Total Synthesis of an Antitumor Agent RA-VII via an Efficient Preparation of Cycloisodityrosine†

Antony Bigot, Marie Elise Tran Huu Dau, and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

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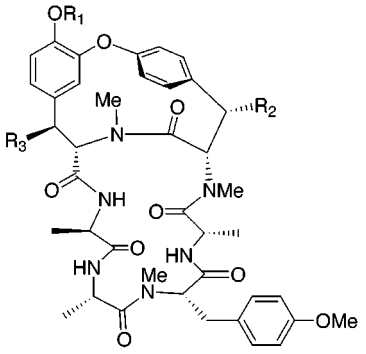
Details of efficient syntheses of (9*S*,12*S*)-cycloisodityrosine (**6**) and a concise total synthesis of RA-VII (**1**) were described. An intramolecular S_NAr-based cycloetherification reaction was employed as the key ring-closure step for construction of the illusive 14-membered *m*,*p*-cyclophane. Treatment of methyl *N*-[*N*-(*tert*-butyloxycarbonyl)-L-(3-hydroxy-4-methoxyphenylalanyl]-L-4-fluoro-3-nitrophenylalaninate ((9*S*,12*S*)-**10**) with potassium carbonate in DMSO at room temperature provided a mixture of two atropdiastereomers **20a** and **20b** in 75% yield that were transformed into cycloisodityrosine **6** in good overall yield. Furthermore, a size-selective ring-forming process was established for methyl *N*-[*N*-(*tert*-butyloxycarbonyl)-L-(3,4-dihydroxyphenylalanyl)]-L-4-fluoro-3-nitrophenylalaninate ((9*S*,12*S*)-**11**). Thus, cyclization of **11** (K_2CO_3, DMSO, rt), followed by in situ methylation, gave exclusively the 14-membered *m*,*p*-cyclphane **20a** and **20b** without competitive formation of the alternative 15-membered *p*,*p*-cyclophane. The selective ring-forming process allowed us to develop one of the shortest and the most efficient synthesis of cycloisodityrosine to date. Computational studies have shown that it was the elimination, but not the addition, step that determined the ring-size selectivity observed in the cyclization of substrate **11**. Coupling of **6** with L-*N*-Boc-Ala (**51**) proceeded efficiently to provide the corresponding tripeptide **52** that, after removal of the *N*-Boc function, was allowed to react with another tripeptide **53** to afford the hexapeptide **50** in good overall yield. Saponification followed by liberation of amino function from **50** gave the *seco*-acid, whose cyclization (DPPA, DMF, $NaHCO_3$) afforded the natural product RA-VII (**1**).

Introduction and Background

RA-VII (**1**) is a bicyclic hexapeptide (Figure 1) isolated from the plants *Rubia akane* and *Rubia cordifolia* (Rubiaceae)[1] whose structure is closely related to bouvardin (NSC 259968, **2**) isolated from *Bouvardia ternifolia*.[2] To date, 16 congeners (RA-I−RA-XVI) have been identified, and their relative and absolute configurations have been determined.[3] A characteristic structural feature of this family of natural products is the presence of an 18-membered peptide ring and a bridged 14-membered cycloisodityrosine unit with an *endo aryl*−*aryl ether* linkage. Both RA-VII (**1**) and bouvardin (**2**) show potent antitumor activity by inhibiting protein synthesis through eukaryotic 80S ribosomal binding.[4,5] Mechanistic studies using purified elongation factors and ribosomes have identified RA-VII as a peptidyltransferase inhibitor. RA-VII has been selected for clinic evaluations in Japan as an anticancer agent.[3] Extensive structure−activity relationship (SAR) studies carried out in Itokawa[6] and Boger's[7] groups elucidated that the 14-membered cycloisodityrosine moiety is the pharmacophore for this class of natural products.



1 RA-VII R_1 = Me, R_2 = R_3 = H
2 Bouvardin, R_1= R_3 = H, R_2 = OH
3 RA-V, Deoxybouvardin R_1 = R_2 = R_3 = H
4 RA-IV, R_1 = Me, R_2 = H, R_3 = OH

Figure 1.

† Dedicated with affection to Professor Yulin Li on the occasion of his 65th birthday.

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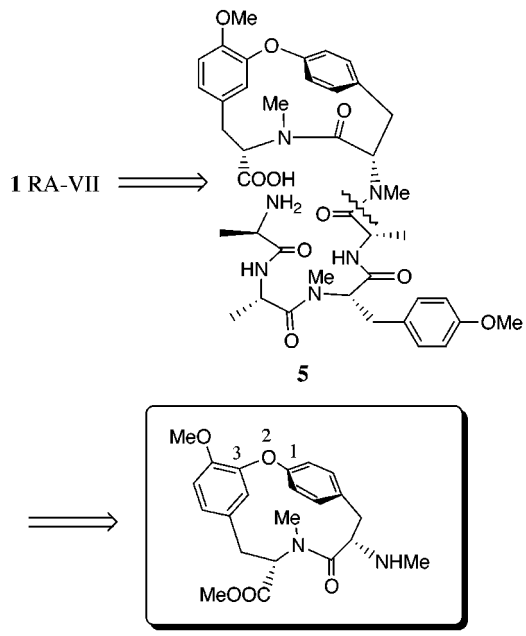
Scheme 1



6 *N*, *N*-dimethylcycloisodityrosine methyl ester

Strongly promoted by RA-VII's significant biological activity, great potential as a chemotherapeutic agent, and its unique structural features, total synthesis of RA-VII and its congeners has attracted a number of research groups, and a variety of synthetic approaches have been investigated.[3,8−10] From the viewpoint of synthetic design, three strategies, namely, (1) transannulation,[7,9] (2) bottom-up,[11] and (3) top-down approaches[7,9,10] were the most evident for the synthesis of the bridged bicyclic system of RAs, and indeed all of them have been investigated. While the first two strategies failed to give the target molecules, the "top-down" approach (Scheme 1) was found to be more operative. Realizing that ring closure of the bottom 18-membered macrocycle from *seco*-acid was relatively easy,[12] synthetic efforts have thus far concentrated on the synthesis of the key subunit, L,L-*N*,*N*-dimethylcycloisodityrosine methyl ester **6**. However, an efficient synthesis of such compound is far from being a trivial problem despite its simple structure. Cyclization via macrolactamization[13] under different activating conditions including polymer-supported agents, ring closure via C3−O2 bond formation based on Ullmann ether synthesis,[9] and intramolecular oxidative phenol coupling[11] have failed to give the elusive 14-membered ring. Alternatively, Inoue and co-workers[10] have devised an ingenious synthesis of **6** based on thallium trinitrate (TTN)-promoted intramolecular phenolic oxidative coupling of tetrahalogenated dipeptide followed by reductive dehalogenation,[14] but the key cyclization step proceeded in only 5% yield. Boger and co-workers[7,9,13] have successfully implemented an intramolecular Ullmann ether synthesis to reach directly the cycloisodityrosine **6** by formation of the C1−O2 bond. However, the yield of this cyclization methodology was still low to moderate and the harsh reaction conditions used were far from ideal. In fact, it has recently been disclosed that epimerization had occurred during the Ullmann ether synthesis and that the synthetic product thus obtained was in fact an *epi*-**6**.[15,16]

In connection with our research project on the total synthesis of vancomycin and related glycopeptide antibiotics, we have developed a novel cycloetherification methodology based on intramolecular S_NAr reaction.[8,17] The power of this ring-forming process has been demonstrated in the synthesis of a variety of complex biologically important macrocycles with an endo aryl−aryl[18] or aryl−alkyl ether[19] linkage, which were otherwise difficultly accessible. We[20] and Boger's group[16,21] have independently applied this technology to the synthesis of cycloisodityrosine by way of cyclization of the linear dipeptide (9*S*,12*S*)-**8** (route a, Scheme 2). Although the synthesis was relatively efficient, partial epimerization

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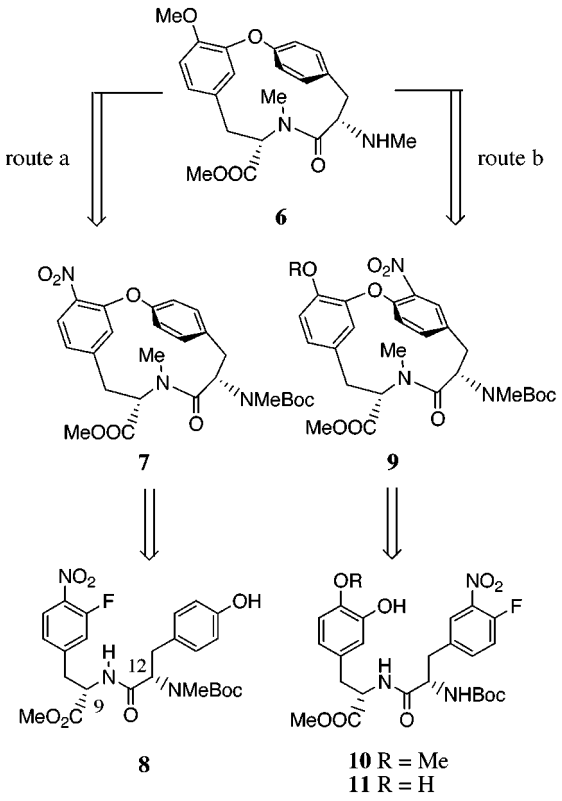
Scheme 2



of the C9 chiral center was encountered even under optimized reaction conditions. While it was surprising to observe facile epimerization under such mild conditions (K_2CO_3, DMF), we were intrigued by the fact that epimerization occurred exclusively at the C9 chiral center rather than at C12. This preference of epimerization site is uncommon, as it is well-known that derivatives of *N*-methylamino acids are more prone to racemization (C-12) than the corresponding amino acid derivatives (C-9).[22] To account for the configurational instability of C9 chiral center, we hypothesized that the presence of a nitro group para to the benzylic position of the dipeptide **7** and/or **8** was responsible for the facile epimerization at C-9.[20b] Thus, both resonance contribution of the nitro group and the inductive effect of the electron-deficient aromatic ring increased the kinetic acidity of the C-9 proton and, consequently, the opportunity of facile enolization and hence epimerization at this chiral center.[23] Based on this assumption, we reasoned that an alternative strategy based on cyclization of dipeptide **10** wherein the nitro group was positioned meta to the benzylic carbon might overcome this problem (route b, Scheme 2).[24] An added bonus to this approach is that the access to natural products would now be achieved by reductive removal of nitro group (**9** to **6**). Previous experiences have shown that this transformation can be realized much easier than the replacement of nitro by a hydroxy function (**7** to **6**, Scheme 2), especially in a larger scale preparation. Furthermore, we also planned to investigate the cyclization of dipeptide **11** (R = H), which contains two nucleophilic phenols and thus raises an interesting issue of ring-size selectivity during the cyclization.[25] The merit of this route is that it would allow the use of commercially available L-Dopa instead of the side-chain selectively protected L-Dopa derivatives for which five steps are required in the until now shortest syntheses.[26] Full details of the successful implementation of these strategies, highlighted by efficient syntheses of cycloisodityrosine (**6**) and, subsequently, a total synthesis of RA-VII (**1**) are reported in the present paper.

Results and Discussion

Cyclization of Dipeptide (9*S*,12*S*)-10. Several syntheses of L-Dopa derivatives bearing a selectively protected catechol have been described.[26] The most direct route involving selective protection of unsymmetric catechol of L-Dopa was unfortunately inefficient due to the similar reactivity of the two phenol groups.[27] Among numerous reported approaches, the shortest syntheses were that developed by Boger and Jung starting from L-tyrosine.[26] Our synthesis based on Evans' asymmetric azidation methodology[28,29] is shown in Scheme 3. Conversion of acid **12** into the mixed anhydride with pivaloyl chloride followed by reaction with the lithium salt of (4*S*)-4-benzyl-2-oxazolidinone (**13**) afforded the imide **14**. Treatment of **14** with KHMDS followed by trisyl azide according to Evans gave the α-azido derivative **15**. The desired diastereoisomer was obtained after flash chromatography in 83% yield. Transesterification of **15** with MeOMgBr[30] furnished azido ester **16** in 90% yield with concomitant recovery of the chiral auxiliary **13**. Hydrogenolysis of **16** afforded L-methyl 3-isopropyloxy-4-methoxyphenylalaninate **17**, which was coupled directly with L-*N*-Boc-4-fluoro-3-nitrophenylalanine (**18**)[31] to give the dipeptide **19** in 90% overall yield. Deprotection of isopropyloxy ether with BCl_3[32] caused partial removal of the *N*-Boc moiety. However, treatment of the crude product with Boc_2O under classic conditions reinstalled the *N*-Boc function, affording the cyclization precursor (9*S*,12*S*)-**10** in excellent overall yield (99% for two steps).

In searching for cycloetherification conditions of compound **10**, a dramatic solvent effect was observed. Treatment of (9*S*,12*S*)-**10** with potassium carbonate (K_2CO_3) in DMF at room temperature for 24 h did not afford any cyclic compound. However, an efficient macrocyclization occurred when the solvent was switched to DMSO[18i,25]

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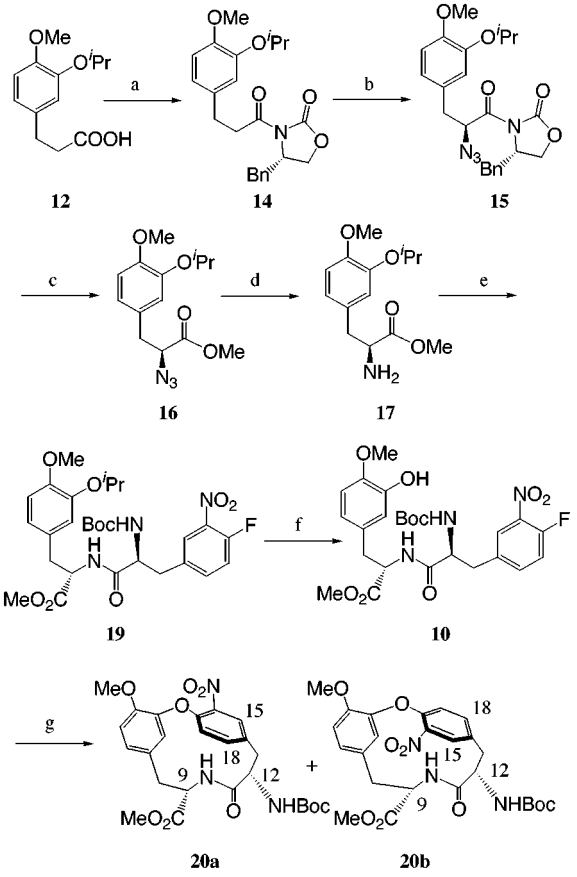
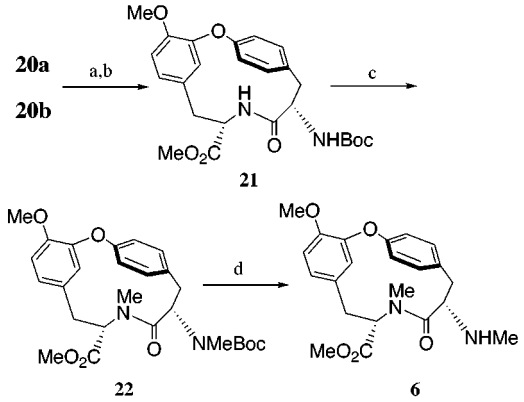
Scheme 3[a]



[a]Reagents and conditions: (a) Et_3N, pivaloyl chloride, -78°C, 1h, then **13**/n-BuLi, -79°C to rt, THF, 84%; (b) KHMDS, THF, -78°C, then, trisylN_3, 2 min, then AcOH, 83%; (c) MeOMgBr, MeOH, 0°C, 10 min, 92%; (d) Pd/C, H_2, MeOH, quantitative; (e) EDC, HOBt, **18**, CH_2Cl_2, 1.5 h, 90%; f) BCl_3, CH_2Cl_2, then, Boc_2O, THF, Et_3N, rt, 2h, 99%; (g) K_2CO_3, DMSO, rt, 75%

to give an atropdiastereomeric mixture of cycloisodityrosine **20a** and **20b**. The atropisomerism of **20a** and **20b** was determined by NOE studies. As observed in the vancomycin series,[33] a NOE cross-peak between protons H12 and H18 was observed in the NOESY spectrum of M atropdiastereomer **20a**, while that of H12 and H15 was found for the P diasteromer **20b**.[34] This stereochemistry assignment was of no consequence in the present synthesis since the planar chirality will be destroyed in subsequent synthetic operations. However, it did provide useful information regarding the stereochemical integrity of these two cyclophanes and supported the notion that compounds **20a** and **20b** did not result from the partial epimerization of the chiral carbon centers (vide infra). In line with the configurational stability of **20a** and **20b**, no epimerization occurred when they were treated with DBU in THF, conditions known to epimerize **7** (degradation was, however, observed).

Scheme 4[a]



[a]Reagents and conditions: (a) Pd/C, H_2, MeOH; (b) H_3PO_2, $NaNO_2$, Cu_2O, H_2O/THF, 75%; (c) NaH, DMF-THF, excess MeI, 0°C to rt, 85%; (d) TFA, 20 min, quantitative.

The transformation of cyclophane **20a** and **20b** into the cycloisodityrosine **6** was straightforward (Scheme 4). Hydrogenation of **20a** in MeOH in the presence of catalytic amount of Pd/C afforded the amino derivative, which was submitted, without further purification, to in situ diazotization and reduction[35] to afford compound (9*S*,12*S*)-**21** ([α_D] = +56, *c* 0.9, $CHCl_3$; lit.[16b] [α_D] = +57, *c* 0.6, $CHCl_3$) in 75% overall yield. The same synthetic sequence applied to compound **20b** afforded a product identical in all respects with that obtained from **20a**, establishing thus firmly the atropisomerism of these two compounds. We have not observed reactivity differences between **20a** and **20b** in the above two-step sequence, and in practical synthesis, we used the mixture of **20a** and **20b** for the preparation of **21** without the erosion of overall yield. Other reductive deamination procedures (^{t}BuONO, DMF;[36] ^{t}BuONO, $BF_3{\cdot}Et_2O$, then $FeSO_4$, DMF[37,19]) were examined, but none of them was found to be suitable in this specific case. The N-bis-methylation of **21** was carried out by adding sodium hydride (NaH) in a mixture of solvents (THF−DMF, 1/1) in the presence of an excess of methyl iodide to provide compound **22** in 85% yield. Under classic conditions, i.e., formation of amide anion of **21** followed by addition of MeI, a poor yield of the desired product **22** was obtained. Removal of the *N*-Boc moiety from **22** under mild acidic conditions gave then L,L-*N*,*N*-dimethylcycloisodityrosine methyl ester **6**, whose physical data were identical in all respects with the literature values.[16b,20b] While compounds **20** and **21** have a single solution conformation in $CDCl_3$ and CD_3OD, the N,N-dimethylated cycloisodityrosine derivatives (**22** and **6**) exist in two rigid solution conformations (cis, trans of internal amide bond). In the case of **6**, the two conformers were even detectable by TLC.[9,20b]

In the case of cyclophane **24** (Scheme 5) where the terminal amino function was protected by benzyloxycarbonyl group, methylation (NaH, MeI, THF−DMF) furnished a bicyclic compound **25** (85% yield) instead of the desired N,N-bismethylated derivative of type **22**. The

(33) (a) Vergne, C.; Bois-Choussy, M.; Beugelmans, R.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 1403−1406. (b) Bois-Choussy, M.; Vergne, C.; Neuville, L.; Beugelmans, R.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 5795−5798.

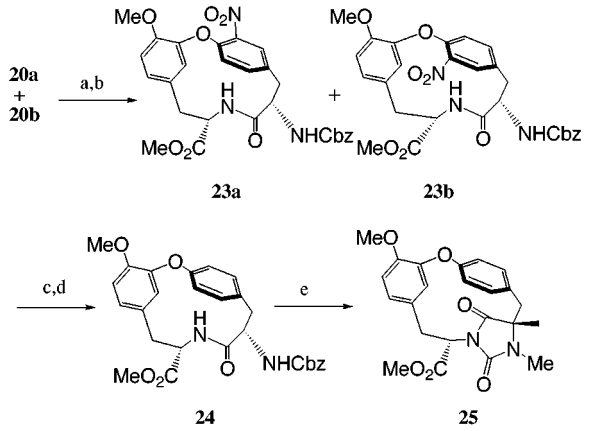
(34) The configuration (P or M) of the atropisomer was determined by viewing the atropisomer as helix. "For this designation, only the ligands of highest priority in front and in the back of the framework are considered. If the turn from the priority front ligand to the priority rear ligand is clockwise, the configuration is P, if counterclockwise it is M". See: Eliel, E. L.; Willen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons Inc.: New York, 1994; Chapter 14.

(35) Rhee, E. S.; Shine, H. J. *J. Am. Chem. Soc.* **1986**, *108*, 1000−1006.

(36) (a) Doyle, M. P.; Dellaria, J. F.; Siegfried, Jr. B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494−3498. (b) Islas-Gonzalez, G.; Zhu, J. *J. Org. Chem.* **1997**, *62*, 7544−7545.

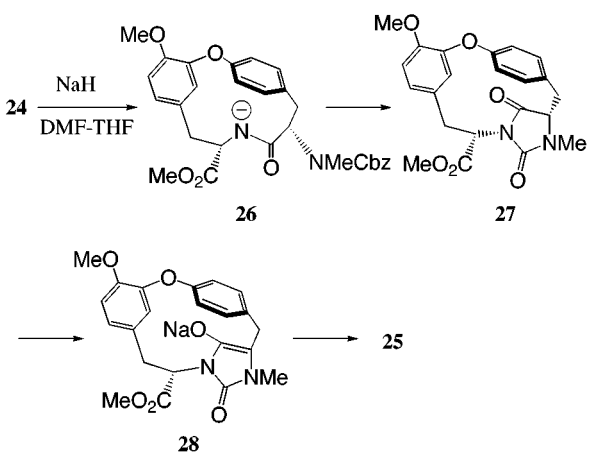
(37) (a) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572−1574. (b) Wassmundt, F. W.; Kiesman, W. F. *J. Org. Chem.* **1995**, *60*, 1713−1719.

Scheme 5[a]



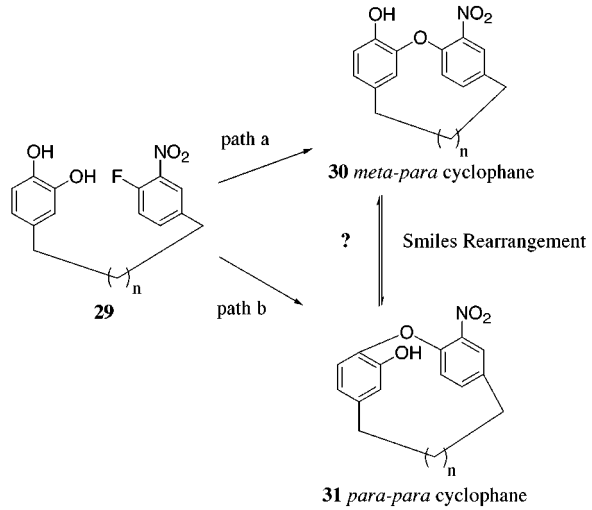
[a]Reagents and conditions: (a) TFA, rt, 20 min; (b) CbzOSu, Et_3N, THF, rt, 2h, 95%; (c) $SnCl_2$, DMF, 50°C, 2h, (d) H_3PO_2, $NaNO_2$, Cu_2O, H_2O/THF, 75%; (e) NaH, DMF-THF, excess MeI, 0°C to rt, 85%.

Scheme 6

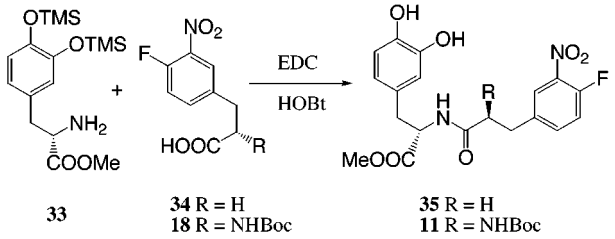


structure of compound **25** was determined by spectroscopic studies. While the formation of imide from peptide is amply precedented and readily explained by intramolecular N-acylation,[38,39] the high stereoselectivity observed for the *C*-methylation was nevertheless intriguing. There were in fact three bond-forming process, i.e., N-acylation, N- and C-methylation, occurred in this transformation, the high stereoselectivity observed led us to draw a reaction cascade as shown in Scheme 6. After formation of dianion, N-methylation occurred first at the terminal amide function leading to **26**. Instead of the second N-methylation, intramolecular N-acylation was favored in this case for both steric and geometric reasons leading to **27**.[39] Finally, formation of enolate followed by C-methylation afforded compound **25**. Due to the rigidity of the bicyclic ring system, only one face of the enolate was accessible to the electrophile leading to the observed high diastereoselectivity (Scheme 6). That C-methylation occurred at C-12 rather than at C-9 was determined by a strong NOE effect observed between two methyl groups. Diminished steric hindrance of the *N*-Cbz in compound **24** vs *N*-Boc in **21** may account for their different reactivity.

Scheme 7



Scheme 8



Size-Selective Ring-Forming Process. Encouraged by these results, we became interested in investigating type **29** substrates (Scheme 7) in order to study the ring-size selectivity during the cyclization (path a vs b) and the possible thermoequilibrium of products **30** and **31** via Smiles rearrangement.[40] If the cyclization could be driven, either kinetically or thermodynamically toward the formation of type **30** *m*,*p*-cyclophane, a desirable feature would be evident since this route would allow the use of commercially available L-Dopa instead of side-chain selectively protected L-Dopa derivatives.[25] Linear compounds **35** and **11** (Scheme 8) were prepared following standard procedures. Thus, temporary protection of two hydroxyl groups of L-Dopa methyl ester (**32**) as TMS ethers (**33**), followed by EDC-mediated coupling with 4-fluoro-3-nitrophenylpropionic acid (**34**)[41] or L-*N*-Boc-4-fluoro-3-nitrophenylalanine (**18**)[31] gave, after acidic aqueous workup, the cyclization precursors (9*S*)-**35** or (9*S*,-12*S*)-**11** in higher than 90% yield.

The initial cyclization study was carried out with model compound **35** (Scheme 9). When a solution of **35** in THF (0.01 M) was treated with NaH at room temperature, a smooth reaction occurred to give a mixture of two atropdiastereomers **36a** and **36b** in reasonable yields (55−65%, entry 1, Table 1). Neither the formation of 15-membered *p*,*p*-cyclophane **37** nor that of the dimer **38** was observed under these conditions. When K_2CO_3 was used as a base in DMF (0.01 M), cyclophanes **36a** and **36b** were produced in 42% yield together with a signifi-

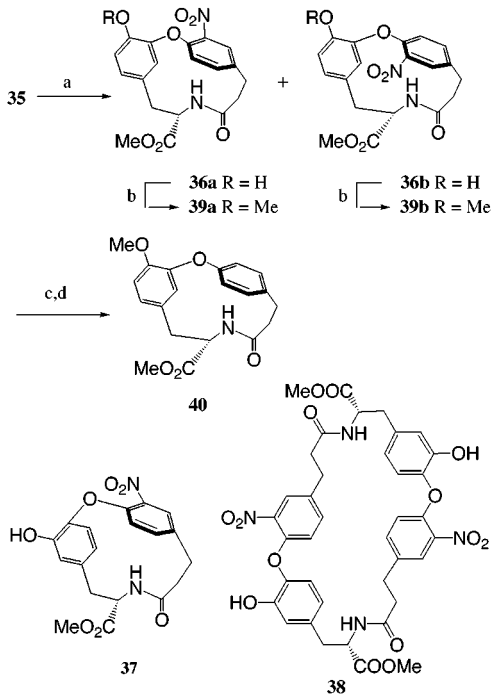
(38) (a) Andrus, M. B.; Li, W. K.; Keyes, R. F. *Tetrahedron Lett.* **1998**, *39*, 5465−5468. (b) Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *Chem. Rev.* **1970**, *70*, 439−469.

(39) A very similar product was obtained in Boger's synthesis of piperazinomycin; see: Boger, D. L.; Zhou, J. *J. Am. Chem. Soc.* **1993**, *115*, 11426−11433 and ref 9b.

(40) (a) Truce, W. E.; Kreider, E. M.; Brand, W. W. The Smiles and related rearrangements of aromatic systems. *Organic Reactions*; John Wiley & Sons Inc.: New York, 1970; Vol. 18, pp 99−215. (b) Borchardt, A.; Still, W. C. *Synlett* **1995**, 539−540 and references therein.

(41) Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535−5542.

Scheme 9[a]



[a]Reagents and conditions: (a) K_2CO_3, DMSO, 0.002 M, rt, 5h, 70%; (b) K_2CO_3, MeI, acetone, reflux, 1h, 90%; (c) Pd/C, H_2, MeOH; (d) H_3PO_2, $NaNO_2$, Cu_2O, H_2O/THF, 73%.

Table 1. Survey of Reaction Conditions for the Cyclization of 35

entry	base	solvent	concn (M)	*T* (°C	time (h)	yield of **36a** + **36b** (%)	yield of **38** (%)
1	NaH	THF	10^{-2}	0−25	2	58	0
2	K_2CO_3	DMF	10^{-2}	25	3	42	20
3	K_2CO_3	DMF	10^{-2}	5	48	0[a]	0[a]
4	K_2CO_3	DMF	2×10^{-3}	25	6	60	10
5	K_2CO_3	DMSO	2×10^{-3}	25	1	70	1
6	K_2CO_3	DMSO	4×10^{-3}	25	1.3	68	5
7	CsF	DMF	10^{-2}	25	23	0	30

[a] Degradation or oligomerization of starting materials.

cant amount of a cyclic dimer **38** (20%).[42] The yields of **36a** and **36b** were increased to 60% when the concentration of **35** was decreased to 0.002 M. The best result was obtained when the cyclization was performed in DMSO at 0.002 M with K_2CO_3 as a base. Under these conditions, compounds **36a** and **36b** were isolated in higher than 70% combined yield and the formation of the dimer **38** was minimized (<2%). Cesium fluoride (CsF) failed to give the desired compounds and only dimer **38** was isolated in less than 30% yield together with the recovered starting materials.

The formation of the 15-membered *p*,*p*-cyclophane **37** was not observed. Furthermore, no Smiles rearrangement was observed when pure cyclophanes **36a** and **36b** were submitted to the cyclization conditions. This result was understandable if one considers the high ring constraints[43] associated with the formation of the *p*,*p*-cyclophane (**37**). A pleasant consequence is that the two otherwise equally reactive hydroxyl functions[26] were successfully differentiated, a phenomenon inherent to the intramolecular process. In a control experiment, we have shown that the reaction of L-*N*-Boc dopamine methyl ester with methyl *N*-trifluoroacetyl-L-4-fluoro-3-nitrophenylalaninate (K_2CO_3, DMF) gave equal amount of the two possible monoarylated compounds.

Table 2. Survey of Reaction Conditions for the Cyclization of 11

entry	base	solvent	concn (M)	*T* (°C)	time (h)	yield of **41a** + **41b** (%)
1	NaH	THF	10^{-2}	0−25	4	0[a]
2	NaH	DMF	10^{-2}	0−25	5	21
3	K_2CO_3	DMF	10^{-2}	5	63	<5
4	K_2CO_3	DMF	10^{-2}	25	7	45
5	K_2CO_3	DMSO	10^{-2}	25	2	43
6	K_2CO_3[b]	THF	10^{-2}	25	21	0[c]
7	K_2CO_3	HMPT	10^{-2}	25	24	ND[d]
8	K_2CO_3	DMF	2×10^{-3}	25	7	44
9	K_2CO_3	DMSO	2×10^{-3}	25	2	56

[a] Starting material was recovered. [b] In the presence of 18-crown-6. [c] A significant amount of acyclic dimer was isolated. [d] Not determined, the conversion was too low to be meaningful.

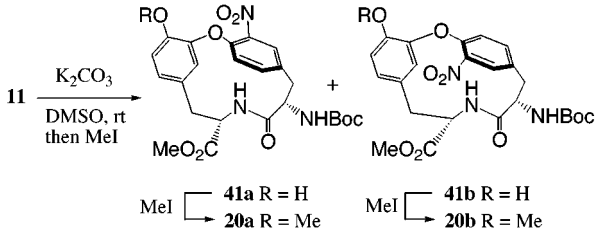
A variable amount of cyclic dimer was obtained when the substrate concentration was higher than 0.005 M. That the intermolecular S_NAr reaction becoming more competitive in the cyclization of **35** than in previously studied substrates such as **10** could partly be explained on statistical grounds as both hydroxyl groups of **35** can participate to an intermolecular process. The atropisomerism between compounds **36a** and **36b** was confirmed by the independent conversion of the individual macrocycles into a common 14-membered cyclophane **40**[13] via a two-step sequence described earlier (vide supra).

With these results in hand, we then turned our attention to the fully functionalized dipeptide **11**. In contrast to (9*S*)-**35**, treatment of (9*S*,12*S*)-**11** in THF (0.01 M) with NaH gave no cyclic product and only starting material was recovered (Table 2). Using DMF under otherwise identical conditions, cyclic compound **41a** and **41b** were isolated in 20% yield. After a survey of reaction parameters varying a base, solvent, and temperature, it was found that no cyclic monomer was produced in THF (dielectric constant $\epsilon = 7.6$) and HMPT ($\epsilon = 30$) with either NaH or K_2CO_3 as a base. The cyclization proceeded smoothly in more polar aprotic solvents such as DMF ($\epsilon = 37$) and DMSO ($\epsilon = 47$), the latter being the best in accord with its higher dielectric constant. A reasonable reaction rate was observed only at room temperature. At 5 °C, the reaction time was substantially prolonged leading to a diminished yield due to partial decomposition of cyclized product. Finally, under optimal conditions we found (K_2CO_3, DMSO, 0.002 M, room temperature), a mixture of cyclic products **41a** and **41b** was isolated in 55−65% yield. It was interesting to note that when the cyclization was carried out in THF (0.01 M) in the presence of potassium carbonate and crown ether 18-C-6, only acyclic dimer was produced. An observation that partial degradation of cyclic products **41a** and **41b** occurred during flash chromatography purification and the fact that both cyclization and methylation steps could, a priori, be carried out under identical conditions prompted us to examine the possibility of combining these two operations in a one-pot fashion. Indeed, treatment of a DMSO solution (0.002 M) of dipeptide (9*S*,12*S*)-**11** with K_2CO_3 at room temperature followed, after 2 h, by addition of MeI (excess) gave compounds **20a** and **20b** in greater than 75% isolated yield (Scheme 10).

(42) While it was a symmetric dimer, the regiochemistry was not determined rigorously.

(43) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312−322.

Scheme 10



Scheme 11

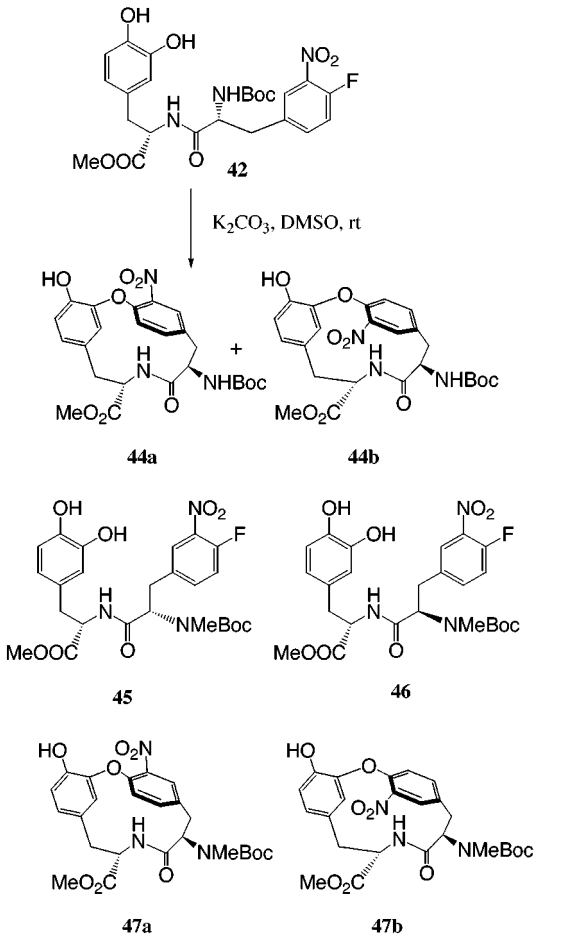
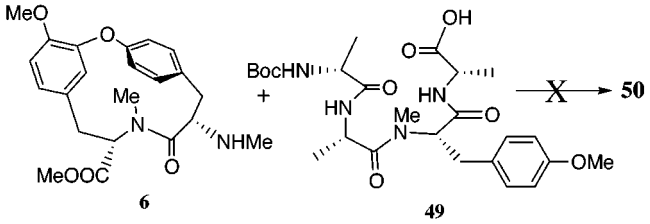


Figure 2.

To verify if any epimerization had occurred during the cyclization, we have synthesized compound (9*S*,12*R*)-**42** by coupling L-Dopa (**33**) with D-4-fluoro-3-nitrophenylalanine (**43**)[31] (Scheme 11). When (9*S*,12*R*)-**42** was submitted to the identical cycloetherification conditions as described for (9*S*,12*S*)-**11**, a mixture of two atropodiastereomers **44a** and **44b** was obtained whose physical data were completely different from those of **41a** and **41b** (Scheme 10). This control experiment indicated that the stereochemical integrity of (9*S*,12*S*)-**11** was preserved in both preparation and cyclization steps, in sharp contrast to the easy epimerization encountered with compound (9*S*,12*S*)-**7**[16,20b] (Scheme 2).

We have also examined the cyclization of dipeptide (9*S*,12*S*)-**45** and (9*S*,12*R*)-**46** wherein a L- or D-*N*-Boc-*N*-methyl-4-fluoro-3-nitrophenylalanine (**48**) was incorporated (Figure 2). Under various conditions examined, compound (9*S*,12*S*)-**45** did not give any cyclic product. Conversely, treatment of (9*S*,12*R*)-**46** with K_2CO_3 in DMSO gave the desired cyclophane **47a** and **47b** in

Scheme 12



reasonable yields. These results were in accord with the previous observation that the 9*S*,12*R* diastereoisomer was more prone to cyclization than the corresponding 9*S*,-12*S* diastereoisomer.[16,20b]

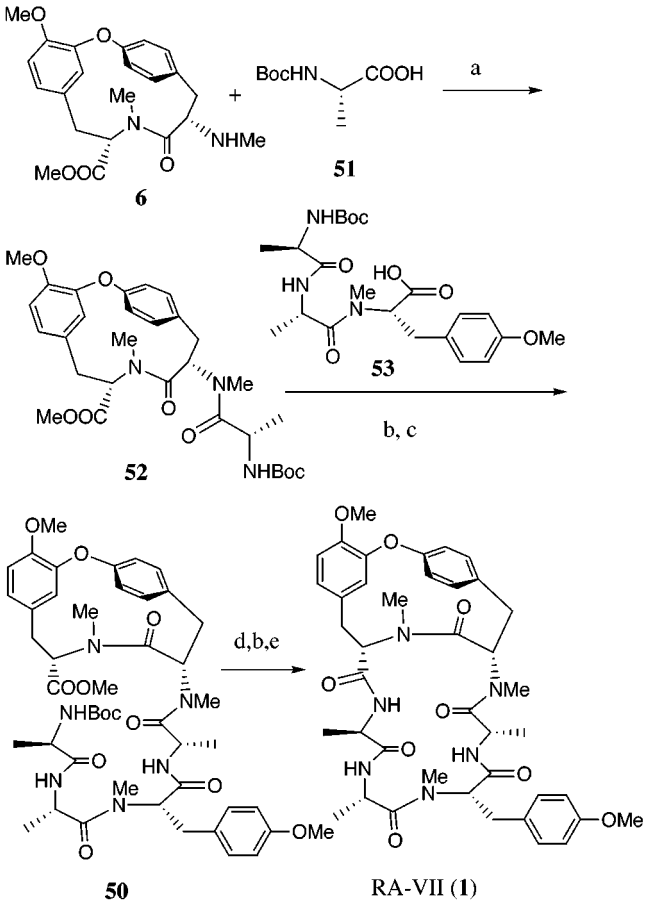
Total Synthesis of RA-VII. With a quantity of cycloisodityrosine methyl ester **6** in hands, the total synthesis of RA-VII was pursued. Following literature precedents, we first tried to prepare the hexapeptide (**50**) by assemblage of cycloisodityrosine (**6**) and tetrapeptide **49**, which was in turn synthesized according to the standard peptide coupling procedures (Scheme 12). However, under conditions prescribed for such transformation[9,10] we were unable to isolate the desired hexapeptide **50**, and degradations of two coupling partners were instead observed. We thought that both the low reactivity of the secondary amine present in **6** and the polypeptide nature of the acid **49** contributed to the failure of this coupling reaction.[44] Reagents such as PyBrop and BOPCl known to be especially successful for coupling of *N*-methylamino acid were attempted without success. To remedy this reactivity problem, we hypothesized that a two-step sequence via coupling of **6** with *N*-Boc-L-alanine **51** followed by coupling of the resulting tripeptide **52** with another linear tripeptide *N*-Boc-D-Ala-L-Ala-*N*,*O*-dimethyl-L-Tyr **53** would be more efficient. The reason for planning this alternative synthesis was that the activated form of amino acid *N*-Boc-L-alanine **51** should be less prone to side reactions and thus have a lifetime longer enough to react with the secondary amine **6**. The [3 + 3] segment coupling between **52** and **53** should also be facilitated by the fact that the nucleophile in this case will be a primary amine, known to be more reactive than the secondary amine. Indeed, coupling of **6** with **51** (PyBroP, $^{i}Pr_2EtN$, DMF) gave the corresponding tripeptide **52** in 97% yield. Removal of *N*-Boc group from **52** followed by its coupling with tripeptide **53** (EDC, HOBt, CH_2Cl_2) afforded hexapeptide **50** in 60% yield. Saponification followed by liberation of amino function gave the *seco*-acid which was cyclized by treatment with DPPA in DMF to provide the natural product RA-VII (**1**) in 20% yield (Scheme 13). Attempts to increase the overall yield of this three-step sequence by varying the deprotection and macrolactamization conditions were unsuccessful. The physical data of this synthetic RA-VII were shown to be identical in all respects with an authentic sample generously provided by Professor Itokawa.

Discussion

A two step, i.e., addition−elimination sequence via formation of a Meisenheimer-type intermediate is a generally accepted mechanism for nucleophilic aromatic

(44) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243−2266.

Scheme 13[a]

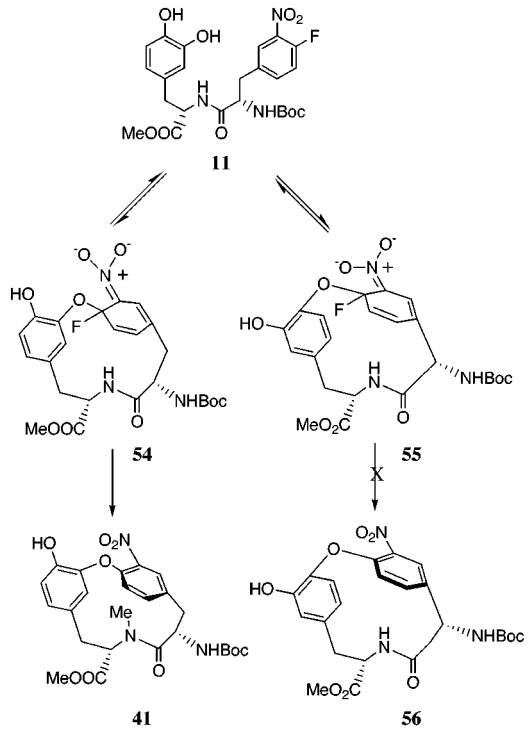


[a]Reagents and conditions: (a) PyBrop, iPr_2EtN, DMF, 0°C to rt, 95%; b) TFA, rt; c) EDC, HOBt, **53**, 62%; (d) LiOH, THF-MeOH-H_2O; (e) DPPA, $NaHCO_3$, DMF, 0°C, 20%.

substitution reaction (S_NAr).[45] Accordingly, the hybridization of the carbon atom bearing the leaving group (fluoride in our case) changes from sp_2 to sp_3 when going from the reactant to the intermediate and back to sp_2 after expelling the fluoride. A consequence of this hybridization change in the intramolecular version of this reaction is that the ring constraint of the intermediate may be lower than that of the macrolactamization intermediate since deformation of a cyclohexadiene system should in principle be energetically easier than that of the planar aromatic ring. This is, in our opinion, one of the reasons why intramolecular S_NAr reaction is more efficient in the construction of highly constrained macrocycles than other methodologies such as macrolactamization technique. This consideration raised an interesting mechanistic question regarding the ring size selectivity observed in the cycloetherification of substrate (9*S*,12*S*)-**11**. Was the formation of the 15-membered Meisenheimer intermediate **55** possible (Scheme 14) although the formation of 15-membered cyclophane **56** was not observed? To understand this point, a computational study was carried out.

Five thousand conformations of each compounds, i.e., the dipeptide **11**, the two zwitterionic intermediate **54**, **55** and two cyclophanes **41**, **56** were generated by random search Monte Carlo method[46] and optimized by TNCG Truncated Newton molecular mechanics minimization[47] using the Macromodel (version 5.5) program[48] with the AMBER force field[49] and GB/SA water solvation. The search was carried out on blocks of 1000 Monte Carlo steps until no additional conformation was found to be of lower energy than the current minimum. Duplicated conformations as well as those that had chirality changes were discarded. From these conformational searches, all the possible conformations within 3 kcal/mol from the global minimum were analyzed.

Scheme 14



First of all, the lowest energy conformers of cyclization precursor **11** were folded and the distance between the two reactive sites O−C_F was close enough to provide entropy driving force for the cyclization and account for the observed facile cyclization according to the proximity theory.[50]

Since the entropy loss in the macrocycle-forming process is considerable, a process that can lower the rotation may be expected to lead to a substantial acceleration of the overall rate of reaction. For this reason, only the lowest energy conformations of **11** that have similar torsional angles related to the intermediates **54**, **55** and the cyclophane **41**, **56** (Figure 3) were considered. The calculated steric energies (AMBER) and the most

(45) For recent books and reviews, see: (a) Terrier, F. *Nucleophilic Aromatic Displacement: The Role of the Nitro Group*; VCH: New York, 1991; Chapter 1. (b) Paradisi, C. Arene Substitution via Nucleophilic Addition to Electron Deficient Arenes. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4, pp 423−450. (c) Vlasov, V. M. *J. Fluorine Chem.* **1993**, *61*, 193-216.

(46) Chang. G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379−4386.

(47) Ponder, J. W.; Richards, F. M. *J. Comput. Chem.* **1987**, *8*, 1016−1024.

(48) Mohamadi, F.; Richards, N. J. G.; Guida, W. C.; Liskamp, R.; Lipton, M. C.; Caufield, M.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(49) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127−8134.

(50) (a) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128−134. (b) Mandolini, L. *Bull. Soc. Chim. Fr.* **1988**, 173−176. (c) Bruice, T. C.; Lightstone, F. C. *Acc. Chem. Res.* **1999**, *32*, 127−136.

Table 3. Calculated Steric Energies and Relevant Geometrical Parameters of Compounds 11, 41, and Related Intermediates

	11A	54	41	11B	55	56
E (kJ/mol)	−413.5	−347.0	−260.0	−423.7	−347.0	−214.9
O2−C1−C16−C15[a]		**−131.3**	**−156.8**		**−107.4**	**−148.4**
C1−C16−C15−C14		1.9	−0.7		−6.6	−0.3
C16−C15−C14−C13		**179.4**	**166.1**		**174.9**	**160.9**
C15−C14−C13−C12	−106.15	−104.7	−103.5	−89.73	−81.9	−81.3
C14−C13−C12−C11	78.46	59.2	58.7	−66.66	−68.9	−62.4
C13−C12−C11−N10	−89.97	−94.2	−101.7	143.97	160.7	142.9
C12−C11−N10−C9	−177.17	−179.2	−176.5	−166.29	−172.6	174.5
C11−N10−C9−C8	170.41	177.1	179.0	135.11	108.0	136.9
N10−C9−C8−C7	60.51	80.9	82.2	−48.97	−50.1	−54.9
C9−C8−C7−C19	−96.74	−57.1	−58.0	89.87	99.4	107.2
C8−C7−C19−C3		**178.5**	**171.1**		**−173.7**	**−165.8**
C7−C19−C3−O2		**−177.9**	**−169.7**			
C7−C19−C3−C4					−0.6	1.0
C19-C3-C4-O2					**174.7**	**152.3**

[a] The torsion angles are in degrees.

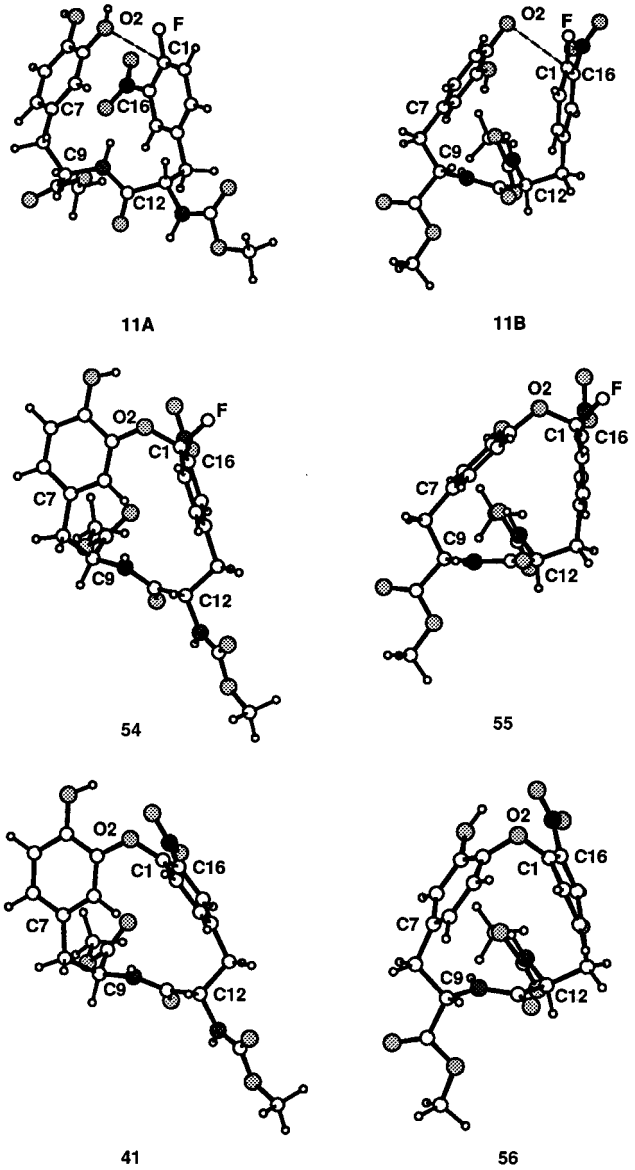


Figure 3.

relevant geometrical parameters of these conformers are summarized in Table 3. It was noticed that the two atropisomers have very similar steric energy, thus for clarity only one atropisomer will be considered in the following discussion.

Energy analysis revealed that in view of their similar steric energy both zwitterionic intermediates **54**, **55** can be produced. However, the energy difference between two cyclophanes **41** and **56** was so enormous that only formation of the former was observed.[51] In fact, both aromatic ring systems of the 15-membered *p*,*p*-cyclophane **56** was perturbed in a great extent than that of the *m*,*p*-cyclophane **41** (Table 3), and consequently, the formation of **41** was largely favored. These considerations suggested that the formation of both Meisenheimer adducts **54** and **55** were energetically allowed. However, in intermediate **55** the departure of fluoride was hampered due to introduction of highly strained ring system. Taking into account the reversibility of the addition step in the S_NAr mechanism, we concluded that it was the elimination, but not the addition step that determined the ring size selectivity observed in the cyclization of substrate **11**.

Conclusion

We described efficient syntheses of cycloisodityrosine (**6**) and subsequently, a total synthesis of bicyclic hexapeptide RA-VII (**1**). An intramolecular S_NAr-based cycloetherification reaction was employed as the key ring-closure step for the construction of the illusive 14-membered *m*,*p*-cyclophane. The selective ring forming process observed for the cyclization of linear dipeptide **11** is until now one of the shortest and the most efficient synthesis of cycloisodityrosine. Computational studies have revealed that the preferential formation of 14-membered *m*,*p*-cyclophane over the alternative 15-membered *p*,*p*-cyclophane is controlled by the elimination step of S_NAr mechanism. The difficult 2 + 4 peptide coupling between cycloisodityrosine **6** and tetrapeptide **49** en route to RA-VII (**1**) was resolved by an alternative 3 + 3 assemblage strategy on a rational basis. The synthetic scheme described in this paper should find application in the synthesis of a range of natural product analogues for detailed SAR studies.

Experimental Section

(4*S*)-3-[3-[3-Isopropyloxy-4-methoxyphenyl]-1-oxopropionyl]-4-(phenylmethyl)-2-oxazolidinone (14). To a precooled solution (−78 °C) of acid **12** (5.0 g, 21.0 mmol) in THF

(51) As pointed out by one of reviewers, we agree that the comparison of energies between **41** and **56** may not be relevant in the present case since compound **56** has never been isolated.

(100 mL) under Ar were added, successively, Et_3N (3.54 mL, 25.20 mmol) and pivaloyl chloride (2.7 mL, 22.1 mmol). The resulting slurry was stirred at −78 °C for 1 h. In a separate flask containing a solution of (4*S*)-4-benzyl-2-oxazolidinone **13** (4.1 g, 23.1 mmol) in THF (75 mL) was added *n*-BuLi (1.6 M in hexane, 15.9 mL, 25.4 mmol) at −78 °C. After being stirred at −78 °C for 30 min, this metalated oxazolidinone solution was transferred to the flask containing the mixed anhydride via cannula, and the resulting white slurry was stirred at −78 °C for 15 min and then overnight at room temperature. The reaction was quenched with aqueous NH_4Cl (60 mL) and extracted five times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in a vacuum to give an oily residue. Crystallization from EtOAc/heptane gave **14** (7.0 g, 84%) as a white solid: mp 100−101 °C (EtOAc−heptane); $[\alpha]_D = +42.0$ ($CHCl_3$, *c* 1.00); IR ($CHCl_3$) 1782, 1702, 1510, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, $J = 6.1$ Hz, 6H), 2.75 (dd, $J = 9.5$, 13.4 Hz, 1H), 2.92−2.98 (m, 2H), 3.15−3.35 (m, 3H), 3.82 (s, 3H), 4.14−4.21 (m, 2H), 4.53 (septet, $J = 6.1$ Hz, 1H), 4.66 (m, 1H), 6.81−6.84 (m, 3H), 7.16−7.18 (m, 2H), 7.26−7.36 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.2, 29.9, 37.4, 37.8, 55.1, 56.1, 66.2, 71.4, 112.2, 116.6, 121.0, 127.4, 129.0, 129.4, 133.0, 135.3, 147.3, 149.0, 153.5, 172.5; MS *m*/*z* 397 (M^+). Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.59; H, 6.95; N, 3.54.

(4*S*,2*S*)-3-[2-Azido-3-[3-isopropyloxy-4-methoxyphenyl]-1-oxopropionyl]-4-(phenylmethyl)-2-oxazolidinone (15). To a stirred solution of the imide **14** (5.0 g, 12.6 mmol) in THF (150 mL) at −78 °C was added KHMDS (0.5 M solution in toluene, 37.8 mL, 18.9 mmol), and the resulting solution was stirred at −78 °C for 30 min. To this solution was added, via cannula, a precooled (−78 °C) solution of trisyl azide (5.1 g, 16.4 mmol) in THF (30 mL). The resulting solution was stirred at −78 °C for 2 min, quenched by addition of glacial acetic acid (3.3 mL, 57.9 mmol), and warmed to room temperature with a water bath. After being stirred at room temperature for 3 h, the reaction mixture was diluted with brine (100 mL) and extracted four times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc/heptane = 1/4) of the crude product gave **15** (4.6 g, 83%) as a colorless oil: $[\alpha]_D = +76.4$ ($CHCl_3$, *c* 1.26); IR ($CHCl_3$) 2113, 1781, 1706, 1513 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (d, $J = 6.1$ Hz, 6H), 2.82 (dd, $J = 9.5$, 13.5 Hz, 1H), 2.97 (dd, $J = 9.0$, 13.6 Hz, 1H), 3.14 (dd, $J = 5.6$, 13.6 Hz, 1H), 3.32 (dd, $J = 3.3$, 13.5 Hz, 1H), 3.83 (s, 3H), 4.11 (t, $J = 9.1$ Hz, 1H), 4.19 (dd, $J = 2.8$, 9.1 Hz, 1H), 4.54 (septet, $J = 6.1$ Hz, 1H), 4.59 (m, 1H), 5.24 (dd, $J = 5.6$, 9.0 Hz, 1H), 6.83−6.88 (m, 3H), 7.19−7.23 (m, 2H), 7.29−7.39 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.1, 37.2, 37.6, 55.4, 56.0, 61.5, 66.6, 71.5, 112.1, 116.9, 121.8, 127.5, 128.0, 128.9, 129.1, 129.4, 134.7, 147.3, 149.7, 152.8, 170.6; MS *m*/*z* 438 (M^+); HRMS *m*/*z* 438.1912 ($C_{23}H_{26}N_4O_5$ requires 438.1903).

(2*S*)-Methyl 2-Aazido-3-(3-isopropyloxy-4-methoxyphenyl)propionate (16). To methanol (20 mL) cooled at 0 °C was added MeMgBr (3 M solution in ether, 6.7 mL, 20.1 mmol). The white slurry was stirred at 0 °C for 2 min and transferred, via cannula, to a precooled (0 °C) solution of compound **15** (4.0 g, 9.1 mmol) in MeOH (20 mL). After being stirred at 0 °C for 10 min, the reaction mixture was diluted with brine (50 mL). The volatile was removed under reduced pressure and the aqueous solution was extracted four times with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc/heptane = 1/3, then EtOAc) gave azido ester **16** (2.58 g, 96%) as a colorless oil and chiral auxiliary **13** (1.4 g, 87%). Compound **16**: $[\alpha]_D = -22.8$ ($CHCl_3$, *c* 1.12); IR ($CHCl_3$) 2107, 1742, 1516 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.36 (d, $J = 6.1$ Hz, 6H), 2.94 (dd, $J = 8.5$, 14.0 Hz, 1H), 3.10 (dd, $J = 5.6$, 14.0 Hz, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.03 (dd, $J = 5.6$, 8.5 Hz, 1H), 4.52 (septet, $J = 6.1$ Hz, 1H), 6.78−6.81 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.1, 37.2, 52.6, 56.0, 63.5, 71.5, 112.1, 117.2, 121.9, 128.2, 147.2, 149.8, 170.5; MS *m*/*z* 293 (M^+); HRMS *m*/*z* 293.1359 ($C_{14}H_{19}N_3O_4$ requires 293.1375).

Methyl *N*-[*N*-(*tert*-Butyloxycarbonyl)-L-(3-isopropyloxy-4-methoxyphenylalanyl]-L-4-fluoro-3-nitrophenylalaninate ((9*S*,12*S*)-19). A solution of **16** (2.0 g, 6.8 mmol) in MeOH (20 mL) was hydrogenated at atmospheric pressure in the presence of 10% Pd/C for 1 h. The mixture was filtered through a short pad of Celite and washed with MeOH. The filtrate was evaporated to dryness in vacuo to give **17** (1.82 g, 99%) as an oil that was used without further purification. To a solution of **17** (1.82 g, 6.83 mmol) in CH_2Cl_2 (40 mL) were added sequentially l-*N*-Boc-4-fluoro-3-nitrophenylalanine **18** (2.24 g, 6.83 mmol), $HOBt \cdot H_2O$ (1.04 g, 6.83 mmol), and EDC (1.6 g, 8.3 mmol) at room temperature. After being stirred at room temperature for 80 min, the reaction mixture was hydrolyzed with aqueous HCl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc/heptane = 1:3 then 1:1) gave **19** (3.54 g, 90%) as a yellow solid: mp 44−45 °C (EtOAc−heptane); $[\alpha]_D = +20.9$ ($CHCl_3$, *c* 0.75); IR ($CHCl_3$) 3425, 1744, 1706, 1681, 1538, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, $J = 6.1$ Hz, 3H), 1.34 (d, $J = 6.1$ Hz, 3H), 1.41 (s, 9H), 2.95−3.02 (m, 3H), 3.15 (dd, $J = 6.8$, 14.0 Hz, 1H), 3.72 (s, 3H), 3.82 (s, 3H), 4.31 (m, 1H), 4.47 (septet, $J = 6.1$ Hz, 1H), 4.78 (m, 1H), 5.07 (d, $J = 7.0$ Hz, NH), 6.20 (d, $J = 7.8$ Hz, NH), 6.58 (dd, $J = 2.0$, 8.1 Hz, 1H), 6.61 (d, $J = 2.0$ Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 7.19 (dd, $J = 8.6$, 10.6 Hz, 1H), 7.45 (ddd, $J = 2.3$, 7.1, 8.6 Hz, 1H), 7.85 (dd, $J = 2.3$, 7.1 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.2, 22.3, 28.5 (3 C), 37.4, 37.6, 52.5, 53.5, 55.3, 56.0, 71.7, 80.7, 112.2, 117.3, 118.5 (d, $J = 20.0$ Hz), 122.0, 126.9, 127.7, 136.6 (d, $J = 9.0$ Hz), 147.4, 150.0, 154.7 (d, $J = 261.0$ Hz), 155.2, 170.1, 171.6; MS *m*/*z* 577 (M^+); HRMS *m*/*z* 577.2435 ($C_{28}H_{36}FN_3O_9$ requires 577.2435).

Methyl *N*-[*N*-(*tert*-Butyloxycarbonyl)-L-(3-hydroxy-4-methoxyphenylalanyl]-L-4-fluoro-3-nitrophenylalaninate ((9*S*,12*S*)-10). To a cooled solution (−78 °C) of dipeptide **19** (100.0 mg, 0.17 mmol) in CH_2Cl_2 (6 mL) was added BCl_3 (1 M solution in CH_2Cl_2 867 μL, 0.87 mmol), and the resulting yellow solution was stirred at −78 °C for 5 min and at 0 °C for 20 min. Five drops of MeOH were added to convert the excess of BCl_3 into $B(OMe)_3$, and the volatile was evaporated to dryness. To the solution of the so-obtained crude reaction mixture in THF (4 mL) were added Et_3N and Boc_2O (42 mg, 0.19 mmol). After being stirred at room temperature for 2 h, the reaction mixture was diluted with aqueous HCl and extracted four times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc/heptane = 1/1.2) gave **10** (92 mg, 99%) as a white solid: mp 159−160 °C (EtOAc−heptane); $[\alpha]_D = +31.8$ ($CHCl_3$, *c* 0.66); IR ($CHCl_3$) 3542, 3422, 1742, 1702, 1682, 1543, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.98−3.04 (m, 3H), 3.14 (dd, $J = 6.7$, 14.0 Hz, 1H), 3.74 (s, 3H), 3.86 (s, 3H), 4.35 (m, 1H), 4.76 (m, 1H), 5.14 (d, $J = 7.1$ Hz, NH), 5.75 (s, OH), 6.24 (d, $J = 7.6$ Hz, NH), 6.50 (dd, $J = 2.1$, 8.1 Hz, 1H), 6.56 (d, $J = 2.1$ Hz, 1H), 6.73 (d, $J = 8.1$ Hz, 1H), 7.18 (dd, $J = 8.6$, 10.6 Hz, 1H), 7.43 (ddd, $J = 2.2$, 7.0, 8.6 Hz, 1H), 7.86 (dd, $J = 2.2$, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5 (3 C), 37.3, 37.8, 52.9, 53.6, 55.3, 56.3, 80.7, 111.6, 116.3, 119.2 (d, $J = 21.0$ Hz), 121.5, 127.7, 129.3, 134.7 (d, $J = 4.0$ Hz), 137.5 (d, $J = 7.0$ Hz), 146.1, 154.6 (d, $J = 263.0$ Hz), 154.8, 155.3, 171.1, 172.6; MS *m*/*z* 535 (M^+). Anal. Calcd for $C_{25}H_{30}FN_3O_9$: C, 56.07; H, 5.65; N, 7.85. Found: C, 55.62; H, 5.71; N, 7.67.

(9*S*,12*S*)-12-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,11-dioxo-4-methoxy-9-methoxycarbonyl-16-nitro-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (20). To a solution of linear dipeptide **10** (140.0 mg, 0.26 mmol) in DMSO (26 mL, 0.01 M) containing 3 Å molecular sieves was added K_2CO_3 (140 mg, 1.05 mmol) at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was quenched by addition of water and extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification by preparative TLC (SiO_2, eluent: EtOAc/heptane = 1:1) afforded atropisomer **20a** (50 mg, 37%) as a colorless oil and atropisomer **20b** (51 mg, 38%) as a colorless oil. For **20a**: $[\alpha]_D = +41.0$

($CHCl_3$, *c* 0.31); IR ($CHCl_3$) 1744, 1682, 1607, 1537, 1494 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 1.47 (s, 9H), 2.78−2.86 (m, 2H), 3.09 (dd, J = 4.0, 13.0 Hz, 1H), 3.47 (dd, J = 5.3, 13.0 Hz, 1H), 3.59 (s, 3H), 3.90 (s, 3H), 4.02 (m, 1H), 4.65 (m, 1H), 5.41 (d, J = 2.0 Hz, 1H), 6.44 (m, NH), 6.73 (dd, J = 2.0, 8.2 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.28 (m, NH), 7.54 (dd, J = 2.1, 8.4 Hz, 1H), 8.12 (br s, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 28.3 (3 C), 34.8, 38.5, 52.6, 54.1, 56.5, 56.8, 80.2, 112.7, 115.3, 123.2, 125.5, 128.5, 135.5, 137.6, 138.0, 147.6, 155.1, 156.3, 170.6, 171.1; MS (FAB) *m*/*z* 538 (M + Na). For **20b**: $[\alpha]_D$ = −115.0 ($CHCl_3$, *c* 0.10); IR ($CHCl_3$) 1736, 1708, 1687, 1602, 1532, 1518, 1497 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 1.45 (s, 9H), 2.79 (m, 1H), 2.87 (m, 1H), 3.01 (dd, J = 6.2, 13.1 Hz, 1H), 3.45 (dd, J = 5.1, 13.1 Hz, 1H), 3.55 (s, 3H), 3.89 (s, 3H), 4.08 (m, 1H), 4.54 (m, 1H), 5.45 (d, J = 2.0 Hz, 1H), 6.22 (m, NH), 6.68 (dd, J = 2.0, 8.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.32 (m, NH), 7.72 (br d, J = 7.9 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H); ^{13}C NMR (50.05 MHz, CD_3COCD_3) δ 28.6 (3 C), 34.9, 39.3, 52.2, 55.5, 56.6, 58.0, 80.1, 113.6, 117.3, 123.5, 123.8, 128.4, 128.7, 129.4, 132.7, 132.9, 136.9, 137.4, 138.9, 145.9, 152.1, 171.1; MS *m*/*z* 516 (M+H), 460, 416; HRMS *m*/*z* 516.1975 (M + H) ($C_{25}H_{29}N_3O_9$ + H requires 516.1982).

(9*S*,12*S*)-12-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,11-dioxo-4-methoxy-9-methoxycarbonyl-10-azatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (21). A solution of a mixture of **20a** and **20b** (240 mg, 0.47 mmol) in MeOH (10 mL) was hydrogenated in the presence of 10% Pd/C at atmospheric pressure for 50 min. The reaction mixture was then filtered through a pad of Celite and washed thoroughly with MeOH. The filtrate was evaporated to dryness to give the aniline (228.0 mg, quantitative) as a brown oil that was immediately used for the next step. To the solution of the so-obtained aniline in THF (2 mL), cooled at 0 °C, were added, successively, water (5 mL), H_3PO_2 (50% solution in water, 0.434 mL, 3.29 mmol), a small amount of Cu_2O, and a solution of $NaNO_2$ (39.0 mg, 0.56 mmol) in water (1 mL). After the mixture was stirred at 0 °C for 5 min and then at room temperature for 30 min, water (10 mL) was added, and the aqueous phase was extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc/heptane = 1:2) afforded **21** (165.2 mg, 75%) as a white solid: mp 114−115 °C (EtOAc−heptane); $[\alpha]_D$ = +56 ($CHCl_3$, *c* 0.90) (li.t[16b] $[\alpha]_D$ = +57° ($CHCl_3$, *c* 0.6)); IR ($CHCl_3$) 3442, 1743, 1695, 1689, 1620, 1532 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.80−2.93 (m, 3H), 3.52 (dd, J = 4.9, 13.5 Hz, 1H), 3.68 (s, 3H), 3.96 (s, 3H), 4.22 (m, 1H), 4.60 (m, 1H), 4.98 (d, J = 8.9 Hz, NH), 5.04 (br s, 1H), 5.88 (br s, NH), 6.62 (dd, J = 2.1, 8.3 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 7.07 (dd, J = 2.4, 8.3 Hz, 1H), 7.15 (dd, J = 2.2, 8.3 Hz, 1H), 7.30 (m, 2H); ^{13}C NMR (50.05 MHz, $CDCl_3$) δ 28.4 (3 C), 34.8, 38.6, 52.4, 53.9, 56.2, 56.8, 81.1, 112.0, 115.2, 116.8, 121.7, 124.0, 125.7, 129.6, 132.9, 133.7, 147.0, 152.5, 154.8, 158.1, 170.8, 171.2; MS *m*/*z* 471 (M + H), 415, 371.

(9*S*,12*S*)-12-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-2,11-dioxo-4-methoxy-9-methoxycarbonyl-10-methyl-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (22). To a precooled (0 °C) solution of **21** (13.0 mg, 0.028 mmol) in THF (1 mL) were added four drops of DMF and excess MeI. NaH (80% dispersion, 1.8 mg, 0.06 mmol, 2.2 equiv) was then added in one portion, and the resulting slurry was stirred at 0 °C for 10 min and at room temperature for 50 min. The reaction was quenched with aqueous HCl. The aqueous solution was extracted three times with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification by preparative TLC (SiO_2, eluent: toluene/EtOAc = 4:1) afforded **22** (11.7 mg, 85%) as a 4:1 mixture of conformers: $[\alpha]_D$ = −160 ($CHCl_3$, *c* 0.4) (lit.[16b] $[\alpha]_D$ = −161 ($CHCl_3$, *c* 0.2)); IR ($CHCl_3$) 1744, 1673, 1648, 1519, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of two conformers A and B (4/1)). Conformer: δ 1.47 (s, 9H), 2.56 (s, 3H), 2.93 (s, 3H), 2.60−3.35 (m, 3H), 3.65 (m, 1H), 3.67 (s, 3H), 3.94 (s, 3H), 4.42 (br. s, 1H), 4.70 (dd, J = 3.6, 12 Hz, 1H), 4.90 (dd, J = 2.8, 11.3 Hz, 1H), 6.60 (m, 1H), 6.81 (br. d, J = 8.3 Hz, 1H), 6.89 (dd, J = 2.5, 8.2 Hz, 1H), 7.17 (dd, J = 2.5, 8.5 Hz, 1H), 7.33 (m, 1H), 7.46 (dd, J = 1.8, 8.4 Hz, 1H); Conformer B: δ 1.50 (s, 9H), 2.76 (s, 3H), 2.87 (s, 3H), 2.60−3.35 (m, 4H), 3.65 (s, 3H), 3.93 (s, 3H), 4.38 (m, 1H), 4.81 (s, 1H), 5.53 (dd, J = 4.8, 11.9 Hz, 1H), 6.63 (m, 1H), 6.75 (br. d, J = 8.1 Hz, 1H), 6.90 (m, 1H), 7.04 (m, 1H), 7.24 (m, 1H), 7.53 (d, J = 8.3 Hz, 1H); MS *m*/*z* 499 (M + H).

(9*S*,12*S*)-12-[*N*-(Benzyloxycarbonyl)amino]-2,11-dioxo-4-methoxy-9-methoxycarbonyl-16-nitro-10-azatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (23). A solution of an equimolar mixture of **20a** and **20b** (43.0 mg, 0.083 mmol) in TFA (2 mL) was stirred a room temperature for 20 min. The volatile was then removed, and the residue was redissolved in THF (1 mL). To this solution were added Et_3N (35 μL, 0.25 mmol) and CbzOSu (62.0 mg, 0.25 mmol). After being stirred at room temperature for 1 h, the reaction mixture was hydrolyzed by addition of aqueous HCl and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Preparative TLC (SiO_2, eluent: EtOAc/heptane = 1.2/1) gave an equimolar mixture of **23a** and **23b** (44 mg, 95%) as a yellow oil: ^1H NMR (250 MHz, CD_3COCD_3) δ 2.77−2.84 (m, 4H), 3.06 (dd, J = 6.3, 13.4 Hz, 1H), 3.14 (dd, J = 3.9, 13.1 Hz, 1H), 3.44−3.52 (m, 2H), 3.54 (s, 3H), 3.58 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.05 (m, 2H), 4.63 (m, 1H), 4.74 (m, 1H), 5.12 (m, 2H), 5.14 (m, 2H), 5.43 (d, J = 2.0 Hz, 1H), 5.46 (br s, 1H), 6.63 (m, 2H), 6.67 (dd, J = 2.2, 8.3 Hz, 1H), 6.72 (dd, J = 2.0, 8.3 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.33−7.43 (m, 12H), 7.54 (dd, J = 2.1, 8.4 Hz, 1H), 7.76 (dd, J = 1.9, 8.2 Hz, 1H), 7.97 (d, J = 1.9 Hz, 1H), 8.15 (br s, 1H); MS *m*/*z* 549 (M); HRMS *m*/*z* 549.1759 (M) ($C_{28}H_{27}N_3O_9$ requires 549.1747).

(9*S*,12*S*)-12-[*N*-(Benzyloxycarbonyl)amino]-2,11-dioxo-4-methoxy-9-methoxycarbonyl-10-azatricyclo[12.2.2.1^{3,7}]-nonadeca-3,5,7(19),14,16,17-hexaene (24). To a stirred solution of a mixture of **23a** and **23b** (15.0 mg, 0.027 mmo) in DMF (1 mL) was added $SnCl_2 \cdot 2H_2O$ (49 mg, 0.22 mmol), and the resulting slurry was stirred at 50 C for 2 h. The reaction mixture was then cooled to room temperature, hydrolyzed, and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to give aniline (13.0 mg, quantitative) as a brown oil that was immediately used for the next step. To a solution of above-obtained amino derivative in THF (1 mL) and water (2 mL) cooled at 0 °C were added sequentially H_3PO_2 (50% solution in water, 23 μL, 0.175 mmol), a catalytic amount of Cu_2O, and $NaNO_2$ (2 mg, 0.03 mmol) in water (1 mL). After being stirred at 0 °C for 5 min and at room temperature for 30 min, the reaction mixture was diluted with water (10 mL) and extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Preparative TLC (TLC (SiO_2, eluent: EtOAc/heptane = 1:1) afforded **24** (10.3 mg, 75%) as a colorless oil: ^1H NMR (300 MHz, CD_3COCD_3) δ 2.78−2.81 (m, 2H), 2.98 (dd, J = 4.2, 13.2 Hz, 1H), 3.37 (dd, J = 5.0, 13.2 Hz, 1H), 3.59 (s, 3H), 3.87 (s, 3H), 3.98 (m, 1H), 4.65 (m, 1H), 5.14 (s, 2H), 5.21 (d, J = 2.2 Hz, 1H), 6.47 (br s, 1H), 6.61 (dd, J = 2.1, 8.2 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.95 (dd, J = 2.5, 8.2 Hz, 1H), 7.05 (dd, J = 2.5, 8.2 Hz, 1H), 7.22 (dd, J = 2.2, 8.4 Hz, 1H), 7.26−7.46 (m, 7H); MS *m*/*z* 504 (M); HRMS *m*/*z* 504.1891 (M) ($C_{28}H_{28}N_2O_7$ requires 504.1897).

Bicyclic Hydantoin 25. To a precooled (0 °C) solution of **24** (12.0 mg, 0.024 mmol) in THF (1 mL) and DMF (1 mL) was added an excess of MeI followed by NaH (75% dispersion, 1.7 mg, 0.052 mmol). After being stirred at 0 °C for 5 min and at room temperature for 70 min, the reaction mixture was quenched with aqueous HCl and extracted four times with EtOAc. The combined organic extracts was washed with brine, dried over Na_2SO_4, and concentrated. Purification by preparative TLC (TLC (SiO_2, eluent: EtOAc/heptane = 1:1) afforded **25** (9.0 mg, 87%) as a white solid: mp 198−199 °C (EtOAc−heptane); $[\alpha]_D$ = +305.0 ($CHCl_3$, *c* 0.20); IR ($CHCl_3$) 1769, 1744, 1713, 1519 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.53 (s, 3H), 3.02 (dd, J = 1.9, 16.1 Hz, 1H), 3.07 (s, 3H), 3.00−3.09 (m,

2H), 3.72 (s, 3H), 3.93 (s, 3H), 4.07 (dd, J = 12.1, 16.1 Hz, 1H), 4.46 (dd, J = 1.9, 12.1 Hz, 1H), 4.91 (d, J = 2.0 Hz, 1H), 6.66 (dd, J = 2.0, 8.2 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.92 (dd, J = 2.4, 8.4 Hz, 1H), 7.03 (dd, J = 2.2, 8.3 Hz, 1H), 7.16 (dd, J = 2.4, 8.3 Hz, 1H), 7.22 (dd, J = 2.2, 8.4 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 22.0, 30.5, 39.7, 53.3, 55.7, 56.3, 67.4, 111.8, 116.3, 122.0, 124.4, 124.9, 129.5, 130.8, 132.0, 133.6, 152.4, 156.2, 158.8, 170.0; MS *m*/*z* 424 (M); HRMS *m*/*z* 424.1653 (M) ($C_{23}H_{24}N_2O_6$ requires 424.1634).

(2*S*)-Methyl 3-(3,4-Dihydroxyphenyl)-2-[3-(4-fluoro-3-nitrophenyl)propionylamino]propionate (35). To a solution of amino ester **33** (500 mg, 1.41 mmol) in 10 mL of CH_2Cl_2 were added sequentially acid **34** (350 mg, 1.64 mmol), HOBt (250.9 mg, 1.64 mmol), and EDC (313.2 mg, 1.64 mmol) at room temperature. After being stirred at room temperature for 30 min, the reaction mixture was diluted with aqueous HCl and extracted four times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc) gave **35** (561.0 mg, 98%) as a yellow oil: $[\alpha]_D = -5.8$ (CH_3OH, *c* 2.10); IR ($CHCl_3$) 3423, 1742, 1676, 1616, 1603, 1536, 1510, 1450 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 2.50 (t, J = 7.3 Hz, 2H), 2.74 (dd, J = 8.8, 13.9 Hz, 1H), 2.89 (t, J = 7.3 Hz, 2H), 2.93 (dd, J = 5.5, 13.9 Hz, 1H), 3.64 (s, 3H), 4.56 (dd, J = 5.5, 8.8 Hz, 1H), 6.43 (dd, J = 2.0, 8.0 Hz, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 7.24 (dd, J = 8.6, 11.0 Hz, 1H), 7.42 (ddd, J = 2.2, 7.2, 8.6 Hz, 1H), 7.87 (dd, J = 2.2, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.3, 37.6, 37.8, 52.6, 55.3, 116.2, 117.1, 119.1 (d, J = 21.0 Hz), 121.5, 126.7, 129.4, 136.9 (d, J = 9.0 Hz), 139.5, 145.2, 146.2, 155.1 (d, J = 258.0 Hz), 173.6, 174.2; MS *m*/*z* 407 (M + H); HRMS *m*/*z* 407.1279 (M + 1) ($C_{19}H_{20}FN_2O_7$ requires 407.1255).

Methyl *N*-[*N*-(*tert*-Butyloxycarbonyl)-L-(3,4-dihydroxyphenylalanyl]-L-4-fluoro-3-nitrophenylalaninate ((9*S*,12*S*)-11). Under the conditions described for the preparation of compound **35**, coupling between amino ester **33** and L-*N*-BOC-4-fluoro-3-nitrophenylalanine (**18**) gave dipeptide **11** as a yellow oil in 90% yield after flash chromatography (SiO_2, eluent: EtOAc/heptane = 2/1): $[\alpha]_D = +41.0$ ($CHCl_3$, *c* 0.33); IR ($CHCl_3$) 3419, 1738, 1686, 1615, 1538, 1506, 1448 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.90−2.99 (m, 3H), 3.11 (dd, J = 6.2, 14.0 Hz, 1H), 3.75 (s, 3H), 4.48 (m, 1H), 4.80 (m, 1H), 5.41 (d, J = 8.9 *H*z, NH), 6.42 (dd, J = 1.9, 8.1 Hz, *1*H), 6.48 (d, J = 1.9 Hz, 1H), 6.63 (d, J = 8.0 Hz, NH), 6.71 (d, J = 8.[1] Hz, 1H), 7.17 (dd, J = 8.5, 10.5 Hz, 1H), 7.43 (ddd, J = 2.0, 7.0, 8.5 Hz, 1H), 7.86 (dd, J = 2.0, 7.0 Hz, 1H); 13C NMR (75 MHz, CD3OD) δ 28.5 (3 C), 37.8, 38.2, 52.6, 55.3, 56.5, 80.8, 116.3, 117.2, 119.0 (d, J = 21.0 Hz), 121.7, 127.8, 129.0, 136.1, 137.9 (d, J = 9.0 Hz), 145.3, 146.2, 155.5 (d, J = 259.0 Hz), 156.8, 172.8, 173.3; MS *m*/*z* 522 (M + H). Anal. Calcd. for $C_{24}H_{28}FN_3O_9$: C, 55.27; H, 5.41; N, 8.06. Found: C, 55.46; H, 5.87; N, 7.87.

Methyl *N*-[*N*-(*tert*-Butyloxycarbonyl)-L-(3,4-dihydroxyphenylalanyl]-D-4-fluoro-3-nitrophenylalaninate ((9*S*,12*R*)-42). Under the conditions described for the preparation of compound **35**, coupling between amino ester **33** and D-*N*-BOC-4-fluoro-3-nitrophenylalanine gave dipeptide **42** as a yellow oil in 90% yield after flash chromatography (SiO_2, eluent: EtOAc/heptane = 2/1): $[\alpha]_D = +12.2$ ($CHCl_3$, *c* 0.49); IR ($CHCl_3$) 3420, 1738, 1680, 1622, 1538, 1519, 1499, 1448, 1370 cm^{-1}; ^{1}H NMR (250 MHz, CD_3COCD_3) δ 1.31 (s, 9H), 2.84 (dd, J = 3.9, 8.0 Hz, 1H), 2.88 (dd, J = 5.1, 8.0 Hz, 1H), 3.00 (dd, J = 5.4, 13.9 Hz, 1H), 3.21 (dd, J = 4.5, 13.9 Hz, 1H), 3.68 (s, 3H), 4.47 (m, 1H), 4.68 (dd, J = 7.8, 13.9 Hz, 1H), 6.11 (d, J = 8.4 Hz, NH), 6.54 (dd, J = 2.0, 8.3 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 7.35 (dd, J = 8.7, 11.0 Hz, 1H), 7.49 (m, 1H), 7.60 (d, J = 8.1 Hz, NH), 7.77 (s, OH), 7.81 (s, OH), 7.99 (br d, J = 6.4, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 28.5 (3 C), 38.0, 38.2, 52.5, 54.7, 55.9, 79.7, 116.2, 117.3, 118.8 (d, J = 21.0 Hz), 121.7, 127.7, 128.2, 136.5, 138.1 (d, J = 10.0 Hz), 145.1, 146.0, 155.1 (d, J = 269.0 Hz), 156.8, 172.1, 173.3; MS *m*/*z* 522 (M + H); HRMS *m*/*z* 522.1896 (M + H) ($C_{24}H_{28}FN_3O_9$ + H requires 522.1888).

Methyl *N*-[*N*-(*tert*-Butyloxycarbonyl-*N*-methylamino)-L-(3,4-dihydroxyphenylalanyl]-L-4-fluoro-3-nitrophenylalaninate ((9*S*,12*S*)-45). Under the conditions described for the preparation of compound **35**, coupling between amino ester **33** and l-*N*-BOC-*N*-methyl-4-fluoro-3-nitrophenylalanine gave dipeptide **45** as a yellow oil in 90% yield after flash chromatography (SiO_2, eluent: EtOAc/heptane = 1.2/1): $[\alpha]_D = -16.4$ ($CHCl_3$, *c* 0.59); IR ($CHCl_3$) 1743, 1680, 1616, 1539, 1518, 1476 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3, mixture of two rotamers) δ 1.30 (br s, 9H), 2.62 (br s, 3H), 2.88 (dd, J = 8.2, 14.2 Hz, 1H), 3.02 (dd, J = 5.4, 13.9 Hz, 1H), 3.04 (m, 1H), 3.34 (dd, J = 5.4, 13.9 Hz, 1H), 3.68 (s, 3H), 4.64 (m, 1H), 5.03 (m, 1H), 6.53 (m, 1H), 6.71 (m, 1H), 6.73 (d, J = 8.0 Hz, 1H), 7.19 (m, NH), 7.42 (m, 1H), 7.76 (m, 1H+2 OH), 8.03 (m, 1H); ^{13}C NMR (50.05 MHz, CD_3COCD_3, mixture of two rotamers) δ 28.3 (3 C), 31.1, 33.9, 37.4, 52.4, 54.5 and 54.6, 59.6, 80.5, 116.1, 117.1, 118.9 (d, J = 19.0 Hz), 121.5, 127.2, 129.1, 136.9, 137.8 (d, J = 8.0 Hz), 144.9, 145.9, 154.8 (d, J = 259.0 Hz), 170.5, 172.6; MS *m*/*z* 536 (M + H); HRMS *m*/*z* 536.2024 (M + H) ($C_{25}H_{30}FN_3O_9$ + H requires 36.2044).

Methyl *N*-[*N*-(*tert*-Butyloxycarbonyl-*N*-methylamino)-L-(3,4-dihydroxyphenylalanyl]-D-4-fluoro-3-nitrophenylalaninate ((9*S*,12*R*)-46). Under the conditions described for the preparation of compound **35**, coupling between amino ester **33** and d-*N*-BOC-*N*-methyl-4-fluoro-3-nitrophenylalanine gave dipeptide **46** as a yellow oil in 90% yield after flash chromatography (eluent: EtOAc/heptane = 1/1): $[\alpha]_D = +41.3$ ($CHCl_3$, *c* 1.95); IR ($CHCl_3$) 1736, 1682, 1616, 1543, 1519, 1450 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3, mixture of two rotamers) δ 1.26 and 1.30 (2 br s, 9H), 2.76 (br s, 3H), 2.84−3.00 (m, 2H), 3.02 (dd, J = 10,6, 14.5 Hz, 1H), 3.32 (m, 1H), 3.69 (s, 3H), 4.67 (m, 1H), 4.93 and 5.03 (2 m, 1H), 6.51 (m, 1H), 6.68 (m, 1H), 6.72 (d, J = 8.0 Hz, 1H), 7.24 (m, 1H), 7.42 (m, 1H), 7.69 (m, 1H), 7.78 (m, 2H), 8.05 (m, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3, mixture of two rotamers) δ 28.3 (3 C), 30.7 and 31.1, 33.9 and 34.0, 37.4, 52.4, 54.6, 59.6 and 61.3, 80.6, 116.1, 117.1, 118.9 (d, J = 19.0 Hz), 121.5, 127.3, 129.1 (d, J = 11.0 Hz), 137.1, 137.8 (d, J = 9.0 Hz), 144.9, 145.9, 154.8 (d, J = 259.0 Hz), 170.3 and 170.5, 172.7; MS *m*/*z* 536 (M + H).

(9*S*)-2,11-Dioxo-4-hydroxy-9-methoxycarbonyl-16-nitro-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (36). To a solution of **35** (10 mg, 0.025 mmol) in DMSO (12.5 mL, 0.002 M) containing 3 Å molecular sieves was added K_2CO_3 (10 mg, 0.074 mmol) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was diluted with water and extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification by preparative TLC (EtOAc) afforded atropisomer **36a** (4 mg, 35%) as a white solid and its atropisomer **36b** (4 mg, 35%) as a yellow oil. Atropisomer **36a**: mp 222−223 °C (EtOAc−heptane); $[\alpha]_D = +121.8$ ($CHCl_3$, *c* 0.62); IR ($CHCl_3$) 3436, 3309, 1749, 1676, 1536, 1516, 1497, 1437, 1350 cm^{-1}; ^{1}H NMR (250 MHz, CD_3COCD_3) δ 2.43 (dt, J = 4.8, 13.1 Hz, 1H), 2.54 (ddd, J = 3.2, 4.7, 13.1 Hz, 1H), 2.73 (m, 1H), 2.88 (br s, 1H), 3.01 (dd, J = 4.8, 12.4 Hz, 1H), 3.17 (dd, J = 4.1, 12.4 Hz, 1H), 3.64 (s, 3H), 4.01 (m, 1H), 5.38 (d, J = 2.0 Hz, 1H), 6.64 (dd, J = 2.0, 8.1 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.45 (dd, J = 2.1, 8.3 Hz, 1H), 7.57 (d, J = 7.2 Hz, NH), 8.10 (d, J = 2.1 Hz, 1H), 8.28 (s, OH); ^{13}C NMR (62.5 MHz, CD_3COCD_3) δ 32.1, 35.0, 40.3, 52.4, 55.2, 116.1, 117.3, 123.9, 126.6, 128.2, 131.3, 138.2, 141.5, 145.7, 151.3, 151.7, 155.7, 172.0; MS *m*/*z* 387 (M+H); HRMS *m*/*z* 387.1170 (M + 1) ($C_{19}H_{19}N_2O_7$ requires 387.1192). Atropisomer **36b**: $[\alpha]_D = +19.3$ ($CHCl_3$, *c* 1.00); IR ($CHCl_3$) 3550, 3423, 1743, 1673, 1532, 1504, 1441, 1356 cm^{-1}; ^{1}H NMR (250 MHz, CD_3COCD_3) δ 2.32 (dt, J = 5.2, 12.1 Hz, 1H), 2.53 (ddd, J = 3.6, 4.9, 13.5 Hz, 1H), 2.75 (m, 1H), 2.89 (br s, 1H), 3.03 (dd, J = 4.8, 12.3 Hz, 1H), 3.14 (ddd, J = 3.4, 5.2, 12.7 Hz, 1H), 3.63 (s, 3H), 4.03 (m, 1H), 5.31 (d, J = 2.1 Hz, 1H), 6.62 (dd, J = 2.1, 8.1 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 6.8 Hz, NH), 7.78 (dd, J = 2.1, 8.3 Hz, 1H), 7.82 (d, J = 2.1 Hz, 1H), 8.20 (s, OH); ^{13}C NMR (62.5 MHz, CD_3COCD_3) δ 32.2, 34.7, 40.0, 52.4, 54.9, 115.0, 117.3, 123.9, 128.4, 128.6, 131.2, 136.3, 141.5, 150.9, 151.3, 171.2, 173.1; MS *m*/*z* 387 (M + H).

A variable amount of cyclic dimer **38** was also isolated under other cyclization conditions (see text) as a white solid: mp 238−239 °C (EtOAc−heptane); ^{1}H NMR (300 MHz, CD3COCD3) δ 2.51 (m, 2H), 2.77−3.05 (m, 8H), 3.09 (dd, J = 4.2, 13.6 Hz, 2H), 3.72 (s, 6H), 4.66 (m, 2H), 6.16 (dd, J = 2.0, 8.0 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 2.0 Hz, 2H), 6.79 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2 NH), 7.40 (dd, J = 2.0, 8.6 Hz, 2H), 7.86 (d, J = 2.0 Hz, 2H), 8.52 (s, 2 OH); MS (FAB + NaCl) m/z 795 (M + Na).

(M) (9*S*)-2,11-Dioxo-4-methoxy-9-methoxycarbonyl-16-nitro-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (39a). To a solution of atropisomer **36a** (22 mg, 0.057 mmol) in acetone (5 mL) were added K_2CO_3 (24 mg, 0.17 mmol) and an excess of MeI. After being refluxed for 15 h, the reaction mixture was filtered through a short pad of Celite, and the filtrate was evaporated to dryness. Purification by preparative TLC (SiO_2, eluent: EtOAc) gave compound **39a** (20 mg, 90%) as a yellow oil: $[\alpha]_D = -173$ ($CHCl_3$, c 0.15); IR ($CHCl_3$) 3438, 3013, 2931, 1744, 1681, 1538, 1494, 1438, 1350 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 2.38 (dt, J = 4.8, 12.5 Hz, 1H), 2.53 (ddd, J = 3.3, 4.7, 13.3 Hz, 1H), 2.79 (m, 2H), 3.04 (dt, J = 4.7, 12.4 Hz, 1H), 3.14 (ddd, J = 3.2, 4.9, 12.6 Hz, 1H), 3.64 (s, 3H), 3.88 (s, 3H), 4.03 (m, 1H), 5.31 (d, J = 2.0 Hz, 1H), 6.72 (dd, J = 2.0, 8.3 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 7.0 Hz, 1H), 7.78 (dd, J = 2.1, 8.4 Hz, 1H, NH), 7.82 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 31.5, 34.5, 40.2, 52.6, 53.7, 56.6, 112.8, 113.8, 122.9, 127.9, 130.3, 134.7, 139.8, 147.4, 150.6, 151.3, 171.5, 172.4; MS (CI) m/z 401 (M + H).

(P) (9*S*)-2,11-Dioxo-4-methoxy-9-methoxycarbonyl-16-nitro-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,-17-hexaene (39b). Methylation of atropisomer **36b** under the above-described conditions gave **39b** as a yellow oil: $[\alpha]_D$ = −90 ($CHCl_3$, c 1.5); IR ($CHCl_3$) 3433, 3020, 2962, 2937, 1744, 1680, 1531, 1493, 1441, 1351 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 2.43 (dt, J = 4.8, 12.6 Hz, 1H), 2.54 (ddd, J = 3.2, 4.8, 13.1 Hz, 1H), 2.74−2.77 (m, 2H), 3.01 (dt, J = 4.8, 12.5 Hz, 1H), 3.18 (dt, J = 3.9, 12.6 Hz, 1H), 3.64 (s, 3H), 3.90 (s, 3H), 4.00 (dt, J = 4.7, 7.8 Hz, 1H), 5.39 (d, J = 2.2 Hz, 1H), 6.73 (dd, J = 2.2, 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.45 (dd, J = 2.2, 8.3 Hz, 1H), 7.59 (dd, J = 7.2 Hz, 1H, NH), 8.11 (d, J = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 31.7, 34.6, 39.8, 52.0, 54.7, 56.3, 113.4, 115.5, 123.0, 126.1, 127.6, 132.2, 137.7, 141.0, 148.0, 151.1, 152.4, 171.5, 173.0; MS (CI) m/z 401 (M + H); HRMS m/z 401.1335 (M + H) ($C_{20}H_{20}N_2O_7$ + H requires 401.1349).

(9*S*)-2,11-Dioxo-4-methoxy-9-methoxycarbonyl-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16, 17-hexaene (40). To a stirred solution of **39a** or **39b** (10 mg, 0.025 mmol) in 5 mL of MeOH were added 2 drops of concentrated HCl and a catalytic amount of 10% Pd/C. The resulting slurry was hydrogenated at atmospheric pressure for 30 min. The reaction mixture was then filtered through a short pad of Celite and washed with MeOH. The filtrate was evaporated to dryness under reduced pressure to give the hydrochloride salt of aniline (10 mg, quantitative) as a white solid that was immediately used for the next step. To the solution of aniline in THF (1 mL) and water (2 mL), cooled to 0 °C, were added sequentially H_3PO_2 (50% solution in water, 23 μL, 0.17 mmol), a catalytic amount of Cu_2O, and $NaNO_2$ (2.0 mg, 0.027 mmol) in water (1 mL). After being stirred at 0 °C for 5 min and at room temperature for 30 min, the reaction mixture was diluted with water (10 mL) and extracted five times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Preparative TLC (SiO_2, EtOAc) afforded **40** (6.5 mg, 73%) as a colorless oil: $[\alpha]_D = -10.0$ (CH_3OH, c 0.50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (m, 1H), 2.68 (m, 2H), 2.88 (dd, J = 1.3, 16.9 Hz, 1H), 3.06 (m, 2H), 3.72 (s, 3H), 3.96 (s, 3H), 4.22 (ddd, J = 1.0, 7.4, 10.4 Hz, 1H), 5.10 (d, J = 2.0 Hz, 1H), 5.30 (d, J = 7.1 Hz, NH), 6.60 (dd, J = 2.0, 8.2 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 7.02 (dd, J = 2.4, 8.2 Hz, 1H), 7.10 (dd, J = 2.4, 8.3 Hz, 1H), 7.26 (dd, J = 2.4, 8.3 Hz, 1H), 7.32 (dd, J = 2.2, 8.4 Hz, 1H); MS m/z 356 (M+H); HRMS m/z 356.1515 (M+1) ($C_{20}H_{22}NO_5$ requires 356.1498).

(9*S*,12*S*)-12-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,11-dioxo-4-hydroxy-9-methoxycarbonyl-16-nitro-10-azatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (41). To a solution of **11** (200.0 mg, 0.38 mmol) in DMSO (200 mL, 0.002 M) containing 3 Å molecular sieves was added K_2CO_3 (212.0 mg, 1.54 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by dropwise addition of water and extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc/heptane = 1/1.5) afforded an inseparable mixture of atropisomer **41a** and atropisomer **41b** (110 mg, 57%) as a white solid: ^{1}H NMR (300 MHz, CD_3COCD_3) for **41a** δ 1.47 (s, 9H), 2.79−2.83 (m, 2H), 3.08 (dd, J = 4.1, 13.3 Hz, 1H), 3.46 (dd, J = 5.3, 13.3 Hz, 1H), 3.58 (s, 3H), 4.05 (m, 1H), 4.65 (m, 1H), 5.41 (d, J = 2.0 Hz, 1H), 6.44 (m, NH), 6.63 (dd, J = 2.0, 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.28 (m, NH), 7.53 (dd, J = 2.1, 8.4 Hz, 1H), 8.11 (br s, 1H); 8.27 (s, OH); for **41b** δ 1.45 (s, 9H), 2.79−2.83 (m, 2H), 3.00 (dd, J = 6.2, 13.1 Hz, 1H), 3.46 (dd, J = 5.3, 13.3 Hz, 1H), 3.55 (s, 3H), 4.05 (m, 1H), 4.55 (m, 1H), 5.47 (d, J = 2.0 Hz, 1H), 6.25 (m, NH), 6.58 (dd, J = 2.0, 8.2 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 7.28 (m, 1H+NH), 7.72 (br d, J = 7.7 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H); 8.24 (s, OH); MS m/z 502 (M + H).

(9*S*,12*R*)-12-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,11-dioxo-4-hydroxy-9-methoxycarbonyl-16-nitro-10-azatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (44). To a solution of **42** (15.0 mg, 0.029 mmol) in DMSO (6.0 mL, 0.002 M) containing 3 Å molecular sieves was added K_2CO_3 (16.0 mg, 1.2 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by dropwise addition of water and extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Preparative TLC (SiO_2, eluent: EtOAc/heptane = 2/1) afforded an inseparable mixture of atropisomer **44a** and atropisomer **44b** (8 mg, 55%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) for **44a** δ 1.45 (s, 9H), 2.59−3.06 (m, 3H), 3.28−3.44 (m, 1H), 3.68 (s, 3H), 4.16 (m, 2H), 5.15 (d, J = 2.1 Hz, 1H), 5.20 (d, J = 6.7 Hz, NH), 5.77 (s, OH), 6.11 (m, NH), 6.62 (br d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.50 (dd, J = 2.2, 8.4 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H); for **44b** δ 1.45 (s, 9H), 2.59−3.06 (m, 3H), 3.28−3.44 (m, 1H), 3.64 (s, 3H), 4.16 (m, 2H), 5.22 (br s, 1H), 5.24 (d, J = 9.1 Hz, NH), 5.77 (s, OH), 6.11 (m, NH), 6.62 (br d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 2.1, 8.5 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H); MS m/z 502 (M + H).

(9*S*,12*S*)-12-[*N*-(*tert*-Butyloxycarbonyl)amino]-2,11-dioxo-4-methoxy-9-methoxycarbonyl-16-nitro-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (20). Method A. To a solution of **41a** and **41b** (14.0 mg, 0.028 mmol) in acetone (5 mL) were added an excess of MeI and K_2CO_3 (13.0 mg, 0.09 mmol), and the resulting reaction mixture was refluxed for 3 h. The volatile was removed, and the residue was taken up in water and extracted five times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Preparative TLC (SiO_2, eluent: EtOAc/heptane = 1:1) afforded **20a** (6 mg, 42%) and **20b** (6 mg, 42%) identical in all respects with those prepared previously. **Method B** (one pot, cyclization−methylation): To a solution of **11** (1.0 g, 2.0 mmol) in DMSO (900 mL, 0.002 M) containing 3 Å molecular sieves was added K_2CO_3 (1.0 g, 7.3 mmol) at room temperature, and the resulting reaction mixture was stirred at room temperature for 2 h. After the total consumption of the starting material, an excess of MeI was then added, and the resulting pale yellow solution was stirred at room temperature for 2 h. The reaction was quenched by addition of water and extracted four times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (SiO_2, eluent: EtOAc/heptane = 1:1) afforded **20a** and **20b** (783.0 mg, 76%) identical in all respects with those prepared previously.

(9*S*,12*R*)-12-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-2,11-dioxo-4-methoxy-9-methoxycarbonyl-16-nitro-10-azatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene (47). The cyclization procedure described for **35** was applied to **46**. Preparative TLC (SiO_2, eluent: EtOAc/heptane = 1:1) afforded atropisomer **47a** (28%) as a white solid and atropisomer **47b** (28%) as yellow oil. For **47a**: mp 252−254 °C (EtOAc−heptane); $[\alpha]_D = +54.5$ ($CHCl_3$, *c* 0.55); IR ($CHCl_3$) 3556, 3419, 1744, 1688, 1675, 1600, 1538, 1519 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.64 (dd, *J* = 11.3, 16.5 Hz, 1H), 2.89 (d, *J* = 15.6 Hz, 1H), 2.98 (s, 3H), 3.01 (dd, *J* = 4.2, 12.0 Hz, 1H), 3.38 (t, *J* = 12.0 Hz, 1H), 3.67 (s, 3H), 4.23 (t, *J* = 9.8 Hz, 1H), 4.61 (dd, *J* = 4.2, 12.1 Hz, 1H), 5.26 (br s, 1H), 5.89 (s, OH), 6.04 (d, *J* = 9.1 Hz, NH), 6.63 (dd, *J* = 2.0, 8.2 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.70 (br d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.5 (3 C), 30.2, 34.6, 34.9, 52.6, 53.2, 61.0, 81.2, 113.8, 116.3, 124.2, 127.7, 130.0, 135.8, 136.8, 144.3, 149.0, 152.0, 156.3, 168.6, 172.0; MS *m*/*z* 516 (M + H). For **47b**: $[\alpha]_D = +204.8$ ($CHCl_3$, *c* 0.84); IR ($CHCl_3$) 3555, 3420, 3059, 2962, 2859, 1744, 1680, 1602, 1538, 1441 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.69 (dd, *J* = 11.3, 16.7 Hz, 1H), 2.96 (d, *J* = 14.0 Hz, 1H), 2.99 (s, 3H), 3.04 (dd, *J* = 4.4, 12.0 Hz, 1H), 3.36 (t, *J* = 12.0 Hz, 1H), 3.68 (s, 3H), 4.30 (t, *J* = 9.8 Hz, 1H), 4.64 (m, 1H), 5.17 (br s, 1H), 5.93 (s, OH), 6.16 (d, *J* = 7.8 Hz, NH), 6.62 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.57 (dd, *J* = 2.2, 8.3 Hz, 1H), 8.13 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (62.5 MHz, CD_3-$COCD_3$) δ 28.5 (3 C), 30.2, 34.4, 35.0, 52.7, 52.8, 61.1, 81.2, 113.7, 116.4, 123.9, 127.2, 127.9, 129.9, 136.8, 138.5, 144.0, 149.0, 150.9, 155.8, 169.0, 171.5; MS *m*/*z* 516 (M + H), 416, 386.

Cycloisodityrosine 6. A solution of compound **22** (380 mg, 0.76 mmol) in CH_2Cl_2 (15 mL) and CF_3COOH (1.50 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O and extracted with Et_2O to remove the neutral species. The aqueous solution was then carefully basified and extracted with EtOAc. The combined organic extracts were washed with brine, dried, and concentrated under reduced pressure to give pure compound **6** (290 mg, 96%) as a colorless oil. Compound **6** was found to exist as a mixture of two distinct conformers that were detectable by TLC (SiO_2, R_f = 0.41 and 0.48 in CH_2Cl_2/MeOH = 10/1): IR ($CHCl_3$) 2985, 1748, 1642, 1522, 1501 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of two conformers A and B (1/1) not assignable) δ 2.59 (s, 3H), 2.62 (s, 3H), 2.66 (s, 3H), 2.75 (s, 3H), 2.79−3.25 (m, 6H), 3.56 (dd, *J* = 4.2, 10.1 Hz, 1H), 3.69 (s, 3H), 3.75 (s, 3H), 3.86 (m, 1H), 3.94 (s, 3H), 3.95 (s, 3H), 4.27 (d, *J* = 2 Hz, 1H), 4.41 (dd, *J* = 3.7, 12.1 Hz, 1H), 4.67 (d, *J* = 2 Hz, 1H), 6.62 (br. d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.93 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.07 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.22−7.29 (m, 1H), 7.3 (m, 1H), 7.4 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.48 (dd, *J* = 2.1, 8.3 Hz, 1H); MS *m*/*z* 399 (M + H); HRMS *m*/*z* 399.1911 (M + H) ($C_{22}H_{26}N_2O_5$ + H requires 399.1920).

NHBoc-(*S*)-Ala-NMe-cycloisodityrosine (52). To a precooled (0 °C) solution of **6** (52.0 mg, 0.13 mmol) in DMF (2 mL) were added **51** (49 mg, 0.26 mmol), PyBrOP (126.0 mg, 0.26 mmol), and ^{i}Pr$_2$NEt (excess), and the resulting solution was stirred at 0 °C for 5 min and at room temperature for 2 h. The reaction mixture was then diluted with aqueous $NaHCO_3$. The aqueous solution was extracted three times with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Purification by preparative TLC (1:1 EtOAc/heptane) afforded **52** (72 mg, 97%, oil) as a mixture of two separable conformers: $[\alpha]_D = -152.0$ ($CHCl_3$, *c* 0.40); IR ($CHCl_3$) 3438, 1744, 1706, 1638, 1519, 1500 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of two conformers 8/1) Major conformer δ 1.29 (d, *J* = 6.8 Hz, 1H), 1.47 (s, 9H), 2.57 (s, 3H), 2.74 (dd, *J* = 2.8, 11.4 Hz, 1H), 2.93 (dd, *J* = 12.0, 18.0 Hz, 1H), 3.22 (s, 3H), 3.35 (dd, *J* = 3.6, 18.0 Hz, 1H), 3.66 (m, 1H), 3.68 (s, 3H), 3.95 (s, 3H), 4.41 (d, *J* = 2.0 Hz, 1H), 4.60 (m, 1H), 4.65 (dd, *J* = 3.7, 12.2 Hz, 1H), 5.33 (dd, *J* = 3.0, 11.4 Hz, 1H), 5.38 (d, *J* = 7.7 Hz, NH), 6.61 (dd, *J* = 2.0, 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.92 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.20 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.28 (dd, *J* = 2.3, 8.4 Hz, 1H), 7.42 (dd, *J* = 2.3, 8.4 Hz, 1H); MS *m*/*z* 570 (M + H); HRMS *m*/*z* 570.2807 (M + H) ($C_{30}H_{39}N_3O_8$ + H requires 570.2815).

Hexapeptide (50). A solution of **52** (15 mg, 0.026 mmol) in TFA (1 mL) was stirred at room temperature for 20 min. The volatile was then evaporated, and the residue was redissolved in CH_2Cl_2 (1 mL). To this solution was added ^{i}Pr$_2$-NEt (excess), HOBt (12.2 mg, 0.08 mmol), EDC (15.3 mg, 0.08 mmol), and the tripeptide **53** (36.0 mg, 0.080 mmol). After being stirred at room temperature for 24 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Preparative TLC (SiO_2, EtOAc) gave **50** (15.0 mg, 63%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of conformers) major conformer δ 0.85−0.98 and 1.22−1.48 (m, 18H), 2.48 (s, 3H), 2.94 (s, 3H), 3.20 (s, 3H), 2.70−3.65 (m, 6H), 3.62 (s, 3H), 3.75 (s, 3H), 3.92 (s, 3H), 4.12 (m, 1H), 4.39 (br s, 1H), 4.61−5.00 (m, 6H), 5.29 (dd, *J* = 2.1, 7.8 Hz, 1H), 6.62 (br d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 3H), 6.91 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.19 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.27 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.42 (dd, *J* = 1.6, 8.4 Hz, 1H); MS (FAB Thioglycerol + NaCl) *m*/*z* 946 (M + H + Na).

RA VII (1). To a stirred solution of **50** (15.0 mg, 0.016 mmol) in a mixture of solvents (THF/MeOH/H_2O = 4/1/1, 2 mL) was added LiOH·H_2O (2 mg, 0.05 mmol), and the reaction mixture was stirred at room temperature for 1 h. The volatile was then removed in vacuo, and the resulting residue was taken up in diluted HCl solution and extracted five times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give acid (12 mg, 82%) as a colorless oil that was used whithout further purification for the following reaction. The so-obtained product was dissolved in 2 mL of a 3 M HCl−EtOAc solution. After 1 h, the solvent was evaporated to give the seco acid as a white solid, MS (FAB Thioglycerol) *m*/*z* 789 (M + H), which was used without further purification for the cyclization reaction. To a precooled solution (5 °C) of seco acid in DMF (1 mL) was added solid $NaHCO_3$ (3.6 mg, 0.04 mmol), DPPA (4 μL, 0.024 mmol), and the resulting slurry was stirred at the same temperature for 72 h. The reaction mixture was then filtrated and washedwith EtOAc, the filtrate was evaporated to dryness, and the resulting residue was submitted directly to preparative TLC (SiO_2, eluent: CH_2Cl_2/MeOH = 10/1) to give 2.5 mg (20%) of RA-VII **1** identical in all respects with natural sample: $[\alpha]_D = -222.0$ ($CHCl_3$, *c* 0.09; $CHCl_3$) (lit.[1a] $[\alpha]_D = -229.0$ ($CHCl_3$, *c* 0.1); li.t[10b] $[\alpha]_D = -209.0$ ($CHCl_3$, *c* 0.39)); IR ($CHCl_3$) 3410−3300, 3006, 2932, 1667, 1644, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of conformers) major conformer δ 1.11 (d, *J* = 6.7 Hz, 3H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.37 (d, *J* = 6.9 Hz, 3H), 2.64 (m, 1H), 2.70 (s, 3H), 2.87 (s, 3H), 2.95−3.10 (m, 2H), 3.14 (s, 3H), 3.32 (dd, *J* = 10.6, 14.0 Hz, 1H), 3.38 (dd, *J* = 5.0, 14.0 Hz, 1H), 3.48 (brd, *J* = 3.2 Hz, 1H), 3.60 (dd, *J* = 5.0, 10.6 Hz, 1H), 3.69 (t, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.95 (s, 3H), 4.35 (d, *J* = 1.9 Hz, 1H), 4.37 (m, 1H), 4.56 (dd, *J* = 3.6, 12.0 Hz, 1H), 4.75−4.88 (m, 2H), 5.43 (dd, *J* = 2.9, 11.5 Hz, 1H), 6.42 (d, *J* = 6.5 Hz, 1H), 6.59 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.79−6.87 (m, 4H), 6.89 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.22 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.27 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.43 (dd, *J* = 1.9, 8.4 Hz, 1H); MS (FAB thioglycerol + NaCl) *m*/*z* 793 (M + Na).

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Supporting Information Available: ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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