Articles

S_NAr-Based Macrocyclization: An Application to the Synthesis of Vancomycin Family Models

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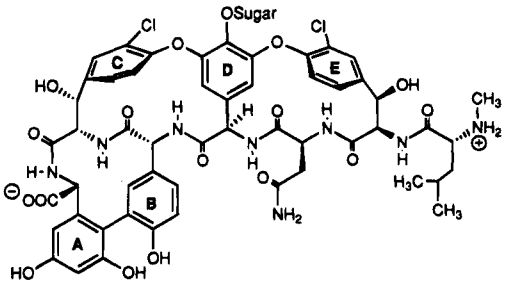
The first examples of macrocyclization using the intramolecular S_NAr reaction are reported. The method has allowed the efficient preparation of the elusive 16-membered macrocyclic COD and DOE rings related to vancomycin. The mild conditions used allow the incorporation of very racemization-prone amino acids, such as *p*-methoxyphenylglycine, into the peptide chain. After serving as an activator, the nitro group *ortho* to the diaryl ether linkage is converted either into a chlorine or a hydrogen atom, thus achieving the substitution pattern found in the vancomycin family of glycopeptides. When compound **20** was submitted to the same macrocyclization conditions, two atropisomers **21** and **22** were isolated and characterized.

The glycopeptide antibiotic, vancomycin **1** (Figure 1), has found extensive clinical use over the last quarter of a century and is the drug "of choice" for the treatment of infections due to methicillin-resistant *staphylococcus aureus* and other Gram-positive organisms in patients allergic to β-lactam antibiotics.[1] The molecular basis for the antibacterial activity of vancomycin and related glycopeptides including, for example, ristocetin,[2] teicoplanin,[3] and β-avoparcin,[4] arise from the specific binding of the glycopeptide to the bacterial cell wall precursors terminating in the sequence D-Ala-D-Ala.[5] Resistance to vancomycin has only recently been reported, and the possible molecular basis of this phenomenon has been addressed.[6]

The molecular architecture of this class of natural products has intrigued synthetic chemists for decades.[7] However, the search for new methodologies for the preparation of the dipeptide binding pocket composed of the COD and DOE 16 membered rings is still an active area. Hamilton *et al.*[8a] and Crimmin *et al.*[8b] have reported the synthesis of model COD and DOE rings by a macrolactamization procedure but in less than 10% yield. Interestingly, in related studies, Williams *et al.*[9a] and Pearson *et al.*[9b] failed to obtain the macrocyclic compound using the same strategy. Yamamura *et al.*[10a] and Evans *et al.*[10b] have developed an elegant approach based on a thallium(III)-promoted intramolecular oxidative coupling procedure. Unfortunately, the use of dichloro- and dibromophenol coupling partners is obligatory, and as a consequence, only the dichloro-substituted



1 Vancomycin

Figure 1.

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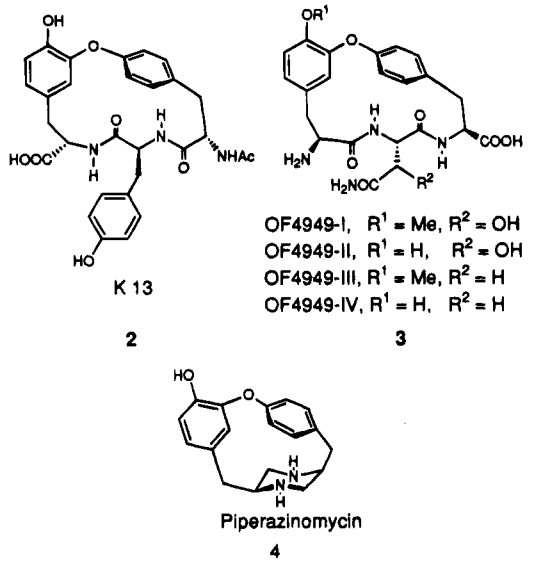


Figure 2.

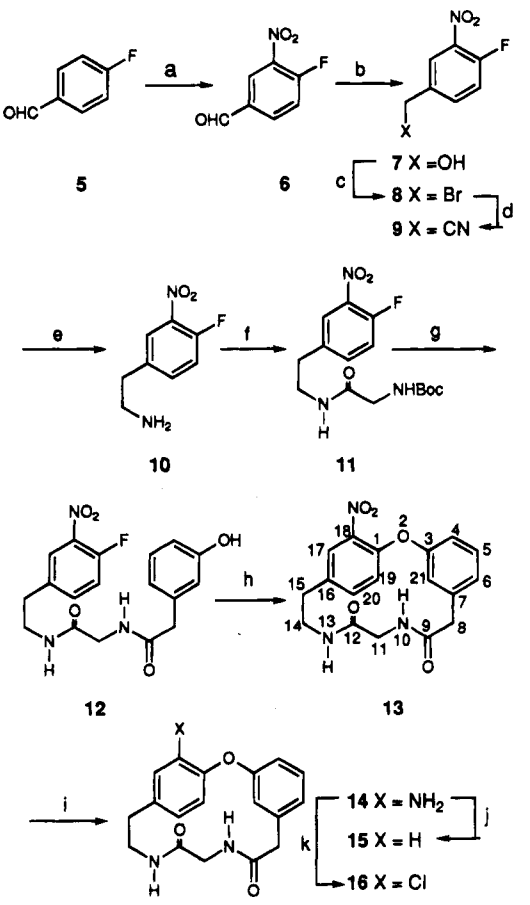
coupling product can be obtained by this approach. Very recently, Boger *et al.*[11] have reported a synthesis using an intramolecular Ullmann reaction. All these methods suffer from the fact that they are only of low to moderate yield, but perhaps their major shortcoming is the very real difficulty which is posed in introducing *a chlorine atom* into the aromatic C and E rings *ortho* to the aryl ether linkage.

Our interest in the synthesis of the vancomycin family of glycopeptides[12] as well as other recently isolated oxidatively cross-linked cyclic tripeptides K-13[13] (**2**), OF4949 I-IV[13] (**3**), and cyclic dipeptide piperazinomycin[14] (**4**) (Figure 2) prompted us to investigate a new ring closure method for the preparation of the 16-membered COD and DOE rings where the macrolactamization technique has proved to be inefficient, and we focused our attention on ring closure *via* biaryl ether formation with the idea that this should also allow a "masked" chlorine atom to be incorporated. Herein, we detail our studies[15] on the implementation of an intramolecular S_NAr reaction for direct closure to the elusive 16-membered diaryl ethers.

Results and Discussion

Aryl halides in which the halogen substituent is *ortho* or *para* to an electron-withdrawing group are activated for nucleophilic substitution via S_NAr mechanism (addition–elimination),[16] and fluoro is the best leaving group, especially when hard nucleophiles, e.g., alkoxides, are involved. As one of the most important reactions for nucleophilc aromatic substitution, the S_NAr reaction has attracted a great deal of mechanistic studies and has been applied to C–C bond as well as C–heteroatom bond formation. However, to the best of our knowledge, there is no single report dealing with macrocyclization based on this reaction.[17]

Scheme 1[a]



[a] Reagents: (a) HNO_3–H_2SO_4; (b) $NaBH_4$; (c) PBr_3; (d) Et_4NCN; (e) AlH_3 or $NaBH_4$, TFA; (f) DCC, Et_3N, *N*-Boc-glycine; (g) TFA, then Et_3N, DCC, *m*-hydroxyphenylacetic acid; (h) K_2CO_3, DMF (i) Fe–$FeSO_4$; (j) ^tBuONO, DMF; (k) $NaNO_2$, HCl, CuCl–$CuCl_2$.

Synthesis of Model COD Rings. The precursor **12** needed for the macrocyclization study was prepared according to Scheme 1. Commercially available 4-fluorobenzaldehyde (**5**) was converted to 4-fluoro-3-nitrobenzaldehyde (**6**) in quantitative yield.[18] Introduction of a nitro group *ortho* to the fluorine atom was based on the assumption that it could not only serve as an activating group but also could be transformed into the desired chlorine or hydrogen atom found in the natural products. Compound **6** was then converted to 4-fluoro-3-nitrobenzylnitrile (**9**) by sequential reduction, bromination, and

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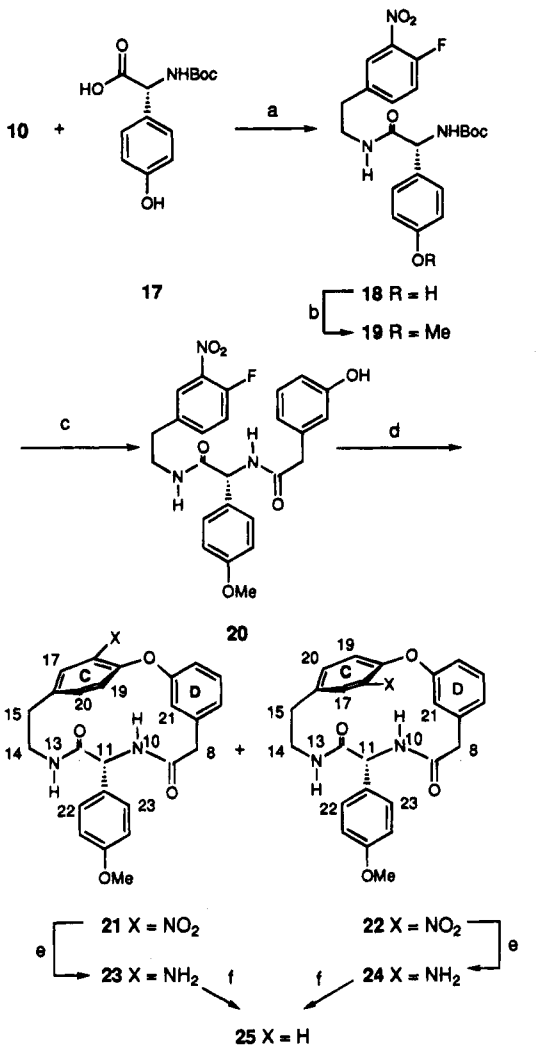
cyanation.[19] Chemoselective reduction of the nitrile group in the presence of the nitro function was problematic until either AlH_3[20] or sodium borohydride in the presence of 1 equiv of trifluoroacetic acid[21] was employed as reducing agent. Without further purification, the crude amine **10** was coupled with *N*-Boc-glycine to afford amide **11** in 87% overall yield. Mild acid deprotection of **11** followed by amide bond formation with 3-hydroxyphenylacetic acid provided compound **12** in 94% yield, without any complication due to free hydroxy group.

Treatment of a DMF solution of **12** with 4 equiv of anhydrous potassium carbonate at room temperature for 6 h afforded a single compound in 95% isolated yield. Macrocyclization was first run in 0.004 M concentration; however, we found that the high dilution technique was, in fact, not needed and that macrocyclization could be carried out routinely at 0.01 M concentration. Under these conditions, possible side products derived from dimerization and O-transacylations (inter- or intramolecular) were not observed. Spectral data (^1H and ^{13}C NMR, IR and elemental analysis) of the product were consistent with the structure assigned to the macrocyclic compound **13**. A comparison of ^1H NMR spectra of **12** with **13** shows an upfield shift of the H-21 signal from δ = 6.75 ppm in **12** to δ = 6.18 ppm in **13**. The equivalent proton in vancomycin is found at 5.65 ppm.[22] The mass spectrum of **13** by electron impact ionization at 70 eV showed the molecular ion peak corresponding to cyclic monomer at 355 together with the expected fragmentations. Further evidence for the structure of **13** was obtained by conversion to the known compound **15** (*vide infra*).[11] It is worth noting that, for compound **13**, geminal protons attached to C-8, C-11, C-14, and C-15 are all magnetically and chemically nonequivalent in contrast to those of compound **15**.[23] We reasoned that the lack of a substituent in the aromatic C ring of compound **15** may cause the molecule to be relatively flexible, and thus rotational freedom of the peptide chain could be expected to average out the shielding effects on geminal protons. Conversely, introduction of a substituent in C ring would be expected to more or less limit the conformational mobility of the molecule. This point will become more clear when we are able to isolate the two atropisomers (*vide infra*).

The potential of this approach was demonstrated by transforming the macrocyclic compound **13** into the model COD ring **15** (X = H) found in ristocetin, actaplanin, and actinoidin or into the model compound **16** (X = Cl) found in vancomycin and teicoplanin. Thus, reduction of nitro compound **13** employing Fe–$FeSO_4$[24] as reducing agent provided the corresponding amine **14** in excellent yield. Direct reductive deamination of **13** under Doyle's conditions[25] gave **14** in 66% yield. Conversion of **14** into **16** was not as straightforward as expected. After repeated trials, we found that the best results were obtained when the Sandmeyer reaction was performed

Scheme 2[a]



[a] Reagents (a) DCC; (b) MeI, K_2CO_3; (c) TFA, then DCC, *m*-hydroxyphenylacetic acid; (d) K_2CO_3, DMF; (e) Fe-$FeSO_4$; (f) ^tBuONO, DMF.

in the presence of both reductant (CuCl) and the ligand transfer agent ($CuCl_2$)[26] *in degassed solvent*. The successful preparation of compound **16** represents the first example where a single chlorine atom was correctly incorporated into the aromatic C ring.[10] The synthesis of a monochlorinated 16-membered lactone related to the DOE ring of vancomycin has been recently reported.[27]

Having established the validity of our approach, we turned our attention to the preparation of the more elaborate COD ring as shown in Scheme 2. Coupling of amine **10** with *N*-Boc-4-hydroxyphenylglycine (**17**) gave **18** in 72% yield. Methylation under usual conditions (K_2CO_3, MeI in Me_2CO) gave **19** in 80% yield. Removal of the Boc protecting group from **19** with trifluoroacetic acid followed by coupling with 3-hydroxyphenylacetic acid provided **20** in 50% yield. Macrocylization under the previously established conditions (4 equiv of K_2CO_3, 0.01 M in DMF) afforded two separable atropisomers **21** and **22** (54/40) in 94% yield.[27]

The mass spectra and the HRMS reveal that compounds **21** and **22** are constitutional isomers calculated

(19) Alternatively, 4-fluoro-3-nitrobenzyl bromide (**8**) can be prepared by bromination of commercially available 4-fluoro-3-nitrotoluene [NBS, $(PhCOO)_2O$, CCl_4] in 55% yield.
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for $C_{25}H_{23}N_3O_6$. ^1H NMR studies were carried out in $CDCl_3$ at 400 MHz at room temperature. The assignments of proton chemical shifts were based on the COSY $^1H-^1H$ spectrum. Both compounds have the characteristic upfield shifted H-21, expected for cyclized products. The major differences between these two isomers lie in the aromatic C ring protons, and the H-21 of the D-ring most likely to be affected by the orientation of C ring substitutents. The most notable difference in chemical shift is observed for proton H-17: an upfield shift from δ = 8.05 ppm in compound **21** to δ = 7.60 ppm in **22**. This large difference may be explained by considering that H-17 in **22** is disposed under the plane of aromatic D ring and that the shielding effect of diamagnetic anisotropy of D ring compensated the deshielding effect of the nitro group. The stereochemistry of compounds **21** and **22** was determined largely on decoupling and NOE studies. The diagnostic NOE crosspeaks were listed as follows. For **21**: H-21/H-20, H11, H-10, H-8; H-20/H-19, H-11; H-17/H-15, H-14; H-8/H-10, H-6 and H11/H-20, H-13. For **22**: H-17/H-21, H-11, H-22, H-13, H-14, H-15; H-21/H-10, H-8, H-23; H-6/H-8, H-8/H-10.

The chemical shift and vicinal coupling constants of the NH-13/H-14 and NH-10/H-11 pairs were also examined. The fact that identical values are observed (**21**: $J_{NH\text{-}13/H\text{-}14}$ = 10 Hz, $J_{NH\text{-}10/H\text{-}11}$ = 7.7 Hz; **22**: $J_{NH\text{-}13/H\text{-}14}$ = 10 Hz, $J_{NH\text{-}10/H\text{-}11}$ = 7.8 Hz) eliminates the possibility that the compounds differ in peptide conformation rather than in orientation of the aromatic rings.

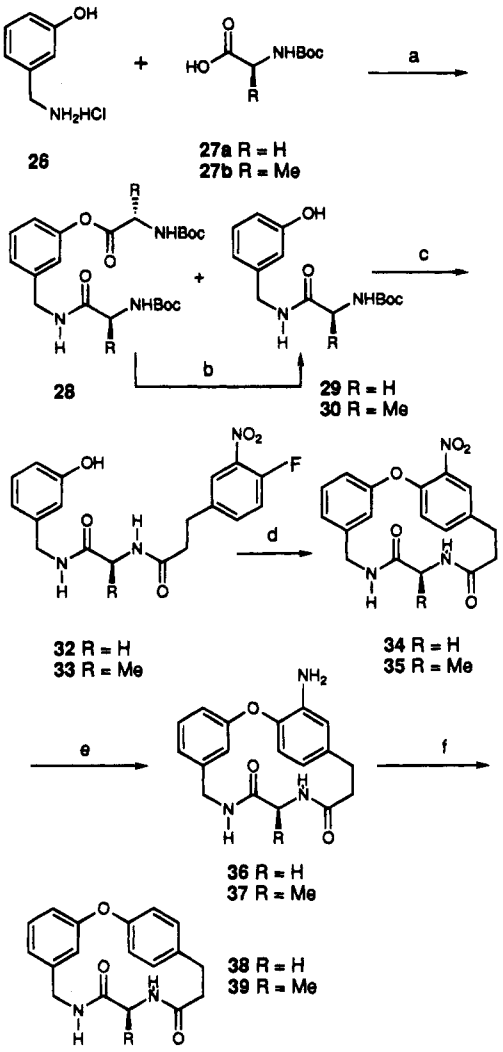
As shown by ^1H NMR experiments conducted in DMSO-d_6, no epimerization occurred at 70 °C after 15 h! However, partial thermal atropisomerization of **21** to **22** as well as **22** to **21** was observed in DMSO-d_6 at 110 °C in favor of the compound **22**, the "unnatural atropisomer". A control experiment showed that there was no such equilibration under the S_NAr reaction conditions, thus confirming that both **21** and **22** are kinetic products. The lack of atropdiastereoselectivity is, however, not suprising.

Reduction of **21** and **22** with Fe–$FeSO_4$ in water at 80 °C gave **23** and **24** in yields of 54% and 80%, respectively. ^1H NMR analysis of **23** and **24** revealed that atropisomerization or racemization of chiral center did not take place under these conditions. Reductive deamination of either **23** or **24** afforded the same compound **25**, identical in all respects (IR; ^1H and ^{13}C NMR; MS and α_D = −30, c = 0.5, DMF). This chemical transformation further supports the structure assignment of compound **21** and **22**.

Synthesis of Model DOE Rings. Extension of the above macrocyclization method to the preparation of model DOE rings is shown in Scheme 3. Coupling of 3-hydroxybenzylamine (**26**), obtained by reduction of 3-hydroxybenzonitrile, with *N*-Boc-glycine using the mixed anhydride method afforded **29** in 54% yield together with **28**. However, **28** can be quantitatively converted to **29** under basic hydrolysis conditions (K_2CO_3, MeOH–H_2O). Another coupling partner, 3-(4′-fluoro-3′-nitrophenyl)propionic acid (**31**), needed for constructing the macrocyclization precursor, was prepared in 94% overall yield by sequential treatment of bromide **8** with diethyl malonate in DMSO followed by acidic hydrolysis and decarboxylation. Removal of the Boc group from **29** followed by coupling with acid **31** then furnished dipeptide **32** in 59% yield.

Cyclization of **32** under standard conditions led to the macrocycle **34** in 88% yield. Its structure was supported

Scheme 3[a]



[a] Reagents (a) ClCOOMe, Et_3N; (b) K_2CO_3, MeOH–H_2O; (c) TFA then 3-(4′-fluoro-3′-nitrophenyl)propionic acid, DCC; (d) K_2CO_3, DMF; (e) Fe–$FeSO_4$; (f) ^{t}BuONO, DMF.

by spectroscopic data and in particular by the characteristic shielded proton signal H-21 at δ = 5.9 ppm in the ^1H NMR spectrum. Transformation of **34** into the known compound **38**[11] *via* a two-step sequence as described for the preparation of compound **15** confirmed its structure.

Macrocyclization of **33** containing the alanine residue, which was prepared according to the same synthetic scheme, afforded the macrocycle **35** in 72% yield. In order to verify the extent of racemization of the central amino acid of the linking amide chain, **35** was converted to the known compound **39**[11] in a straightforward fashion. It is worth noting that in the reduction step (Fe–$FeSO_4$, H_2O, reflux), thermoatropisomerization of **35**, occurred, and thus compound **37** was obtained as a mixture of two diastereoisomers. However, this was of no consequence, as the atropostereocenter was removed in the final compound **39**. The optical rotation of **39** (α_D = +230°, c = 0.5, MeOH) indicates that the enantiomeric excess of **39** is greater than 90% (lit.[11] α_D = +220° when ee = 90% and α_D = +253° when ee > 99.9%), thus confirming again that only little if any racemization took place during the macrocyclization.

Conclusion

We have developed an efficient method for the preparation of 16-membered macrocycles related to the vancomycin family of glycopeptides. The conditions used are so mild that no racemization occurs when a racemization-prone amino acid was incorporated into the acyclic chain. In addition to the high yield obtained, an important advantage of our approach is that the nitro group *ortho* to the diaryl ether linkage, after serving as an activator, allows the possibility to introduce either a chlorine atom or a hydrogen atom, thus providing the substitution pattern found in the vancomycin family of glycopeptides. The isolation and characterization of two atropisomers **21** and **22** is not only in itself extremely interesting but could well be pertinent to our projected total syntheses of these compounds. To the best of our knowledge, this report represents the first examples of a S_NAr-based macrocyclization. Extension of this remarkable macrocyclization reaction to other oxidatively coupled macrocycles of different ring size is being actively pursued in this laboratory, and the results will be reported elsewhere.

Experimental Section

Melting points were determined with a Kofler apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Nicolet-205 spectrometer. ^1H NMR spectra were measured on Brucker AC-200 (200 MHz), Bruker AC-250 (250 MHz), Bruker (300 MHz), and Bruker WM-400 (400 MHz) spectrometers with tetramethylsilane as internal standard (δ ppm). Solvents and reagents were purified according to standard laboratory techniques. All reactions requiring anhydrous conditions or in an inert atmosphere were conducted under an atmosphere of Argon.

4-Fluoro-3-nitrobenzylnitrile (9). To the solution of bromide **8** (12.35 g, 52.8 mmol) in CH_3CN (200mL) was added Et_4NCN (9.88 g, 63.4 mmol). The resulting deep green solution was stirred at room temperature for 4 h. The solvent was removed in *vacuo*, and the residue was purified by flash chromatography (SiO_2, Et_2O/heptane = 3/1) to afford **9** (7.97g, 83.9%) as a white crystalline solid: mp 33 °C (Et_2O/heptane); IR ($CHCl_3$) 2266, 1627, 1542, 1353 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 2H, CH_2CN), 7.38 (dd, J = 8.8 and 10.2 Hz, 1H, H-5), 7.65 (m, 1H, H-6), 8.10 (dd, J = 2.2 and 6.6 Hz, 1H, H-2) 1H; ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 22.6, 116.7, 119.3 (d, J = 16.7 Hz), 125.5, 127.4 (d, J = 4.4 Hz), 133.5, 135.2 (d, J = 7.2 Hz), 154.9 (d, J = 264.4 Hz); MS *m/z* 180, 134, 108.

2-[(*tert*-Butyloxycarbonyl)amino]-*N*-(4-fluoro-3-nitrophenethyl)acetamide (11). To a mixture of $NaBH_4$ (754.7 mg, 19.9 mmol) and TFA (1.53 mL, 19.9 mmol) in dry THF (15 mL) at room temperature was added nitrile **9** (715 mg, 3.9 mmol) in 5 mL of THF. The mixture was stirred for 15 h and cooled to 0 °C, and the excess of reducing agent was decomposed by dropwise addition of water. The volatile was removed in *vacuo*, and the residue was acidified. The aqueous layer was extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4), and evaporated to afford the starting material (309 mg). The aqueous layer was then basified and extracted with CH_2Cl_2 to give, after usual treatment, pure amine **10** (367 mg, 50.2% or 88.5% based on the reacted **9**): ^1H NMR (200 MHz, $CDCl_3$) δ 1.5 (brs, 2H, NH_2), 2.80 (t, J = 6.7 Hz, 2H, CH_2), 3.00 (t, J = 6.7 Hz, 2H, CH_2), 7.21 (dd, J = 8.5, 10.7 Hz, 1H, H-5'), 7.48 (ddd, J = 2.3, 4.3 and 8.5 Hz, 1H, H-6'), 7.90 (dd, J = 2.3 and 7.0 Hz, 1H, H-2'), MS *m/z* 184, 154, 138. On standing in solution, compound **10** rapidly became carbonated. It was thus submitted directly to the following reaction: DCC (1.45 g, 7.1 mmol) was added to the solution of amine **10** (1.3 g, 7.1 mmol) and *N*-Boc-glycine (1.24 g, 7.1 mmol) in CH_2Cl_2 (20 mL) and THF (20 mL). The reaction mixture was stirred for 15 h. After removal of the solvent, CH_2Cl_2 was added, and the precipitate was filtered. The filtrate was washed with aqueous $NaHCO_3$, H_2O and brine successively. The organic phase was concentrated in *vacuo* and purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 98/2, gradient eluent) to afford **11** (2.09 g, 87%): IR ($CHCl_3$) 3300–3500, 1684, 1539, 1516 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H, 3 × CH_3), 2.90 (t, J = 7.0 Hz, 2H, $ArCH_2$), 3.54 (q, J = 7.0 Hz, 2H, $ArCH_2CH_2$), 3.76 (d, J = 5.8 Hz, 2H, $OCCH_2NH$), 5.38 (t, J = 5.8 Hz, 1H, $OCCH_2NH$), 6.70 (brt, J = 7.0 Hz, 1H, $ArCH_2CH_2NH$), 7.24 (dd, J = 8.5 and 10.7 Hz, 1H, H-5'), 7.48 (ddd, J = 2.2, 4.2 and 8.5 Hz, 1H, H-6'), 7.87 (dd, J = 2.2 and 7.0 Hz, 1H, H-2'); ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 28.3, 34.6, 40.1, 44.6, 80.4, 118.5 (d, J = 21.1 Hz), 126.0 (d, J = 2.5 Hz), 136.0 (d, J = 8.8 Hz), 153.9 (d, J = 229.2 Hz), 156.9, 169.9; HRMS *m/z* 342.1438 ($C_{15}H_{20}FN_3O_5$ + H^+, 342.1467).

2-[(3-Hydroxyphenyl)acetamido]-*N*-(4-fluoro-3-nitrophenethyl)acetamide (12). Compound **11** (92 mg, 0.27 mmol) was dissolved in TFA (1 mL) and set aside at room temperature for 30 min. TFA was removed in *vacuo*, and the so-produced amine salt was dissolved in CH_2Cl_2 (3 mL), THF (3 mL), and Et_3N (57 μL, 0.41 mmol). After 30 min, 3-hydroxyphenylacetic acid (41.1 mg, 0.27 mmol), DCC (55.7 mg, 0.27 mmol), and a few drops of DMF was added. The reaction mixture was stirred for 10 h, and following the workup procedure detailed for **11**, compound **12** was obtained in 95% yield after column chromatography (SiO_2, CH_2Cl_2/MeOH = 98/2): mp 180–183 °C (EtOAc–MeOH); ^1H NMR (CD_3OD, 300 MHz) δ 2.83 (t, J = 7.0 Hz, 2H, H-15), 3.42 (t, J = 7.0 Hz, 2H, H-14), 3.46 (s, 2H, H-8), 3.76 (s, 2H, H-11), 6.66 (dd, J = 2.6 and 7.9 Hz, 1H, H-4), 6.75 (m, 2H, H-6 and H-21), 7.11 (t, J = 7.9 Hz, 1H, H-5), 7.28 (dd, J = 8.5 and 11.0 Hz, 1H, H-19), 7.50 (ddd, J = 2.2, 4.4, 8.5 Hz, 1H, H-20), 7.93 (dd, J = 2.2 and 7.0 Hz, 1H, H-17); ^{13}C NMR (CD_3OD–$CDCl_3$) δ 33.3, 39.3, 41.8, 45.9, 113.1, 115.1, 117.3 (d, J = 21.6 Hz), 119.4, 125.1 (d, J = 2.5 Hz), 128.7, 135.3 (d, J = 9.0 Hz), 135.8 (d, J = 4.5 Hz), 153.4 (d, J = 260.6 Hz), 169.6, 172.5; MS *m/z* 375, 268; HRMS *m/z* 375.1236 ($C_{18}H_{18}FN_3O_5$, 375.1231).

9,12-Dioxo-2-oxa-18-nitro-10,13-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (13). To the solution of compound **12** (138 mg, 0.37 mmol) in DMF (37 mL) was added K_2CO_3 (204 mg, 1.48 mmol). The mixture was stirred at room temperature for 6 h and then diluted with 120 mL of CH_2Cl_2, washed with 2 N HCl, H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from $CHCl_3$ to afford **13** (124 mg, 95%): mp 251–253 °C; IR ($CHCl_3$) 3350–3450, 1669, 1596, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.78 (ddd, J = 4.8, 8.7 and 13.6 Hz, 1H, H-15), 2.95 (m, 1H, H-15'), 3.42 (d, J = 14.7 Hz, 1H, H-8), 3.48 (d, J = 14.7 Hz, 1H, H-8'), 3.55 (m, 1H, H-14), 3.68 (dd, J = 3.8, 16.3 Hz, 1H, H-11), 3.79 (m, 1H, H-14'), 3.95 (dd, J = 6.0, 16.3 Hz, 1H, H-11'), 5.95 (brs, 1H, NH), 6.18 (t, J = 1.7 Hz, 1H, H-21), 6.29 (brs, 1H, NH), 6.89 (brd, J = 7.4 Hz, 1H, H-4), 7.03 (d, J = 8.3 Hz, 1H, H-19), 7.12 (dd, J = 2.4, 8.0 Hz, H-6), 7.28 (t, J = 8.0 Hz, 1H, H-5), 7.32 (dd, J = 2.2, 8.3 Hz, 1H, H-20), 7.86 (d, J = 2.2 Hz, 1H, H-17); ^{13}C NMR (CD_3OD), 36.5, 40.1, 42.5, 43.1, 115.0, 117.3, 124.8, 125.6, 127.6, 130.9, 137.2, 139.1, 149.1, 161.1, 170.3, 173.3; MS *m/z* 355, 327, 298, 270, 241. Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83. Found: C, 60.48; H, 5.18; N, 11.53.

9,12-Dioxo-2-oxa-18-amino-10,13-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (14). To the suspension of compound **13** (96 mg, 0.27 mmol) in refluxing H_2O was added Fe (151 mg, 2.7 mmol) and $FeSO_4$ (41 mg, 0.27 mmol). The reaction mixture was refluxed for 3 h, filtered through Celite, and washed thoroughly with CH_2Cl_2 . The aqueous phase was extracted with CH_2Cl_2, dried(Na_2SO_4), and evaporated in *vacuo*. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 40/1) to afford **14** as a slightly yellow solid (79 mg, 90%): mp 235–237 °C (MeOH); IR ($CHCl_3$) 3350–3550, 1666, 1512 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.70 (m, 2H, H-15), 3.38–3.77 (m, 5H, H-8, H-14, H-11), 3.85 (dd, J = 5.8 and 15.7 Hz, 1H, H-11), 4.75 (brs, 2H, NH_2), 6.18 (brs, 1H, H-21), 6.48 (dd, J = 1.6 and 8.0 Hz, 1H, H-20), 6.63 (d, J = 8.0 Hz, 1H, H-19), 6.74 (d, J = 1.6 Hz, 1H, H-17), 6.87 (d, J = 7.4 Hz, 1H, H-4), 7.09 (dd, J = 2.0 and 8.0 Hz, 1H, H-6), 7.33 (t, J = 7.8 Hz, 1H, H-5), 7.80 (t, J = 5.8 Hz, 1H,

NH-10), 8.04 (t, J = 4.8 Hz, 1H, NH-13); ^{13}C NMR (50.03 MHz, CD_3OD–a drop of $CDCl_3$) δ 34.8, 38.2, 41.5, 41.7, 112.2, 114.6, 116.7, 118.2, 121.3, 121.9, 128.9, 135.8, 138.3, 139.0, 140.1, 159.3, 167.4, 169.3; MS m/z 325, 297, 268, 240, 211; HRMS m/z 325.1430 ($C_{18}H_{19}N_3O_3$ requires 325.1427).

9,12-Dioxo-2-oxa-10,13-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (15). To a rapidly stirred solution of ^{t}BuONO (28 mg, 0.086 mmol) in anhydrous DMF, heated to 65 °C, was added dropwise *via* syringe a solution of amine (10.1 μL, 0.13 mmol) in DMF. The reaction mixture was stirred for 10 min, cooled to room temperature and diluted with Et_2O. The resulting solution was poured into 20% aqueous HCl, and the organic layer was separated and washed with HCl, H_2O, and brine successively, dried (Na_2SO_4), and evaporated in *vacuo* to afford a crude mixture which was purified by flash chromatography (SiO_2, EtOAc/MeOH = 40/1) to give **15** (17.6 mg, 66%): mp 255–257 °C (lit.[11] 256–257 °C); IR ($CHCl_3$) 3620, 3400, 1684 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.78 (t, J = 6.0 Hz, 2H, H-15), 3.45 (s, 2H, H-8), 3.56 (t, J = 6.0 Hz, 2H, H-14), 3.77 (s, 2H, H-11), 6.14 (t, J = 2.0 Hz, 1H, H-21), 6.80 (brd, J = 7.4 Hz, 1H, H-4), 6.85 (d, J = 8.4 Hz, 2H, H-18 and H-19), 6.98 (dd, J = 2.6 and 8.2 Hz, 1H, H-4), 7.20 (d, J = 8.4 Hz, 2H, H-17 and H-20), 7.21 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$–a drop of CD_3OD, 50.03 MHz) δ 35.6, 39.7, 42.0, 43.1, 113.9, 116.3, 122.0, 122.7, 129.8, 131.2, 135.4, 136.7, 155.0, 161.1, 168.6, 171.5; MS m/z 310, 282, 255.

9,12-Dioxo-2-oxa-18-chloro-10,13-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (16). To a solution of $NaNO_2$ (10.35 mg, 0.15 mmol) in degassed concd HCl was added compound **14** in degassed HOAc at 0 °C. Stirring was continued for 20 min at the same temperature, and the reaction mixture was then transferred into a solution of CuCl (39.6 mg, 0.4 mmol) and $CuCl_2$ (53.8 mg, 0.4 mmol) in concd HCl at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 3 h at room temperature. The reaction was quenched by addition of NH_4OH in saturated aqueous NH_4Cl untill the blue color persisted. The aqueous solution was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated in *vacuo*. Compounds **15** (9.6 mg, 39.5%) and **16** (14.5 mg, 53.5%) were separated by HPLC (column Nova-Pak C_{18}, 4 μm; mobile phase: heptane/2-isopropanol = 9/1; flow rate: 1 mL/min; retention time: compound **15**, 11.64 min; compound **16**, 16.04 min). Compound **16**: mp 238–240 °C ($CHCl_3$); IR ($CHCl_3$) 3300–3500, 1669, 1594, 1513, 1444 cm^{-1}; ^1H NMR ($CDCl_3$–a drop of CD_3OD) δ 2.7–2.9 (m, 2H, H-15), 3.42 (d, J = 14.5 Hz, 1H, H-8), 3.50 (d, J = 14.5 Hz, 1H, H-8), 3.5–3.6 (m, 1H, H-14), 3.64 (d, J = 16.0 Hz, 1H, H-11), 3.65–3.75 (m, 1H, H-14), 3.77 (d, J = 16.0 Hz, 1H, H-11), 5.97 (t, J = 1.9 Hz, 1H, H-21), 6.83 (d, J = 7.5 Hz, 1H, H-4), 6.93 (d, J = 8.2 Hz, 1H, H-19), 7.08 (dd, J = 2.1, 8.2 Hz, 1H, H-20), 7.10 (m, 1H, H-6), 7.28 (t, J = 7.5 Hz, 1H, H-5) 7.32 (d, J = 2.1 Hz, 1H, H-17); ^{13}C NMR (50.03 MHz, $CDCl_3$–a drop of CD_3OD) δ 35.3, 39.2, 41.9, 42.9, 112.6, 116.1, 123.1, 123.8, 129.8, 130.0, 131.9, 136.8, 150.2, 168.4, 171.2; MS m/z 346, 344, 318, 316, 289, 287; HRMS m/z 344.0948/346.0913 ($C_{18}H_{17}ClN_2O_3$ requires 344.0925/346.0895).

(2*R*)-2-[(*tert*-Butyloxycarbonyl)amino]-*N*-(4-fluoro-3-nitrophenethyl)-*p*-hydroxyphenylacetamide (18). To the solution of *N*-Boc-4-hydroxyphenylglycine (506 mg, 1.9 mmol), DCC (391 mg, 1.9 mmol), and 1-hydroxybenzotriazole (HOBt, 257 mg, 1.9 mmol) in DMF (1 mL) and CH_2Cl_2 was added, at 0 °C, a solution of amine **10** (350 mg, 1.9 mmol) in DMF–CH_2Cl_2 (1/1, 4 mL). The resulting reaction mixture was stirred at room temperature for 12 h. The solvent was removed, and the residue was partitioned with 20 mL of EtOAc. The solid (DCU) was filtered off, and the organic phase was washed with 3 N HCl (20 mL), saturated $NaHCO_3$ (20 mL), H_2O, and brine, dried (Na_2SO_4), and evaporated. Flash chromatography (SiO_2, 5% MeOH–CH_2Cl_2) afforded **18** as an yellow solid (600 mg, 72%): mp 79 °C; α_D = −67° ($CHCl_3$, c = 0.1); IR ($CHCl_3$) 3437, 3337, 1756, 1700, 1537, 1500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 9H, ^{t}Bu), 2.80 (t, J = 7.0 Hz, 2H, CH_2), 3.54 (m, 2H, CH_2), 5.01 (d, J = 7.2 Hz, 1H, OCC*H*(Ar)NH), 5.72 (d, J = 7.2 Hz, 1H, N*H*COOBu^t), 6.25 (t, J = 7.0 Hz, 1H, CH_2NHCO), 6.6, 7.01 (d, J = 8.4 Hz, AB system, 4H) 7.12 (dd, J = 8.5 and 10.6 Hz, 1H, H *ortho* to F), 7.20 (ddd, J = 2.2, 4.2 and 8.5 Hz, 1H, H *meta* to F), 7.75 (dd, J = 2.2 and 7.0 Hz, 1H, H *ortho* to NO_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 34.6, 41.1, 59.0, 81.2, 116.7, 119.2 (d, J = 20.7 Hz), 126.6, 129.1, 129.4, 129.8, 136.5 (d, J = 19.7), 136.7 (d, J = 8.0 Hz), 154.6 (d, J = 219.8 Hz), 157.5, 171.9; MS m/z 433, 376, 360, 317. Anal. Calcd for $C_{21}H_{24}FN_3O_6$: C, 58.20; H, 5.58; N, 9.70. Found: C, 58.42; H, 5.78; N, 9.53.

(2*R*)-2-[(*tert*-Butyloxycarbonyl)amino]-*N*-(4-fluoro-3-nitrophenethyl)-*p*-methoxyphenylacetamide (19). A solution of **18** (600 mg, 1.38 mmol) in acetone, K_2CO_3 (950 mg, 6.92 mmol), and MeI (587 mg, 4.14 mmol) was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate poured into H_2O (100 mL), extracted with EtOAc, dried (Na_2SO_4), and evaporated to afford the crude mixture which was purified by flash chromatography (SiO_2, 5% MeOH–CH_2Cl_2) afforded **19** as a yellow solid (495 mg, 80%): mp 66 °C; α_D = −47° ($CHCl_3$, c = 0.1); IR ($CHCl_3$) 3200–3550, 1706, 1681, 1612, 1550 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 9H, ^{t}Bu), 2.78 (t, J = 6.7 Hz, 2H, CH_2), 3.40 (m, 1H, C*H*H), 3.60 (m, 1H, CH*H*), 3.80 (s, 3H, CH_3O), 5.0 (d, J = 7.3 Hz, 1H, OCC*H*(Ar)NH), 5.70 (d, J = 7.3 Hz, 1H, *NH*COOBu^t), 6.25 (brs, 1H, CH_2NHCO), 6.8 (d, J = 8.4 Hz, AB system, 2H), 7.1 (dd, J = 8.5 and 10.6 Hz, 1H, H *ortho* to F), 7.18 (d, J = 8.4 Hz, AB system, 2H) 7.1–7.2 (m, 1H, H *meta* to F), 7.73 (dd, J = 2.2 and 7.0 Hz, 1H, H *ortho* to NO_2); MS m/z 447, 374, 331. Anal. Calcd for $C_{22}H_{26}FN_3O_6$: C, 59.05; H, 5.86; N, 9.39. Found: C, 58.80; H, 5.57; N, 9.50.

(2*R*)-2-[(3-Hydroxyphenyl)acetamido]-*N*-(4-fluoro-3-nitrophenethyl)-*p*-methoxyphenylacetamide (20). Following the procedure detailed for **12**, compound **20** was isolated in 50% yield: mp 172–173 °C; α_D = −62° (MeOH, c = 1); IR ($CHCl_3$) 3200–3550, 1717, 1675, 1593, 1537 cm^{-1}; ^1H NMR (300 MHz, Me_2CO-d_6) δ 2.85 (t, J = 6.6 Hz, 2H, H-15), 3.35 (m, 1H, H-14), 3.5 (s, 2H, H-8), 3.58 (m, 1H, H-14), 3.75 (s, 3H, MeO), 5.30 (d, J = 7.5 Hz, 1H, H-11), 6.70 (dd, J = 1.8 and 7.8 Hz, 1H, H-4), 6.80 (d, J = 8.7 Hz, 2H, H-24 and H-25), 6.75–6.82 (m, 2H, H-6 and H-21), 7.08 (t, J = 7.8 Hz, 1H, H-5), 7.20 (d, J = 8.7 Hz, 2H, H-22 and H-23), 7.22 (dd, J = 8.6 and 11.1 Hz, 1H, H-19), 7.45 (ddd, J = 2.2, 4.4 and 8.6 Hz, 1H, H-20), 7.48 (brs, 1H, NH-13), 7.60 (d, J = 7.5 Hz, 1H, NH-10), 7.83 (dd, J = 2.2 and 7.2 Hz, 1H, H-17), 8.31 (brs, 1H, OH); ^{13}C NMR (50.03 MHz, Me_2CO-d_6) δ 35.0, 40.9, 43.6, 55.6, 57.5, 114.7, 117.3, 118.8 (d, J = 17.1 Hz), 121.4, 126.9, 130.3, 137.5 (d, J = 6.0 Hz), 138.6, 154.7 (d, J = 206.1), 170.5, 171.3; MS m/z 481, 461, 404; HRMS m/z 481.1710 ($C_{25}H_{24}FN_3O_6$ requires 481.1650).

Macrocycles 21 and 22. Following the procedure detailed for **13**, compounds **21** and **22** were isolated in yields of 54% and 40%, respectively (preparative TLC, eluent: EtOAc). Compound **21**: mp 287–288 °C; α_D = −76° ($CHCl_3$, c = 0.4); IR ($CHCl_3$) 3200–3500, 1676, 1589, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (dt, J = 4.9 and 13.3 Hz, 1H, H-15), 3.00–3.18 (m, 2H, H-15′ and H-14), 3.32 (d, J = 14.0 Hz, 1H, H-8), 3.50 (d, J = 14.0 Hz, 1H, H-8′), 3.77 (s, 3H, OMe), 4.08–4.17 (m, 1H, H-14′), 5.30 (d, J = 7.8 Hz, 1H, H-11), 5.98 (brd, J = 10.0 Hz, 1H, NH-13), 6.31 (s, 1H, H-21), 6.78 (d, J = 8.6 Hz, 2H, H-24 and H-25), 6.83 (d, J = 8.4 Hz, 1H, H-19), 6.88 (d, J = 7.3 Hz, 1H, H-6), 7.02 (d, J = 7.8 Hz, 1H, NH-10), 7.07 (dd, J = 1.8 and 8.4 Hz, 1H, H-20), 7.15 (brd, J = 8.0 Hz, 1H, H-4), 7.18 (d, J = 8.0 Hz, 2H, H-22 and H-23), 7.26 (t, J = 8.0 Hz, 1H, H-5), 8.05 (d, J = 1.8 Hz, 1H, H-17); ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 36.1, 39.9, 43.7, 55.0, 55.8, 114.3, 114.6, 117.2, 124.2, 124.4, 126.5, 128.5, 130.2, 136.0, 137.2, 160.0, 170.0; MS m/z 461, 431, 404; HRMS m/z 461.1560 ($C_{25}H_{23}N_3O_6$ requires 461.1587). Compound **22**: mp 180–182 °C; α_D = +64° ($CHCl_3$, c = 0.2); IR ($CHCl_3$) 3200–3500, 1711, 1662, 1540, 1503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (dt, J = 5.2, 13.5 Hz, 1H, H-15), 2.95–3.00 (m, 1H, H-15′), 3.01–3.08 (m, 1H, H-14), 3.37 (d, J = 14.8, 1H, H-8), 3.50 (d, J = 14.8 Hz, 1H, H-8′), 3.72 (s, 3H, OMe), 4.20 (m, 1H, H-14′), 5.35 (d, J = 7.6 Hz, 1H, H-21), 6.10 (brs, 1H, H-21), 6.51 (brd, J = 10.0 Hz, 1H, NH-13), 6.76 (d, J = 8.7 Hz, 2H, H-24 and H-25), 6.77 (d, J = 8.1 Hz, 1H, H-19), 6.84 (brd, J = 7.7 Hz, 1H, H-6), 6.96 (d, J = 7.7 Hz, 1H, NH-10), 7.13 (dd, J = 2.6 and 8.1 Hz, 1H, H-4), 7.21 (d, J = 8.7 Hz, 1H, H-22 and H-23), 7.22 (dd, J = 2.0 and 8.1 Hz, 1H, H-20), 7.28 (dd, J = 7.7 and 8.1 Hz, 1H, H-5), 7.60 (d, J = 2.0 Hz, 1H, H-17); ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 35.1, 39.0,

43.4, 55.4, 55.9, 111.8, 114.4, 116.8, 123.9, 125.9, 127.7, 128.5, 130.4, 136.1, 136.8, 137.0, 141.5, 147.6, 159.7, 169.1, 170.3; MS *m/z* 461, 431, 404; HRMS *m/z* 461.1619 ($C_{25}H_{23}N_3O_6$ requires 461.1587).

Compound 23. Following the procedure detailed for **14**, compound **23** was isolated in 54% yield (preparative TLC, eluent: $CHCl_3$/MeOH = 9/1): mp 254–255 °C; α_D = −156° (MeOH, *c* = 0.4); IR ($CHCl_3$) 3431, 3387, 1737, 1668, 1593, 1512 cm^{-1}; ^1H NMR (300 MHz, Me_2CO-d_6) δ 2.5 (dt, *J* = 5.0 and 13.3 Hz, 1H, H-15), 2.8–2.85 (m, 1H, H-14), 2.92 –3.02 (m, 1H, H-15′), 3.20 (d, *J* = 14.0 Hz, 1H, H-8), 3.72 (s, 3H, MeO), 3.80 (d, *J* = 14.0 Hz, 1H, H-8′), 4.11 (ddt, *J* = 4.3, 10.5 and 13.3 Hz, 1H, H-14′), 4.42 (brs, 2H, NH_2), 5.25 (d, *J* = 8.0 Hz, 1H, H-11), 6.38 (brs, 1H, H-21), 6.42 (dd, *J* = 2.0 and 8.0 Hz, 1H, H-20), 6.58 (d, *J* = 8.0 Hz, 1H, H-19), 6.78–6.86 (m, 2H, H-6 and H-17), 6.82 (d, *J* = 8.7 Hz, 2H, H-24 and H-25), 6.98 (dd, *J* = 2.4 and 8.0 Hz, 1H, H-4), 7.22 (t, *J* = 8.0 Hz, 1H, H-5), 7.27 (d, *J* = 8.7 Hz, 2H, H-22 and H-23), 7.28 (brd, *J* = 10.5 Hz, 1H, H-13), 7.62 (d, *J* = 8.0 Hz, 1H, NH-10); ^{13}C NMR (50.03 MHz, $CDCl_3$) δ 36.4, 40.1, 43.7, 55.7, 56.5, 113.7, 114.7, 116.2, 117.5, 121.2, 123.0, 123.4, 127.1, 129.2, 130.3, 133.2, 137.1, 137.3, 139.6, 141.7, 160.4, 161.2, 169.5, 170.6; MS *m/z* 431; HRMS *m/z* 431.1869 ($C_{25}H_{25}N_3O_4$ requires 431.1846).

Compound 24. Following the procedure detailed for **14**, compound **24** was isolated in 80% yield by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 96/4): mp 254–255 °C; α_D = −79° (MeOH, *c* = 0.4); IR ($CHCl_3$) 3250–3400, 1668, 1612, 1506 cm^{-1}; ^1H NMR (300 MHz, Me_2CO-d_6 and a drop of MeOH-d_4) δ 2.49 (dt, *J* = 5.1 and 13.5 Hz, 1H, H-15), 2.82–2.92 (m, 1H, H-14), 2.95 (ddd, *J* = 1.5, 5.1 and 11.8 Hz, 1H, H-15′), 3.23 (d, *J* = 14.5 Hz, 1H, H-8), 3.73 (s, 3H, MeO), 3.90 (d, *J* = 14.5 Hz, 1H, H-8′), 4.1–4.24 (m, 3H, H-14′ and NH_2), 5.28 (s, 1H, H-11), 6.29 (brs, 1H, H-21), 6.54 (dd, *J* = 1.9 and 8.1 Hz, 1H, H-20), 6.60 (d, *J* = 1.9 Hz, 1H, H-17), 6.67 (d, *J* = 8.1 Hz, 1H, H-19), 6.80 (d, *J* = 8.7 Hz, 2H, H-24 and H-25), 6.79 (m, 1H, H-4), 6.98 (dd, *J* = 2.4 and 8.0 Hz, 1H, H-6), 7.21 (t, *J* = 8.0 Hz, 1H, H-5), 7.29 (d, *J* = 8.7 Hz, 2H, H-22 and H-23); ^{13}C NMR (50.03 MHz, Me_2CO-d_6 and a drop of CD_3OD) δ 36.8, 39.2, 43.2, 55.2, 56.1, 112.5, 114.6, 115.5, 119.0, 120.1, 123.4, 123.6, 129.0, 130.3, 133.0, 137.5, 139.8, 140.8, 160.1, 160.7, 169.5, 170.4; MS *m/z* 431, 387, 374; HRMS *m/z* 431.1843 ($C_{25}H_{25}N_3O_4$ requires 431.1846).

(11*R*)-9,12-Dioxo-2-oxa-11-(4-methoxyphenyl)-10,13-diazatricyclo[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (25). Following the procedure detailed for **15**, both of the amino compounds **23** and **24** were converted into the same product **25** which was isolated in 72% yield by preparative TLC (SiO_2, CH_2Cl_2/MeOH = 9/1): mp 256–258 °C; α_D = −34° (DMF, *c* = 0.5); IR (KBr) 3306, 1643, 1521, 1512 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.70 (dt, *J* = 4.7 and 13.2 Hz, 1H, H-15), 2.98–3.08 (m, 2H, H-15′ and H-14), 3.13 (d, *J* = 14.0 Hz, 1H, H-8), 3.81 (s, 3H, MeO), 3.92 (d, *J* = 14.0 Hz, 1H, H-8′), 4.0–4.15 (m, 1H, H-14), 5.34 (d, *J* = 8.8 Hz, 1H, H-11), 6.18 (brs, 1H, H-21), 6.83–6.92 (m, 2H, H-4 and H-20), 6.99 (d, *J* = 8.2 Hz, 2H, H-24 and H-25), 7.08–7.15 (m, 2H, H-6 and H-18), 7.28–7.34 (m, 2H, H-5 and H-19), 7.39 (d, *J* = 8.2 Hz, 2H, H-22 and H-23), 7.47 (d, *J* = 8.3 Hz, 1H, H-17), 8.24 (d, *J* = 9.9 Hz, 1H, NH-13), 8.77 (d, *J* = 8.8 Hz, 1H, NH-10); ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.3, 39.5, 42.6, 55.4, 55.9, 114.1, 114.4, 115.7, 121.7, 122.5, 123.1, 128.6, 130.2, 131.0, 132.8, 133.1, 136.4, 139.4, 154.4, 159.4, 161.2, 169.3, 170.1; MS *m/z* 416, 359; HRMS *m/z* 416.1765 ($C_{25}H_{24}N_2O_4$ requires 416.1737).

2-[(*tert*-Butyloxycarbonyl)amino]-*N*-(3-hydroxybenzyl)acetamide (29). To the solution of *N*-Boc-glycine (1.24 g, 7.12 mmol) and Et_3N (1 mL, 7.12 mmol) in THF was added ClCOOEt (681 μL, 7.12 mmol) dropwise at −10 °C. In a separate flask, a solution of **26** (1.14 g, 7.12 mmol) in THF (9 mL) and DMF (1 mL) was treated with Et_3N (1.1 mL, 7.83 mmol) for 20 min at room temperature, and this was transferred into the mixed anhydride solution dropwise via syringe at −10 °C. After the solution was stirred for 2 h at 0 °C, H_2O was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (16 mL) and H_2O (4 mL) and treated with K_2CO_3 for 4 h at room temperature. MeOH was removed, the aqueous solution was acidified with 2 N HCl and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH = 20/1) and recrystallization (EtOAc–MeOH) to afford **29** as a white crystalline solid (1.08 g, 54.4%): mp 146–147 °C (EtOAc–MeOH) (lit.[11] mp 144–145 °C (Et_2O)); IR ($CHCl_3$) 3628, 3447, 1701, 1683 cm^{-1}; ^1H NMR (200 MHz, Me_2CO-d_6) δ 1.45 (s, 9H, ^{t}BuO), 3.78 (d, *J* = 5.9 Hz, 2H, ArCH_2NH), 4.34 (d, *J* = 6.0 Hz, 2H, OCCH_2NH), 6.22 (brs, 1H, NH), 6.7 (m, 3H, aromatic H-2, H-4 and H-6), 7.1 (t, *J* = 7.9 Hz, 1H, H-5), 7.53 (brs, 1H, NH), 8.30 (s, 1H, OH); ^{13}C NMR (50.03 MHz, CD_3OD) δ 28.6, 43.7, 43.8, 80.7, 114.9, 119.3, 130.2, 140.5, 158.0, 171.7.

(2*S*)-2-[(*tert*-Butyloxycarbonyl)amino]-*N*-(3-hydroxybenzyl)propionamide (30). Following the procedure detailed for **29**, compound **30** was isolated as a sticky solid in 51% yield by flash chromatography (SiO_2, EtOAc/heptane = 35/65): α_D = −10° ($CHCl_3$, *c* = 0.3); IR ($CHCl_3$) 3450, 3325, 1687, 1600, 1493 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.3 (s, 3H, ^{t}BuO), 1.4 (d, *J* = 7.0 Hz, 1H, Me), 4.13 (m, 1H, *CH*Me), 4.3–4.5 (m, 2H, CH_2), 5.13 (brs, 1H, NH), 6.59 (brs, 1H, NH), 6.72 (m, 3H, H-2, H-4 and H-6), 7.12 (t, *J* = 7.6 Hz, 1H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 28.2, 43.6, 50.0, 113.8, 115.0, 119.2, 129.8, 138.7, 155.8, 157.0, 173.9; MS *m/z* 294, 238, 221; HRMS *m/z* 295.168 ($C_{15}H_{22}N_2O_4$ + H requires 295.1659).

4-Fluoro-3-nitro-phenylpropionic Acid (31). In a flame-dried flask, purged by argon, was added NaH (480 mg, 50% oil dispension, 10 mmol) which was washed two times with pentane and then DMSO (40 mL). To this solution was introduced diethyl malonate (763 μL, 5 mmol). After 5 min bromide **8** (1.17 g, 5 mmol) was added. The mixture was stirred for 5 min and then diluted with CH_2Cl_2 and washed with H_2O, and the organic layer was dried (Na_2SO_4) and evaporated in *vacuo*. The crude mixture was purified by flash chromatography (heptane/ether = 5/1) to afford 2-(4′-fluoro-3′-nitrobenzyl)malonate as an oil (1.48 g, 94%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 6H, 2 × Me), 3.26 (d, *J* = 7.0 Hz, 2H, CH_2), 3.63 (t, 1H, *J* = 7 Hz, 1H, CH), 4.20 (q, *J* = 7.0 Hz, 4H, 2 × CH_3CH_2O), 7.23 (dd, *J* = 8.0 and 10 Hz, 1H, H-5), 7.50 (m, 1H, H-6), 7.93 (dd, *J* = 2.0 and 8.0 Hz, 1H, H-2); MS *m/z* 313, 268, 240. The ester was dissolved in concd HCl (10 mL) and was refluxed overnight. The aqueous solution was extracted with EtOAc, and the organic phase was dried (Na_2SO_4) and evaporated to give pure compound **31** after recrystallization from CH_2Cl_2–pentane (1.05 g, 100%): mp 97–99 °C; IR ($CHCl_3$) 3250, 1718, 1537 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.73 (t, *J* = 6.0 Hz, 2H, CH_2), 3.0 (t, *J* = 6.0 Hz, 2H, CH_2), 7.23 (t, *J* = 8.0 Hz, 1H, H-5), 7.50 (m, 1H, H-6), 7.90 (dd, *J* = 2.0 and 8.0 Hz, 1H, H-2); ^{13}C NMR (75 MHz, CD_3OD) δ 31.3, 36.5, 119.9 (d, *J* = 21 Hz), 127.3, 137.5 (d, *J* = 8.2 Hz), 140.4, 155.8 (d, *J* = 255 Hz), 176.5. Anal. Calcd for $C_9H_8FNO_4$: C, 50.70; H, 3.75. Found: C, 50.52; H, 3.95.

***N*-(3-Hydroxybenzyl)-2-[3-(4-fluoro-3-nitrophenyl)propionamido]acetamide (32).** Following the procedure detailed for **12**, compound **32** was isolated as a sticky solid in 59% yield by flash chromatography (SiO_2, MeOH/CH_2Cl_2 = 2/98): IR ($CHCl_3$) 3200–3600, 1743, 1718, 1675, 1531 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 2.6 (t, *J* = 7.5 Hz, 2H, H-15), 3.01 (t, *J* = 7.5 Hz, 2H, H-14), 3.80 (s, 2H, H-8), 4.3 (s, 2H, H-11), 6.80 (m, 3H, H-4, H-6 and H-21), 7.20 (t, *J* = 7.6 Hz, 1H, H-5), 7.40 (dd, *J* = 8.6 and 11.0 Hz, 1H, H-19), 7.65 (m, 1H, H-20), 8.05 (dd, *J* = 2.2 and 6.9 Hz, 1H, H-17); ^{13}C NMR (75 MHz, CD_3OD) δ 31.8, 38.4, 44.1, 44.5, 115.7 (d, *J* = 5.9 Hz), 119.7 (d, *J* = 20.8), 120.1, 127.21, 131.1, 137.5 (d, *J* = 8.4 Hz), 140.8, 156.2 (d, *J* = 225 Hz), 159.3, 172.0, 175.5; MS *m/z* 376 (M + H), 356; HRMS *m/z* 376.1341 ($C_{18}H_{18}FN_3O_5$ + H requires 376.131).

(2*S*)-*N*-(3-Hydroxybenzyl)-2-[3-(4-fluoro-3-nitrophenyl)propionamido]propionamide (33). Following the procedure detailed for **12**, compound **33** was isolated as a sticky solid in 31% yield by preparative TLC (SiO_2, EtOAc): IR ($CHCl_3$) 3200–3600, 1720, 1630, 1515, 1400 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 1.3 (d, *J* = 7.2 Hz, 3H, CHCH_3), 2.55 (t, *J* = 7.6 Hz, 2H, H-15), 2.96 (t, *J* = 7.6 Hz, 2H, H-14), 4.28 (s, 2H, H-8), 4.31 (m, 1H, H-11), 6.68 (m, 3H, H-4, H-6 and H-21),

7.10 (t, J = 8.0 Hz, 1H, H-5), 7.25 (dd, J = 8.4 and 11.1 Hz, 1H, H-19), 7.55 (ddd, J = 2.2, 4.4 and 8.4 Hz, 1H, H-20), 7.95 (dd, J = 2.2 and 7.2 Hz, 1H, H-17); ^{13}C NMR (50.03 MHz, CD_3OD) δ 18.2, 31.3, 37.7, 43.9, 50.5, 115.1, 119.2 (d, J = 21.0 Hz), 126.6 (d, J = 3.0 Hz), 130.5, 136.9 (d, J = 9.2 Hz), 137.0, 141.2, 155.2 (d, J = 259.1 Hz), 174.0, 174.9; MS m/z 389, 359; HRMS m/z 389.1384 ($C_{19}H_{20}FN_3O_5$ requires 389.1387).

10,13-Dioxo-2-oxa-18-nitro-9,12-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (34). Following the procedure detailed for **13**, compound **34** was isolated (reaction time 24 h) as a white crystalline solid in 84% yield by preparative TLC (SiO_2, MeOH/CH_2Cl_2 90%): IR ($CHCl_3$) 3200–3500, 1731, 1656, 1600, 1531 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 2.6 (m, 2H, H-15), 3.06 (t, J = 6.5 Hz, 2H, H-14), 3.75 (d, J = 2.4 Hz, 2H, H-8), 4.30 (s, 2H, H-11), 5.90 (s, 1H, H-21), 6.87 (d, J = 7.1 Hz, 1H, H-4), 7.06 (dd, J = 2.3 and 8.3 Hz, 1H, H-6), 7.15 (d, J = 8.3 Hz, 1H, H-19), 7.30 (t, J = 7.9 Hz, 1H, H-5), 7.56 (dd, J = 2.2 and 8.2 Hz, 1H, H-20), 7.90 (d, J = 2.2 Hz, 1H, H-17); ^{13}C NMR (62.5 MHz, CD_3OD) δ 31.9, 38.4, 42.7, 43.1, 112.1, 116.4, 121.4, 126.9, 127.2, 130.8, 136.6, 140.0, 141.3, 161.4, 171.1, 173.4; MS m/z 356 (M + H), 326, 309; HRMS m/z 356.1243 ($C_{18}H_{17}N_3O_5$ + H requires 356.1248).

(11*S*)-10,13-Dioxo-2-oxa-18-nitro-11-methyl-9,12-diazatricyclo[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (35). Following the procedure detailed for **13**, compound **35** was isolated (reaction time 24 h) as a white crystalline solid in 72% yield by preparative TLC (SiO_2, MeOH/CH_2Cl_2 = 1/10): mp 158–160 °C; α_D = +152° (c = 0.58, MeOH); IR ($CHCl_3$) 3350–3450, 1706, 1656, 1600, 1537, 1512 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3 (d, J = 6.8 Hz, 3H, Me), 2.3 (dt, J = 5.5 and 12.8 Hz, 1H, H-15), 2.70 (td, J = 3.9 and 12.8 Hz, 1H, H-15′), 3.01 (m, 2H, H-14), 3.73 (dd, J = 3.5 and 15.8 Hz, 1H, H-8), 4.29 (m, 1H, H-11), 4.93 (dd, J = 9.4 and 15.8 Hz, 1H, H-8′), 5.91 (s, 1H, H-21), 6.26 (brs, 2H, NH-9 and NH-12), 6.83 (d, J = 7.3 Hz, 1H, H-4), 6.93 (d, J = 8.3 Hz, 1H, H-19), 7.13 (dd, J = 2.1 and 7.8 Hz, 1H, H-6), 7.25–7.33 (m, 2H, H-5 and H-20), 7.89 (d, J = 2.0 Hz, 1H, H-17); ^{13}C NMR (50.3 MHz, CD_3OD) δ 19.4, 31.7, 38.7, 42.2, 49.8, 112.3, 116.4, 121.1, 125.9, 126.1, 130.4, 136.6, 139.7, 141.2, 148.0, 161.1; MS m/z 369, 352, 341; HRMS m/z 370.1413 ($C_{19}H_{19}N_3O_5$ + H requires 370.1404). Chiral phase HPLC analysis (OD Daicel 4 × 250 mm) of **35** revealed a 98.7:1.3 ratio of enantiomers.

10,13-Dioxo-2-oxa-18-amino-9,12-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7(21),16,18,19-hexaene (36). Following the procedure detailed for **14**, compound **36** was isolated as a white crystalline solid in 82% yield by preparative TLC (SiO_2, MeOH/CH_2Cl_2 90%): mp 236–238 °C; IR ($CHCl_3$) 3200–3600, 1710, 1655, 1510 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.51 (m, 2H, H-15), 2.85 (m, 2H, H-14), 3.68, 3.82 (d, J = 15.2 Hz, AB system, 2H, H-8), 4.22, 4.35 (d, J = 15.8 Hz, AB system, 2H, H-11), 6.05 (s, 1H, H-21), 6.55 (dd, J = 2.0 and 8.0 Hz, 1H, H-20), 6.65–6.75 (m, 2H, H-17, H-19), 6.78 (d, J = 7.3 Hz, 1H, H-4), 7.05 (dd, J = 2.3 and 8.2 Hz, 1H, H-6), 7.28 (t, J = 7.8 Hz, 1H, H-5); MS m/z 325, 297, 267; HRMS m/z 325.1431 ($C_{18}H_{19}N_3O_3$ requires 325.1427).

(11*S*)-10,13-Dioxo-2-oxa-18-amino-11-methyl-9,12-diazatricyclo[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (37). Following the procedure detailed for **14**, compound **37** was obtained as a inseparable mixture of two atropisomers in 72% yield by preparative TLC (SiO_2, MeOH/CH_2Cl_2 = 1/9): IR ($CHCl_3$) 3350–3450, 1712, 1525 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28, 1.31 (2 × d, J = 6.7 Hz, 3H, Me), 2.25 (m, 1H, H-15), 2.50–2.68 (m, 2H, H-15′ and H-14), 2.80–2.90 (m, 1H, H-14′), 3.58 (brs, 2H, NH_2), 3.72–3.85 (m, 1H, H-8), 4.3 (q, J = 6.7 Hz, 1H, H-11), 4.92 (dd, J = 9.0 and 16.0 Hz, 1H, H-8′), 5.95, 6.02 (2 × s, 1H, H-21), 6.18–7.22 (m, 8H, H-aromatics and 2 × NH); MS m/z 339, 268, 253, 225, 211; HRMS m/z 339.1588 ($C_{19}H_{21}N_3O_3$ requires 339.1583).

10,13-Dioxo-2-oxa-9,12-diazatricyclo[14.2.2.1^{3,7}]-heneicosa-3,5,7 (21),16,18,19-hexaene (38). Following the procedure detailed for **15**, compound **38** was obtained in 70% yield by preparative TLC (SiO_2, MeOH/CH_2Cl_2 90%): mp 258–260 °C lit.[11] mp 260 °C; IR ($CHCl_3$) 3200–3450, 1661, 1582 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 2.80 (t, J = 6.0 Hz, 2H, H-15), 3.45 (s, 2H, H-11), 3.55 (t, J = 6.0 Hz, 2H, H-14), 3.77 (s, 2H, H-8), 6.15 (s, 1H, H-21), 6.84 (d, J = 8.4 Hz, 2H, H-17 and H-20), 6.82–6.84 (m, 1H, H-4), 6.92 (dd, J = 1.6 and 8.4 Hz, 1H, H-4), 7.20 (d, J = 8.4 Hz, 2H, H-18 and H-19), 7.18–7.22 (m, 1H, H-5); MS m/z 310, 282, 253.

(11*S*)-10,13-Dioxo-2-oxa-11-methyl-9,12-diazatricyclo-[14.2.2.1^{3,7}]heneicosa-3,5,7(21),16,18,19-hexaene (39). Following the procedure detailed for **15**, compound **39** was obtained in 55% yield by flash chromatography (SiO_2, 2% MeOH/CH_2Cl_2): mp 256 °C dec (lit.[11] mp 256 °C dec); IR ($CHCl_3$) 3200–3450, 1737, 1718, 1681, 1656, 1587 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.20 (d, J = 6.9 Hz, 3H, Me), 2.50 (m, 2H, H-15), 2.92 (m, 2H, H-14), 3.77 (d, J = 16.0 Hz, 1H, H-8), 4.30 (q, J = 6.9 Hz, 1H, H-11), 4.67 (d, J = 16 Hz, 1H, H-8′), 5.85 (s, 1H, H-21), 6.71 (d, J = 7.7 Hz, 1H, H-4), 6.77 (dd, J = 2.5 and 8.4 Hz, 1H, H-18 or H-19), 6.92 (dd, J = 2.5 and 8.4 Hz, 1H, H-19 or H-18), 6.91–6.92 (m, 1H, H-6), 7.05 (dd, J = 2.2 and 8.4 Hz, 1H, H-17 or H-20), 7.19 (t, J = 7.7 Hz, 1H, H-5), 7.31 (dd, J = 2.2 and 8.4 Hz, 1H, H-20 or H-17); ^{13}C NMR (CD_3OD, 75 MHz) δ 19.9, 32.3, 39.2, 42.5, 49.7, 112.4, 116.2, 120.2, 123.2, 123.8, 130.5, 130.9, 132.2, 138.1, 140.7, 155.3, 162.5, 173.4, 174.5; MS m/z 324, 296, 269, 225.

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Supplementary Material Available: ^{1}H NMR spectra of **12–16**, **20–25**, and **32–39** (19 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.