Vancomycin and Ristocetin Models: Synthesis via the Ullmann Macrocyclization Reaction

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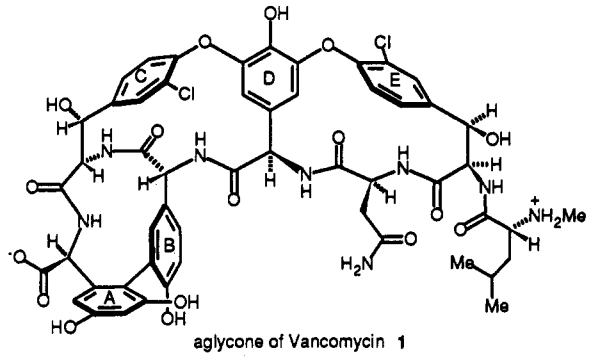
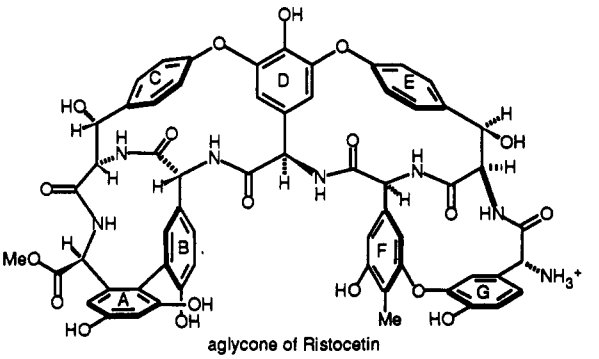
The preparations of **2** and **3**, the parent skeletons of the CD and DE diphenyl ether 16-membered ring systems of vancomycin and ristocetin, based on the implementation of an intramolecular Ullmann macrocyclization reaction are detailed. Additional studies which define the scope of substrates suitable for use in the Ullmann macrocyclization reaction are described including a limited study of those bearing centers capable of racemization. Within the limited series of agents examined, Ullmann macrocyclization closure of the DE ring system was found to occur at a faster rate and in higher overall yields than those providing the CD ring system. N-Methylation of the amide linking chain decelerates or inhibits Ullmann macrocyclization and α-substitution of the central amino acid of the linking chain significantly *increases* the cyclization conversions. Racemization of the central amino acid of the linking amide chain was found to be minimal (5%) under reaction conditions where the secondary amides are deliberately deprotonated prior to exposure of the substrate to the thermal, basic reaction conditions.

Vancomycin (**1**)[2] represents the most widely recognized member of a family of clinically effective glycopeptide antibiotics[3] including ristocetin, β-avoparcin, and teicoplanin that express their properties through inhibition of bacterial cell wall biosynthesis by selectively binding to mucopeptides terminating in the sequence D-Ala-D-Ala.[4] Consequently, the binding affinity and selectivity of such agents with D-Ala-D-Ala and related dipeptides have been the subject of extensive investigation.[5,6] However, due to the structural complexity of the agents and the inherent difficulty associated with the preparation of the dipeptide binding pocket composed of the CD and DE 16-membered rings, most studies to date have been constrained to the natural products and their chemical derivatives.[5] The exception is the recent study of Hamilton using the model agent **4**.[6]

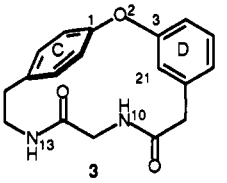
Deceptively simple efforts to prepare the characteristic 16-membered macrocyclic ring through amide bond closure have been unsuccessful[7,8] or found to proceed in very modest conversions[6,9] (<10%), Scheme I. More successful have been the efforts to effect macrocyclization through use of a two-step, thallium trinitrate promoted oxidative



aglycone of Vancomycin **1**



aglycone of Ristocetin



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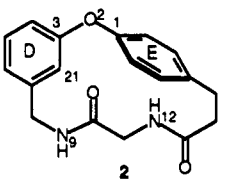

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(1) On sabbatical leave (1991–1992) from Kyowa Hakko Kogyo Co., Ltd., Japan.

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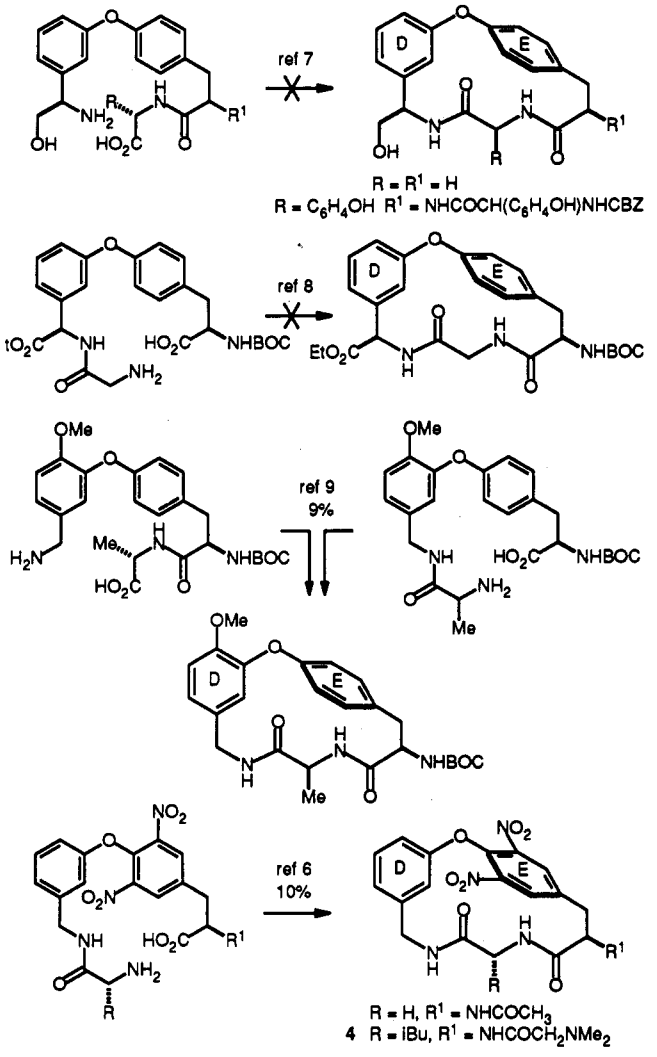
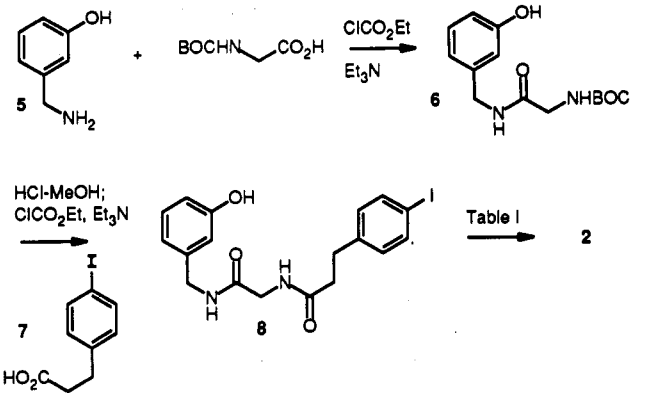
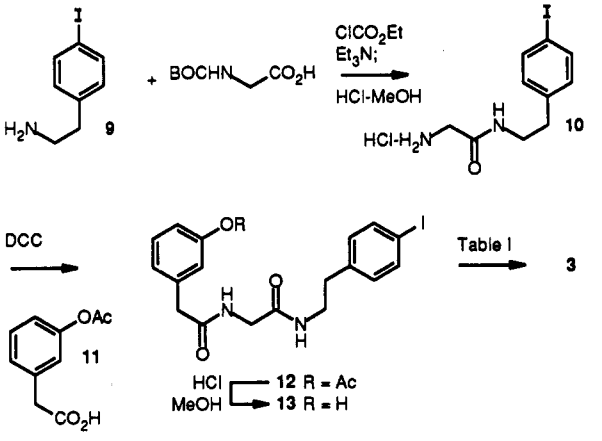
Scheme I



Scheme II



Scheme III



cyclization[10] of dibromo-/dichlorophenols with formation of the key diphenyl ether.[11,12] As a consequence of our disclosure of an intramolecular Ullmann macrocyclization reaction[13] effective in forming refractory 14-membered and 15-membered cyclic diphenyl ethers including those found in RA-VII, deoxybouvardin,[14,15] and combretastatin D2,[16] we have extended the investigations to the study of the vancomycin and ristocetin 16-membered ring system. Through use of such an approach, it is anticipated that simplified vancomycin or ristocetin models[17] may be made available from readily accessible starting materials without recourse to the use of dibromo- or dichlorophenol coupling partners.[11,12] This may prove especially appropriate for ristocetin which lacks the aryl halogen substitution characteristic of vancomycin. Herein we detail the synthesis of **2** and **3**, constituting the parent skeletons of the CD and DE 16-membered ring systems of vancomycin and ristocetin, based on the implementation of the intramolecular Ullmann macrocyclization reaction[13-16] which establishes the viability of the approach. Additional studies which define the scope of substrates suitable for use in the Ullmann macrocyclization reaction are described along with the empirical observation that closure of the DE ring system occurs at a faster rate and in higher conversions than does the corresponding CD ring system.

Ullmann Macrocyclization Reaction To Prepare 2 and 3. The appropriately substituted substrates **8** and **13** for study of the Ullmann macrocyclization reaction to provide **2** and **3** were prepared in a straightforward fashion as illustrated in Schemes II and III.

Ullmann macrocyclization of **8** to provide **2** was examined under a range of experimental conditions, Table I. Modest conversions of 15–20% were obtained by employing NaH or K_2CO_3 with CuBr–SMe_2 as the source of Cu(I) in pyridine at 130 °C under the dilute reaction conditions of 0.004 M. Significant improvements were observed with the use of methylcopper[16] (3 equiv) to generate the initial cuprous phenoxide and yields of 35–40% of **2** were routinely obtained in the Ullmann macrocyclization reaction (6 h, 130 °C, 0.004 M pyridine). As in past studies, the conversion of **8** to **2** was found to be temporally sensitive and shorter or longer reaction times led to diminished conversions, indicating that **2** is not fully stable to the reaction conditions. Unlike substrates employed in our prior studies of the Ullmann macrocyclization reaction, the chain linking the aryl iodide and

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Table I. Representative Results of a Study of the Ullmann Macrocyclization Reactions for Formation of 2 and 3

entry	Cu(I) source (equiv)	solvent	temp (°C), time (h)	product (% yield)
1	MeCu (3)	pyridine	130, 6	2, 40
2	MeCu (3)	pyridine	130, 9	2, 32–35
3	MeCu (3)	pyridine	130, 5	2, 35[a]
4	NaH (3), CuBr–SMe_2 (10)	pyridine	130, 9	2, 15[b]
5	NaH (3), CuBr–SMe_2 (3)	pyridine	130, 18	2, 18[b]
6	K_2CO_3 (5), CuBr–SMe_2 (10)	pyridine	130, 19	2, 17[b]
7	NaH (3), CuI–$(SBu_2)_2$ (10)	pyridine	130, 20	2, trace
8	NaH (3), CuBr–SMe_2 (10)	pyridine	95, 19	2, 0[b,c]
9	MeCu (3)	dioxane–pyridine (24:1)	110, 20	2, no reaction
10	MeCu (3)	pyridine	130, 9	3, 31
11	MeCu (3)	pyridine	130, 12	3, 23
12	MeCu (3)	pyridine	130, 6	3, 23[a]
13	MeCu (3)	pyridine	130, 5	3, 13[a]

[a] Starting material present or recovered. [b] p-$IC_6H_4CH_2CH_2CONH_2$ isolated as major product. [c] Run at 0.1 M.

phenol of 8 possesses the capabilities for intramolecular O- and N-acylation prior to cyclization which may lead to cleavage of the linking amides. The low yields encountered with the use of NaH or K_2CO_3/CuBr–SMe_2 may reflect this competitive cleavage reaction under basic reaction conditions. Macrocyclization with 16-membered ring formation was established by the characteristic appearance of the shielded H-21 aromatic proton signal in the ^1H NMR at 5.82 ppm (DMSO-d_6) and further supported by 2D ^1H–^1H NOESY NMR which exhibited diagnostic NOE crosspeaks for H-19 and H-18/H-21, H-17 and H-20/H-21, H-9/H-21, H-8/H-21, H-9/H-11, H-6/H-8, H-12/H-14, H-14/H-17 and H-20, and H-15/H-17 and H-20. Confirmation of the structure 2 was derived from the mass spectrum which exhibited the expected m/e 443.0389 for the monomeric macrocyclic 16-membered ring.

Extension of these observations to the cyclization of 13 to provide 3 proved straightforward with the exception that complete cyclization required longer reaction times. Optimal conversions for this slower cyclization reaction were observed after 9 h (3 equiv of MeCu, 130 °C, 0.004 M pyridine, 31%), Table I. Macrocyclization to provide 3 was established by the appearance of the shielded H-21 aromatic proton signal in the ^1H NMR at 6.03 ppm (DMSO-d_6), further supported by 2D ^1H–^1H NOESY NMR which exhibited diagnostic NOE crosspeaks for H-10/H-21, H-8/H-21, H-11/H-21, H-17 and H-20/H-21, H-18 and H-19/H-21, H-10/H-8, H-10/H-18 and H-19, H-10/H-17 and H-20, H-13/H-15, H-13/H-11, H-13/H-18 and H-19, H-13/H-17 and H-20, H-15/H-17 and H-20, H-14/H-17 and H-20, H-11/H-17 and H-20, and H-8/H-6, and confirmed with the mass spectrum of 3 which exhibited the expected m/e 443.0377.

Unambiguous confirmation of the 16-membered macrocyclic structures of 2 and 3 was established in single-crystal X-ray structure determinations, Figure 1. Like the DE ring system of vancomycin, 2 was found to possess trans N^9–C^{10} and N^{12}–C^{13} amide bonds. In addition, both the para-substituted and meta-substituted phenyl rings of 2 exhibit little perceptible deformation unlike the diphenyl ether of the related 14-membered macrocyclic systems of bouvardin,[18] piperazinomycin,[19] RA-VII,[20] and their simplified models.[13] For 2, C-1 and C-16 deviate in the same direction from the plane defined by the central four atoms of the para-substituted aryl ring (C-17, C-18, C-19, and C-20) by 0.02 and 0.03 Å, respectively, while O-2 and C-15 deviate from this plane by only 0.12 and 0.12 Å, respectively. Unlike the CD ring system of vancomycin but like 2, 3 was found to possess trans N^{13}–C^{12} and N^{10}–C^9 amide bonds in the X-ray crystal structure. The meta-substituted phenyl ring of 3 showed no deformation resulting from incorporation into the 16-membered macrocyclic ring. The para-substituted phenyl ring exhibited only minor puckering with C-1 and C-16 deviating from the plane defined by the central four atoms of the phenyl ring (C-17, C-18, C-19, and C-20) by 0.03 and 0.02 Å, respectively, and with O-2 and C-15 deviating from this plane by only 0.04 and 0.14 Å, respectively.

Conformational searches revealed a limited number of conformations available within 5–7 kcal/mol of the lowest energy conformations for each 2 and 3, Table II. For 2, like the solution-phase conformation of the DE ring system of vancomycin, each of the four available conformations located was found to possess trans amide bonds. The lowest energy conformation located proved to be substantially more stable than the next available conformation and constitutes the predicted predominant or near exclusive conformation available to the agent. Consistent with this expectation, the lowest energy conformation of 2 located corresponds to the conformation of 2 observed in the X-ray crystal structure (RMS = 0.31 Å for all non-hydrogen atoms; RMS = 0.22 Å for inner ring atoms),[21] Figure 1.

Unlike the solution-phase conformation of the CD ring system of vancomycin which maintains a N^{13}–C^{12} cis amide, the low energy conformation of 3 located in the conformational searches was found to possess two trans amide bonds. The lowest energy conformation proved to be substantially more stable than the next available conformation and consequently constitutes the predicted predominant or near exclusive solution conformation available to the agent, Figure 1. Consistent with this expectation, the lowest energy conformation of 3 located corresponds to the conformation of 3 in the X-ray crystal structure (RMS = 0.28 Å for all non-hydrogen atoms; RMS = 0.18 Å for inner ring atoms, Figure 1). Two conformations 4.5 and 6.3 kcal/mol higher in energy were located that possessed the characteristic vancomycin N^{13}–C^{12} cis amide which, like vancomycin, are directionally oriented under

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(21) The significant distinction in the X-ray crystal structure and the OPLSA low energy conformation for 2 is the pitch of the E ring relative to the plane of the D ring presumably subject to crystal packing forces.

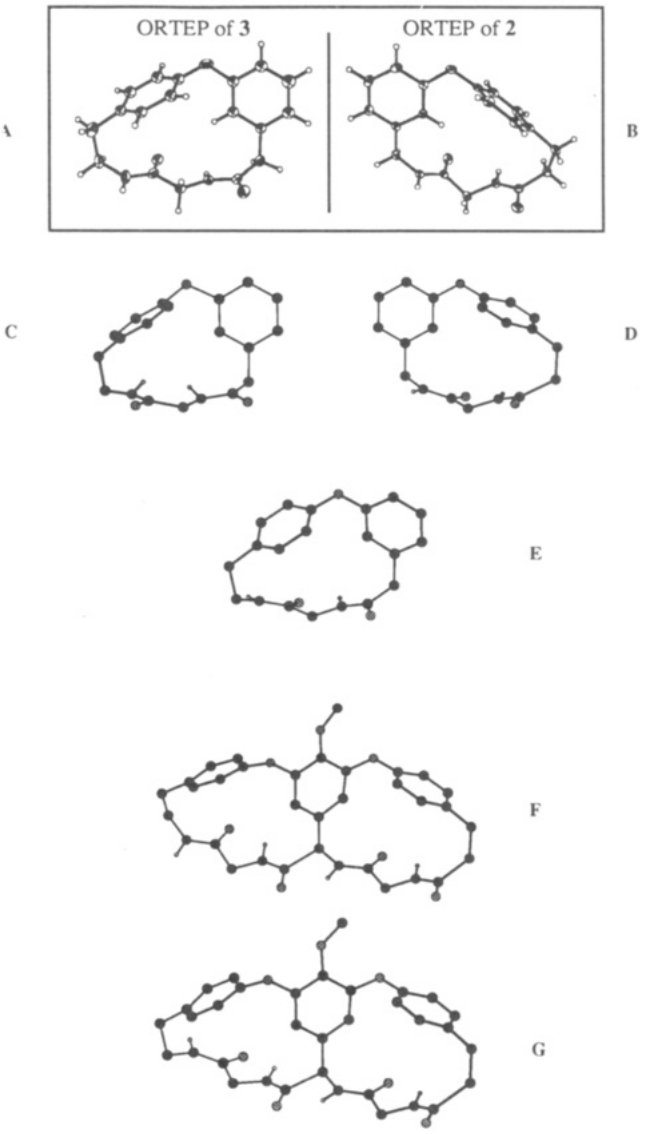
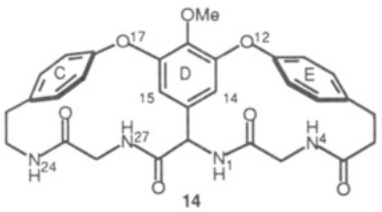


Figure 1. A: ORTEP of X-ray structure of **3**. B: ORTEP of X-ray structure of **2**. C: Conformation 1 of **3**. D: Conformation 1 of **2**. E: Conformation 2 of **3**. F: Conformation 1 of **14**. G: Conformation 9 of **14**.

the aryl C ring, Figure 1. Thus, upon incorporation into vancomycin, the 16-membered CD ring system adopts the inherently disfavored N^{13}–C^{12} cis amide stereochemistry. We attribute this to the influence of the 12-membered vancomycin AB ring system which induces and maintains the inherently disfavored cis amide with forced incorporation into an unusual type-VI β-turn[22] conformation.

Similar observations were made in a conformational search of **14**, Table II. Each of the low lying conformations was found to possess four trans amides and the fusion of the CD and DE ring systems was found to have little effect on the preferred conformational properties of the individual ring systems, Table III. Like **3**, conformations of **14** that possess the cis N^{24}–C^{25} amide characteristic of vancomycin were located only at much higher energies (5.7 and 6.1 kcal), Figure 1. Consequently, the adoption of a disfavored cis N^{24}–C^{25} amide appears to be the consequence of the incorporation into the vancomycin 12-membered AB ring system. Global and low lying minima (≤5–7 kcal) were located in the conformational searches by repetitive use-directed Monte Carlo sampling and subsequent minimization of conformations (MacroModel,[23] Batchmin Version 3.5a, OPLSA force field,[24] MCMM = 1000, MCSS = 2, 7 kcal window) generated by random variations (0–180°) in 8 of the 11 (**2**–**3**) or 15 of 21 (**14**) available tortional angles[25] excluding those originating in the phenyl rings. The global minima were located 23 times (**2**),[26] 960 times (**3**),[26] and 53 times (**14**).



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Scope of Suitable Substrates. In the course of the studies of the Ullmann macrocyclization reactions to provide **2** and **3**, two prominent side reactions were considered as potential limiting features of the reaction. The first side reaction provides products derived from intramolecular N- or O-transacylation within the chain linking the aryl phenol and aryl iodide under the reaction conditions. The second provides products potentially derived from oxidative cleavage of the CH_2–NHCO bonds in the linking amide chain observed on occasion when the Ullmann macrocyclization reaction proved slow. This is observed most prominently when excess CuBr–SMe_2 (10 equiv) in conjunction with NaH (1–3 equiv) was used to generate the cuprous phenoxide and presumably results from in situ oxidation to the imine followed by hydrolytic cleavage of the imine upon workup. An important and third competitive reaction not addressed with substrates **2** and **3** is the potential racemization of substrates and products bearing substituents on the carbon adjacent to the central amide carbonyls. The three independent issues were addressed with the preparation of substrates **15**–**17**, **21**, and **23** and the study of their Ullmann macrocyclization reaction. N-Methylation was anticipated to prevent the base-catalyzed N- or O-transacylation reactions within the linking amide chain as well as diminish or eliminate the potential oxidative cleavage reaction. The effect of N-methylation of the amides in the linking chain was first examined for the macrocyclization reaction providing the vacomycin and ristocetin DE ring system and was addressed with the study of substrates **15**–**17**, Scheme IV. Although this was not examined in exhaustive detail, each of the substrates bearing an *N*-methyl amide exhibited reduced capabilities for Ullmann macrocyclization, Table IV. The two substrates **15** and **16** possessing a N^{12}–C^{13} *N*-methyl amide failed to undergo macrocyclization. In each case, the reaction provided recovered starting materials and extending the reaction times failed to provide detectable amounts of the cyclization products **18**–**19**. Subjection of the substrate possessing only the N^9–C^{10}

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(26) Use of AMBER as a force field also provided this conformation as the lowest energy conformation.

Table II

conf	compound 2: ΔE (kcal),[a] % pop,[b] RMS (Å)[c]	compound 2: stereochem: N^9–C^{10}, N^{12}–C^{13}	compound 3: ΔE (kcal),[a] % pop,[b] RMS (Å)[c]	compound 3: stereochem: C^9–N^{10}, C^{12}–N^{13}	compound 14: ΔE (kcal),[a] % pop,[b] RMS (Å)[c]	compound 14: stereochem: C^5–N^4, C^2–N^1, N^{24}–C^{25}, N^{27}–C^{28}
1	0.0, 99.98, 0.0	t, t	0.0, 99.93, 0.0	t, t	0.0, 40.4, 0.0	t, t, t, t
2	5.3, 0.01, 0.40	t, t	4.5, 0.05, 1.19	t, c	0.3, 23.9, 1.07	t, t, t, t
3	6.2, 0.0, 0.72	t, t	5.4, 0.01, 1.00	t, t	0.4, 22.1, 1.10	t, t, t, t
4	6.2, 0.0, 1.16	t, t,	6.0, 0.0, 1.15	t, t	0.7, 13.6, 0.37	t, t, t, t
5			6.3, 0.0, 1.18	t, c	4.5, 0.02, 0.35	t, t, t, t
6			6.6, 0.0, 0.68	t, t	4.6, 0.02, 1.28	t, t, t, t
7					4.8, 0.01, 0.39	t, t, t, t
8					4.9, 0.01, 0.54	t, t, t, t
9					5.7, 0.0, 0.82	t, t, c, t
10					6.1, 0.0, 0.46	t, t, c, t
X-ray	–, –, 0.31 (0.22)[d]	t, t	–, –, 0.28 (0.18)[d]	t, t		

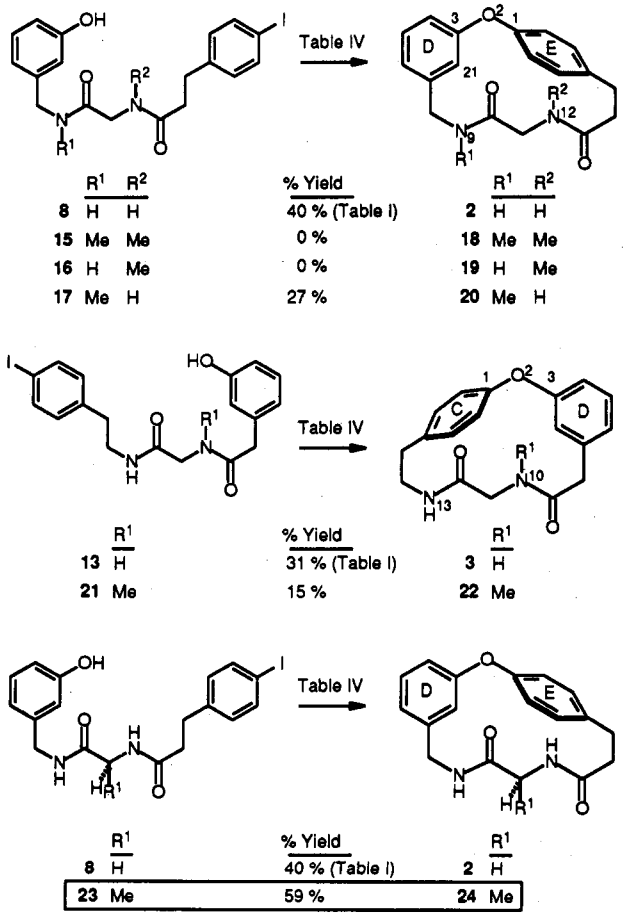
[a] OPLSA force field. [b] % pop = Boltzmann distribution at 37 °C. [c] RMS difference relative to conformation 1. [d] RMS in parentheses denotes the inner ring atom deviation.

Table III

compd, conf	14 conf	RMS (Å)[a]	compd, conf	14 conf	RMS (Å)[a]
2, 1	1	0.26	3, 1	2	0.25
2, 1	2	0.64	3, 1	3	0.23
2, 1	3	0.64	3, 1	4	0.22
2, 1	4	0.24	3, 2	9	0.60
3, 1	1	0.66	3, 2	10	0.60

[a] RMS difference calculated using the conserved heavy atoms from each molecule.

Scheme IV



N-methyl amide to the Ullmann macrocyclization conditions provided **20** but in conversions (27%) reduced from that observed in the generation of **2** (40%). Thus, the use of tertiary versus secondary amides in the linking chain significantly reduces the rate and conversions of the intramolecular Ullmann macrocyclization reactions leading to the 16-membered diphenyl ethers.[27] In addition, the use of a N^{12}–C^{13} tertiary amide appears to prevent Ullmann macrocyclization leading to the vancomycin DE ring system while use of a N^9–C^{10} tertiary amide diminishes but does not preclude cyclization.

Similar results were obtained in the case of the single extension of these observations to the incorporation of a *N*-methyl amide within the key amide site of the linking chain of the vancomycin or ristocetin CD ring system, Scheme IV. Ullmann macrocyclization of **21** provided **22** (14–15%) but in conversions diminished from that observed in the closure to provide **3** (31%), Table IV. Exhaustive efforts to optimize the Ullmann macrocyclization ring closures of **15–17** and **21** were not conducted and may be subject to improvements beyond what we detail herein. Importantly, however, the studies have shown that the use of tertiary versus secondary amides does not offer the immediate advantages that accompany the enhanced stability of the linking chain amides.

More significant were the observations made with substrate **23**. In efforts conducted initially to simply establish the extent of racemization of the central amino acid of the linking amide chain, the key observation was made that the conversions in the Ullmann macrocyclization reaction *further and significantly improved and* ***23*** *provided* ***24*** *in yields of 60%*. This empirical observation that substitution of the amino acid linking chain carbon significantly *increases* the observed conversions in the Ullmann macrocyclization reaction further verifies the viability of the approach, provides preparatively useful conversion yields for a refractory synthetic problem, and locates the origin or at least sites responsible for the modest conversions observed with the simplified systems leading to **2** and **3**. Moreover, the extent of racemization proved minimal even for reactions conducted in pyridine (95:5 L:D, 6 h at 130 °C bath, 59%) and was not observed in reactions conducted in collidine (>99:1 L:D, 6 h at 130 °C bath). The 5% racemization in pyridine and the lack of detectable racemization in collidine is much lower than might be initially anticipated. However, the Ullmann macrocyclization reaction is conducted under conditions where the linking chain secondary amides are deliberately deprotonated prior to exposure to the thermal, basic reaction conditions. Subsequent racemization of **23** or **24** then requires anion generation α to and cross-conjugated

(27) Notably, this is in distinct contrast to studies of a related Ullmann macrocyclization reaction employed to form 14-membered diphenyl ethers[13-15] in which secondary or tertiary amides at the single linking amide closed with equivalent facility.

Table IV. Representative Results of the Ullmann Macrocyclization Reactions of 15–17, 21, and 23

substrate	Cu(I) source (equiv)	solvent	temp (°C), time (h)	product (% yield)
15	MeCu (1.2)	pyridine	130, 7.5	18, 0
15	MeCu (3)	pyridine	130, 24	18, 0
15	NaH (2), CuBr–SMe_2 (10)	pyridine	130, 9	18, 0
16	MeCu (3)	pyridine	130, 9	19, 0
17	MeCu (3)	pyridine	130, 9	20, 27
21	MeCu (2)	pyridine	130, 9	22, 14
21	NaH (3), CuBr–SMe_2 (10)	pyridine	130, 6	22, 15
23	MeCu (3)	pyridine	130, 9	24, 28[a]
23	MeCu (3)	pyridine	130, 6	24, 55[a]
23	NaH (3), CuBr–SMe_2 (10)	pyridine	130, 6	24, 59[b]
23	NaH (3), CuBr–SMe_2 (10)	collidine	130, 6	24, 09[c]
23	NaH (3), CuBr–SMe_2 (10)	pyridine–diglyme (1:4)	130, 6	24, trace[a]

[a] Racemization not assayed. [b] 95:5 L:D (5% racemization). [c] >99:1 L:D (<1% racemization).

with the amide anion. Presumably even pyridine at 130 °C may not be sufficiently basic to deprotonate the central linking amino acid α site with required trianion generation.

With appropriate macrocyclization technology developed for the preparation of model CD and DE ring systems, the scope of substrates amenable to use defined and preliminary studies which successfully address potential racemization under the reaction conditions in hand, studies of simple models capable of addressing the vancomycin structural features contributing to its characteristic molecular recognition and functional biological activity may be undertaken. The application of the approach detailed herein to advanced vancomycin and ristocetin models is in progress and will be reported in due course.

Experimental Section[28]

2-[(*tert*-Butyloxycarbonyl)amino]-*N*-(3-hydroxybenzyl)-acetamide (6). A stirred mixture of *N*-(*tert*-butyloxycarbonyl)-glycine (1.54 g, 8.8 mmol) and Et_3N (1.23 mL, 8.8 mmol) in THF (15 mL) was treated with $ClCO_2Et$ (0.84 mL, 8.8 mmol) dropwise at −10 °C. After the mixture was stirred for 5 min, a solution of 3-hydroxybenzylamine[29] (5, 1.08 g, 8.8 mmol) in 50% THF–H_2O (24 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 15 min. H_2O (10 mL) and saturated aqueous NaCl (10 mL) were added and the mixture was extracted with EtOAc (20 mL × 2). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was crystallized from Et_2O to afford 6 (1.20 g, 49%) as a white crystalline solid: mp 144–145 °C (MeOH–Et_2O); ^1H NMR ($CDCl_3$, 400 MHz, ppm) 8.95 (s, 1 H, OH), 7.62 (bs, 1 H, NH), 7.09 (dd, 1 H, J = 8, 8 Hz, C5-H), 6.74–6.68 (m, 3 H, C2-H, C4-H, and C6-H), 6.18 (bs, 1 H, NH), 4.32 (d, 2 H, J = 6 Hz, CH_2), 3.77 (d, 2 H, J = 6 Hz, CH_2), 1.43 (s, 9 H, $C(CH_3)_3$); IR (KBr) ν_{max} 3333, 1720, 1695, 1630, 1559, 1519, 1425, 1317, 1265, 1175 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 413.0477 ($C_{14}H_{20}N_2O_4$ + Cs^+ requires 413.0477).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.33; H, 7.00; N, 10.11.

***N*-(3-Hydroxybenzyl)-2-[3-(4-iodophenyl)propionamido]-acetamide (8).** A solution of 6 (1.20 g, 4.3 mmol) in 2 N HCl–MeOH (30 mL) was stirred at 50 °C for 30 min and concentrated in vacuo. The residue was dissolved in THF (10 mL), Et_3N (0.90 mL, 6.5 mmol) and H_2O (3 mL) were added, and the resulting solution was added to a mixture of 3-(4-iodophenyl)propionic acid[30] (7, 1.20 g, 4.3 mmol), Et_3N (0.66 mL, 4.7 mmol) and $ClCO_2Et$ (0.41 mL, 4.3 mmol) in THF (20 mL) at −10 °C. After 10 min of stirring at 0 °C, the mixture was diluted with EtOAc (30 mL) and washed with saturated aqueous NaCl (10 mL × 2). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was crystallized from MeOH to afford 8 (1.20 g, 64%) as a white crystalline solid: mp 199–200 °C (EtOH); ^1H NMR (DMSO-d_6, 400 MHz, ppm) 9.33 (s, 1 H, OH), 8.24 (t, 1 H, J = 6 Hz, NH), 8.12 (t, 1 H, J = 6 Hz, NH), 7.60 (d, 2 H, J = 8 Hz, C2-H and C6-H), 7.10 (dd, 1 H, J = 7, 8 Hz, C5′-H), 7.03 (d, 2 H, J = 8 Hz, C3-H and C5-H), 6.65–6.60 (m, 3 H, C2′-H, C4′-H and C6′-H), 4.17 (d, 2 H, J = 6 Hz, CH_2), 3.70 (d, 2 H, J = 6 Hz, CH_2), 2.76 (t, 2 H, J = 8 Hz, $ArCH_2CH_2$), 2.42 (t, 2 H, J = 8 Hz, $ArCH_2CH_2$); IR (KBr) ν_{max} 3390, 1655, 1587, 1534, 1488, 1428, 1321, 1219, 1152 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 570.9495 ($C_{18}H_{19}IN_2O_3$ + Cs^+ requires 570.9495).

Anal. Calcd for $C_{18}H_{19}IN_2O_3$: C, 49.33; H, 4.37; N, 6.39. Found: C, 49.55; H, 4.46; N, 6.09.

General Procedure for the Ullmann Macrocyclization Reactions: 10,13-Dioxo-2-oxa-9,12-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (2). A solution of CuI-$(SBu_2)_2$[31] (290 mg, 0.60 mmol) in dry Et_2O (7 mL) under Ar in a flame-dried test tube at −78 °C was treated with methyllithium (1.4 M, 0.43 mL, 0.60 mmol) and the solution was allowed to warm to 22 °C. The precipitated methylcopper was collected by removal of supernatant and washed with dry Et_2O (7 mL × 3). After removal of the Et_2O in vacuo, pyridine (4 mL) was added to the methylcopper at −78 °C. A solution of 8 (88 mg, 0.20 mmol) in pyridine (2 mL) was added dropwise to the mixture at −78 °C and the resulting brown mixture was stirred at 22 °C for 1 h. The mixture was diluted further with pyridine (44 mL) and warmed at 130 °C (bath temperature) for 6 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (50 mL), and washed with saturated aqueous NH_4Cl (20 mL × 2), 3 N aqueous HCl (20 mL × 2), and H_2O (20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 7 g, 2% MeOH–$CHCl_3$) afforded 2 (25 mg, 40%) as a white crystalline solid: mp 260 °C (MeOH–Et_2O); ^1H NMR (DMSO-d_6, 400 MHz, ppm) 8.50 (t, 1 H, J = 6 Hz, N9-H), 7.54 (t, 1 H, J = 5 Hz, N12-H), 7.29 (dd, 1 H, J = 7, 8 Hz, C5-H), 7.23 (d, 2 H, J = 8 Hz, C17-H and C20-H), 7.01 (dd, 1 H, J = 2, 8 Hz, C4-H), 6.91 (d, 2 H, J = 8 Hz, C18-H and C19-H), 6.82 (d, 1 H, J = 7 Hz, C6-H), 5.82 (s, 1 H, C21-H), 4.19 (d, 2 H, J = 6 Hz, C8-H_2), 3.66 (d, 2 H, J = 5 Hz, C11-H_2), 2.86 (t, 2 H, J = 6 Hz, C15-H_2), 2.52 (t, 2 H, J = 6 Hz, C14-H_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 170.3, 168.9, 160.7, 152.8, 145.6, 140.4, 130.8, 129.3, 122.0, 119.2, 114.6, 111.1, 41.6, 40.8, 37.0, 30.9; IR (KBr) ν_{max} 3323, 3261, 1667, 1641, 1590, 1533, 1508, 1441, 1241 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 443.0389 ($C_{18}H_{18}N_2O_3$ + Cs^+ requires 443.0372).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 70.00; H, 5.81; N, 9.01.

The ^1H–^1H NOESY NMR (DMSO-d_6) displayed diagnostic NOE crosspeaks for N9-H/C11-H, N9-H/C8-H, N9-H/C21-H,

(28) Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (0.00 ppm). Infrared spectra (IR) were recorded as KBr pellets. Melting points are uncorrected. Pyridine was distilled from CaH. Et_2O was distilled from sodium benzophenone ketyl. Flash chromatography was performed on silica gel (SiO_2, 230–400 mesh, ASTM). Methyllithium (1.4 M in Et_2O) was purchased from Aldrich Chemical Company. All reactions requiring anhydrous conditions or an inert atmosphere were conducted under an atmosphere of Ar.

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N12-H/C14-H, N12-H/C11-H, C17,20-H/C-21H, C14-H/C17,20-H, C15-H/C17,20-H, C4-H/C21-H, C18,19-H/C21-H, C6-H/C8-H, C8-H/C-21H, and C14-H/C15-H.

The structure of **2** was unambiguously established in a single-crystal X-ray structure determination conducted with colorless prisms grown from MeOH–Et_2O.[32]

2-Amino-*N*-(4-iodophenethyl)acetamide Hydrochloride (10). Ethyl chloroformate (0.44 mL, 4.5 mmol) was added to a mixture of *N*-(*tert*-butyloxycarbonyl)glycine (810 mg, 4.6 mmol) and Et_3N (0.65 mL, 4.6 mmol) in THF (20 mL) at −10 °C and the solution was stirred for 10 min. A solution of 4-iodophenethylamine·HCl[33] (**9**, 1.30 g, 4.6 mmol) and Et_3N (0.64 mL, 4.6 mmol) in THF (20 mL) and H_2O (5 mL) was added to the mixture which was stirred for 15 min at 22 °C. After removal of solvent in vacuo, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (20 mL × 2). The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was treated with 2 N HCl–MeOH (5 mL) and the mixture was stirred at 60 °C for 10 min. Et_2O was added to the cooled reaction mixture to precipitate the crystalline product. The crystalline product was collected by filtration, washed with Et_2O, and dried to give **10** (1.23 g, 80%) as a white crystalline solid: mp 215–220 °C (MeOH–Et_2O); ^1H NMR (CD_3OD, 400 MHz, ppm) 7.62 (d, 2 H, J = 8 Hz, ArH), 7.03 (d, 2 H, J = 8 Hz, ArH), 3.62 (s, 2 H, $COCH_2$), 3.46 (t, 2 H, J = 7 Hz, CH_2), 2.78 (t, 2 H, J = 7 Hz, CH_2); IR (KBr) ν_{max} 3313, 3005, 1662, 1559, 1482, 1436, 1267, 1118, 1005 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 305.0155 ($C_{10}H_{14}ClIN_2O$ + H^+ requires 305.0151).

Anal. Calcd for $C_{10}H_{14}ClIN_2O$: C, 35.27; H, 4.14; N, 8.22. Found: C, 35.27; H, 4.14; N, 8.22.

2-(3-Hydroxyphenylacetamido)-*N*-(4-iodophenethyl)-acetamide (13). DCC (410 mg, 2.0 mmol) was added to a mixture of **10**·HCl (680 mg, 2.0 mmol), 3-acetoxyphenylacetic acid[34] (**11**, 380 mg, 2.0 mmol), and Et_3N (0.28 mL, 2.0 mmol) in THF (15 mL) and H_2O (1 mL) at 0 °C. The reaction mixture was allowed to warm to 23 °C and stirred for 24 h. After removal of the solvent, 2 N HCl–MeOH (5 mL) was added and the mixture was stirred at 23 °C for 4 h. Removal of the solvent in vacuo followed by flash chromatography (SiO_2, 10 g, 2–4% MeOH–CH_2Cl_2) and crystallization from MeOH–Et_2O afforded **13** (400 mg, 46%) as a white crystalline solid: mp 181–183 °C (EtOH–hexane); ^1H NMR (DMSO-d_6, 400 MHz, ppm) 9.27 (s, 1 H, OH), 8.15 (t, 1 H, J = 6 Hz, NH), 7.88 (t, 1 H, J = 5 Hz, NH), 7.62 (d, 2 H, J = 8 Hz, C2-H and C6-H), 7.05 (dd, 1 H, J = 8, 8 Hz, C5′-H), 7.01 (d, 2 H, J = 8 Hz, C3-H and C5-H), 6.68–6.66 (m, 2 H, C2′-H, C4′- or C6′-H), 6.59 (m, 1 H, C4′- or C6′-H), 3.62 (d, 2 H, J = 6 Hz, $COCH_2N$), 3.56 (s, 2 H, $ArCH_2CO$), 3.24 (m, 2 H, CH_2CH_2N-), 2.64 (t, 2 H, J = 7 Hz, $ArCH_2CH_2$); IR (KBr) ν_{max} 3280, 1664, 1630, 1602, 1560, 1485, 1456, 1288, 1249, 1163, 1007 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 570.9481 ($C_{18}H_{19}IN_2O_3$ + Cs^+ requires 570.9495).

Anal. Calcd for $C_{18}H_{19}IN_2O_3$: C, 49.33; H, 4.37; N, 6.39. Found: C, 49.31; H, 4.38; N, 6.42.

9,12-Dioxo-2-oxa-10,13-diazatricyclo[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (3). Following the procedure detailed for **2**, subjection of **13** to the conditions of the Ullmann macrocyclization reaction provided **3** (Table I): mp 256–257 °C (EtOH–Et_2O); ^1H NMR (DMSO-d_6, 400 MHz, ppm) 7.91 (t, 1 H, J = 5 Hz, N10-H), 7.83 (t, 1 H, J = 6 Hz, N13-H), 7.22 (dd, 1 H, J = 8, 8 Hz, C5-H), 7.20 (d, 2 H, J = 8 Hz, C17-H and C20-H), 6.98 (dd, 1 H, J = 8, 2 Hz, C4-H), 6.81 (d, 2 H, J = 8 Hz, C18-H and C19-H), 6.77 (d, 1 H, J = 8 Hz, C6-H), 6.03 (s, 1 H, C21-H), 3.62 (d, 2 H, J = 5 Hz, C11-H_2), 3.47 (dt, 2 H, J = 6, 6 Hz, C14-H_2), 3.39 (s, 2 H, C8-H_2), 2.70 (t, 2 H, J = 6 Hz, C15-H_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) 169.4, 167.8, 160.2, 153.6, 138.7, 135.5, 131.2, 129.3, 122.4, 121.1, 114.9, 113.5, 41.7, 41.3, 38.6, 34.9; IR (KBr) ν_{max} 3426, 3313, 1636, 1590, 1544, 1508, 1441, 1236 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 443.0377 ($C_{18}H_{18}N_2O_3$ + Cs^+ requires 443.0372).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.78; H, 5.88; N, 9.01.

The ^1H–^1H NOESY NMR (DMSO-d_6) displayed diagnostic NOE peaks for N10-H/C8-H, N10-H/C11-H, N10-H/C21-H, N10-H/C18,19-H, N10-H/C17,20-H, N13-H/C15-H, N13-H/C14-H, N13-H/C11-H, N13-H/C18,19-H, N13-H/C17,20-H, C17,20H/C15-H, C17,20-H/C14-H, C17,20H/C11-H, C8-H/C6-H, C8-H/C21-H, C21-H/C4-H, C21-H/C18,19-H, C21-H/C17,20-H, C21-H/C11-H, and C14-H/C15-H.

The structure of **3** was unambiguously established in a single-crystal X-ray structure determination conducted with colorless plates grown from EtOH-H_2O.[32]

***N*-(3-Hydroxybenzyl)-*N*-methyl-2-[3-(4-iodophenyl)-*N*′-methylpropionamido]acetamide (15).** A mixture of **8** (0.22 g, 0.50 mmol), 2,3-dihydropyran (0.48 mL, 6.0 mmol), and *p*-TsOH (20 mg) in THF (5 mL), CH_2Cl_2 (5 mL), and DMF (2 mL) was stirred at 23 °C for 1 h. Additional 2,3-dihydrofuran (0.48 mL, 6.0 mmol) was added, and the mixture was stirred at 23 °C for 1 h. The reaction mixture was diluted with Et_2O (50 mL), washed with concentrated NH_4OH (10 mL) and H_2O (10 mL × 3), dried ($MgSO_4$), and concentrated. The residue was crystallized from Et_2O to afford *N*-[3-(2-tetrahydropyranyloxy)benzyl]-2-[3-(4-iodophenyl)propionamido]acetamide (0.20 g, 75%): mp 129.5–130.0 °C (MeOH–Et_2O); ^1H NMR ($CDCl_3$, 400 MHz, ppm) 7.54 (d, 2 H, J = 8 Hz, C2-H and C4-H), 7.21 (t, 1 H, J = 8 Hz, C5′-H), 6.96–6.84 (m, 5 H, C2′-H, C4′-H, C6′-H, C3-H, and C5-H), 6.42 (bs, 1 H, NH), 6.33 (bs, 1 H, NH), 5.38 (m, 1 H, OCHO), 4.36 (d, 2 H, J = 6 Hz, CH_2), 3.89 (d, 2 H, J = 5 Hz, CH_2), 3.86 (m, 1 H, CH_2), 3.57 (m, 1 H, CH_2), 2.85 (t, 2 H, J = 8 Hz, CH_2), 2.48 (t, 2 H, J = 8 Hz, CH_2), 2.05–1.50 (m, 6 H, CH_2); IR (KBr) ν_{max} 3307, 2942, 1634, 1540, 1487, 1458, 1256, 1038, 1007 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 655.0061 ($C_{23}H_{27}IN_2O_4$ + Cs^+ requires 655.0070).

A solution of the THP ether (0.18 g, 0.36 mmol) in DMF (1 mL) was treated with NaH (60% in oil, 44 mg, 1.1 mmol) and the reaction mixture was stirred at 23 °C for 30 min. MeI (0.062 mL, 1.0 mmol) was added and the mixture was stirred at 23 °C for 15 min before 3 N HCl (1 mL) was added. The resulting mixture was stirred at 23 °C for 30 min, diluted with EtOAc (50 mL), and washed with H_2O (20 mL × 3). The EtOAc layer was dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2, 5 g, 4% MeOH–CH_2Cl_2) afforded **15** (92 mg, 55%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz, ppm) of major rotamer 7.70 (bs, 1 H, OH), 7.56 (d, 2 H, J = 8 Hz, ArH), 7.14 (t, 1 H, J = 8 Hz, ArH), 6.87 (d, 2 H, J = 8 Hz, ArH), 6.78–6.66 (m, 3 H, ArH), 4.52 (s, 2 H, CH_2), 4.27 (s, 2 H, CH_2), 3.05 (s, 3 H, CH_3), 2.89 (s, 3 H, CH_3), 2.78 (m, 2 H, CH_2), 2.60 (m, 2 H, CH_2); IR (KBr) ν_{max} 3159, 2962, 1658, 1618, 1587, 1483, 1409, 1328, 1279, 1005 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 598.9808 ($C_{20}H_{23}IN_2O_3$ + Cs^+ requires 598.9808).

***N*-(3-Hydroxybenzyl)-2-[3-(4-iodophenyl)-*N*′-methylpropionamido]acetamide (16).** A solution of 3-(4-iodophenyl)-propionic acid[30] (1.8 g, 6.5 mmol) and Et_3N (1.0 mL, 7.1 mmol) in THF (30 mL) was treated with $ClCO_2Et$ (0.60 mL, 6.5 mmol) at −10 °C. The reaction mixture was stirred at −10 °C for 5 min before a solution of sarcosine (0.58 g, 6.5 mmol) and Et_3N (1.0 mL, 7.1 mmol) in H_2O (10 mL) was added. The mixture was allowed to warm to 23 °C during 15 min and concentrated to half volume. The residual solution was adjusted to pH 1 with the addition of 3 N HCl and extracted with EtOAc (50 mL). The extract was washed with saturated aqueous NaCl (20 mL × 2), dried ($MgSO_4$), and concentrated. The residue was crystallized from MeOH–Et_2O–hexane to afford *N*-[3-(4-iodophenyl)propionyl]sarcosine (0.79 g): mp 143–144 °C; ^1H NMR ($CDCl_3$, 400 MHz, ppm) 7.58 (d, 2 H, J = 8 Hz, ArH), 6.96 (d, 2 H, J = 8 Hz, ArH), 4.90 (bs, 1 H), 4.12 (s, 2 H, CH_2), 3.02 (s, 2 H, CH_3), 2.90 (t, 2 H, J = 8 Hz, CH_2), 2.65 (t, 2 H, J = 8 Hz, CH_2); IR (KBr) ν_{max} 3015, 1746, 1616, 1498, 1405, 1199, 1128, 1006, 865 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 348.0093 ($C_{12}H_{14}INO_3$ + H^+ requires 348.0093).

A mixture of the carboxylic acid (0.24 g, 0.69 mmol), 3-hydroxybenzylamine[29] (85 mg, 0.69 mmol), and EDCI (132 mg, 0.69 mmol) in THF (20 mL), H_2O (2 mL), and DMF (2 mL) was stirred at 23 °C for 16 h. The solvent was removed, EtOAc (35

(32) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates may be obtained upon request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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mL) was added to the residue, and the mixture was washed with 3 N HCl (10 mL × 2), saturated aqueous $NaHCO_3$ (10 mL × 2), and H_2O (10 mL × 2). The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2, 5 g, 4% MeOH–CH_2Cl_2) afforded **16** (84 mg) as a white solid: mp 152–153 °C (MeOH–Et_2O); ^1H NMR ($CDCl_3$, 400 MHz, ppm) 8.38 (bs, 1 H, OH), 7.65 (t, 1 H, J = 5 Hz, NH), 7.51 (d, 2 H, J = 8 Hz, C2-H and C6-H) 7.10 (t, 1 H, J = 8 Hz, C5'-H), 6.79 (d, 2 H, J = 8 Hz, C3-H and C5-H), 6.73 (dd, 1 H, J = 2, 8 Hz, ArH), 6.68 (d, 1 H, J = 8 Hz, ArH), 6.50 (s, 1 H, C2'-H), 4.31 (d, 2 H, J = 5 Hz, CH_2), 4.15 (s, 2 H, CH_2), 3.07 (s, 3 H, CH_3), 2.47 (m, 4 H, CH_2); IR (KBr) ν_{max} 3336, 3086, 1694, 1628, 1590, 1551, 1483, 1420, 1274 cm^{-1}; FABHRMS (NBA–CsI), m/e 584.9651 ($C_{19}H_{21}IN_2O_3$ + Cs^+ requires 584.9651).

Anal. Calcd for $C_{19}H_{21}IN_2O_3$: C, 50.46; H, 4.68; N, 6.19. Found C, 50.31; H, 4.88; N, 6.20.

***N*-(3-Hydroxybenzyl)-*N*-methyl-2-[3-(4-iodophenyl)propionamido]acetamide (17).** A mixture of 3-(4-iodophenyl)-propionic acid[30] (3.6 g, 13 mmol) and Et_3N (2.0 mL, 14 mmol) in THF (60 mL) was treated with $ClCO_2Et$ (1.2 mL, 13 mmol) at −10 °C and the mixture was stirred for 5 min. A solution of glycine (1.0 g, 13 mmol) and Et_3N (2.0 mL, 14 mmol) in H_2O (10 mL) was added to the mixture. The reaction mixture was allowed to warm to 23 °C over 30 min before being concentrated to half volume. The residual solution was adjusted to pH 1 with the addition of 3 N HCl and extracted with EtOAc (50 mL). The organic layer was washed with saturated aqueous NaCl (10 mL × 3), dried ($MgSO_4$), and concentrated. The residue was crystallized from Et_2O–hexane to afford *N*-[3-(4-iodophenyl)-propionyl]glycine (2.0 g, 46%); mp 157.5–159 °C (Et_2O–hexane): ^1H NMR (5% d_6-DMSO–$CDCl_3$, 400 MHz, ppm) 7.45 (d, 2 H, J = 8 Hz, ArH), 6.84 (d, 2 H, J = 8 Hz, ArH), 6.60 (bs, 1 H, NH), 3.82 (d, 2 H, J = 5 Hz, CH_2), 3.80 (bs, 1 H), 2.78 (t, 2 H, J = 7 Hz, CH_2), 2.39 (t, 2 H, J = 7 Hz, CH_2); IR (KBr) ν_{max} 3297, 3072, 1724, 1649, 1550, 1485, 1254, 1224, 1007 cm^{-1}; FABHRMS (NBA), m/e 333.9949 ($C_{11}H_{12}INO_3$ + H^+ requires 333.9940).

A mixture of the carboxylic acid (0.33 g, 1.0 mmol), 3-hydroxy-*N*-methylbenzylamine[35] (0.14 g, 1.0 mmol), HOBT (0.15 g, 1.0 mmol), and DCC (0.21 g, 1.0 mmol) in DMF (10 mL) was stirred at 23 °C for 14 h. The mixture was diluted with EtOAc (50 mL) and the insoluble material was removed by filtration. The filtrate was washed with 3 N HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL × 2), and H_2O (5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, 7 g, 4% MeOH–CH_2Cl_2) followed by crystallization from MeOH–Et_2O afforded **17** (0.32 g, 71%): mp 143.5–144.0 °C (MeOH–Et_2O); ^1H NMR ($CDCl_3$, 400 MHz, ppm) of major rotamer 7.54 (d, 2 H, J = 8 Hz, ArH), 7.13 (t, 1 H, J = 8 Hz, ArH), 6.89 (d, 2 H, J = 8 Hz, ArH), 6.76–6.58 (m, 5 H, ArH, OH, NH), 4.47 (s, 2 H, CH_2), 4.04 (d, 2 H, J = 4 Hz, CH_2), 2.85 (t, 2 H, J = 8 Hz, CH_2), 2.81 (s, 3 H, CH_3), 2.49 (t, 2 H, J = 8 Hz, CH_2); IR (KBr) ν_{max} 3308, 3220, 1671, 1634, 1587, 1483, 1413, 1278, 1006 cm^{-1}; FABHRMS (NBA–CsI), m/e 584.9666 ($C_{19}H_{21}IN_2O_3$ + Cs^+ requires 584.9651).

Anal. Calcd for $C_{19}H_{21}IN_2O_3$: C, 50.46; H, 4.68; N, 6.19. Found: C, 50.50; H, 4.68; N, 6.19.

10,13-Dioxo-9-methyl-2-oxa-9,12-diazatricyclo[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (20). Following the procedure detailed for **2**, subjection of **17** to the conditions of the Ullmann macrocyclization reaction provided **20** (Table IV): ^1H NMR ($CDCl_3$, 400 MHz, ppm) 7.19 (t, 1 H, J = 8 Hz, C5-H), 7.10 (bs, 2 H, ArH), 7.00 (dd, 1 H, J = 3, 8 Hz, ArH), 6.75 (bs, 2 H, ArH), 6.70 (dd, 1 H, J = 1, 7 Hz, ArH), 6.16 (bs, 1 H, NH), 5.75 (d, 1 H, J = 2 Hz, C21-H), 5.35 (m, 1 H, C*H*H), 4.10 (m, 1 H, CH*H*), 3.40 (m, 2 H, CH_2), 2.94 (m, 2 H, CH_2), 2.73 (s, 3 H, CH_3), 2.63 (m, 1 H, C*H*H), 2.25 (m, 1 H, CH*H*); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 171.9, 169.3, 161.5, 154.0, 137.4, 137.0, 131.3, 130.1, 123.1, 122.2, 120.2, 116.2, 111.9, 51.4, 40.7, 39.7, 34.8, 32.0, 29.7; IR (KBr) ν_{max} 3444, 2926, 1629, 1541, 1505, 1458, 1241, 1210 cm^{-1}; FABHRMS (NBA–CsI), m/e 457.0528 ($C_{19}H_{20}N_2O_3$ + Cs^+ requires 457.0528).

***N*-(4-Iodophenethyl)-2-[*N*'-methyl-2-(3-hydroxyphenyl)-acetamido]acetamide (21).** Ethyl chloroformate (0.7 mL, 7.5 mmol) was added to a mixture of *N*-(*tert*-butyloxycarbonyl)-sarcosine (1.4 g, 7.5 mmol) and Et_3N (1 mL, 7.8 mmol) in THF (30 mL) at −10 °C and the mixture was stirred for 10 min. A solution of 4-iodophenethylamine[33] (1.85 g, 7.5 mmol) in THF (15 mL) and H_2O (2 mL) was added to the mixture which was allowed to warm to 23 °C during 20 min. After concentration to half volume, the mixture was extracted with EtOAc (50 mL). The organic layer was washed with H_2O (20 mL × 2), dried ($MgSO_4$), and concentrated. The residue was treated with 2 N HCl–MeOH (10 mL) and the mixture was stirred at 60 °C for 30 min. After removal of solvent in vacuo, the residue was crystallized from Et_2O to afford 2-(methylamino)-*N*-(4-iodophenethyl)acetamide·HCl (1.5 g, 56%): mp 217–221 °C (MeOH–EtOAc); ^1H NMR (DMSO-d_6, 400 MHz, ppm) 9.00 (bs, 2 H, NH or HCl), 8.65 (bs, 1 H, NH or HCl), 7.66 (d, 2 H, J = 8 Hz, ArH), 7.08 (d, 2 H, J = 8 Hz, ArH), 3.64 (s, 2 H, CH_2), 3.35 (t, 2 H, J = 7 Hz, CH_2), 2.72 (t, 2 H, J = 7 Hz, CH_2), 2.52 (s, 3 H, CH_3); IR (KBr) 3424, 3310, 2937, 1666, 1562, 1458, 1401, 1267, 1194 cm^{-1}; FABHRMS (NBA), m/e 319.0307 ($C_{11}H_{15}IN_2O$ + H^+ requires 319.0307).

A mixture of the amine (0.35 g, 1.0 mmol), 3-hydroxyphenylacetic acid (0.12 g, 1.0 mmol), Et_3N (0.14 mL, 1.0 mmol), HOBT (0.15 g, 1.0 mmol), and DCC (0.21 g, 1.0 mmol) in DMF (10 mL) was stirred at 0 °C for 5 min before being allowed to warm to 23 °C and further stirred for 1 h. EtOAc (50 mL) was added and the insoluble material was removed by filtration. The filtrate was washed with saturated aqueous $NaHCO_3$ (5 mL × 2) and H_2O (5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, 5 g, 4% MeOH–CH_2Cl_2) afforded **21** (85 mg) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz, ppm) 7.55 (d, 2 H, J = 8 Hz, ArH), 7.16 (t, 1 H, J = 8 Hz, C5'-H), 6.84 (d, 2 H, J = 8 Hz, ArH), 6.73 (m, 3 H, C2'-H, C4'-H, and C6'-H), 6.60 (bs, 1 H, OH), 6.19 (bs, 1 H, NH), 3.90 (s, 2 H, CH_2), 3.64 (s, 2 H, CH_2), 3.42 (m, 2 H, CH_2), 2.97 (s, 3 H, CH_3), 2.66 (t, 2 H, J = 7 Hz, CH_2); IR (KBr) ν_{max} 3292, 1635, 1587, 1485, 1456, 1401, 1242, 1006, 773 cm^{-1}; FABHRMS (NBA–CsI), m/e 584.9650 ($C_{19}H_{21}IN_2O_3$ + Cs^+ requires 584.9651).

9,12-Dioxo-10-methyl-2-oxa-10,13-diazatricyclo[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (22). Following the procedure detailed for **2**, subjection of **21** to the conditions of the Ullmann macrocyclization reaction provided **22** (Table IV): ^1H NMR ($CDCl_3$, 400 MHz, ppm) 7.22 (d, 2 H, J = 8 Hz, ArH), 7.22 (t, 1 H, J = 8 Hz, C5-H), 7.02 (dd, 1 H, J = 2, 8 Hz, ArH), 6.99 (d, 2 H, J = 8 Hz, ArH), 6.72 (dd, 1 H, J = 1, 8 Hz, ArH), 5.87 (bs, 1 H, NH), 5.58 (s, 1 H, C21-H), 3.89 (m, 1 H, C*H*H), 3.67 (s, 2 H, CH_2), 3.64 (m, 1 H, CH*H*), 3.58 (m, 2 H, CH_2), 2.93 (t, 2 H, J = 6 Hz, CH_2), 2.90 (s, 3 H, CH_3); IR (KBr) ν_{max} 3447, 2923, 1662, 1631, 1559, 1510, 1456, 1226, 1169 cm^{-1}; FABHRMS (NBA–CsI), m/e 457.0528 ($C_{19}H_{20}N_2O_3$ + Cs^+ requires 457.0528).

(2*S*)-*N*-(3-Hydroxybenzyl)-2-[3-(4-iodophenyl)propionamido]propionamide (23). Ethyl chloroformate (0.62 mL, 6.5 mmol) was added to a mixture of 3-(4-iodophenyl)propionic acid[30] (1.80 g, 6.5 mmol) and Et_3N (1.0 mL, 7.1 mmol) in THF (30 mL) at −10 °C and the mixture was stirred at −10 °C for 10 min. A solution of L-alanine (0.58 g, 6.5 mmol) and Et_3N (1.0 mL, 7.1 mmol) in H_2O (10 mL) was added to the mixture at −10 °C, and the mixture was allowed to warm to 23 °C during 15 min before being concentrated to half volume. The mixture was adjusted to pH 1 with the addition of 3 N HCl and extracted with EtOAc (50 mL). The organic layer was washed with saturated aqueous NaCl (20 mL × 2), dried ($MgSO_4$), and concentrated. The residue was crystallized from Et_2O–hexane to give the carboxylic acid (1.40 g, 62%): mp 153.0–153.5 °C (Et_2O–hexane); $[\alpha]^{23}_D$ −16° (*c* 0.96, MeOH); ^1H NMR (5% d_6-DMSO–$CDCl_3$, 400 MHz, ppm) 7.45 (d, 2 H, J = 7 Hz, ArH), 6.84 (d, 2 H, J = 7 Hz, ArH), 6.55 (br, 1 H, NH), 4.36 (m, 1 H, C*H*CH_3), 3.77 (bs, 1 H), 2.77 (t, 2 H, J = 8 Hz, CH_2), 2.38 (t, 2 H, J = 8 Hz, CH_2), 1.24 (d, 3 H, J = 7 Hz, CH_3); IR (KBr) ν_{max} 3463, 3328, 1704, 1609, 1557, 1452, 1265, 1165, 808 cm^{-1}; FABHRMS (NBA), m/e 348.0097 ($C_{12}H_{14}INO_3$ + H^+ requires 348.0097).

DCC (1.3 g, 9.5 mmol) was added to a mixture of the carboxylic acid (3.3 g, 14 mmol), 3-hydroxybenzylamine[29] (0.78 g, 6.3 mmol), and HOBT (0.32 g, 9.5 mmol) in DMF (15 mL) at 0 °C. The mixture was allowed to warm to 23 °C and was stirred for 14 h. EtOAc (50 mL) was added and insoluble material was removed by filtration. The filtrate was washed with saturated aqueous

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$NaHCO_3$ (10 mL × 2) and H_2O (5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, 10 g, 4% MeOH–CH_2Cl_2) and crystallization from Et_2O–MeOH provided **23** (0.91 g): mp 165.0–165.5 °C (MeOH–Et_2O); $[\alpha]^{23}_D$ +11.8° (*c* 0.71, MeOH); ^1H NMR (10% d_6-DMSO–$CDCl_3$, 400 MHz, ppm) 8.63 (s, 1 H, OH), 7.31 (br t, 1 H, *J* = 5 Hz, NH), 7.23 (d, 2 H, *J* = 8 Hz, ArH), 7.13 (br d, 1 H, *J* = 7 Hz, NH), 6.78 (t, 1 H, *J* = 8 Hz, ArH), 6.65 (d, 2 H, *J* = 8 Hz, ArH), 6.38 (m, 3 H, ArH), 4.16 (m, 1 H, C*H*CH_3), 4.00 (dd, 1 H, *J* = 7.15 Hz, CH*H*), 3.92 (dd, 1 H, *J* = 7.15 Hz, C*H*H), 2.55 (t, 2 H, *J* = 8 Hz, CH_2), 2.16 (t, 2 H, *J* = 8 Hz, CH_2), 0.99 (d, 3 H, *J* = 7.0 Hz, CH_3); IR (KBr) ν_{max} 3318, 3006, 1663, 1560, 1486, 1436, 1269, 1008, 830 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 584.9644 ($C_{19}H_{21}IN_2O_3$ + Cs^+ requires 584.9651).

Anal. Calcd for $C_{19}H_{21}IN_2O_3$: C, 50.46; H, 4.68; N, 6.19. Found: C, 50.46; H, 4.71; N, 6.30.

(11*S*)-10,13-Dioxo-11-methyl-2-oxa-9,12-diazatricyclo-[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (24). Following the procedure detailed for **2**, subjection of **23** to the conditions of the Ullmann macrocyclization reaction provided **24** (Table IV). Chiral phase HPLC analysis of **24** revealed a 95:5 ratio of enantiomers: $[\alpha]^{25}_D$ +220° (*c* 0.04, CH_3OH), **24** t_R = 1.4 min (+**24**) and 1.7 min (−**24**) respectively (J. T. Baker Bakerbond DNPG (covalent) column 2.0 mL/min, 50% EtOAc/hexane eluant). Recrystallization (*i*-PrOH–Et_2O) provided pure (+)-**24** (>99.9% ee, HPLC): mp 257 °C dec (*i*-PrOH–Et_2O); $[\alpha]^{25}_D$ +253° (*c* 0.1, CH_3OH); ^1H NMR (CD_3OD, 400 MHz, ppm) 7.47 (bd, 1 H, NH), 7.35 (dd, 1 H, *J* = 2, 8 Hz C17- or C20-H), 7.23 (t, 1 H, *J* = 8 Hz, C5-H), 7.10 (dd, 1 H, *J* = 2, 8 Hz, C17- or C20-H), 6.98 (dd, 1 H, *J* = 2, 8 Hz, C18- or C19-H), 6.96 (dd, 1 H, *J* = 2, 7 Hz, C4-H), 6.82 (dd, 1 H, *J* = 2, 8 Hz, C18- or C19-H), 6.78 (bd, 1 H, J = 8 Hz, C6-H), 5.88 (s, 1 H, C21-H), 4.71 (d, 1 H, *J* = 16 Hz, ArC*H*HNH), 4.31 (m, 1 H, C*H*CH_3), 3.81 (d, 1 H, *J* = 16 Hz, ArCH*H*NH), 2.91 (m, 2 H, $ArCH_2$), 2.52 (m, 2 H, $COCH_2$), 1.20 (d, 3 H, *J* = 7 Hz, CH_3); ^1H NMR (5% d_6-DMSO–$CDCl_3$, 400 MHz, ppm) 7.87 (br, 1 H, NH), 7.22 (m, 1 H, ArH), 7.16 (t, 1 H, J = 8 Hz, ArH), 7.04 (m, 1 H, ArH), 6.94 (m, 2 H, ArH), 6.74 (m, 1 H, ArH), 6.68 (d, 1 H, *J* = 8 Hz, ArH), 6.45 (bs, 1 H, NH), 5.81 (s, 1 H, C21-H), 4.73 (dd, 1 H, *J* = 9, 16 Hz, C*H*H), 4.29 (m, 1 H, C*H*CH_3), 3.70 (dd, 1 H, *J* = 4, 16 Hz, CH*H*), 2.91 (m, 2 H, CH_2), 2.55 (m, 1 H, C*H*H), 2.28 (m, 1 H, CH*H*), 1.18 (d, 3 H, *J* = 7 Hz, CH_3); ^{13}C NMR (5% d_6-DMSO–$CDCl_3$, 100 MHz, ppm) 172.7, 170.1, 160.7, 153.3, 139.5, 136.6, 130.9, 129.1, 122.4, 121.7, 118.8, 114.8, 111.1, 48.0, 41.3, 38.7, 31.1, 19.5; IR (KBr) ν_{max} 3287, 2928, 2635, 1559, 1540, 1506, 1447, 1236, 1164, 1017 cm^{-1}; FABHRMS (NBA–CsI), *m/e* 457.0539 ($C_{19}H_{20}N_2O_3$ + Cs^+ requires 457.0528).

Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.20; N, 8.60. Found: C, 70.35; H, 6.21; N, 8.64.

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Supplementary Material Available: ^1H NMR of **15** and **20–22** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.