Synthesis of (9*R*,12*S*)- and (9*S*,12*S*)-Cycloisodityrosine and Their *N*-Methyl Derivatives

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Received July 16, 1996 (Revised Manuscript Received January 29, 1997[⊗]*)*

Full details of the synthesis of (9*R*,12*S*)- and (9*S*,12*S*)-cycloisodityrosine and their *N*-methyl derivatives are detailed based on an intramolecular nucleophilic aromatic substitution reaction for formation of the key biaryl ether with 14-membered ring macrocyclization. Their comparison with prior samples and the documentation of a facile C9 epimerization within the natural 9*S* series are described.

Deoxybouvardin (**1**) and RA-VII (**2**), bicyclic hexapeptides containing an unusual *N*-methylcycloisodityrosine subunit, constitute prototypical members of a growing class of naturally occurring potent antitumor agents (Figure 1).[1−3] In recent communications,[4,5] we and Inoue disclosed the assessment of the stereochemistry of prior cycloisodityrosine intermediates employed in the total synthesis of **1** and **2**[6,7] which resulted in the reassignment of the stereochemistry of our past intermediates. This was carried out concurrent with efforts[8] on the development of an alternative synthesis of the cycloisodityrosine subunit of **1** and **2** based on an intramolecular nucleophilic aromatic substitution reaction[9] for formation of the biaryl ether modeled on our original Ullmann coupling reaction.[10] Herein, we report full details of this work and the extension of the studies to the preparation of the partially *N*-methylated derivatives including cycloisodityrosine itself and their comparison with our previously reported samples. In these studies, we provide documentation of a remarkably facile and efficient base-catalyzed epimerization that went undetected in our prior efforts.

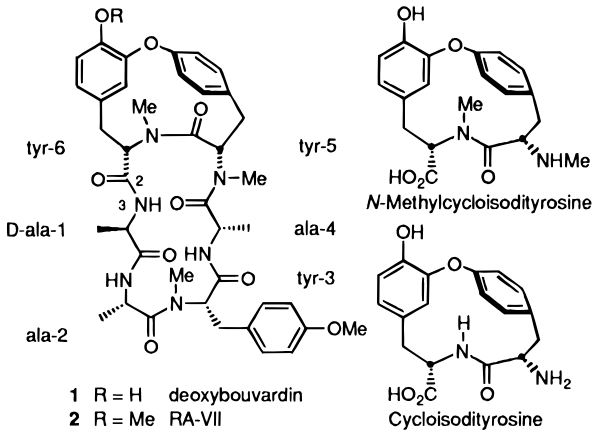

Figure 1.

Preparation and Characterization of the Amino Acid and Dipeptide Building Blocks. (*S*)- and (*R*)-3-Fluoro-4-nitrophenylalanine methyl ester (**6**) were prepared by benzylic bromination[11] of 2-fluoro-4-methylnitrobenzene[12] effected by treatment with 1,3-dibromo-5,5-dimethylhydantoin and alkylation with both enantiomers of the higher order cuprate of Schöllkopf's reagent **4**[13] to provide the enantiomers of **5** with high diastereoselectivity (≥99:1). In our hands, the best conversions achieved with this procedure were 40−45% which do not approach those disclosed in related efforts.[14] Although the corresponding lithium reagent provided **5** in lower conversions (30−35%), it makes more effective use of the valuable chiral reagent, and this was generally employed in our preparations of **6**. Hydrolysis of **5** followed by liberation of the free amine provided the (*S*)- and (*R*)-**6**[5,14] directly (Scheme 1).

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1997.

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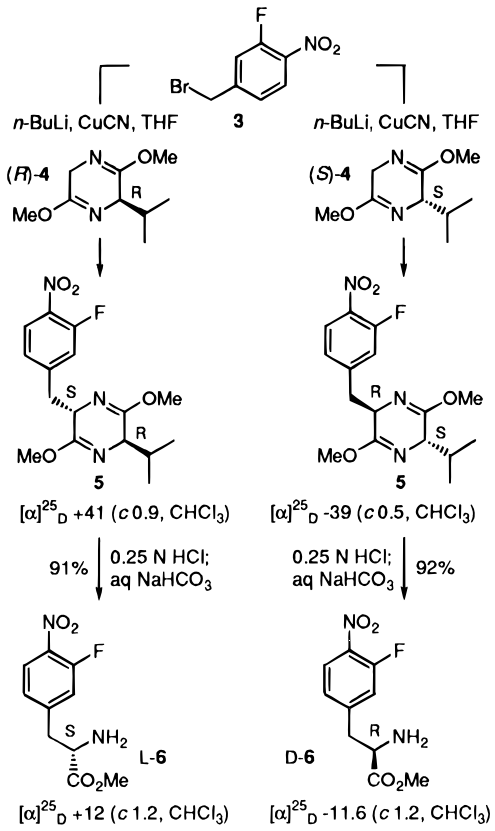
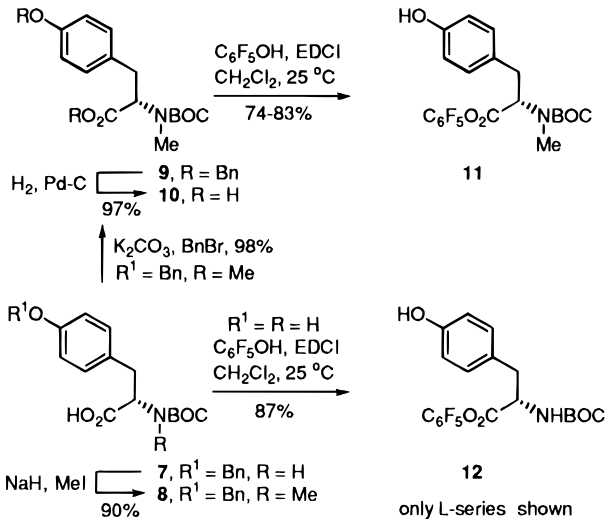
S0022-3263(96)01346-1 CCC: $14.00

Scheme 1



Scheme 2



The preparation of L- and D-BOC-NMe-Tyr-OH (**10**) and their conversion to the corresponding active esters, L- and D-BOC-NMe-Tyr-OC_6F_5 (**11**), were accomplished as outlined in Scheme 2. Direct *N*-methylation[15] of L- or D-BOC-Tyr(OBn)-OH[16] conducted in THF−DMF (20:1) with limiting amounts of NaH (2.2 equiv) provided **8** (90%, 92% ee). This proved much more effective than *N*-methylation of the corresponding benzyl ester (82−89%, 47−55% ee) or when this reaction was run using excess NaH (1:10 DMF−THF) under conditions that generate the corresponding methyl ester (82% ee). In the latter efforts, substantial racemization was observed. This was most easily assessed by direct chromatographic

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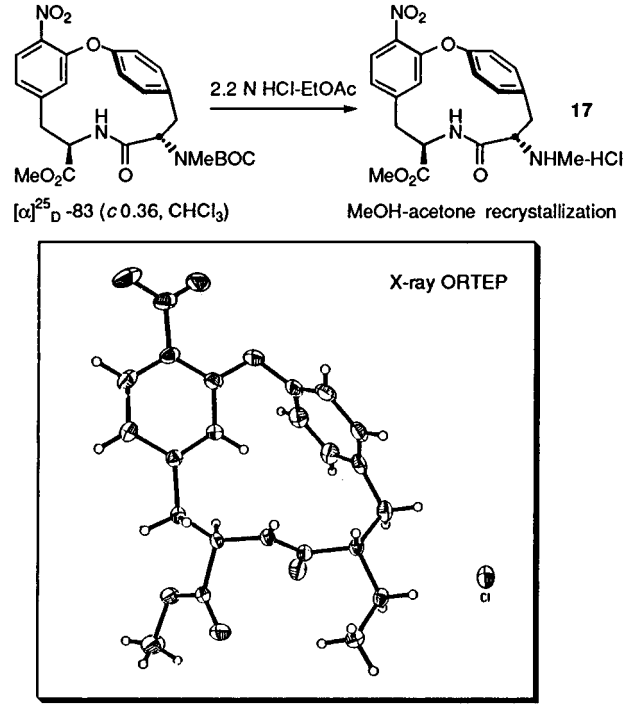


Figure 2.

resolution of the enantiomers of **11** on an analytical ChiralCel OD-H HPLC column (t_R = 17.9 min for L and 16.0 min for D, 4% *i*-PrOH/hexane, 1.0 mL/min).

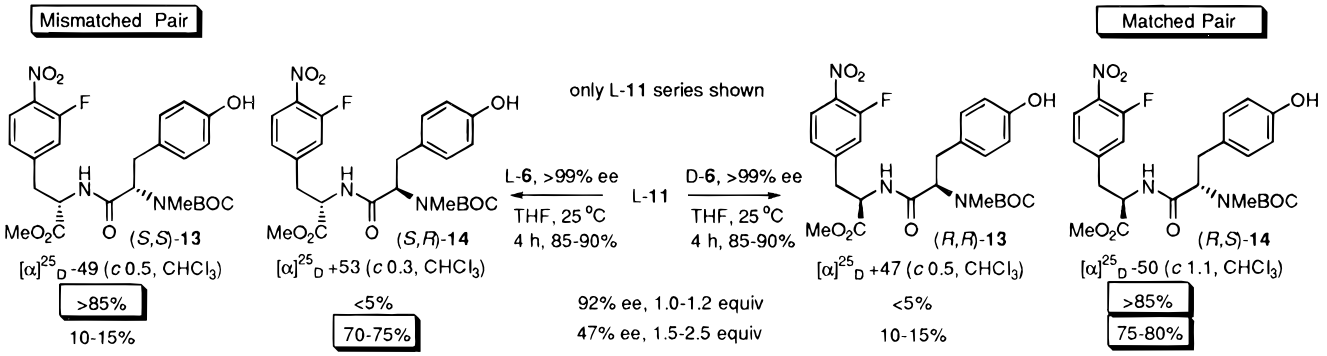
Both (*S*)- and (*R*)-3-fluoro-4-nitrophenylalanine methyl ester (**6**) were coupled with L- and D-BOC-NMe-Tyr-OC_6F_5 (**11**) in THF (25 °C, 4 h, 80−90%), and this reaction exhibited a significant kinetic preference for formation of the (*S*,*R*)- or (*R*,*S*)-diastereomer (Scheme 3). The use of excess amounts of optically enriched but impure active ester (47−55% ee) in the formation of the (*S*,*S*)- or (*R*,*R*)-diastereomer was found to preferentially provide the mixed (*S*,*R*)- or (*R*,*S*)-diastereomer, respectively.

Macrocyclization of 13 and 14. Consistent with prior observations[8] on the 14-membered ring macrocyclization reaction with formation of a biaryl ether,[9] treatment of **13** and **14** with either K_2CO_3 (5 equiv, 0.008 M DMF, 45−50 °C, 2−4 h) or NaH (2.2 equiv, 0.004 M THF, 0−25 °C, 2−6 h) led to smooth 14-membered ring closure under remarkably mild conditions (Scheme 4). In the case of (*R*,*S*)- or (*S*,*R*)-**14**, both conditions provided a single product **15** in superb conversions (76−78%), and the relative stereochemistry of the former was unambiguously established upon *N*-BOC deprotection and X-ray analysis of crystals grown from CH_3OH−acetone (Figure 2).[17] The closure of (*R*,*S*)-**14** was found to occur even at 25 °C in the presence of K_2CO_3, albeit requiring 24 h (72%), and the reaction could be accelerated by the addition of 0.1 equiv of 18-crown-6 (25 °C, 8 h, 70%). CsF also proved to be an excellent reagent for promoting the macrocyclization reaction and provided results comparable to those observed with K_2CO_3 (Table 1). Both KF and $NaHCO_3$ were less effective.

In contrast, (*S*,*S*)- or (*R*,*R*)-**13** only provided the desired macrocyclization product diastereomer **16** under carefully defined reaction conditions where potential epimerization was minimized (2.2 equiv of NaH, 0.004 M THF, 0−25

(17) The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EW, UK.

Scheme 3



Scheme 4

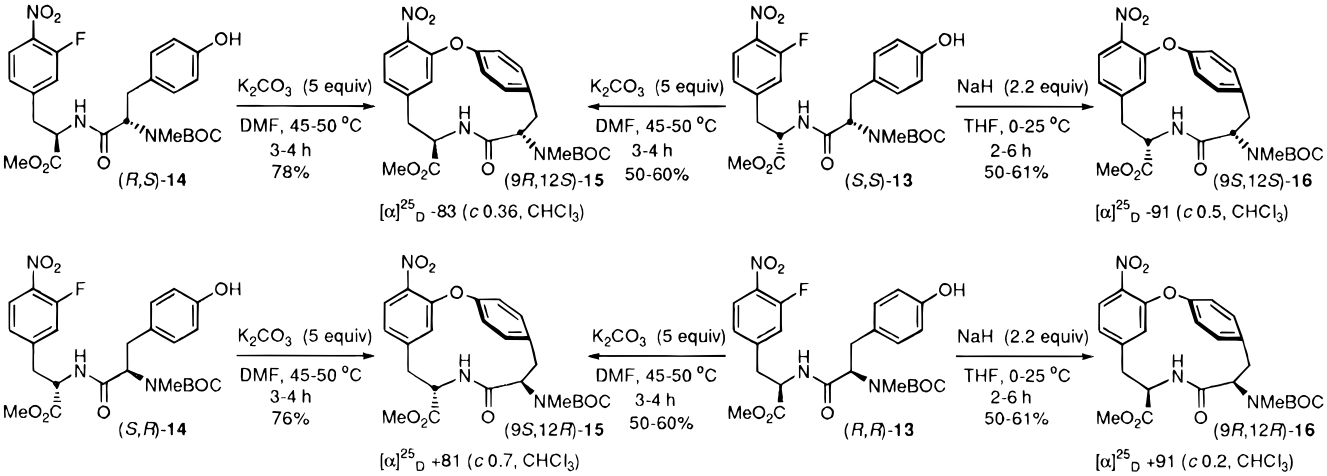


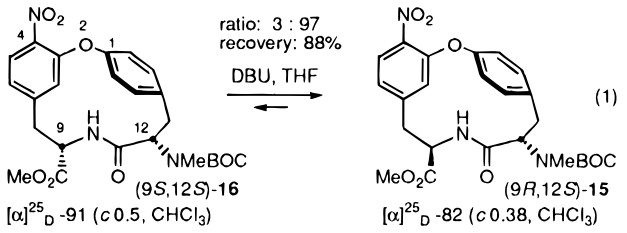
Table 1. Representative Results of the Macrocyclization Reaction of 14 To Provide 15[a]

entry	base (equiv)	catalyst (equiv)	temp (°C)	time (h)	yield (%)
1	K_2CO_3 (3)	none	25	24	72
2	K_2CO_3 (3)	none	45	3	76
3	K_2CO_3 (3)	18-c-6 (0.1)	25	8	70
4	NaH (2.2)[b]	none	0−25	4−6	76−78
5	CsF (3)	none	25	24	74
6	CsF (3)	18-c-6 (0.1)	25	8	68
7	KF (3)	none	25	24	15−20
8	KF (3)	18-c-6 (0.1)	25	24	55[c]
9	$NaHCO_3$ (6)	none	25	24	trace
10	$NaHCO_3$ (6)	18-c-6 (0.1)	25	24	17[d]

[a] All reactions were run in 0.007−0.008 M anhydrous, degassed DMF. [b] The reaction was run in 0.008 M anhydrous THF. [c] <10% recovered **14**. [d] >50% recovered **14**.

°C, 2−6 h, 50−61%). Moreover, increasing amounts of the diastereomer **15** were observed if the reaction was extended to longer reaction times or conducted with excess NaH. Conducting this reaction under the apparently milder conditions of K_2CO_3−DMF (5.0 equiv, 45−50 °C, 0.008 M, 3−4 h) provided the undesired and epimerized diastereomer **15** nearly exclusively (45−55%) with only a trace of the desired product **16** (5−10%) being detected at any time during the course of the reaction. Even more remarkable, the epimerized diastereomer **15** was detected as the major cyclization product when this reaction was conducted at 25 °C (5.0 equiv of DMF, 0.008 M K_2CO_3, 25 °C, 36 h). Under such conditions, the macrocyclization reaction was found to proceed very slowly and provided mainly recovered starting material (>60%) without its epimerization. Addition of a catalytic amount of 18-crown-6 (0.1−0.2 equiv) to the reaction mixture provided a much faster reaction and significantly improved conversions at 25 °C, but with product epimerization, and the isolated ratio of undesired diastereomer **15** to desired **16** was 2.5−3 to 1 under such conditions.

Equilibration studies conducted on (9*S*,12*S*)-**16** confirmed the unusually facile epimerization which could be effected by treatment with K_2CO_3, K_2CO_3/18-c-6, or KF in DMF as well as DBU or Et_3N in THF. However, the epimerization of **16** was found to occur with greater facility in the reaction itself, indicating that the liberated fluoride in the reaction mixture may be contributing to the generation of **15**. The studies also established an equilibrium ratio of ≥97:3 in favor of the unnatural diastereomer **15** and that this epimerization occurs at the C9 center adjacent to the methyl ester (eq 1). This facile epimerization of **16** is analogous to similar but



(1)

unrecognized observations made in closely related efforts[14] but is in sharp contrast to the observations made in systems which are not constrained to the cycloisodityrosine 14-membered ring where epimerization is minimal under comparable[8,9] or more vigorous reaction conditions[10] (Figure 3).

(*S,S*)-*N*-Methylcycloisodityrosine Methyl Ester (22) and Its Unnatural Diastereomer, (*R,S*)-*N*-Meth-

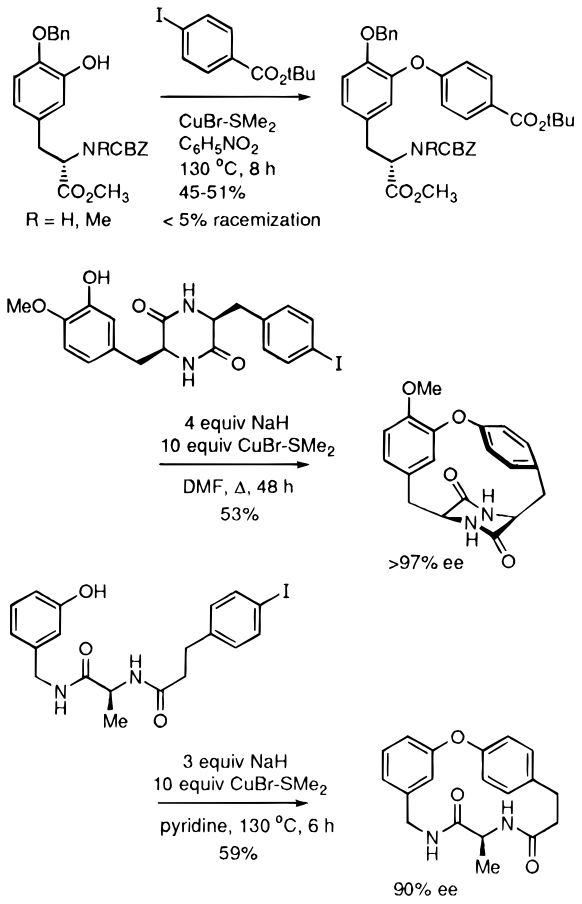
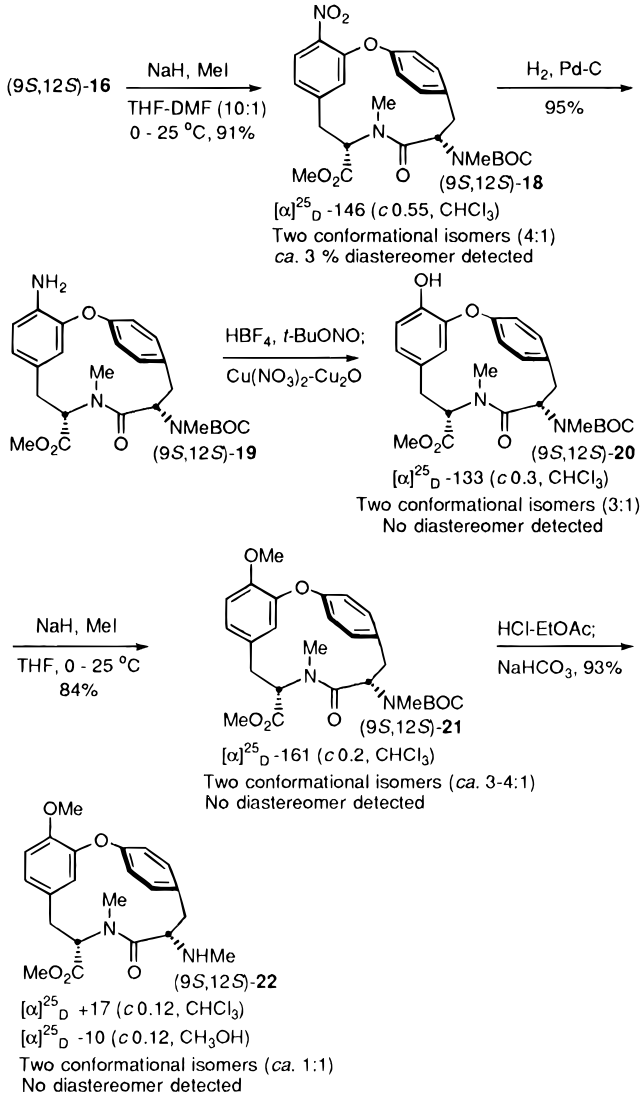


Figure 3.

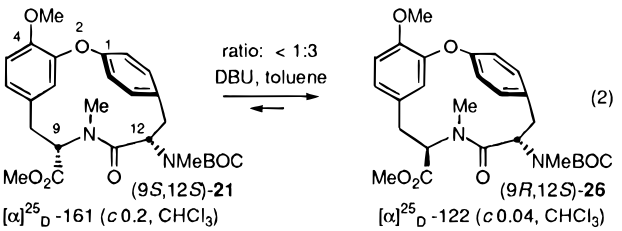
ylcycloisodityrosine Methyl Ester (27). Conversions of (9*S*,12*S*)-**16** and (9*R*,12*S*)-**15** to (*S*,*S*)-*N*-methylcycloisodityrosine methyl ester (9*S*,12*S*)-**22** and its unnatural (*R*,*S*)-diastereomer, (9*R*,12*S*)-**27**, were accomplished as outlined in Schemes 5 and 6. N^{10}-Methylation (1.2 equiv of NaH, 10 equiv of CH_3I, 20:1 THF−DMF, 0−25 °C, 3 h, 84−92%) of **16** and **15** provided **18** and **23**, respectively. No epimerization of **23** was detected under the reaction conditions while the more sensitive **18** suffered trace detectable epimerization (≤3%). Increasing amounts of diastereomer **23** were observed if the latter reaction was conducted with excess NaH (1.5−2.0 equiv), with increasing amounts of DMF (THF−DMF 10:1), or if the reaction time was extended. Nitro reduction to the aryl amines **19** and **24** (H_2, 10% Pd-C, 95%) followed by diazotization (2 equiv of *t*-BuONO, 2 equiv of HBF_4, THF−H_2O, 0 °C, 1 h) and subsequent oxidative hydrolysis of the diazonium salt using $Cu(NO_3)_2$−Cu_2O (0−25 °C, 1 h) afforded the phenols **20** and **25** (40−50%) accompanied by minor amounts of *N*-BOC deprotection and competitive formation of the reduced products (10−20%). Although not extensively examined, the use of THF versus CH_3OH[18] as the reaction solvent provided significant improvements in the relative ratio of phenol to reduction products and limiting the amount of HBF_4 diminished competitive *N*-BOC deprotection. *O*-Methylation provided **21** and **26**, respectively, and subsequent acid-catalyzed *N*-BOC deprotection followed by liberation of the free amines provided **22** and **27**. With care, (*S*,*S*)-**16** could be taken through this sequence without competitive epimerization. With

Scheme 5



the samples of **21**, **22** and **26**, **27** in hand, their comparison with our prior intermediates[7] and those reported by Inoue[4,6] revealed that our past intermediates possess the (*R*,*S*)-stereochemistry of **26** and **27**.[7,19−21]

(9*S*,12*S*)-**21** was subjected to epimerization (DBU, toluene) which established an equilibrium ratio of >3:1 in favor of the (*R*,*S*)- versus (*S*,*S*)-isomer with epimerization occurring cleanly at the C9 center adjacent to the methyl ester (eq 2). This epimerization study of **21**,



which was not driven to equilibrium, was slower and less effective than that of **16** but did confirm that it occurs

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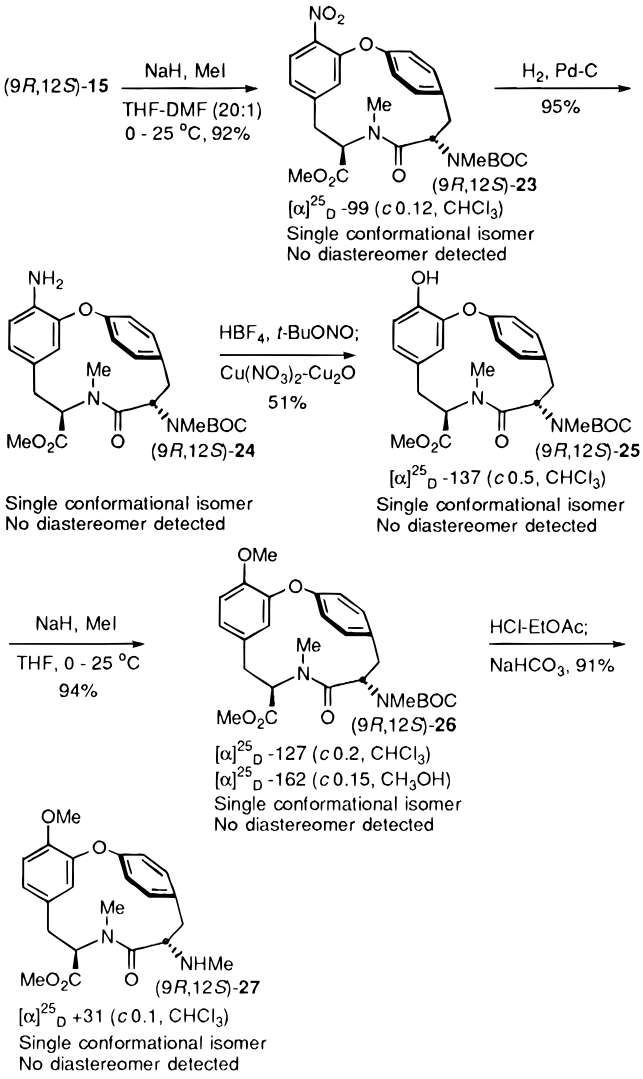
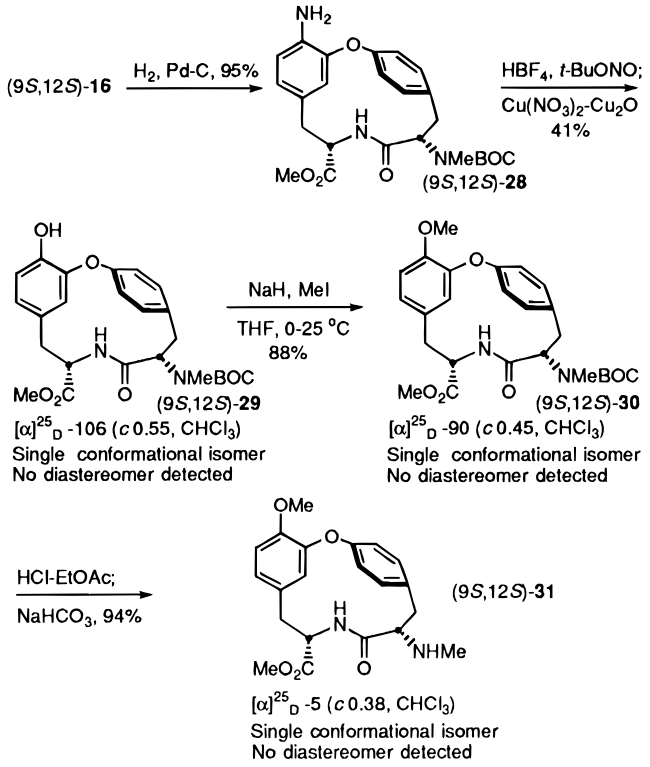
Scheme 6



Scheme 7



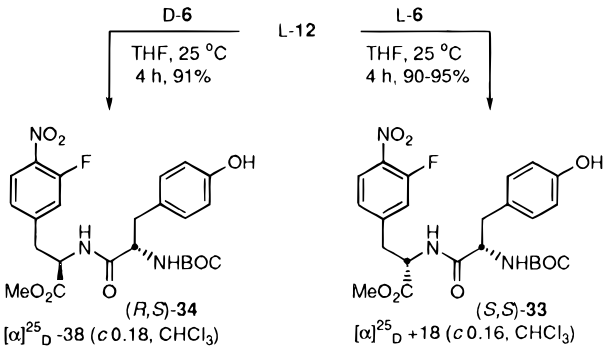
cleanly at the ester center. A similar treatment of **26** led to recovered starting material with little or no detection of **21**, indicating the true equilibrium ratio lies close to that observed with **15**/**16** and explains why prior attempts at deliberate epimerization with our original samples[7] did not afford a second diastereomer.

The intermediates **15** and **23**−**27** were all found to exist in a single, rigid solution conformation that is analogous to that observed with the X-ray structures of **17** and **26**[4] which possess a trans amide central to the 14-membered ring. Thus, N^{10}-methylation of **15** did not alter this inherent preference for a central trans amide. Similarly, **16** adopts a single rigid solution conformation containing a trans secondary amide central to the 14-membered ring, and its backbone conformation proved nearly identical with that of **15**. Although this was established by ^{1}H NMR and is consistent with modeling studies of the low energy conformations available to **15**, **16** and **23**−**27**, it is most apparent in the comparison X-ray of **45**.[17] Superimposition of **17** and **45** revealed that the adopted backbone conformations are essentially indistinguishable (RMS = 0.23 Å excluding substituents).

In contrast, **18**−**22** derived from *N*-methylation of **16** adopt two rigid solution conformations. This was more closely examined with the free amine **22** which was found to exist as a near 1:1 mixture of the two conformations in $CDCl_3$ and acetone-d_6 whereas **18**−**21** exist as 3−4:1 mixtures with one conformation dominating. For one conformation, the 2D ^{1}H−^{1}H ROESY NMR spectrum of the free amine **22** exhibited diagnostic H-9/N10-CH_3, H-12/N10-CH_3, and H-19/N10-CH_3 NOE cross peaks and lacked a strong H-9/H-12 NOE establishing the trans amide configuration and the N-CH_3 orientation proximate to C19 analogous to that found in the X-ray structures of **17**, **26**, and **45**. For the second conformation, an intense H′-12/H′-9 NOE was observed and is diagnostic of a cis amide central to the 14-membered ring. Thus, **22** adopts two rigid conformations, one of which possesses a cis amide in the 14-membered ring analogous to that found in the natural products **1** and **2**. Moreover, the two conformational isomers of **22** are sufficiently stable to be chromatographically detected (TLC) and even separated although they rapidly reequilibrate at 25 °C upon isolation. For **18**−**21**, the major conformation (3−4:1) adopted corresponds to the cis amide conformation central to the 14-membered ring analogous to that found in **1** and **2** and was established with the observation of the characteristic H-9/H-12 and H-9/H-19 NOEs in the ^{1}H−^{1}H ROESY NMR spectra.

***N*$^\alpha$-Methylcycloisodityrosine Methyl Ester (31).** The partially methylated agents **29**−**31** containing a secondary amide central to the 14-membered ring and a C12 *N*-methyl group were prepared following an identical sequence (Scheme 7). Without optimization, reduction of (9*S*,12*S*)-**16** followed by conversion to the diazonium salt and its immediate conversion to a phenol provided **29**. Subsequent *O*-methylation provided *N*-BOC-*N*$^\alpha$-methylcycloisodityrosine methyl ester (**30**) and *N*-BOC deprotection followed by liberation of the free amine afforded **31**. The intermediates **29**−**31** adopt a single rigid solution conformation possessing a trans secondary amide central to the 14−membered ring. The comparison of **30** and **31** with our prior intermediates revealed that those previously disclosed[7,19−20,22] possess the (*R*,*S*)- versus (*S*,*S*)-stereochemistry.

Scheme 8



Natural (9*S*,12*S*)-Cycloisodityrosine Methyl Ester (40) and Its Unnatural (9*R*,12*S*)-Diastereomer 44. The parent cycloisodityrosine derivatives **38**−**40** lacking both the N^{10} and C^{12} *N*-methylation were prepared and required the dipeptide macrocyclization substrate **33**. For this purpose and in efforts to distinguish the extent and site of epimerization, both L- and D-**6** were coupled (THF, 25 °C, 4 h, 90−95%) with L-BOC-NH-Tyr-OC_6F_5 (**12**) to provide (*S*,*S*)-**33** and (*R*,*S*)-**34** (Scheme 8). When this reaction was conducted with L-BOC-Tyr-OH activated for coupling with EDCI−HOBt, a 4:1 mixture of (*S*,*S*)-**33** and (*S*,*R*)-**34** was obtained resulting from the kinetic preference for formation of the mixed (*S*,*R*)- or (*R*,*S*)-diastereomer. Unrecognized, but analogous, observations have been made in closely related efforts.[14,23]

Smooth macrocyclization of (*R*,*S*)-**34** was observed upon exposure to K_2CO_3 (5 equiv, 0.005 M DMF, 70 °C, 10 h, 63%) to provide a single, stable diastereomer, (9*R*,-12*S*)-**35**, in excellent conversions. Exposure of (*S*,*S*)-**33** to the same reaction conditions provided an approximate 1:1 mixture of (9*S*,12*S*)-**36** and the epimerized diastereomer (9*R*,12*S*)-**35** in 50−60% combined yield (Scheme 9). Conducting this latter reaction at 25 °C (3 equiv of K_2-CO_3, 0.01 M DMF, 20−24 h, 59%, 1:1 **35**:**36**) provided similar results but required a more extended reaction time for completion. Analogous, but unrecognized, observations have been disclosed in the work of Zhu and Beugelmans.[24] Similar to our observations with **13**, macrocyclization of (*S*,*S*)-**33** effected by treatment with NaH (3.3 equiv, 0.004 M THF, 6−12 h, 0−25 °C) under conditions that minimize epimerization provided predominately the desired (9*S*,12*S*)-**36** (50−60%) and smaller but significant amounts of the undesired (9*R*,12*S*)-diastereomer (15−20%). The pure diastereomers were obtained by chromatographic separation.

Characterization of the minor diastereomer **35** derived from closure of (*S*,*S*)-**33**, its comparison with authentic

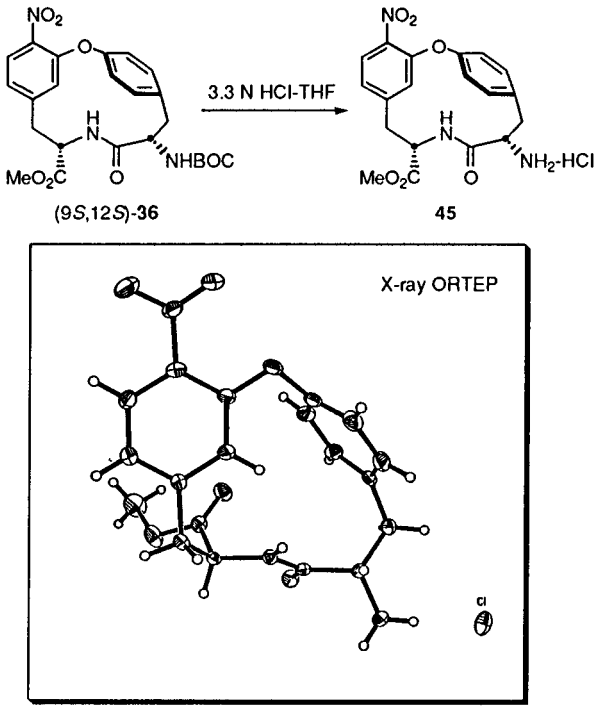
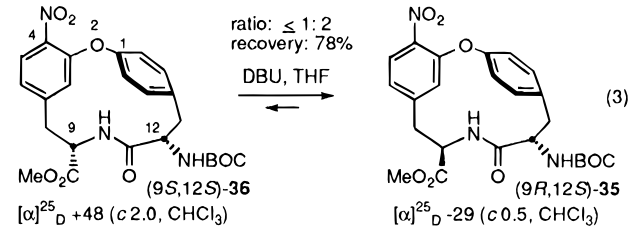


Figure 4.

(9*R*,12*S*)-**35**, and epimerization studies conducted on (9*S*,12*S*)-**36** confirmed the unusually facile epimerization, established an equilibrium ratio of ≥2:1 in favor of the unnatural diastereomer **35**, and established that this epimerization occurs at the C9 center adjacent to the methyl ester (eq 3). The true equilibrium ratio was not



(3)

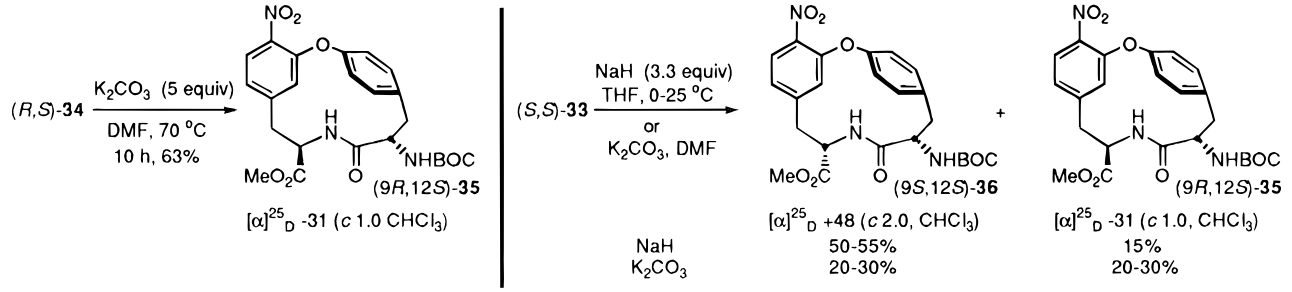
able to be assessed due to base-catalyzed decomposition derived from nucleophilic attack of the deprotonated central amide onto the C-12 N^{α}-BOC in a reaction that is not competitive upon C-12 *N*-methylation.[7,10] The structure of **36** was unambiguously established upon *N*-BOC deprotection and subsequent single-crystal X-ray structure determination of the resulting HCl salt (Figure 4). The comparison of the X-ray structure conformation of **45** with that of **17** revealed the structural origin of the preferential epimerization of the (9*S*,12*S*) diastereomers to the more stable (9*R*,12*S*) diastereomers. Both **45** and **17** exist in rigid conformations containing a trans secondary amide central to the 14-membered ring and contain nearly indistinguishable backbone conformations (RMS = 0.23 Å excluding substituents). Both adopt perpendicular arrangements of the two aryl rings with the strongly shielded C19-H imbedded in the face of the right-hand aryl ring which is slightly puckered to accommodate the strain in the macrocyclic ring. In **17**, as well as **26**,[4] which are representative of the (9*R*,12*S*)-diastereomers, the C9 methyl ester adopts a pseudoequatorial position on the rigid 14-membered ring avoiding transannular

(22) Boger, D. L.; Yohannes, D.; Myers, J. B. *J. Org. Chem.* **1992**, *57*, 1319.

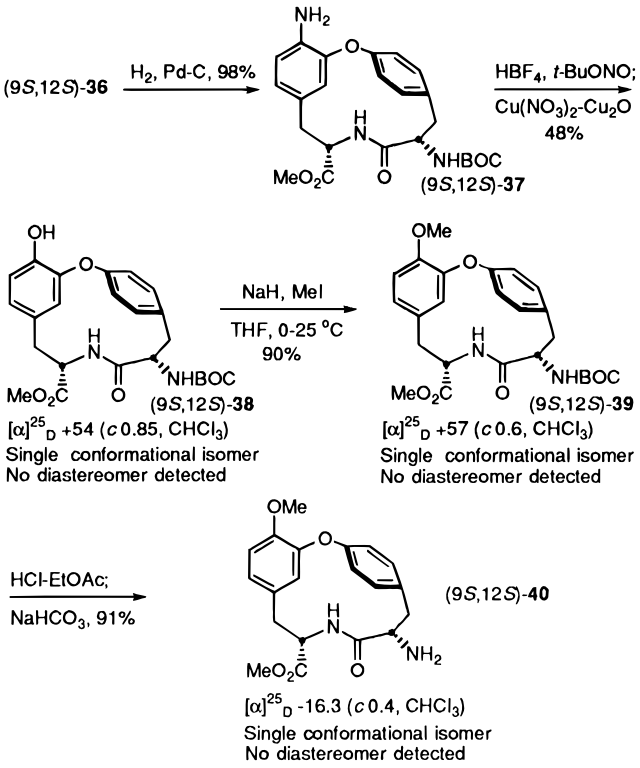
(23) Similar, but unrecognized, observations with EDCI−HOBt were disclosed, lit.[14] $[\alpha]^{25}_D$ +12 (*c* 0.13, $CHCl_3$) versus $[\alpha]^{25}_D$ +18 (*c* 0.16, $CHCl_3$) for (*S*,*S*)-**33**.

(24) Identical, but unrecognized, observations were disclosed[14] but misrepresented as thermally stable, noninterconvertable atropisomers. The report[14] that the starting materials and products are stable to base and the macrocyclization conditions is incorrect and the two diastereomers are related by C9 epimerization. The ^1H NMR spectra disclosed in this work[14] for atropisomers match those of the diastereomers **35** and **36**. However, the specific rotations are not coincident with those disclosed herein: (9*S*,12*S*)-**36** $[\alpha]^{25}_D$ +48 (*c* 2.0, $CHCl_3$) versus +35 (*c* 0.28, $CHCl_3$)[14] and (9*R*,12*S*)-**35** $[\alpha]^{25}_D$ −31 (*c* 1.0, $CHCl_3$) versus −9 (*c* 0.1, $CHCl_3$).[14] This would seem to further confirm the contamination of (*S*,*S*)-**33** with (*S*,*R*)-**34** which was derived from epimerization during coupling to provide **33**[23] (HOBt−EDCI, C12 center) in addition to that which occurs upon macrocyclization (C9 center).

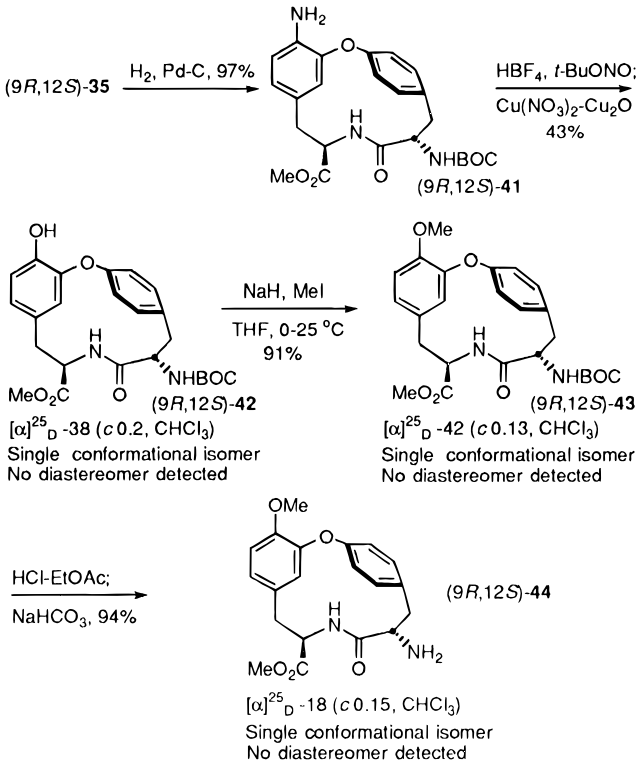
Scheme 9



Scheme 10



Scheme 11



interactions and adopting an anti relationship to the C7−C8 bond. In **45**, which is representative of the (9*S*,12*S*)-diastereomers, the C9 methyl ester adopts a pseudoaxial position on the rigid 14-membered ring exposing it to destabilizing transannular interactions and forcing it to adopt a strongly destabilizing gauche/eclipsed relationship with the C7−C8 bond (dihedral angle = 44°).

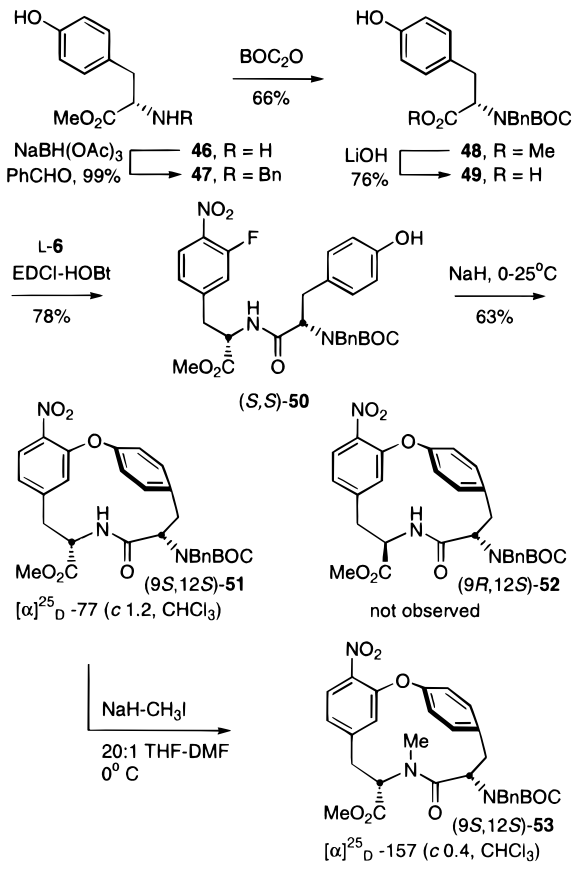
Transformation of **36** and **35** into the (9*S*,12*S*)-cycloisodityrosine derivatives **38**−**40** and their unnatural (9*R*,-12*S*)-diastereomers **42**−**44** was accomplished as outlined in Schemes 10 and 11. Thus, nitro reduction (97−98%), diazotization, and oxidative hydrolysis of the *in situ*-generated diazonium salt (40−55%), followed by selective *O*-methylation (90−91%), provided **39** and **43**, respectively. Subsequent *N*-BOC deprotection provided the free amines **40** and **44**. With care, **36** could be taken through this sequence without epimerization. Analogous to **15**−**17** and **45**, **35**−**44** adopt a single rigid solution conformation possessing a trans secondary amide central to the cycloisodityrosine structure. The comparisons of **39**, **40** and **43**, **44** with our prior reported samples[19,20,25] required their reassignment to the diastereomer **43** and **44** stereochemistry.

In early studies, we had also examined the prospect that **36** might also serve as a precursor to **18** and thus the *N*-methylcycloisodityrosine derivatives required of the natural products **1** and **2**. Although this was not investigated in detail, the double *N*-methylation of **36** was problematic (2.2 equiv of NaH, 10 equiv, CH_3I, 10:1 THF−DMF, 0−25 °C, 12 h) and provided only low yields of **18** (20−30%) along with at least three other compounds, presumably representing the two monomethylated derivatives accompanied by epimerization. Efforts to drive this reaction to completion using more vigorous conditions were not pursued due to this sensitivity to epimerization. In contrast, the unnatural diastereomer (9*R*,12*S*)-**35** proved more amenable to permethylation, requiring a shorter reaction period and providing a satisfactory yield of (9*R*,12*S*)-**23** (50%) under similar conditions (2.2 equiv NaH, 10 equiv of CH_3I, 10:1 THF−DMF, 0−25 °C, 3 h).

Related Studies. The final agents in the series examined were **51**−**53** which selectively differentiates and protects the C12 amine and in principle would permit the preparation of N^{10}-methylcycloisodityrosine. Its preparation incorporated the use of L-BOC-NBn-Tyr-OH (**49**) which allows for protection and subsequent release of a C12 free amine. Coupling of L-**49** which was prepared as shown in Scheme 12 with L-**6** cleanly provided (*S*,*S*)-

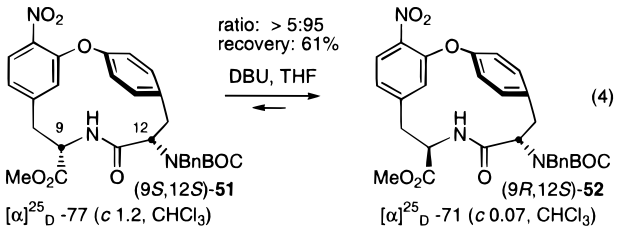
(25) Boger, D. L.; Zhou, J. *Bioorg. Med. Chem.* **1995**, *3*, 1579.

Scheme 12



50 (78%) along with a trace of the separable (*R*,*S*)-diastereomer (5%). Treatment of (*S*,*S*)-**50** with NaH (2.2 equiv, 20:1 THF:DMF, 0 to 25 °C, 4.5 h) cleanly provided (*S*,*S*)-**51** (63%) without detection of the epimerized diastereomer (*R*,*S*)-**52**.

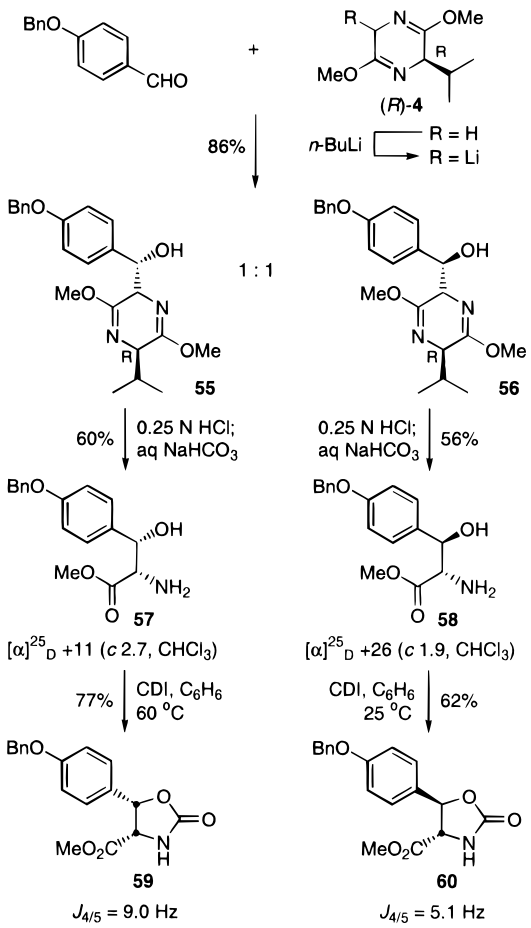
Subjection of (*S*,*S*)-**51** to epimerization (DBU, THF, 50 °C) led to rapid and complete epimerization to (*R*,*S*)-**52** (eq 4). These observations are analogous to those made with **15** and **16**. Both **51** and **52** adopt a single, rigid solution conformation containing a trans amide central to the cyclic structure.

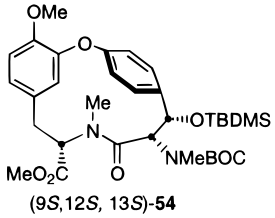


Similar to efforts with **16**, N^{10}-methylation was effected by NaH−CH_3I and could be accomplished without C9 epimerization (Scheme 12). However, extending the reaction times, use of higher reaction temperatures (25 °C) or excess NaH, and employment of larger amounts of DMF cosolvent led to increased levels of C9 epimerization.

Attempted Preparation of the Cycloisodityrosine Subunit of Bouvardin: (9*S*,12*S*,13*S*)-N^{10},N^{α}-Dimethyl-13-hydroxycycloisodityrosine. In preliminary efforts, the extension of these studies to the preparation of **54**, a protected derivative of the *N*,*N*-dimethyl-13(*S*)-hydroxycycloisodityrosine subunit found in bouvardin[1] has not yet proven sufficiently successful for implementation.

Scheme 13

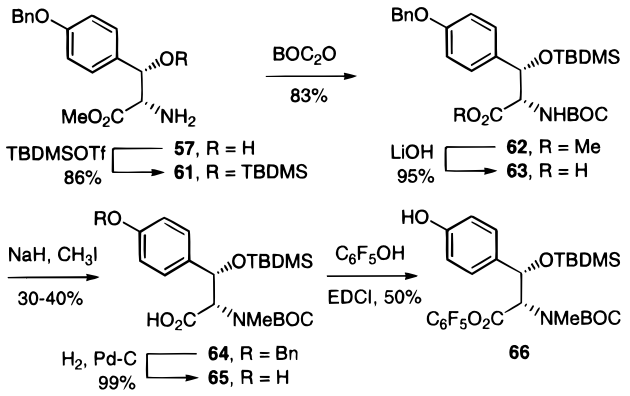




The protected 3(*S*)-*β*-hydroxy-BOC-NMe-L-Tyr required for incorporation into **54** was prepared from 3(*S*)-*β*-hydroxy-L-Tyr(OBn)-OMe (**57**) which in turn is available in two steps as shown in Scheme 13. The direct condensation of 4-(benzyloxy)benzaldehyde with the lithium anion of the Schöllkopf reagent (*R*)-**4** (THF, −78 to −30 °C, 1.5 h) provided a separable mixture (86%) of the diastereomers **55** and **56** epimeric at the alcohol center. Without optimization, independent hydrolysis (2 equiv of 0.25 N aqueous HCl, 1:3 CH_3CN−THF, 25 °C, 5 h, 56−60%) provided the free amino alcohols **57** and **58** which were converted (1.2 equiv of carbonyldiimidazole, C_6H_6, 60 and 25 °C, 12−14 h) to the corresponding cyclic carbamates **59** and **60**, respectively. The large (J = 9.0 Hz) and small (J = 5.1 Hz) C4-H/C5-H coupling constants of **59** and **60**, respectively, established the erythro (*cis*) and threo (*trans*) stereochemistry of the respective intermediates.

Without optimization, **57** was converted to **65** for coupling with L-**6** (Scheme 14). Thus, TBDMS protection of the alcohol (5.0 equiv of TBDMSOTf, 6.0 equiv of Et_3N,

Scheme 14



CH_2Cl_2, −10 to 4 °C, 24 h, 75−86%), *N*-BOC protection (1.1 equiv of BOC_2O, 2.0 equiv of K_2CO_3, 1:1 THF−H_2O, 25 °C, 3 h, 83%), methyl ester hydrolysis (2.0 equiv of LiOH, 2:1 *t*-BuOH−H_2O, 5−25 °C, 4.5 h, 95%), and *N*-methylation (2.2 equiv of NaH, 5.0 equiv of CH_3I, THF, −20 to 25 °C, 7 h, 30−40%) provided **64**. In the latter reaction, significant amounts (23−30%) of OTBDMS elimination was observed. Benzyl ether deprotection by hydrogenolysis (H_2, 10% Pd−C, CH_3OH, 3−4 h, 99%) provided **65** and, for comparison purposes, the pentafluorophenyl ester **66** was prepared from **65**.

Coupling of either **65** (1.6 equiv of EDCI, 1.1 equiv HOBt, DMF, 0−25 °C, 14 h, 80%) or **66** (1:1 THF−DMF, 60 °C, 18 h, 48%) with L-**6** provided the key cyclization substrate **67** (Scheme 15). In both instances, an approximately 4:1 mixture of separable diastereomers was obtained upon coupling resulting from epimerization of **65** or **66** upon activation and prior to coupling. Treatment of **67** with NaH (2.2 equiv, 0.008 M THF, 25 °C, 6 h, <10%) or K_2CO_3 (5 equiv, 0.008 M DMF, 45 °C, 6 h (no reaction), 80 °C, 12 h, < 10%) provided only trace amounts of **68** and predominantly the degradation product **69**. Thus, **68** presently fails to withstand the conditions utilized to effect ring closure and these observations are in interesting contrast to the stability of **15**/**16**, **35**/**36** and the related products successfully prepared in a set of vancomycin ring systems.[8,9]

In an alternative approach to **54** which entails the reverse macrocyclization reaction with closure conducted with formation of the O^2-C^1 biaryl ether bond and ultimately with reductive removal of the aryl nitro group, the preparation of **80** was also examined (Scheme 16). Analogous to the route employed for **65** and without optimization, the erythro β-hydroxy amino acid **73** was prepared and the stereochemistry confirmed upon cyclic carbamate formation. However, following conversion of **73** to **79**, exposure of **79** to the successful *N*-methylation conditions above (2.2 equiv of NaH, 5 equiv CH_3I, THF−DMF 20:1, −10 to 25 °C, 6 h) afforded only recovered starting material and trace amounts of methyl ester **78**. Increasing the amount of DMF cosolvent to 13:1 THF:DMF led to a complex mixture including products of elimination, and no *N*-methylated products were observed.

The ramifications of these studies are under investigation and will be disclosed in due course. Most notable of these is the accessible adoption of a conformation possessing a cis tertiary amide central to the 14-membered ring of the 9*S*,12*S* diastereomers of the N^{10}-methylcycloisodityrosines analogous to that found in the natural products **1** and **2**.

Experimental Section

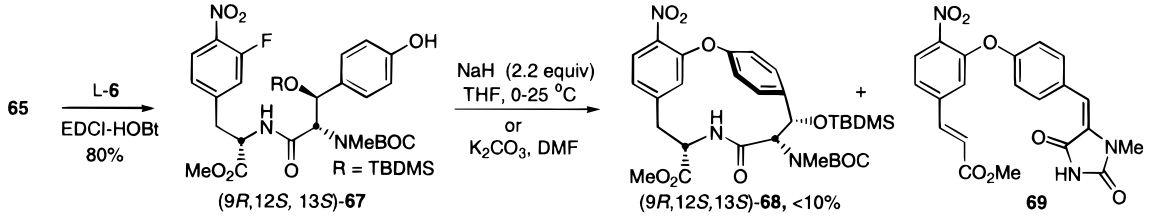
3-Fluoro-4-nitro-*N*-[*N*-(*tert*-butyloxycarbonyl)-*N*-methyl-L-tyrosyl]-L-phenylalanine Methyl Ester ((*S*,*S*)-13). A solution of L-**6** (203 mg, 0.84 mmol) in anhydrous THF (5 mL) was treated with L-**11** (426 mg, 0.924 mmol, 1.1 equiv, 92% ee) at 25 °C under Ar, and the resulting reaction mixture was stirred at 25 °C for 4 h under Ar before the solvent was removed in vacuo. Flash chromatography (SiO_2, 2 × 10 cm, 20−50% EtOAc−hexane gradient elution) afforded (*S*,*S*)-**13** (376 mg, 436 mg theoretical, 86%) as a pale-yellow oil which solidified upon standing and (*S*,*R*)-**14** (18.2 mg, 436 mg theoretical, 4%) as a pale-yellow oil which solidified upon standing. For (*S*,*S*)-**13**: $[\alpha]^{25}_D$ −49 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) mixture of two rotamers, δ 7.95 and 7.93 (two t, 1H, *J* = 7.8 Hz, C5-H), 6.90−7.04 (m, 5H), 6.51−6.72 (m, 3H), 4.75−4.83 (m, 1H, $ArCH_2CH$), 4.72 (dd, 1H, *J* = 7.0, 9.0 Hz, $ArCH_2CH$), 3.74 and 3.68 (two s, 3H, CO_2CH_3), 3.24 (dd, 1H, *J* = 5.2, 14.0 Hz, ArC*H*H), 3.11 (dd, 1H, *J* = 7.3, 14.0 Hz, ArCH*H*), 3.03 (dd, 1H, *J* = 7.6, 13.4 Hz, ArC*H*H), 2.84 (dd, 1H, *J* = 8.0, 13.4 Hz, ArCH*H*), 2.76 and 2.66 (two s, 3H, NCH_3), 1.40 and 1.30 (two s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major rotamer) 170.6 (2C), 155.3 (d, *J* = 263.0 Hz, C3), 154.6, 145.8 (d, *J* = 9.0 Hz, C1), 145.4, 135.9 (d, *J* = 20 Hz, C4), 130.3 (2C), 128.6, 126.2, 125.4, 119.1 (d, *J* = 20 Hz, C2), 115.3 (2C), 81.1, 59.8, 52.7, 52.6, 37.6, 33.3, 31.0, 28.2 (3C); IR (neat) ν_{max} 3342, 3016, 2978, 1744, 1670, 1605, 1518, 1441, 1392, 1349, 1222, 1163, 840, 753 cm^{-1}; FABHRMS (NBA−CsI) *m*/*e* 652.1093 (M^+ + Cs, $C_{25}H_{30}N_3O_8F$ requires 652.1071).

(*R*,*R*)-13: $[\alpha]^{25}_D$ +47 (*c* 0.5, $CHCl_3$).

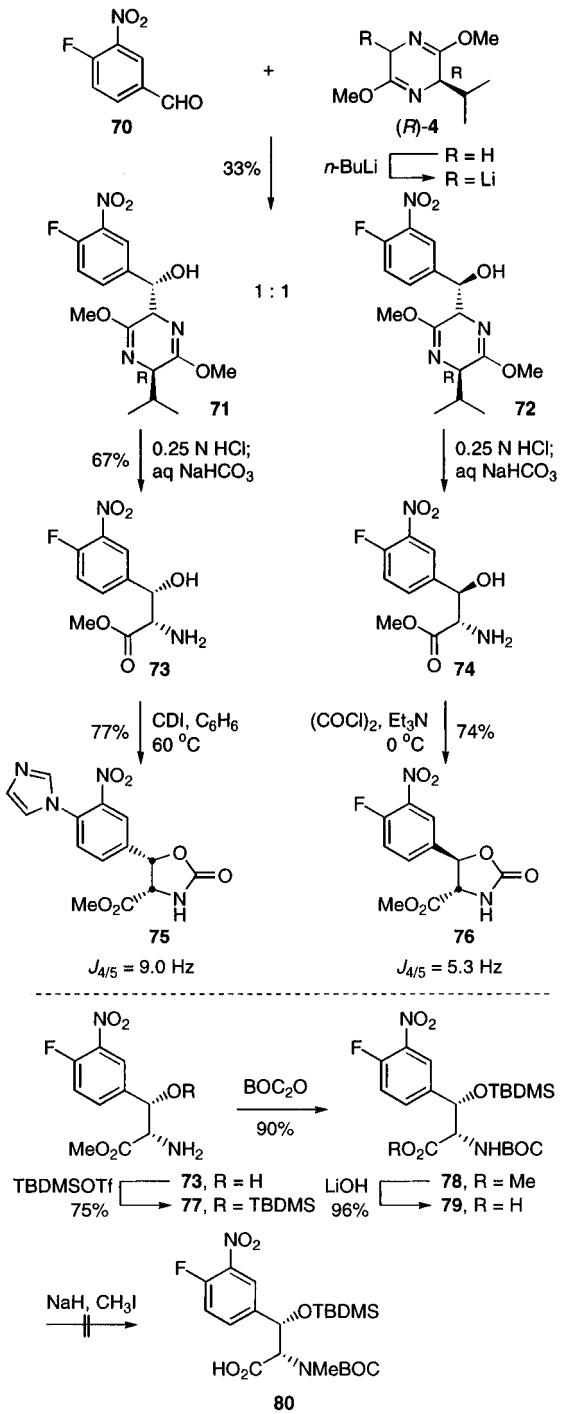
3-Fluoro-4-nitro-*N*-[*N*-(*tert*-butyloxycarbonyl)-*N*-methyl-L-tyrosyl]-D-phenylalanine Methyl Ester ((*R*,*S*)-14). Following the procedure described for (*S*,*S*)-**13**, D-**6** (100 mg, 0.41 mmol) and L-**11** (210 mg, 0.45 mmol, 1.1 equiv, 92% ee) afforded (*R*,*S*)-**14** (192 mg, 213 mg theoretical, 90%) and (*R*,*R*)-**13** (8 mg, 213 mg theoretical, 4%). For (*R*,*S*)-**14**: $[\alpha]^{25}_D$ −50 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) mixture of two rotamers, δ 7.95 and 7.87 (two t, 1H, *J* = 7.8 Hz, C5-H), 6.44−7.06 (m, 7H), 5.14 (br s, 1H, ArOH), 4.71−4.86 (m, 2H, two $ArCH_2CH$), 3.75 and 3.71 (two s, 3H, CO_2CH_3), 3.24 (dd, 1H, *J* = 5.6, 14.0 Hz, ArC*H*H), 3.14 (dd, 1H, *J* = 5.0, 14.0 Hz, ArCH*H*), 3.03 (dd, 1H, *J* = 6.2, 13.7 Hz, ArC*H*H), 2.78 (dd, 1H, *J* = 8.4, 13.7 Hz, ArCH*H*), 2.77 and 2.74 (two s, 3H, NCH_3), 1.39 and 1.31 (two s, 9H, $CO_2C(CH_3)_3$); IR (KBr) ν_{max} 3410, 2968, 2929, 1742, 1670, 1609, 1521, 1442, 1388, 1344, 1250, 1221, 1162, 838 cm^{-1}; FABHRMS (NBA−CsI) *m*/*e* 652.1051 (M^+ + Cs, $C_{25}H_{30}FN_3O_8$ requires 652.1071). Anal. Calcd for $C_{25}H_{30}N_3O_8F$: C, 57.80; H, 5.78; N, 8.09. Found: C, 57.48; H, 5.99; N, 7.89.

(*S*,*R*)-14: $[\alpha]^{25}_D$ +53 (*c* 0.3, $CHCl_3$).

Scheme 15



Scheme 16



Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-nitro-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]-nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-15). A solution of (*R*,*S*)-**14** (104 mg, 0.2 mmol) in anhydrous DMF (25 mL, 0.008 M) was treated with K_2CO_3 (138 mg, 1.0 mmol, 5.0 equiv) at 25 °C under Ar. The resulting reaction mixture was warmed to 45−50 °C for 4 h before the solvent was removed in vacuo. Flash chromatography (SiO_2, 1 × 10 cm, 15−30% EtOAc−hexane gradient elution) afforded (9*R*,12*S*)-**15** (77.8 mg, 99.8 mg theoretical, 78%) as a white solid: mp 228−230 °C (white powder, EtOAc−hexane); $[\alpha]^{25}_D$ −83 (*c* 0.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 1H, *J* = 8.4 Hz, C5-H), 7.50 (dd, 1H, *J* = 2.2, 8.4 Hz, C18−H), 7.32 (dd, 1H, *J* = 2.2, 8.4 Hz, C15-H), 7.09 (dd, 1H, *J* = 2.2, 8.4 Hz, C17-H), 7.00 (dd, 1H, *J* = 2.2, 8.4 Hz, C16-H), 6.73 (dd, 1H, *J* = 2.2, 8.4 Hz, C6-H), 5.96 (d, 1H, *J* = 8.3 Hz, N10-H), 5.41 (d, 1H, *J* = 2.2 Hz, C19-H), 4.56 (dd, 1H, *J* = 5.0, 12.0 Hz, C12-H), 4.23 (t, 1H, *J* = 10.0 Hz, C9−H), 3.67 (s, 3H, CO_2CH_3), 3.28 (t, 1H, *J* = 12.0 Hz, C13-Hα), 2.98−3.03 (m, 2H, C8-Hβ and C13−Hβ), 2.99 (s, 3H, NCH_3), 2.75 (dd, 1H, *J* = 11.8, 16.8 Hz, C8-Hα), 1.49 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 169.8, 156.4, 156.3, 155.6, 145.2, 136.7, 135.8, 133.8, 131.6, 125.6, 123.9, 123.7, 121.6, 116.4, 80.7, 61.1, 52.7, 52.1, 35.2, 34.8, 30.1, 28.4 (3C); IR (KBr) ν_{max} 3279, 2958, 2919, 1750, 1670, 1589, 1522, 1432, 1364, 1347, 1255, 1227, 1196, 1142, 1093, 985, 882, 839, 749 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 632.0985 (M^+ + Cs, $C_{25}H_{29}N_3O_8$ requires 632.1009). Anal. Calcd for $C_{25}H_{29}N_3O_8$: C, 60.12; H, 5.81; N, 8.42. Found: C, 59.86; H, 6.25; N, 8.11.

(9*S*,12*R*)-15: $[\alpha]^{25}_D$ +81 (*c* 0.7, $CHCl_3$).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methyl]-amino-4-nitro-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]-nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-16). A solution of (*S*,*S*)-**13** (156 mg, 0.3 mmol) in anhydrous THF (2 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 26.4 mg, 0.66 mmol, 2.2 equiv) in anhydrous THF (73 mL) at 0 °C under Ar, and the resulting reaction mixture was stirred at 0 °C for 30 min before being warmed to 25 °C for 6 h. The reaction was quenched with the addition of H_2O (5.0 mL) and EtOAc (50 mL). The aqueous solution was extracted with EtOAc (3 × 10 mL), and the combined organic solution was washed with H_2O (15 mL) and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 3 × 10 cm, 20−40% EtOAc−hexane gradient elution) afforded (9*S*,12*S*)-**16** (81.3 mg, 150 mg theoretical, 54%) and (9*R*,12*S*)-**15** (21.4 mg, 150 mg theoretical, 14%). For (9*S*,12*S*)-**16**: pale-yellow oil, which solidified upon standing; $[\alpha]^{25}_D$ −91 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, 1H, *J* = 8.4 Hz, C5-H), 7.51 (dd, 1H, *J* = 2.6, 8.4 Hz, C15- or C18-H), 7.46 (dd, 1H, *J* = 2.6, 8.4 Hz, C18- or C15-H), 7.15 (dd, 1H, *J* = 2.6, 8.4 Hz, C16- or C17-H), 7.13 (dd, 1H, *J* = 2.6, 8.4 Hz, C17- or C16-H), 6.67 (dd, 1H, *J* = 1.3, 8.4 Hz, C6-H), 5.56 (d, 1H, *J* = 1.3 Hz, C19-H), 5.35 (br s, 1H, N10-H), 4.54 (dd, 1H, *J* = 4.4, 11.9 Hz, C12-H), 4.27 (m, 1H, C9-H), 3.55 (s, 3H, CO_2CH_3), 3.22 (t, 1H, *J* = 12.2 Hz, C13-Hα), 3.15 (dd, 1H, *J* = 6.3, 12.2 Hz, C13-Hβ), 3.13 (dd, 1H, *J* = 5.4, 16.8 Hz, C8-Hα), 3.07 (s, 3H, NCH_3), 2.98 (dd, 1H, *J* = 3.1, 16.8 Hz, C8-Hβ), 1.45 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 168.5, 156.6, 156.0, 155.9, 142.9, 136.8, 135.7, 133.8, 130.7, 125.9, 125.7, 124.0, 121.8, 119.5, 80.6, 61.8, 52.9, 52.1, 36.5, 34.9, 31.0, 28.4 (3C); IR (neat) ν_{max} 3363, 3012, 2976, 2931, 1760, 1682, 1611, 1588, 1519, 1502, 1440, 1391, 1349, 1229, 1193, 1169, 1148, 1098, 1055, 992, 844, 755 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 632.0985 (M^+ + Cs, $C_{25}H_{29}N_3O_8$ requires 632.1009).

Following the K_2CO_3 procedure described for (*R*,*S*)-**14**, (*S*,*S*)-**13** (38 mg, 0.073 mmol) afforded the expected (9*S*,12*S*)-**16** (4.0 mg, 36.4 mg theoretical, 11%) and its diastereomer (9*R*,12*S*)-**15** (19.7 mg, 36.4 mg theoretical, 54%).

(9*R*,12*R*)-16: $[\alpha]^{25}_D$ +91 (*c* 0.2, $CHCl_3$).

Equilibration Epimerization of (9*S*,12*S*)-16. A solution of (9*S*,12*S*)-**16** (12.3 mg, 0.025 mmol, $[\alpha]^{25}_D$ −91 (*c* 0.5, $CHCl_3$)), in anhydrous THF (2 mL), was treated with DBU (37.5 mg, 37 μL, 0.25 mmol, 10.0 equiv) at 25 °C, and the resulting mixture was warmed at 50−55 °C for 36 h under Ar. The solvent was removed in vacuo, and the residue was purified by flash chromatography (SiO_2, 1 × 10 cm, 20−40% EtOAc−hexane gradient elution) to afford (9*R*,12*S*)-**15** (10.5 mg, 12.3 mg theoretical, 85.4%) as a white solid ($[\alpha]^{25}_D$ −82 (*c* 0.38, $CHCl_3$)), which was identical in all respects to an authentic sample, and recovered (9*S*,12*S*)-**16** (0.3 mg, 2.4%).

Methyl 12(*S*)-(*N*-Methylamino)-4-nitro-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]-nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-17). A solution of (9*R*,12*S*)-**15** (27 mg, 0.054 mmol) in 2.2 N HCl −EtOAc (2 mL) was stirred at 25 °C for 30 min before the volatiles were removed in vacuo. The residue was then dried thoroughly under vacuum to afford the crude HCl salt (23.5 mg, 23.5 mg theoretical, 100%) as a white solid, which afforded white crystals after recrystallization from CH_3OH.

The crude HCl salt (20 mg, 0.046 mmol) was dissolved in saturated aqueous $NaHCO_3$ (2 mL), and the aqueous solution was extracted with EtOAc (4 × 5 mL). The combined EtOAc extracts were washed with H_2O (2 mL) and saturated aqueous

NaCl (2 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 10 cm, 0−5% CH_3OH−$CHCl_3$ gradient elution) afforded the free amine (17.0 mg, 18.4 mg theoretical, 93%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, 1H, J = 8.4 Hz, C5-H), 7.38 (dd, 1H, J = 2.4, 8.4 Hz, C15- or C18-H), 7.23 (dd, 1H, J = 2.4, 8.4 Hz, C18- or C15-H), 7.02−7.05 (m, 2H, C16- and C17-H), 6.72 (dd, 1H, J = 1.5, 8.4 Hz, C6-H), 5.68 (d, 1H, J = 7.2 Hz, N10-H), 5.34 (d, 1H, J = 1.5 Hz, C19-H), 4.20 (dd, 1H, J = 8.0, 10.4 Hz, C9-H), 3.72 (s, 3H, CO_2CH_3), 3.26 (dd, 1H, J = 4.9, 12.2 Hz, C12-H), 3.04 (dd, 1H, J = 4.9, 11.3 Hz, C13-Hβ), 2.99 (d, 1H, J = 17.4 Hz, C8-Hβ), 2.80 (dd, 1H, J = 11.3, 17.4 Hz, C8-Hα), 2.75 (t, 1H, J = 11.8 Hz, C13-Hα), 2.44 (s, 3H, NCH_3); IR (neat) ν_{max} 3297, 3026, 2953, 2851, 1746, 1663, 1590, 1519, 1436, 1349, 1228, 1196, 1106, 988, 840, 753 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 532.0468 (M^+ + Cs, $C_{20}H_{21}N_3O_6$ requires 532.0485).

A single crystal X-ray structure determination conducted on the HCl salt confirmed the structure and relative stereochemistry of **17**.[17]

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-10-methyl-4-nitro-11-oxo-10-aza-2-oxotricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-18). Following the procedure described for **23**, (9*S*,12*S*)-**16** (81 mg, 0.16 mmol, 20:1 THF−DMF, 0−25 °C, 1 h) afforded (9*S*,12*S*)-**18** (73 mg, 80 mg theoretical, 91%), which was contaminated with *ca*. 3% of **23**, as a colorless oil which solidified upon standing: $[\alpha]^{25}_D$ −146 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two conformational isomers (conformer A:B = 3.8:1), δ (for conformer A) 7.87 (d, 1H, J = 8.4 Hz, C5-H), 7.49 (dd, 1H, J = 1.9, 8.4 Hz, C15- or C18-H), 7.29 (dd, 1H, J = 1.9, 8.4 Hz, C18- or C15-H), 7.17 (dd, 1H, J = 2.3, 8.4 Hz, C16- or C17-H), 6.90 (dd, 1H, J = 2.3, 8.4 Hz, C17- or C16-H), 6.72 (dd, 1H, J = 1.6, 8.4 Hz, C6-H), 4.88 (d, 1H, J = 2.8, 11.2 Hz, C9- or C12-H), 4.71 (dd, 1H, J = 3.6, 12.0 Hz, C12- or C9-H), 4.63 (d, 1H, J = 1.6 Hz, C19-H), 3.68 (s, 3H, CO_2CH_3), 3.65 (dd, 1H, J = 3.8, 14.8 Hz, C13-Hβ), 3.42 (dd, 1H, J = 3.3, 18.4 Hz, C8-Hβ), 3.03 (dd, 1H, J = 12.8, 18.4 Hz, C8-Hα), 2.93 (s, 3H, NCH_3), 2.73 (dd, 1H, J = 12.3, 14.8 Hz, C13-Hα), 2.53 (s, 3H, NCH_3), 1.45 (s, 9H, $CO_2C(CH_3)_3$); δ (for conformer B) 7.83 (d, 1H, J = 8.3 Hz, C5-H), 7.56 (dd, 1H, J = 1.9, 8.4 Hz, C15- or C18-H), 7.37 (dd, 1H, J = 1.9, 8.4 Hz, C18- or C15-H), 7.28 (dd, 1H, J = 2.3, 8.4 Hz, C16- or C17-H), 7.01 (dd, 1H, J = 2.3, 8.4 Hz, C17- or C16-H), 6.77 (dd, 1H, J = 1.6, 8.4 Hz, C6-H), 5.51 (dd, 1H, J = 5.0, 12.0 Hz, C9- or C12-H), 5.10 (d, 1H, J = 1.6 Hz, C19-H), 4.62 (m, 1H, C12- or C9-H, partially obscured by C19-H of conformer A), 3.64 (s, 3H, CO_2CH_3), 3.16−3.27 (m, 2H, C8- and/or C13-H), 2.92−3.11 (m, 2H, C8- and/or C13-H), 2.91 (s, 3H, NCH_3), 2.76 (s, 3H, NMe), 1.48 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 2927, 2851, 1745, 1686, 1655, 1589, 1522, 1495, 1441, 1347, 1278, 1221, 1196, 1168, 1145, 1096, 1026, 840, 713 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 646.1184 (M^+ + Cs, $C_{26}H_{31}N_3O_8$ requires 646.1165).

Methyl 4-Amino-12(*S*)-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-10-methyl-11-oxo-10-aza-2-oxatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-19). Following the procedure detailed for the reduction of **15**, (9*S*,12*S*)-**18** (67 mg, 0.16 mmol) afforded **19** (60 mg, 63 mg theoretical, 95%) as a pink oil, which solidified upon standing: ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two conformational isomers, δ (for major isomer) 7.41 (dd, 1H, J = 1.9, 8.4 Hz, C15- or C18-H), 7.29 (dd, 1H, J = 1.9, 8.4 Hz, C18- or C15-H), 7.21 (dd, 1H, J = 2.1, 8.4 Hz, C16- or C17-H), 7.11 (dd, 1H, J = 2.1, 8.4 Hz, C17- or C16-H), 6.77 (d, 1H, J = 8.4 Hz, C5-H), 6.48 (dd, 1H, J = 1.6, 8.4 Hz, C6-H), 4.85 (dd, 1H, J = 2.4, 11.2 Hz, C9- or C12-H), 4.64 (dd, 1H, J = 3.4, 14.9 Hz, C12- or C9-H), 4.34 (d, 1H, J = 1.6 Hz, C19-H), 3.64 (s, 3H, CO_2CH_3), 2.56−3.29 (m, 4H, C8-H_2 and C13-H_2), 2.89 (s, 3H, NCH_3), 2.52 (s, 3H, NCH_3), 1.44 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3365, 2927, 2851, 1743, 1686, 1654, 1589, 1519, 1500, 1445, 1367, 1335, 1304, 1210, 1144, 1026, 866, 837, 736, 705 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 616.1450 (M^+ + Cs, $C_{26}H_{33}N_3O_6$ requires 616.1424).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-hydroxy-10-methyl-11-oxo-10-aza-2-oxatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-20). Colorless oil, which solidified upon standing; $[\alpha]^{25}_D$ −133 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two conformational isomers (conformer A:B = 3:1), δ (for conformer A) 7.46 (dd, 1H, J = 2.1, 8.3 Hz, C15- or C18-H), 7.26 (dd, 1H, J = 2.1, 8.3 Hz, C18- or C15-H), 7.15 (dd, 1H, J = 2.2, 8.3 Hz, C16- or C17-H), 6.83 (dd, 1H, J = 2.2, 8.3 Hz, C17- or C16-H), 6.80 (d, 1H, J = 8.3 Hz, C5-H), 6.53 (dd, 1H, J = 1.6, 8.3 Hz, C6-H), 5.55 (br s, 1H, ArOH), 4.87 (dd, 1H, J = 2.6, 11.2 Hz, C9- or C12-H), 4.67 (dd, 1H, J = 3.9, 12.2 Hz, C12- or C9-H), 4.40 (d, 1H, J = 1.6 Hz, C19-H), 3.66 (s, 3H, CO_2CH_3), 3.62 (dd, 1H, J = 5.0, 11.2 Hz, C13-Hα), 3.29 (dd, 1H, J = 3.6, 17.8 Hz, C8-Hβ), 2.90 (s, 3H, NCH_3), 2.83−2.88 (m, 1H, C8-Hα), 2.70 (dd, 1H, J = 2.4, 11.2 Hz, C13-Hβ), 2.54 (s, 3H, NCH_3), 1.46 (s, 9H, $CO_2C(CH_3)_3$); δ (for conformer B) 7.51 (dd, 1H, J = 2.1, 8.3 Hz, C15- or C18-H), 7.34 (dd, 1H, J = 2.1, 8.3 Hz, C18- or C15-H), 6.96 (dd, 1H, J = 2.2, 8.3 Hz, C16- or C17-H), 6.88 (dd, 1H, J = 2.2, 8.3 Hz, C17- or C16-H), 6.77 (d, 1H, J = 8.3 Hz, C5-H), 6.57 (dd, 1H, J = 1.6, 8.3 Hz, C6-H), 5.55 (br s, 1H, ArOH), 5.48 (dd, 1H, J = 4.9, 12.2 Hz, C9- or C12-H), 4.91 (d, 1H, J = 1.6 Hz, C19-H), 4.40 (m, 1H, C12- or C9-H), 3.63 (s, 3H, CO_2CH_3), 3.38 (dd, 1H, J = 4.4, 11.4 Hz, C8- or C13-H), 2.84−3.18 (m, 3H, C8- and C13-H), 2.89 (s, 3H, NCH_3), 2.67 (s, 3H, NCH_3), 1.48 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3344, 2923, 2852, 1742, 1657, 1586, 1441, 1282, 1256, 1178, 1096, 1021, 860, 756 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 617.1286 (M^+ + Cs, $C_{26}H_{32}N_2O_7$ requires 617.1264).

For the reduced product, methyl 12(*S*)-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-10-methyl-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate: colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two conformational isomers (conformer A:B = 3:1), δ (for conformer A) 7.44 (dd, 1H, J = 1.8, 8.3 Hz, C15- or C18-H), 7.25 (dd, 1H, J = 1.8, 8.3 Hz, C18- or C15-H), 7.14 (t, 1H, J = 7.8 Hz, C5-H), 6.96 (dd, 2H, J = 2.0, 8.3 Hz, C16- and C17-H), 6.84 (dd, 1H, J = 2.1, 8.3 Hz, C4-H), 6.62 (dd, 1H, J = 2.1, 8.3 Hz, C6-H), 4.89 (dd, 1H, J = 2.7, 11.3 Hz, C9- or C12-H), 4.72 (dd, 1H, J = 3.4, 12.0 Hz, C12- or C9-H), 4.39 (d, 1H, J = 2.1 Hz, C19-H), 3.66 (s, 3H, CO_2CH_3), 3.61 (m, 1H, C13-Hβ), 3.36 (dd, 1H, J = 2.8, 18.2 Hz, C8-Hβ), 3.18 (t, 1H, J = 12.0 Hz, C13-Hα), 2.95 (dd, 1H, J = 12.0, 18.2 Hz, C8-Hα), 2.92 (s, 3H, NCH_3), 2.55 (s, 3H, NCH_3), 1.46 (s, 9H, $CO_2C(CH_3)_3$); δ (for conformer B) 7.51 (dd, 1H, J = 1.8, 8.3 Hz, C15- or C18-H), 7.32 (dd, 1H, J = 1.8, 8.3 Hz, C18- or C15-H), 7.12 (t, 1H, J = 7.8 Hz, C5-H), 6.96 (dd, 2H, J = 2.0, 8.3 Hz, C16- and C17-H), 6.89 (dd, 1H, J = 2.1, 8.3 Hz, C4-H), 6.67 (dd, 1H, J = 2.1, 8.3 Hz, C6-H), 5.49 (dd, 1H, J = 5.0, 12.0 Hz, C9- or C12-H), 4.87 (d, 1H, J = 2.1 Hz, C19-H), 4.46 (dd, 1H, J = 2.7, 11.2 Hz, C12- or C9-H), 3.62 (s, 3H, CO_2CH_3), 3.42 (dd, 1H, J = 4.2, 11.4 Hz, C13-Hβ), 2.90−3.23 (m, 3H, C8-H_2 and C13-Hα), 2.91 (s, 3H, NCH_3), 2.70 (s, 3H, NCH_3), 1.49 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (for major conformational isomer) 171.3, 170.9, 164.0, 157.7, 155.5, 137.0, 136.1, 132.6, 131.1, 129.1, 125.9, 124.0, 121.0, 114.1, 112.7, 80.1, 57.0, 56.8, 52.6, 37.3, 33.5, 31.2, 29.8, 28.5 (3C); IR (neat) ν_{max} 2973, 2929, 2854, 1747, 1688, 1650, 1587, 1492, 1445, 1367, 1335, 1313, 1281, 1257, 1208, 1143, 1096, 1020, 964, 898, 863, 837, 793, 736 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 601.1287 (M^+ + Cs, $C_{26}H_{32}N_2O_6$ requires 601.1315).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-methoxy-10-methyl-11-oxo-10-aza-2-oxatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-21). Following the procedure described for **26**, (9*S*,12*S*)-**20** (12 mg, 0.025 mmol) afforded (9*S*,12*S*)-**21** (10.5 mg, 12.5 mg theoretical, 84%) as a white solid: $[\alpha]^{25}_D$ −161 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two conformational isomers (conformer A:B = 3.6:1), δ (for conformer A) 7.44 (dd, 1H, J = 1.8, 8.3 Hz, C15- or C18-H), 7.32 (dd, 1H, J = 1.8, 8.3 Hz, C18- or C15-H), 7.15 (dd, 1H, J = 2.2, 8.3 Hz, C16- or C17-H), 6.87 (dd, 1H, J = 2.2, 8.3 Hz, C17- or C16-H), 6.79 (d, 1H, J = 8.3 Hz, C5-H), 6.59 (dd, 1H, J = 1.6, 8.3 Hz, C6-H), 4.88 (dd, 1H, J = 2.7, 11.2 Hz, C9- or C12-H), 4.68 (dd, 1H, J = 3.7, 12.2 Hz, C12- or C9-H), 4.40 (d, 1H, J = 1.6 Hz, C19-H), 3.93 (s, 3H, $ArOCH_3$), 3.66 (s, 3H, CO_2CH_3), 3.62 (t, 1H, J = 12.0 Hz, C13-Hα), 3.31 (dd, 1H, J = 3.3, 18.0 Hz, C8-Hβ), 2.93 (dd, 1H, J = 12.0, 18.0 Hz, C8-Hα),

2.91 (s, 3H, NCH_3), 2.70 (dd, 1H, J = 2.7, 12.0 Hz, C13-Hβ), 2.55 (s, 3H, NCH_3), 1.45 (s, 9H, $CO_2C(CH_3)_3$); δ (for conformer B) 7.53 (dd, 1H, J = 1.8, 8.3 Hz, C15- or C18-H), 7.22 (dd, 1H, J = 1.8, 8.3 Hz, C18- or C15-H), 7.03 (dd, 1H, J = 2.2, 8.3 Hz, C16- or C17-H), 6.91 (dd, 1H, J = 2.2, 8.3 Hz, C17- or C16-H), 6.73 (d, 1H, J = 8.3 Hz, C5-H), 6.63 (dd, 1H, J = 1.6, 8.3 Hz, C6-H), 5.51 (dd, 1H, J = 4.8, 12.2 Hz, C9- or C12-H), 4.79 (d, 1H, J = 1.6 Hz, C19-H), 4.30 (dd, 1H, J = 3.7, 12.2 Hz, C12- or C9-H), 3.92 (s, 3H, $ArOCH_3$), 3.61 (s, 3H, CO_2CH_3), 3.40 (dd, 1H, J = 4.2, 11.4 Hz, C13-Hβ), 2.67−3.22 (m, 3H, C8-H_2 and C13-Hα), 2.85 (s, 3H, NCH_3), 2.74 (s, 3H, NCH_3), 1.49 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 2972, 2932, 2855, 1747, 1683, 1652, 1585, 1517, 1443, 1368, 1335, 1312, 1263, 1211, 1144, 1096, 1027, 899, 862, 838, 798, 756 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 631.1448 (M^+ + Cs, $C_{27}H_{34}N_2O_7$ requires 631.1420).

Methyl 4-Methoxy-12(*S*)-(*N*-methylamino)-10-methyl-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),-14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-22). Following the procedure described for **27**, (9*S*,12*S*)-**21** (10.5 mg, 0.021 mmol) afforded (9*S*,12*S*)-**22** (7.8 mg, 8.4 mg theoretical, 93%) as a white solid, which consisted of two separable conformational isomers (conformer A: R_f 0.36, 5.2 mg, 62%; conformer B: R_f 0.29, 2.6 mg, 31%; 5% CH_3OH−$CHCl_3$) and each separated conformer slowly reverted to an equilibrium mixture of two conformational isomers when they were allowed to stand in $CHCl_3$ solution: $[\alpha]^{25}_D$ +17 (*c* 0.12, $CHCl_3$), −10 (*c* 0.12, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two conformational isomers (conformer A:B = 9:8), δ (for conformer A) 7.35 (dd, 1H, J = 2.0, 8.4 Hz, C15- or C18-H), 7.25 (dd, 1H, J = 2.1, 8.3 Hz, C18- or C15-H), 7.14 (dd, 1H, J = 2.2, 8.3 Hz, C16- or C17-H), 6.91 (dd, 1H, J = 2.2, 8.4 Hz, C17- or C16-H), 6.80 (d, 1H, J = 8.3 Hz, C5-H), 6.60 (dd, 1H, J = 2.0, 8.3 Hz, C6−H), 4.34 (dd, 1H, J = 3.4, 11.4 Hz, C9-H), 4.26 (d, 1H, J = 2.0 Hz, C19-H), 3.93 (s, 3H, $ArOCH_3$), 3.70 (s, 3H, CO_2CH_3), 3.47 (dd, 1H, J = 3.9, 10.3 Hz, C12-H), 2.72−3.26 (m, 4H, C8-H_2 and C13−H_2), 2.72 (s, 3H, N10-CH_3), 2.39 (s, 3H, C12-NCH_3); δ (for conformer B) 7.43 (dd, 1H, J = 2.0, 8.4 Hz, C15- or C18-H), 7.21 (dd, 1H, J = 2.1, 8.4 Hz, C18- or C15-H), 7.19 (dd, 1H, J = 2.2, 8.4 Hz, C16- or C17-H), 7.04 (dd, 1H, J = 2.1, 8.4 Hz, C17- or C16-H), 6.74 (d, 1H, J = 8.1 Hz, C5-H), 6.60 (dd, 1H, J = 2.0, 8.3 Hz, C6-H), 4.70 (d, 1H, J = 2.0 Hz, C19-H), 3.92 (s, 3H, $ArOCH_3$), 3.92 (m, 1H, C9-H, partially obscured by $ArOCH_3$), 3.67 (s, 3H, CO_2CH_3), 3.53 (dd, 1H, J = 3.7, 10.2 Hz, C12-H), 2.72−3.26 (m, 4H, C8-H_2 and C13-H_2), 2.69 (s, 3H, N10-CH_3), 2.49 (s, 3H, C12−NCH_3); IR (neat) ν_{max} 3344, 2922, 2841, 1741, 1641, 1517, 1442, 1253, 1201, 1128, 1024, 838, 805 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 399.1908 (conformer A) and 399.1914 (conformer B) (M^+ + H, $C_{22}H_{26}N_2O_5$ requires 399.1920).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-10-methyl-4-nitro-11-oxo-10-aza-2-oxatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-23). A suspension of NaH (60% dispersion in mineral oil, 6.9 mg, 0.173 mmol, 1.2 equiv) in anhydrous THF (5 mL) was treated dropwise with a solution of (9*R*,12*S*)-**15** (72 mg, 0.144 mmol) in anhydrous THF (1 mL) at 0 °C under Ar, and the resulting mixture was stirred for 10 min at 0 °C before being treated with CH_3I (204 mg, 90 μL, 1.44 mmol, 10.0 equiv) and anhydrous DMF (0.3 mL). The reaction mixture was stirred at 0 °C for 30 min before being warmed to 25 °C for 3 h. The reaction was quenched by addition of H_2O (2 mL), and the aqueous solution was extracted with EtOAc (4 × 5 mL). The combined EtOAc extracts were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 8 cm, 20−40% EtOAc−hexane gradient elution) afforded (9*R*,12*S*)-**23** (67.8 mg, 73.8 mg theoretical, 92%) as a colorless oil, which solidified as a white solid upon standing: $[\alpha]^{25}_D$ −99 (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 1H, J = 8.3 Hz, C5-H), 7.51 (dd, 1H, J = 2.2, 8.3 Hz, C18-H), 7.33 (dd, 1H, J = 2.2, 8.3 Hz, C15-H), 7.04 (dd, 1H, J = 2.2, 8.3 Hz, C17-H), 7.01 (dd, 1H, J = 2.2, 8.3 Hz, C16-H), 6.76 (dd, 1H, J = 2.2, 8.3 Hz, C6-H), 5.37 (dd, 1H, J = 5.0, 12.0 Hz, C12-H), 5.01 (d, 1H, J = 2.2 Hz, C19-H), 4.81 (d, 1H, J = 12.0 Hz, C9-H), 3.68 (s, 3H, CO_2CH_3), 3.26 (t, 1H, J = 12.0 Hz, C13-Hα), 3.20 (d, 1H, J = 18.6 Hz, C8-Hβ), 3.03 (dd, 1H, J = 12.0, 18.6 Hz, C8-Hα), 2.98 (dd, 1H, J = 5.0, 12.0 Hz, C13-Hβ), 2.92 (s, 3H, C12-NCH_3), 2.78 (s, 3H, N10-CH_3), 1.50 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 170.6, 156.6, 156.0, 154.9, 145.0, 136.1, 133.8, 131.4, 130.8, 125.5, 124.1, 122.9, 121.2, 115.0, 80.5, 56.7, 55.3, 52.6, 35.6, 31.4, 30.3, 29.8, 28.3 (3C); IR (KBr) ν_{max} 2968, 2919, 1742, 1683, 1653, 1590, 1521, 1442, 1344, 1255, 1221, 1201, 1172, 1147, 1019, 902, 838 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 646.1139 (M^+ + Cs, $C_{26}H_{31}N_3O_8$ requires 646.1165).

Following the procedure described above, (9*R*,12*S*)-**35** (9.7 mg, 0.02 mmol) treated with 2.2 equiv of NaH (1.8 mg, 0.044 mmol) afforded (9*R*,12*S*)-**23** (5.1 mg, 10.3 mg theoretical, 50%).

Methyl 4-Amino-12(*S*)-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-10-methyl-11-oxo-10-aza-2-oxatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-24). A solution of (9*R*,12*S*)-**23** (51.3 mg, 0.1 mmol) in anhydrous CH_3OH (5 mL) was treated with 10% Pd−C (10 mg, 20% wt equiv) at 25 °C and stirred under an atmosphere of H_2 (1 atm) for 1 h. The reaction mixture was filtered through Celite (CH_3OH wash), concentrated in vacuo, and dried thoroughly under vacuum to afford (9*R*,12*S*)-**24** (46 mg, 48.3 mg theoretical, 95%) as a white foam: ^{1}H NMR (acetone-d_6, 400 MHz) mixture of two rotamers, δ 7.52 and 7.45 (two dd, 1H, J = 2.2, 8.0 Hz, C18-H), 7.24 (dd, 1H, J = 2.2, 8.0 Hz, C15-H), 7.03 (dd, 1H, J = 2.2, 8.0 Hz, C17−H), 6.95 (dd, 1H, J = 2.2, 8.0 Hz, C16-H), 6.78 and 6.64 (two d, 1H, J = 8.2 Hz, C5-H), 6.58 and 6.48 (two dd, 1H, J = 2.2, 8.2 Hz, C6-H), 5.97 and 4.67 (two m, 1H, C12-H), 5.36 and 5.17 (two m, 1H, C9-H), 4.74 and 4.51 (two d, 1H, J = 2.2 Hz, C19-H), 4.72 and 4.68 (two s, 2H, C4-NH_2), 3.61 (s, 3H, CO_2CH_3), 3.23 (t, 1H, J = 11.0 Hz, C13-Hα), 2.85−3.00 (m, 3H, C13-Hβ and C8-H_2), 2.83 (s, 3H, C12-NCH_3), 2.79 (s, 3H, N10-CH_3), 1.54 and 1.48 (two s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3405, 2954, 2862, 1698, 1615, 1538, 1462, 1431, 1348, 1242, 1195, 1082, 1005, 913, 826, 790 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 616.1451 (M^+ + Cs, $C_{26}H_{33}N_3O_6$ requires 616.1424).

Methyl (12*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-hydroxy-10-methyl-11-oxo-10-aza-2-oxatricyclo-[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-25). A solution of (9*R*,12*S*)-**24** (22 mg, 0.046 mmol) in anhydrous THF (1.0 mL) was treated dropwise with HBF_4 (48% aqueous solution, 17 mg, 12 μL, 0.092 mmol, 2.0 equiv) at 0 °C under Ar, and the resulting mixture was stirred at 0 °C for 30 min before being warmed to 25 °C for 1 h. The reaction mixture was recooled to 0 °C and treated dropwise with *tert*-butyl nitrite (10 mg, 11.5 μL, 0.092 mmol, 2.0 equiv), and the resulting reaction mixture was stirred at 0 °C for 1 h. The solvent was removed in vacuo at 0 °C, the residue was immediately treated with 10 mL of an aqueous solution containing $Cu(NO_3)_2 \cdot 3H_2O$ (1.11 g, 4.6 mmol, 100 equiv) and Cu_2O (33 mg, 0.23 mmol, 5.0 equiv) at 0 °C under Ar, and the mixture was warmed to 25 °C for 1 h. The reaction mixture was filtered through Celite (H_2O and CH_2Cl_2 wash), and the filtrate was extracted with CH_2Cl_2 (5 × 10 mL). The combined CH_2Cl_2 extracts were washed with saturated aqueous NH_4Cl (5 mL), H_2O (5 mL), and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 8 cm, 10−30% EtOAc−hexane gradient elution) afforded (9*R*,12*S*)-**25** (11.4 mg, 22.3 mg theoretical, 51%) and the corresponding reduced product (3.0 mg, 21.5 mg theoretical, 14%). For (9*R*,12*S*)-**25**: colorless oil, which solidified upon standing; $[\alpha]^{25}_D$ −137 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (dd, 1H, J = 2.0, 8.2 Hz, C18-H), 7.31 (dd, 1H, J = 2.0, 8.2 Hz, C15-H), 6.99 (dd, 2H, J = 2.0, 8.2 Hz, C16- and C17-H), 6.82 (d, 1H, J = 8.2 Hz, C5-H), 6.58 (dd, 1H, J = 1.6, 8.2 Hz, C6-H), 5.55 (s, 1H, C4-OH), 5.33 (dd, 1H, J = 5.0, 11.6 Hz, C12-H), 4.81 (d, 1H, J = 11.7 Hz, C9-H), 4.71 (d, 1H, J = 1.6 Hz, C19-H), 3.66 (s, 3H, CO_2CH_3), 3.24 (t, 1H, J = 11.6 Hz, C13-Hα), 3.07 (d, 1H, J = 17.5 Hz, C8-Hβ), 2.94 (dd, 1H, J = 11.7, 17.5 Hz, C8−Hα), 2.90−2.97 (m, 1H, C13-Hβ, partially obscured by C12-NCH_3 and C8-Hα), 2.90 (s, 3H, C12−NCH_3), 2.77 (s, 3H, N10-CH_3), 1.50 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 170.2, 155.8, 150.3, 142.9, 135.6, 133.6, 131.2, 130.6, 129.4, 124.5, 123.5, 121.7, 115.2, 112.6, 80.4, 56.9, 56.0, 52.3, 35.6, 30.6, 30.1, 29.8, 28.4 (3C); IR (neat) ν_{max} 3374, 2964, 2923, 2851, 1743, 1682,

1652, 1595, 1518, 1441, 1364, 1333, 1282, 1213, 1180, 1139, 1108, 1021, 836, 805, 754 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 617.1277 (M^+ + Cs, $C_{26}H_{32}N_2O_7$ requires 617.1264).

For the reduced product, methyl 12(*S*)-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-10-methyl-11-oxo-10-aza-2-oxatricyclo[12.2.2.$1^{3,7}$]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate: colorless oil, which solidified upon standing; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, 1H, J = 2.0, 8.2 Hz, C18-H), 7.29 (dd, 1H, J = 2.0, 8.2 Hz, C15-H), 7.15 (t, 1H, J = 8.0 Hz, C5-H), 6.98 (d, 3H, J = 8.2 Hz, C6-, C16- and C17-H), 6.67 (dd, 1H, J = 1.6, 8.0 Hz, C4-H), 5.35 (dd, 1H, J = 5.0, 11.6 Hz, C12-H), 4.81 (d, 1H, J = 12.0 Hz, C9-H), 4.73 (d, 1H, J = 1.6 Hz, C19-H), 3.66 (s, 3H, CO_2CH_3), 3.23 (t, 1H, J = 11.6 Hz, C13-Hα), 3.14 (d, 1H, J = 17.8 Hz, C8-Hβ), 3.01 (dd, 1H, J = 12.0, 17.8 Hz, C8-Hα), 2.95 (dd, 1H, J = 5.0, 11.6 Hz, C13-Hβ), 2.92 (s, 3H, C12-NCH_3), 2.80 (s, 3H, N10-CH_3), 1.50 (s, 9H, $CO_2C(CH_3(CH_3)_3)$; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 170.3, 163.5, 156.2, 155.8, 138.8, 135.1, 133.4, 131.1, 129.0, 124.6, 123.5, 121.2, 114.3, 112.4, 80.4, 56.7, 55.8, 52.3, 35.7, 31.2, 30.2, 29.8, 28.4 (3C); IR (KBr) ν_{max} 2974, 2928, 1744, 1682, 1645, 1587, 1487, 1445, 1364, 1333, 1221, 1147, 1026, 862, 835, 780, 687 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 601.1337 (M^+ + Cs, $C_{26}H_{32}N_2O_6$ requires 601.1315).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-methoxy-10-methyl-11-oxo-10-aza-2-oxatricyclo-[12.2.2.$1^{3,7}$]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-26). A suspension of NaH (60% dispersion in mineral oil, 1.0 mg, 0.025 mmol, 1.2 equiv) in anhydrous THF (0.5 mL) was treated dropwise with a solution of (9*R*,-12*S*)-**25** (10.0 mg, 0.021 mmol) in anhydrous THF (100 μL) at 0 °C under Ar, and the resulting mixture was stirred for 10 min at 0 °C before being treated with CH_3I (28.4 mg, 13.0 μL, 0.21 mmol, 10.0 equiv). The reaction mixture was stirred at 0 °C for 10 min and at 25 °C for 1 h. The reaction was quenched by addition of H_2O (0.5 mL), and the aqueous solution was extracted with EtOAc (4 × 4 mL). The combined EtOAc extracts were washed with H_2O (2 mL) and saturated aqueous NaCl (2 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 6 cm, 20−30% EtOAc−hexane gradient elution) afforded (9*R*,12*S*)-**26** (9.7 mg, 10.5 mg theoretical, 92%) as a colorless oil, which solidified upon standing: $[\alpha]^{25}_D$ −127 (*c* 0.2, $CHCl_3$), −162 (*c* 0.15, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, 1H, J = 2.0, 8.2 Hz, C18-H), 7.29 (dd, 1H, J = 2.0, 8.2 Hz, C15-H), 7.03 (dd, 1H, J = 2.0, 8.2 Hz, C16-H), 7.00 (dd, 1H, J = 2.0, 8.2 Hz, C17-H), 6.80 (d, 1H, J = 8.3 Hz, C5-H), 6.63 (dd, 1H, J = 1.6, 8.3 Hz, C6-H), 5.35 (dd, 1H, J = 5.0, 11.6 Hz, C12-H), 4.76 (d, 1H, J = 11.8 Hz, C9-H), 4.74 (d, 1H, J = 1.6 Hz, C19-H), 3.93 (s, 3H, $ArOCH_3$), 3.65 (s, 3H, CO_2CH_3), 3.23 (t, 1H, J = 11.6 Hz, C13-Hα), 3.07 (d, 1H, J = 17.5 Hz, C8-Hβ), 2.96 (dd, 1H, J = 11.8, 17.5 Hz, C8-Hα), 2.92−2.96 (m, 1H, C13-Hβ, partially obscured by C12-NCH_3 and C8-Hα), 2.91 (s, 3H, C12-NCH_3), 2.80 (s, 3H, N10-CH_3), 1.49 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 170.3, 156.2, 154.4, 152.4, 146.5, 135.1, 133.5, 131.0, 130.1, 124.6, 123.6, 121.1, 113.2, 111.8, 80.6, 56.8, 56.2, 56.1, 52.3, 35.7, 30.6, 30.4, 29.7, 28.4 (3C); IR (neat) ν_{max} 2923, 2851, 1739, 1682, 1646, 1513, 1446, 1262, 1215, 1025, 795 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 631.1443 (M^+ + Cs, $C_{27}H_{34}N_2O_7$ requires 631.1420).

Methyl 4-Methoxy-12(*S*)-(*N*-methylamino)-10-methyl-11-oxo-10-aza-2-oxatricyclo[12.2.2.$1^{3,7}$]nonadeca-3,5,7(19),-14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-27). A solution of (9*R*,12*S*)-**26** (12 mg, 0.024 mmol) in 2.2 M HCl−EtOAc (1.0 mL) was stirred at 25 °C for 30 min before the volatiles were removed in vacuo. The residue was neutralized by addition of saturated aqueous $NaHCO_3$ (2.0 mL). The aqueous solution was extracted with EtOAc (3 × 5 mL), and the combined EtOAc extracts were washed with H_2O (2.0 mL) and saturated aqueous NaCl (2 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1 × 6 cm, 0−5% CH_3OH−$CHCl_3$ gradient elution) afforded (9*R*,12*S*)-**27** (8.9 mg, 9.6 mg theoretical, 93%) as a white solid: $[\alpha]^{25}_D$ +31 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (dd, 1H, J = 2.2, 8.3 Hz, C18-H), 7.20 (dd, 1H, J = 2.2, 8.3 Hz, C15-H), 7.05 (dd, 1H, J = 2.2, 8.3 Hz, C17-H), 7.03 (dd, 1H, J = 2.2, 8.3 Hz, C16-H), 6.81 (d, 1H, J = 8.3 Hz, C5-H), 6.63 (dd, 1H, J = 2.2, 8.3 Hz, C6-H), 4.73 (d, 1H, J = 2.2 Hz, C19-H), 4.64 (dd, 1H, J = 2.6, 12.6 Hz, C9-H), 4.06 (dd, 1H, J = 5.5, 10.8 Hz, C12-H), 3.94 (s, 3H, $ArOCH_3$), 3.69 (s, 3H, CO_2CH_3), 3.47 (dd, 1H, J = 5.5, 12.5 Hz, C13-Hβ), 3.08 (dd, 1H, J = 2.6, 18.1 Hz, C8-Hβ), 2.94 (dd, 1H, J = 12.6, 18.1 Hz, C8-Hα), 2.78 (dd, 1H, J = 10.8, 12.5 Hz, C13-Hα), 2.77 (s, 3H, N10-CH_3), 2.48 (s, 3H, C12-NCH_3); IR (KBr) ν_{max} 3447, 2919, 2848, 1738, 1652, 1555, 1533, 1516, 1459, 1266, 1212, 1161, 1125, 1069, 1023, 875, 839, 808 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 531.0883 (M^+ + Cs, $C_{22}H_{26}N_2O_5$ requires 531.0896).

Methyl 4-Amino-12(*S*)-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-11-oxo-10-aza-2-oxatricyclo[12.2.2.$1^{3,7}$]-nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-28). Following the procedure detailed for **24**, (9*S*,-12*S*)-**16** (43 mg, 0.086 mmol) afforded (9*S*,12*S*)-**28** (38.3 mg, 40.3 mg theoretical, 95%) as a pink solid: ^{1}H NMR (acetone-d_6, 400 MHz) mixture of two rotamers, δ 7.47−7.51 (m, 1H, C15- or C18-H), 7.28−7.34 (m, 1H, C18- or C15-H), 7.12 and 7.10 (two dd, 1H, J = 2.0, 8.4 Hz, C16- or C17-H), 6.81−6.93 (m, 2H, C17- or C16-H and C5-H), 6.31−6.59 (m, 2H, C6-H and N10-H), 5.54 and 5.39 (two br s, 1H, C19-H), 4.57−4.62 (m, 1H, C9- or C12-H), 4.04−4.09 (m, 1H, C12- or C9-H), 3.42 and 3.40 (two s, 3H, CO_2CH_3), 3.05 and 3.04 (two s, 3H, NCH_3), 2.79−3.17 (m, 4H, C8-H_2 and C13-H_2), 1.43 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3358, 2931, 1761, 1726, 1676, 1627, 1587, 1519, 1502, 1440, 1366, 1202, 1147, 1097, 1054, 988, 859, 735 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 602.1252 (M^+ + Cs, $C_{25}H_{31}N_3O_6$ requires 602.1267).

Methyl 12(*S*)-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-4-hydroxy-11-oxo-10-aza-2-oxatricyclo[12.2.2.$1^{3,7}$]-nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-29). Following the procedure described for **25**, (9*S*,-12*S*)-**28** (32 mg, 0.068 mmol) afforded (9*S*,12*S*)-**29** (13.4 mg, 32 mg theoretical, 41%) and the corresponding reduced product (5.2 mg, 30.9 mg theoretical, 17%). For (9*S*,12*S*)-**29**: white solid; $[\alpha]^{25}_D$ −106 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (dd, 1H, J = 2.0, 8.2 Hz, C15- or C18-H), 7.41 (dd, 1H, J = 2.0, 8.2 Hz, C18- or C15−H), 7.09 (dd, 1H, J = 2.2, 8.4 Hz, C16- or C17-H), 7.00 (dd, 1H, J = 2.4, 8.4 Hz, C17- or C16-H), 6.72 (d, 1H, J = 8.2 Hz, C5-H), 6.44 (dd, 1H, J = 1.6, 8.2 Hz, C6-H), 5.94 (s, 1H, ArOH), 5.32 (br s, 1H, N10-H), 5.28 (d, 1H, J = 1.6 Hz, C19-H), 4.56 (m, 1H, C12-H), 4.25 (m, 1H, C9-H), 3.51 (s, 3H, CO_2CH_3), 3.19 (t, 1H, J = 12.4 Hz, C13-Hα), 3.12 (dd, 1H, J = 4.2, 12.4 Hz, C13-Hβ), 3.06 (s, 3H, NCH_3), 2.99 (dd, 1H, J = 5.4, 16.2 Hz, C8-Hα), 2.82 (dd, 1H, J = 2.8, 16.2 Hz, C8-Hβ), 1.46 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 169.1, 158.3, 156.0, 149.9, 143.5, 135.0, 133.7, 130.2, 127.4, 126.2, 124.6, 122.6, 117.7, 115.5, 80.5, 61.8, 57.7, 51.8, 36.7, 34.6, 31.0, 28.3 (3C); IR (neat) ν_{max} 3316, 2961, 2927, 2862, 1761, 1725, 1677, 1442, 1366, 1259, 1195, 1146, 1082, 1025, 860, 803, 757 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 603.1120 (M^+ + Cs, $C_{25}H_{30}N_2O_7$ requires 603.1107).

For the reduced product, methyl 12(*S*)-[*N*-(*tert*-butyloxycarbonyl)-*N*-methylamino]-11-oxo-10-aza-2-oxatricyclo-[12.2.2.$1^{3,7}$]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate: colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, 1H, J = 2.0, 8.2 Hz, C15- or C18-H), 7.42 (dd, 1H, J = 2.0, 8.2 Hz, C18- or C15-H), 7.12 (dd, 1H, J = 2.2, 8.4 Hz, C16- or C17-H), 7.11 (t, 1H, J = 8.0 Hz, C5-H), 7.03 (dd, 1H, J = 2.4, 8.4 Hz, C17- or C16-H), 6.99 (dd, 1H, J = 2.2, 8.0 Hz, C4-H), 6.56 (dd, 1H, J = 1.6, 8.0 Hz, C6-H), 5.28 (br s, 1H, N10-H), 5.22 (d, 1H, J = 1.6 Hz, C19-H), 4.58 (dd, 1H, J = 4.0, 11.0 Hz, C12-H), 4.32 (m, 1H, C9-H), 3.52 (s, 3H, CO_2CH_3), 3.19 (t, 1H, J = 12.4 Hz, C13-Hα), 3.14 (dd, 1H, J = 4.0, 12.4 Hz, C13-Hβ), 3.10 (dd, 1H, J = 5.4, 16.4 Hz, C8-Hα), 3.07 (s, 3H, NCH_3), 2.89 (dd, 1H, J = 2.8, 16.4 Hz, C8-Hβ), 1.46 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3314, 3055, 2976, 2930, 1761, 1727, 1678, 1586, 1500, 1444, 1366, 1230, 1201, 1164, 1098, 1055, 1000, 859, 777, 737 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 587.1145 (M^+ + Cs, $C_{25}H_{30}N_2O_6$ requires 587.1158).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-*N*-methylamino]-4-methoxy-11-oxo-10-aza-2-oxatricyclo[12.2.2.$1^{3,7}$]-nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-30). Following the procedure detailed for **26**, selective *O*-methylation of (9*S*,12*S*)-**29** (12.0 mg, 0.025 mmol) with NaH (1.5 mg, 0.038 mmol, 1.5 equiv) afforded (9*S*,12*S*)-**30** (10.8

mg, 12.3 mg theoretical, 88%) as a white solid: $[\alpha]^{25}_D$ −90 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, 1H, *J* = 2.0, 8.2 Hz, C15- or C18-H), 7.42 (dd, 1H, *J* = 2.0, 8.2 Hz, C18- or C15-H), 7.16 (dd, 1H, *J* = 2.1, 8.2 Hz, C16- or C17-H), 7.06 (dd, 1H, *J* = 2.1, 8.2 Hz, C17- or C16-H), 6.72 (d, 1H, *J* = 8.2 Hz, C5-H), 6.51 (dd, 1H, *J* = 1.6, 8.2 Hz, C6-H), 5.27 (br s, 1H, N10-H), 5.23 (d, 1H, *J* = 1.6 Hz, C19-H), 4.56 (m, 1H, C12-H), 4.28 (m, 1H, C9-H), 3.92 (s, 3H, $ArOCH_3$), 3.51 (s, 3H, CO_2CH_3), 3.20 (t, 1H, *J* = 12.4 Hz, C13-Hα), 3.13 (dd, 1H, *J* = 4.4, 12.4 Hz, C13-Hβ), 3.07 (s, 3H, NCH_3), 3.00 (dd, 1H, *J* = 5.5, 16.4 Hz, C8-Hα), 2.85 (dd, 1H, *J* = 2.4, 16.4 Hz, C8-Hβ), 1.45 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 169.1, 158.4, 151.8, 147.0, 142.7, 134.6, 133.5, 130.1, 127.8, 126.3, 124.7, 122.0, 117.8, 111.9, 80.4, 61.9, 56.0, 53.7, 51.8, 36.7, 34.5, 31.1, 28.4 (3C); IR (neat) ν_{max} 3356, 2974, 2932, 2841, 1733, 1681, 1516, 1441, 1366, 1260, 1200, 1148, 1098, 1029, 858, 832, 800, 756, 735 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 617.1248 (M^+ + Cs, $C_{26}H_{32}N_2O_7$ requires 617.1264).

On occasions, a small amount of the C9 epimer (**32**) was generated (0−7%): white solid; $[\alpha]^{25}_D$ −131 (*c* 0.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (dd, 1H, *J* = 2.0, 8.3 Hz, C15-H), 7.28 (dd, 1H, *J* = 2.0, 8.3 Hz, C18-H), 7.10 (dd, 1H, *J* = 2.0, 8.3 Hz, C16-H), 6.98 (dd, 1H, *J* = 2.0, 8.3 Hz, C17-H), 6.77 (d, 1H, *J* = 8.2 Hz, C5-H), 6.59 (dd, 1H, *J* = 1.8, 8.2 Hz, C6-H), 5.83 (d, 1H, *J* = 7.5 Hz, N10-H), 5.12 (d, 1H, *J* = 1.8 Hz, C19-H), 4.56 (m, 1H, C12-H), 4.19 (t, 1H, *J* = 9.8 Hz, C9-H), 3.93 (s, 3H, $ArOCH_3$), 3.65 (s, 3H, CO_2CH_3), 3.26 (t, 1H, *J* = 12.0 Hz, C13-Hα), 2.98 (s, 3H, NCH_3), 2.96 (m, 1H, C13-Hβ, partially obscured by NCH_3), 2.87 (d, 1H, *J* = 16.3 Hz, C8-Hα), 2.69 (dd, 1H, *J* = 11.0, 16.3 Hz, C8-Hβ), 1.49 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3360, 2931, 2841, 1747, 1678, 1585, 1516, 1441, 1367, 1262, 1210, 1146, 1027, 980, 838, 755 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 617.1247 (M^+ + Cs, $C_{26}H_{32}N_2O_7$ requires 617.1264).

Methyl 4-Methoxy-12(*S*)-(*N*-methylamino)-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-31). Following the procedure detailed for **27**, (9*S*,12*S*)-**30** (10.0 mg, 0.021 mmol) afforded (9*S*,12*S*)-**31** (7.6 mg, 8.1 mg theoretical, 94%) as a yellow solid: $[\alpha]^{25}_D$ −5 (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (dd, 2H, *J* = 2.4, 8.4 Hz, C15- and C18-H), 7.08 (dd, 1H, *J* = 2.4, 8.4 Hz, C16- or C17-H), 6.96−7.02 (m, 2H, C17- or C16-H and N10-H), 6.75 (d, 1H, *J* = 8.2 Hz, C5-H), 6.59 (dd, 1H, *J* = 1.6, 8.2 Hz, C6-H), 5.01 (d, 1H, *J* = 1.6 Hz, C19-H), 4.12 (dd, 1H, *J* = 8.1, 9.5 Hz, C9-H), 3.93 (s, 3H, $ArOCH_3$), 3.69 (s, 3H, CO_2CH_3), 3.38−3.41 (m, 1H, C12-H), 3.36 (dd, 1H, *J* = 4.9, 12.0 Hz, C13-Hα), 2.95 (dd, 1H, *J* = 2.0, 12.0 Hz, C13-Hβ), 2.83 (d, 1H, *J* = 16.4 Hz, C8-Hβ), 2.70 (dd, 1H, *J* = 14.8, 16.4 Hz, C8-Hα), 2.55 (s, 3H, $NHCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4 (2C), 157.7, 152.5, 146.7, 134.1, 132.8, 130.3, 130.1, 125.1, 123.4, 121.2, 115.1, 111.5, 65.7, 56.1, 53.8, 52.4, 37.5, 35.3, 34.8; IR (neat) ν_{max} 3337, 2921, 2850, 1745, 1658, 1582, 1496, 1435, 1262, 1201, 1125, 1024, 912, 861, 795, 729 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 517.0724 (M^+ + Cs, $C_{21}H_{24}N_2O_5$ requires 517.0740).

3-Fluoro-4-nitro-*N*-[*N*-(*tert*-butyloxycarbonyl)-L-tyrosyl]-L-phenylalanine Methyl Ester ((*S*,*S*)-33). Following the procedure detailed for (*S*,*S*)-**13**, L-**6** (48 mg, 0.2 mmol) and L-**12** (98 mg, 0.22 mmol, 1.1 equiv) afforded (*S*,*S*)-**33** (95 mg, 101 mg theoretical, 94%) as a pale-yellow solid: $[\alpha]^{25}_D$ −34 (*c* 0.1, acetone), +18 (*c* 0.16, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.14 (s, 1H, OH), 8.03 (t, 1H, *J* = 8.0 Hz, C5-H), 7.56 (d, 1H, *J* = 6.8 Hz, NH), 7.40 (d, 1H, *J* = 12.3 Hz, C2-H), 7.30 (d, 1H, *J* = 8.3 Hz, C6-H), 7.04 (d, 2H, *J* = 8.4 Hz, C2′- and C6′-H), 6.72 (d, 2H, *J* = 8.4 Hz, C3′- and C5′-H), 5.97 (d, 1H, *J* = 7.6 Hz, NHBOC), 4.80 (m, 1H, $ArCH_2CH$), 4.25 (m, 1H, $ArCH_2CH$), 3.69 (s, 3H, CO_2CH_3), 3.33 (dd, 1H, *J* = 5.0, 14.0 Hz, ArC*H*H), 3.15 (dd, 1H, *J* = 8.2, 13.7 Hz, ArCH*H*), 2.97 (dd, 1H, *J* = 5.2, 14.0 Hz, ArC*H*H), 2.76 (dd, 1H, *J* = 9.0, 13.7 Hz, ArCH*H*), 1.32 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR (acetone-d_6, 100 MHz) δ 172.6, 171.7, 157.1, 156.9, 155.3 (d, *J* = 271 Hz, C3), 147.9 (d, *J* = 7.0 Hz, C1), 136.9 (d, *J* = 20 Hz, C4), 131.1 (2C), 129.0, 127.0 (d, *J* = 4.0 Hz, C6), 126.7 (C5), 120.0 (d, *J* = 21 Hz, C2), 115.9 (2C), 79.3, 57.0, 53.5, 52.6, 37.7 (2C), 28.4 (3C); IR (KBr) ν_{max} 3333, 2968, 2860, 1737, 1664, 1612, 1519, 1442, 1349, 1295, 1246, 1162, 1093, 1049, 1015, 965, 892, 839, 749 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 638.0938 (M^+ + Cs, $C_{24}H_{28}N_3O_8F$ requires 638.0915).

3-Fluoro-4-nitro-*N*-[*N*-(*tert*-butyloxycarbonyl)-L-tyrosyl]-D-phenylalanine Methyl Ester ((*R*,*S*)-34). Following the procedure detailed for (*S*,*S*)-**13**, D-**6** (5.0 mg, 0.021 mmol) and L-**12** (11.1 mg, 0.025 mmol, 1.2 equiv) afforded (*R*,*S*)-**34** (9.6 mg, 10.6 mg theoretical, 91%) as a pale-yellow oil, which solidified upon standing: $[\alpha]^{25}_D$ −38 (*c* 0.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (t, 1H, *J* = 8.0 Hz, C5-H), 7.00 (d, 2H, *J* = 8.3 Hz, C2′- and C6′-H), 6.88 (d, 1H, *J* = 11.6 Hz, C2−H), 6.84 (d, 1H, *J* = 8.5 Hz, C6-H), 6.71 (d, 2H, *J* = 8.3 Hz, C3′- and C5′-H), 6.70 (br s, 1H, NH), 5.84 (br s, 1H, ArOH), 4.94 (d, 1H, *J* = 6.5 Hz, NHBOC), 4.84 (dd, 1H, *J* = 6.0, 13.0 Hz, $ArCH_2CH$), 4.29 (m, 1H, $ArCH_2CH$), 3.70 (s, 3H, CO_2CH_3), 3.10 (dd, 1H, *J* = 5.8, 14.0 Hz, ArC*H*H), 3.05 (dd, 1H, *J* = 6.4, 14.0 Hz, ArC*H*H), 2.98 (dd, 1H, *J* = 7.6, 14.0 Hz, ArC*H*H), 2.91 (dd, 1H, *J* = 6.6, 14.0 Hz, ArC*H*H), 1.38 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3327, 2976, 2931, 1744, 1695, 1667, 1612, 1518, 1441, 1349, 1250, 1167, 1101, 1048, 1022, 910, 840, 732 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 638.0931 (M^+ + Cs, $C_{24}H_{28}N_3O_8F$ requires 638.0915).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-nitro-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-35). A solution of (*R*,*S*)-**34** (8.0 mg, 0.016 mmol) in anhydrous DMF (4 mL, 0.004 M) was treated with K_2CO_3 (11 mg, 0.08 mmol, 5.0 equiv) at 25 °C under Ar. The resulting reaction mixture was warmed at 70 °C for 10 h before the solvent was removed in vacuo. Flash chromatography (SiO_2, 1 × 5 cm, 20−40% EtOAc−hexane gradient elution) afforded (9*R*,12*S*)-**35** (4.9 mg, 7.7 mg theoretical, 63%) as a white solid: mp > 230 °C; $[\alpha]^{25}_D$ −32 (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 1H, *J* = 8.4 Hz, C5-H), 7.45 (dd, 1H, *J* = 2.0, 8.4 Hz, C18-H), 7.26 (dd, 1H, *J* = 2.0, 8.4 Hz, C15-H), 7.09 (dd, 1H, *J* = 2.0, 8.4 Hz, C17-H), 7.03 (dd, 1H, *J* = 2.0, 8.4 Hz, C16-H), 6.73 (dd, 1H, *J* = 1.7, 8.4 Hz, C6-H), 6.04 (d, 1H, *J* = 7.7 Hz, N10-H), 5.35 (d, 1H, *J* = 1.7 Hz, C19-H), 5.16 (d, 1H, *J* = 9.2 Hz, NHBOC), 4.08−4.17 (m, 2H, C9- and C12-H), 3.68 (s, 3H, CO_2CH_3), 3.27 (dd, 1H, *J* = 5.1, 12.0 Hz, C13-Hβ), 2.99 (d, 1H, *J* = 17.4 Hz, C8-Hβ), 2.89 (t, 1H, *J* = 12.0 Hz, C13-Hα), 2.77 (dd, 1H, *J* = 11.3, 17.4 Hz, C8-Hα), 1.45 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 171.0, 156.5, 155.9, 155.2, 144.7, 136.6, 135.5, 133.0, 131.0, 125.7, 124.5, 124.0, 121.4, 116.6, 80.5, 58.2, 52.9, 52.7, 38.7, 34.7, 28.3 (3C); IR (neat) ν_{max} 3299, 2976, 2933, 1749, 1703, 1676, 1589, 1520, 1500, 1435, 1349, 1287, 1233, 1195, 1171, 1097, 1052, 1015, 987, 841, 732 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 618.0872 (M^+ + Cs, $C_{24}H_{27}N_3O_8$ requires 618.0852).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-nitro-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-36). A solution of (*S*,*S*)-**33** (200 mg, 0.4 mmol) in anhydrous THF (2 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 53 mg, 1.32 mmol, 3.3 equiv) in anhydrous THF (98 mL) at 0 °C under Ar, and the resulting reaction mixture was stirred at 0 °C for 30 min and 25 °C for 12 h. The reaction was quenched by addition of H_2O (10 mL) and EtOAc (50 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL) and saturated aqueous NaCl (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2 × 15 cm, 20−40% EtOAc−hexane gradient elution) afforded (9*S*,12*S*)-**36** (111 mg, 194 mg theoretical, 57%) and (9*R*,12*S*)-**35** (35 mg, 194 mg theoretical, 18%). For (9*S*,12*S*)-**36**: white solid; mp > 230 °C; $[\alpha]^{25}_D$ +48 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 1H, *J* = 8.4 Hz, C5-H), 7.34 (dd, 2H, *J* = 2.2, 8.4 Hz, C15- and C18-H), 7.15 (dd, 1H, *J* = 2.2, 8.4 Hz, C16- or C17-H), 7.06 (dd, 1H, *J* = 2.2, 8.4 Hz, C17- or C16-H), 6.73 (dd, 1H, *J* = 1.5, 8.4 Hz, C6-H), 5.84 (br s, 1H, N10-H), 5.31 (d, 1H, *J* = 1.5 Hz, C19-H), 4.97 (br s, 1H, NHBOC), 4.56 (m, 1H, C12-H), 4.24 (m, 1H, C9-H), 3.68 (s, 3H, CO_2CH_3), 3.51 (dd, 1H, *J* = 5.2, 13.4 Hz, C13-Hβ), 2.98 (dd, 1H, *J* = 2.0, 17.4 Hz, C8-Hβ), 2.87−2.93 (m, 2H, C8-Hα and C13-Hα), 1.50 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0 (2C), 156.5, 156.3, 154.7, 144.5, 136.7, 134.8, 133.0, 130.1, 125.8, 124.8, 123.5, 121.6,

117.0, 80.5, 56.8, 52.7, 52.6, 38.6, 35.0, 28.2 (3C); IR (KBr) ν_{max} 3374, 3303, 2974, 2933, 1754, 1703, 1667, 1605, 1585, 1519, 1497, 1431, 1344, 1226, 1195, 1164, 1092, 1046, 1015, 985, 841 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 618.0838 (M^+ + Cs, $C_{24}H_{27}N_3O_8$ requires 618.0852).

Following the procedure detailed for (*R*,*S*)-**34**, (*S*,*S*)-**33** (25.3 mg, 0.05 mmol) afforded (9*S*,12*S*)-**36** (7.0 mg, 24.3 mg theoretical, 29%) and (9*R*,12*S*)-**35** (6.4 mg, 24.3 mg theoretical, 26%).

Equilibration Epimerization of (9*S*,12*S*)-36. Following the procedure described for **16**, (9*S*,12*S*)-**36** (9.7 mg, 0.02 mmol, $[\alpha]^{25}_D$ +48 (*c* 2.0, $CHCl_3$)) after 72 h afforded (9*R*,12*S*)-**35** (5.0 mg, 9.7 mg theoretical, 52%), which was identical in all respects with an authentic sample, as a white solid ($[\alpha]^{25}_D$ −31 (*c* 0.25, $CHCl_3$)) and recovered (9*S*,12*S*)-**36** (2.5 mg, 26%).

Methyl 4-Amino-12(*S*)-[*N*-(*tert*-butyloxycarbonyl)amino]-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-37). Following the procedure detailed for **24**, (9*S*,12*S*)-**36** (123 mg, 0.25 mmol) afforded (9*S*,12*S*)-**37** (113 mg, 116 mg theoretical, 98%) as a pink solid: ^{1}H NMR (acetone-d_6, 400 MHz) mixture of two rotamers, δ (for major rotamer) 7.36 (dd, 1H, *J* = 2.2, 8.4 Hz, C15- or C18-H), 7.17 (dd, 1H, *J* = 2.2, 8.4 Hz, C18- or C15-H), 7.03 (dd, 1H, *J* = 2.3, 8.2 Hz, C16- or C17-H), 6.92 (dd, 1H, *J* = 2.3, 8.4 Hz, C17- or C16-H), 6.57 (d, 1H, *J* = 8.0 Hz, C5-H), 6.40 (dd, 1H, *J* = 2.0, 8.0 Hz, C6-H), 6.19 (br s, 1H, N10-H), 5.05 (d, 1H, *J* = 2.0 Hz, C19-H), 4.56 (br s, 1H, NHBOC), 4.52 (m, 1H, C12-H), 3.96 (ddd, 1H, *J* = 1.6, 6.4, 9.3 Hz, C9-H), 3.57 (s, 3H, CO_2CH_3), 3.22 (dd, 1H, *J* = 5.0, 13.2 Hz, C13-Hβ), 2.90 (dd, 1H, *J* = 8.1, 13.2 Hz, C13-Hα), 2.78 (dd, 1H, *J* = 9.1, 16.4 Hz, C8-Hα), 2.67 (dd, 1H, *J* = 1.6, 16.4 Hz, C8-Hβ), 1.46 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR (acetone-d_6, 100 MHz) mixture of two rotamers, δ (for major rotamer) 172.3, 170.9, 159.3, 155.5, 152.7, 151.8, 136.0, 135.0, 133.4, 130.7, 125.7, 124.7, 122.3, 116.3, 115.2, 79.9, 57.6, 55.7, 52.1, 39.4, 35.3, 34.9 (3C); IR (neat) ν_{max} 3351, 2978, 2932, 1709, 1663, 1588, 1516, 1500, 1438, 1368, 1204, 1164, 1098, 1050, 1017, 984, 870, 736 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 588.1124 (M^+ + Cs, $C_{24}H_{29}N_3O_6$ requires 588.1111).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-hydroxy-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-38). Following the procedure detailed for **25**, (9*S*,12*S*)-**37** (36.4 mg, 0.08 mmol) afforded (9*S*,12*S*)-**38** (17.6 mg, 36.4 mg theoretical, 48%) and the corresponding reduced product (4.2 mg, 35.2 mg theoretical, 12%). For (9*S*,12*S*)-**38**: white solid; $[\alpha]^{25}_D$ +54 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd, 2H, *J* = 2.0, 8.2 Hz, C15- and C18-H), 7.09 (dd, 1H, *J* = 2.3, 8.4 Hz, C16- or C17-H), 7.02 (dd, 1H, *J* = 2.3, 8.4 Hz, C17- or C16-H), 6.79 (d, 1H, *J* = 8.2 Hz, C5-H), 6.52 (dd, 1H, *J* = 2.1, 8.2 Hz, C6-H), 5.85 (br s, 1H, N10-H), 5.78 (s, 1H, ArOH), 4.99 (br s, 2H, C19-H and NHBOC), 4.56 (m, 1H, C12-H), 4.20 (m, 1H, C9-H), 3.65 (s, 3H, CO_2CH_3), 3.50 (dd, 1H, *J* = 4.9, 13.5 Hz, C13-Hβ), 2.70−2.90 (m, 3H, C13-Hα and C8-H_2), 1.50 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.7, 157.7, 154.8, 150.3, 143.3, 134.1, 132.8, 129.7, 129.0, 125.5, 123.8, 122.2, 115.4, 114.7, 81.2, 56.6, 53.6, 52.4, 38.5, 34.6, 28.2 (3C); IR (neat) ν_{max} 3345, 2958, 2854, 1724, 1664, 1595, 1496, 1441, 1367, 1256, 1205, 1162, 1113, 1051, 1021, 869, 736 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 589.0968 (M^+ + Cs, $C_{24}H_{28}N_2O_7$ requires 589.0951).

For the reduced product, methyl 12(*S*)-[*N*-(*tert*-butyloxycarbonyl)amino]-11-oxo-10-aza-2−oxatricyclo[12.2.2.1^{3,7}]-nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate: pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd, 2H, *J* = 2.2, 8.4 Hz, C15- and C18-H), 7.13 (t, 1H, *J* = 8.0 Hz, C5-H), 7.05 (dd, 1H, *J* = 2.2, 8.4 Hz, C16- or C17-H), 7.01 (dd, 1H, *J* = 2.2, 8.4 Hz, C17- or C16−H), 6.99 (dd, 1H, *J* = 2.3, 8.4 Hz, C4-H), 6.61 (dd, 1H, *J* = 2.3, 8.4 Hz, C6-H), 5.99 (br s, 1H, N10−H), 5.08 (d, 1H, *J* = 9.1 Hz, NHBOC), 5.03 (d, 1H, *J* = 2.3 Hz, C19-H), 4.54 (m, 1H, C12-H), 4.22 (m, 1H, C9-H), 3.63 (s, 3H, CO_2CH_3), 3.47 (dd, 1H, *J* = 4.9, 13.4 Hz, C13-Hβ), 2.80−2.89 (m, 3H, C13-Hα and C8-H_2), 1.48 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.7, 163.2, 157.9, 154.8, 138.3, 133.8, 132.6, 129.7, 129.3, 125.5, 123.8, 121.6, 114.8, 114.3, 81.1, 56.7, 53.3, 52.4, 38.5, 35.0, 28.2 (3C); IR (neat) ν_{max} 3313, 2976, 2924, 1675, 1582, 1562, 1423, 1367, 1321, 1252, 1164, 1065, 1025 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 573.1026 (M^+ + Cs, $C_{24}H_{28}N_2O_6$ requires 573.1002).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-methoxy-11-oxo-10-aza-2-oxo-tricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-39). Following the procedure detailed for **26**, *O*-methylation of (9*S*,12*S*)-**38** (13.7 mg, 0.03 mmol) with NaH (1.8 mg, 0.045 mmol, 1.5 equiv) afforded (9*S*,12*S*)-**39** (12.7 mg, 14.1 mg theoretical, 90%) as a white solid: $[\alpha]^{25}_D$ +57 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (dd, 2H, *J* = 2.2, 8.2 Hz, C15- and C18-H), 7.10 (dd, 1H, *J* = 2.2, 8.2 Hz, C16- or C17-H), 7.04 (dd, 1H, *J* = 2.2, 8.2 Hz, C17- or C16-H), 6.77 (d, 1H, *J* = 8.2 Hz, C5-H), 6.59 (dd, 1H, *J* = 1.7, 8.2 Hz, C6-H), 5.88 (br s, 1H, N10−H), 5.00 (d, 1H, *J* = 1.7 Hz, C19-H), 4.98 (br s, 1H, NHBOC), 4.57 (m, 1H, C12-H), 4.19 (m, 1H, C9-H), 3.93 (s, 3H, $ArOCH_3$), 3.65 (s, 3H, CO_2CH_3), 3.49 (dd, 1H, *J* = 4.9, 13.4 Hz, C13-Hβ), 2.74−2.89 (m, 3H, C13-Hα and C8-H_2), 1.49 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.7, 157.9, 154.7, 152.3, 146.9, 133.8, 132.9, 129.4, 125.6, 123.8, 121.6, 116.8, 114.9, 111.7, 81.1, 56.5, 56.1, 53.7, 52.4, 38.4, 34.7, 28.2 (3C); IR (neat) ν_{max} 3356, 3058, 2931, 2852, 1752, 1719, 1672, 1586, 1517, 1499, 1439, 1367, 1263, 1222, 1203, 1162, 1129, 1025, 870, 803, 735 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 603.1125 (M^+ + Cs, $C_{25}H_{30}N_2O_7$ requires 603.1107).

Methyl 12(*S*)-Amino-4-methoxy-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*S*)-carboxylate ((9*S*,12*S*)-40). Following the procedure detailed for **27**, (9*S*,12*S*)-**39** (12.5 mg, 0.0266 mmol) afforded (9*S*,12*S*)-**40** (8.9 mg, 9.8 mg, 91%) as a white solid: $[\alpha]^{25}_D$ −16 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (dd, 1H, *J* = 1.9, 8.2 Hz, C15- or C18−H), 7.23 (dd, 1H, *J* = 1.9, 8.2 Hz, C18- or C15-H), 7.12 (d, 1H, *J* = 8.6 Hz, N10-H), 7.10 (dd, 1H, *J* = 2.0, 8.3 Hz, C16- or C17-H), 6.99 (dd, 1H, *J* = 2.0, 8.3 Hz, C17- or C16-H), 6.75 (d, 1H, *J* = 8.2 Hz, C5-H), 6.59 (dd, 1H, *J* = 1.6, 8.2 Hz, C6-H), 5.02 (d, 1H, *J* = 1.6 Hz, C19-H), 4.13 (t, 1H, *J* = 8.8 Hz, C9-H), 3.93 (s, 3H, $ArOCH_3$), 3.90 (m, 1H, C12-H), 3.69 (s, 3H, CO_2CH_3), 3.49 (dd, 1H, *J* = 4.0, 13.3 Hz, C13-Hβ), 2.81 (t, 1H, *J* = 13.3 Hz, C13-Hα), 2.80 (dd, 1H, *J* = 2.1, 16.5 Hz, C8-Hβ), 2.71 (dd, 1H, *J* = 10.6, 16.5 Hz, C8-Hα), 1.70 (br s, 2H, C12-NH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 172.4, 157.8, 152.5, 146.7, 133.7, 133.0, 130.3, 130.0, 125.2, 123.0, 121.3, 114.8, 111.4, 56.1, 55.7, 53.7, 52.4, 40.4, 34.8; IR (neat) ν_{max} 3384, 2924, 2853, 1744, 1687, 1605, 1502, 1442, 1261, 1200, 1155, 1099, 1035, 843 cm^{-1}; MS (ion spray) *m/e* 371 (M^+ + H, $C_{20}H_{22}N_2O_5$).

Methyl 4-Amino-12(*S*)-[*N*-(*tert*-butyloxycarbonyl)amino]-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-41). Following the procedure detailed for **24**, (9*R*,12*S*)-**35** (26 mg, 0.054 mmol) afforded (9*R*,12*S*)-**41** (23.8 mg, 24.6 mg theoretical, 97%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (dd, 1H, *J* = 2.0, 8.2 Hz, C15- or C18-H), 7.19 (dd, 1H, *J* = 2.0, 8.2 Hz, C18- or C15-H), 7.04 (dd, 1H, *J* = 2.0, 8.2 Hz, C16- or C17-H), 6.97 (dd, 1H, *J* = 2.0, 8.2 Hz, C17- or C16-H), 6.74 (d, 1H, *J* = 8.2 Hz, C5-H), 6.62 (dd, 1H, *J* = 1.8, 8.2 Hz, C6-H), 6.46 (d, 1H, *J* = 8.0 Hz, N10-H), 5.17 (d, 1H, *J* = 9.1 Hz, NHBOC), 4.86 (d, 1H, *J* = 1.8 Hz, C19-H), 4.06−4.14 (m, 2H, C9- and C12-H), 3.68 (s, 3H, CO_2CH_3), 3.24 (dd, 1H, *J* = 4.7, 12.0 Hz, C13-Hβ), 2.88 (t, 1H, *J* = 12.0 Hz, C13-Hα), 2.79 (d, 1H, *J* = 16.0 Hz, C8-Hα), 2.65 (dd, 1H, *J* = 11.0, 16.0 Hz, C8-Hβ), 1.45 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3322, 2976, 2933, 1739, 1692, 1660, 1516, 1439, 1367, 1282, 1208, 1163, 1016, 908, 837, 732 cm^{-1}; FABHRMS (NBA−NaI) *m/e* 455.2051 (M^+, $C_{24}H_{29}N_3O_6$ requires 455.2056).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-hydroxy-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-42). Following the procedure detailed for **25**, (9*R*,12*S*)-**41** (21 mg, 0.046 mmol) afforded (9*R*,12*S*)-**42** (9.0 mg, 21 mg theoretical, 43%) and the corresponding reduced product (3.8 mg, 19%). For (9*R*,12*S*)-**42**: white solid; $[\alpha]^{25}_D$ −38 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (dd, 1H, *J* = 2.4, 8.4 Hz, C15- or C18-H), 7.22 (dd, 1H, *J* = 2.4, 8.4 Hz, C18- or C15-H), 7.06 (dd, 1H, *J* = 2.4, 8.4 Hz, C16- or C17-H), 6.96 (dd, 1H, *J* = 2.4, 8.4 Hz, C17- or C16-H), 6.79 (d, 1H, *J* = 8.2 Hz, C5-H),

6.53 (dd, 1H, J = 1.6, 8.2 Hz, C6-H), 5.78 (d, 1H, J = 7.6 Hz, N10-H), 5.59 (br s, 1H, C4-OH), 5.15 (d, 1H, J = 9.2 Hz, NHBOC), 5.04 (d, 1H, J = 1.6 Hz, C19-H), 4.08−4.14 (m, 2H, C9- and C12-H), 3.66 (s, 3H, CO_2CH_3), 3.25 (dd, 1H, J = 5.0, 12.1 Hz, C13-Hβ), 2.88 (t, 1H, J = 12.1 Hz, C13-Hα), 2.85 (d, 1H, J = 16.7 Hz, C8-Hα), 2.65 (dd, 1H, J = 11.2, 16.7 Hz, C8-Hβ), 1.45 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3317, 2974, 2933, 1723, 1659, 1595, 1497, 1435, 1364, 1282, 1162, 1108, 1051, 1010, 836, 728 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 589.0933 (M^+ + Cs, $C_{24}H_{28}N_2O_6$ requires 589.0951).

For the reduced product, methyl 12(*S*)-[*N*-(*tert*-butyloxycarbonyl)amino]-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate: pale-yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (dd, 1H, J = 2.2, 8.4 Hz, C15- or C18-H), 7.21 (dd, 1H, J = 2.2, 8.4 Hz, C18- or C15-H), 7.13 (t, 1H, J = 8.0 Hz, C5-H), 7.05 (dd, 1H, J = 2.2, 8.4 Hz, C16- or C17-H), 7.01 (dd, 1H, J = 2.2, 8.4 Hz, C17- or C16-H), 6.98 (dd, 1H, J = 2.0, 8.0 Hz, C4-H), 6.61 (dd, 1H, J = 2.0, 8.0 Hz, C6-H), 6.00 (d, 1H, J = 7.6 Hz, N10-H), 5.17 (d, 1H, J = 9.2 Hz, NHBOC), 5.06 (d, 1H, J = 2.0 Hz, C19-H), 4.07−4.15 (m, 2H, C9- and C12-H), 3.65 (s, 3H, CO_2CH_3), 3.26 (dd, 1H, J = 5.0, 12.0 Hz, C13-Hβ), 2.88 (t, 1H, J = 12.0 Hz, C13-Hα), 2.86 (d, 1H, J = 16.6 Hz, C8-Hα), 2.73 (dd, 1H, J = 11.2, 16.6 Hz, C8-Hβ), 1.43 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3301, 2974, 2933, 1733, 1661, 1587, 1533, 1500, 1444, 1368, 1206, 1165, 1017, 836, 757 cm^{-1}; FABHRMS (NBA−NaI) *m/e* 463.1838 (M^+ + Na, $C_{24}H_{28}N_2O_6$ requires 463.1845).

Methyl 12(*S*)-[*N*-(*tert*-Butyloxycarbonyl)amino]-4-methoxy-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7-(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-43). Following the procedure detailed for **26**, (9*R*,12*S*)-**42** (6.4 mg, 0.014 mmol) and NaH (0.9 mg, 0.021 mmol, 1.5 equiv) provided (9*R*,12*S*)-**43** (6.0 mg, 6.6 mg theoretical, 91%): white solid; $[\alpha]^{25}_D$ −42 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (dd, 1H, J = 2.1, 8.4 Hz, C15- or C18-H), 7.21 (dd, 1H, J = 2.1, 8.4 Hz, C18- or C15-H), 7.10 (dd, 1H, J = 2.2, 8.4 Hz, C16- or C17-H), 6.99 (dd, 1H, J = 2.2, 8.4 Hz, C17- or C16-H), 6.76 (d, 1H, J = 8.2 Hz, C5-H), 6.58 (dd, 1H, J = 2.2, 8.2 Hz, C6-H), 5.76 (d, 1H, J = 7.4 Hz, N10-H), 5.15 (d, 1H, J = 9.2 Hz, NHBOC), 5.05 (d, 1H, J = 2.2 Hz, C19-H), 4.07−4.13 (m, 2H, C9- and C12-H), 3.93 (s, 3H, $ArOCH_3$), 3.67 (s, 3H, CO_2CH_3), 3.25 (dd, 1H, J = 5.1, 12.1 Hz, C13-Hβ), 2.87 (t, 1H, J = 12.2 Hz, C13-Hα), 2.84 (d, 1H, J = 16.6 Hz, C8-Hα), 2.68 (dd, 1H, J = 11.0, 16.6 Hz, C8-Hβ), 1.45 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 171.5, 157.2, 155.2, 152.3, 146.0, 134.5, 132.5, 130.5, 129.8, 125.0, 124.7, 121.2, 115.0, 111.5, 80.3, 58.2, 56.1, 54.0, 52.5, 38.9, 34.3, 28.3 (3C); IR (KBr) ν_{max} 3347, 3300, 2954, 2853, 1748, 1718, 1664, 1587, 1517, 1436, 1367, 1264, 1205, 1162, 1130, 1015, 978, 891, 869, 838, 797, 762, 729 cm^{-1}; FABHRMS (NBA) *m/e* 471.2125 (M^+ + H, $C_{25}H_{30}N_2O_7$ requires 471.2131).

Methyl 12(*S*)-Amino-4-methoxy-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9(*R*)-carboxylate ((9*R*,12*S*)-44). Following the procedure for **27**, (9*R*,12*S*)-**43** (4.6 mg, 0.01 mmol) afforded (9*R*,12*S*)-**44** (3.4 mg, 3.6 mg theoretical, 94%): $[\alpha]^{25}_D$ −18 (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (dd, 1H, J = 2.1, 8.3 Hz, C18-H), 7.19 (dd, 1H, J = 2.1, 8.3 Hz, C15-H), 7.10 (dd, 1H, J = 2.1, 8.3 Hz, C17-H), 6.99 (dd, 1H, J = 2.1, 8.3 Hz, C16−H), 6.77 (d, 1H, J = 8.3 Hz, C5-H), 6.58 (dd, 1H, J = 2.1, 8.3 Hz, C6-H), 6.26 (br s, 1H, N10-H), 5.07 (d, 1H, J = 2.1 Hz, C19-H), 4.09 (ddd, 1H, J = 1.4, 7.0, 11.4 Hz, C9-H), 3.93 (s, 3H, $ArOCH_3$), 3.73 (s, 3H, CO_2CH_3), 3.54 (m, 1H, C12-H), 3.22 (dd, 1H, J = 4.7, 12.4 Hz, C13-Hβ), 2.74−2.88 (m, 3H, C8-H_2 and C13-Hα); IR (KBr) ν_{max} 3436, 3046, 2954, 1718, 1667, 1590, 1513, 1436, 1415, 1267, 1225, 1205, 1128, 1021, 980, 882, 836, 805, 765 cm^{-1}; FABHRMS (NBA−CsI) *m/e* 503.0598 ((M^+ + Cs, $C_{20}H_{22}N_2O_5$ requires 503.0583).

Methyl (9*S*,12*S*)-12-Amino-4-nitro-11-oxo-10-aza-2-oxatricyclo[12.2.2.1^{3,7}]nonadeca-3,5,7(19),14,16,17-hexaene-9-carboxylate Hydrochloride ((9*S*,12*S*)-45). A solution of (9*S*,12*S*)-**36** (6.4 mg, 13 μmol) in 3.3 N HCl−THF (0.5 mL) was stirred at 25 °C for 3 h before the volatiles were removed in vacuo. The residue was then thoroughly dried under vacuum to afford the crude HCl salt (5.5 mg, 5.5 mg theoretical, 100%) as a white solid, which afforded colorless parallel piped shaped crystals after recrystallization from CH_3OH−Et_2O. A single crystal X-ray structure determination of **45** confirmed the structure and relative stereochemistry of **45**.[17]

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA41101), The Skaggs Institute for Chemical Biology, and the award of predoctoral (SLC, NSF GER-9253922) and postdoctoral fellowships (RMB, NIH GM17548; SN, Pfizer, Japan).

Supporting Information Available: 2D ^{1}H−^{1}H ROESY NMR and/or 1D decoupling NMR experimental results for **15**, **16**, **25**, **26**, **35**, and **36**, experimental procedures and characterization for **3**, **5**, **6**, **8**−**12**, **47**−**69**, **73**−**79**, and ^{1}H NMR spectra of **3**, (2*S*,5*R*)- and (2*R*,5*S*)-**5**, L- and D-**6**, **9**−**53**, and the corresponding reduced products of **20**, **25**, **29**, and **38** (83 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.

JO961346O