= 1) as an oil. Compounds **2b-d** (n = 1) and **2a-d** (n = 2) were similarly prepared form **12b-d** and **13a-d**, respectively.

[4(*R*)-[1β,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2a, n = 1): ^{1}H NMR (300 MHz) δ 5.69 (m, 1 H), 5.39 (t, 1 H), 3.81 (d, 1 H, J = 10.9 Hz), 3.22 (q, 2 H), 2.3-2.2 (m, 1 H), 2.08-1.21 (13 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 439 ($M^+ + 1 - H_2O$, 10), 347 (50), 143 (20), 123 (15), 93 (70), 75 (100); $[\alpha]^{20}_D$ +23.9° (c 0.66, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.83; H, 9.55.

[4(*R*)-[1β,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2a, n = 2): white powder, 64% from **13a**; mp 121-123 °C; ^{1}H NMR (300 MHz) δ 5.63 (m, 1 H), 5.38 (t, 1 H), 3.62 (d, 1 H, J = 10.9 Hz), 2.76-2.60 (m, 4 H), 2.29-2.19 (m, 1 H), 2.07-1.21 (33 H), 0.88 (t, 3 H); IR (KBr) 3600-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 25), 365 (60), 347 (40), 193 (20), 143 (25), 123 (50), 107 (70), 89 (100), 73 (50); $[\alpha]^{20}_D$ +32.0° (c 0.95, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}O_5S$: C, 66.34; H, 9.85. Found: C, 66.15; H, 9.75.

[4(*S*)-[1β,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2b, n = 1): clear oil, 63% from **12b**; ^{1}H NMR (300 MHz) δ 5.68 (m, 1 H), 5.36 (t, 1 H), 3.82 (d, 1 H, J = 11 Hz), 3.22 (q, 2 H), 2.25 (m, 1 H), 2.09-1.12 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 457 ($M^+ + 1$, 10), 439 (70), 375 (25), 365 (40), 347 (100), 239 (10), 143 (15), 93 (30), 75 (45); $[\alpha]^{20}_D$ -11.5° (c 1.42, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.83; H, 9.55.

[4(*S*)-[1β,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2b, n = 2): white powder, 89% from **13b**; mp 122-123 °C; ^{1}H NMR (300 MHz) δ 5.63 (m, 1 H), 5.39 (t, 1 H), 3.62 (d, 1 H, J = 10.9 Hz), 2.75-2.60 (m, 4 H), 2.29-2.20 (m, 1 H), 2.07-1.22 (33 H), 0.88 (t, 3 H); IR (KBr) 3400-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 30), 347 (60), 239 (25), 193 (30), 143 (50), 125 (40), 107 (60), 89 (100); $[\alpha]^{20}_D$ -38.1° (c 0.89, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}O_5S$: C, 66.34; H, 9.85. Found: C, 66.19; H, 9.76.

[4(*R*)-[1α,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2c, n = 1): clear oil, 60% form **12c**; ^{1}H NMR (300 MHz) δ 5.73 (m, 1 H), 5.42 (t, 1 H), 4.26 (d, 1 H, J = 11 Hz), 3.17 (q, 2 H), 2.44 (m, 1 H), 2.11-1.18 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 439 ($M^+ + 1 - H_2O$, 75), 365 (25), 347 (100), 314 (15), 143 (25), 125 (10), 93 (10), 83 (20), 75 (15); $[\alpha]^{20}_D$ +3.3° (c 0.73, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.51; H, 9.74.

[4(*R*)-[1α,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2c, n = 2): clear oil, 77% from **13c**; ^{1}H NMR (300 MHz) δ 5.66 (m, 1 H), 5.41 (t, 1 H), 3.75 (d, 1 H, J = 10.7 Hz), 2.75-2.59 (m, 5 H), 2.08-1.26 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 25), 365 (20), 347 (20), 143 (30), 125 (15), 107 (25), 89 (100), 75 (40); $[\alpha]^{20}_D$ +34.8° (c 0.81, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}O_5S$: C, 66.34; H, 9.85. Found: C, 66.44; H, 9.96.

[4(*S*)-[1α,4β,4(*Z*)]]-4-[1-[(Carboxymethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2d, n = 1): clear oil, 25% from **12d**; ^{1}H NMR (300 MHz) δ 5.72 (m, 1 H), 5.49 (t, 1 H), 4.26 (d, 1 H, J = 11 Hz), 3.16 (m, 2 H), 2.50-2.40 (m, 1 H), 2.30-1.17 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 439 ($M^+ + 1 - H_2O$, 30), 365 (20), 347 (100), 314 (20), 143 (40), 125 (20), 107 (10), 93 (40), 75 (50); $[\alpha]^{20}_D$ -11.8° (c 0.97, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}O_5S$: C, 65.75; H, 9.71. Found: C, 65.99; H, 9.72.

[4(*S*)-[1α,4β,4(*Z*)]]-4-[1-[(2-Carboxyethyl)thio]-2-hexadecenyl]-4-hydroxycyclohexanecarboxylic acid (2d, n = 2): clear oil, 38% from **13d**; ^{1}H NMR (300 MHz) δ 5.63 (m, 1 H), 5.42 (t, 1 H), 3.76 (d, 1 H, J = 10.9 Hz), 2.75-2.58 (m, 5 H), 2.09-1.22 (33 H), 0.88 (t, 3 H); IR (neat) 3600-2400, 1700 cm^{-1}; MS m/z 453 ($M^+ + 1 - H_2O$, 30) 365 (20), 347 (40), 239 (15), 193 (15), 143 (20), 125 (15), 107 (20), 89 (100), 75 (20); $[\alpha]^{20}_D$ -41.5° (c 1.26, $CHCl_3$). Anal. Calcd for $C_{26}H_{46}OS$: C, 66.34; H, 9.85. Found: C, 66.47; H, 9.85.

Acknowledgment. We wish to thank Bob Barbuch and Dr. Michael R. Whalon of the MDRI Analytical Department for spectral data and Dr. Jack Martin for helpful discussions.

Supplementary Material Available: X-ray data for compound **9b** and ^{1}H NMR spectra of all new compounds (53 pages); structure factor tables (4 pages). Ordering information is given on any current masthead page.

Intramolecular Ullmann Condensation Reaction: An Effective Approach to Macrocyclic Diaryl Ethers

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The demonstration and definition of the scope of the intramolecular Ullmann condensation reaction suitable for use in macrocyclization reactions leading to 14-membered para- and metacyclophanes possessing a diaryl ether are detailed.

Bouvardin (1, NCS 259968) and deoxybouvardin (2), bicyclic hexapeptides isolated initially from *Bouvardia ternifolia* (Rubiacea) and unambiguously identified by single-crystal X-ray structure analysis (bouvardin) and chemical correlation (deoxybouvardin),[1] constitute the initial members of a class of potent antitumor antibiotics now including 1-8.[1-7] The unusual 14-membered para- and metacyclophane of the naturally occurring agents has been suggested to arise from the oxidative coupling of two adjacent L-tyrosine residues in cyclic hexapeptide precursors, although the direct incorporation of naturally derived isodityrosine (9)[8] has not been excluded. Related isodityrosine-derived 17-membered and 14-membered diaryl ether structural subunits have been found in a number of additional naturally occurring agents now in-

(1) 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.

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

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

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

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

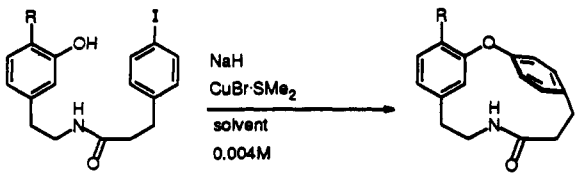
(6) Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann* **1984**, *75*, 929.

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

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

0022-3263/91/1956-1763$02.50/0

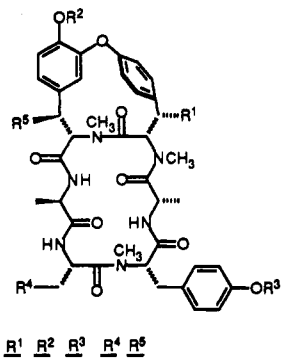
Table I



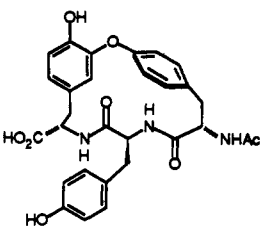
entry		R	NaH (equiv)	CuBr·SMe$_2$[a] (equiv)	Solvent	Time[b]		Yield (RSM)[c]
1	**18a**	H	2.0	1.4	pyridine	18h	**19a**	12%
2	**18a**	H	2.0	2	pyridine	18h	**19a**	58%
3	**18a**	H	2.0	10	pyridine	18h	**19a**	58%
4	**18a**	H	2.0	10	pyridine	3h	**19a**	23%
5	**18a**	H	2.0	10	pyridine	9h	**19a**	61%
6	**18a**	H	2.0	10	pyridine	18h	**19a**	58%
7	**18a**	H	2.0	10	pyridine	36h	**19a**	19%
8	**18a**	H	2.0	10	DMSO	18h	**19a**	0% (94%)
9	**18a**	H	2.0	10	DMF	18h	**19a**	0% (66%)
10	**18a**	H	2.0	10	chlorobenzene	18h	**19a**	trace (91%)
11	**18a**	H	2.0	10	diglyme	18h	**19a**	5% (85%)
12	**18a**	H	2.0	10	nitrobenzene	18h	**19a**	33% (21%)
13	**18a**	H	2.0	10	dioxane	18h	**19a**	51% (24%)
14	**18c**	OCH_3	2.0	10	collidine	9h	**19c**	58% (16%)

[a] Attempts to employ CuO (K_2CO_3, CuO, pyridine, 130 °C) afforded no evidence of cyclic product. [b] All reactions were conducted at 130 °C (bath) temperature except entry 13 (dioxane), which was conducted at 115 °C (bath) temperature. [c] All yields are based on product isolated by chromatography (SiO_2); RSM = recovered starting material.

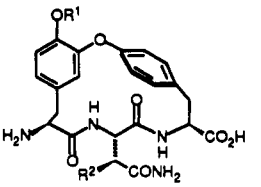
cluding K-13 (10),[9] OF4949-I–OF4949-IV (11–14),[10] and piperazinomycin (15).[11]



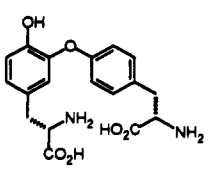
	R^1	R^2	R^3	R^4	R^5	
1	OH	H	CH_3	H	H	bouvardin
2	H	H	CH_3	H	H	deoxybouvardin, (RA-V)
3	H	H	CH_3	OH	H	RA-I
4	H	CH_3	H	H	H	RA-II
5	H	CH_3	CH_3	OH	H	RA-III
6	H	CH_3	CH_3	H	OH	RA-IV
7	OH	CH_3	CH_3	H	H	O-methyl bouvardin, (RA-VI)
8	H	CH_3	CH_3	H	H	O-methyl deoxybouvardin, (RA-VII)



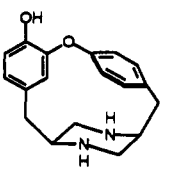
10 K-13



	R^1	R^2	
11	CH_3	OH	OF4949-I
12	H	OH	OF4949-II
13	CH_3	H	OF4949-III
14	H	H	OF4949-IV



9 Isodityrosine



15 piperazinomycin

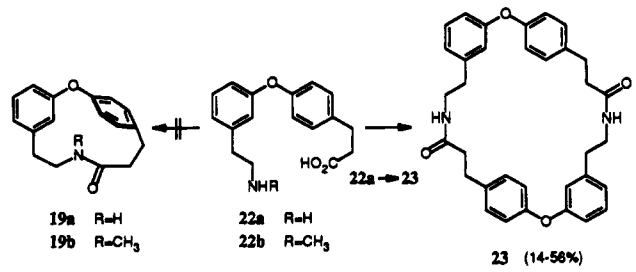
(9) K-13 structure determination: Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455. K-13 fermentation, isolation, and biological properties: Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450.

Synthetic efforts on **1–8** have been characterized by the failure of conventional macrolactamization techniques[12] and direct cyclization procedures for diaryl ether formation (intramolecular Ullmann condensation reaction or oxidative phenol coupling) to provide the elusive 14-membered ring.[13,14] Consequently, an indirect thallium trinitrate promoted two-step method for achieving the intramolecular phenol coupling has been introduced by Yamamura and co-workers[15–17] and applied in the total syntheses of deoxybouvardin (**2**) and RA-VII (**8**) albeit in modest yields (2.2% and 5% respectively).[18,19] In the course of synthetic studies on deoxybouvardin and structurally related agents including K-13[20] and OF4949-III–OF4949-IV,[21,22] we have examined a number of approaches to macrocyclization for formation of the key 14-membered isodityrosine-derived cyclophane subunit.[12] In contrast to earlier reports,[14,15] herein we detail successful studies on the implementation of an intramolecular Ullmann condensation reaction[23] for closure of 14-membered diaryl ethers that have proven

(10) OF4949-I–OF4949-IV structure elucidation: Saño, 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.

(11) Piperazinomycin fermentation, isolation, characterization, and biological properties: Tamai, S.; Kaneda, M.; Nakamura, S. *J. Antibiot.* **1982**, *35*, 1130. Piperazinomycin X-ray structure determination: Kaneda, M.; Tamai, S.; Nakamura, S.; Hirata, T.; Kushi, Y.; Suga, T. *J. Antibiot.* **1982**, *35*, 1137.

(12) Initial and repeated efforts to close **22** to the 14-membered macrocycle **19** employing a range of macrolactamization techniques (DPPA, $NaHCO_3$, DMF, 0 °C, 72 h, 0.08 M; active (C_6F_5O) ester, pyridine, 90 °C, 12 h, 0.0003 M; EDCI, HOBt, DMF, 0 °C, 72 h, 0.02 M; DCC, pyridine, 25 °C, 12 h, 0.02 M) including polymer-supported reagents (Insoluble polymeric carbodiimide: Weinshenker, N. M.; Chen, C.-M. *Tetrahedron Lett.* **1972**, *32*, 3281. Polymer-supported aryl sulfonyl chlorides: Patchornik, A. *Nouv. J. Chim.* **1982**, 639) failed to provide **19** and provided **23** (14–56%) as the only cyclization product. For **23**: ^1H NMR (pyridine-d_5, 300 MHz, ppm) 8.48 (bs, 2 H, NH), 7.50–6.88 (m, 16 H, ArH), 3.55 (dd, 4 H, J = 6.8, 12.9 Hz, CH_2NH), 3.05 (t, 4 H, J = 6 Hz, CH_2Ar), 2.75 (t, 4 H, J = 6.8 Hz, CH_2Ar), 2.55 (t, 4 H, J = 6.4 Hz, CH_2CON); IR (neat) ν_{max} 3338, 3055, 2956, 2931, 2868, 1642, 1605, 1586, 1538, 1508, 1485, 1442, 1420, 1359, 1253, 1218, 1173, 1142, 1109, 1077, 1049, 1014, 969, 911, 830 cm^{-1}; EIMS, m/e 534 (M^+, 5), 267 (base), 223 (13), 167 (4); CIMS (isobutane), m/e (relative intensity) 535 (M^+ + H, 33), 534 (M^+, base).



19a R=H
19b R=CH_3

22a R=H
22b R=CH_3

23 (14-56%)

(13) Bates, R. B.; Gin, G. L.; Hassen, M. A.; Hruby, V. J.; Janda, K. D.; Kriek, G. R.; Michaud, J.-P.; Vine, D. B. *Heterocycles* **1985**, *22*, 785. See also: Bates, R. B.; Janda, K. D. *J. Org. Chem.* **1982**, *47*, 4374.

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

(15) Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481.

(16) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559.

(17) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 379.

(18) Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957.

(19) Itokawa, H.; Inoue, T.; Umezawa, I.; Yuasa, M.; Inaba, T. Jpn. Pat. 63 05,0098; *Chem. Abstr.* **1989**, *110*, 213344s.

(20) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498.

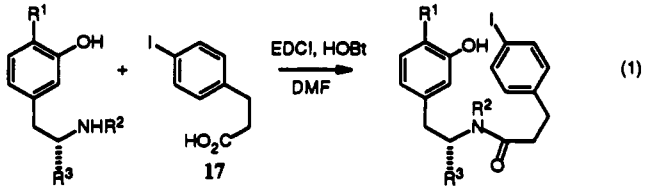
(21) Boger, D. L.; Yohannes, D. *Tetrahedron Lett.* **1989**, *30*, 5061.

(22) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *54*, 6000.

(23) Moroz, A. A.; Shvartsberg, M. S. *Russ. Chem. Rev.* **1974**, *43*, 679. See also: Bird, C. W.; Singh, M. *Chem. Ind. (London)* **1974**, 749.

inaccessible[12-14] or less accessible[18,19] by the alternative routes.

Intramolecular Ullmann Condensation. Substrates for use in the study of the intramolecular Ullmann condensation were prepared as detailed in eq 1 (1–1.1 equiv of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 1.0 equiv of 1-hydroxybenzotriazole (HOBt), 0.3 M in DMF).[24] Initial studies con-



(1)

	R^1	R^2	R^3	
16a	H	H	H	**18a**
16b	H	CH_3	H	**18b**
16c	OCH_3	H	H	**18c**
16d	OCH_3	CH_3	H	**18d**
16e	OH	H	CO_2CH_3	**18e**
16f	OCH_3	H	CO_2CH_3	**18f**

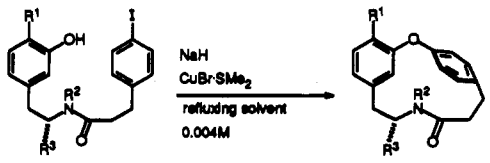
ducted with **18a** are summarized in Table I and include representative results secured in the optimization of the macrocyclization reaction. Reaction conditions requiring 2 equiv of the copper(I) source ($CuBr-SMe_2$) under moderately dilute conditions (0.004 M) provided near-optimal conversions although the presence of a substantial excess of reagent (10 equiv) did not alter the reaction results (Table I, entries 1–3). As with the classical intermolecular Ullmann reaction, pyridine proved to be a satisfactory solvent although sensitive substrates prone to racemization and products sensitive to mild base at elevated temperatures (130 °C) proved sensitive to the reaction conditions and particularly the reaction time (Table I, entries 4–7). In anticipation that the Ullmann condensation reaction enroute to a subunit of deoxybouvardin would suffer competitive racemization when conducted in pyridine,[20,22] alternative nonbasic solvents suitable for use in the reaction were examined (Table I, entries 8–14). Of those examined, dioxane (110 °C) proved to be a suitable nonbasic solvent for conduct of the macrocyclization reaction of **18a**.

In efforts to ensure that the generality of the observations extend to substrates comparable to those required for use in the total synthesis of deoxybouvardin or piperazinomycin, the Ullmann macrocyclization reactions of **18b–f** were examined. Substrates **18c–f** possess an alkoxy *or* hydroxy substituent ortho to the phenol participating in the Ullmann reaction and, as such, constitute rigorous tests of the generality of the potential macrocyclization reaction for formation of the elusive 14-membered para- and metacyclophanes of **1–8**. The results of this study are summarized in Table II and highlight the generality of the observations made with **18a**. Routine macrocyclization conversions in the range of 45–60% were realized with the full range of substrates including those bearing an alkoxy or hydroxy substituent ortho to the participating phenol, and racemization of the optically active substrate **18f** was suppressed with reactions conducted in collidine or dioxane.

Confirmation of the 14-membered cyclic structure of **19b** was established unambiguously in a single-crystal X-ray structure determination (Figure 1).[25] In contrast to

(24) Experimental details for the preparation of **18a–f** and their spectroscopic/physical characterization are provided in supplementary material.

Table II



	R^1	R^2	R^3	NaH (equiv)	CuBr·SMe_2 (equiv)	Solvent[a]	Time		Yield (RSM)[b]	S:R[c]
18a	H	H	H	2.0	10	pyridine	18h	**19a**	58% (20%)	-
18a	H	H	H	2.0	10	dioxane	18h	**19a**	51% (24%)	-
18b	H	CH_3	H	1.2	10	pyridine	18h	**19b**	49% (36%)	-
18c	OCH_3	H	H	2.0	10	pyridine	18h	**19c**	46% (29%)	-
18d	OCH_3	CH_3	H	1.2	10	pyridine	18h	**19d**	45% (22%)	-
18e	OH	H	CO_2CH_3	2.0	10	pyridine	9h	**19e**	51% (20%)	nd
18f	OCH_3	H	CO_2CH_3	2.0	10	pyridine	9h	**19f**	51% (8%)	55:45
18f	OCH_3	H	CO_2CH_3	2.0	10	dioxane	9h	**19f**	31% (17%)	96:4
18f	OCH_3	H	CO_2CH_3	2.0	10	collidine	9h	**19f**	50% (12%)	93:7

[a] Reaction temperatures: pyridine, 130 °C (bath); collidine, 185 °C (bath); dioxane, 115 °C (bath). [b] All yields are based on product isolated by chromatography (SiO_2); RSM = recovered starting material. [c] Ratio of *S* to *R* enantiomers; nd = not determined.

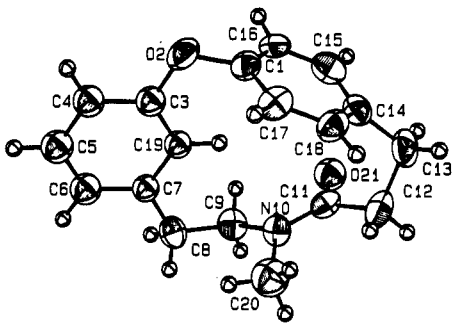


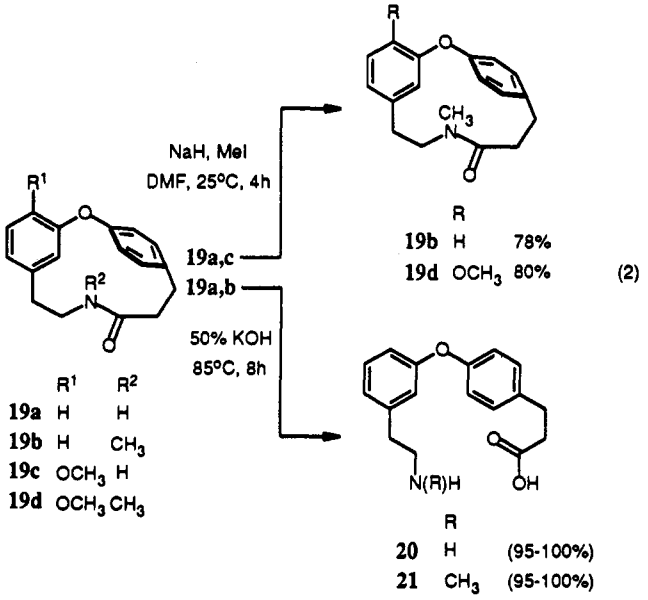
Figure 1. ORTEP of the X-ray crystal structure of **19b**.

bouvardin (**1**) and deoxybouvardin (**2**), which possess a $C^{11}-N^{10}$ cis *N*-methylamide bond in the 14-membered cyclic isodityrosine subunit,[1] **19b** possesses the $C^{11}-N^{10}$ trans *N*-methylamide.[26] Like **1** and **15**,[11] the meta-substituted aryl ring of **19b** is undistorted while the para-substituted aryl ring is slightly distorted with the substituted carbons of the puckered aryl ring lying out of the plane defined by the central four carbons of the ring. Comparable to that detailed for piperazinomycin,[11] C-1 and C-14 deviate in the same direction from the plane defined by the central four atoms (C-15, C-16, C-17, C-18) by 0.10 and 0.08 Å, respectively, and O-2 and C-13 deviate from

(25) The single-crystal X-ray structure determination of **19b** (supplementary material) was conducted by Dr. P. Fanwick of the Purdue University X-ray crystallography facility.

(26) Conformational searches of **19a** and **19b** revealed a total of three available conformations within 5 kcal of the lowest energy conformation for **19a** and a total of four conformations for **19b**. In both cases, the lowest energy conformation contains the trans amide bond and calculation of the relative population (Boltzman distribution) among the available conformations revealed that trans amide stereochemistry would be expected to be exclusively populated (>99%, 25 °C) in each case. The cis amide stereochemistry is observed at 4.7 kcal higher energy from the lowest energy conformation for **19a** and at 3.0 kcal above the lowest energy conformation for **19b**. The lowest energy conformation for **19b** corresponds with the conformation found in the X-ray crystal structure for **19b** (comparison of the ring atoms of the X-ray structure of **19b** with the lowest energy conformation for **19b** revealed an RMS deviation of 0.17 Å). Global minima and close, low-lying minima (≤5 kcal) were located by use of directed Monte Carlo sampling of two starting conformations (cis and trans amides) for **19a** and **19b** each (MacroModel, Version 2.5, OPLSA force field, MCMM = 500, MCSS = 2) generated by random variations (0–180°) in two to four of the available tortional angles excluding those originating in the aryl rings. See: Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. The global minima were located 89 times (**19a**) and 74 times (**19b**).

this plane by 0.42 and 0.52 Å, respectively. Despite this aryl deformation, the amide bond of **19** proved surprisingly stable to cleavage,[27] and pertinent to synthetic endeavors on the natural products **1–8**, the secondary amides of **19a** and **19c** could be N-methylated under appropriate conditions[28] to provide **19b** and **19d** without event (eq 2).



(2)

Thus, in contrast to the related efforts in which the intramolecular Ullmann condensation reaction of substrates bearing a 3-iodotyrosine has proven unsuccessful,[13,14,29] presumably due to the decelerating effect of the *o*-alkoxy group on the aryl iodide partner of the Ullmann reaction, the macrocyclization reaction of **18a–f** with 14-membered ring formation has proven synthetically useful and applicable with substrates bearing an alkoxy or hydroxy substituent ortho to the participating phenol. Application of these observations in the total syntheses of **1–8** and piperazinomycin are in progress and will be reported in due course.

Experimental[30] Section

General Procedure for the Preparation of Cyclic Ethers. 11-Oxo-2-oxa-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene (19a). A solution of **18a** (80 mg, 0.20 mmol) in 1 mL of freshly distilled pyridine was added to a suspension of sodium hydride (60% dispersion in mineral oil, 18 mg, 0.44 mmol, 2.3 equiv) in 1 mL of freshly distilled pyridine at 0 °C. Cuprous bromide–dimethyl sulfide complex (0.580 g, 2.05 mmol, 10.0 equiv) was added, and the reaction mixture was stirred at 24 °C (0.5 h). Pyridine was added (48 mL), and the reaction mixture was warmed at reflux (125 °C bath temperature; 18 h). The cooled reaction mixture was concentrated in vacuo to a volume of 5 mL, poured onto ethyl acetate (15 mL), and washed with saturated aqueous ammonium chloride (3 × 15 mL), 10% aqueous hydrochloric acid (3 × 15 mL), and saturated aqueous sodium chloride (30 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 10 cm, Et_2O) afforded **19a** (32 mg, 55 mg theoretical yield, 58%) as a fine, crystalline solid: mp 191–193 °C (EtOH–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.31–7.26 (m, 2 H, Ar-H), 7.14 (t, 1 H, J = 7.8 Hz, C5-H), 7.04–6.95 (m, 3 H, Ar-H), 6.64 (bd, 1 H, J = 7.4 Hz, C6-H), 5.11 (d, 1 H, J = 1.7 Hz, C19-H), 4.89 (bs, 1 H, NH), 3.33 (dt, 2 H, J = 4.2, 10 Hz, CH_2), 3.06 (t, 2 H, J = 6 Hz, CH_2Ar), 2.74 (t, 2 H, J = 5 Hz, CH_2Ar), 2.32 (t, 2 H, J = 6 Hz); APT ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 171.7 (e, C=O), 163.7 (e), 156.9 (e), 140.8 (e), 138.7 (e), 131.0 (o), 129.2 (o), 124.9 (o), 121.4 (o), 114.1 (o), 41.4 (e), 39.8 (e), 32.2 (e), 31.3 (e); IR (KBr) ν_{max} 3568, 2926, 1636, 1618, 1576, 1560, 1542, 1522, 1508, 1498, 1490, 1474, 1458, 1438, 1420, 1398 cm^{-1}; EIMS, m/e (relative intensity) 267 (M^+, base), 222 (23), 209 (66), 196 (74), 181 (6), 167 (14), 153 (15); CIMS (isobutane), m/e 268 (M^+ + H, base); EIHRMS, m/e 267.1252 ($C_{17}H_{17}NO_2$ requires 267.1259). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 73.88; H, 6.52; N, 5.07. Found: C, 73.78; H, 6.54; N, 5.05.

10-Methyl-11-oxo-2-oxa-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (19b): mp 167–174 °C (EtOH–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.34–7.27 (m, 2 H, Ar-H), 7.14 (t, 1 H, J = 8 Hz, C5-H), 7.05–6.95 (m, 3 H, Ar-H), 6.65 (bd, 1 H, J = 7.4 Hz, C6-H), 4.83 (d, 1 H, J = 1.7 Hz, C19-H), 4.19 (ddd, 1 H, J = 1, 13.2, 14.8 Hz, CH*H*N), 3.33–2.28 (m, 6 H, 3 CH_2), 2.66 (s, 3 H, NCH_3); APT ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 172.9 (e, C=O), 163.9 (e), 156.4 (e), 141.0 (e), 138.8 (e), 132.9 (o), 131.0 (o), 129.7 (o), 128.9 (o), 123.9 (o), 121.4 (o), 114.0 (o), 113.4 (o), 43.7 (e), 35.6 (e), 32.1 (e), 32.0 (o), 29.4 (e); IR (KBr) ν_{max} 3650, 3300, 3000, 2926, 1700, 1636, 1560, 1542, 1522, 1508, 1490, 1474, 1458, 1398, 1210 cm^{-1}.

The structure of **19b** was unambiguously established in a single-crystal X-ray structure determination.[25]

4-Methoxy-11-oxo-2-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene (19c): mp 92–95 °C (EtOH–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.28 (d, 2 H, J = 8 Hz, C15-H and C18-H), 7.06 (d, 2 H, J = 8 Hz, C16-H and C17-H), 6.77 (d, 1 H, J = 8 Hz, C5-H), 6.58 (dd, 1 H, J = 2, 8 Hz, C6-H), 5.07 (d, 1 H, J = 2 Hz, C19-H), 4.86 (bs, 1 H, NH), 3.94 (s, 3 H, OCH_3), 3.28 (dt, 2 H, J = 4, 10 Hz, CH_2CH_2NH), 3.04 (t, 2 H, J = 6 Hz, CH_2Ar), 2.65 (t, 2 H, J = 5.5 Hz, CH_2Ar), 2.30 (t, 2 H, J = 6 Hz, CH_2CO); APT ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 171.7 (e, C=O), 156.9 (e), 152.7 (e), 146.5 (e), 138.7 (e), 132.2 (e), 131.0 (o), 125.0 (o), 121.3 (o), 114.8 (o), 111.9 (o), 56.4 (o), 41.5 (e), 40.3 (e), 32.3 (e), 30.9 (e); IR (KBr) ν_{max} 3632, 3280, 2928, 1638, 1586, 1514, 1460, 1438, 1264, 1210, 1128, 1028, 886, 832, 800, 730 cm^{-1}; EIMS, m/e (relative intensity) 297 (M^+, base), 252 (12), 239 (67), 225 (18), 211 (33), 150 (19); CIMS (isobutane), m/e (relative intensity) 298 (M^+ + H, base); EIHRMS, m/e 297.1366 ($C_{18}H_{19}NO_3$ requires 297.1365).

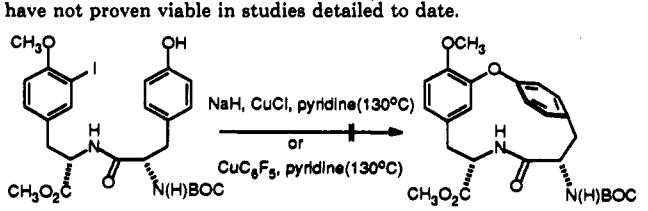
4-Methoxy-10-methyl-11-oxo-2-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (19d): mp 115–118 °C (EtOH–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.34–7.25 (m, 2 H, C15-H and C18-H), 6.97–6.94 (m, 2 H, C16-H and C17-H), 6.71 (d, 1 H, J = 8 Hz, C5-H), 6.53 (dd, 1 H, J = 2, 8 Hz, C6-H), 4.75 (d, 1 H, J = 2 Hz, C19-H), 4.07 (ddd, 1 H, J = 3, 14, 15 Hz, CH*H*N), 3.87 (s, 3 H, OCH_3), 3.04–2.28 (m, 6 H, 3 CH_2), 2.57 (s, 3 H, NCH_3); APT ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 172.8 (e, C=O), 156.3 (e), 152.8 (e), 146.3 (e), 138.6 (e), 132.9 (o), 132.3 (e), 129.6 (o), 124.7 (o), 124.0 (o), 121.2 (o), 114.1 (o), 111.9 (o), 56.4 (o), 44.1 (e), 35.7 (e), 32.1 (e), 32.0 (o), 28.6 (e); IR (KBr) ν_{max} 3568, 2926, 1718, 1636, 1508, 1474, 1458, 1264, 1218, 1128 cm^{-1}; EIMS, m/e (relative intensity) 311 (M^+, base), 279 (2), 268 (2), 252 (22), 239 (36); CIMS (isobutane), m/e (relative intensity) 312 (M^+ + H, base); EIHRMS, m/e 311.1519 ($C_{19}H_{22}NO_3$ requires 311.1521).

Methyl 4-hydroxy-11-oxo-2-oxa-10-azatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9-carboxylate (19e): mp 275–277 °C dec (benzene); ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) 7.32 (m, 2 H, C15-H and C18-H), 7.05 (m, 2 H, C16-H and C17-H), 6.79 (d, 1 H, J = 8 Hz, C5-H), 6.52 (dd, 1 H, J = 2, 8

(27) No amide cleavage was observed upon exposure of **19b,d** to 20% NH_3–MeOH (25 °C, 18 h) or 1 M LiOH–MeOH (25 °C, 18 h; 55 °C, 18 h).

(28) Coggins, J. R.; Benoiton, N. L. *Can. J. Chem.* **1971**, *49*, 1968.

(29) The Ullmann closure detailed below (DY) and related systems (Kriek, G. R. Ph.D. Dissertation, University of Arizona, Tucson, AZ, 1980) have not proven viable in studies detailed to date.



(30) General experimental details are provided in supplementary material. HPLC analysis was performed on a Waters Model 501 dual-pump chromatograph equipped with a Waters Model 484 variable-wavelength absorbance detector. Chiral-phase HPLC analysis employing a J. T. Baker Bakerbond DNPG (covalent) chiral column of **19f** revealed the enantiomeric ratios given in Table II; L:D–**19f**, t_R = 4 min/8.7 min, 2.0 mL/min, EtOAc–hexane gradient elution 50:50 to 5:95 over 10 min, 258-nm detection.

Hz, C6-H), 5.55 (bd, 1 H, J = 7 Hz, NH), 5.05 (d, 1 H, J = 1.8 Hz, C19-H), 4.21 (bt, 1 H, J = 15 Hz, CHN), 3.69 (s, 3 H, OCH_3), 3.09–2.01 (m, 6 H, 3 CH_2); IR (KBr) ν_{max} 3304, 1654, 1560, 1508, 1438, 1214, 1116 cm^{-1}; EIMS, m/e (relative *intensity*) 341 (M^+, 83), 309 (base), 282 (67), 265 (71), 253 (10), 240 (29), 226 (28), 212 (45), 197 (10); CIMS (isobutane), m/e (relative intensity) 342 (M^+ + H, base); EIHRMS, m/e 341.1264 ($C_{19}H_{19}NO_5$ requires 342.1263).

Methyl (9*S*)-4-methoxy-11-oxo-2-oxa-10-azatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9-carboxylate (19f): oil; $[\alpha]^{22}_D$ −7.14° (c 0.7, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 7.30 (dd, 1 H, J = 2.2, 8.3 Hz, C16-H or C17-H), 7.23 (dd, 1 H, J = 2.2, 8.2 Hz, C16-H or C17-H), 7.08 (dd, 1 H, J = 2.4, 8.3 Hz, C15-H or C18-H), 6.99 (dd, 1 H, J = 2.3, 8.2 Hz, C15-H or C18-H), 6.77 (d, 1 H, J = 8.3 Hz, C5-H), 6.58 (dd, 1 H, J = 2.1, 8.2 Hz, C6-H), 5.51 (d, 1 H, J = 7.2 Hz, NH), 5.08 (d, 1 H, J = 2.0 Hz, C19-H), 4.19 (ddd, 1 H, J = 1.5, 7.3, 10 Hz, C9-H), 3.94 (s, 3 H, $ArOCH_3$), 3.70 (s, 3 H, CO_2CH_3), 3.06–2.04 (m, 6 H, 3 CH_2); APT ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 172.7 (e), 172.2 (e), 156.9 (e), 152.8 (e), 146.9 (e), 138.5 (e), 132.4 (o), 130.0 (e), 129.9 (o), 124.9 (o), 124.8 (o), 121.4 (o), 114.8 (o), 111.9 (o), 56.3 (o), 53.9 (o), 52.7 (o), 41.0 (e), 34.7 (e), 32.1 (e); IR (neat) ν_{max} 3360, 3270, 1718, 1654, 1560, 1542, 1508, 1458, 1266, 1206, 1130 cm^{-1}; EIMS, m/e (relative intensity) 357 (M^+, 90), 341 (26), 324 (base), 297 (59), 283 (69), 280 (58), 268 (10); CIMS (isobutane), m/e (relative intensity) 358 (M^+ + H, base); EIHRMS, m/e 357.3876 ($C_{20}H_{21}NO_5$ requires 357.3876).

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Supplementary Material Available: Experimental details and full spectroscopic and physical characterization of **18a–f**, ^{1}H NMR spectra of **18a–f** and **19a–f**, and details of the single-crystal X-ray structure determination of **19b** (30 pages). Ordering information is provided on any current masthead page.

Reactions of the Serotonergic Neurotoxin 5,6-Dihydroxytryptamine with Glutathione

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At physiological pH the serotonergic neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) catalyzes the oxidation of the cellular antioxidant glutathione (GSH) by molecular oxygen to give GSSG. At the stage when GSH is depleted, 5,6-DHT is then autoxidized to give first 2,7′-bi(5,6-dihydroxytryptamine) (**2**) and ultimately indolic melanin. In the presence of an excess of GSH and enzymes such as tyrosinase or ceruloplasmin, the oxidation of 5,6-DHT to its corresponding *o*-quinone (**1**) is greatly accelerated. Under such conditions, **1** is attacked by GSH to give 4-*S*-glutathionyl-5,6-dihydroxytryptamine (A), which is further oxidized to the corresponding quinone **4**. Further attack by GSH or A on **4** gives 4,7-diglutathionyl-5,6-dihydroxytryptamine (B) and 4,4′-di-*S*-glutathionyl-2,7′-bi(5,6-dihydroxytryptamine) (C), respectively. Reaction between **4** and B yields 4,7,4′-tri-*S*-glutathionyl-2,7′-bi(5,6-dihydroxytryptamine) (D).

5,6-Dihydroxygtryptamine (5,6-DHT) is a pharmacological tool used in neurobiology for the selective chemical lesioning of serotonergic neurons.[1] The selectivity of 5,6-DHT derives from the transport of the drug into a target neuron by the uptake mechanism normally used for the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). The molecular mechanism(s) by which 5,6-DHT expresses its neurodegenerative effect is still an open question. However, it is widely believed that the neurotoxicity of 5,6-DHT results from an inherent chemical property, namely ease of oxidation by molecular oxygen, i.e., autoxidation. Two principal theories have been advanced to relate the autoxidation of 5,6-DHT to its neurodegenerative activity.[2-9] The first postulates that the autoxidation reaction converts the indolamine into an electrophilic *o*-quinone that alkylates and cross-links neuronal proteins. Such processes would be expected to compromise the normal functions of such proteins, leading to cell death. However, reactions between putative electrophilic intermediates generated upon autoxidation of 5,6-DHT with protein nucleophiles or even with model peptides have never been demonstrated. The second theory proposes that cytotoxic reduced oxygen species such as H_2O_2, $O_2^{\bullet-}$, and $HO^{\bullet}$ are formed as byproducts of autoxidation of 5,6-DHT and attack neuronal lipids and proteins or other susceptible structures.

In recent reports[10,11] we have shown that at physiological pH 5,6-DHT is indeed autoxidized to *o*-quinone **1** with concomitant formation of H_2O_2 as a byproduct (Scheme I). Nucleophilic attack by 5,6-DHT on **1** gives 2,7′-bi-(5,6-dihydroxytryptamine) (**2**), which is the major initial product of the autoxidation reaction. Dimer **2** is autoxidized to diquinone **3** with formation of 2 mol more of H_2O_2. Diquinone **3** can chemically oxidize 5,6-DHT to quinone **1** so that an autocatalytic cycle is established. The

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