Total Synthesis of (+)-Piperazinomycin

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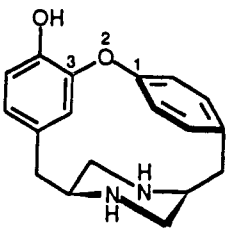
Abstract: A concise total synthesis of (+)-piperazinomycin (**1**), a novel naturally occurring macrocyclic piperazine possessing antimicrobial and antifungal activity, is detailed with implementation of an improved Ullmann macrocyclization reaction conducted on a diketopiperazine (53%).

Piperazinomycin (**1**), a novel macrocyclic piperazine isolated as a minor metabolite of *Streptoverticillium olivoreticuli* subsp. *neoenacticus*[1] and unambiguously identified by single-crystal X-ray analysis,[2] constitutes the simplest naturally occurring agent possessing the parent 14-membered para- and metacyclophane diaryl ether structural subunit found in bouvardin,[3] deoxybouvardin,[3] RA-I-X,[4] OF4949-I-OF494-IV,[5] and K-13.[6] Our interest in the synthesis of the naturally occurring agents[7-19] including those possessing potent cytotoxic and antitumor properties[20,21] led to recent disclosure that the 14-membered cycloisodityrosine subunit of bouvardin, deoxybouvardin, and RA-I-X constitutes the pharmacophore.[11,13,16] This has renewed interest in the synthesis and evaluation of piperazinomycin and structurally related agents since **1** and notably **10**, a potential biosynthetic precursor, more closely mimic the structural and conformational properties of the cycloisodityrosine subunit found in the biologically more potent natural products (cis amide) than that of cycloisodityrosine itself (trans amide). However, efforts to critically examine the importance of the cycloisodityrosine subunit have been hampered by the synthetic inaccessibility of such systems.[11,22-29] Characteristic of this synthetic inaccessibility, efforts to prepare **1** through 14-membered macrolactamization have proven unsuccessful[11] and attempts to implement an Ullmann macrocyclization reaction with C^3–O^2 bond formation have not provided **1**.[23] As a result, an indirect thallium trinitrate-promoted



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two-step procedure for achieving the intramolecular phenol coupling has been introduced by Yamamura and co-workers[30-32] and was employed successfully in the single existing total synthesis of **1**.[30] However, it required the use of dichloro- and dibromophenol coupling partners, the three key steps of the indirect

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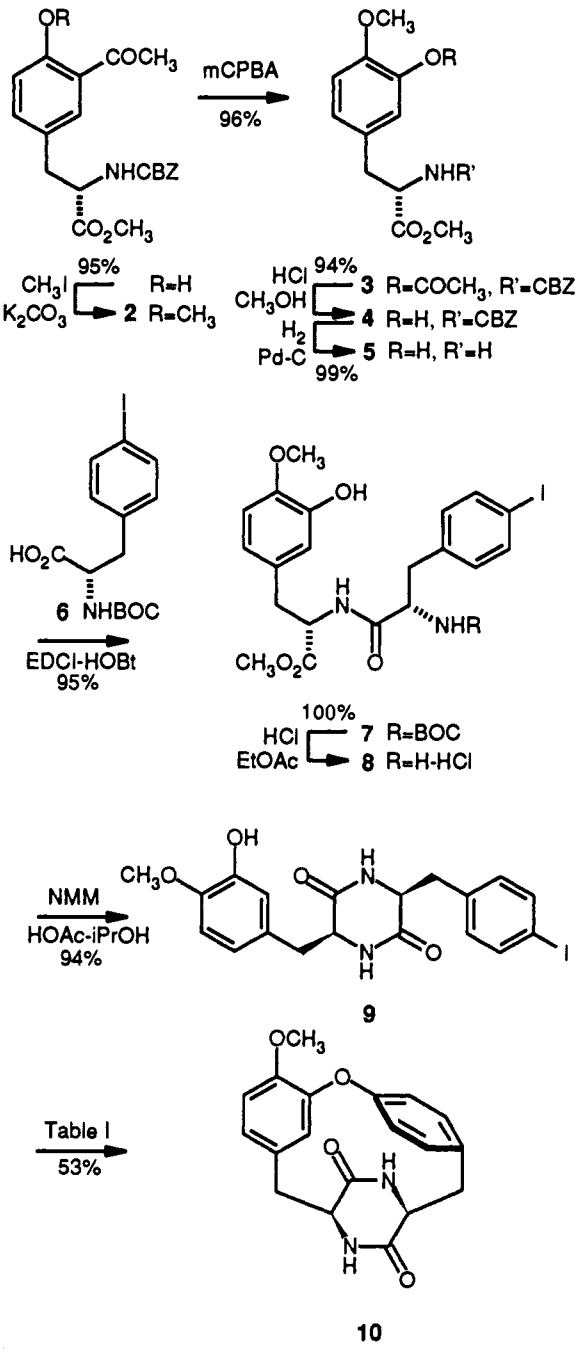
oxidative phenol coupling proceeded in low overall yields (19%), and the protocol employed provided a regioisomeric mixture of cyclization products.

In conjunction with efforts designed to address whether conformational as well as structural features of cycloisodityrosine contribute to its inherent biological properties,[11] herein we detail a concise total synthesis of (+)-piperazinomycin (**1**) based on the implementation of an improved and effective intramolecular Ullmann macrocyclization reaction for *direct* preparation of the elusive 14-membered ring. In addition to the introduction and use of improved reaction conditions, the C^1–O^2 Ullmann macrocyclization reaction, which could be anticipated to be more facile than C^3–O^2 bond formation as a consequence of the decelerating effect of the electron-donating substituent ortho to the aryl iodide necessarily present in C^3–O^2 Ullmann closure, proved uniquely successful when conducted with a diketopiperazine substrate. In addition to the improved conversions available through use of this procedure, the Ullmann reaction permitted the use of readily available amino acids, directly provided the appropriately functionalized diaryl ethers without resorting to the use of the less accessible dichloro- and dibromophenols, provided a single regioselective cyclization reaction product in high yield (>50%), and may be conducted under conditions which minimize the extent of substrate racemization (<3%).

Total Synthesis of (+)-Piperazinomycin (1). *O*-Methylation of *N*-CBZ-3-acetyl-L-tyrosine methyl ester[33] followed by Baeyer–Villiger oxidation and subsequent methanolysis of the resulting acetate **3** provided *O*-methyl *N*-CBZ-L-DOPA methyl ester (**4**) (Scheme I). Catalytic hydrogenolysis of **4** and coupling (1.3 equiv EDCI, 1.3 equiv HOBt, DMF, 25 °C, 16 h, 95%) of the resultant amine **5** with *N*-BOC-4-iodophenylalanine (**6**)[34] provided **7** (Scheme I). Acid-catalyzed deprotection of the *tert*-butyloxycarbonyl group (3.25 M HCl–EtOAc, 25 °C, 30 min, 100%) followed by treatment of the crude amine hydrochloride salt **8** with *N*-methylmorpholine[35] (1.3 equiv, 0.1 M HOAc in *i*PrOH, reflux, 2 h, 94%) provided the diketopiperazine **9** in excellent conversion. Ullmann macrocyclization of **9** was conducted most effectively by treatment with NaH (4 equiv) and CuBr–SMe_2 (10 equiv) in dry DMF under moderately dilute reaction conditions (0.004 M, reflux, 48 h, 53%). Use of lower reaction temperatures and shorter reaction periods led to diminished conversions of **9** to **10**. Macrocyclization with closure of the 14-membered ring to provide **10** ($[\alpha]^{25}_D$ +182 (*c* 0.05, CH_3OH)) was established by the characteristic appearance of the shielded C19–H proton signal in the ^1H NMR spectrum at 4.13 ppm (DMSO-d_6) and was ultimately confirmed with the conversion of **10** to **1**. The extent of racemization under the reaction conditions was carefully assessed and found to be <3%. Given the importance of the Ullmann macrocyclization reaction, we examined the conversion of **9** to **10** in detail (Table I). Initial attempts to conduct the reaction under more conventional reaction conditions in pyridine (0.004 M, reflux, 9–24 h, 10–15% **10**) or under the modified reaction conditions we disclosed in recent studies in either collidine[11,18] (0.004 M, 130 °C, 9–24 h, trace **10**) or dioxane[18] (0.004 M, 110 °C, 9 h, 0%) failed to provide **10** in competitive conversions. Similarly, the use of methylcopper (4 equiv, 0.004 M pyridine, reflux, 9 h) to stoichiometrically generate the cuprous phenoxide[11,12] failed to provide **10** in more than trace amounts. Consequently, the Ullmann macrocyclization reaction conducted in DMF at reflux proved uniquely successful at providing **10**. In part, this may be attributed to the effect of the increased reaction temperature (*ca.* 156 °C, reflux) and the relatively nonbasic polar, aprotic nature of the reaction solvent (vs pyridine or collidine), resulting in enhanced substrate and product stability under the thermal reaction conditions. An added benefit of the mild, nonbasic reaction conditions was the minimization of the extent of substrate racemization prior to cyclization. The Ullmann macrocyclization reaction is conducted under conditions where the secondary amides are deliberately deprotonated prior to exposure to the thermal reaction conditions. Subsequent racemization of **9** requires anion generation α to and cross-conjugated with the amide anions. Presumably, subjection of the trianion of **9** to refluxing DMF under the conditions of the Ullmann reaction is not sufficient to lead to further deprotonation and racemization of the diketopiperazine.

Scheme I



The final conversion of **10** to piperazinomycin was accomplished by two complementary approaches (Scheme II). First, demethylation of **10** (48% HBr–HOAc, reflux, 45 min, 84%) followed by acetylation of **11a** (excess Ac_2O, pyridine, 25 °C, 4 h, 94%) provided **11b** ($[\alpha]^{25}_D$ +188 (*c* 0.15, pyridine)), identical in all comparable respects with authentic **11b** (^1H NMR, IR, $[\alpha]_D$).[30] The conversion of **11b** to **1** following the five-step sequence detailed by Yamamura[30] formally completes a total synthesis of (+)-

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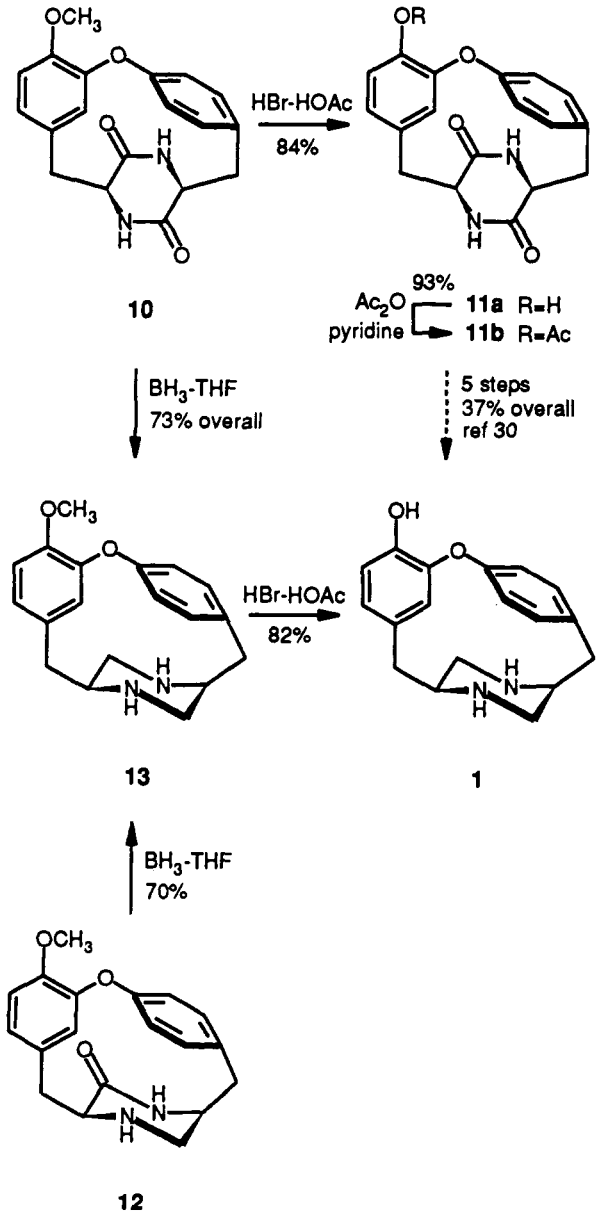
Table I. Representative Results of the Ullmann Macrocyclization Reaction of 9 to 10

entry	base (equiv)	Cu(I) reagent (equiv)	solvent[a]	temp (bath, °C)	reaction time (h)	10 (%)	recovered 9 (%)
1	NaH (4)	CuBr–SMe_2 (10)	DMF	170	48	53	0
2	NaH (4)	CuBr–SMe_2 (10)	DMF	170	36	42	9
3	NaH (4)	CuBr–SMe_2 (10)	DMF	170	24	35–40	15
4	NaH (4)	CuBr–SMe_2 (10)	pyridine	130	9	10–15	65
5	NaH (4)	CuBr–SMe_2 (10)	pyridine	130	24	10	50
6	NaH (4)	CuBr–SMe_2 (10)	collidine	130	9	trace	>50
7	NaH (4)	CuBr–SMe_2 (10)	collidine	130	24	trace	40
8	NaH (4)	CuBr–SMe_2 (10)	pyridine/collidine (1:1)	130	15	trace	60
9	NaH (4)	CuBr–SMe_2 (10)	HMPA/collidine	130	9	trace	75
10	NaH (4)	CuBr–SMe_2 (10)	dioxane	110	9	0	72
11		MeCu (4)	pyridine	130	9	trace	>50

[a] Conducted at 0.004 M at reflux (pyridine 115 °C, dioxane 101 °C, DMF 156 °C) or at the indicated bath temperature.

Scheme II



piperazinomycin. Alternatively, **10** was converted to piperazinomycin more directly in two steps. In contrast to the report of Yamamura, we have found that the direct reduction of **10** to **13** may be accomplished upon treatment with diborane (15 equiv BH_3–THF, THF, 45–50 °C, 72 h, 43%) under the conditions detailed by Jung.[23] The initial treatment of **10** with BH_3–THF provided a mixture of **13** (43%) and **12** (43%). Efforts to drive the reaction to completion employing longer reaction times, higher reaction temperatures, or larger excesses of reagent did not provide further conversion to **13**. However, isolation of **12** and its resubjection to the reduction conditions provided **13** (70%), and the conversion of **10** to **13** with this recycling of **12** provided **13** in 73% overall yield. Alternative reduction conditions with $LiAlH_4$, BH_3–SMe_2, $NaBH_3(OAc)$, or $LiBH_3(iPr_2N)$ failed to provide **13** in competitive conversions. Subsequent demethylation of **13** upon treatment with 48% HBr–HOAc (reflux, 1.5 h, 82%) provided (+)-piperazinomycin (**1**) ($[\alpha]^{25}_D$ +31 (*c* 0.2, CH_3OH)), identical in all respects with authentic material (^1H NMR, ^{13}C NMR, IR, UV, MS, $[\alpha]_D$).[2]

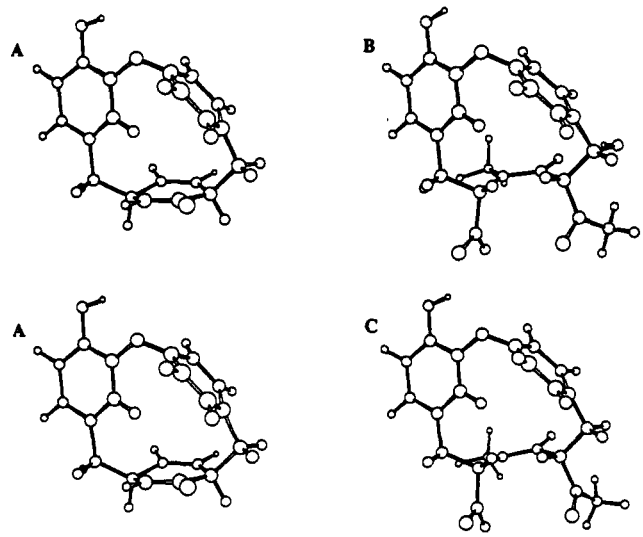


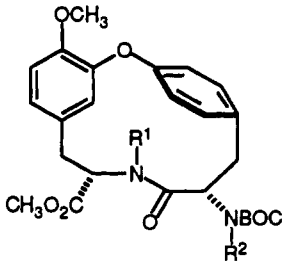
Figure 1. (A) OPLSA low-energy conformation of **11a**. (B) Cycloisodityrosine conformation taken from X-ray crystal structure of bouvardin. (C) Cycloisodityrosine conformation taken from OPLSA lowest energy conformation of deoxybouvardin.

Conformational analysis revealed a single low-energy conformation available to **11a** (within 12 kcal/mol), and it was found to possess a partial or flattened boat diketopiperazine ring. Consequently, this single conformation constitutes the predicted exclusive conformation available to the agent. Consistent with this expectation, the conformation of **11a** located proved compatible with the observed NOEs in the 2D ^1H–^1H NOESY NMR spectra and corresponds precisely to the conformation of the cycloisodityrosine subunit of bouvardin observed in the single-crystal X-ray structure determination (RMS = 0.18 Å for all non-hydrogen atoms)[3] (Figure 1). This precise adoption of the cis amide conformation of cycloisodityrosine found within bouvardin (RMS = 0.18 Å), deoxybouvardin (RMS = 0.14 Å), and the related RA-I–X is especially important and suggests that derivatives of **10–11** may substitute nicely for the active conformation of the natural product pharmacophore. Consistent with this expectation, **10** and the related agent **11a** exhibited in vitro cytotoxic activity at a level nearly equivalent to that of the parent cycloisodityrosine derivatives (Figure 2). Global and low-lying minima (≤12 kcal/mol) were located in the conformational searches by repetitive use directed Monte Carlo sampling and

Table II. Representative Additional Ullmann Macrocyclization Studies

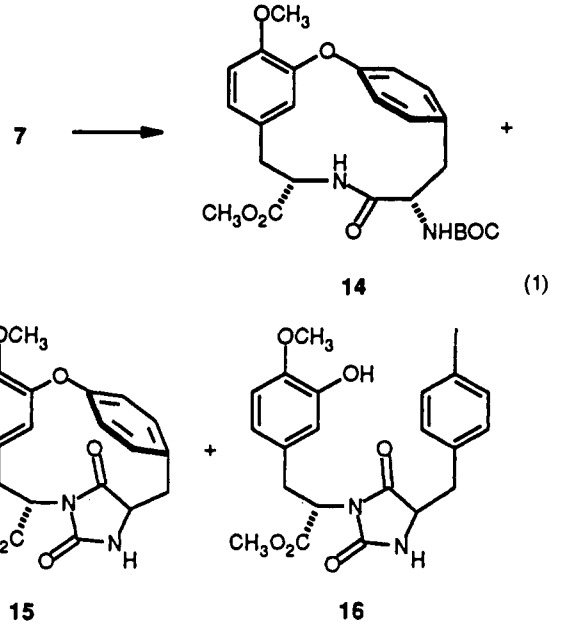
agent	R	base (equiv)	Cu(I) reagent (equiv)	solvent[a]	temp (bath, °C)	reaction time (h)	products (% yield)
7	BOC	NaH (3)	CuBr–SMe_2 (10)	pyridine	130	9	**14** (5–10), **15** (10–15), **16** (4–9), **7** (20–40)
7	BOC	NaH (3)	CuBr–SMe_2 (10)	pyridine	130	20	**14** (5), **15** (12), **16** (6), **7** (13)
7	BOC	NaH (3)	CuBr–SMe_2 (10)	collidine	130	9	**16** (12), **7** (22)
7	BOC		MeCu (3)	dioxane	110	9	**7** (79)
7	BOC		MeCu (3)	pyridine	130	9	**16** (10), **7** (28)
7	BOC		MeCu (3)	collidine	130	9	**16** (25), **7** (24)
17	CBZ	NaH (3)	CuBr–SMe_2 (10)	pyridine	130	9	**16** (12), **17** (35)
17	CBZ	NaH (3)	CuBr–SMe_2 (10)	collidine	130	9	**16** (30), **17** (20)
18	SES	NaH (3)	CuBr–SMe_2 (10)	pyridine	130	9	no cyclization
18	SES	NaH (3)	CuBr–SMe_2 (10)	collidine	130	9	no cyclization
19	H	NaH (2)	CuBr–SMe_2 (10)	pyridine	130	9	**9** + **19** (nd)
19	H	NaH (2)	CuBr–SMe_2 (10)	collidine	130	9	**9** (32)
19	H		MeCu (3)	pyridine	130	9	**9** (nd)
19	H		MeCu (3)	collidine	130	9	**9** (22)
24		NaH (3)	CuBr–SMe_2 (10)	pyridine	130	24	no cyclization
25-27		NaH (1–3)	CuBr–SMe_2 (10)	DMF	170	36	no cyclization

[a] Conducted at 0.004 M at reflux (pyridine 115 °C, DMF 156 °C) or at the indicated bath temperature.



	Agent	rel IC_{50} (L1210)
	$R^1 = R^2 = CH_3$	1.0[3]
	$R^1 = H$ $R^2 = CH_3$	2.0[3]
14	$R^1 = R^2 = H$	0.5
15		0.9
10		1.5
11a		3.0
11b		inactive

Figure 2.

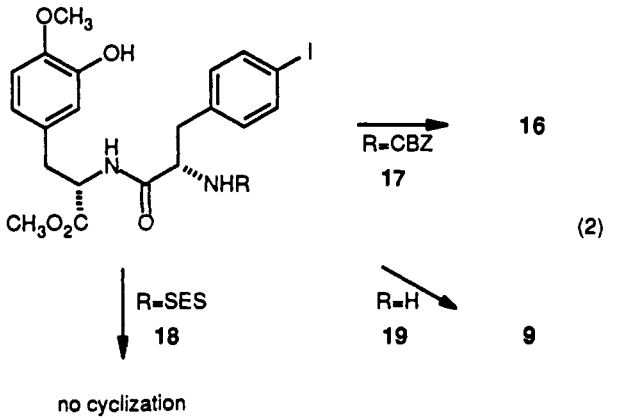


subsequent minimization of conformations generated by random variations (0–180 °C) in 8 of the 10 available torsional angles excluding those originating in the phenyl rings (MacroModel, Batchmin Version 3.5a, OPLSA and AMBER force fields, MCMM = 1000, MCSS = 2, 12 kcal/mol window). The global minimum for **11a** was located 290 times.

Additional Studies on the 14-Membered-Ring Ullmann Macrocyclization Reaction. Prior to and concurrent with the implementation of the successful Ullmann macrocyclization of **9** to provide **10**, a number of alternatives were examined. The results of these studies merit a detailed discussion since they provide an important perspective on the successful efforts leading to the formation of the piperazinomycin 14-membered ring. Our initial efforts focused on attempts to conduct the Ullmann macrocyclization prior to diketopiperazine or piperazine introduction. Subjection of **7** to a range of conditions for effecting the Ullmann macrocyclization reaction provided **14**[36] in low yield (5–10%) under optimal conditions, and its generation was always accompanied by the competitive formation of **15** (5–15%)[37] and **16** (4–25%)[38] (eq 1 and Table II). While the combined yield of macrocyclization product approached 15–20%, extensive but not exhaustive efforts to define reaction conditions where the intramolecular *N*-acylation (**7** → **14/16** → **15**) might be minimized including the use of methylcopper for stoichiometric generation of the cuprous phenoxide[11,12] were not successful. Moreover, this competitive reaction proved to be an inherent problem with all acyclic substrates examined under the thermal conditions of the Ullmann reaction. Although not pursued, it is also likely that *O*- versus *N*-acylation may occur under the reaction conditions and that products derived from amide and/or carbamate intramolecular *O*-acylation were present but not isolated from the reaction mixtures.

The CBZ derivative **17**[39] (eq 2) proved to be even more prone to competitive intramolecular acylation, presumably due to the diminished steric hindrance of the carbamate derivative. Subjection of **17** to a select set of conditions for effecting the Ullmann macrocyclization reaction provided only **16** and recovered **17**. In

(36) For **14**: mp 189–190 °C; $[\alpha]^{25}_D$ –32 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (dd, 1H, *J* = 2.1, 8.4 Hz, C^{15}– or C^{18}–H), 7.21 (dd, 1H, *J* = 2.1, 8.4 Hz, C^{18}– or C^{15}–H), 7.08 (dd, 1H, *J* = 2.4, 8.4 Hz, C^{16}– or C^{17}–H), 6.98 (dd, 1H, *J* = 2.4, 8.4 Hz, C^{17}– or C^{16}–H), 6.75 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.57 (dd, 1H, *J* = 2.0, 8.2 Hz, C^6–H), 5.87 (d, 1H, *J* = 7.4 Hz, N^{10}–H), 5.17 (d, 1H, *J* = 9.2 Hz, NHBOC), 5.05 (d, 1H, *J* = 2.0 Hz, C^{19}–H), 4.07–4.15 (m, 2H, C^9– and C^{12}–H), 3.93 (s, 3H, $ArOCH_3$), 3.66 (s, 3H, CO_2CH_3), 3.25 (dd, 1H, *J* = 5.0, 12.2 Hz, C^8– or C^{13}–H), 2.86 (t, 1H, *J* = 12.0 Hz, C^{13}– or C^8–H), 2.84 (d, 1H, *J* = 16.6 Hz, C^8– or C^{13}–H), 2.67 (dd, 1H, *J* = 11.0, 16.7 Hz, C^{13}– or C^8–H), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 171.5, 157.2, 155.2, 152.3, 146.0, 134.5, 132.5, 130.5, 129.8, 125.0, 124.7, 121.2, 115.0, 111.5, 80.3, 58.2, 56.1, 54.0, 52.5, 38.9, 34.3, 28.3; IR (KBr) ν_{max} 3347, 3300, 2954, 2932, 2853, 1748, 1718, 1664, 1587, 1517, 1436, 1367, 1264, 1205, 1162, 1130, 1015, 978, 891, 869, 838, 797, 762, 729 cm^{-1}; FABHRMS (NBA) *m/e* 471.2125 (M^+ + H, $C_{25}H_{30}N_2O_7$ requires 471.2131).



deliberate efforts to avoid the intramolecular acylation, efforts to effect the Ullmann macrocyclization of the β-(trimethylsilyl)-ethylsulfonyl carbamate **18**[40] did not prove promising and the free amine **19**[41] preferentially closed to the diketopiperazine **9** under conventional Ullmann macrocyclization conditions. Consequently, the use of the diketopiperazine **9** in the Ullmann macrocyclization served the additional purpose of incorporating the substrate functionality in a protected form, precluding prevalent competitive reactions that may be observed with common acyclic precursors.

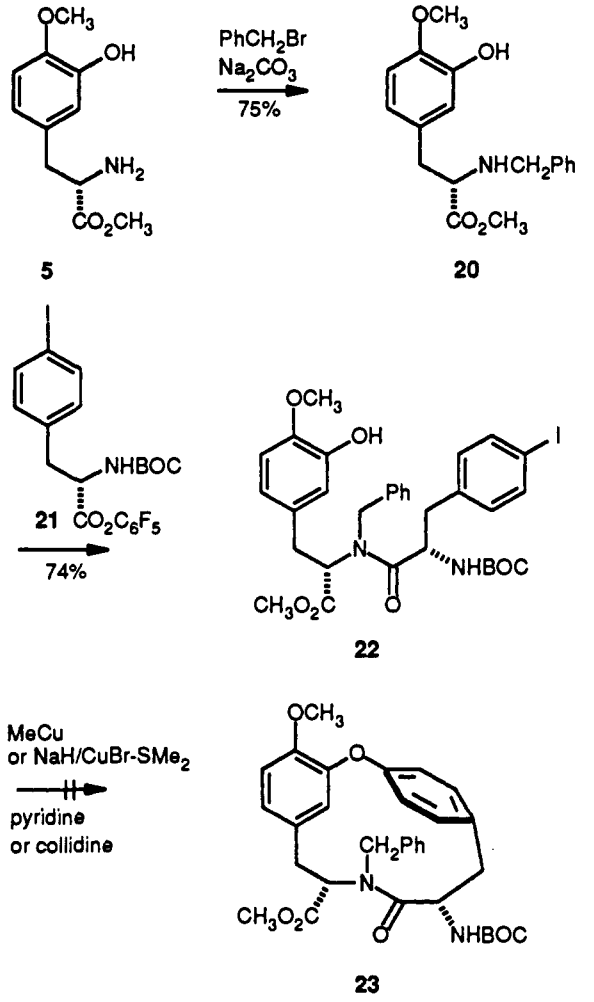
(37) For **15**: white needles, mp 228–229 °C; $[\alpha]^{25}_D$ –25 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25 (dd, 1H, *J* = 2.2, 8.3 Hz, C^{16}– or C^{19}–H), 7.21 (dd, 1H, *J* = 2.2, 8.3 Hz, C^{19}– or C^{16}–H), 6.92 (dd, 1H, *J* = 2.4, 8.4 Hz, C^{17}– or C^{18}–H), 6.77 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.66 (dd, 1H, *J* = 2.0, 8.2 Hz, C6–H), 6.21 (two s, 1H, NH), 4.85 (d, 1H, *J* = 2.0 Hz, C^{20}–H), 4.44–4.47 (m, 2H, C^9– and C^{13}–H), 4.06 (dd, 1H, *J* = 12.1, 16.2 Hz, C^8– or C^{14}–H), 3.93 (s, 3H, $ArOCH_3$), 3.73 (s, 3H, CO_2CH_3), 3.31 (dd, 1H, *J* = 3.6, 13.9 Hz, C^8– or C^{14}–H), 3.03 (dd, 1H, *J* = 3.2, 12.4 Hz, C^{14}– or C^8–H), 3.00 (dd, 1H, *J* = 1.9, 14.1 Hz, C^{14}– or C^8–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 169.9, 158.7, 157.8, 152.4, 147.0, 133.4, 130.7, 130.6, 130.5, 124.7, 123.0, 121.9, 115.8, 111.7, 58.2, 56.1, 55.5, 53.3, 36.1, 30.3; IR (KBr) ν_{max} 3336, 3028, 2938, 2841, 1769, 1741, 1720, 1586, 1517, 1502, 1412, 1265, 1206, 1129, 1024, 1005, 926, 875, 834, 790, 759, 667, 631 cm^{-1}; FABHRMS (NBA) *m/e* 396.1333 (M$^+$, $C_{21}H_{20}N_2O_6$ requires 396.1321).

(38) For **16**: pale-yellow solid, mp 180–181 °C; $[\alpha]^{25}_D$ –196 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, 2H, *J* = 8.3 Hz, C$^{3'}$– and C$^{5'}$–H), 6.89 (d, 2H, *J* = 8.3 Hz, C$^{2'}$– and C$^{6'}$–H), 6.75 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.72 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.68 (dd, 1H, *J* = 2.0, 8.2 Hz, C^6–H), 5.58 (s, 1H, OH), 5.29 (br s, 1H, NH) 4.84 (dd, 1H, *J* = 6.5, 10.4 Hz, C*H*COOMe), 4.06 (ddd, 1H, *J* = 1.2, 3.8, 10.2 Hz, C*H*NH), 3.83 (s, 3H, $ArOCH_3$), 3.76 (s, 3H, CO_2CH_3), 3.30–3.40 (m, 2H, CH_2Ar), 3.01 (dd, 1H, *J* = 3.8, 13.9 Hz, CH_2Ar), 2.30 (dd, 1H, *J* = 10.2, 13.9 Hz, CH_2Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 168.9, 155.6, 145.53, 145.48, 138.1, 135.2, 131.1, 129.6, 120.6, 115.3, 110.8, 92.9, 57.9, 55.9, 53.5, 53.0, 37.7, 33.4; IR (KBr) ν_{max} 3429, 3349, 2955, 2925, 2849, 1743, 1718, 1693, 1592, 1513, 1431, 1267, 1149, 1133, 1010, 959, 872, 798, 767, 669, 625 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 656.9486 (M$^+$ + Cs, $C_{21}H_{21}N_2O_6I$ requires 656.9499).

(39) For **17**: pale-yellow solid, mp 168–169 °C; $[\alpha]^{25}_D$ +29 (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, 2H, *J* = 8.2 Hz, C$^{3'}$– and C$^{5'}$–H), 7.25–7.35 (m, 5H, PhH), 6.86 (d, 2H, *J* = 8.2 Hz, C$^{2'}$– and C$^{6'}$–H), 6.66 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.57 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.44 (dd, 1H, *J* = 2.0, 8.0 Hz, C^6–H), 5.88 (br s, 1H, OH), 5.42 (d, 1H, *J* = 8.0 Hz, NH), 5.07 (d, 1H, *J* = 12.3 Hz, CO_2CHH), 5.02 (d, 1H, *J* = 12.3 Hz, CO_2CHH), 4.72 (dd, 1H, *J* = 5.7, 13.3 Hz, C*H*CH_2), 4.42 (dd, 1H, *J* = 5.5, 13.0 Hz, C*H*CH_2), 3.79 (s, 3H, $ArOCH_3$), 3.69 (s, 3H, CO_2CH_3), 2.88–3.02 (m, 4H, CH_2Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 170.2, 155.9, 145.8, 145.5, 137.6, 135.9, 131.3, 128.5, 128.3, 128.2, 127.9, 120.6, 115.5, 110.7, 92.4, 67.1, 55.8, 55.6, 53.8, 52.5, 37.9, 37.0; IR (KBr) ν_{max} 3303, 3033, 2950, 2840, 1740, 1701, 1651, 1591, 1534, 1512, 1441, 1341, 1272, 1214, 1132, 1027, 1007, 792, 752, 738, 697 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 765.0081 (M$^+$ + Cs, $C_{28}H_{29}N_2O_7I$ requires 765.0074).

(40) For **18**: white solid, mp 149–150 °C; $[\alpha]^{25}_D$ +34 (*c* 0.5, $CHCl_3$), ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, 2H, *J* = 8.3 Hz, C$^{3'}$– or C$^{5'}$–H), 6.95 (d, 2H, *J* = 8.3 Hz, C$^{2'}$– or C$^{6'}$–H), 6.73 (d, 1H, *J* = 8.0 Hz, $NHSO_2$), 6.89 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.61 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.48 (dd, 1H, *J* = 2.0, 8.2 Hz, C^6–H), 5.83 (s, 1H, OH), 5.21 (d, 1H, *J* = 9.0 Hz, HNCO), 4.73–4.77 (m, 1H, C*H*CH_2), 4.03–4.08 (m, 1H, C*H*CH_2), 3.81 (s, 3H, $ArOCH_3$), 3.70 (s, 3H, CO_2CH_3), 2.92–3.08 (m, 3H, $CHCH_2$), 2.85 (dd, 1H, *J* = 8.7, 14.0 Hz, CHC*H*H), 2.49–2.56 (m, 2H, CH_2SO_2), 0.72–0.78 (m, 2H, CH_2TMS), –0.062 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 170.2, 146.0, 145.5, 137.8, 135.9, 131.8, 128.2, 120.9, 115.6, 110.9, 92.9, 58.3, 55.8, 53.6, 52.5, 50.0, 38.4, 37.1, 9.9, –2.2; IR (KBr) ν_{max} 3330, 2953, 2842, 1740, 1663, 1591, 1512, 1438, 1319, 1274, 1260, 1215, 1135, 1026, 1008, 963, 895, 856, 831, 761, 698 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 795.0033 (M$^+$ + Cs, $C_{25}H_{35}N_2O_7SiSI$ requires 795.0033).

Scheme III

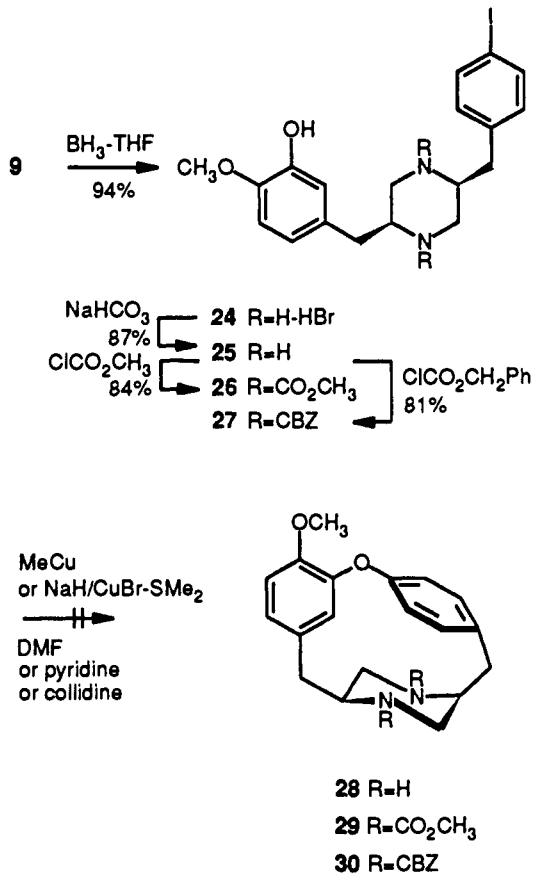


In a final effort to avoid the intramolecular *N*-acylation reaction, the substrate **22**[42] was prepared in which the linking amide was converted to tertiary *N*-benzylamide (Scheme III) and unsuccessfully subjected to four representative Ullmann macrocyclization reaction conditions (Table II). Although this was not investigated in detail, the observation was not unexpected. It is likely that substitution of the linking amide with the bulky benzyl group further decelerates the inherently slow macrocyclization reaction[19] in addition to serving its prescribed role of blocking the intramolecular *N*-acylation reaction.

More surprising were the unexpected comparisons of the highly successful Ullmann closure of **9** with the unsuccessful Ullmann macrocyclization reactions of **24-27**[43] (Scheme IV). With the piperazines **24-27**, there is no potential of competitive substrate racemization under the reaction conditions and, consequently, they were viewed as more appropriate Ullmann macrocyclization substrates. However, no traces of **28-30** were detected even with the piperazine substrates which incorporate the key C^1–O^2 Ullmann ring closure and with use of the optimized reaction conditions (NaH, 10 equiv CuBr–SMe_2, DMF, 0.004 M, reflux, 12–48 h).

(41) For **19**: pale yellow solid, mp 279–280 °C; $[\alpha]^{25}_D$ +12.5 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, 1H, *J* = 8.1 Hz, NH), 7.59 (d, 2H, *J* = 7.7 Hz, C$^{3'}$– and C$^{5'}$–H), 6.92 (d, 2H, *J* = 7.7 Hz, C$^{2'}$– and C$^{6'}$–H), 6.71 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.61 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.48 (dd, 1H, *J* = 2.0, 8.2 Hz, C^6–H), 4.78 (dd, 1H, *J* = 6.0, 13.6 Hz, C*H*CH_2), 3.83 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, CO_2CH_3), 3.52–3.56 (m, 1H, C*H*CH_2); 2.91–3.10 (m, 3H, $CHCH_2$), 2.60 (dd, 1H, *J* = 9.0, 13.6 Hz, CHC*H*H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 171.9, 145.7, 145.5, 137.7, 137.3, 131.4, 128.9, 120.6, 115.6, 110.7, 92.2, 56.0, 55.9, 52.8, 52.3, 40.2, 37.3; IR (KBr) ν_{max} 3379, 3299, 2944, 2840, 1734, 1653, 1586, 1543, 1512, 1442, 1356, 1283, 1218, 1207, 1132, 1026, 1005, 960, 894, 842, 785, 643 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 630.9725 (M$^+$ + Cs, $C_{20}H_{23}N_2O_5I$ requires 630.9706).

Scheme IV



The extension of the studies detailed herein to the preparation of structural and conformational analogs of piperazinomycin and cycloisodityrosine are in progress and will be reported in due course.

Experimental Section

3-Acetyl-*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosine Methyl Ester (2). A solution of 3-acetyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosine methyl ester[33] (3.0 g, 8.1 mmol) in dry DMF (15 mL) was treated with CH_3I (3.45 g, 1.5 mL, 24 mmol, 3.0 equiv) and K_2CO_3 (2.23 g, 16.2 mmol, 2.0 equiv) at 25 °C under Ar. The reaction mixture was stirred at 25 °C for 6 h and filtered. The filtrate was poured into H_2O (15 mL) and extracted with EtOAc (3 × 30 mL). The organic phase was washed with H_2O (15 mL) and saturated aqueous NaCl (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 20 cm, 15–30% EtOAc–hexane gradient elution) afforded **2** (2.92 g, 3.11 g theoretical, 94%) as a colorless oil which solidified upon standing: mp 84–85 °C; $[\alpha]^{25}_D$ +61 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, 1H, *J* = 2.4 Hz, C^2–H), 7.30 (m, 5H, PhH), 7.19 (dd, 1H, *J* = 2.4, 8.4 Hz, C^6–H), 6.85 (d, 1H, *J* = 8.4 Hz, C^5–H), 5.29 (d, 1H, *J* = 8.0 Hz, NH), 5.07 (s, 2H, CH_2Ph), 4.60 (dd, 1H, *J* = 5.8, 7.9 Hz, C*H*CH_2), 3.86 (s, 3H, $ArOCH_3$), 3.72 (s, 3H, CO_2CH_3), 3.06 (dq, 2H, *J* = 6.0, 14.0 Hz, CHCH_2), 2.57 (s, 3H, $COCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.3, 171.8, 158.1, 155.5, 136.1, 134.4, 131.1, 128.4, 128.1, 128.0, 127.8, 127.7, 111.8, 66.9, 55.5, 54.8, 52.4, 37.1, 31.8; IR (KBr) ν_{max} 3366, 2938, 2838, 1753, 1727, 1667, 1610, 1520, 1504, 1427, 1359, 1265, 1219, 1182, 1057, 1022, 976, 815, 794, 745, 700 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 518.0602 (M^+ + Cs, $C_{21}H_{23}NO_6$ requires 518.0580). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.45; H, 5.97; N, 3.64. Found: C, 65.08; H, 5.86; N, 4.00.

3-Acetoxy-*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosine Methyl Ester (3). A solution of **2** (2.92 g, 7.5 mmol) in dry CH_2Cl_2 (30 mL) was treated with *m*-chloroperbenzoic acid (*m*CPBA, 55–60% grade, 5.18 g, 16.5 mmol, 2.2 equiv) and warmed at 40 °C for 20 h. The cooled reaction mixture was concentrated in vacuo, dissolved in EtOAc (60 mL), washed with saturated aqueous Na_2SO_3 (3 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 20 cm, 10–30% EtOAC–hexane gradient elution) afforded **3** (2.87 g, 3.00 g theoretical, 96%) as a colorless oil which solidified upon standing: mp 86–87 °C; $[\alpha]^{25}_D$ +45 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.37 (m, 5H, PhH), 6.93 (dd, 1H, *J* = 2.0, 8.4 Hz, C^6–H), 6.85 (d, 1H, *J* = 8.4 Hz, C^5–H), 6.78 (d, 1H, *J* = 2.0 Hz, C^2–H), 5.26 (d, 1H, *J* = 8.0 Hz, NH), 5.09 (dd, 2H, *J* = 2.0, 12.4 Hz, CH_2Ph), 4.61 (dd, 1H, *J* = 5.8, 8.0 Hz, C*H*CH_2), 3.79 (s, 3H, $ArOCH_3$), 3.70 (s, 3H, CO_2CH_3), 2.99-3.10 (m, 2H, CHCH_2), 2.28 (s, 3H, $OCOCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 168.9, 155.6, 150.2, 139.5, 136.2, 131.1, 128.5, 128.1, 128.0, 127.5, 123.7, 112.4, 66.9, 55.8, 54.8, 52.4, 37.3, 20.6; IR (KBr) ν_{max} 3346, 2955, 2841, 1766, 1738, 1716, 1514, 1440, 1367, 1265, 1209, 1119, 1056, 1022, 904, 813, 750, 697 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 534.0529 (M^+ + Cs, $C_{21}H_{23}NO_7$ requires

(42) For **20**: pale-blue solid, mp 84.5–85 °C; $[\alpha]^{25}_D$ –1.6 (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.27 (m, 5H, PhH), 6.74 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.73 (d, 1H, *J* = 2.2 Hz, C^2–H), 6.62 (dd, 1H, *J* = 2.2, 8.2 Hz, C^6–H), 5.70 (br s, 1H, OH), 3.85 (s, 3H, $ArOCH_3$), 3.80 (d, 1H, *J* = 13.4 Hz, C*H*HPh), 3.65 (s, 3H, CO_2CH_3), 3.63 (d, 1H, *J* = 13.4 Hz, CH*H*Ph), 3.50 (t, 1H, *J* = 6.8 Hz, C*H*CH_2), 2.82–2.91 (m, 2H, CHCH_2), 1.78 (br s, 2H, NH and OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.0, 145.4, 139.5, 130.3, 128.6, 128.3, 128.1, 127.0, 120.6, 115.4, 110.5, 62.0, 55.9, 52.0, 51.6, 39.0; IR (KBr) ν_{max} 3300, 3026, 2932, 1734, 1585, 1508, 1444, 1275, 1226, 1175, 1139, 1030, 991, 820, 749, 699 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 448.0522 (M^+ + Cs, $C_{18}H_{21}NO_4$ requires 448.0525). For **21**: white solid, mp 119.5–120.5 °C; $[\alpha]^{25}_D$ –6.1 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, *J* = 8.1 Hz, C^3– and C^5–H), 6.97 (d, 2H, *J* = 8.1 Hz, C^2– and C^6–H), 4.85–4.95 (m, 1H, C*H*CH_2), 3.27 (dd, 1H, *J* = 5.7, 14.0 Hz, CHC*H*H), 3.13 (dd, 1H, *J* = 5.7, 14.0 Hz, CHCH*H*), 1.42 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2, 154.8, 142.1, 141.0, 139.8, 139.2, 138.5, 136.6, 137.9, 134.6, 131.3, 93.0, 80.8, 54.1, 37.4, 28.2; IR (KBr) ν_{max} 3358, 2982, 2938, 1782, 1690, 1519, 1368, 1328, 1252, 1170, 1132, 1033, 993, 893, 848, 809 cm^{-1}. For **22**: pale-yellow oil, $[\alpha]^{25}_D$ +17 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, 2H, *J* = 8.2 Hz, $C^{3'}$– and $C^{5'}$–H), 7.22–7.28 (m, 5H, PhH), 7.02 (d, 2H, *J* = 8.2 Hz, $C^{2'}$– and $C^{6'}$–H), 7.01 (dd, 1H, *J* = 2.2, 8.4 Hz, C^6–H), 6.86 (d, 1H, *J* = 8.4 Hz, C^5–H), 6.78 (d, 1H, *J* = 2.2 Hz, C^2–H), 5.02 (d, 1H, *J* = 8.3 Hz, NH), 4.82 (dd, 1H, *J* = 6.0, 14.2 Hz, C*H*NHBOC), 3.82 (d, 1H, *J* = 13.4 Hz, C*H*HPh), 3.81 (s, 3H, $ArOCH_3$), 3.64 (s, 3H, CO_2CH_3), 3.62 (d, 1H, *J* = 13.4 Hz, CH*H*Ph), 3.46 (t, 1H, *J* = 6.8 Hz, C*H*COOMe), 3.11–3.30 (m, 2H, CHCH_2), 2.87 (d, 2H, *J* = 6.8 Hz, CHCH_2), 1.42 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.0, 169.8, 155.0, 149.6, 139.5, 138.9, 137.5, 135.7, 131.7, 130.0, 128.4, 128.1, 127.9, 127.0, 123.4, 112.2, 92.5, 80.1, 61.9, 55.8, 54.0, 52.0, 51.8, 38.7, 37.7, 28.3; IR (KBr) ν_{max} 3364, 2964, 2843, 1764, 1725, 1710, 1587, 1513, 1484, 1443, 1367, 1267, 1158, 1121, 1026, 1008, 899, 860, 809, 734 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 821.0730 (M^+ + Cs, $C_{32}H_{37}N_2O_7I$ requires 821.0700).

(43) For **24**: ^1H NMR (DMSO-d_6, 400 MHz) δ 9.35 (br s, 4H, two NH–HBr), 9.05 (br s, 1H, OH), 7.77 (d, 2H, *J* = 8.1 Hz, $C^{3''}$– and $C^{5''}$–H), 7.25 (d, 2H, *J* = 8.1 Hz, $C^{2''}$– and $C^{6''}$–H), 6.93 (d, 1H, *J* = 8.0 Hz, $C^{5'}$–H), 6.79 (br s, 1H, $C^{6'}$–H), 6.77 (d, 1H, *J* = 8.0 Hz, C^2–H), 3.86 (m, 2H, C*H*CH_2), 3.77 (s, 3H, $ArOCH_3$), 3.07–3.17 (m, 8H); IR (KBr) ν_{max} 3415, 2931, 1596, 1508, 1440, 1276, 1250, 1331, 1062, 1025, 1008, 969, 883, 800, 763 cm^{-1}. For **25**: pale-yellow oil which solidified upon standing, mp 194–196 °C; $[\alpha]^{25}_D$ –10.1 (*c* 0.3, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 7.58 (d, 2H, *J* = 8.1 Hz, $C^{3''}$– and $C^{5''}$–H), 6.99 (d, 2H, *J* = 8.1 Hz, $C^{2''}$– and $C^{6''}$–H), 6.78 (d, 1H, *J* = 8.1 Hz, $C^{5'}$–H), 6.64 (d, 1H, *J* = 2.0 Hz, $C^{2'}$–H), 6.61 (dd, 1H, *J* = 2.0, 8.1 Hz, $C^{6'}$–H), 3.73 (s, 3H, $ArOCH_3$), 3.12–3.14 (m, 2H, C*H*CH_2), 2.70–2.90 (m, 8H); ^{13}C NMR (CD_3OD, 100 MHz) δ 148.2, 147.9, 139.0, 138.2, 132.5, 130.7, 121.4, 117.1, 113.0, 92.9, 56.4, 55.6, 55.2, 45.3, 37.3, 36.6; IR (KBr) ν_{max} 3405, 2933, 2834, 1590, 1508, 1441, 1276, 1251, 1224, 1134, 1026, 1007, 873, 801, 761 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 570.9859 (M^+ + Cs, $C_{19}H_{23}N_2O_2I$ requires 570.9859). For **26**: colorless oil which solidified upon standing, mp 69–70 °C; $[\alpha]^{25}_D$ +43 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, 2H, *J* = 8.1 Hz, $C^{3''}$– and $C^{5''}$–H), 6.82 (d, 2H, *J* = 8.1, Hz, $C^{2'}$– and $C^{6'}$–H), 6.74 (d, 1H, *J* = 8.2 Hz, $C^{5'}$–H), 6.66 (d, 1H, *J* = 2.0 Hz, $C^{2'}$–H), 6.53 (dd, 1H, *J* = 2.0, 8.2 Hz, $C^{6'}$–H), 5.62 (s, 1H, OH), 4.05–4.10 (m, 2H, C*H*CH_2), 3.88 (s, 3H, $ArOCH_3$), 3.78–3.82 (m, 2H, CHCH_2 or NHCH_2), 3.68 (s, 3H, CO_2CH_3), 3.63 (s, 3H, CO_2CH_3), 2.55–2.78 (m, 6H, CHCH_2 and NHCH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 145.5, 145.3, 137.5, 136.4, 131.4, 129.7, 120.8, 115.5, 110.6, 91.9, 56.1, 54.3, 54.1, 52.74, 52.72, 41.2, 37.2; IR (KBr) ν_{max} 3383, 3016, 2955, 2840, 1715, 1713, 1682, 1667, 1589, 1505, 1451, 1409, 1350, 1295, 1263, 1169, 1121, 1027, 1007, 962, 789, 750, 731 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 686.9975 (M^+ + Cs, $C_{23}H_{27}N_2O_6I$ requires 686.9968). For **27**: colorless oil which solidified upon standing, mp 66–67 °C; $[\alpha]^{25}_D$ +33 (*c* 0.88, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, 2H, *J* = 8.1 Hz, $C^{3''}$– and $C^{5''}$–H), 7.27–7.38 (m, 10H, PhH), 6.72 (d, 1H, *J* = 8.2 Hz, $C^{5'}$–H), 6.68 (d, 2H, *J* = 8.1 Hz, $C^{2''}$– and $C^{6''}$–H), 6.62 (d, 1H, *J* = 2.0 Hz, $C^{2'}$–H), 6.46 (dd, 1H, *J* = 2.0, 8.2 Hz, $C^{6'}$–H), 5.56 (s, 1H, OH), 5.12 (s, 2H, CH_2OCO), 5.08 (s, 2H, CH_2OCO), 4.04–4.12 (m, 2H, C*H*CH_2), 3.87 (s, 3H, $ArOCH_3$), 3.81–3.92 (m, 2H, CHCH_2 or NCH_2), 2.59–2.76 (m, 6H, CHCH_2 and NCH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 145.6, 145.3, 137.4, 136.4, 136.3, 131.3, 129.6, 128.6, 128.5, 128.2, 128.1, 127.9, 120.8, 115.5, 110.6, 91.9, 67.4, 56.0, 54.5, 41.3, 37.2; IR (KBr) ν_{max} 3516, 3382, 3031, 2935, 1682, 1675, 1589, 1511, 1414, 1353, 1271, 1160, 1118, 1025, 1007, 754, 733, 697, 667 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 839.0611 (M^+ + Cs, $C_{35}H_{35}N_2O_6I$ requires 839.0594).

534.0529). Anal. Calcd for $C_{21}H_{23}NO_7$: C, 62.84; H, 5.74; N, 3.49. Found: C, 62.47; H, 5.78; N, 3.84.

3-Hydroxy-*O*-methyl-*N*-[(phenylmethoxy)carbonyl]-L-tyrosine Methyl Ester (4). A solution of **3** (2.97 g, 7.42 mmol) in CH_3OH (10 mL) was added to a solution of 0.25 N HCl–CH_3OH (30 mL) prepared by dropwise addition of CH_3COCl (583 mg, 0.53 mL, 7.42 mmol, 1.0 equiv) to 30 mL of CH_3OH at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 10 h before being concentrated in vacuo. Flash chromatography (SiO_2, 3 × 20 cm, 15–30% EtOAc–hexane gradient elution) afforded **4** (2.59 g, 2.66 g theoretical, 97%) as a clear, pale-yellow oil: $[\alpha]^{25}_D$ +48 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.36 (m, 5H, PhH), 6.72 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.67 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.56 (dd, 1H, *J* = 2.0, 8.2 Hz, C^6–H), 5.74 (br s, 1H, OH), 5.29 (d, 1H, *J* = 8.0 Hz, NH), 5.09 (br s, 2H, CH_2Ph), 4.61 (dd, 1H, *J* = 5.8, 8.1 Hz, C*H*CH_2), 3.82 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, CO_2CH_3), 2.90–3.05 (m, 2H, CHC*H*$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 155.6, 145.7, 145.6, 136.7, 128.6, 128.4, 128.04, 127.98, 120.6, 115.4, 110.7, 66.9, 55.7, 54.8, 52.2, 37.4; IR (neat) ν_{max} 3333, 2940, 2842, 1734, 1709, 1592, 1514, 1443, 1343, 1273, 1208, 1126, 1049, 1020, 908, 761, 732 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 492.0431 (M^+ + Cs, $C_{19}H_{21}NO_6$ requires 492.0423). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.51; H, 5.85; N, 3.90. Found: C, 63.60; H, 5.62; N, 4.08.

3-Hydroxy-*O*-methyl-L-tyrosine Methyl Ester (5). A solution of **4** (2.59 g, 7.2 mmol) in dry CH_3OH (40 mL) was treated with 10% Pd/C (260 mg, 10% wt equiv) and stirred under an atmosphere of H_2 (1 atm) at 25 °C for 10 h. The reaction mixture was filtered through Celite (CH_3OH wash), concentrated in vacuo, and dried thoroughly under vacuum to afford **5** (1.60 g, 1.62 g theoretical, 99%) as a pale-blue solid: mp 78–79 °C; $[\alpha]^{25}_D$ –11.6 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.77 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.74 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.65 (dd, 1H, *J* = 2.0, 8.2 Hz, C^6–H), 3.85 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, CO_2CH_3), 3.68 (dd, 1H, *J* = 5.0, 7.9 Hz, C*H*CH_2), 2.99 (dd, 1H, *J* = 5.0, 13.6 Hz, CHC*H*H), 2.75 (dd, 1H, *J* = 7.9, 13.6 Hz, CHCH*H*), 2.30–2.60 (br s, 3H, NH_2 and OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.4, 145.71, 145.67, 130.1, 120.7, 115.5, 110.8, 55.9, 55.8, 52.0, 40.3; IR (KBr) ν_{max} 3370, 3301, 2953, 2828, 1730, 1582, 1509, 1440, 1375, 1320, 1286, 1221, 1206, 1165, 1131, 1028, 994, 932, 877, 812, 785, 759, 652 cm^{-1}; FABHRMS (NBA/NaI) *m/e* 248.0899 (M^+ + Na, $C_{11}H_{15}NO_4$ requires 248.0899).

3-Hydroxy-*O*-methyl-*N*-[4-iodo-*N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-L-tyrosine Methyl Ester (7). A solution of **5** (1.35 g, 6.0 mmol) in dry DMF (5 mL) was added to a solution of **6**[34] (2.35 g, 6.0 mmol, 1.0 equiv), EDCI (1.50 g, 7.8 mmol, 1.3 equiv), and HOBt (1.05 g, 7.8 mmol, 1.3 equiv) in DMF (15 mL) at 0 °C under Ar. The resulting reaction solution was allowed to warm to 25 °C and stirred for 16 h. The reaction mixture was poured into 10% aqueous HCl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined EtOAc extracts were washed with 10% aqueous HCl (2 × 10 mL), H_2O (10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 25 cm, 10–30% EtOAc–hexane gradient elution) afforded **7** (3.39 g, 3.59 g theoretical, 95%) as a white solid: mp 170–171 °C (80% EtOAc–hexane, white powder); $[\alpha]^{25}_D$ +36 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, 2H, *J* = 8.2 Hz, $C^{3'}$– and $C^{5'}$–H), 6.90 (d, 2H, *J* = 8.2 Hz, $C^{2'}$– and $C^{6'}$–H), 6.69 (d, 1H, *J* = 8.2 Hz, C^5–H), 6.57 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.44 (dd, 1H, *J* = 2.0 8.2 Hz, C^6–H), 6.35 (d, 1H, *J* = 6.4 Hz, NHCO), 5.92 (br s, 1H, OH), 5.07 (d, 1H, *J* = 6.0 Hz, NHBOC), 4.68–4.72 (m, 1H, CH_2CH), 4.28–4.32 (m, 1H, CH_2CH), 3.82 (s, 3H, $ArOCH_3$), 3.68 (s, 3H, CO_2CH_3), 2.96 (dt, 2H, *J* = 5.9, 14.0 Hz, CH_2Ar), 2.93 (dt, 2H, *J* = 5.7, 13.9 Hz, CH_2Ar), 1.39 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 170.5, 155.3, 145.9, 145.6, 137.5, 136.1, 131.3, 128.4, 120.6, 115.6, 110.7, 92.3, 80.3, 55.8, 55.3, 53.3, 52.4, 37.8, 37.0, 28.2; IR (KBr) ν_{max} 3504, 3334, 3297, 2977, 2931, 1736, 1683, 1664, 1513, 1438, 1365, 1298, 1270, 1249, 1172, 1131, 1024, 1007, 965, 895, 841, 801, 762, 623 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 731.0237 (M^+ + Cs, $C_{25}H_{31}N_2O_7I$ requires 731.0230). Anal. Calcd for $C_{25}H_{31}N_2O_7I$: C, 50.17; H, 5.18; N, 4.68. Found: C, 50.37; H, 5.26; N, 5.05.

***cyclo*-(4-Iodo-L-phenylalanyl)-3-hydroxy-4-*O*-methyl-L-tyrosine (9).** A solution of **7** (2.30 g, 3.85 mmol) in 3.25 M HCl–EtOAc (30 mL) was stirred at 0 °C for 10 min and allowed to warm to 25 °C over 30 min. The volatiles were removed in vacuo and the residue was dried thoroughly under vacuum to afford the corresponding amine hydrochloride salt **8** (2.06 g, 2.06 g theoretical, 100%) as a white solid. A suspension of the hydrochloride salt **8** (2.06 g, 3.85 mmol) in 0.1 M HOAc–*i*PrOH (20 mL) was treated with *N*-methylmorpholine (NMM, 505 mg, 0.55 mL, 5.0 mmol, 1.3 equiv) at 25 °C, and the resulting weakly acidic reaction mixture was warmed at reflux for 2 h. The diketopiperazine began to crystallize from the hot reaction solution. The mixture was cooled at 0 °C (4 h) and filtered, and the collected product was washed with Et_2O (3 × 20 mL). Recrystallization from 2-propanol afforded **9** (1.69 g, 1.79 g theoretical, 94%) as a white solid: mp 281-283 °C dec (2-propanol, white powder); $[\alpha]^{25}_D$ –203 (*c* 0.05, CH_3OH); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.94 (s, 1H, OH), 7.95 (d, 1H, *J* = 2.2 Hz, NH), 7.90 (d, 1H, *J* = 2.2 Hz, NH), 7.63 (d, 2H, *J* = 8.2 Hz, $C^{3'}$– and $C^{5'}$–H), 6.86 (d, 1H, *J* = 8.3 Hz, C^5–H), 6.83 (d, 2H, *J* = 8.2 Hz, $C^{2'}$– and $C^{6'}$–H), 6.58 (d, 1H, *J* = 2.0 Hz, C^2–H), 6.47 (dd, 1H, *J* = 2.0, 8.3 Hz, C^6–H), 3.94–3.98 (m, 1H, C*H*CH_2), 3.86–3.90 (m, 1H, C*H*CH_2) 3.71 (s, 3H, $ArOCH_3$), 2.58 (dd, 1H, *J* = 4.6, 13.6 Hz, CHC*H*H), 2.48 (dd, 1H, *J* = 5.0, 13.6 Hz, CHCH*H*), 2.37 (dd, 1H, *J* = 5.6, 13.6 Hz, CHC*H*H), 2.01 (dd, 1H, *J* = 7.0, 13.6 Hz, CHCH*H*); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.3, 166.1, 146.6, 146.4, 136.9, 136.7, 132.2, 128.9, 120.7, 117.5, 112.3, 92.5, 55.8, 55.7, 55.3, 38.6; IR (KBr) ν_{max} 3427, 3209, 2989, 2831, 1672, 1585, 1513, 1461, 1400, 1328, 1267, 1128, 1005, 969, 805, 764, 662 cm^{-1}; FABHRMS (NBA/CsI) *m/e* 598.9444 (M^+ + Cs, $C_{19}H_{19}N_2O_4I$ requires 598.9444). Anal. Calcd for $C_{19}H_{19}N_2O_4I$: C, 48.93; H, 4.08; N, 6.01. Found: C, 49.02; H, 4.34; N, 5.63.

(3*S*,6*S*)-11-Methoxy-5,21-dioxo-13-oxa-4,20-diazatetracyclo-[12.2.2.2^{3,6}.1^{8,12}]heniecosa-8,10,12(19),14,16,17-hexaene (10). A solution of **9** (466 mg, 1.0 mmol) in dry DMF (5 mL) was added dropwise to a 0 °C suspension of NaH (60% dispersion in mineral oil, 160 mg, 4.0 mmol, 4.0 equiv) in dry DMF (2 mL) under Ar, and the solution was allowed to stir for 20 min at 0 °C. The solution was treated with CuBr–SMe_2 (2.06 g, 10.0 mmol, 10.0 equiv) and allowed to stir for 1 h at 25 °C. The mixture was diluted with additional dry, degassed DMF to 0.004 M (243 mL) and warmed at 170 °C (bath temperature) for 48 h. The cooled reaction mixture was concentrated in vacuo, and the residue was treated with saturated aqueous NH_4Cl–concentrated NH_4OH (9:1, 40 mL) and 10% CH_3OH–$CHCl_3$ (40 mL). The mixture was stirred for 30 min at 25 °C before the two layers were separated and the aqueous phase was extracted with 10% CH_3OH–$CHCl_3$ (5 × 40 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (2 × 20 mL), H_2O (20 mL), and saturated aqueous NaCl (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 3 × 10 cm, 2–10% CH_3OH–$CHCl_3$ gradient elution) afforded **10** (180 mg, 338 mg theoretical, 53%) as a white solid: mp 284–286 °C dec (95% EtOH–H_2O, white powder); $[\alpha]^{25}_D$ +182 (*c* 0.05, CH_3OH); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.11 (br s, 1H, N^4–H), 7.92 (br s, 1H, N^{20}–H), 7.46 (dd, 1H, *J* = 2.1, 8.4 Hz, C^{16}–H), 7.23 (dd, 1H, *J* = 2.1, 8.4 Hz, C^{17}–H), 7.04 (dd, 1H, *J* = 2.4, 8.3 Hz, C^{15}–H), 6.91 (dd, 1H, *J* = 2.4, 8.4 Hz, C^{18}–H), 6.88 (d, 1H, *J* = 8.3 Hz, C^{10}–H), 6.55 (dd, 1H, *J* = 2.1, 8.3 Hz, C^9–H), 4.25–4.28 (m, 1H, C^3–H), 4.15–4.18 (m, 1H, C^6–H), 4.13 (d, 1H, *J* = 2.1 Hz, C^{19}–H), 3.81 (s, 3H, $ArOCH_3$), 3.49 (dd, 1H, *J* = 2.3, 12.8 Hz, C^2–H_β), 3.07 (dd, 1H, *J* = 3.2, 17.7 Hz, C^7–H_β), 2.89 (dd, 1H, *J* = 4.7, 12.8 Hz, C^2–H_α), 2.74 (dd, 1H, *J* = 4.7, 17.7 Hz, C^7–H_α); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.3, 166.2, 157.9, 152.2, 145.1, 133.6, 133.1, 131.9, 129.2, 124.1, 123.2, 121.6, 114.8, 112.6, 56.2, 55.8, 51.7, 36.7, 31.1; IR (KBr) ν_{max} 3443, 3204, 3075, 2966, 2897, 1671, 1585, 1517, 1500, 1438, 1325, 1265, 1216, 1127, 1024, 965, 933, 830, 807, 746, 713 cm^{-1}; FABHRMS (NBA) *m/e* 338.1281 (M^+, $C_{19}H_{18}N_2O_4$ requires 338.1267).

The 2D ^1H–^1H NOESY NMR spectrum of **10** (DMSO-d_6, 400 MHz) displayed diagnostic NOE crosspeaks for N^4–H/C^3–H, N^4–H/C^2–H_α, N^4–H/C^{16}–H, N^{20}–H/C^6–H, N^{20}–H/C^7–H_β, C^{16}–H/C^{15}–H, C^{16}–H/C^2–H_α, C^{17}–H/C^{18}–H, C^{17}–H/C^2–H_β, C^{10}–H/C^9–H, C^{10}–H/C^{11}–OCH_3, C^3–H/C^2–H_β, C^3–H/C^2–H_α, C^6–H/C^7–H_β, C^6–H/C^7–H_α, C^2–H_α/C^2–H_β, C^7–H_α/C^7–H_β.

Chiral-phase HPLC analysis of **10** revealed a single peak (t_R 8.1 min; 1 mL/min, 2% *i*PrOH–CH_2Cl_2 elution, 258-nm detection).

(3*S*,6*S*)-5,21-Dioxo-13-oxa-4,20-diazatetracyclo[12.2.2.2^{3,6}.1^{8,12}]-heniecosa-8,10,12(19),14,16,17-hexaen-11-ol (11a). A solution of **10** (6.8 mg, 0.02 mmol) in HOAc (0.5 mL) was treated with HBr (48%, 0.1 mL) at 25 °C, and the resulting reaction solution was warmed at reflux for 40 min. The volatiles were removed in vacuo, and the residue was treated with saturated aqueous $NaHCO_3$ (3 mL). The aqueous phase was extracted with 10% CH_3OH–$CHCl_3$ (6 × 5 mL). The combined extracts were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 3 cm, 5–10% CH_3OH–$CHCl_3$ gradient elution) afforded **11a** (5.5 mg, 6.5 mg theoretical, 85%) as a white solid: mp 294–296 °C dec (95% EtOH–H_2O, white powder); $[\alpha]^{25}_D$ +125 (*c* 0.25, pyridine); ^1H NMR (CD_3OD, 400 MHz) δ 7.33 (dd, 1H, *J* = 2.2, 8.3 Hz, C^{16}–H),

7.29 (dd, 1H, J = 2.2, 8.3 Hz, C^{17}–H), 7.06 (dd, 1H, J = 2.2, 8.3 Hz, C^{15}–H), 6.91 (dd, 1H, J = 2.2, 8.3 Hz, C^{18}–H), 6.65 (d, 1H, J = 8.2 Hz, C^{10}–H), 6.45 (dd, 1H, J = 2.2, 8.2 Hz, C^{9}–H), 4.35-4.37 (m, 1H, C^{3}–H), 4.24–4.27 (m, 1H, C^{6}–H), 4.21 (d, 1H, J = 2.2 Hz, C^{19}–H), 3.53 (dd, 1H, J = 2.4, 13.3 Hz, C^{2}–H_β), 3.24 (dd, 1H, J = 3.0, 17.6 Hz, C^{7}–H_β), 2.94 (dd, 1H, J = 4.8, 13.3 Hz, C^{2}–H_α), 2.79 (dd, 1H, J = 4.8, 17.6 Hz, C^{7}–H_α); ^{13}C NMR (CD_3OD, 100 MHz) δ 170.1, 169.2, 160.6, 152.8, 144.1, 134.2, 133.9, 133.1, 128.4, 125.9, 124.9, 123.3, 117.2, 116.3, 58.1, 53.8, 38.3, 32.6; IR (KBr) ν_{max} 3422, 3214, 3102, 2964, 2929, 1670, 1517, 1437, 1324, 1265, 1213, 1117, 1024, 964, 932, 854, 744, 708 cm^{-1}; FABHRMS (NBA) m/e 325.1188 (M^+ + H, $C_{18}H_{16}N_2O_4$ requires 325.1188).

(3*S*,6*S*)-11-Acetoxy-5,21-dioxo-13-oxa-4,20-diazatetracyclo-[12.2.2.2^{3,6}.1^{8,12}]heniecosa-8,10,12(19),14,16,17-hexaene (11b). A solution of **11a** (5.5 mg, 0.017 mmol) in dry pyridine (0.5 mL) was treated with Ac_2O (87 mg, 80 μL, 0.85 mmol, 50 equiv) at 25 °C under Ar. The resulting reaction solution was stirred for 4 h at 25 °C. The volatiles were removed in vacuo, and the residue was purified by flash chromatography (SiO_2, 1.5 × 2 cm, 2–10% CH_3OH–$CHCl_3$ gradient elution) to afford **11b** (5.8 mg, 6.2 mg theoretical, 93%) as a white solid: mp 292–294 °C dec (EtOH, white powder); $[\alpha]^{25}_D$ +188 (c 0.15, pyridine), [lit^{30} $[\alpha]^{20}_D$ +190 (c 0.19, pyridine)]; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.25 (dd, 1H, J = 2.2, 8.3 Hz, C^{16}–H), 7.22 (dd, 1H, J = 2.1, 8.3 Hz, C^{17}–H), 6.97 (dd, 1H, J = 2.2, 8.3 Hz, C^{15}–H), 6.84 (dd, 1H, J = 2.2, 8.3 Hz, C^{18}–H), 6.78 (d, 1H, J = 8.2 Hz, C^{10}–H), 6.55 (dd, 1H, J = 2.0, 8.2 Hz, C^{9}–H), 4.28–4.30 (m, 1H, C^{3}–H), 4.26 (d, 1H, J = 2.0 Hz, C^{19}–H), 4.21–4.24 (m, 1H, C^{6}–H), 3.46 (dd, 1H, J = 2.3, 13.2 Hz, C^{2}–H_β), 3.24 (dd, 1H, J = 3.0, 17.6 Hz, C^{7}–H_β), 2.87 (dd, 1H, J = 4.6, 13.2 Hz, C^{2}–H_α), 2.79 (dd, 1H, J = 4.6, 17.6 Hz, C^{7}–H_α), 2.23 (s, 3H, $OCOCH_3$); ^{13}C NMR (CD_3OD, 100 MHz) δ 170.7, 170.1, 169.0, 160.2, 156.0, 137.9, 136.0, 134.8, 134.1, 133.2, 125.6, 124.7, 123.5, 123.3, 117.1, 58.1, 53.6, 38.4, 32.9, 20.5; IR (KBr) ν_{max} 3448, 3226, 2926, 2855, 1758, 1671, 1591, 1500, 1427, 1322, 1247, 1195, 1113, 1014, 967, 932, 906, 855, 753, 730, 644 cm^{-1}; FABHRMS (NBA) m/e 367.1299 (M^+ + H, $C_{20}H_{18}N_2O_5$ requires 367.1294).

(3*S*,6*S*)-11-Methoxy-13-oxa-4,20-diazatetracyclo[12.2.2.2^{3,6}.1^{8,12}]-heniecosa-8,10,12(19),14,16,17-hexaene (13). A well-stirred suspension of **10** (33.8 mg, 0.1 mmol) in dry THF (1.0 mL) was treated with 1 M BH_3–THF (3 mL, 3 mmol, 15 equiv) at 25 °C under Ar. The reaction mixture was stirred at 25 °C for 1 h and warmed to 45–50 °C for 72 h. The volatiles were removed in vacuo, and the residue was treated with 2 N aqueous HCl (2 mL) at 25 °C for 30 min. The clear acidic solution was neutralized with the addition of 6N aqueous NaOH (0.8 mL), and the mixture was stirred at 25 °C for 20 min. The mixture was extracted with 10% CH_3OH–$CHCl_3$ (8 × 5 mL). The combined organic extracts were washed with H_2O (2 × 5 mL) and saturated aqueous NaCl (2 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 5 cm, 0–15% CH_3OH–$CHCl_3$ gradient elution) afforded **13** (13.2 mg, 31.0 mg theoretical, 43%) and a monoreduced product **12** (13.9 mg, 43%). The monoreduced product **12** was recycled through the reduction reaction conditions a second time (70% conversion) to provide **13** (73% overall). For **13**: white solid, mp 89–91 °C (95% EtOH–H_2O, white powder); $[\alpha]^{25}_D$ –43 (c 0.23, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.53 (dd, 1H, J = 2.2, 8.4 Hz, C^{17}–H), 7.50 (dd, 1H, J = 2.2, 8.4 Hz, C^{16}–H), 7.10 (dd, 1H, J = 2.4, 8.3 Hz, C^{18}–H), 6.92 (dd, 1H, J = 2.4, 8.3 Hz, C^{15}–H), 6.77 (d, 1H, J = 8.3 Hz, C^{10}–H), 6.49 (dd, 1H, J = 2.2, 8.3 Hz, C^{9}–H), 5.89 (d, 1H, J = 2.2 Hz, C^{19}–H), 3.86 (s, 3H, $ArOCH_3$), 3.40 (d, 1H, J = 13.4 Hz, C^{21}–H_β), 3.04–3.23 (m, 4H, C^{2}–H_α, C^{2}–H_β, C^{3}–H_α, C^{21}–H_α), 2.87 (m, 1H, C^{6}–H_α), 2.76 (dd, 1H, J = 4.2, 17.0 Hz, C^{7}–H_β), 2.56 (t, 1H, J = 12.2 Hz, C^{5}–H_β), 2.53 (dd, 1H, J = 3.2, 17.0 Hz, C^{7}–H_α), 2.32 (dd, 1H, J = 2.8, 12.2 Hz, C^{5}–H_α); ^{13}C NMR (CD_3OD, 100 MHz) δ 162.7, 153.9, 148.1, 137.8, 133.3, 132.6, 131.0, 126.4, 125.7, 124.1, 121.9, 114.0, 56.9, 55.0, 50.6, 49.6, 45.5, 41.8, 36.7; IR (KBr) ν_{max} 3445, 2927, 2851, 1605, 1516, 1457, 1430, 1384, 1262, 1196, 1127, 1025, 996, 840, 808, 751, 720, 686 cm^{-1}; FABHRMS (NBA) m/e 311.1766 (M^+ + H, $C_{19}H_{22}N_2O_2$ requires 311.1760).

The 2D ^{1}H–^{1}H NOESY NMR spectrum of **13** (CD_3OD, 400 MHz) displayed diagnostic NOE crosspeaks for C^{17}–H/C^{18}–H, C^{17}–H/C^{21}–H_β, C^{17}–H/C^{2}–H_β, C^{16}–H/C^{15}–H, C^{16}–H/C^{2}–H_α, C^{18}–H/C^{19}–H, C^{10}–H/C^{9}–H, C^{10}–H/C^{11}–OCH_3, C^{9}–H/C^{7}–H_α, C^{19}–H/C^{5}–H_β, C^{21}–H_β/C^{21}–H_α, C^{21}–H_β/C^{3}–H_α, C^{21}–H_α/C^{6}–H_α, C^{21}–H_α/C^{3}–H_α, C^{3}–H_α/C^{2}–H_β, C^{3}–H_α/C^{2}–H_α, C^{2}–H_α/C^{2}–H_β, C^{6}–H_α/C^{5}–H_α, C^{6}–H_α/C^{5}–H_β, C^{6}–H_α/C^{7}–H_α, C^{6}–H_α/C^{7}–H_β, C^{7}–H_β/C^{7}–H_α, C^{5}–H_β/C^{5}–H_α.

For **12**: white solid, mp 279–281 °C dec (CH_3OH, white powder); $[\alpha]^{25}_D$ +278 (c 0.23, CH_3OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.58 (br s, 1H, N^4–H), 7.55 (dd, 1H, J = 2.1, 8.3 Hz, C^{17}–H), 7.38 (dd, 1H, J = 2.1, 8.3 Hz, C^{16}–H), 7.06 (dd, 1H, J = 2.1, 8.2 Hz, C^{15}–H), 6.91 (dd, 1H, J = 2.1, 8.2 Hz, C^{18}–H), 6.83 (d, 1H, J = 8.2 Hz, C^{10}–H), 6.52 (dd, 1H, J = 2.1, 8.2 Hz, C^{9}–H), 4.74 (d, 1H, J = 2.1 Hz, C^{19}–H), 3.80 (s, 3H, $ArOCH_3$), 3.63 (m, 1H, C^{3}–H_α), 3.30 (m, 1H, N^{20}–H, partially obscured by H_2O), 3.25 (dd, 1H, J = 4.4, 17.6 Hz, C^{7}–H_β), 3.19 (dd, 1H, J = 1.2, 16.8 Hz, C^{21}–H_β), 3.14 (m, 1H, C^{6}–H_α), 3.04 (m, 1H, C^{21}–H_α), 2.92 (dd, 1H, J = 4.9, 13.2 Hz, C^{2}–H_α), 2.84 (dd, 1H, J = 1.2, 12.8 Hz, C^{2}–H_β), 2.52 (dd, 1H, J = 4.6, 16.8 Hz, C^{7}–H_α); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.6, 158.6, 152.1, 145.2, 135.2, 132.5, 131.4, 130.1, 124.2, 123.7, 121.5, 117.2, 112.6, 56.5, 55.9, 50.5, 46.5, 40.7, 31.5; IR (KBr) ν_{max} 3431, 2933, 2830, 1660, 1587, 1518, 1499, 1267, 1206, 1131, 1027, 967, 837, 793, 727, 704 cm^{-1}; FABHRMS (NBA) m/e 325.1552 (M^+ + H, $C_{19}H_{20}N_2O_3$ requires 325.1552).

The 2D ^{1}H–^{1}H NOESY NMR spectrum of **12** (DMSO-d_6, 400 MHz) displayed diagnostic NOE crosspeaks for N^4–H/C^{16}–H, N^4–H/C^{3}–H_α, N^4–H/C^{2}–H_α, C^{17}–H/C^{18}–H, C^{17}–H/C^{21}–H_β, C^{17}–H/C^{2}–H_β, C^{16}–H/C^{15}–H, C^{16}–H/C^{2}–H_α, C^{15}–H/C^{19}–H, C^{18}–H/C^{19}–H, C^{10}–H/C^{9}–H, C^{10}–H/C^{11}–OCH_3, C^{9}–H/C^{19}–H, C^{9}–H/C^{7}–H_α, C^{3}–H_α/C^{21}–H_α, C^{3}–H_α/C^{2}–H_α, C^{3}–H_α/C^{2}–H_β, N^{20}–H/C^{19}–H, C^{7}–H_β/C^{7}–H_α, C^{7}–H_β/C^{6}–H_α, C^{21}–H_β/C^{21}–H_α, C^{21}–H_β/C^{2}–H_β, C^{6}–H_α/C^{7}–H_α, C^{2}–H_α/C^{2}–H_β.

(3*S*,6*S*)-13-Oxa-4,20-diazatetracyclo[12.2.2.2^{3,6}.1^{8,12}]heniecosa-8,10,-12(19),14,16,17-hexaen-11-ol (1, (+)-Piperazinomycin). A solution of **13** (6.2 mg, 0.02 mmol) in HOAc (0.5 mL) was treated with HBr (48%, 0.1 mL) at 25 °C, and the resulting reaction solution was warmed at reflux for 1 h. The volatiles were removed in vacuo, and the residue was treated with saturated aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with 10% CH_3OH–$CHCl_3$ (8 × 5 mL). The combined organic extracts were washed with H_2O (5 mL) and saturated aqueous NaCl (2 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 3 cm, 5–15% CH_3OH–$CHCl_3$ gradient elution) afforded **1** (4.8 mg, 5.9 mg theoretical, 82%) as a white solid: mp 103–104 °C (lit^1 mp 102–104 °C); $[\alpha]^{25}_D$ +31 (c 0.2, CH_3OH), [lit^1 $[\alpha]^{23}_D$ +31 (c 0.74, CH_3OH)]; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.56 (dd, 1H, J = 2.2, 8.3 Hz, C^{16}–H), 7.51 (dd, 1H, J = 2.2, 8.3 Hz, C^{17}–H), 7.06 (dd, 1H, J = 2.2, 8.3 Hz, C^{18}–H), 7.03 (dd, 1H, J = 2.2, 8.3 Hz, C^{15}–H), 6.62 (d, 1H, J = 8.1 Hz, C^{10}–H), 6.41 (dd, 1H, J = 2.1, 8.1 Hz, C^{9}–H), 5.76 (d, 1H, J = 2.0 Hz, C^{19}–H), 3.33 (d, 1H, J = 13.2 Hz, C^{21}–H_β), 2.97–3.12 (m, 4H, C^{2}–H_β, C^{2}–H_α, C^{3}–H_α, C^{21}–H_α), 2.75 (m, 1H, C^{6}–H_α), 2.70 (dd, 1H, J = 4.9, 16.3 Hz, C^{7}–H_β), 2.53 (t, 1H, J = 12.3 Hz, C^{5}–H_β), 2.49 (dd, 1H, J = 3.0, 16.3 Hz, C^{7}–H_α), 2.26 (dd, 1H, J = 3.0, 12.3 Hz, C^{5}–H_α); ^{13}C NMR (CD_3OD, 100 MHz) δ 163.4, 152.8, 145.5, 139.4, 132.9, 132.1, 129.9, 126.2, 125.9, 124.9, 122.0, 117.5, 55.8, 49.9, 49.1, 45.9, 43.8, 37.2; IR (KBr) ν_{max} 3300, 2928, 2864, 1602, 1509, 1430, 1380, 1265, 1195, 1130, 1024, 990, 938, 825, 786, 680 cm^{-1}; FABHRMS (NBA/NaI) m/e 297.1613 (M^+ + H, $C_{18}H_{20}N_2O_2$ requires 297.1603).

The 2D ^{1}H–^{1}H NOESY NMR spectrum of **1** (CD_3OD, 400 MHz) displayed diagnostic NOE crosspeaks for C^{16}–H/C^{19}–H, C^{16}–H/C^{15}–H, C^{16}–H/C^{5}–H_β, C^{16}–H/C^{2}–H_α, C^{17}–H/C^{18}–H, C^{17}–H/C^{21}–H_β, C^{17}–H/C^{2}–H_β, C^{15}–H/C^{19}–H, C^{10}–H/C^{9}–H, C^{9}–H/C^{7}–H_β, C^{9}–H/C^{7}–H_α, C^{19}–H/C^{5}–H_β, C^{21}–H_β/C^{21}–H_α, C^{21}–H_β/C^{3}–H_α, C^{2}–H_β/C^{2}–H_α, C^{2}–H_β/C^{3}–H_α, C^{2}–H_α/C^{3}–H_α, C^{21}–H_α/C^{3}–H_α, C^{21}–H_α/C^{6}–H_α, C^{6}–H_α/C^{7}–H_α, C^{6}–H_α/C^{7}–H_β, C^{6}–H_α/C^{5}–H_β, C^{6}–H_α/C^{5}–H_α, C^{7}–H_β/C^{7}–H_α, C^{5}–H_β/C^{5}–H_α.

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