Total Synthesis of Bouvardin, *O*-Methylbouvardin, and *O*-Methyl-N^9-desmethylbouvardin

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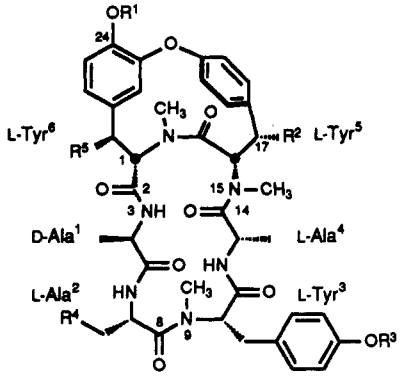
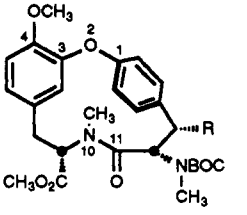
Abstract: Concise total syntheses of bouvardin (**1**) and *O*-methylbouvardin (**2**) are described based on the asymmetric synthesis of the *N*-methyl-*erythro*-β-hydroxy-L-4-iodophenylalanine derivative **24**, its coupling with the selectively protected *N*,O^4-dimethyl-L-DOPA methyl ester to provide **40**, and subsequent incorporation into a surprisingly successful key Ullmann macrocyclization reaction for preparation of the 14-membered 13(*S*)-hydroxycycloisodityrosine subunit **15** of the bicyclic hexapeptides. Coupling of **15** with BOCNH-D-Ala-Ala-NMe-Tyr(OMe)-Ala-OC_6F_5 followed by 18-membered-ring macrocyclization strategically conducted with formation of a secondary amide at a D-amino acid amine terminus (C^2–N^3 amide) provided *O*-methylbouvardin (**2**). Selective demethylation (BBr_3) of **2** provided bouvardin (**1**) in excellent conversion (86%). The extensions of the studies to the preparation of *O*-methyl-N^9-desmethylbouvardin (**51**) are detailed and its solution-phase conformational properties examined by ^1H NMR in efforts which confirm that the additional minor conformation of **1** and **2** (*ca.* 10–15%) observed in nonpolar solvents ($CDCl_3$, THF-d_8), arise from a cis N^9–C^8 *N*-methylamide conformation.

Bouvardin (**1**, NSC 259968) and deoxybouvardin (**3**), bicyclic hexapeptides isolated from *Bouvardia ternifolia* (Rubiaceae) and identified by X-ray structure analysis (bouvardin) and chemical correlation (deoxybouvardin),[1] constitute the initial members of a growing class of potent antitumor antibiotics now including *O*-methylbouvardin (**2**)[1] and RA-I–RA-XIV[2-14] (Figure 1). Studies of the properties of RA-VII (**8**) have revealed efficacious antitumor activity including a demonstration of complete cures in a solid tumor, colon adenocarcinoma 38.[15] Both bouvardin and RA-VII have been shown to inhibit protein synthesis[15-17] through eukaryotic 80S ribosomal binding[18,19] with inhibition of both amino acyl-*t*RNA binding and peptidyl-*t*RNA translocation, and this is presently thought to be the site of action for the agent antitumor activity.



	R^1	R^2	R^3	R^4	R^5	
1	H	OH	Me	H	H	bouvardin
2	Me	OH	Me	H	H	*O*-methyl bouvardin
3	H	H	Me	H	H	deoxybouvardin (RA-V)
4	H	H	Me	OH	H	RA-I
5	Me	H	H	H	H	RA-II
6	Me	H	Me	OH	H	RA-III
7	Me	H	Me	H	OH	RA-IV
8	Me	H	Me	H	H	RA-VII
9	Me	H	Me	(OH)Me	H	RA-VIII
10	Me	H	Me	CH_2CO_2H	H	RA-X
11	H	H	Me	CH_2CO_2H	H	RA-XI
12	β-D-glucose	H	Me	H	H	RA-XII
13	β-D-glucose	H	Me	CH_2CO_2H	H	RA-XIII



14, R=H
15, R=OSi^{t}BuMe$_2$
16, R=OH

Figure 1.

Although the initial examination of structures **1–3** led to the logical proposal that the cycloisodityrosine-derived 14-membered ring serves the functional role of inducing and maintaining a rigid, normally inaccessible conformation within a biologically

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active tetrapeptide housed in the 18-membered cyclic hexapeptide,[1,20] more recent studies have suggested that it is the cycloisodityrosine subunit that constitutes the agent pharmacophore.[21-27] However, efforts to critically examine the role of the cycloisodityrosine subunit have been hampered by the synthetic inaccessibility of such systems. Conventional macrolactamization techniques including transannular lactamizations,[23] Ullmann macrocyclizations with C^3–O^2 bond closure,[23,28-30] and intramolecular oxidative phenol couplings[20] have failed to provide the 14-membered cycloisodityrosine subunit.[31] We recently disclosed the implementation of a general C^1–O^2 Ullmann macrocyclization reaction for the preparation of such 14-membered biaryl ethers (45–60%)[32] and have reported the successful extension of the methodology to the total syntheses of RA-VII and deoxybouvardin,[23,33] *N*-methylcycloisodityrosine,[23,33] piperazinomycin,[34] and related agents.[35-37] In these studies, the direct Ullmann macrocyclization reaction with C^1–O^2 ring closure has proven uniquely successful even with functionalized, base-sensitive substrates (30–55% yields)[33-37] and surprisingly more effective than an indirect, two-step thallium trinitrate-promoted phenol coupling reaction introduced by Yamamura and co-workers.[38-43] This process, which requires the use of dichloro- and dibromophenol coupling partners, was employed by Inoue and co-workers[38,39] in the first total synthesis of RA-VII (**8**) and deoxybouvardin (**3**) albeit with the key steps proceeding in low yields (*ca.* 2–5%). Herein, we detail the surprisingly successful extension of the Ullmann macrocyclization methodology to the preparation of the highly functionalized and more sensitive 13-hydroxy-*N*-methylcycloisodityrosine derivatives **15** and **16** and their incorporation into the first total syntheses of bouvardin (**1**) and *O*-methylbouvardin (**2**).

Two complementary asymmetric syntheses of *N*-methyl-*erythro*-β-hydroxy-L-4-iodophenylalanine derivatives based on asymmetric epoxidation[44-50] and asymmetric the Sharpless dihydroxylation[51-61] reactions, their conversion to **24**, and its coupling with the selectively protected *N*,O^4-dimethyl-L-DOPA methyl ester[23,62] preceded Ullmann macrocyclization to provide the 13-hydroxy-*N*-methylcycloisodityrosine derivative **15**. Notably, the Ullmann macrocyclization reaction conducted strategically with C^1–O^2 bond closure was found to occur without perceptible racemization, without additional significant side reactions introduced resulting from substrate incorporation of a β-alkoxy group, and with use of readily available amino acid derivatives, and it directly provided the appropriately functionalized biaryl ether without resorting to the use of the less accessible dichloro- or dibromophenols.[38-43]

N-Methyl-*erythro*-β-hydroxy-L-4-iodophenylalanine. Two approaches to the synthesis of *N*-methyl-*erythro*-β-hydroxy-L-4-iodophenylalanine derivatives required for use as the Ullmann cyclization acceptor were pursued based on complementary applications of the Sharpless asymmetric epoxidation and asymmetric dihydroxylation reactions. The initial approach was based on the catalytic asymmetric epoxidation of (*E*)-4-iodocinnamyl alcohol (**18**),[63] which was cleanly converted to the 2(*S*),3(*S*)-epoxide **19** (90%, ≥98% ee) upon treatment with *t*-BuOOH (2.0 equiv), Ti(O-*i*-Pr)$_4$ (0.05 equiv), and (+)-DIPT (0.075 equiv) in CH_2Cl_2 (0.1 M, –20 °C, 4 h) in the presence of 4-Å molecular sieves (1.0 g/mmol), Scheme 1. The crystallinity of this intermediate proved exceptional, and it served as a useful point to further enhance the enantiomeric purity of the synthetic intermediates. Simple purification of **19** by recrystallization (40%

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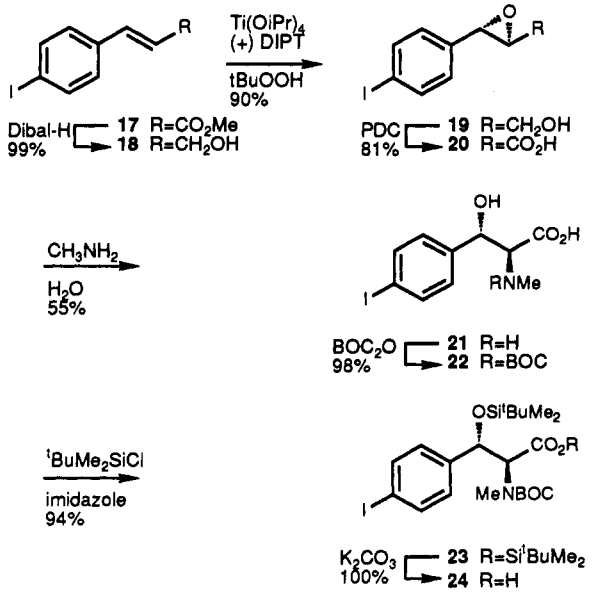
(63) The agents **17** and **18** were conveniently prepared on a large scale from 4-iodobenzoic acid by the following sequence: (1) 1.5 equiv of BH_3–THF, THF, 0 °C to reflux, 10 h, 99%; (2) 5 wt equiv of MnO_2, CH_2Cl_2, 25 °C, 8 h, 99%; (3) 1.2 equiv of $Ph_3P{=}CHCO_2CH_3$, C_6H_6, reflux, 3 h, 81% (40:1 *trans*:*cis* readily separable by SiO_2 chromatography); (4) 1.2 equiv of *i*-Bu_2AlH, 1:2.5 hexane–CH_2Cl_2, –78 °C, 20 min, 99%.

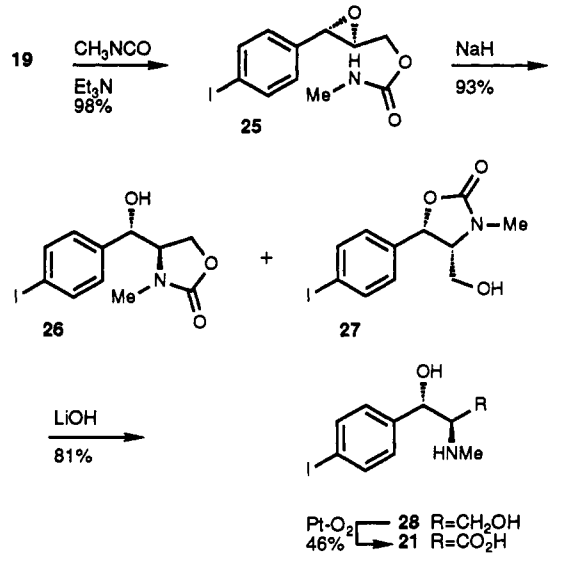
Scheme 1



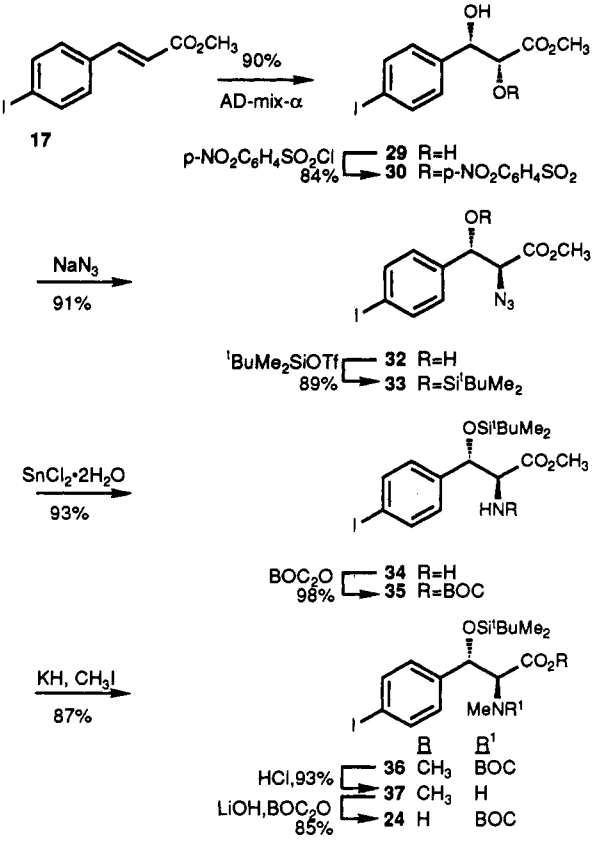
EtOAc–hexane) provided the epoxide with excellent recovery (93%) in high chemical and enhanced enantiomeric (>99% ee) purity. The enantiomeric purity of **19** was assessed after recrystallization upon conversion to its (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate (3.5 equiv of (*R*)-MTPACl, 2.5 equiv of Et_3N, 1.0 equiv of DMAP, 0.1 M CH_2Cl_2, 25 °C, 0.5 h, 97%) and analysis by ^1H and ^{19}F NMR. Oxidation of the primary alcohol to the carboxylic acid **20** was accomplished cleanly and directly upon treatment with PDC[64] (4.5 equiv, 25 °C, 10 h, 81%) in DMF. Oxidation of **19** with H_5IO_6–$RuCl_3$ (2.2 equiv and 0.02 equiv, 0.15 M 1:1:1.5 CCl_4–CH_3CN–H_2O, −5 to 0 °C, 3 h, 50%)[45b] or PDC–Celite also provided **20** but in lower conversions.

Regiospecific nucleophilic ring opening of the epoxide[65-68] was accomplished upon treatment of **20** with aqueous methylamine (0.15 M in H_2O, 90 °C, 4 h, 55%) and provided *N*-methyl-*erythro*-β-hydroxy-L-4-iodophenylalanine **21**, $[\alpha]^{25}_D$ −38 (*c* 0.8, H_2O), as a single detectable regioisomer (>10:1). Alternative, less direct approaches to introduce the *N*-methylamine were explored and included base-catalyzed epoxide ring opening by *N*-methylcarbamate **25**[72] (4.0 equiv of NaH, 0.1 M THF, 25 °C, 10 h, 93%), derived from reaction of epoxy alcohol **19** with methyl isocyanate[69-71] (2.0 equiv, 2.5 equiv of Et_3N, 0.1 M CH_2Cl_2, 25 °C, 8 h, 98%), which provided a 3:1 mixture of **26**[72] and **27**[72] (Scheme 2). Exhaustive hydrolysis of the mixture of **26** and **27** (5.0 equiv of LiOH, 1:3 EtOH–H_2O, reflux, 13 h, 81%) followed by oxidation of **28**[72] with Pt–O_2 (1:1 acetone–H_2O, 12 h, 46%)[73] also provided in **21**.

Scheme 2



Scheme 3



N-BOC formation (1.0 equiv of $(BOC)_2O$, 3.0 equiv of K_2CO_3, 1:1 THF–H_2O, 98%), concurrent alcohol and carboxylate *O*-silylation (2.0 equiv of *t*-$BuMe_2SiCl$, 2.0 equiv of imidazole, DMF, 25 °C, 48 h, 94%),[74] and subsequent silyl ester hydrolysis[75] (5.0 equiv of K_2CO_3, 2:1:1 THF–CH_3OH–H_2O, 25 °C, 1 h, 97–100%) provided **24** suitably protected for carboxylate coupling and incorporation into the total synthesis of **1** and **2** (Scheme 1). An initial attempt to conduct the silyl ester hydrolysis with LiOH (5.0 equiv, 3:1:1 THF–CH_3OH–H_2O, 25 °C, 3 h) led to **24** (58%) and additional competitive alcohol desilylation (38% **22**).

A second approach to *N*-methyl-*erythro*-β-hydroxy-L-4-iodophenylalanine was developed based on the Sharpless asymmetric

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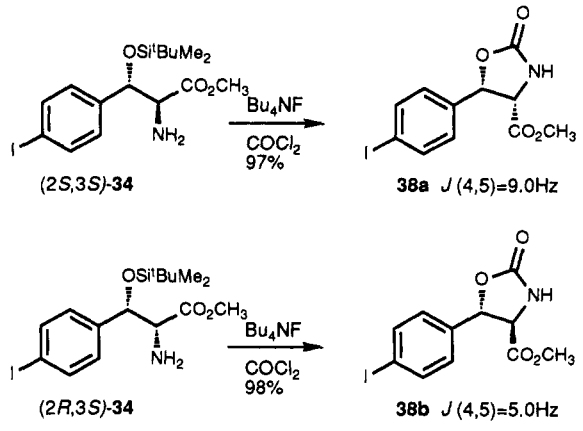
(72) For **25**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, 2H, *J* = 8.3 Hz, Ar C3- and C5-H), 6.96 (d, 2H, *J* = 8.3 Hz, Ar C2- and C6-H), 4.89 (br s, 1H, NH), 4.43 (dd, 1H, *J* = 3.1, 12.3 Hz, C1-C*H*H), 4.03 (dd, 1H, *J* = 5.6, 12.3 Hz, C1-CH*H*), 3.70 (d, 1H, *J* = 1.2 Hz, C3-H), 3.16 (ddd, 1H, *J* = 1.2, 3.6, 5.6 Hz, C2-H), 2.77 (d, 1H, *J* = 6.4 Hz, NCH_3). For **26**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.65 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.07 (d, 2H, *J* = 8.4 Hz, Ar C2-H and C6-H), 5.00 (d, 1H, *J* = 3.6 Hz, C*H*OH), 4.01 (m, 2H, C5-H), 3.55 (dt, 1H, *J* = 3.6, 8.4 Hz, C4-H), 2.53 (s, 3H, NCH_3). For **27**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.65 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.07 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 5.02 (d, 1H, *J* = 4.6 Hz, C5-H), 4.05 (m, 2H, CH_2OH), 3.59 (dt, 1H, *J* = 4.6, 11.8 Hz, C4-H), 2.74 (s, 3H, NCH_3). For **28**: ^1H NMR (CD_3OD, 250 MHz) δ 7.62 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.06 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 4.75 (m, 1H, partially obscured by H_2O, C3-H), 3.54 (d, 2H, partially obscured by CH_3OH, C1-H_2), 2.68 (m, 1H, C2-H), 2.33 (s, 3H, NCH_3).

dihydroxylation reaction (Scheme 3). Treatment of methyl (*E*)-4-iodocinnamate (**17**)[63] with the AD-mix α reagent[60] (1.4 g/mmol, 1.0 equiv of $CH_3SO_2NH_2$, 1:1 *t*-BuOH–H_2O, 25 °C, 20 h) provided methyl (2*R*,3*S*)-2,3-dihydroxy-3-(4-iodophenyl)propionate (**29**, 90%, ≥95% ee). Again, the crystallinity of this intermediate proved exceptional, and simple purification of crude **29** by direct recrystallization from EtOAc–hexane (1:1) provided the diol in high chemical yield (90%) and of enriched enantiomeric purity (>99% ee). The enantiomeric purity of **29** was determined by capillary GLC analysis[59] (CDX-B cyclodextrin, 30 m × 0.32 mm, 175 °C) alongside racemic **29**. Reaction of **29** with 1.0 equiv of 4-nitrobenzenesulfonyl chloride (2.0 equiv of Et_3N, CH_2Cl_2, 0–4 °C, 24 h) as described by Fleming and Sharpless[56] selectively provided α-hydroxy sulfonate **30** (80–85%) resulting from reaction of the more acidic alcohol. Only traces of starting material (2–3%) and the elimination product **31** (3–7%) derived from additional C3 alcohol sulfonylation and elimination were detected, and alternative efforts to conduct this sulfonylation with pyridine versus Et_3N as base (1.0 equiv, 4 °C, 24 h, 36–41% **30** and 45–50% **29**) were less successful. Subsequent NaN_3 displacement of the sulfonate[56] (1.2 equiv of NaN_3, DMF, 55 °C, 12 h, 91%) provided **32** (≥17:1 anti:syn) in a reaction in which the crude product was contaminated with less than 2% of the corresponding epoxide. Attempts to conduct this reaction under similar conditions using a larger excess of NaN_3 (6.0 equiv, 55 °C, 10 h, 46%) resulted in significant scrambling of the C2 stereochemistry and provided a 2:1 mixture of anti:syn **32**. Although the anti and syn diastereomers (≥17:1) were not separable at this stage, they proved readily separable after protection of the C3 hydroxy group as its *tert*-butyldimethylsilyl ether **33** (1.5 equiv of *t*-$BuMe_2SiOTf$, 2.0 equiv of Et_3N, CH_2Cl_2, 5 h, 89%).[76,77] Subsequent reduction of azide **33** to the corresponding amine **34** (2.0 equiv of Ph_3P, 10 equiv of H_2O, THF, 45–50 °C, 10 h, 83%, or 2.0 equiv of $SnCl_2$–$2H_2O$, CH_3OH, 25 °C, 2.5 h, 93%) and BOC protection (1.1 equiv of $(BOC)_2O$, 2.0 equiv of K_2CO_3, 1:1 THF–H_2O, 25 °C, 3 h, 98%) provided **35**. *N*-Methylation of **35** was accomplished upon treatment with KH–CH_3I (1.1 and 5.0 equiv, THF, 25 °C, 10 h, 87%) to provide **36**, and efforts to conduct this *N*-alkylation reaction with NaH (1.0 equiv, 4.0 equiv of CH_3I, 10:1 THF–DMF, 25 °C, 24 h)[78] provided only recovered starting material. As revealed in subsequent efforts to hydrolyze the methyl ester of **36**, this may be attributed to the increased steric hindrance surrounding the amine and carboxylate centers once the amine is both methylated and protected. Although the hydrolysis of **35** could be conducted under conventional reaction conditions (2.0 equiv of LiOH, 3:1:1 THF–CH_3OH–H_2O, 25 °C, 4 h, 91%), classical saponification of **36** with 2 N NaOH (1–3 equiv, 3:1 THF–CH_3OH, 25 °C, 24 h), 2 N KOH (1–3 equiv, 3:1 THF–CH_3OH, 25 °C, 24 h), and LiOH (1–5 equiv, 3:1:1 THF–CH_3OH–H_2O, 25 °C, 12–48 h) provided low yields of **24** (15–28%) together with the product derived from ester hydrolysis and (*tert*-butyldimethylsilyl)oxy elimination (45–60%).[79] Attempts to conduct the ester hydrolysis with anhydrous hydroxide (8.0 equiv of *t*-BuOK, 2.0 equiv of H_2O, Et_2O, 25 °C, 12 h), superoxide (2.0 equiv of KO_2, 2.0 equiv of 18-crown-6, benzene, reflux 4 h), or lithium hydroperoxide (1–5 equiv of LiOOH, 3:1:1 THF–CH_3OH–H_2O, 25 °C, 12–60 h) proved even less successful. Alternative approaches to the hydrolysis of **36** including the use of $(Bu_3Sn)_2O$ under neutral conditions (2.0 equiv, benzene, reflux, 24–48 h, 10–15% **24** and >50% **36**), LiI (2.0 equiv, pyridine, reflux, 12 h), LiCl (2–10 equiv, DMF, 90 °C, 3 days), EtSNa (2.0 equiv, DMF, 90 °C, 12 h), and TMSI (2.0 equiv, CCl_4, 50 °C, 6 h, 19% **24** and 64% **37**) also failed to improve on the initial results. Consequently, the conversion of **36** to **24** was accomplished by first selective deprotection of the *N*-BOC group (3.25 N HCl–EtOAc, 0 °C, 20 min, 93%) to provide **37**, hydrolysis of **37** under standard conditions (2.2 equiv of LiOH, 3:1:1 THF–CH_3OH–H_2O, 25 °C, 3 h), and subsequent reprotection of the amine (1.1 equiv of $(BOC)_2O$, 1:1 THF–H_2O, 25 °C, 6 h, 85% for two steps).

Scheme 4



Confirmation of the relative stereochemistry was derived upon conversion of (2*S*,3*S*)-**34** and (2*R*,3*S*)-**34** to the corresponding cyclic carbamates **38a** and **38b**, respectively, and observation of the diagnostic C4-H/C5-H ^{1}H NMR coupling constants (Scheme 4). It has been shown in studies of the 2-oxazolidinone derivatives of 2-amino-3-hydroxy carboxylic acids that the vicinal coupling constant ($J_{4,5}$) for the erythro (cis) isomer is 9.6 ± 0.6 Hz and that of the threo (trans) isomer is 5.0 ± 1.0 Hz.[80] The observed coupling constants for **38a** (9.0 Hz) and **38b** (5.0 Hz) were in excellent agreement with expectations and with those reported by Rich and Dufour.[81]

Synthesis of *N*-Methyl-13(*S*)-hydroxycycloisodityrosine. Key to the total synthesis of **1** and **2** was the manner in which the 14-membered ring was closed and the stage at which it was assembled. Moreover, recent studies have suggested that simple derivatives of *N*-methyl-13(*S*)-hydroxycycloisodityrosine itself may prove important to examine.[21-24] Consequently, we elected to adopt an approach in which the 14-membered cycloisodityrosine subunit **15** was first prepared and subsequently incorporated into the 18-membered ring of **1** and **2**. Coupling of the *N*-methyl-*erythro*-β-hydroxy-L-4-iodophenylalanine derivative **24** with *N*,*O*^{4}-dimethyl-L-DOPA methyl ester[23] provided **40** and set the stage for study of the key Ullmann macrocyclization reaction (Scheme 5). A number of methods for the direct coupling of **24** and *N*,*O*^{4}-dimethyl-L-DOPA methyl ester were investigated. The use of EDCI–HOBt provided low yields of the desired amide **40**, recovered starting material, and *tert*-butyldimethylsilyl deprotection byproducts including **41**. Additional reagents typically employed for the coupling of *N*-methylamines including BOPCl–

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(77) Efforts to conduct this *O*-silylation under alternative reaction conditions (1.2 equiv *t*-$BuMe_2SiCl$, 1.2 equiv of imidazole, DMF, 55 °C, 10 h, 40–46%, or 1.2 equiv of *t*-$BuMe_2SiCl$, 1.5 equiv of Et_3N, 0.1 equiv of DMAP, CH_2Cl_2, 40–45 °C, 24 h, 70–75%) were not as successful.
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(79) For 2-[*N*-[(*tert*-butyloxy)carbonyl]-*N*-methylamino]-3-(4-iodophenyl)propenoic acid: white powder, mp 143–144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, 2H, J = 8.5 Hz, Ar C3- and C5-H), 7.35 (s, 1H, C3-H), 7.27 (d, 2H, J = 8.5 Hz, Ar C2- and C6-H), 2.94 (s, 3H, NCH_3), 1.36 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 154.7, 138.2, 137.4, 134.7, 132.2, 131.5, 96.8, 81.1, 34.5, 28.1; IR (KBr) ν_{max} 3448, 2976, 2927, 1718, 1637, 1582, 1483, 1397, 1368, 1257, 1154, 1062, 1005, 862, 778 cm^{-1}; FABHRMS (NBA–NaI) *m*/*e* 426.0170 (M^+ + Na, $C_{15}H_{18}INO_4$ requires 426.0178).
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Scheme 5

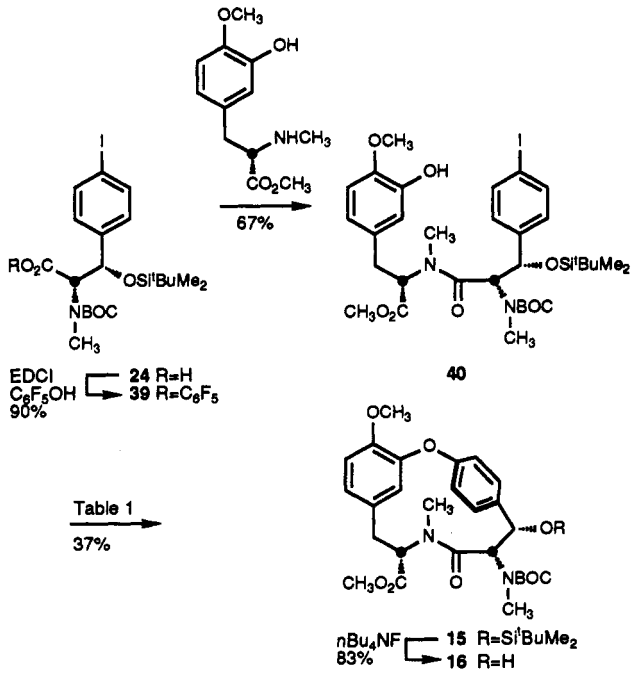


Table 1. Ullmann Closure of **40**

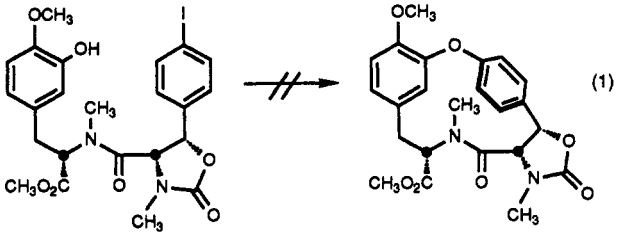
Cu(I) source	conditions	time (h)	% yield of **15**
NaH (1.1),[a] CuBr–SMe_2 (10)	130 °C, 2,6-lutidine	9	37
	130 °C, collidine	9	25–30
NaH (2.0), CuBr–SMe_2 (10)	130 °C, DMF	18, 9	0
	180 °C, DMF	9	0
MeCu	130 °C, collidine	9	13

[a] The number of equivalents is in parentheses.

i-Pr_2NEt provided moderate yields (*ca.* 40%) of the desired amide with the main product being derived from phenol coupling (*ca.* 60%) even in the absence of added base. Similarly, DCC and DCC–DMAP provided mainly the phenol ester. The coupling was most effectively accomplished through conversion of **24** to pentafluorophenyl ester **39** (EDCI, C_6F_5OH, CH_2Cl_2, 8 h, 25 °C, 90%) and its subsequent reaction with the L-DOPA free amine (1:1 THF–DMF, 70 °C, 36 h, 67%) to provide **40**. Although no reaction was observed at room temperature in THF, THF–DMF, and DMF even after prolonged reaction times, simply warming a THF–DMF (1:1) mixture at 70 °C for 24–48 h provided the desired amide **40** in 67% yield.

In preceding studies of such Ullmann macrocyclization reactions we have shown that closure with C^1–O^2 bond formation is uniquely successful while closure with O^2–C^3 bond formation is not observed due to the decelerating effect of the aryl iodide *o*-alkoxy group necessarily present with the latter approach.[29,32-34] Additional studies have illustrated that the degree of racemization and the chemical conversions may be influenced substantially by the choice of thermal reaction conditions. At least three different sets of conditions may be employed which are sufficiently nonbasic as to permit effective Ullmann macrocyclization without significant amino acid racemization.[32,34,36,37] Each of these sets of conditions was examined with the highly functionalized and more sensitive substrate **40**. While we were anticipating that β-elimination of the silyl ether would preclude successful cyclization under the thermal, mildly basic conditions of the Ullmann reaction conducted in collidine or 2,6-lutidine, we were pleasantly surprised with the quality and yield of the experimentally observed conversion, Table 1. Cyclization of cuprous phenoxide salt of **40** generated *in situ* (1.1 equiv of NaH, 10 equiv of CuBr–SMe_2) under moderately dilute reaction conditions (0.004 M) in anhydrous 2,6-lutidine was effected at 130 °C (bath temperature, 9 h) to provide **15** in yields (35–37%) competitive with those observed in Ullmann closures to provide the less functionalized cycloisodityrosine derivative **14**. Key to the successful cyclization were the use of rigorously dried 2,6-lutidine, the use of purified CuBr–SMe_2 complex, and careful degassing of the reaction solvent immediately prior to the reaction. Because of the dilute reaction conditions, the former and latter precautions are thought to be most critical. 2,6-Lutidine proved more suitable as a solvent than collidine (30% **15**) principally because of the enhanced solubility of the initial cuprous phenoxide. Alternative attempts to promote the closure in DMF[34] (130 °C, 9–18 h, or 180 °C, 9 h, 0.004 M) were not successful, and the use of MeCu[23,36] to stoichiometrically generate the cuprous phenoxide did not prove as successful although this was not investigated in detail. The successful Ullmann closure of **40** to provide **15** was surprising especially in light of the ease with which (*tert*-butyldimethylsilyl)-oxy elimination was observed in the attempted conversions of **36** to **24**. Nonetheless, the observations attest to the low level of α-deprotonation observed under the reaction conditions and served to independently verify the unusual and unexpected stability of such substrates and products to the thermal, mildly basic Ullmann reaction conditions. *O*-Silyl deprotection of **15** (3.0 equiv of Bu_4-NF, THF, 0 °C, 30 min, 83%) provided the 13(*S*)-hydroxycycloisodityrosine derivative **16**.

In the course of these studies, we also examined the potential, but unsuccessful, Ullmann closure of cyclic carbamate **41**[82] (1.1 equiv of NaH, 10 equiv of CuBr–SMe_2, 0.004 M collidine, 130 °C, 9 h, 0%) under the conditions devised for **40** (eq 1).



The generation of the 14-membered ring in the cyclization of **40** to **15** was confirmed upon observation of the diagnostic, strongly shielded aryl C19-H (d, J = 1.7 Hz) at 4.77 ppm and unambiguously established upon its incorporation into **1** and **2**. Like **14**,[23] **15** and **16** adopt rigid solution conformations possessing a trans N^{10}–C^{11} amide. Consistent with expectations based on conformational analysis,[83-85] the global and an additional two out of the three low-lying conformations (≤2.5 kcal/mol) of **16** possess a trans N^{10}–C^{11} amide. The conformational search of **16** revealed a single, low-energy conformation that was 1.6 kcal/mol lower in energy than the next located conformation, which was found to possess a cis amide. The calculated coupling constants for the C9 and C12 hydrogens in the lowest energy conformation of **16** are 3.5, 12.7 (dd), and 8.8 Hz (d), respectively,

(82) For **41**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.99 (d, 1H, J = 8.4 Hz, ArH), 7.42 (m, 2H, ArH), 7.19 and 7.11 (two d, 1H, J = 8.4 Hz, ArH), 6.70–6.90 (m, 3H, ArH), 5.78 (br s, 1H, ArOH), 5.07 and 4.89 (two d, 1H, J = 9.0 Hz, C*H*O), 3.90 (s, 3H, $ArOCH_3$), 3.83 (m, 1H, C*H*CH_2), 3.82 (s, 3H, CO_2CH_3), 3.35 (m, 1H, C*H*NCH_3), 3.17 (s, 3H, NCH_3), 3.06 (br s, 2H, CH_2Ar), 3.00 (s, 3H, NCH_3).

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(85) Global and close low-lying minima (≤12 kcal/mol) were located in conformational searches with use-directed Monte Carlo sampling and subsequent minimization of conformations generated by random variations (0–180°) in 8 of the 10 available torsional angles[84] excluding those originating in the phenyl rings (MacroModel,[83] version 3.5a, OPLSA force field, MCMM = 1000, MCSS = 2, 12 kcal/mol window). The global minimum for **16** was located 117 times.

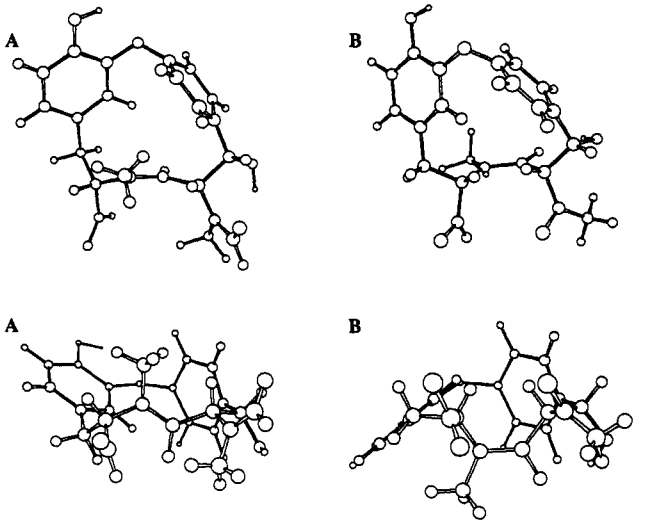
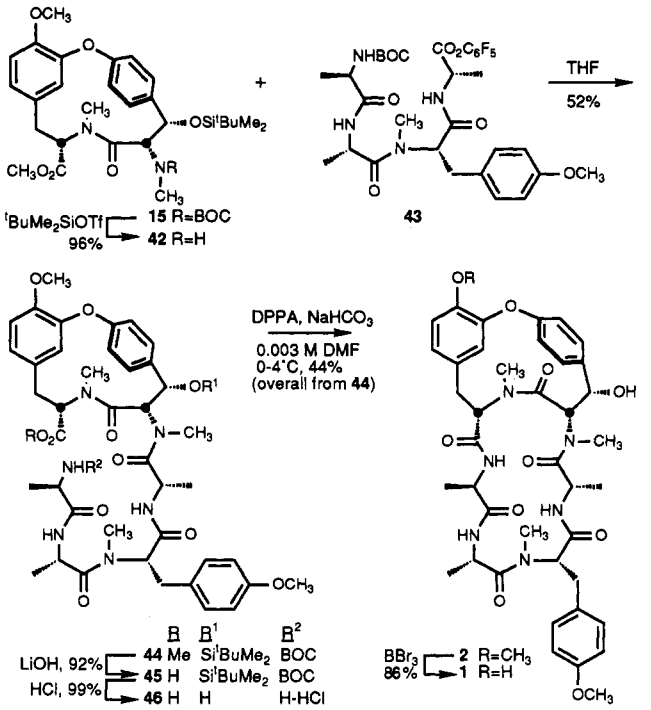


Figure 2. (A) OPLSA low-energy conformation of **16**. (B) 14-Membered-ring conformation taken from X-ray crystal structure of bouvardin (**1**).

and match the experimentally measured values of 2.4, 12.0 (dd), and 9.3 Hz (d). In contrast, the calculated C9-H and C12-H coupling constants for the cis amide conformation (relative E = 1.6 kcal/mol) were found to be 4.4, 11.3 (dd), and 1.3 Hz (d), respectively, and those of the next lowest trans amide conformation (relative E = 1.8 kcal/mol) were determined to be 4.1, 11.5 (dd), and 6.0 Hz (d), respectively. Confirmation that **15** and **16** adopt solution conformations which possess a trans amide was derived from the 2D ^{1}H–^{1}H NOESY NMR of **15**. Strong NOE cross peaks were observed for C9-H/N10-Me and C12-H/N10-Me and are uniquely diagnostic of the trans N^{10}–C^{11} amide stereochemistry. Notably, a C9-H/C12-H NOE cross peak was not observed and would be uniquely diagnostic of a cis N^{10}–C^{11} amide stereochemistry.[23] Consequently, **15** and **16** adopt a single, rigid solution conformation possessing a trans N^{10}–C^{11} *N*-methylamide but upon incorporation into the bicyclic natural products adopt a conformation possessing the inherently disfavored cis N^{29}–C^{30} *N*-methylamide. Comparisons of the lowest energy conformation of **16** possessing the trans amide with the conformation of the *N*-methylcycloisodityrosine subunit of bouvardin (**1**) taken from the X-ray crystal structure[1] may be found in Figure 2.

Completion of the Total Synthesis of *O*-Methylbouvardin (2) and Bouvardin (1). Deprotection of the *N*-BOC group to provide **42** without competitive *O*-desilylation was accomplished through treatment of **15** with *t*-BuMe$_2$SiOTf (3.0 equiv, 0.1 M CH_2Cl_2, 0 °C, 1 h, 96–98%), Scheme 6. Coupling of **42** with BOCNH-D-Ala-Ala-NMe-Tyr(OMe)-Ala-OC$_6$F$_5$ (**43**,[25,35] 0.3 M THF, 25 °C, 72 h, 52%) provided **44**. The use of pentafluorophenyl active ester **43** for this coupling proved more successful than attempts to directly couple the corresponding carboxylic acid activated with carbodiimide reagents including EDCI–HCl. The latter reagent led to coupling and competitive *O*-desilylation providing a mixture of **44** and the corresponding free alcohol. Sequential hydrolysis of methyl ester **44** to provide **45** (3.0 equiv of LiOH, 0.3 M 3:1:1 THF–CH_3OH–H_2O, 25 °C, 3.5 h, 92%), acid-catalyzed *N*-BOC and *O*-silyl deprotection (2 N HCl–EtOAc, 25 °C, 50 min, *ca.* 100%), and subsequent macrocyclization of **46** upon treatment with diphenyl phosphorazidate (2.0 equiv of DPPA, 10.0 equiv of $NaHCO_3$, 0.003 M DMF, 0 °C, 72 h, 44% overall) provided *O*-methylbouvardin (**2**, mp 244–246 °C, CH_3OH, colorless plates), $[\alpha]^{25}_D$ –191 (*c* 0.05, $CHCl_3$), identical in all compared respects with the properties (^{1}H NMR, IR, MS, mp, $[\alpha]_D$) reported[1] for authentic material, mp 244–247 °C (CH_3OH, colorless plates), $[\alpha]^{25}_D$ –191 (*c* 1.0, $CHCl_3$). Notably, the C^2–N^3 amide macrocyclization reaction with closure of the 18-membered ring was conducted strategically at the one available secondary amide site that possesses a D-amino acid amine

Scheme 6



terminus[86,87] under the improved DPPA reaction conditions recently disclosed.[88]

Selective C24 methyl ether deprotection of **2** (2.5 equiv of BBr_3, CH_2Cl_2, –78 °C to 0 °C, 1 h, 86%) provided bouvardin (**1**) in excellent yield despite the potential sensitivity of the substrate to the reagent. Presumably, the adjacent ortho C23 oxygen substituent directs the regioselective demethylation reaction through proximal bidentate complexation and activation of C24 methyl ether cleavage.[89] Synthetic (mp 253–255 °C, CH_3OH–$CHCl_3$, colorless needles; $[\alpha]^{25}_D$ –181 (*c* 0.02, $CHCl_3$)) and natural bouvardin[1,90] (mp 254–255 °C, CH_3OH–$CHCl_3$, colorless needles; $[\alpha]^{25}_D$ –181 (*c* 1.0, $CHCl_3$)) proved identical in side by side comparisons (^{1}H NMR, IR, MS, mp, mixed mp 253.5–255 °C, $[\alpha]_D$; TLC: 5% CH_3OH–$CHCl_3$ R_f 0.42, 7% CH_3OH–$CHCl_3$ R_f 0.50, 10% CH_3OH–$CHCl_3$ R_f 0.73).

***N*^{29}-Desmethyl-*O*-methylbouvardin (51).** In preceding studies of the X-ray structure and solution conformation of natural agents including bouvardin (**1**),[1] deoxybouvardin (**3**), and RA-VII (**8**) as well as *N*^{29}-desmethyl-RA-VII,[23] a single predominant solution conformation was observed by ^{1}H NMR which possesses the characteristic N^{29}–C^{30} cis amide and corresponds closely to the X-ray structure found for **1**.[1] This proved to be observed even with *N*^{29}-desmethyl-RA-VII, which was also shown to possess an inherently less stable cis secondary N^{29}–C^{30} amide. In contrast to the *N*-methyl or N–H cycloisodityrosine derivatives including **14–16** which adopt a trans amide solution conformation,[23] these studies clearly demonstrated that the bicyclic natural products

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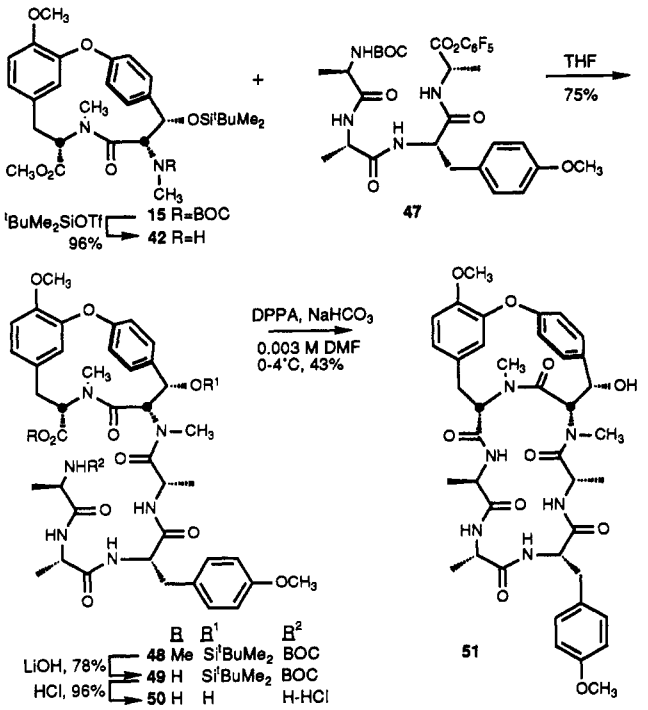
(90) We thank Professors Hoffmann and Bates for a generous comparison sample of natural bouvardin.

Scheme 7



adopt a conformation possessing the inherently disfavored N^{29}–C^{30} cis amide. Nonetheless, one additional minor conformation may be detected by ^1H NMR for **1** and **2** (10–15%) in nonpolar solvents including $CDCl_3$. In efforts to distinguish the site of this conformational equilibrium, which presumably is associated with one of the remaining two *N*-methylamides, N^9-desmethyl-*O*-methylbouvardin (**51**) was prepared for comparative evaluation.

Extensive conformational searches[23,27] conducted on deoxybouvardin (**3**) suggested that minor conformations were not expected to be derived from a N^{29}–C^{30} trans *N*-methylamide and that, of the two remaining *N*-methylamides, it was the N^9–C^8 amide that appeared most likely to adopt an accessible cis amide conformation. Careful ^1H NMR studies of the agents including diagnostic differences in the readily assignable *N*-methyl chemical shifts and NOEs observed in the 2D ^1H–^1H NMR with the major and minor conformation supported this expectation.[91] In efforts to confirm that this is the site and origin of the detectable minor amide conformation and to unambiguously establish the stereochemistry of the major and minor amides, we elected to prepare and examine N^9-desmethyl-*O*-methylbouvardin (**51**) since it would assuredly adopt only N^9–C^8 trans amide conformations.

Coupling of **42** with BOCNH-D-Ala-Ala-Tyr(OMe)-Ala-OC_6F_5 (**47**,[35] 0.3 M THF, 25 °C, 48 h, 75%) provided **48** (Scheme 7). Sequential methyl ester hydrolysis (3.0 equiv of LiOH, THF–CH_3OH–H_2O, 0–25 °C, 4 h, 78%), *N*-BOC and *O*-silyl deprotection (2 N HCl–EtOAc, 25 °C, 50 min, 96%), and macrocyclization of **50** (4.0 equiv of DPPA, 10 equiv of $NaHCO_3$, 0.003 M DMF, 0 °C, 72 h, 43% overall) provided **51**.

The ^1H NMR spectrum of **51** clearly revealed a single solution conformation for the agent and lacked the diagnostic signals observed for the minor conformations of **1–3**. The minor conformation of **1** or **2** in $CDCl_3$ is clearly detected with duplicate ^1H NMR signals (*ca.* 1:10 ratio) in a number of regions. For **1**, the $tyr^{3\delta}$ (δ 7.08 and 7.05), tyr^3-OCH_3 (δ 3.78 and 3.76), tyr^3-NCH_3 (δ 2.89 and 2.84), tyr^6-NCH_3 (δ 2.71 and 2.70), and especially the ala^{β}-H (δ 1.28 and 1.24) exhibit duplicate signals derived from a less populated cis N^9–C^8 amide conformation. This is especially apparent in the ala^{β}-H region of the ^1H NMR spectra of **1** versus **51** which is illustrated in an expanded form in Figure 3. Since **51** incorporates a secondary N^9–C^8 amide capable of adopting only a trans amide stereochemistry and no longer adopts the minor conformation of **1** and **2**, the minor conformation of **1–3** can now be unambiguously localized to the N^9–C^8 amide and assigned a cis N^9–C^8 *N*-methylamide.

(91) Boger, D. L.; Patane, M. A. Unpublished observations.

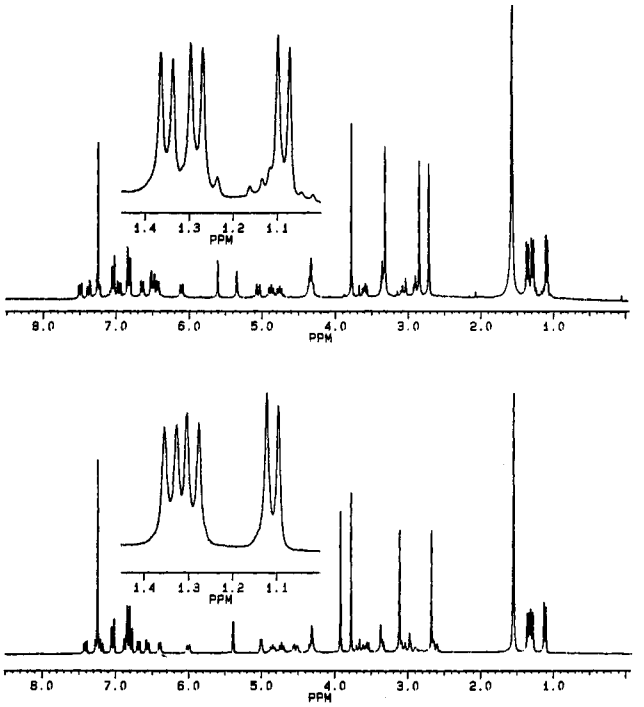


Figure 3. Comparison ^1H NMR spectra of bouvardin (**1**, top) and N^9-desmethyl-*O*-methylbouvardin (**51**, bottom).

Table 2. *In Vitro* Cytotoxic Activity

agent	IC_{50} (L1210, μg/mL)
1, bouvardin	0.005
2, *O*-methylbouvardin	0.005
3, deoxybouvardin	0.002
8, RA-VII	0.002
51, N^9-desmethyl-*O*-methylbouvardin	0.0007

***In Vitro* Cytotoxic Activity.** The comparative *in vitro* cytotoxic activity of **1–3**, **8**, and **51** is detailed in Table 2. Bouvardin (**1**) and *O*-methylbouvardin (**2**) proved indistinguishable in our assays and slightly less potent (2–3×) than deoxybouvardin (**3**) and RA-VII (**8**), which are structurally identical to **1** and **2** but which lack the C17 hydroxy group. Interestingly, N^9-desmethyl-*O*-methylbouvardin (**51**) proved to be perceptibly more potent than **1** and **2** and comparable in potency to deoxybouvardin and RA-VII. Thus, the restriction of **1** and **2** to a single detectable conformation that corresponds to their major solution and X-ray conformation (*i.e.*, **51**) resulted in enhanced biological potency. Similar to prior observations, the *N*-methyl-13(*S*)-hydroxycycloisodityrosine derivatives **15** and **16** exhibited cytotoxic activity comparable to that of **14** albeit being slightly more potent.[24]

Experimental Section

(*E*)-3-(4-Iodophenyl)prop-2-en-1-ol (18). A solution of methyl (*E*)-4-iodocinnamate[63] (**17**, 8.24 g, 27.2 mmol) in distilled CH_2Cl_2 (100 mL) was treated with *i*-Bu_2AlH (82 mL, 1.0 M hexane solution, 82 mmol, 3.0 equiv) in three portions at −78 °C, and the mixture was stirred at −78 °C for 20 min. The reaction mixture was quenched by the addition of CH_3OH (25 mL), warmed to 25 °C, diluted with saturated aqueous sodium potassium tartrate (100 mL), and partitioned. The aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic layers were washed with saturated aqueous sodium potassium tartrate (150 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chroma-

tography (SiO_2, 5 × 20 cm, 20–40% EtOAc–hexane) afforded **18** (7.07 g, 7.43 g theoretical, 95%) as a white crystalline solid: mp 108–110 °C (1:2 EtOAc–hexane, white needles); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.63 (d, 2H, J = 8.4 Hz, Ar C3- and C5-H), 7.10 (d, 2H, J = 8.4 Hz, Ar C2- and C6-H), 6.53 (d, 1H, J = 15.8 Hz, C3-H), 6.36 (dt, 1H, J = 5.4, 15.8 Hz, C2-H), 4.30 (dd, 2H, J = 1.3, 5.4 Hz, C1-H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 137.7, 136.2, 129.9, 129.4, 128.2, 92.9, 63.5; IR (neat) ν_{max} 3310, 2926, 2847, 1651, 1478, 1395, 1084, 1060, 1006, 971, 848, 799, 774 cm^{-1}.

Anal. Calcd for C_9H_9IO: C, 41.56; H, 3.49. Found: C, 41.75; H, 3.34.

(2*S*,3*S*)-2-(Hydroxymethyl)-3-(4-iodophenyl)oxirane (19). A solution of **18** (7.49 g, 26.0 mmol) in anhydrous CH_2Cl_2 (250 mL) containing activated powdered 4-Å molecular sieves (25 g, 1 g/mmol) was treated sequentially with (+)-diisopropyl L-tartrate (457 mg, 1.9 mmol, 0.41 mL, 0.075 equiv) and Ti(O-*i*-Pr)$_4$ (314 mg, 1.30 mmol, 0.33 mL, 0.05 equiv) at –20 °C (30 min). After this reagent aging was complete, *t*-BuOOH (3.5 M CH_2Cl_2 solution, 52.0 mmol, 14.9 mL, 2.0 equiv) was added dropwise (15 min). After 4 h, the mixture was warmed from –20 to 0 °C (20 min), quenched by the addition of H_2O (25 mL), and allowed to warm to 25 °C (45 min). Aqueous NaOH (25%) (20 mL) was added and the mixture stirred at 25 °C (45 min). Following the addition of CH_3OH (10 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (SiO_2, 5.0 × 30.0 cm, 20–50% EtOAc–hexane) afforded **19** (6.43 g, 7.18 g theoretical, 90%) as a white solid. Recrystallization (40% EtOAc–hexane) provided 5.98 g (84%) of **19** (>99% ee): mp 80–82 °C (40% EtOAc–hexane, white powder); $[\alpha]^{25}_D$ –37 (*c* 0.5, CH_3OH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.66 (d, 2H, J = 8.4 Hz, Ar C3- and C5-H), 7.01 (d, 2H, J = 8.4 Hz, Ar C2- and C6-H), 4.02 (ddd, 1H, J = 2.0, 3.6, 12.9 Hz, C1-H), 3.87 (d, 1H, J = 5.1 Hz, C3-H), 3.79 (ddd, 1H, J = 3.6, 7.6, 12.9 Hz, C1-H), 3.14 (m, 1H, C2-H), 1.74 (t, 1H, J = 6.2 Hz, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.6, 136.4, 127.5, 93.7, 62.4, 60.9, 55.0; IR (neat) ν_{max} 3315, 2922, 2851, 1484, 1451, 1395, 1262, 1195, 1072, 1027, 1009, 878, 820 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 276.9720 (M$^+$ + H, $C_9H_9IO_2$ requires 276.9726).

Anal. Calcd for $C_9H_9IO_2$: C, 39.11; H, 3.64. Found: C, 39.45; H, 3.49.

A solution of **19** (5.0 mg, 0.0164 mmol), DMAP (2.0 mg, 0.0164 mmol, 1.0 equiv), and Et_3N (10 μL, 7.3 mg, 0.717 mmol, 4.3 equiv) in CH_2Cl_2 (50 μL) was treated with (*R*)-MTPACl (13 μL), and the solution was stirred for 10 min (25 °C). The reaction mixture was quenched by the addition of Et_3N (0.3 mL) and concentrated *in vacuo*. Flash chromatography (SiO_2, 1.0 × 5.0 cm, 10–25% EtOAc–hexane) afforded the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate of **19** (8.1 mg, 8.2 mg theoretical, 99%), which proved to be >99% optically pure: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, 2H, J = 8.4 Hz, Ar C3- and C5-H), 7.51 (br d, 2H, J = 9.2 Hz, ArH), 7.39 (m, 3H, ArH), 6.95 (d, 2H, J = 8.4 Hz, Ar C2- and C6-H), 4.66 (dd, 1H, J = 5.6, 19.5 Hz, C1-H), 4.36 (dd, 1H, J = 8.6, 19.5 Hz, C1′-H), 3.70 (d, 1H, J = 3.0 Hz, C3-H), 3.56 (s, 3H, OCH_3), 3.19 (ddd, 1H, J = 3.0, 5.6, 8.6 Hz, C2-H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ 10.85.

(2*R*,3*S*)-3-(4-Iodophenyl)oxirane-2-carboxylic Acid (20). A solution of **19** (250 mg, 0.90 mmol) in anhydrous DMF (4.0 mL) was treated with PDC[64] (1.10 g, 2.87 mmol, 3.5 equiv) at 25 °C. After 5 h, additional PDC (348 mg, 0.90 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 25 °C for an additional 5 h before the addition of H_2O (50 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (4 × 50 mL), and the combined organic layers were washed with H_2O (3 × 75 mL) and saturated aqueous NaCl (3 × 75 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was dissolved in saturated aqueous $NaHCO_3$ (10 mL) and EtOAc (10 mL). The organic phase was further extracted with saturated aqueous $NaHCO_3$ (3 × 10 mL), and the combined aqueous layers were acidified to pH 4 with the addition of 5% aqueous HCl and extracted with EtOAc (4 × 20 mL). The combined organic phase was washed with H_2O (3 × 20 mL) and saturated aqueous NaCl (3 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford **20** (212 mg, 262 mg theoretical, 81%) as a white solid: mp 263–265 °C (EtOAc, white powder); $[\alpha]^{25}_D$ –6.9 (*c* 0.30, CH_3OH); ^{1}H NMR (CD_3OD, 250 MHz) δ 7.85 (d, 2H, J = 8.5 Hz, Ar C3- and C5-H), 7.11 (d, 2H, J = 8.5 Hz, Ar C2- and C6-H), 4.01 (br s, 1H, C3-H), 3.49 (br s, 1H, C2-H); ^{13}C NMR (acetone-d_6, 62.5 MHz) δ 170.6, 137.4, 136.6, 128.0, 93.6, 80.1, 56.4; IR (neat) ν_{max} 3360, 2964, 2922, 2841, 1677, 1585, 1482, 1431, 1392, 1294, 1180, 1103, 1008, 928, 849, 805, 754 cm^{-1}; FABMS (NBA) *m/e* 289 (M$^+$ + H, $C_9H_7IO_3$ requires 289).

Anal. Calcd for $C_9H_7IO_3$: C, 37.27; H, 2.43. Found: C, 37.07; H, 2.20.

(2*S*,3*S*)-3-Hydroxy-3-(4-iodophenyl)-2-(methylamino)propionic Acid (21). A solution of **20** (516 mg, 1.78 mmol) in 40% aqueous CH_3NH_2 (12 mL) was warmed at 105 °C (bath) for 4 h, cooled, concentrated *in vacuo*, and thoroughly dried. The resulting residue was triturated with anhydrous Et_2O (3 × 15 mL), dried under high vacuum, treated with 3 N aqueous HCl at 25 °C (30 min), and concentrated *in vacuo*. After thorough drying, the residue was dissolved in EtOH–propylene oxide (20 mL:15 mL) and warmed at reflux (15–20 min), and the white precipitate was filtered, affording **21** (306 mg, 570 mg theoretical, 54%) as white crystals: mp 320–325 °C (H_2O, white needles); $[\alpha]^{25}_D$ –38 (*c* 0.8, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 7.65 (br s, 2H, Ar C3- and C5-H), 6.99 (br s, 2H, Ar C2- and C6-H), 4.80 (br s, 1H, C3-H), 3.85 (br s, 1H, C2-H), 2.38 (br s, 3H, NCH_3); ^{13}C NMR (D_2O, 100 MHz) δ 169.6, 140.5, 140.1, 130.7, 96.9, 74.3, 61.7, 28.1; IR (KBr) ν_{max} 3448, 2921, 1643, 1391, 1109, 533 cm^{-1}; FABHRMS (NBA) *m/e* 321.9956 (M$^+$ + H, $C_{10}H_{12}INO_3$ requires 321.9940).

Anal. Calcd for $C_{10}H_{12}INO_3$: C, 33.59; H, 3.66; N, 3.92. Found: C, 33.52; H, 4.06; N, 3.51.

(2*S*,3*S*)-2-[*N*-[(*tert*-Butyloxy)carbonyl]-*N*-methylamino]-3-hydroxy-3-(4-iodophenyl)propionic Acid (22). A solution of **21** (356 mg, 1.11 mmol) in THF–H_2O (1:1, 4 mL) was treated with $(BOC)_2O$ (244 mg, 0.26 mL, 1.11 mmol, 1.0 equiv) and K_2CO_3 (470 mg, 3.33 mmol, 3.0 equiv) at 25 °C under Ar and the mixture stirred for 4 h. The reaction mixture was quenched by the addition of saturated aqueous citric acid (pH 4) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and saturated aqueous NaCl (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford **22** (458 mg, 467 mg theoretical, 98%) as a colorless oil: $[\alpha]^{25}_D$ –45 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.67 (d, 2H, J = 8.3 Hz, Ar C3- and C5-H), 7.08 (d, 2H, J = 8.3 Hz, Ar C2- and C6-H), 5.32 (br d, 1H, J = 9.1 Hz, C3-H), 4.98 (d, 1H, J = 6.7 Hz, OH), 3.90 (d, 1H, J = 9.1 Hz, C2-H), 2.54 (s, 3H, NCH_3), 1.40 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 177.7, 171.0, 138.6, 136.0, 130.0, 93.2, 85.2, 73.5, 71.0, 30.4, 29.1; IR (neat) ν_{max} 3341, 2971, 1694, 1483, 1385, 1365, 1248, 1164, 1125, 875 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}INO_5$: C, 42.77; H, 4.79; N, 3.33. Found: C, 43.08; H, 4.45; N, 3.23.

(2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[*N*-[(*tert*-butyloxy)carbonyl]-*N*-methylamino]-3-(4-iodophenyl)propionic Acid (24). A solution of **22** (272 mg, 0.646 mmol) in anhydrous DMF (1.0 mL) was treated with imidazole (89 mg, 1.29 mmol, 2.0 equiv) and *t*-BuMe$_2$SiCl (200 mg, 1.29 mmol, 2.0 equiv), and the resulting mixture was stirred at 25 °C (48 h). The reaction mixture was quenched with the addition of ice–water (15 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and saturated aqueous NaCl (3 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. A short SiO_2 plug (3.0 × 5.0 cm, 30% EtOAc–hexane) afforded **23** (395 mg, 420 mg theoretical, 94%), which was used directly in the next reaction. For **23**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.65 (br d, 2H, J = 8.3 Hz, Ar C3- and C5-H), 7.07 (br d, 2H, J = 8.3 Hz, Ar C2- and C6-H), 5.13 (m, 1H, C3-H), 4.30 (m, 1H, C2-H), 2.59 and 2.53 (two s, 3H, NCH_3), 1.44 and 1.29 (two s, 9H, $CO_2C(CH_3)_3$), 0.89 and 0.78 (two s, 18H, $SiC(CH_3)_3$), 0.31 and 0.04 (two s, 12H, $SiCH_3$).

A solution of **23** (395 mg, 0.608 mmol) in THF–CH_3OH–H_2O (3 mL, 2:1:1) was treated with K_2CO_3 (420 mg, 3.04 mmol, 5.0 equiv), and the mixture was stirred at 25 °C (1 h). The reaction mixture was quenched by the addition of saturated aqueous citric acid (pH 4) and extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with H_2O (3 × 30 mL) and saturated aqueous NaCl (3 × 30 mL), dried (Na_2SO_4), and concentrated *in vacuo* affording **24** (316 mg, 325 mg theoretical, 97%; typically 97–100%) as a white solid: mp 138–140 °C (1:4 EtOAc–hexane, white powder); $[\alpha]^{25}_D$ –48 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) mixture of two rotamers δ 7.65 (d, 2H, J = 8.3 Hz, Ar C3- and C5-H), 7.07 (d, 2H, J = 8.3 Hz, Ar C2- and C6-H), 5.30 and 5.04 (two d, 1H, J = 9.5 Hz, C3-H), 4.27 and 4.02 (two d, 1H, J = 9.5 Hz, C2-H), 2.67 and 2.48 (two s, 3H, NCH_3), 1.38 and 1.31 (two s, 9H, $CO_2C(CH_3)_3$), 0.89 and 0.82 (two s, 9H, $SiC(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), –0.24 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9 and 171.7, 156.7 and 154.2, 140.48 and 140.45, 137.3 and 137.1, 128.8 and 128.5, 93.91 and 93.85, 81.7 and 81.0, 72.7 and 72.1, 69.1 and 65.9, 36.1, 28.1 and 27.8, 25.7 and 25.6, 17.9, –4.51 and –4.58, –5.3 and –5.5; IR (neat) ν_{max} 3159, 2955, 2929, 2856, 1692, 1679, 1483, 1444, 1391, 1367, 1304, 1252, 1151, 1092, 1006, 898, 839, 778 cm^{-1}; FABHRMS (NBA) *m/e* 536.1338 (M$^+$ + H, $C_{21}H_{34}INO_5Si$ requires 536.1329).

Anal. Calcd for $C_{21}H_{34}INO_5Si$: C, 47.10; H, 6.40; N, 2.62. Found: C, 47.38; H, 6.71; N, 2.67.

Methyl (2*R*,3*S*)-2,3-Dihydroxy-3-(4-iodophenyl)propionate (29). A stirred mixture of AD-mix-α[60] (21 g, 1.4 g/mmol) and methanesulfonamide (1.43 g, 15.0 mmol, 1.0 equiv) in *t*-BuOH–H_2O (1:1, 150 mL) was treated with methyl (*E*)-4-iodocinnamate[63] (**17**, 4.32 g, 15.0 mmol) at 25 °C, and the resulting reaction mixture was stirred vigorously at 25 °C for 20 h. Sodium sulfite (Na_2SO_3, 22.5 g) was added, and the mixture was stirred at 25 °C for 30 min before EtOAc (100 mL) was added. After separation of the layers, the aqueous phase was further extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with aqueous 2 N KOH (75 mL), H_2O (75 mL), and saturated aqueous NaCl (75 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude, white solid was purified by direct recrystallization from EtOAc–hexane (1:1) to afford **29** (4.33 g, 4.83 g theoretical, 90%, >99% ee[92]) as white needles: mp 145–146 °C (50% EtOAc–hexane, white needles); $[\alpha]^{25}_D$ +9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, *J* = 8.3 Hz, Ar C3- and C5-H), 7.14 (d, 2H, *J* = 8.3 Hz, Ar C2- and C6-H), 4.97 (dd, 1H, *J* = 2.6, 7.2 Hz, C3-H), 4.33 (dd, 1H, *J* = 2.8, 5.2 Hz, C2-H), 3.82 (s, 3H, CO_2CH_3), 3.09 (br s, 2H, two OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 139.7, 137.5, 128.2, 93.7, 74.4, 73.8, 53.0; IR (KBr) ν_{max} 3445, 2958, 1737, 1584, 1482, 1442, 1395, 1225, 1104, 1058, 1000, 933, 785, 733, 659, 600 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 344.9600 (M^+ + Na, $C_{10}H_{11}IO_4$ requires 344.9660).

Anal. Calcd for $C_{10}H_{11}IO_4$: C, 37.26; H, 3.41. Found: C, 36.93; H, 3.70.

Methyl (2*R*,3*S*)-3-Hydroxy-3-(4-iodophenyl)-2-[[(4-nitrophenyl)sulfonyl]oxy]propionate (30). A solution of **29** (1.288 g, 4.0 mmol) in CH_2Cl_2 (20 mL) was treated with 4-nitrobenzenesulfonyl chloride (985 mg, 90% pure, 4.0 mmol, 1.0 equiv) and Et_3N (810 mg, 1.12 mL, 8.0 mmol, 2.0 equiv) at 0 °C under Ar. The resulting reaction mixture was stirred at 4 °C for 24 h. The solvent was removed *in vacuo*, and the residue was dissolved in THF (40 mL), washed with 1 N aqueous HCl (2 × 10 mL), H_2O (10 mL), and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 3 × 15 cm, 20–40% EtOAc–hexane gradient elution) afforded **30** (1.70 g, 2.02 g theoretical, 84%) as a white powder and traces of **31** (127 mg, 6.5%) derived from additional β-alcohol sulfonylation and elimination as well as recovered **29** (31 mg, 2%). For **30**: mp 198–199 °C (40% EtOAc–hexane, white powder); $[\alpha]^{25}_D$ +57 (*c* 0.2, absolute EtOH); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.21 (d, 2H, *J* = 8.8 Hz, Ar C3′- and C5′-H), 7.74 (d, 2H, *J* = 8.8 Hz, Ar C2′- and C6′-H), 7.32 (d, 2H, *J* = 8.2 Hz, Ar C3- and C5-H), 6.96 (d, 2H, *J* = 8.2 Hz, Ar C2- and C6-H), 6.16 (d, 1H, *J* = 5.8 Hz, C2-H), 5.33 (d, 1H, *J* = 2.5 Hz, OH), 5.09 (dd, 1H, *J* = 2.5, 5.8 Hz, C3-H), 3.76 (s, 3H, CO_2CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.0, 150.1, 140.3, 138.9, 136.4, 129.0, 128.3, 124.5, 93.8, 82.7, 71.3, 52.8; IR (KBr) ν_{max} 3534, 2960, 1741, 1532, 1357, 1295, 1183, 1090, 1010, 905, 823, 742, 626 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 529.9380 (M^+ + Na, $C_{16}H_{14}INO_8S$ requires 529.9383).

Anal. Calcd for $C_{16}H_{14}INO_8S$: C, 37.87; H, 2.76; N, 2.76. Found: C, 37.90; H, 2.84; N, 2.78.

For **31**: white powder, mp 196–197 °C (60% EtOAc–hexane, white powder); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29 (d, 2H, *J* = 9.0 Hz, Ar C3′- and C5′-H), 8.07 (d, 2H, *J* = 9.0 Hz, Ar C2′- and C6′-H), 7.67 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.33 (s, 1H, C3-H), 7.31 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 3.78 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4, 142.5, 138.0, 131.7, 130.3, 129.9, 129.6, 128.1, 124.3, 123.9, 97.5, 53.0; IR (KBr) ν_{max} 3107, 1720, 1648, 1529, 1381, 1289, 1197, 1068, 885, 819, 742, 687 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 489.9460 (M^+ + H, $C_{16}H_{12}INO_7S$ requires 489.9458).

Methyl (2*S*,3*S*)-2-Azido-3-hydroxy-3-(4-iodophenyl)propionate (32). A solution of **30** (2.0 g, 3.94 mmol) in anhydrous DMF (15 mL) was treated with NaN_3 (308 mg, 4.73 mmol, 1.2 equiv) at 25 °C under Ar. The resulting reaction mixture was warmed at 55 °C for 12 h before 30 mL of H_2O was added. The aqueous solution was extracted with EtOAc (3 × 30 mL), and the combined EtOAc extracts were washed with H_2O (20 mL) and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 3 × 20 cm, 10–25% EtOAc–hexane gradient elution) afforded **32** (1.25 g, 1.37 g theoretical, 91%) as a colorless oil that solidified as a waxy solid and was determined to be an inseparable 17:1 mixture of C2 epimers by ^1H NMR analysis. Also isolated were traces of the corresponding epoxide[93] (19 mg, 1.6%) and **31** (36 mg, 1.9%). For (2*S*,3*S*)-**32**:[94] ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.10 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 4.93 (dd, 1H, *J* = 4.5, 6.8 Hz, C3-H), 4.08 (d, 1H, *J* = 6.8 Hz, C2-H), 3.77 (s, 3H, CO_2CH_3), 3.10 (d, 1H, *J* = 4.5 Hz, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 138.5, 137.6, 128.5, 94.5, 73.5, 66.6, 53.0; IR (neat) ν_{max} 3443, 3051, 2949, 2909, 2849, 2112, 1732, 1589, 1485, 1285, 1212, 1076, 1006, 917, 795, 750, 665 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 347.9840 (M^+ + H, $C_{10}H_{10}IN_3O_3$ requires 347.9845).

Anal. Calcd for $C_{10}H_{10}IN_3O_3$: C, 34.58; H, 2.88; N, 12.10. Found: C, 34.84; H, 2.64; N, 12.03.

Methyl (2*S*,3*S*)-2-Azido-3-[(*tert*-butyldimethylsilyl)oxy]-3-(4-iodophenyl)propionate (33). A solution of **32** (624 mg, 1.80 mmol, anti:syn = 17:1) in CH_2Cl_2 (5 mL) was treated with *t*-$BuMe_2SiOTf$ (714 mg, 0.62 mL, 2.70 mmol, 1.5 equiv) and Et_3N (364 mg, 0.50 mL, 3.60 mmol, 2.0 equiv) at 0 °C under Ar. The resulting reaction mixture was stirred at 4 °C for 5 h before saturated aqueous $NaHCO_3$ (15 mL) was added. The mixture was stirred at 0 °C for 10 min and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined CH_2Cl_2 extracts were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 3 × 10 cm, 5–10% EtOAc–hexane gradient elution) afforded (2*S*,3*S*)-**33** (736 mg, 830 mg theoretical, 89%) as a colorless oil and its C2 epimer (2*R*,3*S*)-**33** (49 mg, 5.9%) as a colorless oil that solidified as a waxy solid upon standing. For (2*S*,3*S*)-**33**: $[\alpha]^{25}_D$ +55 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.08 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 4.91 (d, 1H, *J* = 7.2 Hz, C3-H), 3.95 (d, 1H, *J* = 7.2 Hz, C2-H), 3.74 (s, 3H, CO_2CH_3), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 3H, $SiCH_3$), –0.20 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 139.6, 137.4, 128.7, 94.3, 74.9, 68.1, 52.4, 25.5, 18.1, –4.5, –5.2; IR (neat) ν_{max} 2952, 2930, 2109, 1748, 1589, 1472, 1253, 1171, 1092, 838, 780 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 462.0710 (M^+ + H, $C_{16}H_{24}IN_3O_3Si$ requires 462.0710).

Anal. Calcd for $C_{16}H_{24}IN_3O_3Si$: C, 41.65; H, 5.21; N, 9.11. Found: C, 42.02; H, 5.15; N, 9.02.

For the minor C2 epimer [(2*R*,3*S*)-**33**]: low-melting colorless waxy solid; $[\alpha]^{25}_D$ +142 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.12 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 5.25 (d, 1H, *J* = 3.1 Hz, C3-H), 3.78 (s, 3H, CO_2CH_3), 3.55 (d, 1H, *J* = 3.1 Hz, C2-H), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 3H, $SiCH_3$), –0.17 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 140.1, 137.4, 128.1, 93.9, 76.4, 67.7, 52.6, 25.4, 17.8, –4.8, –5.6; IR (neat) ν_{max} 2953, 2118, 1732, 1585, 1469, 1248, 1087, 998, 923, 778 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 484.0530 (M^+ + Na, $C_{16}H_{24}IN_3O_3Si$ requires 484.0529).

Anal. Calcd for $C_{16}H_{24}IN_3O_3Si$: C, 41.65; H, 5.21; N, 9.11. Found: C, 41.49; H, 5.18; N, 8.73.

Methyl (2*S*,3*S*)-2-Amino-3-[(*tert*-butyldimethylsilyl)oxy]-3-(4-iodophenyl)propionate (34). Method A. A solution of (2*S*,3*S*)-**33** (230 mg, 0.5 mmol) in THF (2 mL) was treated with Ph_3P (260 mg, 1.0 mmol, 2.0 equiv) and H_2O (90 mg, 90 μL, 5.0 mmol, 10 equiv) at 25 °C under Ar. The resulting reaction mixture was warmed at 45 °C for 10 h. The volatiles were removed *in vacuo*, and the residue was purified by flash chromatography (SiO_2, 2 × 10 cm, 15–40% EtOAc–hexane gradient elution) to afford (2*S*,3*S*)-**34** (180 mg, 217 mg theoretical, 83%) as a colorless oil: $[\alpha]^{25}_D$ +20 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.01 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 4.74 (d, 1H, *J* = 6.3 Hz, C3-H), 3.66 (s, 3H, CO_2CH_3), 3.59 (d, 1H, *J* = 6.3 Hz, C2-H), 0.83 (s, 9H, $SiC(CH_3)_3$), –0.01 (s, 3H, $SiCH_3$), –0.20 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2, 140.2, 137.0, 128.7, 93.6, 76.6, 62.0, 51.7, 25.4, 17.9, –4.8, –5.2;

(92) The enantiomeric excess was determined by capillary GLC (β-cyclodextrin, J & W CDX-B, 30 m × 0.32 mm i.d., 175 °C); retention times: (2*S*,3*S*)-**29**, 77.6 min; (2*R*,3*R*)-**29**, 79.9 min).

(93) For methyl (2*S*,3*S*)-2-(hydroxymethyl)-3-(4-iodophenyl)oxirane: colorless oil which solidified as a low-melting waxy solid upon standing: $[\alpha]^{25}_D$ –27 (*c* 2.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, *J* = 8.2 Hz, Ar C3- and C5-H), 7.14 (d, 2H, *J* = 8.2 Hz, Ar C2- and C6-H), 4.18 (d, 1H, *J* = 4.6 Hz, C3-H), 3.82 (d, 1H, *J* = 4.6 Hz, C2-H), 3.57 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 137.1, 132.5, 128.7, 94.5, 57.1, 55.7, 52.2; IR (neat) ν_{max} 3102, 2957, 1743, 1591, 1485, 1438, 1393, 1209, 1116, 1062, 891, 786 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 304.9680 (M^+ + H, $C_{10}H_9IO_3$ requires 304.9675).

(94) For methyl (2*R*,3*S*)-2-azido-3-hydroxy-3-(4-iodophenyl)propionate: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.10 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 5.13 (t, 1H, *J* = 4.5 Hz, C3-H), 3.99 (d, 1H, *J* = 4.5 Hz, C2-H), 3.78 (s, 3H, CO_2CH_3), 2.89 (d, 1H, *J* = 4.5 Hz, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 137.6, 129.7, 128.0, 94.5, 73.8, 67.3, 53.0.

IR (neat) ν_{max} 3389, 2953, 2857, 1740, 1588, 1473, 1256, 1170, 1085, 1006, 840, 777, 757, 669 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 436.0810 (M^+ + H, $C_{16}H_{26}INO_3Si$ requires 436.0805).

Anal. Calcd for $C_{16}H_{26}INO_3Si$: C, 44.14; H, 5.98; N, 3.22. Found: C, 44.40; H, 6.13; N, 3.43.

Method B. A solution of (2*S*,3*S*)-**33** (1.76 g, 3.82 mmol) in CH_3OH (20 mL) was treated with $SnCl_2$–$2H_2O$ (1.73 g, 7.64 mmol, 2.0 equiv) at 25 °C under Ar. The resulting reaction mixture was stirred at 25 °C for 2.5 h before the solvent was removed *in vacuo*. The residue was treated with H_2O (10 mL) and aqueous 6 N NaOH (pH 10), and the mixture was stirred at 25 °C for 20 min before EtOAc (30 mL) was added. The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were washed with H_2O (20 mL) and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), filtered through Celite, and concentrated *in vacuo*. Flash chromatography (SiO_2, 3 × 15 cm, 15–40% EtOAc–hexane gradient elution) afforded (2*S*,3*S*)-**34** (1.55 g, 1.66 g theoretical, 93%) as a colorless oil identical in all respects with the product obtained by method A.

A solution of the minor C2 epimer (2*R*,3*S*)-**33** (138.3 mg, 0.30 mmol) in CH_3OH (5 mL) was treated with $SnCl_2$–$2H_2O$ (method B, 135 mg, 0.60 mmol, 2.0 equiv) at 25 °C under Ar. The resulting reaction mixture was stirred at 25 °C for 10 h before the solvent was removed *in vacuo*. The residue was treated with H_2O (3 mL) and 6 N aqueous NaOH (pH 10), and the mixture was stirred at 25 °C for 20 min before EtOAc (10 mL) was added. The two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), filtered through Celite, and concentrated *in vacuo*. Flash chromatography (SiO_2, 2 × 8 cm, 15–40% EtOAc–hexane gradient elution) afforded (2*R*,3*S*)-**34** (119.4 mg, 130.5 mg theoretical, 92%) as a colorless oil: $[\alpha]^{25}_D$ +28 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.07 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 5.09 (d, 1H, *J* = 2.4 Hz, C3-H), 3.69 (s, 3H, CO_2CH_3), 3.44 (d, 1H, *J* = 2.4 Hz, C2-H), 0.86 (s, 9H, $SiC(CH_3)_3$), –0.05 (s, 3H, $SiCH_3$), –0.20 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 141.3, 137.1, 128.1, 93.1, 75.3, 61.9, 52.0, 25.5, 18.0, –4.7, –5.6; IR (neat) ν_{max} 3390, 2953, 2857, 1745, 1588, 1478, 1255, 1079, 1006, 838, 756 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 436.0800 (M^+ + H, $C_{16}H_{26}INO_3Si$ requires 436.0805).

Anal. Calcd for $C_{16}H_{26}INO_3Si$: C, 44.14; H, 5.98; N, 3.22. Found: C, 43.85; H, 6.04; N, 3.58.

Methyl (2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[*N*-[(*tert*-butyloxy)-carbonyl]amino]-3-(4-iodophenyl)propionate (35). A solution of **34** (330 mg, 0.76 mmol) in THF–H_2O (1:1, 4 mL) was treated with $(BOC)_2O$ (182 mg, 0.19 mL, 0.84 mmol, 1.1 equiv) and K_2CO_3 (209 mg, 1.52 mmol, 2.0 equiv) at 25 °C under Ar, and the resulting reaction mixture was stirred at 25 °C for 2 h. EtOAc (5 mL) was added, the two layers were separated, and the aqueous phase was extracted with EtOAc (2 × 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, 2 × 10 cm, 5–10% EtOAc–hexane gradient elution) afforded **35** (398 mg, 406 mg theoretical, 98%) as a colorless oil: $[\alpha]^{25}_D$ +66 (*c*, 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, 2H, *J* = 8.3 Hz, Ar C3- and C5-H), 7.08 (d, 2H, *J* = 8.3 Hz, Ar C2- and C6-H), 5.25 (d, 1H, *J* = 8.1 Hz, C3-H), 4.98 (d, 1H, *J* = 3.7 Hz, NH), 4.46 (dd, 1H, *J* = 3.7, 8.1 Hz, C2-H), 3.60 (s, 3H, CO_2CH_3), 1.41 (s, 9H, $CO_2C(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), –0.14 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 154.7, 140.5, 137.0, 128.1, 93.2, 79.9, 75.1, 60.7, 51.8, 28.3, 25.5, 18.0, –4.9, –5.4; IR (neat) ν_{max} 3442, 2954, 2858, 1713, 1495, 1364, 1255, 1167, 1093, 1009, 842, 759 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 536.1330 (M^+ + H, $C_{21}H_{34}INO_5Si$ requires 536.1329).

Anal. Calcd for $C_{21}H_{34}INO_5Si$: C, 47.10; H, 6.36; N, 2.62. Found: C, 47.46; H, 6.60; N, 2.54.

Methyl (2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[*N*-[(*tert*-butyloxy)-carbonyl]-*N*-methylamino]-3-(4-iodophenyl)propionate (36). A suspension of KH (4.4 mg, 0.11 mmol, 1.1 equiv) in anhydrous THF (1 mL) at 0 °C was treated with a solution of **35** (53.5 mg, 0.10 mmol) in dry THF (1 mL) under Ar. The resulting mixture was stirred at 0 °C for 10 min before CH_3I (71 mg, 31 μL, 0.50 mmol, 5.0 equiv) was added. The reaction mixture was warmed to 25 °C and stirred for 10 h before H_2O (2 mL) was added. EtOAc (3 mL) was added, the two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic phases were washed with H_2O (3 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 1.5 × 5 cm, 5–10% EtOAc–hexane gradient elution) afforded **36** (48 mg, 54.9 mg theoretical, 87%) as a white solid and a trace amount of the elimination product (3–5%).[95] For **36**: mp 124–125 °C (30% EtOAc–hexane, white powder); $[\alpha]^{25}_D$ –38 (*c* 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two rotamers, δ 7.61 and 7.59 (two d, 2H, *J* = 8.2 Hz, Ar C3- and C5-H), 7.07 and 7.03 (two d, 2H, *J* = 8.2 Hz, Ar C2- and C6-H), 5.03 and 4.97 (two d, 1H, *J* = 8.9 Hz, C3-H), 4.65 and 4.40 (two d, 1H, *J* = 8.9 Hz, C2-H), 3.71 (s, 3H, CO_2CH_3), 2.73 and 2.64 (two s, 3H, NCH_3), 1.22 (s, 9H, $CO_2C(CH_3)_3$), 0.77 (s, 9H, $SiC(CH_3)_3$), 0.01 (s, 3H, $SiCH_3$), –0.23 and –0.27 (two s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 and 169.9, 155.0 and 154.3, 140.8 and 140.6, 137.2 and 136.9, 129.2 and 128.9, 93.6 and 93.5, 80.5 and 80.1, 75.1, 73.0 and 72.5, 65.4 and 64.2, 51.9, 28.0, 25.6, 17.92 and 17.87, –4.58 and –4.62, –5.36 and –5.40; IR (KBr) ν_{max} 2956, 2855, 1737, 1683, 1444, 1392, 1255, 1146, 1104, 990, 896, 844, 775 cm^{-1}; FABHRMS (NBA) *m/e* 550.1499 (M^+ + H, $C_{22}H_{36}INO_5Si$ requires 550.1486).

Anal. Calcd for $C_{22}H_{36}INO_5Si$: C, 48.09; H, 6.56; N, 2.55. Found: C, 47.96; H, 6.54; N, 2.44.

(2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[*N*-[(*tert*-butyloxy)carbonyl]amino]-3-(4-iodophenyl)propionic Acid. A solution of **35** (1.12 g, 2.1 mmol) in THF–CH_3OH–H_2O (3:1:1, 10 mL) was treated with LiOH–H_2O (176.4 mg, 4.2 mmol, 2.0 equiv) at 25 °C under Ar, and the reaction mixture was stirred at 25 °C for 4 h. The organic solvents were removed under a stream of N_2 before H_2O (10 mL) and EtOAc (20 mL) were added to the residue. The solution was treated dropwise at 0 °C with 15% aqueous citric acid until the pH was equal to 3. The two layers were separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined EtOAc extracts were washed with H_2O (20 mL) and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (1.07 g) was recrystallized from 70% EtOAc–hexane to afford the free acid (994 mg, 1.09 g theoretical, 91%) as a white solid: mp 183–184 °C (70% EtOAc–hexane, white needles); $[\alpha]^{25}_D$ +75 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, 2H, *J* = 8.3 Hz, Ar C3- and C5-H), 7.12 (d, 2H, *J* = 8.3 Hz, Ar C2- and C6-H), 5.17 (d, 1H, *J* = 7.8 Hz, NH), 5.05 (br s, 1H, C3-H), 4.50 (m, 1H, C2-H), 1.41 (s, 9H, $CO_2C(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), –0.12 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 154.9, 140.0, 137.0, 128.2, 93.4, 80.2, 74.9, 60.7, 28.3, 25.7, 18.1, –5.3, –5.5; IR (KBr) ν_{max} 3321, 2931, 1724, 1650, 1479, 1392, 1256, 1162, 1090, 841, 777 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 522.1170 (M^+ + H, $C_{20}H_{32}INO_5Si$ requires 522.1173).

Anal. Calcd for $C_{20}H_{32}INO_5Si$: C, 46.07; H, 6.14; N, 2.69. Found: C, 46.11; H, 6.41; N, 2.64.

Methyl (2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-3-(4-iodophenyl)-2-(*N*-methylamino)propionate (37). A solution of **36** (55 mg, 0.1 mmol) in 3.25 N HCl–EtOAc (1.0 mL) was stirred at 0 °C for 20 min. The volatiles were removed *in vacuo*, and crude **37**–HCl was treated with saturated aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL), and 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, 2 × 5 cm, 15–40% EtOAc–hexane gradient elution) afforded **37** (42 mg, 45 mg theoretical, 93%) as a colorless oil: $[\alpha]^{25}_D$ +78 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.03 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 4.68 (d, 1H, *J* = 7.1 Hz, C3-H), 3.69 (s, 3H, CO_2CH_3), 3.28 (d, 1H, *J* = 7.1 Hz, C2-H), 2.26 (s, 3H, NCH_3), 0.83 (s, 9H, $SiC(CH_3)_3$), –0.01 (s, 3H, $SiCH_3$), –0.25 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 141.5, 137.2, 128.8, 93.6, 75.9, 71.0, 51.6, 35.0, 25.5, 17.9, –4.6, –5.4; IR (neat) ν_{max} 3335, 2950, 2857, 2799, 1738, 1587, 1475, 1254, 1172, 1090, 1006, 843, 779 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 450.0955 (M^+ + H, $C_{17}H_{28}INO_3Si$ requires 450.0961).

Anal. Calcd for $C_{17}H_{28}INO_3Si$: C, 45.43; H, 6.24; N, 3.12. Found: C, 45.62; H, 6.19; N, 3.02.

(95) For methyl 2-[*N*-[(*tert*-butyloxy)carbonyl]-*N*-methylamino]-3-(4-iodophenyl)propenoate: colorless oil which was determined to be an inseparable mixture of *Z*- and *E*-isomers: ^{1}H NMR ($CDCl_3$, 400 MHz, for major isomer) δ 7.72 (d, 2H, *J* = 8.5 Hz, Ar C3- and C5-H), 7.23 (d, 2H, *J* = 8.5 Hz, Ar C2- and C6-H), 7.22 (s, 1H, C3-H), 3.82 (s, 3H, CO_2CH_3), 2.91 (s, 3H, NCH_3), 1.34 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 154.8, 138.1, 137.2, 132.8, 131.3, 130.0, 96.2, 80.8, 52.5, 34.6, 28.1; ^{1}H NMR ($CDCl_3$, 400 MHz, for minor isomer) δ 7.63 (d, 2H, *J* = 8.3 Hz, Ar C3- and C5-H), 6.94 (d, 2H, *J* = 8.3 Hz, Ar C2- and C6-H), 6.46 (br s, 1H, C3-H), 3.63 (s, 3H, CO_2CH_3), 3.23 (s, 3H, NCH_3), 1.49 (s, 9H, $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 154.9, 137.9, 134.1, 132.5, 132.1, 131.3, 96.1, 81.8, 51.9, 35.8, 28.3; IR (neat) ν_{max} 2977, 2950, 1724, 1639, 1582, 1482, 1434, 1346, 1260, 1153, 1066, 1005, 864, 777 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 418.0520 (M^+ + H, $C_{16}H_{20}INO_4$ requires 418.0515).

(2S,3S)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[*N*-[(*tert*-butyloxy)carbonyl]-*N*-methylamino]-3-(4-iodophenyl)propionic Acid (24). A solution of **37** (36 mg, 0.08 mmol) in THF–CH_3OH–H_2O (3:1:1, 1 mL) was treated with LiOH–H_2O (7.4 mg, 0.18 mmol, 2.2 equiv) at 25 °C under Ar, and the reaction mixture was stirred at 25 °C for 3 h. The organic solvents were removed under a stream of N_2 before H_2O (0.8 mL) and THF (1 mL) were added to the residue. The solution was treated with $(BOC)_2O$ (19.2 mg, 21 μL, 0.088 mmol, 1.1 equiv), and the reaction mixture was stirred at 25 °C under Ar for 6 h. The mixture was acidified to pH 3 with the addition of 15% aqueous citric acid at 0 °C. EtOAc (2 mL) was added, and the two layers were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phases were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product (39.4 mg, 42.8 mg theoretical) was directly recrystallized (30% EtOAc–hexane) to afford **24** (36 mg, 43 mg theoretical, 85% for two steps) as a white powder identical in all respects with the material prepared from **22–23**.

(4S,5S)-5-(4-Iodophenyl)-4-(methoxycarbonyl)-2-oxazolidinone (38a). A solution of (2*S*,3*S*)-**34** (43.5 mg, 0.1 mmol) in THF (1.0 mL) at 0 °C was treated dropwise with a 1.0 M solution of Bu_4NF in THF (110 μL, 0.12 mmol, 1.2 equiv) under Ar. The resulting reaction mixture was stirred at 0 °C for 30 min before being treated with Et_3N (20.2 mg, 28 μL, 0.20 mmol, 2.0 equiv) and $COCl_2$ (20% solution in toluene, 63 μL, 0.12 mmol, 1.2 equiv) at 0 °C. The mixture was stirred at 0 °C for an additional 1 h. H_2O (2 mL) and EtOAc (5 mL) were added, the two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic phases were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 2 × 5 cm, 20–50% EtOAc–hexane gradient elution) afforded **38a** (33.5 mg, 34.7 mg theoretical, 97% for two steps) as a white solid: mp 134–135 °C (70% EtOAc–hexane, white powder); $[\alpha]^{25}_D$ +92 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.05 (d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 5.77 (d, 1H, *J* = 9.0 Hz, C5-H), 5.49 (s, 1H, NH), 4.65 (d, 1H, *J* = 9.0 Hz, C4-H), 3.29 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 158.7, 137.5, 133.7, 128.0, 95.2, 78.6, 59.7, 52.4; IR (KBr) ν_{max} 3389, 1763, 1738, 1408, 1356, 1222, 1117, 1006, 810, 760 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 347.9730 (M^+ + H, $C_{11}H_{10}INO_4$ requires 347.9733).

Anal. Calcd for $C_{11}H_{10}INO_4$: C, 38.04; H, 2.88; N, 4.03. Found: C, 38.18; H, 3.09; N, 4.14.

(4R,5S)-5-(4-Iodophenyl)-4-(methoxycarbonyl)-2-oxazolidinone (38b). A solution of (2*R*,3*S*)-**34** (29.5 mg, 0.07 mmol) in THF (1.0 mL) at 0 °C was treated dropwise with a 1.0 M solution of Bu_4NF in THF (84 μL, 0.084 mmol, 1.2 equiv) under Ar. The resulting reaction mixture was stirred at 0 °C for 30 min before being treated with Et_3N (14.1 mg, 20 μL, 0.14 mmol, 2.0 equiv) and $COCl_2$ (20% solution in toluene, 44 μL, 0.084 mmol, 1.2 equiv) at 0 °C. The mixture was stirred at 0 °C for an additional 1 h. H_2O (2 mL) and EtOAc (5 mL) were added, the two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic phases were washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 2 × 5 cm, 20–40% EtOAc–hexane gradient elution) afforded **38b** (23.7 mg, 24.3 mg theoretical, 98% for two steps) as a colorless oil: $[\alpha]^{25}_D$ –74 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, *J* = 8.3 Hz, Ar C3- and C5-H), 7.16 (d, 2H, *J* = 8.3 Hz, Ar C2- and C6-H), 5.99 (s, 1H, NH), 5.60 (d, 1H, *J* = 5.0 Hz, C5-H), 4.22 (d, 1H, *J* = 5.0 Hz, C4-H), 3.86 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 157.8, 138.2, 137.7, 127.1, 95.0, 78.7, 61.1, 53.3; IR (neat) ν_{max} 3345, 2954, 1768, 1732, 1592, 1487, 1381, 1221, 1005, 821, 761 cm^{-1}; FABHRMS (NBA) *m/e* 347.9730 (M^+ + H, $C_{11}H_{10}INO_4$ requires 347.9733).

Anal. Calcd for $C_{11}H_{10}INO_4$: C, 38.04; H, 2.88; N, 4.03. Found: C, 38.23; H, 2.95; N, 3.87.

Pentafluorophenyl (2S,3S)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-[*N*-[(*tert*-butyloxy)carbonyl]-*N*-methylamino]-3-(4-iodophenyl)propionate (39). A solution of **24** (180.6 mg, 0.337 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C was treated with EDCI (66.0 mg, 0.337 mmol, 1.0 equiv) and C_6F_5OH (63.4 mg, 0.337 mmol, 1.0 equiv) under Ar. The resulting mixture was stirred at 25 °C (8 h) and quenched by the addition of 5% aqueous HCl (15 mL) and CH_2Cl_2 (15 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic extracts were washed with 5% aqueous HCl (3 × 20 mL), 10% aqueous K_2CO_3 (3 × 20 mL), H_2O (3 × 20 mL), and saturated aqueous NaCl (3 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (PCTLC, SiO_2, 2 mm, 0–15% EtOAc–hexane) afforded **39** (211 mg, 236 mg theoretical, 90%) as a pale yellow oil: $[\alpha]^{25}_D$ –43 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 and 7.66 (two d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.12 and 7.08 (two d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 5.23 (d, 1H, *J* = 8.4 Hz, C3-H), 4.63 (br d, 1H, *J* = 8.4 Hz, C2-H), 2.65 (s, 3H, NCH_3), 1.33 and 1.31 (two s, 9H, $CO_2C(CH_3)_3$), 0.84 and 0.79 (two s, 9H, $SiC(CH_3)_3$), 0.03 and 0.02 (two s, 3H, $SiCH_3$), –0.24 and –0.25 (two s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 178.5, 165.8, 155.5, 143.4, 140.1, 137.4, 137.1, 129.1, 128.8, 93.8, 80.9, 72.3, 65.7, 34.2, 28.0, 25.5, 17.9, –4.6, –5.4; IR (neat) ν_{max} 2954, 2862, 1790, 1703, 1518, 1472, 1390, 1370, 1251, 1159, 1092, 990, 841, 780 cm^{-1}; FABMS (NBA–NaI) *m/e* 724 (M^+ + Na, $C_{27}H_{33}F_5INO_5Si$ requires 724).

Anal. Calcd for $C_{27}H_{33}F_5INO_5Si$: C, 46.23; H, 4.74. Found: C, 46.58; H, 4.70.

3-Hydroxy-*N*,*O*^{4}-dimethyl-*N*-[3(*S*)-[(*tert*-butyldimethylsilyl)oxy]-*N*-[(*tert*-butyloxy)carbonyl]-*N*-methyl-4′-iodo-L-phenylalanyl]-L-tyrosine Methyl Ester (40). A solution of *N*,*O*^{4}-dimethyl-L-DOPA methyl ester[23] (32.5 mg, 0.136 mmol) in anhydrous THF–DMF (0.5 mL, 1:1) was treated with **39** (95.4 mg, 0.136 mmol), and the mixture was warmed at 70 °C (36 h) under Ar. The reaction mixture was cooled and concentrated *in vacuo*. Chromatography (PCTLC, SiO_2, 2 mm, 5–50% EtOAc–hexane) afforded **40** (69 mg, 103 mg theoretical, 67%) as a white foam: $[\alpha]^{25}_D$ –22 (*c* 0.34, CH_3OH); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.70–7.50 (m, 3H, ArH), 7.20–6.95 (m, 3H, ArH), 5.80–6.50 (m, 2H, ArH and OH), 5.20–4.60 (br m, 3H, C*H*CO_2CH_3, C*H*$N(CH_3)$(BOC), and C*H*OR), 3.80–3.60 (several s, 6H, $ArOCH_3$ and CO_2CH_3), 3.30–3.10 (m, 2H, $ArCH_2$), 3.00–2.80 (several s, 3H, NCH_3), 2.70–2.60 (several s, 3H, NCH_3), 1.44 (m, 9H, $CO_2C(CH_3)_3$), 0.90–0.70 (several s, 9H, $SiC(CH_3)_3$), –0.04 (several s, 3H, $SiCH_3$), –0.24 (several s, 3H, $SiCH_3$); IR (neat) ν_{max} 3444, 2954, 2930, 2856, 1745, 1694, 1688, 1659, 1651, 1590, 1514, 1482, 1444, 1392, 1366, 1258, 1174, 1150, 1092, 1030, 1006, 939, 895, 839, 779, 762, 715, 668 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 779.2215 (M^+ + Na, $C_{33}H_{49}IN_2O_8Si$ requires 779.2201).

Alternatively, a solution of *N*,*O*^{4}-dimethyl-L-DOPA methyl ester[23] (257 mg, 1.08 mmol) and **24** (576 mg, 1.07 mmol) in distilled CH_2Cl_2 (3.6 mL) was treated with bis(2-oxo-3-oxazolidinyl)phosphinic chloride[96] (BOP-Cl, 339 mg, 1.29 mmol, 1.2 equiv) and diisopropylethylamine (0.4 mL, 1.29 mmol, 1.2 equiv) at 0 °C, and the mixture was stirred at 0 °C (10 h). The reaction mixture was quenched by the addition of 2% aqueous HCl (20 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with H_2O (3 × 25 mL), saturated aqueous $NaHCO_3$ (3 × 25 mL), and saturated aqueous NaCl (3 × 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (PCTLC, SiO_2, 4 mm, 15–50% EtOAc–hexane) afforded **40** (318 mg, 813 mg theoretical, 40%) and the corresponding *O*-acylation product (351 mg, 813 mg theoretical, 43%). For the *O*-acylation product: mp 142–145 °C (foam); $[\alpha]^{25}_D$ –49 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.66 and 7.63 (two d, 2H, *J* = 8.4 Hz, Ar C3- and C5-H), 7.14 and 7.11 (two d, 2H, *J* = 8.4 Hz, Ar C2- and C6-H), 6.97 (br s, 1H, ArH), 6.80 (m, 2H, ArH), 5.39 (d, 1H, *J* = 5.0 Hz, C*H*OR), 5.23 (d, 1H, *J* = 5.0 Hz, C*H*NCH_3(BOC)), 5.19 (br s, 1H, C*H*CO_2CH_3), 3.71 (s, 3H, $ArOCH_3$), 3.63 (s, 3H, CO_2CH_3), 3.37 (m, 1H, C*H*$NHCH_3$), 3.13 and 3.09 (two s, 3H, NCH_3), 2.65–2.90 (m, 2H, $ArCH_2$), 2.33 (s, 3H, $NHCH_3$), 1.32 and 1.21 (two s, 9H, $CO_2C(CH_3)_3$), 0.86 and 0.85 (two s, 9H, $SiC(CH_3)_3$), 0.04 and 0.02 (two s, 3H, $SiCH_3$), –0.24, –0.25, and –0.26 (three s, 3H, $SiCH_3$); IR (neat) ν_{max} 3450, 2928, 1744, 1692, 1656, 1513, 1440, 1391, 1252, 1156, 1123, 1006, 838, 779 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 757.2380 (M^+ + H, $C_{33}H_{49}IN_2O_8Si$ requires 757.2381).

Methyl 13(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-12(*S*)-[*N*-[(*tert*-butyloxy)carbonyl]-*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 (15). A solution of **40** (64.1 mg, 0.0847 mmol) in anhydrous 2,6-lutidine (0.5 mL) was added dropwise to a suspension of NaH (60% oil dispersion in mineral oil, 3.8 mg, 0.0932 mmol, 1.1 equiv) in anhydrous 2,6-lutidine (0.5 mL) under Ar at 0 °C, and the solution was stirred for 10 min. The solution was treated with CuBr–SMe_2 (178 mg, 0.847 mmol, 10 equiv) and was stirred at 25 °C for 50 min before the mixture was diluted with anhydrous degassed 2,6-lutidine to 0.004 M (21.2 mL) and warmed at 130 °C (bath) for 9 h. The cooled reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (30

(96) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547. Tung, R. D.; Rich, D. R. *J. Am. Chem. Soc.* **1985**, *107*, 4342.

mL) and saturated aqueous NH_4Cl/concentrated NH_4OH (9:1, pH = 9.5, 30 mL). The aqueous phase was additionally extracted with EtOAc (4 × 30 mL), and the combined organic extracts were washed with 5% aqueous HCl (3 × 25 mL), H_2O (3 × 25 mL), and saturated aqueous NaCl (3 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 1.5 × 10 cm, 0–35% EtOAc–hexane gradient elution) afforded **15** (19.8 mg, 53.2 mg theoretical, 37%) as a pale yellow oil: $[\alpha]^{25}_D$ +45 (*c* 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (dd, 1H, *J* = 2.2, 8.5 Hz, C15-H), 7.27 (dd, 1H, *J* = 2.2, 8.5 Hz, C18-H), 7.09 (dd, 1H, *J* = 2.2, 8.5 Hz, C16-H), 6.96 (dd, 1H, *J* = 2.2, 8.5 Hz, C17-H), 6.79 (d, 1H, *J* = 8.2 Hz, C5-H), 6.62 (br d, 1H, *J* = 8.2 Hz, C6-H), 5.27 (d, 1H, *J* = 9.1 Hz, C13-H), 5.01 (d, 1H, *J* = 9.1 Hz, C12-H), 4.72 (d, 1H, *J* = 1.7 Hz, C19-H), 4.68 (dd, 1H, *J* = 2.7, 11.6 Hz, C9-H), 3.93 (s, 3H, $ArOCH_3$), 3.63 (s, 3H, CO_2CH_3), 3.01 (m, 2H, C8-H), 2.93 (s, 3H, NCH_3), 2.82 (s, 3H, NCH_3), 1.47 (s, 9H, $CO_2C(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.12 (s, 3H, $SiCH_3$), –0.07 (s, 3H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 170.4, 157.3, 152.2, 146.4, 138.6, 131.1, 130.5, 129.4, 123.9, 121.1, 118.2, 113.2, 80.2, 72.5, 63.5, 62.4, 56.1, 55.9, 52.3, 30.4, 29.7, 28.3, 25.7, 18.1, –4.1, –5.1; IR (neat) ν_{max} 2957, 2928, 2856, 1744, 1692, 1650, 1585, 1516, 1461, 1442, 1392, 1366, 1333, 1303, 1260, 1175, 1152, 1130, 1090, 1007, 874, 838, 778 cm^{-1}; FABHRMS (NBA) *m/e* 629.3250 (M^+ + H, $C_{33}H_{48}N_2O_8Si$ requires 629.3258).

The 2D ^1H–^1H NOESY NMR spectrum ($CDCl_3$, 400 MHz) of **15** displayed the following diagnostic NOE cross peaks: C15-H/C16-H, C15-H/C13-H, C18-H/C17-H, C18-H/C12-H, C16-H/C20-H, C17-H/C20-H, C17-H/C19-H, C5-H/C6-H, C5-H/C4-OCH_3, C6-H/C8-H, C13-H/C12-H, C13-H/NCH_3, C12-H/N10-CH_3, C12-H/NCH_3, C9-H/N10-CH_3, C9-H/C8-H, $SiC(CH_3)$/$SiCH_3$.

Methyl 12(*S*)-[*N*-[(*tert*-Butyloxy)carbonyl]-*N*-methylamino]-13(*S*)-hydroxy-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 (16). A solution of **15** (2.1 mg, 0.0033 mmol) in THF (50 μL) at 0 °C was treated with a 1.0 M solution of Bu_4NF in THF (1 μL, 0.01 mmol, 3 equiv) under Ar, and the resulting mixture was stirred at 0 °C for 30 min. Saturated aqueous NH_4Cl (0.5 mL) and EtOAc (0.5 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 0.5 mL). The combined organic phases were washed with H_2O (3 × 1.0 mL) and saturated aqueous NaCl (3 × 1.0 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.5 × 4.0 cm, 30–50% EtOAc–hexane) afforded **16** (1.4 mg, 1.7 mg theoretical, 83%) as a clear viscous oil: $[\alpha]^{25}_D$ –71 (*c* 0.14, $CDCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (dd, 1H, *J* = 2.2, 8.3 Hz, C15-H), 7.33 (dd, 1H, *J* = 2.2, 8.3 Hz, C18-H), 7.13 (dd, 1H, *J* = 2.2, 8.3 Hz, C16-H), 7.01 (dd, 1H, *J* = 2.2, 8.3 Hz, C17-H), 6.80 (d, 1H, *J* = 8.3 Hz, C5-H), 6.63 (dd, 1H, *J* = 2.1, 8.3 Hz, C6-H), 5.23 (br d, 1H, *J* = 9.3 Hz, C13-H), 5.11 (br d, 1H, *J* = 9.3 Hz, C12-H), 4.75 (d, 1H, *J* = 2.1 Hz, C19-H), 4.69 (dd, 1H, *J* = 2.4, 12.0 Hz, C9-H), 3.93 (s, 3H, $ArOCH_3$), 3.65 (s, 3H, CO_2CH_3), 3.00 (s, 3H, NCH_3), 2.94 (br s, 2H, C8-H), 2.80 (s, 3H, NCH_3), 1.47 (s, 9H, $CO_2C(CH_3)_3$); IR (neat) ν_{max} 3458, 2956, 2926, 2857, 1730, 1690, 1646, 1513, 1459, 1267, 1124, 1070 cm^{-1}; FABHRMS (NBA–CsI) *m/e* 647.1345 (M^+ + Cs, $C_{27}H_{34}N_2O_8$ requires 647.1369).

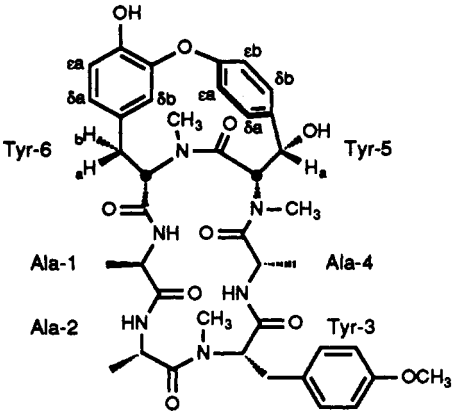
BOC-D-Alanyl-L-alanyl-*N*,*O*-dimethyl-L-tyrosyl-L-alanyl-*N*-methyl-3-(*S*)-[(*tert*-butyldimethylsilyl)oxy]-L-tyrosyl-*N*,*O*-dimethyl-L-tyrosine Cyclic 5^4→6^3 Ether, Methyl Ester (44). A solution of **15** (5.6 mg, 0.0089 mmol) in anhydrous CH_2Cl_2 (0.1 mL) was treated with *t*-$BuMe_2SiOTf$ (7.1 mg, 6.1 μL, 0.027 mmol, 3.0 equiv) at 0 °C, and the mixture was stirred at 0 °C (1 h). The reaction mixture was quenched by the addition of 5% aqueous HCl (2 mL) and stirred for 30 min before saturated aqueous $NaHCO_3$ (4.0 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 4.0 mL). The combined CH_2Cl_2 extract was washed with H_2O (3 × 4.0 mL) and saturated aqueous NaCl (3 × 4.0 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide crude **42** (4.6 mg, 4.7 mg theoretical, 98%), which was used directly in the next reaction.

A solution of **42** (4.6 mg, 0.0087 mmol) in anhydrous THF (0.1 mL) was treated with BOCNH-D-Ala-Ala-NMe-Tyr(OCH_3)-Ala-OC_6F_5 (**43**,[35] 6.0 mg, 0.0087 mmol, 1 equiv) at 25 °C and the mixture was stirred at 25 °C (72 h) before being concentrated *in vacuo*. Flash chromatography (SiO_2, 1.0 × 6.0 cm, 10% EtOAc–hexane and 0–7% CH_3OH–$CHCl_3$) afforded **44** (4.6 mg, 8.9 mg theoretical, 52%) as a pale yellow foam: ^1H NMR ($CDCl_3$, 400 MHz), 7.86 (br d, 1H, *J* = 8.4 Hz, C15-H), 7.41 (br d, 1H, *J* = 8.3 Hz, C18-H), 7.25–6.40 (br m, 10H), 6.09 (br s, 1H, NH(BOC)), 5.50–4.00 (br m, 8H), 3.93 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, $ArOCH_3$), 3.73 (s, 3H, CO_2CH_3), 3.40–2.60 (m, 13H), 1.40 (br s, 9H, $CO_2C(CH_3)_3$), 1.30–1.10 (br m, 9H, ala$^\beta$), 0.90 (br m, 9H, $SiC(CH_3)_3$), 0.05 and 0.04 (two s, 6H, $SiCH_3$); IR (neat) ν_{max} 3297, 2918, 2857, 1737, 1711, 1691, 1665, 1640, 1512, 1456, 1369, 1261, 1169, 1020 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 1055.5142 (M^+ + Na, $C_{53}H_{76}N_6O_{13}Si$ requires 1055.5137).

***O*-Methylbouvardin (2).** A solution of **44** (3.7 mg, 0.0036 mmol) in THF–CH_3OH–H_2O (0.5 mL, 3:1:1) was treated with LiOH (0.5 mg, 0.011 mmol, 3.0 equiv) at 0 °C, and the mixture was allowed to warm to 25 °C gradually. After 3.5 h (25 °C), the reaction mixture was quenched with the addition of saturated aqueous citric acid (1.0 mL, pH 3) and the mixture was extracted with EtOAc (4 × 1.0 mL). The combined organic layers were washed with H_2O (3 × 1.0 mL) and saturated aqueous NaCl (3 × 1.0 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **45** (3.3 mg, 3.6 mg theoretical, 92%), which was used directly in the following reaction.

A solution of **45** (3.3 mg, 0.0032 mmol) in 2.0 N HCl–EtOAc (0.5 mL) was stirred at 25 °C (50 min). The volatiles were removed *in vacuo*, the resulting solid was triturated with anhydrous Et_2O (3 × 1.0 mL), and the residue was dried thoroughly to afford **46** (2.6 mg, 2.6 mg theoretical, 100%), which was used directly in the following reaction.

A solution of **46** (2.6 mg, 0.0032 mmol) in anhydrous degassed DMF (1.2 mL) was cooled to 0 °C and treated with diphenyl phosphorazidate (DPPA, 1.8 mg, 0.0065 mmol, 2.0 equiv) and $NaHCO_3$ (2.8 mg, 0.0323 mmol, 10.0 equiv), and the mixture was stirred at 0 °C for 72 h. The reaction mixture was quenched by the addition of H_2O (1.0 mL) and extracted with EtOAc (4 × 1.0 mL). The organic phase was washed with 5% aqueous HCl (3 × 1.0 mL), saturated aqueous $NaHCO_3$ (3 × 1.0 mL), H_2O (3 × 1.0 mL), and saturated aqueous NaCl (3 × 1.0 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.5 × 7.0 cm, 0–7% CH_3OH–$CHCl_3$) afforded **2** (1.1 mg, 2.5 mg theoretical, 44%) as a white solid: mp 244–246 °C (CH_3OH, colorless plates), lit.[1] mp 244–247 °C (CH_3OH, colorless plates); $[\alpha]^{25}_D$ –191 (*c* 0.055, $CHCl_3$), lit.[1] $[\alpha]^{25}_D$ –191 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (dd, 1H, *J* = 2.2, 8.6 tyr$^{5\delta a}$), 7.36 (dd, 1H, *J* = 2.2, 8.6 Hz, tyr$^{5\delta b}$), 7.23 (dd, 1H, *J* = 2.2, 8.6 Hz, tyr$^{5\varepsilon a}$), 7.03 (d, 2H, *J* = 8.5 Hz, tyr$^{3\delta}$), 6.99 (dd, 1H, *J* = 2.2, 8.6 Hz, tyr$^{5\varepsilon b}$), 6.82 (d, 2H, *J* = 8.5 Hz, tyr$^{3\varepsilon}$), 6.80 (d, 1H, *J* = 8.4 Hz, tyr$^{6\varepsilon a}$), 6.64 (d, 1H, *J* = 7.7 Hz, ala^4 NH), 6.56 (dd, 1H, *J* = 2.1, 8.4 Hz, tyr$^{6\delta a}$), 6.41 (d, 1H, *J* = 6.2 Hz, ala^1 NH), 6.06 (br s, 1H, ala^2 NH), 5.36 (d, 1H, *J* = 1.8 Hz, tyr$^{5\alpha}$), 5.04 (br s, 1H, tyr$^{5\beta}$ OH), 4.86 (dq, 1H, *J* = 7.1 Hz, ala$^{2\alpha}$), 4.77 (br s, 1H, ala$^{4\alpha}$), 4.40 (p, 1H, *J* = 7.0 Hz, ala$^{1\alpha}$), 4.34 (dd, 1H, *J* = 3.0, 11.7 Hz, tyr$^{6\alpha}$), 4.31 (d, 1H, *J* = 2.1 Hz, tyr$^{6\delta b}$), 3.93 (s, 3H, tyr^6 OCH_3), 3.78 (s, 3H, tyr^3 OCH_3), 3.59 (dd, 1H, *J* = 5.9, 9.6 Hz, tyr$^{3\alpha}$), 3.34 (br d, 2H, tyr$^{3\beta}$), 3.32 (s, 3H, tyr^5 NCH_3), 3.13 (dd, 1H, *J* = 11.4, 18.1 Hz, tyr$^{6\beta b}$), 2.94 (dd, 1H, *J* = 3.0, 18.1 Hz, tyr$^{6\beta a}$), 2.84 (s, 3H, tyr^3 NCH_3), 2.72 (s, 3H, tyr^6 NCH_3), 1.35 (d, 3H, *J* = 6.4 Hz, ala$^{2\beta}$), 1.28 (d, 3H, *J* = 6.3 Hz, ala$^{1\beta}$), 1.09 (d, 3H, *J* = 6.6 Hz, ala$^{4\beta}$); IR (neat) ν_{max} 3318, 2927, 2858, 1729, 1664, 1514, 1446, 1412, 1263, 1110, 1037, 800 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 787.3630 (M^+ + H, $C_{41}H_{50}N_6O_{10}$ requires 787.3667).



Bouvardin (1)

Bouvardin (1). A solution of **2** (0.5 mg, 0.0006 mmol) in anhydrous CH_2Cl_2 (0.1 mL) was cooled to –78 °C and treated with BBr_3 (0.1 M solution in CH_2Cl_2, 16 μL, 0.0016 mmol, 2.5 equiv). The reaction mixture was allowed to warm gradually to 0 °C (1 h), quenched with the addition of saturated aqueous $NaHCO_3$, and extracted with EtOAc (4 × 3.0 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.5 × 4.0 cm, 0–7%

CH_3OH–$CHCl_3$) afforded **1** (0.42 mg, 0.49 mg theoretical, 86%) as a white solid identical in all respects with a sample of authentic material:[90] mp 253–255 °C (1:1 $CHCl_3$:CH_3OH, white needles), lit.[1] mp 254–255 °C (CH_3OH–$CHCl_3$, white needles); $[\alpha]^{25}_D$ –181 (*c* 0.02, $CHCl_3$), lit.[1] $[\alpha]^{25}_D$ –181 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) 7.49 (dd, 1H, J = 2.2, 8.6 Hz, tyr$^{5\delta a}$), 7.37 (dd, 1H, J = 2.2, 8.6 Hz, tyr$^{5\delta b}$), 7.23 (dd, 1H, J = 2.2, 8.6 Hz, tyr$^{5\epsilon a}$), 7.03 (d, 2H, J = 8.6 Hz, tyr$^{3\delta}$), 6.95 (dd, 1H, J = 2.2, 8.6 Hz, tyr$^{5\epsilon b}$), 6.83 (d, 2H, J = 8.6 Hz, tyr$^{3\epsilon}$), 6.81 (d, 1H, J = 8.3 Hz, tyr$^{6\epsilon a}$), 6.63 (d, 1H, J = 7.9 Hz, ala^4 NH), 6.50 (dd, 1H, J = 2.0, 8.3 Hz, tyr$^{6\delta a}$), 6.41 (d, 1H, J = 6.8 Hz, ala^1 NH), 6.00 (d, 1H, J = 8.3 Hz, ala^2 NH), 5.67 (br s, 1H, tyr^6 OH), 5.34 (d, 1H, J = 1.9 Hz, tyr$^{5\alpha}$), 5.04 (dd, 1H, J = 1.8, 10.2 Hz, tyr$^{5\beta}$), 4.85 (dq, 1H, J = 6.8 Hz, ala$^{2\alpha}$), 4.76 (dq, 1H, J = 7.3 Hz, ala$^{4\alpha}$), 4.34 (dd, 1H, J = 3.1, 11.8 Hz, tyr$^{6\alpha}$), 4.33 (d, 1H, J = 2.0 Hz, tyr$^{6\delta b}$), 4.32 (dq, 1H, J = 6.7 Hz, ala$^{1\alpha}$), 3.78 (s, 3H, tyr^3 OCH_3), 3.59 (dd, 1H, J = 5.3, 10.6 Hz, tyr$^{3\alpha}$), 3.35 (br d, 2H, J = 4.5 Hz, tyr$^{3\beta}$), 3.32 (s, 3H, tyr^5 NCH_3), 3.08 (dd, 1H, J = 11.8, 18.8 Hz, tyr$^{6\beta b}$), 3.06 (dd, 1H, J = 5.2, 18.8 Hz, tyr$^{6\beta a}$), 2.84 (s, 3H, tyr^3 NCH_3), 2.71 (s, 3H, tyr^6 NCH_3), 1.35 (d, 3H, J = 6.8 Hz, ala$^{2\beta}$), 1.28 (d, 1H, J = 6.9 Hz, ala$^{1\beta}$), 1.09 (d, 3H, J = 6.7 Hz, ala$^{4\beta}$); IR (neat) ν_{max} 3373, 3283, 2930, 1660, 1608, 1514, 1446, 1406, 1351, 1287, 1246, 1213, 1179, 1109, 1036, 926, 780 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 773.3525 (M^+ + H, $C_{40}H_{48}N_6O_{10}$ requires 773.3510).

BOC-D-Alanyl-L-alanyl-*O*-methyl-L-tyrosyl-L-alanyl-*N*-methyl-3(*S*)-[(*tert*-butyldimethylsilyl)oxy]-L-tyrosyl-*N*,*O*-dimethyl-L-tyrosine Cyclic 5^4→6^3 Ether, Methyl Ester (48). A solution of **15** (7.3 mg, 0.0116 mmol) in anhydrous CH_2Cl_2 (50 μL) was treated with *t*-$BuMe_2SiOTf$ (9.4 mg, 8.2 μL, 0.035 mmol, 3 equiv) at 0 °C, and the mixture was stirred at 0 °C (1 h). The reaction mixture was quenched by the addition of 5% aqueous HCl (2 mL). The mixture was stirred for 30 min before saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture extracted with CH_2Cl_2 (4 × 4.0 mL). The combined CH_2Cl_2 extract was washed with H_2O (3 × 3.0 mL) and saturated aqueous NaCl (3 × 3.0 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide crude **42** (6.0 mg, 6.1 mg theoretical, 98%), which was used directly in the next reaction.

A solution of **42** (6.0 mg, 0.011 mmol) in anhydrous THF (50 μL) was treated with BOCNH-D-Ala-Ala-Tyr(OCH_3)-Ala-OC_6F_5[35] (**47**, 7.7 mg, 0.011 mmol) at 25 °C, and the mixture was stirred at 25 °C (48 h). Chromatography (PCTLC, SiO_2, 1.0 mm, 0–7% CH_3OH–$CHCl_3$) afforded **48** (8.8 mg, 11.5 mg theoretical, 75%) as a pale yellow foam: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.80–7.50 (m, 14H), 5.50–3.50 (m, 8H), 3.92 (s, 3H, $ArOCH_3$), 3.72 (br s, 6H, $ArOCH_3$ and CO_2CH_3), 3.30–2.00 (m, 10H), 1.39 and 1.30 (two s, 9H, $CO_2C(CH_3)_3$), 1.30–1.00 (br s, 9H, ala$^\beta$), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 3H, $SiCH_3$), –0.02 (s, 3H, $SiCH_3$); IR (neat) ν_{max} 3308, 2920, 2853, 1740, 1643, 1597, 1513, 1462, 1374, 1260, 1028 cm^{-1}; FABHRMS (NBA–NaI) *m/e* 1018.5054 (M^+ + H, $C_{52}H_{74}N_6O_{13}Si$ requires 1018.5082).

Cyclo(D-alanyl-L-alanyl-*O*-methyl-L-tyrosyl-L-alanyl-*N*-methyl-3(*S*)-hydroxy-L-tyrosyl-*N*,*O*-dimethyl-L-tyrosyl) Cyclic 5^4→6^3 Ether (*N*^{9}-Desmethyl-*O*-methylbouvardin, 51). A solution of **48** (5.0 mg, 0.0049 mmol) in THF–CH_3OH–H_2O (0.5 mL, 3:1:1) was treated with LiOH (0.7 mg, 0.015 mmol, 3 equiv) at 0 °C, and the mixture was warmed gradually to 25 °C (4 h). The reaction mixture was quenched by the addition of H_2O (2 mL), washed with EtOAc (2 × 2.0 mL), acidified to pH 4 with the addition of saturated aqueous citric acid, and extracted with EtOAc (4 × 4.0 mL). The combined organic layers were washed with H_2O (3 × 5.0 mL) and saturated aqueous NaCl (3 × 5.0 mL), dried (Na_2SO_4), concentrated *in vacuo*, and dried thoroughly to afford **49** (3.8 mg, 4.9 mg theoretical, 78% yield), which was used directly in the next reaction.

A solution of **49** (6.9 mg, 0.0069 mmol) in 2.0 N HCl–EtOAc (1.0 mL) was stirred at 25 °C (1 h). The volatiles were removed *in vacuo*, and the resulting solid was triturated with anhydrous Et_2O (3 × 1.0 mL) and dried thoroughly to afford **50** (5.2 mg, 5.4 mg theoretical, 96% yield), which was used directly in the next reaction.

A solution of **50** (5.2 mg, 0.0066 mmol) in distilled degassed DMF (2.2 mL) was treated with DPPA (7.3 mg, 0.026 mmol, 5.7 μL, 4 equiv) and $NaHCO_3$ (5.6 mg, 0.66 mmol, 10 equiv), and the resulting mixture was stirred at 0–4 °C (72 h). The reaction mixture was concentrated *in vacuo*, and H_2O (2.0 mL) and EtOAc (2.0 mL) were added. The aqueous phase was extracted with EtOAc (4 × 2.0 mL), and the combined organic layers were washed with 5% aqueous HCl (3 × 3.0 mL), saturated aqueous $NaHCO_3$ (3 × 3.0 mL), H_2O (3 × 3.0 mL), and saturated aqueous NaCl (3 × 3.0 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (SiO_2, 0.5 × 6.0 cm, 0–7% CH_3OH–$CHCl_3$) afforded **51** (2.2 mg, 5.1 mg theoretical, 43%) as a white solid: mp 241–243 °C; $[\alpha]^{25}_D$ –180 (*c* 0.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) 7.40 (dd, 1H, J = 2.3, 8.5 Hz, tyr$^{5\delta a}$), 7.28 (dd, 1H, J = 2.3, 8.5 Hz, tyr$^{5\delta b}$), 7.22 (dd, 1H, J = 2.3, 8.5 Hz, tyr$^{5\epsilon a}$), 7.03 (d, 2H, J = 8.6 Hz, tyr$^{3\delta}$), 6.84 (dd, 1H, J = 2.3, 8.5 Hz, tyr$^{5\epsilon b}$), 6.82 (d, 2H, J = 8.6 Hz, tyr$^{3\epsilon}$), 6.81 (d, 1H, partially obscured by tyr$^{3\epsilon}$, tyr^3 NH), 6.80 (d, 1H, J = 8.2 Hz, tyr$^{6\epsilon a}$), 6.68 (br d, 1H, J = 7.4 Hz, ala^4 NH), 6.56 (dd, 1H, J = 1.8, 8.2 Hz, tyr$^{6\delta a}$), 6.40 (d, 1H, J = 6.9 Hz, ala^1 NH), 6.18 (d, 1H, J = 8.8 Hz, ala^2 NH), 5.37 (br s, 1H, tyr$^{5\alpha}$), 4.99 (br s, 1H, tyr$^{5\beta}$), 4.84 (p, 1H, J = 7.1 Hz, ala$^{2\alpha}$), 4.75 (p, 1H, J = 7.4 Hz, ala$^{4\alpha}$), 4.52 (dd, 1H, J = 3.0, 11.7 Hz, tyr$^{6\alpha}$), 4.35 (p, 1H, J = 7.0 Hz, ala$^{1\alpha}$), 4.31 (d, 1H, J = 1.8 Hz, tyr$^{6\delta b}$), 3.92 (s, 3H, tyr^6 OCH_3), 3.77 (s, 3H, tyr^3 OCH_3), 3.59 (m, 1H, tyr$^{3\alpha}$), 3.36 (br s, 2H, tyr$^{3\beta}$), 3.11 (s, 3H, tyr^5 NCH_3), 3.06 (dd, 1H, J = 11.3, 18 Hz, tyr$^{6\beta b}$), 2.94 (dd, 1H, J = 3.0, 18.0 Hz, tyr$^{6\beta a}$), 2.67 (s, 3H, tyr^6 NCH_3), 1.33 (d, 3H, J = 6.9 Hz, ala$^{2\beta}$), 1.28 (d, 3H, J = 7.1 Hz, ala$^{1\beta}$), 1.10 (d, 3H, J = 6.6 Hz, ala$^{4\beta}$); IR (neat) ν_{max} 3332, 2963, 2923, 2851, 1730, 1666, 1651, 1514, 1445, 1415, 1261, 1092, 1021, 801 cm^{-1}; FABHRMS (NBA) *m/e* 773.3510 (M^+ + H, $C_{40}H_{48}N_6O_{10}$ requires 773.3511).

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