 129150-89-6; **67**, 129150-90-9; **68**, 129150-91-0; **69**, 129150-92-1; **70**, 129150-93-2; **71**, 129150-94-3; **72**, 129150-95-4; **73**, 120363-31-7; **74**, 120363-32-8; **75**, 120385-12-8; **76**, 120363-33-9; **77**, 129150-96-5; **78**, 129150-97-6; **79**, 129150-98-7; **80**, 129150-99-8; **81**, 129174-03-4; **82**, 129174-04-5; **83**, 120363-40-8; **84**, 120363-41-9; **85**, 120363-42-0; **86**, 129151-00-4; **87**, 129151-01-5; **88**, 129151-02-6; **89**, 120363-46-4; **90**, 129213-55-4; **91**, 129213-56-5; **92**, 129213-57-6; **93**, 129213-58-7; **94**, 129151-03-7; *N*-BOC-**94**, 129151-13-9; **95**, 129151-04-8; **96**, 129151-05-9; **97**, 129151-06-0; **98**, 129151-07-1; **99**, 129151-08-2; **100**, 127559-26-6; **101**, 127559-27-7; **102**, 127559-29-9; **103**, 127559-30-2; **104**, 127559-31-3; **105**, 120363-19-1; **106**, 120363-20-4; **107**, 120363-21-5; **108**, 120363-22-6; **109**, 120363-23-7; **110**, 120363-24-8; **111**, 120363-25-9; **112**, 120363-51-1; **113**, 120363-52-2; **114**, 120363-26-0; **115**, 129151-09-3; **116**, 120363-27-1; **117**, 127559-15-3; **118**, 127559-16-4; **119**, 127559-17-5; **120**, 127578-76-1; **121**, 127559-18-6; *N*-BOC-**121**, 129151-14-0; **122**, 7536-55-2; **123**, 127559-19-7; **124**, 127559-20-0; **125**, 127559-21-1; **127**, 127559-28-8; **128**, 127559-23-3; **129**, 127559-24-4; **130**, 127559-32-4; **131**, 129151-10-6; **132**, 129151-11-7; ACE, 9015-82-1; APB, 9073-92-1; 4-IC_6H_4CHO, 15164-44-0; $(EtO)_2P(O)CH_2COOH$, 3095-95-2; 4-$HOC_6H_4CH_2CH_2NH(BOC)$, 64318-28-1; 3-IC_6H_4CH=CHCOOMe, 58586-58-6; 3-HOC_6H_4CH=CHCOOH, 588-30-7; 4-IC_6H_4CH=CHCOOMe, 93677-03-3; H-Gly-OMe, 616-34-2; H-Tyr-OMe, 1080-06-4; BOC-Gly-OH, 4530-20-5; BOC-Tyr-OH, 3978-80-1; BOC-Asn-OH, 7536-55-2; (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, 109838-85-9.

Supplementary Material Available: Two tables summarizing results of Ullmann condensation diaryl ether coupling studies, experimental details and full spectroscopic and physical characterization of **34–66**, details of the biological evaluation of key agents (cytotoxic activity, ACE and APB inhibitory activity), and ^1H NMR spectra of **25–28**, **34–35**, **37–41**, **43**, **45–69**, **74–75**, **84**, **105**, **108**, **114**, **116**, **118**, **120**, **128–129**, and **132** (64 pages). Ordering information is given on any current masthead page.