Simplified Cyclic Analogues of Bastadin-5. Structure−Activity Relationships for Modulation of the RyR1/FKBP12 Ca^{2+} Channel Complex

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Bastadin-5, a brominated macro-dilactam from the marine sponge *Ianthella basta*, enhances release of Ca^{2+} from stores within the sarcoplasmic reticulum (SR) of muscle and nonmuscle cells by modulating RyR1/FKBP12 complex. Analogues of bastadin-5 present desirable targets for SAR studies to shed light on the gating mechanism and locus of bastadin-5 binding on these heteromeric channels that mediate essential steps in early coupling of membrane excitation to Ca^{2+} signaling cascades. Simple, ring-constrained analogues of bastadin-5 were synthesized from substituted benzaldehydes in a convergent manner, featuring an efficient S_NAr macroetherification, and evaluated in an assay that measures [^{3}H]-ryanodine that is known to correlate with the functional open state of the Ca^{2+} channel. The simplified 14-membered ring, atropisomeric analogue (±)-**7**, like bastadin-5, enhanced ryanodine binding to the RyR1/FKBP12 complex (EC_{50} 11 μM), however, unexpectedly, the corresponding achiral 18-membered ring analogue **14** potently *inhibited* binding (IC_{50} 6 μM) under the same conditions. Structure−activity relationships of both families of cyclic analogues showed activity in a ryanodine binding assay that varied with substitutions of the Br atom on the trisubstituted aryl ring by various functional groups. The most active analogues were those that conserved the dibromocatechol ether moiety that corresponds to the 'western edge' of the bastadin-5 structure. These data suggest that cyclic analogues of bastadin-5 interact with the channel complex in a complex manner that can either enhance or inhibit channel activity.

Introduction

Natural products have played a major role in our current understanding of how FKBP12, an immunophilin, regulates both cellular signal processing and Ca^{2+} efflux within the junctional sarcoplasmic reticulum (JSR) of skeletal muscle tissue. Regulated Ca^{2+} release from the SR is critical for normal striated muscle contractility and dysfunctional Ca^{2+} channel conductance carries important consequences in disease states of skeletal and cardiac muscle. The immunophillins rapamycin (**1**) and FK506 (**2**) are two macrolide immunosuppressant compounds that bind to FKPB12 with high affinity and have been used to explore the RyR1/FKBP12 complex.[1−8] Bastadins are known compounds possessing newly identified properties: allosteric interactions with the RyR1/FKBP12 complex.[9−13]

Bastadin-5 (**3**) is one member of a family of over 20 bromotyrosine-derived macrolactams that have been isolated from the Verongid marine sponges *Ianthella basta* (Pallas), *I. flabeliformis*, *I. quadrangulata*, *I.* sp. and *Psammaplysilla purpurea*.[12,14−24] Our previous studies show that several, but not all, bastadins stimulate Ca^{2+} release from stores in the JSR by binding to the RyR1/FKBP12 channel in skeletal muscle. The most active member of the family is bastadin-5 (**3**, EC_{50} = 2.2 μM), while a constitutional isomer of **3**, bastadin-19 (**3a**), does not mobilize Ca^{2+} from the channel (EC_{50} > 100 μM), but competes for the binding site of bastadin-5.[13] Bastadin-5 also facilitates FK506-induced release of FKBP12 from RyR1, indicating the former may influence stability of the RyR1/FKBP12 complex.[13] Although these effects are concentration-dependent and follow saturable sigmoidal binding isotherms, the locus of binding of bastadin-5 to the RyR1/FKBP12 complex is not yet known.

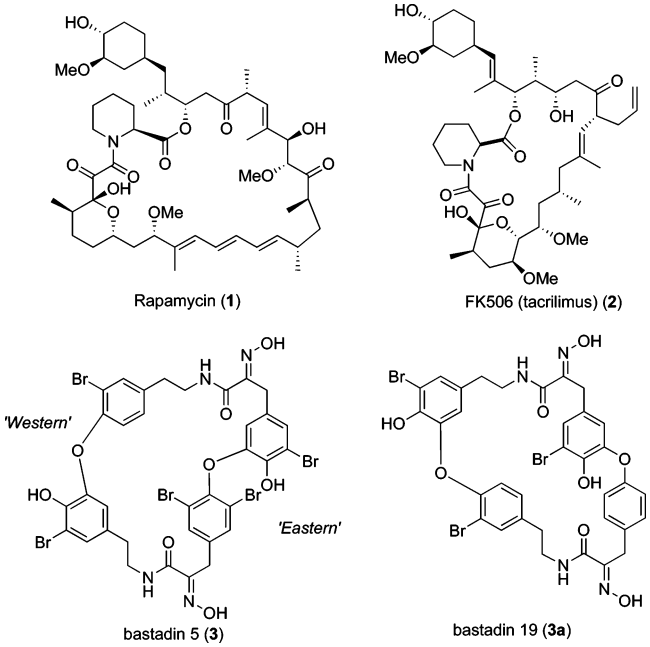

Figure 1. Natural products that interact with FKBP12 or the RyR1/FKBP12 complex.

The structure of **3** is comprised of four brominated, modified tyrosines and tyramines arrayed within a 28-membered macrodilactam. Biosynthetically, each half of the 28-membered ring macrocycle that is common to most bastadins appears to derive from oxidative coupling of one unit each of bromotyramine and bromotyrosine. The two halves are united through two amide

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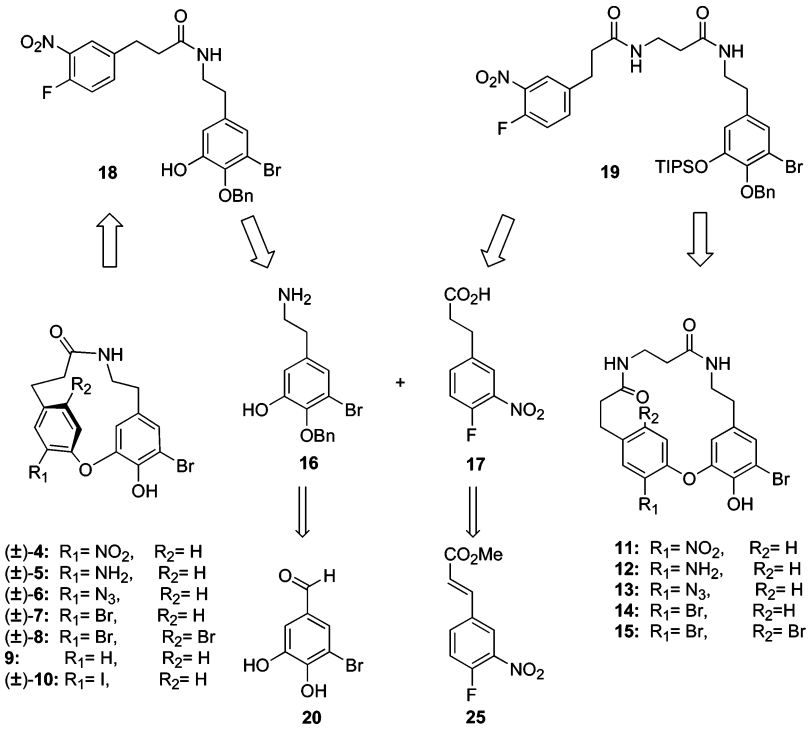
Scheme 1. Retrosynthetic Analysis for 14- and 18-Membered Ring Analogues of Bastadin-5



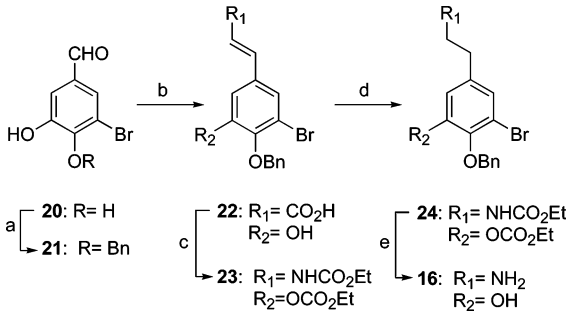
bonds to give a pseudo-tetrameric macrodilactam. Each of the 21 bastadins has an α-ketoxime that appears to derive from α-oxidation of the bromotyrosine. Oxidative modification may also occur at C5/C6 to introduce a vinyl bond (e.g. bastadin-4) or a C6 hydroxyl group (e.g. bastadin-7). The most active member of this family, bastadin-5 (**3**), stimulates release of Ca^{2+} from stores in the SR by binding to an as-yet unidentified site of the intact RyR1/FKBP12 complex in skeletal muscle tissues.[11,13] The RyR1/FKBP12 complex is a ~2.2 MDa heterotetrameric protein anchored within the junctional sarcoplasmic reticulum (JSR) and spans the 100 nm gap between the JSR and transverse tubule membranes. The RyR1 complex is therefore essential for orchestrating physiological Ca^{2+} release during excitation contraction coupling of skeletal muscle. Each monomeric polypeptide is composed of ~5000 amino acid residues folded into several transmembrane domains. Competition studies have revealed that the binding site of **3** is distinct from sites on the channel surface that are recognized as other SR Ca^{2+} channel effectors, such as Ca^{2+}, Mg^{2+}, ATP, caffeine, or the plant alkaloid ryanodine.[13] Bastadins mediate their effects upon the Ca^{2+} channel without compromising the RyR1/FKBP12 association, unlike FK506 which promotes the dissociation of FKBP12 from RyR1. While the macrolide FK506 was useful in revealing the nature of interaction of the large tetrameric channel complex with FKBP12, the bastadins have provided information on the intact RyR1/FKBP12 Ca^{2+} channel complex. For example, addition of **3** to Ca^{2+} channel preparations revealed the function of the RyR1/FKBP12 complexes as a regulator in the filling capacity of the Ca^{2+} stores by influencing the "leak state" conformation of RyR1.[10]

Members of the bastadin family show a range of potency (EC_{50} 2.3 to >100 μM) for binding to the RyR1/FKBP12 complex. Since the functional groups present in each bastadin are essentially the same, we hypothesize that this structural−activity relationship (SAR) is attributable to different preferred solution conformers of bastadins as a result of differences in nonbonded interactions (e.g. Br-steric interactions) in the 'western' and 'eastern' parts of the bastadins. Consequently, the altered torsional angles and even the overall shape of the molecule, may affect the receptor binding energy. We proposed the synthesis of simple rationally designed cyclic analogues of **3** (e.g. **4**−**15**), which embody the substituted catechol ethers of the 'western' hemisphere of **3** within two families of macrocycles bearing 14- and 18-membered ring sizes. Ring-constrained macrocycles with constrained aryl C−O−C−C torsional angles may reveal preferential ryanodine-binding agonism, which in turn may shed light on the minimum pharmacophore of **3**. We report here the results of a study which shows the minimal analogue **7** (EC_{50} = 11 μM), which embodies the bromocatechol ether unit found in **3**, has comparable activity to the natural product **3** in the ryanodine binding assay. Unexpectedly, compound **14**, a synthetic 18-membered ring analogue of **3**, was a potent antagonist in the same binding assay (IC_{50} = 6 μM) which suggests brominated catechol ethers exhibit a bimodal activity that varies with nonbonded interactions. Interestingly, the ketoximino group found in the natural products appears not to be required for activity. Our studies suggest a complex interplay of stereoelectronic factors in binding of bastadin-5 analogues to the RyR1/FKBP12 receptor, which suggests a bimodal model for Ca^{2+} gating, which may be tunable by a selection of properly designed 'second generation' analogues.

Synthesis

The retrosynthetic analysis shown in Scheme 1 reveals the design for preparation of cyclic analogues. We envisioned the 14-membered cyclic analogues, a smaller, ring-constrained macrocycle embodying a single amide bond, would derive from common intermediates **16** and **17**. The larger 18-membered analogues would include an additional β-alanine as a spacer. The units would be assembled by amide bond formation and the pivotal macrocyclization would be accomplished by S_NAr coupling according to Zhu and co-workers.[25,26] The nitro group in compounds **18** and **19** would activate the leaving group and serve as a handle to introduce variable functionality at this position through diazonium salt displacements.

Scheme 2. Synthesis of Substituted Phenethylamine **16**[a]



[a] Key: (a) i. Li_2CO_3, DMF, 45 °C, 1 h; ii. BnBr, 88% (b) i. malonic acid, pyridine, piperidine (cat.), toluene, reflux, 12 h; ii. 1 N HCl, 86%; (c) ethyl chloroformate, Hünig's base, acetone, 0 °C, 2 h; ii. NaN_3, H_2O, 0 °C; iii. EtOH, toluene, reflux, 12 h, 65%; (d) i. TFA, Et_3SiH, −10 °C, 0.5 h; ii. $NaHCO_3$ (aq), 94%; (e) hydrazine, KOH, 1,4-dioxane, reflux, 1 h, 92%

Simple Dreiding molecular models predicted that the 14-membered analogues would be locked into fixed conformations as atropisomers due to severe torsional strain that arises from rotation about the long axis of the *p*-*O*-aryl linkage, while the 18-membered ring analogues should retain relative conformational mobility.

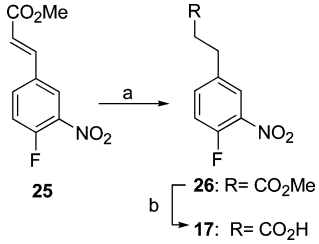
The synthesis of common intermediate **16** is illustrated in Scheme 2. Key considerations in the synthesis included management of the reductively sensitive aryl Br groups and *O*-benzyl protecting groups. Synthesis of substituted phenethylamine **16** was carried out using methodology we had optimized earlier to satisfy these criteria.[27]

The method is amenable to radio-labeling of analogues by insertion of tritium.[28] Selective benzylation of the more acidic hydroxyl of **20** was performed through a modification of a published procedure.[29] Pretreatment of catechol **20** with base (DMF, Li_2CO_3, 45 °C, 1 h) prior to the addition of benzyl bromide achieved selective benzylation of the *p*-OH group to provide **21** in good yield (88%). The position of benzylation was confirmed by NOE experiments. A Doebner-modified Knoevenagel reaction of **21** led to the requisite α,*β*-unsaturated acid **22** in 86% yield which was converted to enamide **23** by a Curtius rearrangement of the corresponding acyl azide (65% over three steps).[30] Cationic hydrogenation of enamide **23** gave carbamate **24 (**94%).[27] Standard conditions for hydrolysis of methyl/ethyl carbamates (e.g. (KOH, H_2O, EtOH, reflux) were ineffective when applied to **24**: either starting material or the corresponding oxazolidone, formed by cyclization/elimination of MeOH/EtOH, were returned. More forcing conditions (NH_2NH_2, KOH, 1,4-dioxane, 80 °C) gave phenethylamine **16** in good yield (92%).

Hydrogenation of methyl 4-fluoro-3-nitrocinnamate (**25**) in the presence of Wilkinson's catalyst[31] with careful control of H_2 pressure and temperature gave methyl ester **26** in excellent yield (95%)[32] without reduction of the nitro functionality. Saponification of ester **26** completed the synthesis of the dihydrocinnamic acid **17** (86%) (Scheme 3).

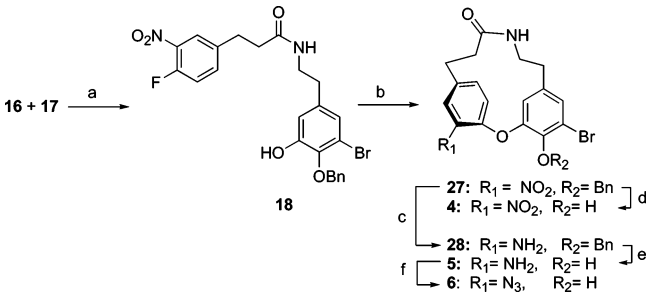
Two possible routes to the cyclic intermediates were considered: S_NAr coupling of a suitable aryl fluoride with a phenol followed by macrolactamization, or the reverse sequence of reactions. In the event, the latter method proved to be the most efficient (Scheme 4) whereas the former resulted in uniformly poor yields of cyclic product (<10%). Amide coupling of intermediates **16** and **17** afforded the macroetherification precursor **18** in 72% yield. Macroetherification of **18** under dilute conditions (2 mM, K_2CO_3, 4 Å sieves, DMSO, RT) smoothly converted **18** to lactam **27** in high yield (85%).

Scheme 3. Synthesis of Common Intermediate **17**[a]



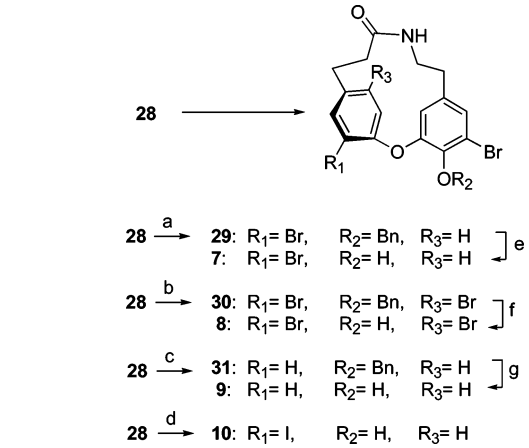
[a] Key: (a) $RhCl(PPh_3)_3$, H_2 (3 atm), toluene, 8 h, 95%; (b) i. LiOH, THF, H_2O, MeOH (4:1:1); ii. HCl aq (0.5 M), 86%.

Scheme 4. Synthesis of 14-Membered Analogues **4**, **5,** and **6** via Macroetherification[a]



[a] Key: (a) i. EDCI, HOBT, CH_2Cl_2, RT, 12 h; ii. 0.5 N HCl, 72%; (b) i. K_2CO_3, DMSO (2 mM), 4 Å sieves, 2 h; ii. 1 N HCl, 85%; (c) i. $CrCl_2$, DMF, RT, 12 h; ii. 1 N HCl, 73%; (d) BBr_3, −78 °C, 1 h, 91%; (e) BBr_3 −78 °C, 1 h, 58%; (f) i. AcOH/H_2O, 9:1, $NaNO_2$, 0 °C; ii. NaN_3, 0 °C, 66%.

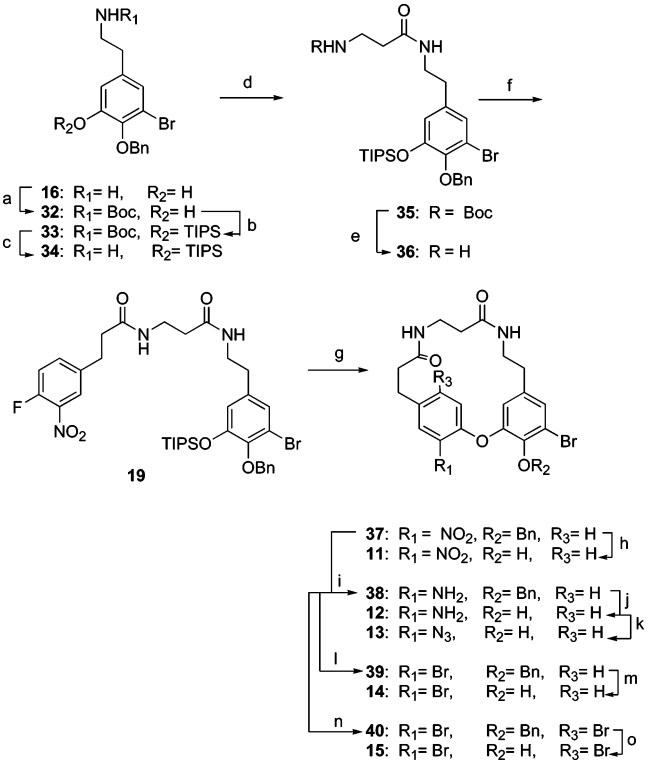
Scheme 5. Preparation of *C*-Aryl-Substituted 14-Membered Ring Analogues[a]



[a] Key: (a) i. $CuBr_2$ (0.8 equiv), ^tBuONO, CH_3CN, 0 °C, 1 h; ii. **27** in portions, 0 °C, 2 h then warmed to room temperature; iii. 1 N HCl, 66% (b) i. $CuBr_2$ (10 equiv), ^tBuONO, CH_3CN, 0 °C, 1 h; ii. **28** in portions, 0 °C, 2 h then warmed to room temperature; iii. 1 N HCl, 32%; (c) i. ^tBuONO, THF, 0 °C, 1 h; ii. **28** in portions, 0 °C, 2 h then warmed to room temperature; iii. 1 N HCl, 39%; (d) i. H_2SO_4, AcOH, $NaNO_2$, 0 °C, 0.5 h; ii. **28** in portions, 0 °C, 1 h then warmed to room temperature, 20 min; iii. KI, H_2O, rt, 15 min then warmed to 70 °C, 15 min, 16%; (e) BBr_3, −78 ° C, 1 h, 91%; (f) TFA, rt, 24 h, 70%; (g) TFA, rt, 24 h, 75%.

Removal of the benzyl group provided the 14-membered ring-constrained analogue **4**. Reduction of lactam **27** to the aniline derivative **28** under conditions that preserved the reductively sensitive aryl Br groups ($CrCl_2$, DMF, room temperature, 73%) and set the stage for the synthesis of several analogues via diazonium salts (Scheme 5). Removal of the benzyl group from **28** gave aniline **5**. The diazonium salt prepared from **5** was quenched with sodium azide to give the azido analogue **6** in 66% yield.[33] The dibromo or tribromide compounds **29** and **30** were procured in acceptable yields by Sandmeyer-type reaction

Scheme 6. Synthesis of 18-Membered Analogues by S_NAr Macroetherification[a]



[a] Key: (a) i. Boc_2O, CH_3CN, rt, 12 h; ii. Na_2CO_3, MeOH, H_2O (4:1), rt, 76%; (b) TIPSCl, DMF, rt, 24 h, 95%; (c) i. TFA, CH_2Cl_2, (1:1), rt, 1h; ii. $NaHCO_3$ (aq), 95%; (d) i. *N*-Boc-*β*-alanine, EDCI, HOBt, CH_2Cl_2, rt, 12 h; ii. 0.5 N HCl, 92%; (e) i. TFA, CH_2Cl_2, (1:1), rt, 1 h; ii. $NaHCO_3$ (aq), 97%; (f) i. **17**, EDCI, HOBt, CH_2Cl_2, rt, 12 h; ii. 0.5 N HCl; 93%; (g) CsF, DMSO (2 mM), 4 Å sieves, rt, 20 h, 84%; (h) BBr_3, CH_2Cl_2, rt, 8 h, 82%; (i) $CrCl_2$, DMF, rt, 12h, 55%; (j) BBr_3, CH_2Cl_2, rt, 8 h, 54%; (k) i. AcOH/H_2O, 9:1, $NaNO_2$ 0 °C; ii. NaN_3, 0 °C, 69%; (l) i. $CuBr_2$ (0.8 equiv), ^tBuONO, CH_3CN, 0 °C, 1 h; ii. 40 in portions, 0 °C, 2 h then warmed to room temperature; iii. 1 N HCl, 25%; (m) BBr_3, CH_2Cl_2, rt, 8 h, 94%; (l) i. $CuBr_2$ (3.0 equiv), ^tBuONO, CH_3CN, 0 °C, 1 h; ii. 40 in portions, 0 °C, 2 h then warmed to room temperature; iii. 1 N HCl, 29%; (m) BBr_3, CH_2Cl_2, rt, 8 h, 72%.

of the corresponding diazonium salts prepared from **28** (*tert*-$BuNO_2$, CH_3CN) and use of carefully controlled amounts of $CuBr_2$ (0.8 or 10 equiv; respectively). The use of substoichiometric $CuBr_2$ (0.8 equiv) resulted in formation of **29**, however, excess $CuBr_2$ (10 equiv) gave the brominated product **30**.[34] Compound **28** suffered unexpected reductive deamination when the corresponding diazonium salt was prepared with *tert*-$BuNO_2$ in the presence of THF to give compound **31**, presumably by hydride abstraction from the solvent.[34b] Quenching the latter diazonium salt potassium iodide resulted in aryl iodide **10**. Removal of the benzyl protecting group in **29**, **30**, and **31**, as before, yielded the corresponding phenolic 14-membered analogues **7**, **8**, and **9**, respectively.

Synthesis of the 18-membered ring analogues is illustrated in Scheme 6. Phenol **32** was protected as a triisopropylsilyl ether (95%) followed by removal of the *N*-Boc under standard conditions to provide amine **34** (97%), which was coupled, in turn, with *N*-Boc-*β*-alanine to afford amide **35** in 92% yield. Removal of the Boc group from **35** as before (97%) followed by coupling of the resultant free-amine **36** to acid **17** (EDCI, HOBt, CH_2Cl_2) provided the precursor for cyclization **19** in 92% yield. One-pot, tandem removal of the TIPS protecting group and macroetherification of **19** with CsF smoothly produced the 18-membered cyclic product **37** in excellent yield (84%). The nitro group in lactam **37** was reduced as before to provide the aniline **38** (58%) which was deprotected to provide phenolic amine **12** (54%). Diazotization, substitution, and deprotection reactions were carried out using similar sequences to those described above to provide azido analogue **13** (69%), dibromo analogue **14**, and tribromide **15**.

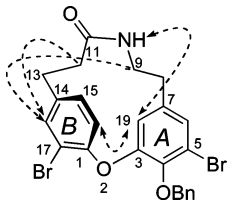


Figure 2. Representative NOEs of **29**.

Structure and Biological Evaluation

For the purpose of discussion, the 14-membered analogues are numbered according to Figure 2. The simple cyclic analogues were designed to embody the 'western' portion of **3** but with different ring sizes and substitutions on ring B (C17). It was hypothesized that the 'western' portion of **3** composed the minimum pharmacophore, where variation of the torsional angle (C1−O2−C3−C4) would modulate activity. The highly constrained 14-membered analogues would contain fewer degrees of freedom and simultaneously constrain both the biphenyl ether angle (C1−O2−C3) and the torsional angle (C1−O2−C3−C4) compared to the larger 18-membered analogues. Varying the substitution on ring B may reveal electronic effects upon the binding of bastadin analogues to the RyR1/FKBP12 complex.

Solution and solid-state conformation studies of the analogues **4**-**15** were ascertained from NMR NOE and chemical shift analysis (Figure 2, Table 1), and X-ray crystal structure analysis (Figure 3). With the exception of compound **9**, the 14-membered cyclic analogues are chiral and exhibit atropisomerism due to restricted rotation. Consequently the latter compounds were synthesized as racemates. Evidence for atropisomerism is seen in the NMR data as illustrated by spectral interpretation of lactam **29** (the precursor to **7**) as follows (Figure 2, Table 1). The ^1H NMR spectrum of **29** showed a diagnostic two-proton signal with an 'AB quartet' *J* coupling pattern (δ 5.18, d, 1H, J = 11 Hz; δ 5.34, d, 1H, J = 11 Hz) corresponding to diastereotopic *O*-benzyloxy protons. Restricted rotation about the catechol ether linkage (C1−O2−C3) was also evident from diamagnetism due to ring current effects leading to an exceptionally high field H19 aryl proton signal (δ 5.06, 1H, J = 2.0 Hz).

The constrained conformation of **29** places H19 in ring A within the shielding region that is close to a perpendicular extended from center of ring B. Complexity in ^1H NMR signals of other CH_2 signals in **29** was also consistent with diastereotopic methylene groups and, likewise, seen in the ^1H NMR spectra of **7** and other products derived from **28**, except **9**. The debromo analogue **9**, where free rotation about the 1,4-axis of the disubstitued phenyl ring is allowed and the barrier to macrocyclic torsional inversion is relaxed, shows no atropisomerism.

A rigid, compact conformation of analogue **29** was supported by NOE experiments (Figure 2, Table 1). Representative NOEs of **29** are consistent with a conformation where ring B lies close to parallel with a plane that bisects ring A (Figure 2). The solid-state conformations of **4** and **9** were determined by X-ray crystallography (Figure 3). The catechol ether torsional angles in **4** are 83.0° (C3−O2−C1−C17) and 152.4° (C1−O2−C3−

Table 1. NMR Data for **29** (400 MHz, $CDCl_3$)

no.	^{1}H δ, m, J (Hz)	^{13}C (ppm)	COSY	HMBC	NOE
1		152.9			
3		154.6			
4		136.4			
5		117.9			
6	6.88 dd (2.0, 1.2)	125.8	H19, H8	C5, C7, C19, C8	
7		142.8			
8	2.64 m	30.5	H9		H6, H9, H10; H19
9	3.29 m	39.7	H8; H10		H8, H10; H18
10	4.90 m		H9		H8, H9, H12, H19
11		171.1			
12	2.29 m	41.0	H13	C11, C13, C14	H10, H13, H15, H18
13	3.00 m	31.7	H12	C11, C12, C14; C15, C18	H12, H15; H18
14		140.6			
15	7.23 dd (8.4, 2.4)	130.4	H16; H18	C1, C13, C15; C17	H13, H16
16	7.05 d (8.4)	126.0	H15	C1, C18	H15, H19
17		118.7			
18	7.51 d (2.4)	134.6	H15	C1, C13, C15; C17	H12, H13
19	5.06 d (2.0)	113.1	H6	C3, C7, C8, C6	H9, H10; H16
20a	5.34 d (10.8)	75.2	H20b	C4, C21; C (22−26)	
20b	5.18 d (10.8)	75.2	H20a	C4, C21, C (22−26)	
21		137.0			
22−26	7.3−7.4 m; 7.61−7.64 m	128.8, 128.4, 128.2	H22−26	C20, C22−C26)	

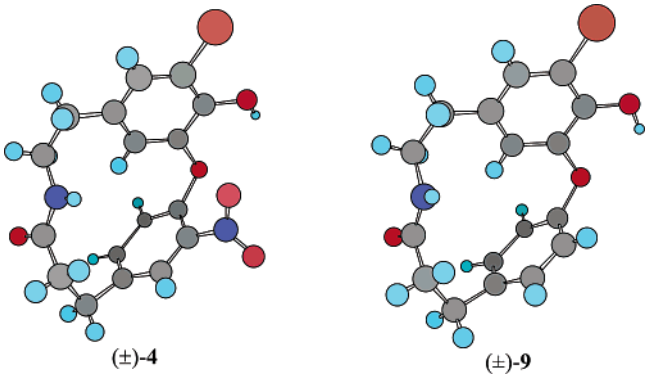


Figure 3. X-ray crystal structures of (±)-**4** and **9**.

C4). The bond angle (C1−O2−C3) of 110.7° deviated slightly from that expected from sp^3 hybridization. Slight bending of the aromatic ring B from planarity (C15−C14−C18−C17, 9.5°) was also evident, compensating in part for the ring strain. Few differences between the solution state conformation and the solid conformation were ascertained; this is not unexpected due to the rigidity imposed by torsional strain within these compounds. Comparison of the X-ray crystal structures of analogues **4** and **9** revealed identical bond angles and distances of their respective carbon skeletons. As expected, the 18-membered counterparts **11**−**15** did not show atropisomerism due to the additional degrees of freedom conferred by the β-alanine linker.

The barrier to rotation in the 14-membered ring analogue **29** was briefly examined by temperature dependent ^{1}H NMR (d_6-DMSO). At temperatures up to T = 105 °C the ^{1}H NMR line shapes of the *O*-Bn signals in **29** remained sharp and revealed no tendency toward coalescence or broadening which suggests a barrier to rotation >17 kcal/mol.[35]

Biological Activity

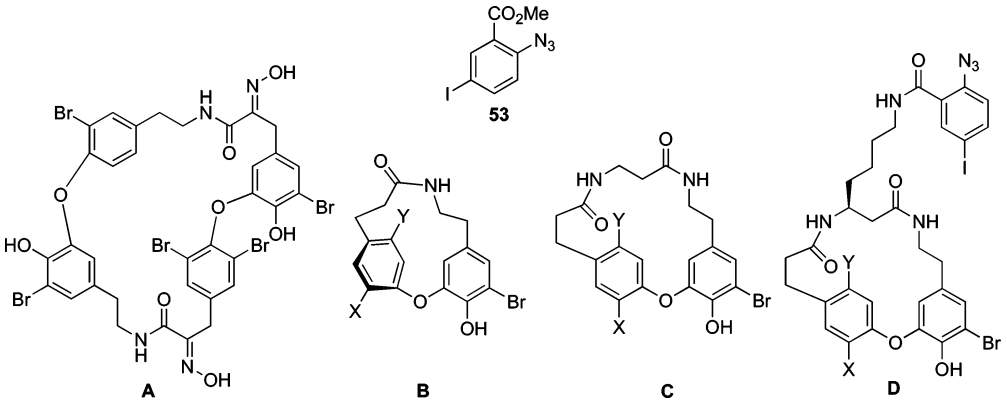
Biological evaluation of the synthetic analogues **4**−**15**, together with bastadin-5 (**3**), was carried out using the [^{3}H]-ryanodine binding assay (Table 2). The assay provides a 'readout' of the open state of the Ca^{2+} channel by detection of [^{3}H]-ryanodine bound to the protein which occurs only in the open state.[13] In earlier studies, we showed that [^{3}H]-ryanodine binding correlates with the functional properties of bastadin-5 (**3**), in particular, transport of Ca^{2+} across the channel and alteration of channel gating (open state probability).[13]

Equilibrium binding of [^{3}H]-ryanodine to skeletal JSR was measured in the presence of analogue and solvent DMSO, or solvent alone (DMSO, 0.5% v/v final concentration), together with assay buffer containing 250 mM KCl, 15 mM NaCl, 20 mM HEPES, 20 μM Ca^{2+}, pH 7.4. Nonspecific binding was determined in the presence of 1 μM cold ryanodine.

Most of the 14-membered ring analogues retained at least some of the potency of **3** on the ryanodine binding to the RyR1/FKBP12 complex. The most potent agonist was **7** (EC_{50} = 11 μM) with a structure corresponding to the substitution pattern of bastadin-5. Substitution of the bromine at C17 in ring B by different functional groups (NO_2, NH_2, H, I, N_3) diminished ryanodine binding. Replacement of the bromine with a nitro group in compound **4** resulted in a 2-fold loss of activity (EC_{50} = 21 μM), whereas the amino analogue **5** (EC_{50} = 33 μM) and the iodo analogue **10** (EC_{50} = 28 μM) retained only a third of the activity of **7**. The debromo analog **9** (EC_{50} < 100 μM) was nearly inactive underscoring the importance of the dibromocatechol ether moiety at the western edge of the bastadin-5 structure. Despite almost identical conformations (X-ray), analogues **4** and **9** showed the largest difference in ryanodine binding among the 14-membered ring analogues (EC_{50} = 21 and >100 μM, respectively). Since the nitro group is expected to occupy space equivalent to the van der Waals radius of a Br atom, it is tempting to speculate that stereoelectronic effects may be responsible for differences in biological activity. Unfortunately, we cannot be more definitive without additional data on the locus of binding of bastadin-5 at the receptor surface and knowledge of the putative amino acid residue contacts that mediate the binding contacts. The addition of a third Br atom on ring B in analogue **8** resulted in total loss of agonist activity in this 14-membered ring analogue (EC_{50} < 100 μM) although, curiously, this was not the case in the corresponding 18-membered ring analogue (see below).

An unexpected trend was revealed by measurements of ryanodine binding in the presence of the 18-membered ring analogues: two of the five compounds were *inhibitors* of ryanodine binding, which suggests inhibition of Ca^{2+} channel opening. While the amino- and azido-substituted 18-membered ring compounds (**12** and **13**, respectively) showed weak activity in promoting channel activation (EC_{50} 21 μM and 24 μM),

Table 2. Structure−Activity Relationships of Bastadin-5 (**3**) and Analogues[a]



entry	compound	skeleton	X	Y	EC_{50} (μM)[b]	IC_{50} (μM)[c]
1	**3**	A	−	−	2.2 ± 0.1	−
2	(±)-**4**	B	NO_2	H	20.9 ±10.8	−
4	(±)-**5**	B	NH_2	H	33.0 ±12.2	−
5	(±)-**6**	B	N_3	H	−	63 ±8.1
6	(±)-**7**	B	Br	H	10.9 ±2.6	−
7	(±)-**8**	B	Br	Br	>100	−
8	(±)-**9**	B	H	H	>100	−
9	(±)-**10**	B	I		28.6 ±14.2	−
10	**11**	C	NO_2	H	24 ± 3.9	−
11	**12**	C	NH_2	H	21 ±5.7	−
12	**13**	C	N_3	H	20.0 ± 2.3	−
13	**14**	C	Br	H	−	6.2 ±1.2
14	(±)-**15**	C	Br	Br	−	47 ± 15
15	**49**	D	Br	H	>100	
16	**52**	D	Br	Br	6.5 ±0.7	
17	**53**				>100	

[a] Equilibrium binding of 1 nM [^{3}H]-ryanodine to skeletal junctional sarcoplasmic reticulum (SR) was performed in assay buffer containing 250 mM KCl, 15 mM NaCl, 20 mM HEPES, 20 μM Ca^{2+}, pH 7.4. Nonspecific binding was determined in the presence of 1 μM cold ryanodine. [b]Agonist-like activity (enhanced ^{3}[H]-ryanodine binding). [c]Antagonist-like (reduced ^{3}[H]-ryanodine binding)

compound **14** with the bastadin-5-like substitution pattern was a more potent inhibitor (IC_{50} = 6 μM, Figure 4), in diametric opposition to that of the 14-membered ring **7** with the same aryl substitution pattern which is agonist-like (EC_{50} 11 μM). The remaining compounds in the 18-membered ring series showed weaker agonist-like activity (EC_{50}s 24−58 μM).

These results suggest the interaction of simple bastadin-5 analogues with the RyR1/FKBP12 is more complex and shows a broader range of action than expected. Each of the active 14-membered ring analogues were synthesized as racemic mixtures, but we predict that specific protein−drug contacts with the binding site should favor only one of the two enantiomers of each compound. Consequently, it would be of interest to investigate the ryanodine binding and Ca^{2+} transport activity of an enantiopure preparation of the most active analogue, **7**.

Photoaffinity Analogues. With the ryanodine-binding properties of both 14-membered and 18-membered ring analogues in hand, we asked the question, 'can a simple photoaffinity analogue of **3** be designed which retains high potency for the RyR1/FKBP12 complex?' Using the key design principles from the 18-membered ring series, we replaced the β-alanine with a β-lysine residue to prepare an 18-membered macrolactam that contains a primary amino group that would could be acylated at the ϵ-NH_2 group with a photoreactive azidobenzoic acid. Photolysis of the derived azidobenzamide analogue of **3** would produce a nitrene that may covalently bond to the RyR1/FKPB12 complex. Tryptic digestion and MS analysis of the photolabeled RyR1/FKPB12-derived peptides from the exposed surface may reveal the consensus amino acid sequence of the bastadin binding site.

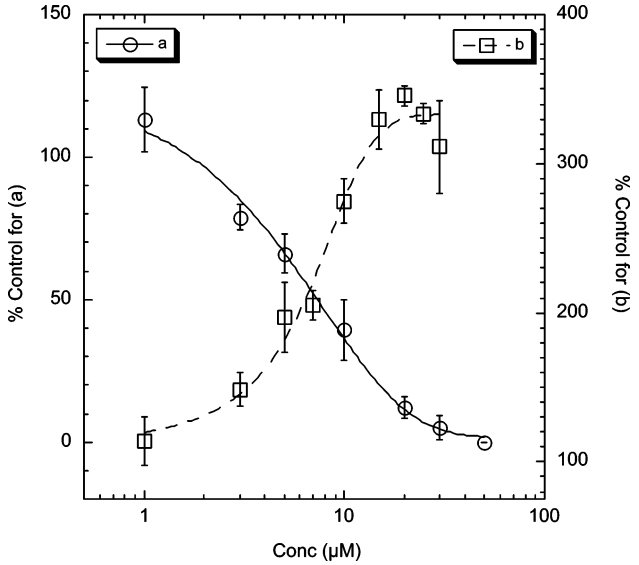
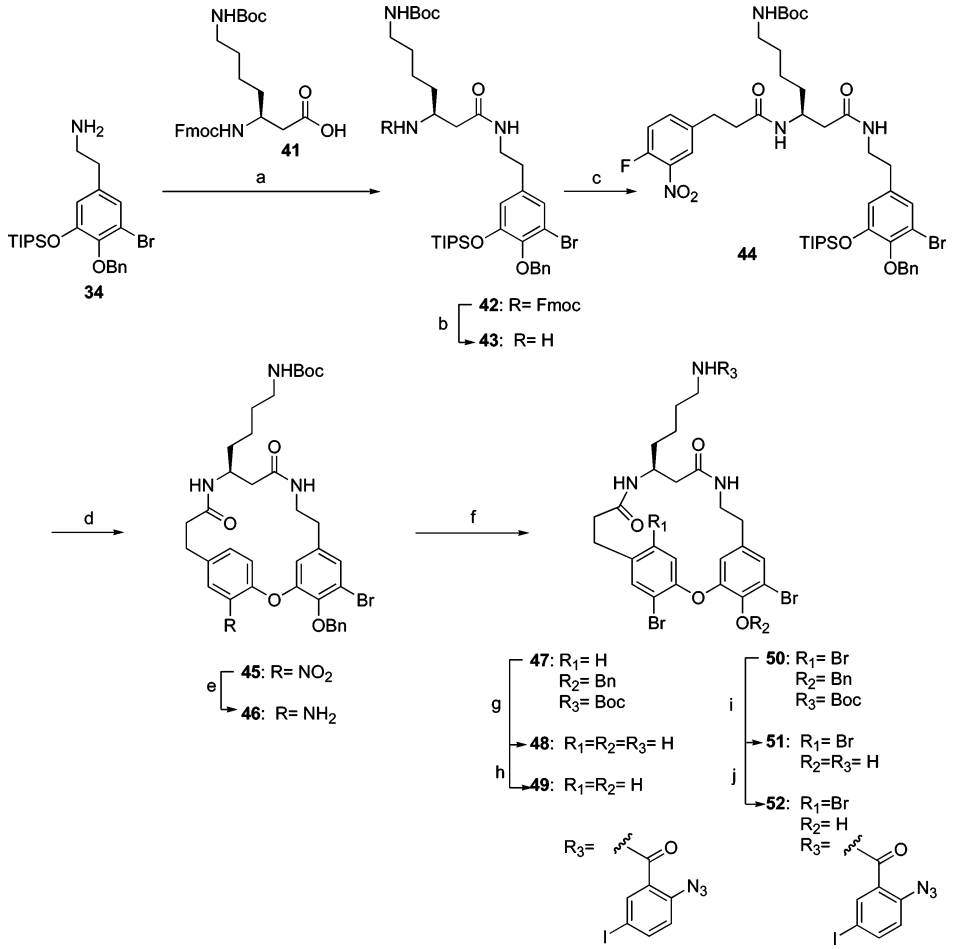


Figure 4. Concentration-dependent enhancement/inhibition of the binding of 1 nM [^{3}H]-ryanodine to RyR1−FKBP12 in skeletal SR by bastadin analogues (a) **14** and (b) **52**. Equilibrium binding of 1 nM [^{3}H]-ryanodine to skeletal junctional sarcoplasmic reticulum (SR) was performed in assay buffer containing 250 mM KCl, 15 mM NaCl, 20 mM HEPES, 20 μM Ca^{2+}, pH 7.4. Control (1% DMSO aq) = 0.175 pmol [^{3}H]-ryanodine/mg SR. Nonspecific binding was determined in the presence of 1 μM cold ryanodine. Measurements were carried out in triplicate; error bars represent ± SD.

Differentially *N*-protected β-lysine (**41**) was coupled (EDCI, HOBt) to bromotyramine **34** (Scheme 7), followed by removal of the β-*N* Fmoc protecting group (81%) and coupling to the

Scheme 7. Synthesis of Photoaffinity Analogues by S_NAr Macroetherification[a]



[a] a. i. EDCI, HOBt, CH_2Cl_2, **41**;[36] ii. H^+, 81%; b. *N*,*N*,*N*,*N*-tetramethylethylenediamine, CH_2Cl_2; c. EDCI, HOBt, CH_2Cl_2, **17** 86% two steps; d. K_2CO_3, 4 Å mol. sieves, DMSO, 75%; e. $CrCl_2$, DMF, 85%; f. *t*-BuONO, $CuBr_2$, CH_3CN, 38% of **47,** 42% of **50**; g. BBr_3, CH_2Cl_2; h. 2-azido-5-iodobenzoic acid,[37] EDCI, HOBt, DMF, **48**, 33% two steps; i. BBr_3, CH_2Cl_2 j. 2-azido-5-iodobenzoic acid,[37] EDCI, HOBt, DMF, **51**, 48% two steps.

substituted dihydrocinnamic acid **17** to give the *N*,*N*′-diacyl *β*-lysine **44** (86% over two steps). Exposure of **44** to standard S_NAr macroetherification conditions gave cyclic analogue **45** in very good yield (75%). Transformation of the NO_2 group in **44** to the corresponding analogues (replacement of NO_2 by Br (**47**) and the overbrominated product **50**) was achieved, as before, by reduction−diazonium salt displacements. Finally, simultaneous deprotection of the aryl ethers and *ϵ*-*N*-Boc protecting group in each of the latter compounds, followed by coupling to 2-azido-5-iodobenzoic acid[37] (EDCI, HOBt) gave the corresponding photoaffinity analogues **49** and **52**, respectively, in acceptable yields (two steps, 33% and 48%, respectively).

When tested in the ryanodine binding assay, each of the photoaffinity analogues gave very different results. Compound **49** was essentially inactive (EC_{50} >100 μM), however, dibromo compound **52** showed very potent agonist-like activity (EC_{50} = 6 μM, Figure 4). It should be noted that the methyl ester **53** prepared from 2-azido-5-iodobenzoic acid (CH_2N_2, Et_2O, 0 °C), was inactive in this assay. Compound **52** shows binding affinity for the receptor similar to that of bastadin-5 (**3**), and its synthesis is amenable to introduction of radiolabel for preparation of [^{125}I]-**52**. Consequently, **52** should provide a suitable probe for photoaffinity labeling of the RyR−FKBP12 complex.

Conclusion

The synthesis of simple, ring-constrained cyclic analogues of bastadin-5, with structures that embody the 'western' edge of **3**, was accomplished by an efficient, macrocyclization based on intramolecular S_NAr substitution. Assay of two classes of analogues that differ in ring size and aryl substitution patterns in the [^{3}H]-ryanodine binding assay, which detects the open state of the RyR1/FKBP12 Ca^{2+} channel, revealed an interesting bimodal range of activity represented by compounds with agonistic and antagonistic properties. In each of the two families, the compound structures that embodied the same 'western edge' substitution pattern found in native bastadin-5 (dibromocatechol ether) showed the highest activities. Members of the smaller 14-membered ring family, constrained by a conformationally rigid macrocycle, exhibited atropisomerism. The synthesis of an active photoaffinity probe **52**, based on the structure of bastadin-5, has been achieved. The synthetic design of **52** should facilitate preparation of [^{125}I]-**52** for use in defining the bastadin-5 binding locus on the surface of the heterotetrameric RyR1/FKBP12 complex that constitutes the membrane bound Ca^{2+} channel of the SR. The unexpected antagonistic activity of the 18-membered ring analogues suggests more complex interactions occur between the receptor site and this family of ligands. A bimodal gating model that accommodates binding−activation−inactivation of the RyR1/FKBP12 complex by bastadin-5 analogues suggests the possibility that Ca^{2+} release from the SR may be modulated by 'fine-tuning' of stereoelectronic factors. Tuned release of Ca^{2+} from stores by custom-designed ligand-gate interactions between small molecule analogues of **3** and the RyR1/FKBP12 complex is an attractive idea that may have practical benefits in treatment of disease

conditions that arise from complications of defective SR Ca^{2+} channel activity, including arrythmias, heart failure, and malignant hypothermia.[38]

Experimental Section

General. TLC was carried out on aluminum plates coated with silica (0.2 mm) containing a fluorescent indicator. Spots were visualized was under a UV lamp then sprayed with a solution of vanillin in ethanolic-H_2SO_4, or ninhydrin in ethanol followed by heating. Purity of each compound was established as >95% by ^{1}H NMR and HPLC. Pyridine, triethylamine, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) were distilled from glass over CaH_2. Dichloromethane, acetonitrile, toluene, tetrahydrofuran, and 1,4-dioxane were dried through commercial alumina cartridge. Optical rotations were recorded on a Jasco DIP-370 instrument. IR spectra were recorded on a Mattson Galaxy FTIR. ^{1}H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, in the stated solvent (≥99.5% atom D) and referenced to residual protonated solvent signal (δ_H $CDCl_3$ 7.24 ppm; CD_3OD, 3.30 ppm; $\delta_C CDCl_3$ 77.00 ppm, CD_3OD, 49.00 ppm).

[^{3}H]-Ryanodine Binding Asssay. Specific binding of [^{3}H]-ryanodine to high affinity sites on rabbit skeletal membrane vesicles[13,39] was determined by incubating SR protein (25 μg), containing the RyR1−FKBP12 complex, with [^{3}H]-ryanodine (1 nM) for 3.5 h at 37 °C in binding assay buffer containing KCl (250 mM), NaCl (15mM), HEPES (20 mM), and $CaCl_2$ (20 μM) and at pH 7.4 (500 μL, final volume). The binding reaction was initiated by addition of a solution of the drug in DMSO (final DMSO concentration ~1%) to the complete assay medium, and the incubation was terminated by filtration through Whatman GF/B glass fiber filters using a Brandel cell harvester (Gaithersburg, MD). Separation of bound and free [^{3}H]-ryanodine was performed by washing the filters with ice-cold buffer (3 × 500 μL) containing Tris-HCl (20 mM), KCl (250 mM), and NaCl (15 mM) at pH 7.4. Filters were placed in scintillation vials containing scintillant (5 mL). Treatments and controls were measured in triplicate, and bound radioactivity (dpm) was measured by scintillation counting and corrected for background. Ryanodine affinity curves were plotted and fitted to sigmoidal functions (Origin, Microcal Software, Inc., Northampton, MA). Error bars represented in Figure 4 are ±1 standard deviation. Positive controls were bastadin-5 (EC_{50} 2.0 μM) and PCB95 (2,2′,3,5′,6-pentachlorobiphenyl),[40,41] and nonspecific binding was determined in the presence of 100-fold 'cold' ryanodine.

5-Bromo-4-hydroxy-17-nitro-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (4). BBr_3 (20 μL, 0.21 mmol) was added to a solution of lactam **27** (20 mg, 0.04 mmol) in CH_2Cl_2 (300 μL) at −78 C. The orange solution was stirred (1 h, −78 °C), quenched with $NaHCO_3$ (aq, satd), and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **4**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) gave **4** (15.0 mg, 91%) as an amorphous solid: mp 259−260 °C (CH_2Cl_2/MeOH); IR (ZnSe, neat) ν 3282, 2933, 1642, 1531, 1346 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 2.40 (t, J = 6.3 Hz, 2H), 2.60−2.64 (m, 2H), 3.00−3.20 (m, 4H), 5.28 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.93 (brs, 1H) 7.29 (d, J = 8.4 Hz, 1H), 7.63 (dd, J = 8.4, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 8.90 (brs, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 30.8 (CH_2), 32.0 (CH_2), 40.2 (CH_2), 40.6 (CH_2), 110.3 (C), 114.3 (CH), 126.7 (CH), 127.4 (CH), 127.9 (CH), 134.0 (C), 137.4 (C), 141.9 (C), 142.3 (C), 144.9 (C), 150.3 (C), 151.1 (CH), 170.9 (C); HRMS (DEI) found m/z 406.0179 [M]$^+$, $C_{17}H_{15}N_2O_5Br$ requires 406.0164.

17-Amino-5-bromo-4-hydroxy-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (5). BBr_3 (2 μL, 0.02 mmol) was added to a solution of lactam **28** (3 mg, 0.006 mmol) in CH_2Cl_2 (300 μL) at −78 °C. The orange solution was stirred (1 h, −78 °C), quenched with a $NaHCO_3$ (aq, satd), and extracted with EtOAc (3 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **5**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) gave **5** (1.4 mg, 58%) as an amorphous solid: IR (ZnSe, neat) ν 3371, 2927, 1635, 1502, 1434 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.15−2.23 (m, 1H), 2.32−2.38 (m, 1H), 2.57−2.71 (m, 2H), 2.86−2.94 (m, 2H), 3.25−3.57 (m, 2H), 4.89 (brs, 1H), 5.36 (d, J = 1.6 Hz, 1H), 5.79 (brs, 1H), 6.62−6.67 (m, 2H), 6.82−6.84 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 30.2 (CH_2), 32.2 (CH_2), 39.7 (CH_2), 41.1 (CH_2), 109.2, 112.7, 120.2, 124.7, 125.06, 131.3, 132.4, 140.3, 141.0, 142.2, 171.8; HRMS (DEI) found m/z 376.0434 [M]$^+$, $C_{17}H_{17}N_2O_3Br$ requires 376.0423.

17-Azido-5-bromo-4-hydroxy-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (6). $NaNO_2$ (0.2 mg, 3 μmol) was added in one portion into a chilled solution (0 °C, ice bath) of arylamine **5** (1.0 mg, 0.003 mmol) in AcOH/H_2O (20 μL, 9:1). The solution was allowed to stir 15 min followed by the addition of NaN_3 (1.0 mg, 0.015 mmol) in one portion. After 0.5 h, the reaction was quenched with H_2O and was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **6**. HPLC purification (C_{18} 5 μm Microsorb 10 × 250 mm, MeOH/H_2O, 3:2, 4 mL/min, rt, 6.4 min) provided **6** (0.7 mg, 66%) as an oil: IR (neat) ν 3241, 2923, 2115, 1639, 1500 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.33−2.38 (m, 2H), 2.63−2.67 (m, 2H), 2.94−2.99 (m, 2H), 3.13−3.17 (m, 2H), 5.18 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 7.01−7.11 (m, 3H), 7.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.7 (CH_2), 32.6 (CH_2), 40.5 (CH_2), 41.4 (CH_2), 114.0 (CH), 123.3 (CH), 126.7 (CH), 127.1 (CH), 128.6 (CH), 134.0 (C), 136.2 (C), 141.9 (C), 174.4 (C); HRMS (DEI) found m/z 402.0336 [M]$^+$, $C_{17}H_{15}N_4O_3Br$ requires 402.0327.

5,17-Dibromo-4-hydroxy-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (7). BBr_3 (2 μL, 0.02 mmol) was added to a solution of lactam **29** (4.0 mg, 7 μmol) in CH_2Cl_2 (200 μL) at −78 C. The orange solution was stirred (1 h, −78 °C), quenched with a $NaHCO_3$ (aq, satd), and extracted with EtOAc (3 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **7**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) gave **7** (3.0 mg, 91%) as an amorphous solid: IR (ZnSe, neat) ν 3291, 2933, 1637, 1504, 1224 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.18−2.25 (m, 1H), 2.32−2.38 (m, 1H), 2.61−2.64 (m, 2H), 2.98−3.02 (m, 2H), 3.20−3.36 (m, 2H), 4.85 (brs, 1H), 5.07 (d, J = 2.0 Hz, 1H), 5.85 (brs, 1H), 6.85 (d, J = 2.0 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.24 (dd, J = 8.4, 2.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 30.3 (CH_2), 31.6 (CH_2), 39.5 (CH_2), 41.0 (CH), 112.7 (CH), 118.5 (C), 125.6 (CH), 126.0 (CH), 130.3 (CH), 132.0 (C), 134.3 (CH), 140.9 (C), 148.5 (C); HRMS (DCI/NH_3) found m/z 439.9493 [M]$^+$, $C_{17}H_{16}O_3NBr_2$ requires 439.9497.

5,15,17-Tribromo-4-hydroxy-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (8). Trifluoroacetic acid (0.5 mL) was added to lactam **30** (5 mg, 8 μmol) and was allowed to stir at room temperature for 24 h. The trifluoroacetic acid was removed under reduced pressure, and traces of trifluoroacetic acid were removed by reevaporation from toluene to give crude **8**. Reversed phase HPLC purification (C_{18}, 5 μm Microsorb, 10 × 250 mm, MeOH/H_2O, 60:40, 3 mL/min) provided **8** (3.2 mg, 75%) as a colorless amorphous solid: IR (ZnSe, neat) ν 3284, 2937, 1644, 1503, 1463, 1232, 1058 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.28−2.36 (m, 1H), 2.47−2.70 (m, 3H), 3.00−3.09 (m, 1H), 3.20−3.26 (m, 2H), 3.38−3.47 (m, 1H), 4.90 (d, J = 6.8 Hz, 1H), 5.14 (d, J = 1.6 Hz, 1H), 5.78 (brs, 1H), 6.87 (d, J = 1.6 Hz, 1H), 7.35 (s, 1H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 30.5 (CH_2), 32.0 (CH_2), 37.1 (CH_2), 39.9 (CH_2), 109.6 (C), 112.5 (CH), 118.1 (C), 122.5 (C), 125.9 (CH), 129.4 (CH), 132.6 (C), 136.8 (CH), 139.5 (C), 140.6 (C), 148.1 (C), 153.2 (C), 170.8 (C); HRMS (DCI/NH_3) found m/z 517.8594 [M]$^+$, $C_{17}H_{15}O_3NBr_3$ requires 517.8602.

5-Bromo-4-hydroxy-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (9). Trifluoroacetic acid (0.5 mL) was added to lactam **31** (4 mg, 9 μmol) and was allowed to stir at room temperature for 24 h. The trifluoroacetic acid was removed under reduced pressure, and traces of trifluoroacetic acid were removed by reevaporation from toluene. Reversed phase HPLC purification (C_{18}, 5 μm Microsorb, 10 × 250 mm, MeOH/H_2O, 60:40, 3 mL/min) provided **9** (2.2 mg, 70%) as a colorless solid: mp 250−251 °C (CH_2Cl_2/MeOH); IR (ZnSe, neat) ν 2929, 1627, 1501, 1429 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.34−2.37 (m, 2H), 2.58−2.63 (m, 2H), 2.96−3.00 (m, 2H), 3.10−3.13 (m, 2H), 4.60 (brs, 1H), 5.03 (d, J = 2.0 Hz, 1H), 6.79 (dd, J = 2.0, 0.8 Hz, 1H), 7.02, (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 30.7 (CH_2), 32.7 (CH_2), 40.7 (CH_2), 41.4 (CH_2), 110.8 (C), 115.4 (CH), 125.4 (CH), 125.8 (CH), 132.2 (CH), 133.8 (C), 140.0 (C), 153.3 (C), 158.3 (C), 174.7 (C); HRMS (DCI/NH_3) found m/z 362.0399 [M + H]$^+$, $C_{17}H_{17}O_3NBr$ requires 362.0392.

5-Bromo-4-hydroxy-17-iodo-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (10). Sodium nitrite (1.6 mg, 0.023 mmol) was added in one portion to concentrated sulfuric acid (50 μL) chilled with an ice bath. AcOH (60 μL) was added dropwise to this solution at 0 °C. The solution was stirred for 30 min and then treated with lactam **28** (9.4 mg, 0.021 mmol) in portions over 1 h. This mixture was stirred for 1 h at 0 °C and then room temperature for 20 min. KI (5.6 mg, 0.034 mmol) in 2 M HCl (0.2 mL) was added to this mixture, and the mixture was stirred at room temperature for 15 min, then 70 °C for 10 min. The mixture was chilled by ice bath and treated with Na_2SO_3 (aq, satd) followed by extraction with EtOAc (4 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **10**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) followed by reversed phase HPLC (C_{18}, 5 μm Microsorb, 10 × 250 mm, MeOH/H_2O, 65:35, 3 mL/min) gave **10** (1.6 mg, 16%) as a pale yellow amorphous solid: IR (ZnSe, neat) ν cm^{-1} 3289, 2928, 1643, 1502, 1433, 1217; ^{1}H NMR (400 MHz, CD_3OD) δ 2.50−2.54 (m, 2H), 2.78−2.84 (m, 2H), 3.10−3.16 (m, 2H), 3.30−3.36 (m, 2H), 5.20 (d, J = 2.0 Hz, 1H), 7.02, (d, J = 2.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.49 (dd, J = 2.0, 8.4 Hz, 1H), 7.92, (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 24.7 (CH_2), 26.1 (CH_2), 34.6 (CH_2), 35.4 (CH_2), 108.4 (CH), 119.9 (CH), 120.5 (CH), 126 (C), 135.8 (CH), 135.9 (CH), 151.9 (C); HRMS (DEI) found m/z 486.9296 [M]$^+$, $C_{17}H_{15}NO_3Br$ requires 486.9280.

5-Bromo-4-hydroxy-20-nitro-2-oxa-10,14-diaza-tricyclo-[16.2.2.1^{0,0}]tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (11). BBr_3 (4 μL, 0.042 mmol) was added to a solution of lactam **37** (8 mg, 0.014 mmol) in CH_2Cl_2 (100 μL) at −78 °C. The orange solution was stirred (1 h, −78 °C), quenched with $NaHCO_3$ (aq, satd), and extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **11**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) gave **11** (6 mg, 82%) as an oil: IR (ZnSe, neat) ν 3405, 3303, 1648, 1533 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.16−2.13 (m, 2H), 2.40−2.34 (m, 2H), 2.65−2.60 (m, 2H), 3.10−3.00 (m, 2H), 3.31−3.27 (m, 2H), 3.51−3.46 (m, 4H), 5.29−5.25 (m, 1H), 5.95 (d, J = 2.0 Hz, 1H), 6.20 (bs, 1H), 6.23 (brt, J = 2.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1 H), 7.47 (dd, J = 8.4, 2.4 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 31.3 (CH_2), 33.4 (CH_2), 34.0 (CH_2), 35.4 (CH_2), 38.9 (CH_2), 41.0 (CH_2), 110.3 (C), 114.2 (CH), 124.7 (CH), 126.1 (CH), 126.9 (CH), 131.8 (C), 135.1 (CH), 139.8 (C), 141.8 (C), 142.1(C), 145.7 (C), 145.9 (C), 170.6 (C), 171.9 (C); HRMS (DCI) found m/z 478.0629 [M + H]$^+$, $C_{20}H_{21}O_6N_3Br$ requires 478.0614.

21-Amino-4-hydroxy-5-bromo-2-oxa-10,14-diaza-tricyclo-[16.2.2.1^{0,0}]tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (12). BBr_3 (4 μL, 0.042 mmol) was added to a solution of lactam **38** (7 mg, 0.013 mmol) in CH_2Cl_2 (100 μL) at −78 °C. The orange solution was stirred (1 h, −78 °C), quenched with $NaHCO_3$ (aq, satd), and extracted with EtOAc (3 × 10 mL). The organic solution was combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **12**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) gave **12** (3 mg, 51%) as an oil: IR (ZnSe, neat) ν 3328, 2929, 1648, 1509, 1423, 1278 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.07−2.10 (m, 2H), 2.35−2.38 (m, 2H), 2.52−2.55 (m, 2H), 2.81−2.84 (m, 2H), 3.19−3.21 (m, 2H), 3.28−3.20 (m, 2H), 3.37−3.40 (m, 2H), 6.10 (d, J = 2.0 Hz, 1H), 6.54 (dd, J = 2.0, 8.4 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.4, 1H), 6.96 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 32.8, (CH_2), 34.5 (CH_2), 35.0 (CH_2), 36.3 (CH_2), 39.5 (CH_2), 42.4 (CH_2), 111.4 (C), 115.7 (CH), 118.9 (CH), 120.3 (CH), 123.3 (CH), 126.8 (CH), 133.4 (C), 139.9 (C), 140.8 (C), 141.8 (C), 143.8 (C), 148.2 (C), 173.8 (C), 174.9 (C); LRMS (ESI) found m/z 448.0 [M + H]$^+$, $C_{20}H_{23}N_3BrO_3$ requires 448.0.

21-Azido-4-hydroxy-5-bromo-2-oxa-10,14-diaza-tricyclo-[16.2.2.1^{0,0}]tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (13). $NaNO_2$ (0.8 mg, 12 μmol) was added in one portion to a chilled solution (0 °C, ice bath) of arylamine **12** (4.8 mg, 11 μmol) in AcOH/H_2O (60 μL, 9:1). The solution was stirred for 15 min and treated with NaN_3 (4.0 mg, 62 μmol) in one portion. After 0.5 h, the reaction was quenched with H_2O and was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **13**. Purification by HPLC (C_{18} 5 μm Microsorb 10 × 250 mm, MeOH/H_2O, 3:2, 4 mL/min, t_R 6.0 min) provided **13** (3.5 mg, 68%) as an oil: IR (neat) ν 3303, 2925, 2117, 1648, 1500 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.05−2.09 (m, 2H), 2.40−2.45 (m, 2H), 2.58−2.62 (m, 2H), 2.91−2.96 (m, 2H), 3.21−3.27 (m, 2H), 3.37−3.42 (m, 2H), 6.05 (d, J = 2.0 Hz, 1H), 6.95−7.10 (m, 4H), 7.67−7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD, 1:1) δ 31.9 (CH_2), 33.8 (CH_2), 34.1 (CH_2), 35.4 (CH_2), 39.1 (CH_2), 41.3 (CH_2), 111.0 (CH), 115.3 (CH), 121.6 (CH), 123.7 (CH), 127.0 (CH), 127.1 (CH), 132.3 (C), 133.0 (C), 139.7 (C), 143.0 (C), 145.7 (C), 147.5 (C), 173.1 (C), 173.4 (C); HRMS (DEI) found m/z 473.0694 [M]$^+$, $C_{20}H_{20}N_5O_4Br$ requires 473.0699.

5,21-Dibromo-4-hydroxy-2-oxa-10,14-diaza-tricyclo[16.2.2.1^{0,0}]-tricosa- 1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (14). BBr_3 (1 μL, 5 μmol) was added to a solution of lactam **39** (1 mg, 2 μmol) in CH_2Cl_2 (20 μL) at −78 °C. The orange solution was stirred (1 h, −78 °C), quenched with a $NaHCO_3$ (aq, satd), and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **14**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) gave **14** (0.8 mg, 94%) as an amorphous solid: ^{1}H NMR (400 MHz, CD_3OD) δ 2.08−2.11 (m, 2H), 2.41−2.44 (m, 2H), 2.58−2.61 (m, 2H), 2.93−2.96 (m, 2H), 3.23−3.24 (m, 2H), 3.38−3.41 (m, 2H), 5.98 (d, J = 1.6 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 1.6, 8.4 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H); HRMS (DCI) found m/z 510.9853 [M + Na]$^+$, $C_{20}H_{21}O_4N_2Br_2$ requires 510.9868.

5,20,22-Tribromo-4-hydroxy-2-oxa-10,14-diaza-tricyclo-[16.2.2.10,0]tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (15). BBr_3 (1M 50 μL) was added to a solution of lactam **40** (4 mg, 6 μmol) in CH_2Cl_2 (50 μL) at −78 °C. The orange solution was stirred (1 h, −78 °C), quenched with $NaHCO_3$ (aq, satd), and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **15**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) gave **15** (2.5 mg, 72%) as an amorphous solid: ^{1}H NMR (400 MHz, CD_3OD) δ 1.92−2.00 (m, 1H), 2.26−2.32, (m, 1H), 2.40−2.50 (m, 2H), 2.54−2.71 (m, 2H), 2.86−2.92 (m, 1H), 3.03−3.23 (m, 3H), 3.55−3.72 (m, 2H), 5.98 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 7.50 (s, 1H), 7.56 (s, 1H); LRMS (DCI) found m/z 610.9 [M + Na]$^+$, $C_{20}H_{19}O_4N_2Br_3Na$ requires 610.9.

5-(2-Aminoethyl)-2-benzyloxy-3-bromophenol (16). KOH (70 mg, 1.3 mmol) and hydrazine (cat.) were added to a solution of carbamate **24** (22 mg, 0.05 mmol) dissolved in dry 1,4-dioxane (1 mL). This heterogeneous mixture was rapidly stirred and heated to 80 °C. After 0.5 h, the mixture was treated with HCl (1 N) until the mixture was neutral by pH paper and was extracted with EtOAc

(3 × 25 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to yield **16** as an oil (14 mg 92% crude). The product was carried forward without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (bs, 2H), 2.85 (bs, 2H), 4.20 (bs, 2H), 4.97 (s, 2H), 6.65 (bs, 1H), 6.89 (bs, 1H), 7.2−7.6 (m, 5H); HRMS (DCI/NH_3) found *m*/*z* 322.0445 $[M + H]^+$, $C_{15}H_{17}O_2NBr$ requires 322.0443.

3-(4-Benzyloxy-3-bromo-5-hydroxyphenyl)-*N*-[2-(4-fluoro-3-nitro-phenyl)-ethyl]propionamide (18). Acid **17** (83 mg, 0.39 mmol), HOBt (55 mg, 0.41 mmol), and EDCI (78 mg, 0.41 mmol) were added sequentially to a solution of amine **16** (120 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 1 h, the reaction was quenched with HCl (1 N, 20 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, washed with brine and dried (Na_2SO_4), and the volatiles were removed to provide crude **18** which was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) yielding **18** (140 mg, 72%) as an amorphous solid: IR (KBr, pellet) ν 3392, 3075, 1639, 1529, 1425, 1349 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 2.52 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 3.01 (t, J = 7.2 Hz), 3.38 (dt, J = 7.2, 6.0 Hz, 2H), 5.01 (s, 2H), 6.78 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 7.25 (brs, 1H), 7.30−7.45 (m, 4H), 7.50−7.60 (m, 2H), 7.64−7.69 (m, 1H), 7.99 (dd, J = 6.9, 2.1 Hz, 1H), 8.68 (bs, 1H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 31.0 (CH_2), 35.0 (CH_2), 37.6 (CH_2), 41.2 (CH_2), 74.8 (CH_2), 117.3 (CH), 117.6 (C), 118.7 (CH, J = 21.0 Hz), 124.3 (CH), 126.2 (CH, J = 3.0 Hz), 128.5 (CH), 128.8 (2 CH), 136.7 (CH, J = 8.0 Hz), 137.7 (C), 138.1 (C, J = 7.0 Hz), 139.6 (C, J = 4.3 Hz), 142.8 (C), 151.9 (C), 154.2 (C, J = 258.0 Hz), 171.9 (C); HRMS (DEI) found *m*/*z* 516.0686 $[M]^+$, $C_{24}H_{22}N_2O_5BrF$ requires 516.0696.

***N*-(2-{2-[4-Benzyloxy-3-bromo-5-triisopropyl-silanyloxy)-phenyl]-ethylcarbamoyl}-ethyl-3-(4-fluoro-3-nitro-phenyl)-propionamide (19).** EDCI (76 mg, 0.40 mmol) was added to a solution of amine **36** (110 mg, 0.20 mmol), HOBt (54 mg, 0.40 mmol), and acid **17** (47 mg, 0.22 mmol) in CH_2Cl_2 (5.0 mL). The solution stirred overnight at room temperature, quenched with HCl (1 N) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **19**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) gave **19** (139 mg, 93%) as an oil: IR (NaCl, neat) ν 3293, 2944, 2867, 1644, 1538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 7.2 Hz, 18H), 1.26 (sept, J = 7.2 Hz, 3H), 2.28 (t, J = 6.0 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 3.50−3.38 (m, 4H), 4.98 (s, 2H), 5.54 (brs, 1H), 6.39 (brs, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 7.15 (dd, J = 10.8, 8.4 Hz, 1H), 7.38−7.29 (m, 3H), 7.48−7.42 (m, 1H), 7.52−7.48 (m, 2H), 7.86 (dd, J = 7.2, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (CH), 17.9 (CH_3), 30.2 (CH_2), 34.8 (CH_2), 35.2 (CH_2), 35.4 (CH_2), 37.2 (CH_2), 40.5 (CH_2), 74.4 (CH_2), 118.0 (C), 118.3 (d, J = 6.2 Hz, CH), 119.7 (CH), 125.1 (CH), 125.3 (d, J = 2.9 Hz, CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 135.5 (C), 135.6 (d, J = 5.1 Hz, CH), 136.0 (d, C), 136.9 (C), 137.8 (d, J = 4.3 Hz, C), 145.4 (C), 150.3 (C), 153.8 (d, J = 260.9 Hz, C), 171.0 (C), 171.4 (C); HRMS (FAB) found *m*/*z* 744.2478 $[M + H]^+$, $C_{36}H_{48}O_6N_3FSiBr$ requires 744.2478.

4-(Benzyloxy)-3-bromo-5-hydroxybenzaldehyde (21). Li_2CO_3 (85 mg, 1.2 mmol) was added to a solution of 3-bromo-4,5-dihydroxybenzaldehyde **20** (100 mg, 0.46 mmol) in DMF (2 mL). This solution was vigorously stirred and heated (45 °C, 1 h) followed by dropwise addition of benzyl bromide (0.14 mL, 1.2 mmol). After 45 min, the reaction was quenched with HCl (aq, 1 N) resulting in precipitation of the crude product **21**. The precipitate was filtered, washed with water, dried under high vacuum, and purified by flash chromatography (SiO_2, CH_2Cl_2/hexane, 9:1) to yield **21** (125 mg, 88%) as a pale yellow solid: mp 92−93 °C; IR (NaCl, neat) ν 3235, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (s, 2H), 5.85 (s, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.38−7.46 (m, 5H), 7.63 (d, J = 2.0 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.1 (CH_2), 115.5 (CH), 117.0 (C), 126.7 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 133.9 (C), 148.3 (C), 150.9 (C), 190.0 (CH); HRMS (DCI/NH_3) found *m*/*z* 306.9963 $[M + H]^+$, $C_{14}H_{12}O_3Br$ requires 306.9969.

4-Benzyloxy-3-bromo-5-hydroxycinnamic Acid (22). Pyridine (0.55 mL, 6.8 mmol) and piperidine (0.16 mL, 1.62 mmol) were added to a solution of 4-benzyloxy-3-bromo-5-hydroxybenzaldehyde **21** (2.0 g, 6.5 mmol) and malonic acid (0.7 g, 6.8 mmol) in toluene (100 mL) within a round-bottom flask equipped with a Dean Stark trap and heated under reflux for 5h. The reaction was quenched with HCl (1 N, 300 mL) resulting in precipitation of **22**. This compound was collected and washed with water and dried under high vacuum to provide **22** (2.0 g, 88%) as a colorless solid: mp 173−174 °C; IR (NaCl, neat) ν 3249, 1650, 1633, 1616 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (s, 2H), 6.3 (d, J = 15.9 Hz, 1H), 7.03 (d, J = 1.8 Hz, 1 H), 7.29 (d, J = 1.8 Hz, 1H), 7.38−7.44 (m, 5H), 7.57 (d, J = 15.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$/drop of DMSO) δ 74.9 (CH_2), 114.9 (CH), 117.5 (C), 118.7 (CH), 123.9 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 131.9 (C), 136.5(C), 143.3 (CH), 145.2 (C), 151.1 (C), 169.0 (C); HRMS (DCI/NH_3) found *m*/*z* 349.0087 $[M]^+$, $C_{16}H_{14}O_4Br$ requires 349.0075.

Ethyl (4-Benzyloxy)-3-bromo-5-(ethoxycarbonyloxy)styryl-carbamate (23). Diisopropylethylamine (1.4 mL) was added dropwise to a chilled solution (−10 °C) of 4-benzyloxy-5-bromo-3-hydroxy-cinnamic acid **22** (1.00 g) dissolved in acetone (40 mL), followed by the dropwise addition of ethylchloroformate (0.6 mL). After stirring for 2 h (−10 °C), a chilled aqueous solution of sodium azide (560 mg, 10 mL H_2O) was added dropwise to the reaction. After stirring for 5 h at 0 °C, the solution was extracted with CH_2Cl_2 (3 × 100 mL). Extracts were combined, dried over anhydrous $MgSO_4$, filtered, and volatiles were removed to give a colorless solid. The resulting solid was azeotroped dried with toluene (3 × 20 mL). Ethanol (5 mL) and toluene (50 mL) were added and this solution was heated to 80 °C for 12 h. The volatiles were removed to give crude **23** that was purified by flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 98:2) to yield **23** (0.89 g, 66%) as an amber viscous oil: IR (NaCl, neat) ν 3324, 2981, 1766, 1729, 1660 1525, 1475, 1257, 1224 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 6H), 4.21 (q, J = 7.2 Hz, 4H), 4.98 (s, 2H), 5.80 (d, J = 14.4 Hz, 1H,), 6.53 (d, J = 10.4 Hz, 1H,), 7.02 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 14.4, 10.4 Hz, 1H,), 7.5−7.3 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (CH_3), 61.8 (CH_2), 65.2 (CH_2), 75.6 (CH_2), 107.7 (CH), 118.3 (C), 118.7 (CH), 125.6 (CH), 127.5 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 134.5 (C), 136.4 (C), 145.3 (C), 146.3 (C), 152.9 (C), 153.5 (C); HRMS (DCI/NH_3) found *m*/*z* 463.0614 $[M]^+$, $C_{21}H_{22}O_6NBr$ requires 463.0630.

Carbonic acid 2-benzyloxy-3-bromo-5-(2-methoxycarbonyl-amino-vinyl)-phenyl ester methyl ester: IR (KBr, neat) ν 3336, 2956, 1770, 1734, 1660, 1477, 1261, 943 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.80 (s, 3H), 4.98 (s, 2H), 5.75 (d, J = 14.0 Hz, 1H), 6.87 (bd, J = 11.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 7.11 (bd, J = 11.0 Hz, 1H), 7.3−7.5 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7 (CH_3), 55.7 (CH_3), 75.6 (CH_2), 107.8 (CH), 118.2 (C), 118.5 (CH), 125.5 (CH), 127.4 (CH), 128.1 (CH), 128.2 (2CH), 134.3 (C), 136.3 (C), 145.1 (C), 146.0 (C), 153.4 (C), 153.8 (C); HRMS (DCI/NH_3) found *m*/*z* 349.0087 $[M]^{+\cdot}$, $C_{16}H_{14}O_4Br$ requires 349.0075.

Carbonic Acid 2-Benzyloxy-3-bromo-5-(2-methoxycarbonyl-amino-ethyl)-phenyl Ester Ethyl Ester (24). Triethylsilane (265 uL, 1.67 mmol) was added to **23** (50 mg, 0.17 mmol), and the resulting heterogeneous mixture was rapidly stirred (−10 °C). Chilled (−10 °C) neat trifluoroacetic acid (1 mL) was rapidly transferred via cannula to the reaction mixture. The heterogeneous mixture was allowed to rapidly stir for 20 min. The reaction was quenched with a $NaHCO_3$ (aq, satd) and was extracted with CH_2Cl_2 (4 × 25 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to provide **24** as a viscous oil (47 mg, 94%): IR (NaCl, neat) ν 3343, 2956, 1770, 1722, 1481, 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (t, J = 7.0 Hz, 2H), 3.40 (dt, J = 7.0, 7.0 Hz, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 4.74 (brs, 1H), 4.98 (s, 2H), 6.96 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.32−7.5 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2 (CH_2), 41.8 (CH_2), 52.1 (CH_3), 55.7 (CH_3), 75.5

(CH_2), 118.0 (C), 122.4 (CH), 128.1 (CH), 128.2 (2CH), 131.0 (CH), 136.2 (C), 136.4 (C), 144.9 (C), 146.6 (C), 153.3 (C), 156.7 (C); HRMS (DCI/NH_3) found *m/z* 466.0864 $[M + H]^+$, $C_{21}H_{25}O_6$-NBr requires 466.0865.

3-(4-Fluoro-3-nitro-phenyl)-propionic Acid Methyl Ester (26). In a glovebox, olefin **25** (300 mg, 1.3 mmol) and Wilkinson's catalyst (44 mg, 0.05 mmol) were dissolved in toluene (25 mL) in a pressure vessel. The vessel was removed from the glovebox and purged with H_2 and pressurized with H_2 (3 atm). The mixture was rapidly stirred and heated (60 °C). After 8 h, the toluene was removed resulting in a brown residue that was passed through a flash column (SiO_2, EtOAc/CH_2Cl_2, 1:50) to provide **26** as an amorphous solid (290 mg, 95%): IR (NaCl, neat) ν 2954, 1735, 1537, 1349 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.2, 2.4 Hz, 1H), 7.45 (m, 1H), 7.17 (dd, J = 10.0, 8.4 Hz, 1H), 3.63 (s, 3H), 2.97 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (s, C), 153.9 (d, J = 348 Hz, C), 137.4 (d, J = 5.7 Hz, C) 136.8 (brs, C), 135.5 (d, J = 11 Hz, CH), 125.4 (d, J = 3.8 Hz, CH), 118.2 (d, J = 28 Hz, CH), 51.8 (s, CH_3), 34.9 (s, CH_2), 29.6 (s, CH_2); HRMS (EI) found *m/z* 227.0601 $[M]^+$, $C_{10}H_{10}FNO_4$ requires 227.0593.

4-Benzyloxy-5-bromo-16-nitro-2-oxa-11-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-10-one (27). K_2CO_3 (500 mg, 3.6 mmol) was added to a solution of phenol **18** (100 mg, 0.19 mmol) in DMSO (100 mL, 2 mM) containing 4 Å sieves at room temperature. After 3 h of vigorous stirring, the reaction mixture was diluted with water (100 mL) and extracted with EtOAc (5 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to provide crude **27** that was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) yielding **27** (86 mg, 85%) as a viscous oil: IR (NaCl, neat) ν 3272, 2933, 1639, 1531, 1346 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.2−2.5 (m, 3H), 3.0−3.4 (m, 5H), 5.05 (d, J = 1.6 Hz, 1H), 5.15 (d, J = 10.4 Hz, 1H), 5.30 (d, J = 10.4 Hz, 1H), 5.34 (brs, 1H), 6.86 (d, J = 1.6 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.3−7.4 (m, 3H), (dd, J = 8.4, 2.0 Hz, 1H), 7.6−7.62 (m, 2H), 7.92 (d, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_2), 31.5 (CH_2), 39.6 (CH_2), 39.9 (CH_2), 75.2 (CH_2), 113.2 (CH), 117.8 (C), 126.3 (CH), 126.4 (CH), 127.4 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 136.8 (C), 136.8 (CH), 137.3 (C), 140.5 (C), 142.6 (C), 143.9 (C), 149.4 (C), 155.2 (C), 171.0 (C); HRMS (DEI) found *m/z* 496.0624 $[M]^+$, $C_{24}H_{21}N_2O_5Br$ requires 496.0634.

17-Amino-4-benzyloxy-5-bromo-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (28). $CrCl_2$ (110 mg, 0.89 mmol) was added to a solution of lactam **27** (34 mg, 0.07 mmol) in DMF (1 mL) and the mixture stirred at room temperature. After 12 h, the volatiles were removed to give a residue that was dissolved in EtOAc (10 mL). The organic solution was washed with brine and dried (Na_2SO_4), and the volatiles were removed to give crude **28** that was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) yielding **28** (23 mg, 73%) as a viscous gum: IR (NaCl, neat) ν 3291, 2927, 1639, 1504, 1270, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.2−2.3 (m, 2H), 2.6−2.7 (m, 2H), 2.8−2.9 (m, 2H), 3.2−3.3 (m, 2H), 4.85 (brs, 1H), 5.17 (d, J = 10.4 Hz, 1H), 5.27 (d, J = 10.4 Hz, 1H), 5.41 (s, 1H), 6.63 (brd, J = 7.2 Hz, 1H), 6.79 (d, J = 7.2 Hz, 1H), 6.88 (s, 1H), 7.3−7.4 (m, 3H), 7.5−7.6 (m, 2H), 7.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (CH_2), 32.2 (CH_2), 39.4 (CH_2), 41.1 (CH_2), 75.3 (CH_2), 113.8 (CH), 117.6 (CH), 120.0 (CH), 124.5 (CH), 125.7 (CH), 128.3 (CH), 128.4 (CH), 128.8 (CH), 136.4 (C), 136.9 (C), 140.0 (C), 141.0 (C), 142.4 (C), 142.7 (C), 154.6 (C), 171.9 (C); HRMS (DEI) found *m/z* 466.0908 $[M]^+$, $C_{24}H_{23}N_2O_3Br$ requires 466.0892.

5,17-Dibromo-4-benzyloxy-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]-nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (29). *tert*-Butyl nitrite (20 μL, 17 μmol) was added to a solution of $CuBr_2$ (3 mg, 14 μmol) in CH_3CN (0.2 mL) at 0 °C. After stirring for 1 h, a heterogeneous mixture of lactam **28** (8 mg, 17 μmol) in CH_3CN (0.8 mL) was added dropwise over 20 min at 0 °C. After stirring for 2 h, the solution was allowed to warm to room temperature, quenched with HCl (1 N, 4 mL), and extracted with CH_2Cl_2 (4 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **29**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) followed by reversed phase HPLC (C_{18}, 5 μm Microsorb 10 × 250 mm, MeOH/H_2O, 65: 35, 3 mL/min) gave **29** (6 mg, 66%) as a colorless amorphous solid: IR (NaCl, neat) ν 3286, 2928, 1640, 1480, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.2−2.4 (m, 2H), 2.6−2.7 (m, 2H), 2.9−3.1 (m, 2H), 3.2−3.4 (m, 2H), 4.90 (brs, 1H), 5.06 (d, J = 2.0 Hz, 1H), 5.18 (d, J = 10.4 Hz, 1H), 5.34 (d, J = 10.4 Hz, 1H), 6.88 (dd, J = 2.0, 1.2 Hz, 1H), 7.05 (d, 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.4 Hz, 1 H), 7.3−7.4 (m, 3H), 7.51 (d, J = 2.4 Hz, 1H), 7.6−7.5 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5 (CH_2), 31.7 (CH_2), 39.7 (CH_2), 41.0 (CH_2), 75.2 (CH_2), 113.1 (CH), 117.9 (C), 118.7 (CH), 125.8 (CH), 125.9 (CH), 128.2 (CH), 128.4 (CH), 128.8 (CH), 130.4 (CH), 134.6 (C), 136.4 (C), 137.0 (C), 140.6 (C), 142.8 (C), 152.9 (C), 154.6 (C), 171.1 (C); HRMS (DEI) found *m/z* 532.9852 $[M]^+$, $C_{24}H_{21}NO_3Br_2$ requires 532.9847.

4-Benzyloxy-5,15,17-tribromo-2-oxa-10-azatricyclo[12.2.2.1^{0,0}]-nonadeca-1 (17),3(19),4,6,14,(18),15-hexaene-11-one (30). *tert*-Butyl nitrite (12 μL, 0.09 mmol) was added to a solution of $CuBr_2$ (56 mg, 0.25 mmol) in CH_3CN (0.5 mL) was added at 0 °C. After stirring for 1 h, a heterogeneous mixture of lactam **28** (12 mg, 0.03 mmol) in CH_3CN (0.8 mL) was added dropwise over 20 min at 0 °C. After stirring for 2 h, the mixture was allowed to warm to room temperature and quenched with HCl (1 N, 4 mL) and extracted with EtOAc (4 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **30**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) followed by reversed phase HPLC (C_{18}, 5 μm Microsorb, 10 × 250 mm, MeOH/H_2O, 75:25, 3 mL/min) gave **30** (5 mg, 32%) as a colorless amorphous solid: IR (NaCl, neat) ν 3273, 2928, 1638, 1463, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.2−2.8 (m, 4H), 3.0−3.5 (m, 4H), 4.93 (bd, J = 7.2 Hz, 1H), 5.16 (d, J = 10.4 Hz, 1H), 5.31 (d, J = 10.4 Hz, 1), 6.92 (d, J = 2.0 Hz, 1H), 7.25 (s, 1H), 7.3−7.4 (m, 3H), 7.55 (s, 1H), 7.59−7.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5 (CH_2), 32.1 (CH_2), 37.1 (CH_2), 39.7 (CH_2), 75.3 (CH_2), 112.9 (CH), 118.1 (C), 118.7 (C), 122.7 (C), 126.2 (CH), 128.3 (CH), 128.4 (CH), 128.8 (CH), 129.4 (CH), 136.5 (CH), 136.7 (C), 136.8 (C), 139.3 (C), 142.7 (C), 153.2 (C), 154.1 (C), 170.9 (C); HRMS (DEI) found *m/z* 606.9021 $[M]^+$, $C_{24}H_{20}$-NO_3Br_3 requires 606.8993.

4-Benzyloxy-5-bromo-2-oxa-10-aza-tricyclo[12.2.2.1^{0,0}]nonadeca-1(17),3(19),4,6,14(18),15-hexaen-11-one (31). *tert*-Butyl nitrite (40 μL, 0.34 mmol) was added to THF (0.3 mL) at 0 °C. After stirring for 1 h, a heterogeneous mixture of lactam **28** (10 mg, 0.02 mmol) in THF (0.4 mL) was added dropwise over 20 min at 0 °C. After stirring for 2 h, the solution was allowed to warm to room temperature, quenched with HCl (1 N, 4 mL), and extracted with EtOAc (4 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **31**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) followed by reversed phase HPLC (C_{18}, 5 μm Microsorb, 10 × 250 mm, MeOH/H_2O, 65:35, 3 mL/min) gave **31** (3.8 mg, 39%) as a colorless powder: IR (NaCl, neat) ν 3286, 2925, 1640, 1567, 1501, 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26−2.29 (m, 2H), 2.58−2.62 (m, 2H), 3.00−3.04 (m, 2H), 3.24−3.28 (m, 2H), 4.77 (brs, 1H), 5.03 (d, J = 2.4 Hz, 1H), 5.22 (s, 2H), 6.83 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.30−7.42 (m, 3H), 7.59−7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5 (CH_2), 32.0 (CH_2), 39.6 (CH_2), 41.2 (CH_2), 75.2 (CH_2), 114.6 (CH), 117.6 (C), 124.4 (CH), 125.0 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 130.8 (CH), 135.9 (C), 136.8 (C), 138.7 (C), 142.2 (C), 156.3 (C), 156.6 (C), 171.4 (C); HRMS (DEI) found *m/z* 451.0795 $[M]^+$, $C_{24}H_{22}NO_3Br$ requires 451.0783.

[2-(4-Benzyloxy-3-bromo-5-hydroxy-phenyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (32). Phenethylamine **16**, (28 mg, 86 μmol) was dissolved in CH_3CN (0.75 mL) and was treated with a solution of di-*tert*-butyl dicarbonate (46 mg, 210 μmol) in CH_3CN (0.25 mL). After 3 h, the volatiles were removed and the resulting residue was redissolved in MeOH (0.5 mL), water (0.2 mL), and treated with sodium carbonate (50 mg). After stirring 12 h, the solution

was extracted with CH_2Cl_2 (4 × 25 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to yield **32** as an oil (28 mg, 76%): IR (NaCl, neat) ν 3359, 2977, 1685, 1500, 1367, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.65 (bt, J = 4.8 Hz, 2H), 3.31 (bd, 2H), 4.59 (bs, 1H), 5.01 (s, 2H), 5.94 (bs, 1H), 6.69 (bs, 1H), 6.90 (bs, 1H), 7.3−7.5 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (CH_3), 35.4 (CH_2), 41.4 (CH_2), 79.4 (C), 115.5 (CH), 116.3 (C), 124.6 (CH), 128.5 (CH), 128.7 (CH), 128.7 (CH), 136.4 (C), 137.3 (C), 141.8 (C), 150.2 (C), 155.9 (C); HRMS (DCI/NH_3) found m/z 439.1221 $[M + NH_4]^+$, $C_{20}H_{28}O_4N_2Br$ requires 439.1232.

{2-[4-Benzyloxy-3-bromo-5-(triisopropyl-silanyloxy)-phenyl]-ethyl}-carbamic Acid *tert*-Butyl Ester (33). TIPSCl (75 μL, 0.35 mmol) was added to a solution of amide **32** (122 mg, 0.299 mmol) and imidazole (50 mg, 0.72 mmol) in DMF (0.5 mL). The yellow solution was stirred overnight at room temperature, quenched with water, and extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **33**. Flash chromatography (SiO_2, CH_2Cl_2) gave **33** (164 mg, 95%) as an oil: IR (NaCl, neat) ν 3434, 3359, 2944, 2867, 1718, 1477, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 7.6 Hz, 18H), 1.27 (sept, J = 7.6, 3H), 1.42 (s, 9H), 2.65 (t, J = 6.4, 2H), 3.36−3.29 (m, 2H), 4.49 (brs, 1H), 4.98 (s, 2H), 6.64 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 7.40−7.30 (m, 3H), 7.53−7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0 (CH), 18.0 (CH_3), 28.4 (CH_3), 74.4 (CH_2), 79.2 (C), 35.5 (CH_2), 41.6 (CH_2), 118.4 (C), 119.9 (CH), 125.3 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 136.0 (C), 137.0 (C), 145.4 (C), 150.2 (C), 155.6 (C); HRMS (FAB) found m/z 600.2131 $[M + Na]^+$, $C_{29}H_{44}O_4NNaSiBr$ requires 600.2121.

2-[4-Benzyloxy-3-bromo-5-(triisopropyl-silanyloxy)-phenyl]-ethylamine (34). TFA (1.0 mL) was added to a solution of carbamate **33** (142 mg, 0.246 mmol) in CH_2Cl_2 (1.0 mL). The solution was stirred for 0.5 h at 0 °C, quenched with $NaHCO_3$ (aq, satd), and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to yield **34** (112 mg, 95%) as an oil: IR (NaCl, neat) ν 2944, 2867, 1556, 1475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 7.2 Hz, 18H), 1.27 (sept, J = 7.2 Hz, 3H), 2.62 (t, J = 6.8 Hz, 2H), 2.92 (bt, J = 6.8 Hz, 2H), 4.98 (s, 2H), 6.66 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.40−7.25 (m, 3H), 7.55−7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0 (CH), 18.0 (CH_3), 39.1 (CH_2), 43.3 (CH_2), 74.4 (CH_2), 118.3 (C), 119.9 (CH), 125.3 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 136.6 (C), 137.1 (C), 145.2 (C), 150.2 (C); HRMS (DCI/NH_3) found m/z 478.1759 $[M + H]^+$, $C_{24}H_{37}O_2NSiBr$ requires 478.1777.

(2-{2-[4-Benzyloxy-3-bromo-5-(triisopropyl-silanyloxy)-phenyl]-ethylcarbamoyl}-ethyl)-carbamic Acid *tert*-Butyl Ester (35). EDCI (88 mg, 0.460 mmol) was added to a solution of amine **34** (110 mg, 0.23 mmol), HOBt (62 mg, 0.46 mmol), and *N*-Boc-β-alanine (65 mg, 0.35 mmol) in CH_2Cl_2 (1.0 mL). The solution was stirred overnight at room temperature, quenched with HCl (1 N), and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **34**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) gave **34** (138 mg, 92%) as an oil: IR (NaCl, neat) ν 3315, 2945, 2867, 1691, 1558, 1477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J = 7.2 Hz, 18H), 1.26 (sept, J = 7.2 Hz, 3H), 1.41 (s, 9H), 2.34 (t, J = 6.0 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 3.37 (dt, J = 6.0, 6.0 Hz, 2H), 3.44 (dt, J = 7.2, 6.0 Hz, 2H), 4.99 (s, 2H), 5.16 (bs, 1H), 5.73 (bs, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 7.40−7.29 (m, 3H), 7.52−7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (CH), 17.8 (CH_3), 28.3 (CH_3), 34.8 (CH_2), 36.1 (CH_2), 36.5 (CH_2), 40.4 (CH_2), 74.3 (CH_2), 79.2 (C), 118.5 (C), 119.7 (CH), 125.2 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 135.8 (C), 137.0 (C), 145.6 (C), 150.4 (C), 156.1 (C), 171.3 (C); HRMS (FAB) found m/z 671.2512 $[M + Na]^+$, $C_{32}H_{49}O_5N_2NaSiBr$ requires 671.2492.

3-Amino-*N*-{2-[4-Benzyloxy-3-bromo-5-(triisopropyl-silanyloxy)-phenyl]-ethyl-propionamide (36). TFA (1.0 mL) was added to a solution of carbamate **35** (136 mg, 0.209 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The solution was stirred for 0.5 h at 0 °C, quenched with $NaHCO_3$ (aq, satd), and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to yield **36** (112 mg, 97%) as a oil: IR (NaCl, neat) ν 3315, 2945, 2867, 1691, 1646, 1558, 1477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 7.2 Hz, 18H), 1.27 (sept, J = 7.2 Hz, 3H), 2.29 (bs, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.97 (bs, 2H), 3.44 (dt, J = 6.8, 6.4 Hz, 2H), 4.99 (s, 2H), 6.65 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.08 (bs, 1H), 7.40−7.28 (m, 3H), 7.52−7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (CH), 17.9 (CH_3), 28.3 (CH_2), 34.9 (CH_2), 37.9 (CH_2), 40.2 (CH_2), 74.4 (CH_2), 118.3 (C), 119.8 (CH), 125.4 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 136.2 (C), 137.1 (C), 145.5 (C), 150.4 (C), 172.4 (C); HRMS (FAB) found m/z 549.2142 $[M + H]^+$, $C_{27}H_{42}O_3N_2NaSiBr$ requires 549.2148.

4-Benzyloxy-5-bromo-21-nitro-2oxa-10,14-diaza-tricyclo-[16.2.2.1^{0,0}]tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (37). CsF (43 mg, 0.29 mmol) was added to a solution of amide **19** (102 mg, 0.140 mmol) and 4 Å sieves in DMSO (75 mL, 2 mM). The solution was rapidly stirred overnight at room temperature, quenched with water, and extracted with CH_2Cl_2 (5 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **37**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) gave **37** (65 mg, 84%) as an oil. IR (NaCl, neat) ν 3299, 2931, 1647, 1533 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12−2.16 (m, 2H), 2.33−2.40 (m, 2H), 2.63−2.69 (m, 2H), 3.05−3.08 (m, 2H), 3.28−3.37 (m, 2H), 3.46−3.52 (m, 2H), 5.14 (s, 2H), 5.36 (brs, 1H), 5.96 (d, J = 1.8 Hz, 1H), 6.22 (brs, 1H), 7.04 (d, J = 1.8 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.30−7.38 (m, 3H), 7.45 (dd, J = 8.4 Hz, 2.1 Hz), 7.54−7.58 (m, 2H), 7.82 (d, J = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2 (CH_2), 33.6 (CH_2), 33.8 (CH_2), 35.3 (CH_2), 38.9 (CH_2), 40.8 (CH_2), 75.3 (CH_2), 115.0 (CH), 118.9 (C), 124.6 (CH), 125.8 (CH), 127.1 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 135.2 (CH), 136.6 (C), 136.7 (C), 139.6 (C), 142.6 (C), 143.8 (C), 146.0 (C), 152.0 (C), 170.8 (C), 172.0 (C); HRMS (FAB) found m/z 568.1061 $[M + H]^+$, $C_{27}H_{27}N_3O_6Br$ requires 568.1083.

21-Amino-4-benzyloxy-5-bromo-2-oxa-10,14-diaza-tricyclo-[16.2.2.1^{0,0}]tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (38). $CrCl_2$ (80 mg, 0.65 mmol) was added to a solution of lactam **37** (40 mg, 0.07 mmol) in DMF (1 mL) at room temperature. After 12 h of stirring, the DMF was removed under reduced pressure followed by dissolving the residue in EtOAc (10 mL). The organic solution was washed with brine and dried (Na_2SO_4), and the volatiles were removed to give crude **38**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) gave **38** (21 mg, 55%) as a yellow viscous oil: IR (NaCl, neat) ν 3320, 2928, 1644, 1479, 1196 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.10−2.14 (m, 2H), 2.38−2.63 (m, 2H), 2.60−2.63 (m, 2H), 2.84−2.87 (m, 2H), 3.25−3.27 (m, 2H), 3.40−3.43 (m, 2H), 5.16 (s, 2H), 6.21 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 8.0, 2.0 Hz, 1H), 6.75 (d, J = 8.0, 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.30−7.39 (m, 3H), 7.55−7.58 (m, 2H), 7.62 (bt, J = 6.0 Hz, 1H), 7.74 (bt, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 32.8 (CH_2), 34.5 (CH_2), 35.2 (CH_2), 36.3 (CH_2), 39.5 (CH_2), 42.1 (CH_2), 76.4 (CH_2), 117.2 (CH), 119.0 (CH), 119.1 (C), 120.8 (CH), 123.0 (CH), 127.2 (CH), 129.3 (CH), 129.4 (CH), 129.8 (CH), 138.4 (C), 139.1 (C), 140.1 (C), 140.2 (C), 141.8 (C), 144.7 (C), 153.4 (C), 173.8 (C), 174.9 (C); HRMS (DCI/NH_3) found m/z 538.1330 $[M + H]^+$, $C_{27}H_{29}O_4N_3Br$ requires 466.0865.

4-Benzyloxy-5,21-dibromo-2-oxa-10,14-diaza-tricyclo[16.2.2.1^{0,0}]-tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (39). *tert*-Butyl nitrite (10 μL, 9 μmol) was added to a solution of $CuBr_2$ (2.5 mg, 10 μmol) in CH_3CN (0.5 mL) at 0 °C and allowed to stir for 1 h. A mixture of lactam **38** (10 mg, 0.02 mmol) in CH_3CN (0.8 mL) was then added dropwise into the above solution over 20 min at 0 °C. After stirring for 2 h, the solution was allowed to warm to room temperature, quenched with HCl (1 N, 4 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **39**. Flash chromatography (SiO_2,

CH_2Cl_2/MeOH, 9:1) followed by reversed phase HPLC (C_{18}, 5 μm Microsorb, 10 × 250 mm, MeOH/H_2O, 65:35, 3 mL/min) gave **39** (2.7 mg, 21%) as a colorless amorphous solid: ^{1}H NMR (400 MHz, CD_3OD) δ 2.15−2.13 (m, 2H), 2.45−2.41 (m, 2H), 2.66−2.63 (m, 2H), 2.98−2.95 (m, 2H), 3.27−3.23 (m, 2H), 3.44−3.36 (m, 2H), 5.18 (s, 2H), 6.05 (d, J = 1.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 7.24 (dd, J = 8.4, 1.6 Hz, 1H), 7.32−7.40 (m, 3H), 7.54−7.57 (m, 3H); HRMS (FAB) found m/z 601.0312 $[M + H]^+$, $C_{27}H_{27}O_4N_2Br_2$ requires 601.0338.

4-Benzyloxy-5,20,22-tribromo-2-oxa-10,14-diaza-tricyclo-[16.2.2.10,0]tricosa-1(21),3(23),4,6,18(22),19-hexaene-11,15-dione (40). *tert*-Butyl nitrite (3.6 μL, 0.04 mmol) was added to a solution of $CuBr_2$ (14 mg, 0.06 mmol) in CH_3CN (0.5 mL) at 0 °C and allowed to stir for 1 h. A mixture of lactam **38** (11 mg, 0.02 mmol) in CH_3CN (0.5 mL) was added dropwise into the above solution over 20 min at 0 °C. After stirring for 2 h, the solution was warmed to room temperature, quenched with HCl (1 N, 4 mL), and extracted with CH_2Cl_2 (4 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **40**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) followed by reversed phase HPLC (C_{18}, 5 μm Microsorb, 10 × 250 mm, MeOH/H_2O, 70:30, 3 mL/min) gave **40** (4 mg, 29%) as a colorless amorphous solid: IR (neat) ν 3307, 2925, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94−2.02 (m, 1H), 2.09−2.16, (m, 1H), 2.31−2.36 (m, 1H), 2.55−2.63 (m, 2H), 2.73−2.81 (m, 2H), 3.08−3.19 (m, 2H), 3.81−3.86 (m, 1H), 3.96−4.02 (m, 3H), 5.23 (d, J = 10.8 Hz, 1H), 5.24 (bs, 1H), 5.28 (d, J = 10.8 Hz, 1H), 5.85 (d, J = 2.0 Hz, 1H), 6.18 (bd, J = 6.8 hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 7.32−7.40 (m, 3H), 7.34 (s, 1H), 7.56−7.59 (m, 2H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4 (CH_2), 33.7 (CH_2), 33.9 (CH_2), 35.6 (CH_2), 36.9 (CH_2), 41.5 (CH_2), 75.1 (CH_2), 114.6 (CH), 115.1 (C), 119.0 (C), 123.2 (C), 126.4 (CH), 128.3 (CH), 128.4 (CH), 128.6 (2 × CH), 135.6 (CH), 136.5 (C), 136.8 (C), 139.6 (C), 143.4 (C), 149.9 (C), 151.7 (C), 171.1 (C), 171.9 (C); LRMS (ESI) found m/z 701.1 $[M + Na]^+$, $C_{27}H_{25}N_2O_4Br_3$ requires 700.9.

***S*-(−)-(6-{2-[4-Benzyloxy-3-bromo-5-(triisopropyl-silanyloxy)-phenyl]-ethylcarbamoyl}-5-*tert*-butoxycarbonylamino-hexyl)-carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (42).** A stirred solution of amine **34** (102 mg, 0.213 mmol) and acid **41**[36] (108 mg, 0.224 mmol) in CH_2Cl_2 (2 mL) was treated with HOBt (58 mg, 0.426 mmol) and EDCI (81 mg, 0.426 mmol) at room temperature. After 3 h, the reaction was quenched with HCl (0.5 N) and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **42**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 5%) gave **42** (163 mg, 81%) as an oil: $[\alpha]^{25}_D$ −3.1° (c 0.75, $CHCl_3$); IR (neat) ν 3313, 2944, 2867, 1687, 1641, 1538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 7.2 Hz, 18H), 1.20−1.34 (m, 4H), 1.41(s, 9H), 2.31−2.43 (m, 2H), 2.66 (dd, J = 6.8 Hz, 2H), 2.85−3.15 (m, 2H), 3.29−3.49 (m, 2H), 3.80−3.90 (m, 1H), 4.19 (dd, J = 7.2 Hz, 1H), 4.35 (d, J = 8.4 Hz, 2H), 4.65 (bs, 1H), 4.99 (s, 2H), 5.87 (bd, J = 8.0 Hz, 1H), 6.18 (bs, 1H), 6.65 (d, J = 1.6 Hz, 1H), 6.94 (d, J = 1.6 Hz, 1H), 7.28−7.37 (m, 8H), 7.51 (d, J = 7.2 Hz, 4H), 7.58 (d, J = 7.2 Hz, 4H), 7.73 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (CH), 17.8 (CH_3), 23.1 (CH_2), 28.3 (CH_2), 29.6 (CH_2), 33.7 (C), 34.8 (CH_2), 39.9 (CH_2), 40.4 (CH_2), 40.5 (CH_2), 47.1 (CH), 48.6 (CH), 66.5 (CH_2), 74.3 (CH_2), 79.0 (C), 118.4 (C), 119.7 (CH), 119.9 (CH), 125.0 (CH), 125.3 (CH), 126.9 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 135.8 (C), 137.1 (C), 141.2 (C), 143.9 (C), 143.9 (C), 145.6 (C), 150.4 (C), 156.1 (C), 156.1 (C), 170.9 (C); HRMS (MALDI) found m/z 964.3905 $[M + Na]^+$, $C_{51}H_{68}N_3O_7BrSiNa$ requires 964.3902.

***S*-(−)-{6-{2-[4-Benzyloxy-3-bromo-5-(triisopropyl-silanyloxy)-phenyl]-ethylcarbamoyl}-5-{3-(4-fluoro-3-nitro-phenyl)-propionylamino]-hexyl}-carbamic Acid *tert*-Butyl Ester (44).** A stirred solution of amine **42** (72 mg, 0.076 mmol) in CH_2Cl_2 (1 mL) was treated with tris(2-amino-ethyl)-amine (TAEA) (0.57 mL, 3.81 mmol) at room temperature. After 5 min, the reaction was quenched with NaCl (sat.) and extracted with CH_2Cl_2 (10 mL). The organic layers were combined, washed with brine (3 × 20 mL), phosphate buffer (pH = 5.5) (3 × 20 mL), and dried (Na_2SO_4), and the volatiles were removed to give crude amine **43**. The crude amine **43** was carried forward without further purification. A stirred solution of amine **43** (55 mg, 0.076 mmol) and acid **17** (96 mg, 0.45 mmol) in CH_2Cl_2 (3 mL) was treated with HOBt (120 mg, 0.92 mmol) and EDCI (180 mg, 0.92 mmol) at room temperature. After 6 h, the reaction was quenched with HCl (0.5 N) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with KOH (0.5 N) (3 × 30 mL), and brine, and dried (Na_2SO_4), and the volatiles were removed to give crude amide **44**. Flash chromatography (SiO_2, CH_2Cl_2/EtOAc 20% then CH_2Cl_2/MeOH 5%) gave **44** (60 mg, 86%) as an amorphous solid: $[\alpha]^{25}_D$ −6.1° (c 0.58, $CHCl_3$); IR (neat) ν 3295, 2942, 2867, 1697, 1646, 1538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J = 7.6 Hz, 18H), 1.21−1.30 (m, 3H), 1.40 (s, 9H), 2.21−2.35 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 3.00−3.07 (m, 2H), 3.41 (q, J = 6.0 Hz, 2H), 4.00−4.10 (m, 1H), 4.58−4.62 (m, 1H), 4.97 (s, 2H), 6.25 (bs, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.98 (bd, J = 7.6 Hz, 1H), 7.15 (dd, J = 8.4, 10.4 Hz, 1H), 7.37−7.28 (m, 3H), 7.44−7.51 (m, 3H), 7.87 (dd, J = 7.2, 2.0 Hz, 1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (CH), 17.9 (CH_3), 23.1 (CH_2), 28.4 (CH_3), 29.6 (CH_2), 30.2 (CH_2), 33.3 (CH_2), 34.8 (CH_2), 37.4 (CH_2), 39.4 (CH_2), 39.8 (CH_2), 40.4 (CH_2), 46.6 (CH), 74.4 (CH), 79.2 (C), 118.2 (d, J = 20.5, CH); 118.5 (C), 119.8 (CH), 125.3 (CH), 125.5 (d, J = 2.3 Hz, CH), 127.9 (CH), 128.2 (CH), 128.2 (CH), 135.6 (d, J = 8.4 Hz, CH), 135.7 (CH), 137.1 (d, J = 8.0 Hz, C), 137.1 (C), 138.0 (d, J = 4.5 Hz, C), 145.7 (C), 150.5 (C), 154.0 (d, J = 261 Hz, C), 156.3 (C), 170.6 (C), 171.3 (C); HRMS (MALDI) found m/z 937.3572 $[M + Na]^+$, $C_{45}H_{64}N_4O_8BrSiNa$ requires 937.3553.

***S*-(−)-[4-(4-Benzyloxy-5-bromo-21-nitro-11,15-dioxo-2-oxa-10,14-diaza-tricyclo[16.2.2.1^{0,0}tricosa-1(21),3(23),4,6,18(22),19-hexaen-13-yl)-butyl]-carbamic Acid *tert*-Butyl Ester (45).** A stirred solution of amide **44** (52 mg, 0.057 mmol) in DMSO (30 mL, 2 mM) containing 4 Å sieves was treated with CsF (86 mg, 0.57 mmol) at room temperature. After 3 h of rapid stirring, the reaction mixture was diluted with water (250 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude amide **45**. Flash chromatography (SiO_2, 9.4: 0.6 CH_2Cl_2/MeOH) gave **45** (31 mg, 75%) as an viscous oil: $[\alpha]^{25}_D$ −65.0° (c 0.600, $CHCl_3$); IR (KBr, neat) ν 3301, 2929, 1683, 1644, 1531, 1284, 1236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.38 (m, 6H), 1.40 (s, 9H), 1.50−1.56 (m, 1H), 1.94−2.18 (m, 3H), 2.56−2.67 (m, 2H), 2.87−3.05 (m, 5H), 3.15−3.23 (m, 1H), 3.74−3.79 (m, 1H), 4.02−4.16 (m, 1H), 4.50−4.58 (m, 1H), 5.09−5.15 (m, 2H), 5.54−5.62 (m, 1H), 6.21 (s, 1H), 6.83 (bd, J = 7.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 7.29−7.36 (m, 3H), 7.52−7.54 (m, 2H), 7.80 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5 (CH_2), 28.4 (CH_2), 29.6 (CH_2), 31.6 (CH_2), 32.7 (CH_2), 32.8 (CH_2), 38.1 (CH_2), 39.3 (CH_2), 39.4 (CH_2), 40.1 (CH_2), 45.3 (CH), 75.4 (CH_2), 79.1 (C), 115.5 (CH), 118.6 (C), 124.1 (C), 125.7 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 135.1 (CH), 136.3 (C), 136.7 (C), 138.9 (C), 142.4 (C), 144.3 (C), 146.6 (C), 151.8 (C), 156.1 (C), 170.5 (C), 171.5 (C); HRMS (MALDI) found m/z 761.2150 $[M + Na]^+$, $C_{36}H_{43}N_4O_8BrNa$ requires 761.2157.

***S*-[4-(20-Amino-4-benzyloxy-5-bromo-11,15-dioxo-2-oxa-10,14-diaza-tricyclo[16.2.2.10,0]tricosa-1(21),3(23),4,6,18(22),19-hexaen-13-yl)-butyl]-carbamic Acid *tert*-Butyl Ester (46).** $CrCl_2$ (140 mg, 1.139 mmol) was added to a solution of lactam **45** (50 mg, 0.066 mmol) in DMF (1 mL) at room temperature. After 12 h of stirring, the DMF was removed under reduced pressure and the residue dissolved in EtOAc (10 mL). The organic solution was washed with brine and dried (Na_2SO_4), and the volatiles were removed to give crude **46**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) gave **46** (40 mg, 85%) as a yellow viscous oil: IR (NaCl, neat) ν 3289, 2929, 1643, 1509, 1278 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD/$CDCl_3$, 1:1) δ 1.25−1.5 (m, 6H), 1.38 (s, 9H), 1.90−2.0 (m, 2H), 2.1−2.3 (m, 1H), 2.50−2.63 (m, 3H), 2.70−3.13 (m, 8H), 3.38−

3.49 (m, 1H), 3.88−4.03 (m, 1H), 5.10 (s, 2H), 6.32 (s, 1H), 6.56 (d, J = 7.2 Hz, 1H), 6.65 (s, 1H), 6.81 (d, J = 7.2 Hz, 1H), 7.03 (s, 1H), 7.25−7.35 (m, 3H), 7.40−7.55 (m, 3H); ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$, 1:1) δ 23.7 (CH_2), 28.2 (CH_3), 29.5 (CH_2), 32.0 (CH_2), 32.9 (CH_2), 33.0 (CH_2), 38.5 (CH_2), 38.9 (CH_2), 39.6 (CH_2), 40.2 (CH_2), 45.9 (CH), 75.7 (CH_2), 79.1 (C), 116.5 (CH), 118,1 (CH), 120.4 (C), 122.1 (CH), 126.8 (CH), 128.5 (CH), 128.9 (CH), 136.8 (C), 137.3 (C), 137.8 (C), 138.3 (C), 141.6 (C), 144.0 (C), 152.0 (C), 157.2 (C), 172.3 (C), 172.9 (C); HRMS (MALDI) found m/z 731.2386 $[M + Na]^+$, $C_{36}H_{45}O_6N_4BrNa$ requires 731.2415.

***S*-(+)-[4-(4-Benzyloxy-5,20-dibromo-11,15-dioxo-2-oxa-10,14-diaza-tricyclo[16.2.2.10,0]tricosa-1(21),3(23),4,6,18(22),19-hexaen-13-yl)-butyl]-carbamic Acid *tert*-Butyl Ester (47).** ^{t}BuONO (2.5 μL, 0.025 mmol) was added to a stirred solution of $CuBr_2$ (5.6 mg, 0.01 mmol) in CH_3CN (0.1 mL) at 0 °C. After 1 h, a mixture of lactam **46** (12 mg, 0.02 mmol) in CH_3CN (0.8 mL) was added dropwise into the above solution over 10 min at 0 °C. After stirring for 2 h, the mixture was allowed to warm to room temperature, quenched with HCl (1 N, 1 mL), and extracted with CH_2Cl_2 (4 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude lactam **47** and **50**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) followed by silca HPLC (SiO_2, 5 μm Microsorb, 10 × 250 mm, CH_2Cl_2/MeOH, 99:1.5, 3 mL/min) gave **47** (4.8 mg, 38%) as a colorless amorphous solid and **50** (5.4 mg, 42%) as a colorless amorphous solid. **47**: $[\alpha]_D^{25}$ +69.4° (c 0.320, $CHCl_3$); IR (KBr) ν 3303, 2927, 1681, 1644, 1527, 1488, 1280 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.18−1.68 (m, 5H), 2.00−2.18 (m, 3H), 2.53−3.20 (m, 9H), 3.68−3.79 (m, 1H), 4.12−4.24 (m, 1H), 4.46−4.58 (m, 1H), 5.16 (d, J = 10.8 Hz, 1H), 5.25 (d, J = 10.8 Hz, 1H), 5.34 (bs, 1H), 5.99 (bs, 1H), 6.85 (bd, J = 10 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 7.17 (dd, J = 8.4, 2.0 Hz, 1H), 7.29−7.38 (m, 3H); 7.48 (d, J = 2.0 Hz,1H), 7.58−7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6 (CH_2), 28.4 (CH_3), 29.6 (CH_2), 31.7 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 38.2 (CH_2), 39.7 (CH_2), 40.2 (CH_2), 40.5 (CH_2), 45.2 (CH), 75.2 (CH_2), 79.0 (C), 115.1 (CH), 116.2 (C), 118.6 (C), 123.7 (CH), 126.2 (CH), 128.2 (CH), 128.4 (CH), 128.7 (CH), 129.6 (CH), 134.2 (CH), 136.1 (C), 136.9 (C), 140.1 (C), 143.6 (C), 150.0 (C), 152.0 (C), 156.1 (C), 171.7 (C); HRMS (MALDI) found m/z 794.1425 $[M + Na]^+$, $C_{36}H_{43}N_3O_6Br_2Na$ requires 794.1441.

***S*-(+)-[4-(4-Benzyloxy-5,20,22-tribromo-11,15-dioxo-2-oxa-10,14-diaza-tricyclo[16.2.2.10,0]tricosa-1(21),3(23),4,6,18(22),19-hexaen-13-yl)-butyl]-carbamic acid *tert*-butyl ester (50)**: $[\alpha]_D^{25}$ +38.3° (c 0.360, $CHCl_3$); IR (KBr) ν 3334, 2925, 1697, 1652, 1513, 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.18−1.68 (m, 7H), 2.00−2.22 (m, 3H), 2.50−2.66 (m, 2H), 2.78−2.88 (m, 1H), 2.96−3.24 (m, 4H), 3.78−3.86 (m, 1H), 4.18−4.28 (m, 1H), 4.48−4.60 (m, 1H), 5.11 (d, J = 10.4 Hz, 1H), 5.28 (d, J = 10.4 Hz, 1H), 5.28 (bs, 1H), 5.95 (d, J = 2.0 Hz, 1H), 6.87 (bd, J = 9.6 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 7.32−7.39 (m, 3H); 7.36 (s,1H), 7.52 (s, 1H), 7.56−7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7 (CH_2), 28.4 (CH_3), 29.7 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 37.3 (CH_2), 38.3 (CH_2), 40.8 (CH_2), 45.2 (CH), 75.2 (CH_2), 79.0 (C), 114.5 (CH), 114.9 (C), 118.8 (C), 123.0 (C), 126.5 (CH), 128.2 (CH), 128.4 (CH), 128.7 (CH), 128.7 (CH), 135.4 (CH), 136.1 (C), 136.9 (C), 139.4 (C), 143.4 (C), 150.0 (C), 151.9 (C), 156.0 (C), 171.8 (C); HRMS (MALDI) found m/z 872.0502 $[M + Na]^+$, $C_{36}H_{42}N_3O_6Br_3Na$ requires 872.0516.

***S*-2-Azido-*N*-[4-(5,20-dibromo-4-hydroxy-11,15-dioxo-2-oxa-10,14-diaza-tricyclo[16.2.2.10,0]tricosa-1(21),3(23),4,6,18(22),19-hexaen-13-yl)-butyl]-5-iodo-benzamide (49).** BBr_3 (1 M, 10 μL, 10 μmol) was added to a solution of lactam **47** (3 mg, 3.8 μmol) in CH_2Cl_2 (50 μL), and the orange solution was allowed to stir overnight at room temperature. The solution was directly transferred onto a flash column (SiO_2, CH_2Cl_2/MeOH/NH_2OH, 10:1:0.1) to give the crude amine **48** (2.2 mg) as an amorphous solid that was immediately carried forward. EDCI (2 mg, 10 μmol) was added to a stirred solution of the crude amine (2.2 mg), HOBt (1.5 mg, 10 μmol) and 2-azido-5-iodo-benzoic acid[37] (3 mg, 10 μmol) in DMF (5.0 mL) at room temperature. After 5 h, the reaction was quenched with HCl (1 N) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **49**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) followed by reversed phase HPLC (C_{18}, MeOH/H_2O, 3:1, 4 mL/min) gave pure **49** (0.56 mg, 33% over two steps) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.60 (m, 7H), 1.94−2.18 (m, 3H), 2.48−2.64 (m, 2H), 2.76−3.00 (m, 3H), 3.04−3.14 (m, 1H), 3.22−3.40 (m, 2H), 3.61−3.74 (m, 1H), 4.06−4.19 (m, 1H), 5.41 (bs, 1H), 5.98 (s, 1H), 6.06 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.19 (dd, J = 8.0, 2.0 Hz, 1H), 7.33 (bs, 1H), 7.75 (dd, J = 8.4, 2.0 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H); HRMS (MALDI) found m/z 874.9709 $[M + Na]^+$, $C_{31}H_{31}N_6O_5Br_2NaI$ requires 874.9660.

***S*-2-Azido-5-iodo-*N*-[4-(5,20,22-tribromo-4-hydroxy-11,15-dioxo-2-oxa-10,14-diaza-tricyclo[16.2.2.10,0]tricosa-1(21),3(23),4,6,18(22),19-hexaen-13-yl)-butyl]-benzamide (52).** BBr_3 (1 M, 10 μL, 10 μmol) was added to a stirred solution of lactam **50** (2 mg, 2.4 μmol) in CH_2Cl_2 (50 μL) at room temperature. The solution was directly transferred onto a flash column (SiO_2, CH_2Cl_2/MeOH/NH_2OH, 10:1:0.1) to give crude amine **51** (1.8 mg) as an amorphous solid that was immediately carried forward. EDCI (2 mg, 10 μmol) was added to a stirred solution of crude amine **51** (2.2 mg), HOBt (1.5 mg, 10 μmol), and 2-azido-5-iodo-benzoic acid[37] (3 mg, 10 μmol) in DMF (5.0 mL) at room temperature. After 5 h, the reaction was quenched with HCl (1 N) and extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4), and the volatiles were removed to give crude **52**. Flash chromatography (SiO_2, CH_2Cl_2/MeOH, 20:1) followed by reversed phase HPLC (C_{18}, MeOH/H_2O, 3:1, 4 mL/min) gave **52** (0.80 mg, 48% over two steps) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.60 (m, 4H), 1.91−2.24 (m, 5H), 2.48−2.62 (m, 2H), 2.91−3.22 (m, 4H), 3.28−3.48 (m, 2H), 3.74−3.84 (m, 1H), 4.12−4.24 (m, 1H), 5.24 (bt, J = 5.6 Hz, 1H), 5.93 (s, 1H), 6.02 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.4, 2.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 7.40 (bt, J = 5.6 Hz, 1H), 7.46 (s, 1H), 7.48 (s, 1H), 7.75 (dd, J = 8.4, 2.0 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H); HRMS (MALDI) found m/z 952.8767 $[M + Na]^+$, $C_{31}H_{30}N_6O_5Br_3NaI$ requires 952.8765.

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Supporting Information Available: Spectral and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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