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Synthesis of Mimics of Pramanicin from Pyroglutamic Acid and Their Antibacterial Activity

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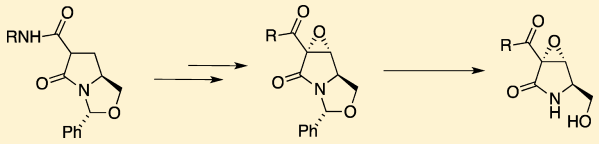
Supporting Information

ABSTRACT: Epoxypyrrolidinones are available by epoxidation of carboxamide-activated bicyclic lactam substrates derived from pyroglutamate using aqueous hydrogen peroxide and tertiary amine catalysis. In the case of an activating Weinreb carboxamide, further chemoselective elaboration leads to the efficient formation of libraries of epoxyketones. Deprotection may be achieved under acidic conditions to give epoxypyroglutaminols, although the ease of this process can be ameliorated by the presence of internal hydrogen bonding. Bioassay against *S. aureus* and *E. coli* indicated that some compounds exhibit antibacterial activity. These libraries may be considered to be structural mimics of the natural products pramanicin and epolactaene. More generally, this outcome suggests that interrogation of bioactive natural products is likely to permit the identification of "privileged" structural scaffolds, providing frameworks suitable for optimization in a short series of chemical steps that may accelerate the discovery of new antibiotic chemotypes. Further optimization of such systems may permit the rapid identification of novel systems suitable for antibacterial drug development.



INTRODUCTION

Pramanicin **1** was isolated from MF5868, a fungus isolated from an unidentified grass collected in New Jersey (typically 12.6 mg/1.8 L of fermentation broth) by Schwartz and co-workers, and was shown to possess a long fatty acyl chain containing an epoxide and enone functional group, along with a polar polyhydroxylated chiral lactam headgroup, by detailed NMR analysis.[1] Full confirmation of the stereochemical assignment came when the total synthesis of pramanicin was accomplished by Barrett and co-workers.[2,3] The synthesis of the fatty acid component has been reported.[4] Pramanicin exhibits antifungal activity against *Candida sp.* (minimum inhibitory concentration (MIC) 4 to >l00 μM), *Aspergillus fumigatus* (100 μM), and *Cryptococcus neoformans* (20 μM) as well as antibacterial activity against *Bacillus subtilis* with an MIC of 4 μM,[1] but it also has significant cytotoxicity at concentrations of 20−100 μM toward Jurkat T lymphoblastic leukemia cells,[5] induces apoptosis in human colon cancer cells,[6] and is able to selectively cause endothelium-dependent vasorelaxation via the nitric oxide pathway.[7] Pramanicin is also reported to increase cell permeability to Ca^{2+} ions and therefore to increase its intracellular concentration, eventually causing endothelial cell injury and death.[7−9] The biosynthesis of pramanicin proceeds via the separate syntheses of two fragments, involving the hydrophobic tail and the tetramic acid head.[10−14] There is no data related to its toxicity or mode of action. Other analogues of pramanicin (pramanicin A, TMC-260) are known,[8,15] and the isolation of the related virgaricin has been reported.[16]

It has recently been recognized that existing strategies for the discovery of new antibacterials have not been effective,[17] probably as a result on overreliance of combinatorial approaches leading to structurally narrow libraries,[18,19] and as a result there is an urgent need for the identification of novel leads for expanding the antibacterial drug development pipeline.[20,21] This has led to a renaissance of interest in natural product-led drug discovery,[22−33] and our contribution to this area has been to show that chemical libraries modeled on natural products,[34] including equisetin,[35] reutericyclin,[36] kibdelomycin,[37] and streptolodygin,[38] which all possess a core tetramate unit, and oxazolomycin,[39] which possesses a β-hydroxyglutamate core, may exhibit significant antibacterial activity and provide useful opportunities for further optimization. One advantage of this approach is that such natural products have been evolutionarily optimized for binding to specific protein domains and might therefore provide better starting points for chemical library design.[40] Given the reported biological activity of pramanicin, and its chemical similarity to tetramate and pyroglutamate systems, of interest was whether related oxygenated chiral lactam scaffolds would also provide structurally novel chemical libraries for antibacterial drug discovery. Noteworthy is that the epoxypyrrolidinone core is also found in other natural products, including epolactaene,[41] and epoxomicin.[42] Bicyclic lactams derived from pyroglutamic acid provide useful scaffolds for modification of the ring

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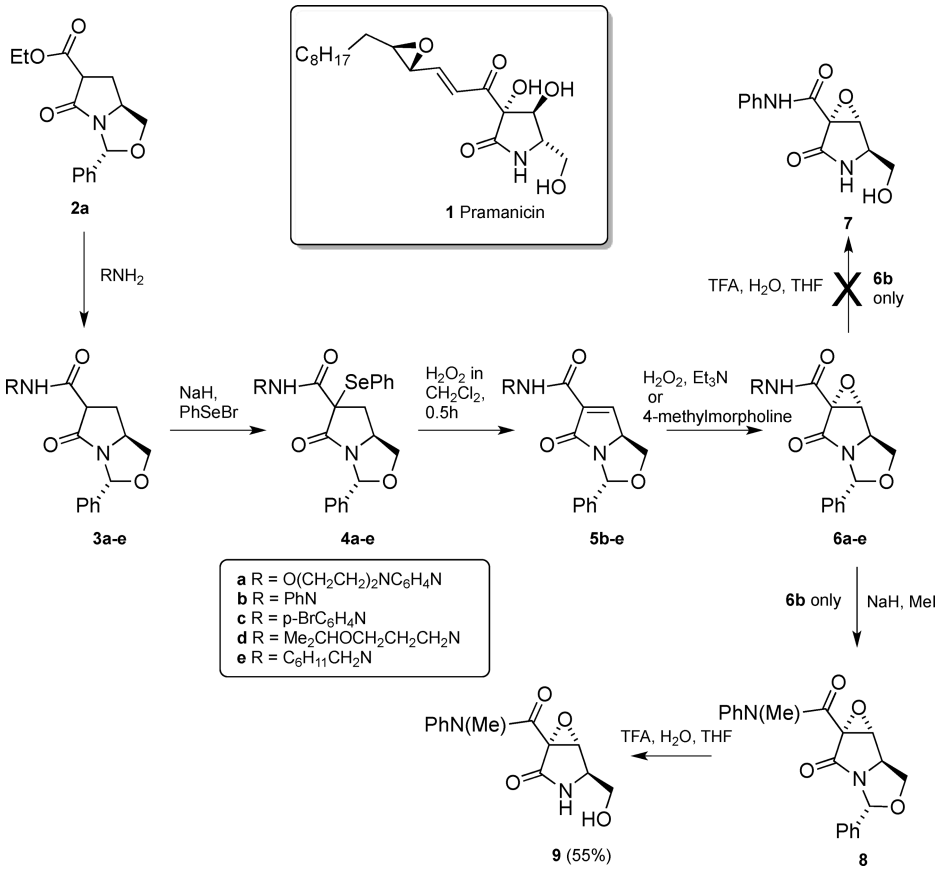
Scheme 1

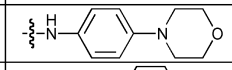
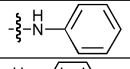
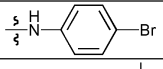
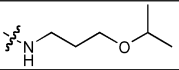
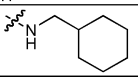


periphery by cycloaddition reactions[43] and by nucleophilic additions of organometallics,[44,45] by amines[46] and for oxygenation processes;[47,48] we report here the successful extension of this strategy for the synthesis of epoxypyrrolidinones, creating libraries that exhibited antibacterial activity against *S. aureus* and/or *E. coli*, thereby providing structurally novel leads for the antibacterial drug discovery process.

RESULTS AND DISCUSSION

Our approach began with ester **2a**, readily prepared from pyroglutamic acid using the literature procedure[43] and which could be easily converted by ester-to-amide exchange to give amides **3a−e**, in excellent yield as a mixture of two diastereomers, by reflux with the respective amine over 20 h (Scheme 1 and Table 1). The synthetic utility of such a transamidation approach has recently been increasingly recognized.[49,50] All of **3a−e** were readily selenylated under standard conditions to give products **4a−e**, also obtained as a mixture of two mainly inseparable diastereomers (although small amounts of pure diastereomers could be isolated for characterization purposes) in good yield (Table 1). Of note is that the 7*R*-isomers of **4a−e** show H-6 signals that are far apart in chemical shift value (typically near δ3.3 and δ2.2), while in the 7*S*-isomers the signals are closer together (near δ2.7); this is in keeping with the related ester system **2a** (although note that the *R*,*S* assignment changes here are due to priority rule alteration).[51] Oxidative elimination, by treatment of **4a−e** with hydrogen peroxide using a standard protocol, gave enones **5b−e** (Table 1) effectively, with the exception of **4a**, which gave epoxide **6a** directly. Noteworthy was the relative stability of

Table 1. Yields of Intermediates and Products in Scheme 1

Substrate		Yield (%)			
Compound Number	R=	3	4	5	6
a		67	40	-	40*
b		92	87	96	74
c		95	77	92	87
d		89	78	100	80
e		89	87	100	73

*Isolated as *N*-oxide and formed directly from **4a**.

enones **5b−e**; it had been earlier found that related ester enones were highly prone to dimerization under basic conditions,[43−46] but this proved not to be a problem with these amide equivalents, except on standing over extended periods or on purification via silica gel column chromatography.

Earlier work had shown that, even though epoxidation of unsaturated lactam systems derived from **2a** was possible under alkaline conditions, the reaction was not without difficulty, because these conditions also favored dimerization.[45] Mild epoxidation conditions were therefore expected to be essential to convert **5b−e** to their corresponding epoxypyrrolidinones. The observation that oxidative elimination of the selenenylated compound **4a** did not give the expected unsaturated compound **5a** but instead directly formed the epoxy *N*-oxide derivative **6a**,

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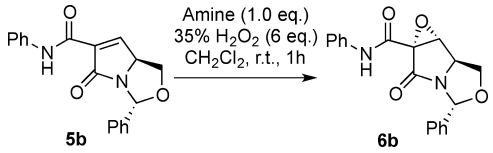
while all of the other substrates listed in Table 1 gave enones **5b–e** cleanly, proved to be fortuitous, suggesting that appropriate base catalysis of the epoxidation might be essential. Thus, the use of amine catalysis for the epoxidation of **5b** was examined, and the results are shown in Table 2. Critically, no

Table 2. Screening of Bases for Epoxidation of 5b



	pK_{aH} in H_2O[a]	reaction duration	yield	remarks
Et_3N	10.75	1 h		complex ^1H NMR of crude
DABCO	2.97, 8.82	40 min	74%	
4-methylmorpholine	7.38	1 h	quant.	
pyridine	5.21	3 h	87%	1.0 equiv of pyridine and 6 equiv of H_2O_2 added after each hour

[a] pK_{aH} in H_2O of H_2O_2 = 11.6.

reaction was observed in the absence of base, and the reaction was generally slow and required excess reagents when pyridine was used; when a more basic amine (Et_3N) was used, the ^1H NMR spectrum of the reaction crude mixture was complex. However, DABCO gave better results in terms of reaction duration and product yield, and when 1 equiv of 4-methylmorpholine was used (chosen for its obvious structural similarity to **6a**), epoxidation was surprisingly rapid and efficient, giving tricycles **6b–e** in excellent yield (Table 1 and Scheme 1); *exo*-oxygen addition was evident from NOE analysis (Figure 1), and noteworthy was that H-6 was a singlet,

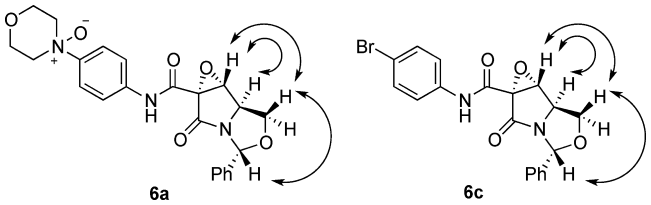


Figure 1. NOE data for selected compounds.

typically at a chemical shift of δ4.57 ± 0.01, indicating its orthogonal relationship to H-5. Epoxidation of related systems using tertiary amine oxides has been reported previously.[52] This stereochemical outcome is consistent with preferred nucleophilic attack at the less hindered face, similar to *exo*-alkylations at the less hindered face of the bicyclic system.[53]

This stereochemical outcome was unequivocally confirmed by single crystal analysis of **6e** (Figure 2),[54] and of interest was the existence of N19···O18 hydrogen bonds forming 1-D chains, but also the close intramolecular proximity of the N–H with the epoxy oxygen (NH···O is 2.394 Å), although appropriate angles for a donor–acceptor intramolecular amide H-bond linking N19–H with O13 do not appear to be possible.

In the case of benzamide **6b**, attempted deprotection using TFA/H_2O/THF failed, conditions which we have previously found to be universally successful in related substrates.[44] However, when *N*-methylated substrate **8** was prepared from **6b** and subject to identical deprotection conditions, clean deprotection in very good yields to alcohol **9** was observed. This unexpected behavior is discussed in more detail later (vide infra).

To extend this work further, a general approach to access longer-chain *C*-acyl rather than amido groups, but making use of the approach thus far developed, was sought; such systems would provide closer mimics to pramanicin. To this end, careful hydrolysis of ester **2a** to acid **2b** could be achieved without spontaneous decarboxylation (Scheme 2), and conversion to Weinreb amide by carbodiimide coupling gave **10a** in 74% yield over the two steps. Introduction of $\Delta^{6,7}$-unsaturation by selenenylation to **10b** and elimination as before gave **11** in high yield, but in this case epoxidation with hydrogen peroxide and 4-methylmorpholine gave **12** with a yield of only 58%, with the reaction being sluggish and excess reagents required for complete conversion. Although a similar result was obtained with DABCO, Et_3N did give the desired product **12** without the use of excess reagents in only 1 h and with an improved isolated yield of 88% (Table 3).

The latter product **12** was in turn readily converted to ketones **13a–g** in moderate to good yield (Scheme 2) using a range of alkyl, aryl, and alkynyl Grignard reagents; the chemoselectivity of this process in such a functionally dense substrate, which left the epoxide and lactam rings fully intact, is noteworthy. An attempt to use ^{n}BuLi instead of the Grignard reagent to synthesize **13d** resulted in only a low yield of product (18%), with several side-products being formed as observed from TLC analysis. The stability of the epoxide in the presence of excess Grignard reagent could be explained from the steric requirements of the bicyclic [3.3.0] system; from the X-ray crystal structure of **6e**, the C–N–C (147.1) and C–C–C (106.1) angles of the bicyclic ring system (see Scheme 2, inset) indicate a high level of nonplanarity,[55] in which the antiperiplanar approach to the epoxy C–O bond at C-6 on the *endo*-face of the bicyclic system is hindered by the C-4 methylene group, whereas the approach of nucleophile at C-7 is hindered by the presence of the two adjacent carbonyl groups.

Deprotection of these compounds under standard acidic conditions proceeded without difficulty, giving products **14a–h** in excellent yield, in contrast to the poor reactivity of system **6b** (Scheme 2). (*E*)-Enones **16a,b** were synthesized from the corresponding ynones **14g,h** via a two-step partial hydrogenation–isomerization sequence involving initial reduction to the (*Z*)-enones **15a,b** using Lindlar's catalyst followed by iodine-catalyzed double-bond isomerization; some fully reduced products **15c,d** were obtained in the initial reduction with 30% yield each. Isolation of the (*E*)-enones was achieved via reverse-phase preparative HPLC to obtain **16a,b** with 50% and 29% yields, respectively.

Several pieces of evidence suggested that there were unusual structural features in these functionally dense systems. From the NMR spectra of Weinreb amide **11**, restricted bond rotation about the exocyclic amide bond was evident from signal broadening, as observed in the ^1H spectra recorded at room temperature, for the –OMe signal and in the ^{13}C spectra for the –NMe, –OMe, C-6, and exocyclic amide carbonyl signals. Additionally, significant differences in the ease of acidic deprotection were observed. Thus, protected epoxyketopyrrolidinones **13a–g** underwent oxazolidine hydrolysis smoothly to give the corresponding pyroglutaminols **14b–h** in good yield.

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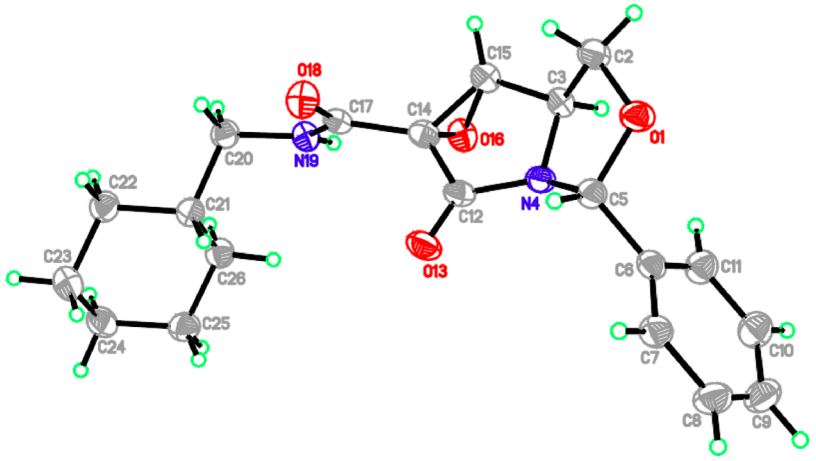


Figure 2. ORTEP plot of **6e**.

Scheme 2

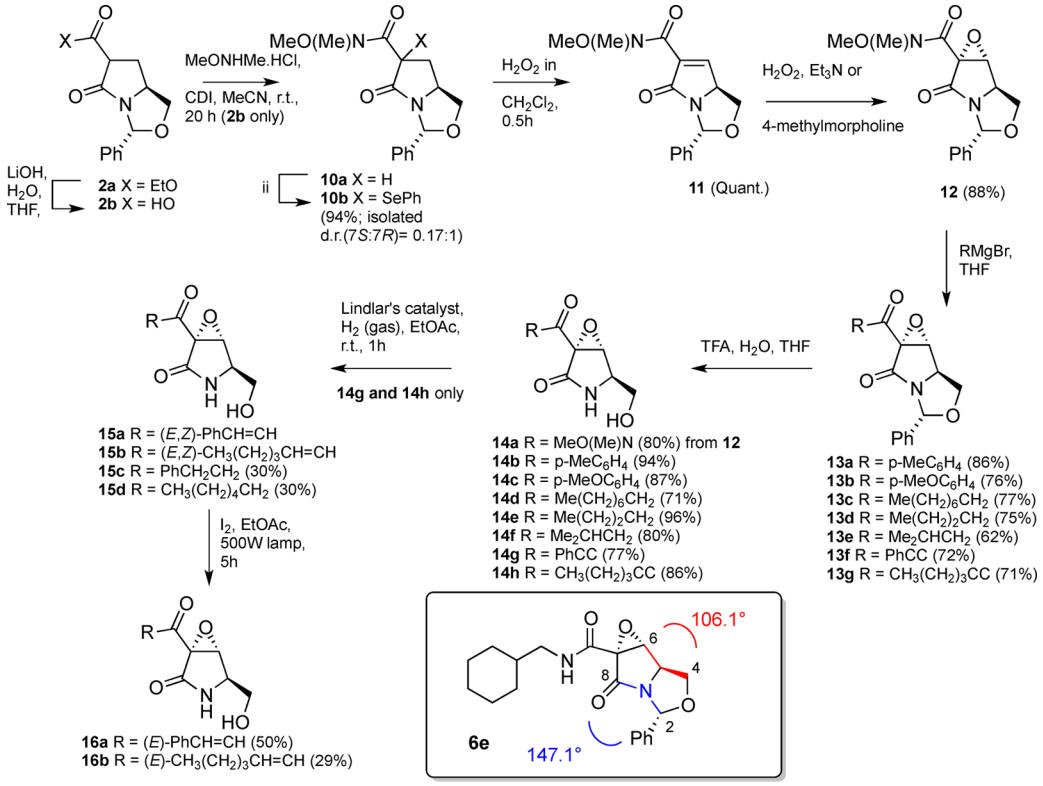
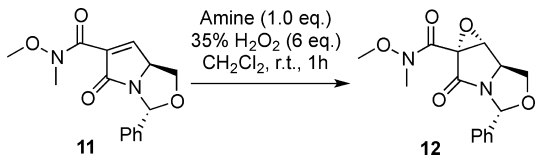


Table 3. Screening of Bases for Epoxidation of 11



	pK_a in H_2O	reaction duration	yield	remarks
4-methylmorpholine	7.38	3 h	58%	1.0 equiv of amine and 6 equiv of H_2O_2 added after each hour
DABCO	2.97, 8.82	6 h	68%	1.0 equiv of amine and 6 equiv of H_2O_2 added four times over 6 h
Et_3N	10.75	1 h	88%	

The behavior of protected carboxamido epoxypyrrolidinones was more variable, so that *N*-methyl **8** and Weinreb amide **12** were readily hydrolyzed, but carboxamido **6b** was resistant to hydrolysis under the same conditions. One possible explanation for this behavior could have been the existence of intramolecular hydrogen bonding of the −NH− group of the amide with the lactam carbonyl oxygen, which would reduce electron density of the lactam nitrogen atom, impeding the acid-catalyzed oxazolidine hydrolysis. To investigate this further, attenuated total reflectance (ATR) IR (neat) and ^{13}C spectra ($CDCl_3$) were obtained, and the data is shown in Table 4.

For the IR data, the tertiary amides **8** and **12** generally showed carbonyl frequencies at a higher resonance frequency than those for the secondary amides **6b−e**, and a similar pattern was observed for the corresponding α,β-unsaturated

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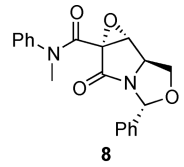
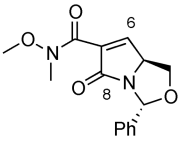
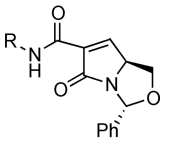
Table 4. Stretching Frequency of Lactam C═O and ^{13}C NMR Chemical Shifts

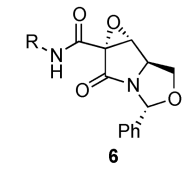


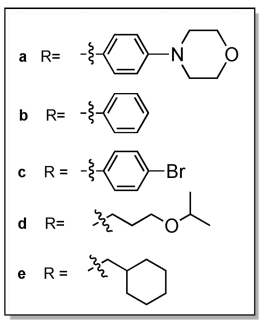
	Epoxy lactams IR frequency (cm^{-1})	^{13}C NMR (ppm)
8	1720	172.13
12	1734	171.82
6b	1716	173.46
6c	1718	173.33
6d	1726	172.89
6e	1714	173.43

	α,β unsaturated lactams IR frequency (cm^{-1})	^{13}C NMR (ppm)
11	1704	C-8: 172.50 C-6: 146.72
5b	1702	C-8: 174.29 C-6: 152.15
5c	1701	C-8: 174.20 C-6: 152.37
5d	1698	C-8: 174.33 C-6: 151.20
5e	1698	C-8: 174.48 C-6: 151.08

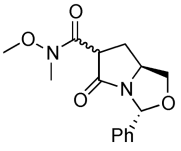


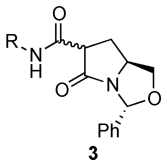


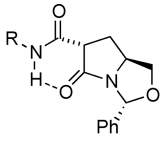


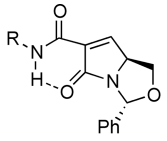


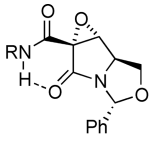
	7-unsubstituted lactam IR frequency (cm^{-1})	^{13}C NMR (7*S*, 7*R*) (ppm)
10a	1703	173.40; 173.52
3a	1697	175.58; 173.81
3b	1699	175.45; 173.62
3c	1700	175.32; 173.41
3d	1699	175.33; 174.02
3e	1697	175.63; 174.04



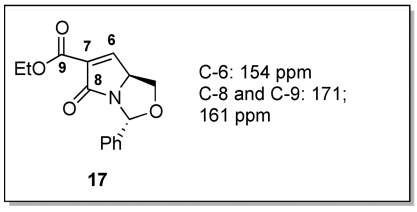








3a-e **5b-e** **6a-e**



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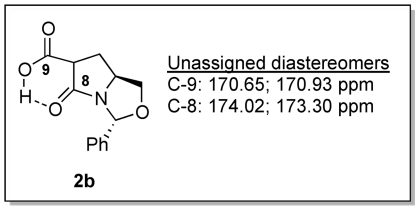

2b

Figure 3. Intramolecular hydrogen bonding and NMR data.

lactams (**11** versus **5b−e**). A similar trend was observed for the ^{13}C NMR data (Table 4). This outcome is consistent with reduced electron density about the carbonyl group that would result from the anticipated intramolecular hydrogen bonding (Figure 3). This characteristic was also manifested in the ease of epoxidation of the *α,β*-unsaturated lactams (**5b−e**) relative to Weinreb amide **11**, which, having the intramolecular hydrogen bonding and therefore reduced electron density at C-6, are better Michael acceptors, so that a weaker base such as 4-methylmorpholine is a sufficient catalyst. Similarly, amides **5b−e** are more reactive and prone to dimerization than Weinreb derivative **11**. This pattern is confirmed from literature data; ester **17** (Figure 3) was found to be highly prone to dimerization under basic conditions and possesses a C-6 ^{13}C NMR chemical shift of 154 ppm, consistent with it being a more reactive Michael acceptor than the corresponding amide derivatives **5b−e**. Without an exocyclic hydrogen-bond donor, the lactam carbonyl group of **17** has a ^{13}C NMR chemical shift of 171 ppm, which is comparable to Weinreb system **11**. By contrast, of interest was the fact that only the exo-diastereomers of 7-unsubstituted lactams **3a−e**[56] exhibited such intramolecular hydrogen bonding, which all showed ^{13}C resonances in excess of 175 ppm (note that the lactam ^{13}C resonance frequency of Weinreb amide **10a**, for which internal hydrogen bonding is not possible, is ∼173 ppm). In this case, the chemical shift difference between **3a−e** and **10a** (ca. 2 ppm) was larger than the difference between **6b−e**, **8**, and **12** (ca. 1.2 ppm), suggesting that the hydrogen bonding was stronger in

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Table 5. Antibacterial Assay Result and Calculated Physicochemical Properties[a]

compound	sample conc. (g/mL)	*S. Aureus* zone size[b,c] (mm)	efficiency ratio (Cpd/CepcC)[d]	*E. coli* zone size[b,c] (mm)	efficiency ratio (Cpd/CepcC)[d]	MW	clogP	PSA	MSA	% PSA
5b	0.5	19	0.61	15	310	320.34	2.71	58.64	419.85	14.0
5c	4	24	3.0	17	1480	399.24	3.48	58.64	440.19	13.3
5d	4	24	3.0	24	670	344.40	1.48	67.87	515.37	13.2
5e	0.5	22	0.44	13.5	160	340.42	2.81	58.64	498.67	11.8
6a[e]	4	NA		16	660	437.44	−2.67	107.28	587.45	18.3
6b	3.3	NA		NA		336.35	2.36	71.17	443.35	16.1
6c	4	18	4.5	17	1400	415.24	3.12	71.17	463.94	15.3
6d	4	NA		12 (halo)		360.41	1.12	80.40	538.65	14.9
6e	4	NA		NA		356.42	2.45	71.17	522.21	13.6
13a	1	20.5	0.96	21.5 (halo)		335.36	3.19	59.14	456.55	13.0
13b	1	NA		22 (halo)		351.35	2.52	68.37	472.51	14.5
13c	2	13	6.8	NA		357.44	4.62	59.14	564.63	10.5
13d	1	17 (halo)		20	350	301.34	2.84	59.14	442.25	13.4
13e	2	18 (halo)		15	2200	301.34	2.68	59.14	440.39	13.4
13f	1	14	2.7	14	400	345.35	3.63	59.14	443.55	13.3
13g	1	13	3.2	14	430	325.36	3.83	59.14	460.41	12.8
14a	4	NA		NA		216.19	−2.03	91.4	301.37	30.3
14b	4	NA		17 (halo)		247.25	0.44	78.93	339.64	23.2
14c	2	NA		13 (halo)		263.25	−0.23	88.16	355.77	24.8
14d	1	14	3.8	18	190	269.34	1.87	78.93	448.09	17.6
14e	1	NA		16 (halo)		213.23	0.10	78.93	325.92	24.2
14f	4	NA		17 (halo)		213.23	−0.06	78.93	323.70	24.4
14g	2	13	8.1	18	620	257.25	0.88	78.93	327.03	24.1
14h	4	14	15.8	14	2340	237.26	1.08	78.93	343.66	23.0
15a	0.5	19	0.51	20	90	259.26	0.86	78.93	339.68	23.2
15b	1	13	4.4	17	330	239.27	0.98	78.93	356.69	22.1
15c	1	12 (halo)		15 (halo)		261.28	0.78	78.93	370.05	21.3
15d	1	NA		19	230	241.29	0.98	78.93	387.03	20.4

[a]MW = molecular weight; PSA = polar surface area; MSA = molecular surface area; %PSA = (PSA/MSA) × 100. [b]NA denotes no observed activity in terms of a distinct clear zone. [c]Halo denotes a ring of reduced bacterial density, but not a distinctly clear zone. [d]Efficiency ratio defined as the ratio of the number of moles of Cephalosporin C to the tested compound, required to produce the same zone size. [e]**6a** tested as a solution in 100% DMSO instead of the usual 70% DMSO/H_2O.

the unsubstituted systems. This intramolecular hydrogen bonding might also be responsible for the lactam carbonyl (C-8) of **2b** resonating further downfield as compared to the carbonyl carbon of its carboxylic acid (C-9) (Figure 3).

The antibacterial activity of the intermediates was assessed using the hole-plate method with agar plates inoculated with either *S. aureus* or *E. coli* (Table 5).[57] In addition to providing cell killing data, the nature of the phenotypic assay is such that cell penetration activity is automatically selected for, identifying active compounds with potential for further development.[58] α,β-Unsaturated lactams (**5b**−**e**, **11**) were found to have good activity toward both *S. aureus* and *E. coli*, but this is perhaps not surprising given their potent Michael addition capability.[59] The unsaturated lactams tested were used in crude form after aqueous workup from the oxidative elimination reaction, as further purification via silica gel column chromatography resulted in significant decomposition. However, the possibility that residual selenium residues (PhSeOH) might confound the bioactivity data was addressed by quickly purifying **5b** on silica gel to obtain a few milligrams of the pure product. A comparison between the activities of crude and purified **5b** showed that the antibacterial activities are very similar, suggesting that toxic selenium residues were unlikely to be causing false positives in the bioassay.[60] By contrast, carboxamido pyrrolidinones **3a**−**e** and carboxamido epoxypyrrolidinones (**6a**−**e**, **12** and **8**, **10a**) exhibited little or no antibacterial activity, with the exceptions of **6a** and **6c**, which both show modest activity toward *E. coli*. However, epoxyketones **13a**−**g** showed significant antibacterial activities, and oxazolidine deprotection gave compounds (amido alcohols **14b**−**h**) that are selective for *E. coli* over *S. aureus*. This outcome suggests that the epoxyketone moiety is important for conferring antibacterial activity.

The calculated physicochemical properties[61] of these small-molecule libraries show that they are within the range for good oral adsorption as described by Lipinski's "rules"[62] and therefore display appropriate "drug likeness". For the α,β-unsaturated lactams **5b**−**e**, having a clogP range of 1.48−3.48 and %PSA range of 11.8−14%, good antibacterial activity was observed for both *S. aureus* and *E. coli*. The epoxypyrrolidinones that are active, **13a**, **d**−**g**, have a clogP range of 2.68−3.83 and %PSA range of 12.8−13.4%. After oxazolidinone hydrolysis, the compounds that retain some of their antibacterial activity (**14d**, **g**, **h**) have a clogP range of 0.88−1.87, with a %PSA range of 17.6−24.1%. Interestingly, the antibacterially active nonpolar compounds (**5b**−**e**, **13a**, and **13d**−**g**) and polar compounds (**14d**, **g**, **h**) each possess clogP and %PSA values similar to other active tetramate libraries reported previously, and the fact that they are bioactive confirms their bacterial cell wall permeability.[63]

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CONCLUSION

Mild and facile epoxidation conditions, utilizing aqueous hydrogen peroxide and a tertiary amine, have been identified to be suitable for construction of epoxypyrrolidinones from a pyroglutamate scaffold. The reactivity of the unsaturated substrate is dependent on intramolecular H-bonding in the substrate, but this can be controlled by changing the basicity of the tertiary amine catalyst. Highly chemoselective modification of a Weinreb amide provides access to a functionalized ketone side-chain on the scaffold. Antibacterial assays have revealed that some of these epoxypyrrolidinones exhibit antibacterial activity toward the Gram-negative *E. coli*, whereas the unsaturated lactams exhibits antibacterial activity toward both *S. aureus* and *E. coli*. We have recently reported that the antibacterial activity of simple pyroglutamates and tetramates is low.[34] The use of natural products for the construction of lead-like libraries has recently been promoted, and the work described herein suggests that, while pramanicin is a valuable start point,[6] ring functionalization is critically important for antibacterial activity. This approach demonstrates that escape from flatland is indeed possible using modular chemistry for the manipulation of 3D templates for rapid library construction,[64,65] and in that regard modified pyroglutamates can provide useful structurally well-defined building blocks.[66−68]

EXPERIMENTAL SECTION

Low-resolution mass spectra (m/z) were recorded using electrospray ionization (ESI), electron impact ionization (EI), or field ionization (FI). High-resolution mass spectra (HRMS) were recorded using TOF (ESI).

General Procedure for Synthesis of Amides 3a−e from 2a. To a solution of the ester **2a** (200 mg, 0.726 mmol, 1.0 equiv) in toluene (15 mL) was added the amine (2.1 equiv) and DMAP (0.1 equiv), and the resulting solution was heated at reflux for 20 h. The solution was then cooled to rt, diluted with ethyl acetate (15 mL), and washed with 1% aq HCl (15 mL). The aqueous layer was extracted with ethyl acetate, and the combined organic layers were combined and washed with water and brine, dried with anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo and purified on silica gel by flash column chromatography to give the amides **3a−e** as an inseparable mixture of diastereomers (at C-7).

(2R,5S,7S)- and (2R,5S,7R)-1-Aza-7-(4′-morpholinophenylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***3a.*** Scale of reaction 200 mg, 0.726 mmol, yield (200 mg, 67%), R_f = 0.11 and 0.19 (5% MeOH/EtOAc); brown oil; ν_{max}/cm^{-1} (film) 1697 (s, C═O), 1682 (s, C═O); diastereomer A (7*S*), diastereomer B (7*R*); δ_H (400 MHz, $CDCl_3$) 9.56 (s, 1H, −NH−$_B$), 8.62 (s, 1H, −NH−$_A$), 7.35−7.51 (m, ArH), 6.84−6.90 (m, ArH), 6.33 (s, 1H, H-2$_A$), 6.30 (s, 1H, H-2$_B$), 4.35 (dd, *J* = 7.2, 8.3 Hz, 1H, H-4$_B$), 4.33 (dd, *J* = 6.3 Hz, 7.8 Hz, 1H, H-4$_A$), 4.20−4.23 (m, 1H, H-5$_A$), 4.16 (m, 1H, H-5$_B$), 3.89 (obscured by morpholinoaniline CH_2 signals, H-7$_B$), 3.84−3.87 (m, morpholinoaniline CH_2), 3.67 (dd, *J* = 5.0, 10.6 Hz, H-7$_A$), 3.58 (t, *J* = 8.3 Hz, 1H, H-4′$_B$), 3.49 (t, *J* = 8.5 Hz, 1H, H-4′$_A$), 3.09−3.13 (m, morpholinoaniline CH_2), 3.05 (ddd, *J* = 5.3, 8.1, 13.6 Hz, H-6$_A$), 2.74 (ddd, *J* = 7.3, 9.6, 13.4 Hz, H-6$_B$), 2.42 (ddd, *J* = 6.8, 10.4, 13.4 Hz, H-6′$_B$), 2.17 (ddd, *J* = 4.0, 10.6, 14.4 Hz, H-6′$_A$); δ_C (100 MHz, $CDCl_3$) 175.6 (C-8$_A$), 173.8 (C-8$_B$), 164.9 (C-9$_B$), 163.9 (C-9$_A$), 148.3, 148.2, 137.9, 130.5, 129.0, 128.6, 128.6, 126.0, 125.9, 121.2, 116.2, 116.2, 87.6 (C-2$_A$), 87.0 (C-2$_B$), 72.2 (C-4$_B$), 71.4 (C-4$_A$), 66.9 (C-11$_A$ and 11$_B$), 57.5 (C-5$_A$), 56.2 (C-5$_B$), 51.3 (C-7$_A$), 50.1 (C-7$_B$), 49.7 (C-10$_B$), 49.7 (C-10$_A$), 26.9 (C-6$_B$), 23.6 (C-6$_A$); m/z (ESI+) 430.21 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{23}H_{25}N_3O_4Na$ ([M + Na]$^+$), 430.1737; found, 430.1723.

(2R,5S,7S)- and (2R,5S,7R)-1-Aza-3-oxa-8-oxo-2-phenyl-7-(phenylcarbamoyl)bicyclo[3.3.0]octane, ***3b.*** Scale of reaction 200 mg, 0.726 mmol, yield (215 mg, 92%), R_f = 0.47 and 0.32 (1:1 PE/EtOAc); brown oil; ν_{max}/cm^{-1} (film) 1699 (br, C═O), 1687 (br, C═O); diastereomer A (7*S*), diastereomer B (7*R*); δ_H (500 MHz, $CDCl_3$) 9.72 (s, 1H, −NH−$_B$), 8.74 (s, 1H, −NH−$_A$), 7.34−7.60 (m, ArH), 7.11−7.14 (m ArH), 6.34 (s, 1H, H-2$_A$), 6.31 (s, 1H, H-2$_B$), 4.36 (dd, *J* = 6.3, 8.2 Hz, 1H, H-4′$_B$), 4.32 (dd, *J* = 6.3, 8.2 Hz, 1H, H-4′$_A$), 4.31−4.38 (m, 1H, H-5$_B$), 4.16−4.31 (m, 1H, H-5$_A$), 3.90 (t, *J* = 9.9 Hz, 1H, H-7$_B$), 3.70 (dd, *J* = 5.4, 10.4 Hz, 1H, H-7$_A$), 3.59 (t, *J* = 8.4 Hz, 1H, H-4$_B$), 3.50 (t, *J* = 8.5 Hz, 1H, H-4$_A$), 3.08 (ddd, *J* = 5.4, 8.2, 13.6 Hz, 1H, H-6$_A$), 2.78 (ddd, *J* = 7.3, 9.5, 13.6 Hz, 1H, H-6$_B$), 2.44 (ddd, *J* = 6.9, 10.4, 13.6 Hz, 1H, H-6′$_B$), 2.20 (ddd, *J* = 4.1, 10.7, 14.5 Hz, 1H, H-6′$_A$); δ_C (125 MHz, $CDCl_3$) 175.5 (C-8$_A$), 173.6 (C-8$_B$), 165.1 (C-9$_B$), 165.0 (C-9$_A$), 137.9, 137.8, 137.6, 137.5, 129.0, 129.0, 128.6, 128.6, 128.5, 126.0, 125.9, 119.9, 119.8, 87.6 (C-2$_A$), 87.0 (C-2$_B$), 72.2 (C-4$_B$), 71.4 (C-4$_A$), 57.5 (C-5$_A$), 56.1 (C-5$_B$), 51.3 (C-7$_A$), 50.1 (C-7$_B$), 26.8 (C-6$_B$), 23.3 (C-6$_A$); m/z (ESI) 321.12 ([M−H]$^-$, 100%); HRMS (FI+): calcd for $C_{19}H_{18}N_2O_3$ ([M]$^+$), 322.1317; found, 322.1314.

(2R,5S,7R)- and (2R,5S,7S)-1-Aza-7-(4′-bromophenylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***3c.*** Scale of reaction 200 mg, 0.726 mmol, yield (275 mg, 95%), R_f = 0.25 and 0.53 (1:1 PE/EtOAc); brown oil; ν_{max}/cm^{-1} (film) 1700 (br, C═O), 1678 (br, C═O); diastereomer A (7*S*), diastereomer B (7*R*); δ_H (500 MHz, $CDCl_3$) 9.80 (s, 1H, −NH−$_B$), 8.81 (s, 1H, −NH−$_A$), 7.35−7.50 (m,ArH), 6.33 (s, 1H, H-2$_A$), 6.30 (s, 1H, H-2$_B$), 4.37 (dd, *J* = 6.0, 8.2 Hz, 1H, H-4$_A$), 4.34 (dd, *J* = 6.3, 8.2 Hz, 1H, H-4$_B$), 4.24−4.30 (m, 1H, H-5$_B$), 4.16−4.23 (m, 1H, H-5$_A$), 3.88 (t, *J* = 10.1 Hz, 1H, H-7$_B$), 3.71 (dd, *J* = 5.7, 10.7 Hz, 1H, H-7$_A$), 3.59 (d, *J* = 8.5 Hz, 1H, H-4′$_B$), 3.51 (t, *J* = 8.8 Hz, 1H, H-4′$_A$), 3.05 (ddd, *J* = 5.4, 8.2, 13.9 Hz, 1H, H-6$_A$), 2.78 (ddd, *J* = 7.3, 9.5, 13.6 Hz, 1H, H-6$_B$), 2.42 (ddd, *J* = 6.9, 10.7, 13.6 Hz, 1H, H-6′$_B$), 2.21 (ddd, *J* = 3.8, 10.7, 14.2 Hz, 1H, H-6′$_A$); δ_C (125 MHz, $CDCl_3$) 175.3 (C-8$_A$), 173.4 (C-8$_B$), 165.2 (C-9$_B$), 164.1 (C-9$_A$), 137.8, 137.7, 136.7, 136.6, 131.9, 129.3, 129.1, 128.6, 128.6, 128.5, 128.5, 125.9, 125.8, 121.40, 121.33, 117.0, 116.9, 87.6 (C-2$_A$), 87.0 (C-2$_B$), 72.2 (C-4$_B$), 71.4 (C-4$_A$), 57.4 (C-5$_A$), 56.1 (C-5$_B$), 51.3 (C-7$_A$), 50.2 (C-7$_B$), 26.9 (C-6$_B$), 23.1 (C-6$_A$); HRMS (FI+): calcd for $C_{19}H_{17}BrN_2O_3$ ([M]$^+$), 400.0423; found, 400.0439.

(2R,5S,7R)- and (2R,5S,7S)-1-Aza-7-(3′-isopropoxypropylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***3d.*** Scale of reaction 200 mg, 0.726 mmol, yield (223 mg, 89%), R_f = 0.38 and 0.26 (EtOAc); colorless oil; ν_{max}/cm^{-1} (film) 1699 (s, C═O), 1672 (br, C═O); diastereomer A (7*S*), diastereomer B (7*R*); δ_H (500 MHz, $CDCl_3$) 7.68 (br s, 1H, −NH−$_B$), 7.31−7.45 (m, ArH), 7.00 (br s, 1H, −NH−$_A$), 6.28 (s, 2H, H-2$_A$ and H-2$_B$), 4.30 (dd, *J* = 6.0, 8.2 Hz, 1H, H-4$_B$), 4.27 (dd, *J* = 6.3, 7.9 Hz, 1H, H-4$_A$), 4.16−4.22 (m, 1H, H-5$_A$), 4.08−4.14 (m, 1H, H-5$_B$), 3.58 (t, *J* = 9.8 Hz, 1H, H-7$_B$), 3.54−3.58 (m, 2H, H-13$_A$ and H-13$_B$), 3.53−3.55 (m, 1H, H-4′$_B$), 3.50−3.47 (m, 5H, H-7$_A$ and H-12$_A$; H-12$_B$), 3.44−3.46 (m, 1H, H-4′$_A$), 3.38−3.45 (m, 2H, H-10$_B$), 3.30−3.37 (m, 2H, H-10$_A$), 2.99 (ddd, *J* = 4.7, 7.9, 13.2 Hz, 1H, H-6$_A$), 2.67 (ddd, *J* = 7.6, 9.8, 13.6 Hz, 1H, H-6$_B$), 2.38 (ddd, *J* = 6.3, 9.8, 13.6 Hz, 1H, H-6′$_B$), 2.10 (ddd, *J* = 4.4, 10.4, 14.5 Hz, 1H, H-6′$_A$), 1.75−1.83 (m, 4H, H-11$_A$ and H-11$_B$), 1.18 (d, *J* = 3.5 Hz, 3H, H-14$_B$), 1.16 (d, *J* = 3.5 Hz, H-14$_A$; d, *J* = 3.5 Hz, H-14′$_B$; 6H), 1.14 (d, *J* = 3.5 Hz, 3H, H-14′$_A$); δ_C (125 MHz, $CDCl_3$) 175.3 (C-8$_A$), 174.0 (C-8$_B$), 167.0 (C-9$_B$), 166.1 (C-9$_A$), 138.2, 128.8, 128.7, 128.5, 128.5, 125.9, 87.4 (C-2$_A$), 86.9 (C-2$_B$), 72.0 (C-4$_B$), 71.7 (C-13$_A$), 71.63 (C-13$_B$), 71.6 (C-4$_A$), 66.2 (C-12$_A$), 66.0 (C-12$_B$), 57.6 (C-5$_A$), 56.2 (C-5$_B$), 51.1 (C-7$_A$), 49.7 (C-7$_B$), 38.1 (C-10$_A$), 37.5 (C-10$_B$), 29.6 (C-11$_B$), 29.4 (C-11$_A$), 26.7 (C-6$_B$), 24.3 (C-6$_A$), 22.0 (C-14$_A$), 22.0 (C-14$_B$); m/z (ESI+) 369.19 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{19}H_{26}N_2O_4Na$ ([M + Na]$^+$), 369.1785; found, 369.1778.

(2R,5S,7R)- and (2R,5S,7S)-1-Aza-7-(cyclohexylmethylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***3e.*** Scale of reaction 200 mg, 0.726 mmol, yield (220 mg, 89%), R_f = 0.20 and 0.28 (1:1 PE/EtOAc); white solid; mp = 138−141 °C; ν_{max}/cm^{-1} (film) 1697 (br, C═O), 1656 (br, C═O); diastereomer A (7*S*), diastereomer B (7*R*); δ_H (500 MHz, $CDCl_3$) 7.65 (br s, 1H, −NH−$_B$), 7.32−7.46 (m, ArH), 6.77 (br s, 1H, −NH−$_A$), 6.29 (s, 1H, H-2$_B$), 6.30 (s, 1H, H-2$_A$), 4.32 (dd, *J* = 6.0, 8.2 Hz, 1H, H-4$_B$), 4.28 (dd, *J* = 6.3, 8.2 Hz, 1H, H-4$_A$), 4.16−4.21 (m, 1H, H-5$_A$), 4.10−4.16 (m, 1H, H-5$_B$), 3.71 (t, *J* = 10.1 Hz, 1H, H-7$_B$), 3.56 (t, *J* = 8.2 Hz, 1H, H-4′$_B$), 3.50 (dd, *J* = 5.0,

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10.4 Hz, 1H, H-7_A), 3.47 (t, J = 8.5 Hz, 1H, H-$4'_A$), 3.10−3.21 (m, 4H, H-10_A and H-10_B), 3.01 (ddd, J = 4.7, 7.9, 12.9 Hz, 1H, H-6_A), 2.70 (ddd, J = 7.3, 9.8, 13.6 Hz, 1H, H-6_B), 2.37 (ddd, J = 6.6, 10.4, 13.6 Hz, 1H, H-$6'_B$), 2.12 (ddd, J = 4.4, 10.4, 14.5 Hz, 1H, H-$6'_A$), 1.64−1.77 (m, 10H, H-12_A, H-13_A, one of H-14_A; H-12_B, H-13_B, one of H-14_B), 1.45−1.55 (m, 2H, H-11_A; H-11_B), 1.10−1.29 (m, 6H, H-$13'_A$ and one of H-14_A; H-$13'_B$ and one of H-14_B), 0.86−1.00 (m, 4H, H-$12'_A$; H-$12'_B$); δ_C (125 MHz, $CDCl_3$) 175.6 (C-8_A), 174.0 (C-8_B), 167.0 (C-9_B), 166.0 (C-9_A), 138.0, 128.9, 128.8, 128.5, 128.5, 125.9, 125.8, 87.3 (C-2_A), 86.9 (C-2_B), 72.1 (C-4_B), 71.5 (C-4_A), 57.6 (C-5_A), 56.2 (C-5_B), 50.9 (C-7_A), 49.5 (C-7_B), 46.1 (C-10_A), 45.8 (C-10_B), 37.8 (C-11_A), 37.7 (C-11_B), 30.8 (C-12_A), 30.7 (C-12_B), 27.0 (C-6_B), 26.4 (C-14_B), 26.3 (C-14_A), 25.8 (C-13_B), 25.8 (C-13_A), 24.0 (C-6_A); m/z (ESI−) 341.20 ([M−H]$^-$, 100%); HRMS (ESI+), calcd for $C_{20}H_{26}N_2O_3Na$ ([M + Na]$^+$), 365.1836; found, 365.1828.

General Procedure for Synthesis of Selenyl Derivatives 4a−e from Amides 3a−e. NaH was prewashed with dry Et_2O and used immediately for the reaction. Amides **3a−e** (1.0 equiv) in anhydrous THF (approximate concentration 0.10−0.13 M) were added dropwise to prewashed NaH (1.0 equiv) at 0 °C, and the mixture was warmed to rt and stirred for 10 min. PhSeBr (1.0 equiv) in anhydrous THF (approximate concentration 0.27−0.40 M) was then added dropwise to the mixture at rt and stirred at rt for a further 30 min. The reaction mixture was then quenched with saturated aq NH_4Cl and extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude. The crude was purified via flash column chromatography on silica gel (eluent = EtOAc/PE) to give the two separate diastereomers. The 7*R* and 7*S* diastereomers were assigned by comparing the chemical shift values of H-6 and H-6′ with those compounds reported by Cossy et al.[69] and Beard et al.[51]

*(2R,5S,7R)-1-Aza-7-(4′-morpholinophenylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7R)-**4a**.* Scale of reaction 125 mg, 0.307 mmol, yield (68 mg, 40%), R_f = 0.26 (1:1 PE/EtOAc); brown oil; $[\alpha]_D^{20}$ = +135.8 (c = 0.55 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1697 (s, C═O), 1663 (s, C═O); δ_H (400 MHz, $CDCl_3$) 8.61 (br s, 1H, −NH−), 7.65−7.68 (m, 2H, ArH), 7.26−7.46 (m, 10H, ArH), 6.82−6.86 (m, 2H, ArH), 6.32 (s, 1H, H-2), 4.26 (t, J = 6.8 Hz, 1H, H-4), 4.05−4.11 (m, 1H, H-5), 3.87 (br t, J = 4.8 Hz, 4H, H-11), 3.61 (t, J = 8.5 Hz, 1H, H-4′), 3.35 (dd, J = 8.5, 15.4 Hz, 1H, H-6), 3.12 (br t, J = 4.8 Hz, 4H, H-10), 2.24 (dd, J = 3.1, 15.4 Hz, 1H, H-6′); δ_C (125 MHz, $CDCl_3$) 175.5 (C-8), 165.0 (C-9), 148.2, 137.9, 137.7, 131.5, 130.2, 130.3, 129.3, 128.9, 128.6, 127.1, 125.9, 121.0, 116.0 (ArC), 88.3 (C-2), 70.7 (C-4), 66.9 (C-11), 55.5 (C-5), 54.6 (C-7), 49.7 (C-10), 30.4 (C-6); m/z (ESI+) 586.14 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{29}H_{29}N_3O_4SeNa$ ([M + Na]$^+$), 586.1215; found, 586.1207.

*(2R,5S,7S)-1-Aza-7-(4′-morpholinophenylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7S)-**4a**.* Scale of reaction 125 mg, 0.307 mmol, yield (68 mg, 40%), R_f = 0.4 (1:1 PE/EtOAc); brown oil; $[\alpha]_D^{20}$ = +32.3 (c = 0.5 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1697 (s, C═O), 1663 (s, C═O); δ_H (400 MHz, $CDCl_3$) 9.36 (br s, 1H, −NH−), 7.55−7.58 (m, 2H, ArH), 7.36−7.47 (m, 8H, ArH), 7.15−7.20 (m, 2H, ArH), 6.85−6.89 (m, 2H, ArH), 6.24 (s, 1H, H-2), 4.33 (dd, J = 6.1, 8.3 Hz, 1H, H-4), 4.00 (m, 1H, H-5), 3.87 (br t, J = 4.8 Hz, 4H, H-11), 3.57 (t, J = 8.2 Hz, 1H, H-4′), 3.13 (br t, J = 4.8 Hz, 4H, H-10), 2.72 (d, J = 7.1 Hz, 2H, H-6, and H-6′); δ_C (125 MHz, $CDCl_3$) 173.3 (C-8), 166.0 (C-9), 148.1, 138.1, 137.6, 130.36, 130.35, 129.0, 129.0, 128.6, 126.3, 126.1, 120.9, 116.1 (ArC), 86.8 (C-2), 72.0 (C-4), 66.9 (C-11), 54.8 (C-5), 53.8 (C-7), 49.7 (C-10), 36.1 (C-6); m/z (ESI+) 586.15 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{29}H_{29}N_3O_4SeNa$ ([M + Na]$^+$), 586.1215; found, 586.1204.

*(2R,5S,7R)-1-Aza-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)-7-(phenylcarbamoyl)bicyclo[3.3.0]octane, (7R)-**4b**.* Scale of reaction 150 mg, 0.465 mmol, yield (237 mg, 87%), R_f = 0.55 (2:1 PE/EtOAc); brown oil; $[\alpha]_D^{20}$ = +47.1 (c = 0.28 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1699 (br, C═O), 1669 (br, C═O); δ_H (500 MHz, $CDCl_3$) 8.74 (br s, 1H, −NH−), 7.67 (d, J = 8.2 Hz, 2H, ArH), 7.28−7.46 (m, 12H, ArH), 7.10 (t, J = 7.3 Hz, 1H, ArH), 6.33 (s, 1H, H-2), 4.27 (t, J = 8.7 Hz, 1H, H-4), 4.06−4.14 (m, 1H, H-5), 3.64 (t, J = 8.0 Hz, 1H, H-4′), 3.37 (dd, J = 8.4, 15.5 Hz, 1H, H-6), 2.26 (dd, J = 2.8, 15.5 Hz, 1H, H-6′); δ_C (125 MHz, $CDCl_3$) 175.4 (C-8), 165.4 (C-9),137.9, 137.7, 137.3, 130.4, 129.3, 128.9, 128.8, 128.6, 127.1, 125.9, 124.4, 119.7 (ArC), 88.4 (C-2), 70.7 (C-4), 55.5 (C-5), 54.4 (C-7), 30.2 (C-6); m/z (ESI +) 477.05 ([M−H]$^-$, 36%); HRMS (ESI+): calcd for $C_{25}H_{22}N_2NaO_3Se$ ([M + Na]$^+$), 501.0689; found, 501.0690.

*(2R,5S,7S)-1-Aza-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)-7-(phenylcarbamoyl)bicyclo[3.3.0]octane, (7S)-**4b**.* Scale of reaction 150 mg, 0.465 mmol, yield (237 mg, 87%), R_f = 0.45 (2:1 PE/EtOAc); brown oil; $[\alpha]_D^{20}$ = +74.0 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1699 (s, C═O), 1669 (s, C═O); δ_H (500 MHz, $CDCl_3$) 9.49 (br s, 1H, −NH−), 7.57 (d, J = 7.9 Hz, 2H, ArH), 7.36−7.50 (m, 7H, ArH), 7.32 (t, J = 8.5 Hz, 1H, ArH), 7.31 (t, J = 8.3 Hz, 2H, ArH), 7.18 (t, J = 7.7 Hz, 2H, ArH), 7.11 (t, J = 7.6 Hz, 1H, ArH), 6.24 (s, 1H, H-2), 4.34 (dd, J = 6.3, 8.5 Hz, 1H, H-4), 4.03 (apparent quintet, J = 6.8 Hz, 1H, H-5), 3.58 (t, J = 8.5 Hz, 1H, H-4′), 2.72 (d, J = 6.9 Hz, 2H, H-6, and H-6′); δ_C (125 MHz, $CDCl_3$) 173.2 (C-8), 166.5 (C-9), 138.2, 137.6, 137.5, 130.4, 129.08, 129.05, 128.9, 128.6, 126.2, 126.1, 124.3, 119.7 (ArC), 86.9 (C-2), 72.0 (C-4), 54.8 (C-5), 53.8 (C-7), 36.0 (C-6); m/z (ESI+) 477.05 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{25}H_{22}N_2NaO_3Se$ ([M + Na]$^+$), 501.0689; found, 501.0691.

*(2R,5S,7R)-1-Aza-7-(4′-bromophenylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7R)-**4c**.* Scale of reaction 235 mg, 0.586 mmol, yield (250 mg, 77%), R_f = 0.49 (2:1 PE/EtOAc); light brown oil; $[\alpha]_D^{20}$ = +215.9 (c = 1.15 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1698 (s, C═O), 1668 (s, C═O); δ_H (500 MHz, $CDCl_3$) 8.74 (s, 1H, −NH−), 7.64 (d, J = 8.2 Hz, 2H, ArH), 7.31−7.46 (m, 11H, ArH), 7.25−7.26 (m, 1H, ArH), 6.33 (s, 1H, H-2), 4.29 (dd, J = 6.3, 7.9 Hz, 1H, H-4), 4.06−4.11 (m, 1H, H-5), 3.68 (dd, J = 7.9, 9.5 Hz, 1H, H-4′), 3.31 (dd, J = 8.5, 15.4 Hz, 1H, H-6), 2.25 (dd, J = 2.8, 15.8 Hz, 1H, H-6′); δ_C (125 MHz, $CDCl_3$) 175.5 (C-8), 165.4 (C-9), 137.9, 137.8, 136.4, 131.8, 130.5, 129.3, 129.2, 129.0, 128.6, 128.4, 127.0, 125.8, 121.2, 117.0 (ArC), 88.5 (C-2), 70.6 (C-4), 55.4 (C-5), 53.9 (C-7), 29.9 (C-6); m/z (ESI−) 554.96 ([M−H]$^-$, 100%); HRMS (ESI−): calcd for $C_{25}H_{20}BrN_2O_3Se$ ([M−H]$^-$), 554.9827; found, 554.9821.

*(2R,5S,7S)-1-Aza-7-(4′-bromophenylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7S)-**4c**.* Scale of reaction 235 mg, 0.586 mmol, yield (250 mg, 77%), R_f = 0.40 (2:1 PE/EtOAc); brown oil; $[\alpha]_D^{20}$ = +50.6 (c = 1.20 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1698 (s, C═O), 1668 (s, C═O); δ_H (500 MHz, $CDCl_3$) 9.50 (s, 1H, −NH−), 7.54 (d, J = 8.2 Hz, 2H, ArH), 7.33−7.47 (m, 10H, ArH), 7.18 (t, J = 7.6 Hz, 2H, ArH), 6.24 (s, 1H, H-2), 4.34 (dd, J = 6.3, 8.5 Hz, 1H, H-4), 4.04−4.10 (m, 1H, H-5), 3.58 (t, J = 8.4 Hz, 1H, H-4′), 2.70 (dd, J = 4.1, 7.6 Hz, 2H, H-6, and H-6′); δ_C (125 MHz, $CDCl_3$) 173.1 (C-8), 166.5 (C-9), 138.1, 137.4, 136.5, 131.9, 130.5, 129.1, 129.0, 128.6, 128.3, 126.1, 126.1, 121.2, 116.8 (ArC), 86.9 (C-2), 72.0 (C-4), 54.9 (C-5), 53.7 (C-7), 36.0 (C-6); m/z (ESI−) 554.95 ([M−H]$^-$, 100%); HRMS (ESI−): calcd for $C_{25}H_{20}BrN_2O_3Se$ ([M−H]$^-$), 554.9827; found, 554.9825.

*(2R,5S,7R)-1-Aza-7-(3′-isopropoxypropylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7R)-**4d**.* Scale of reaction 190 mg, 0.548 mmol, yield (216 mg, 78%), R_f = 0.47 (1:1 PE/EtOAc); pale yellow oil; $[\alpha]_D^{20}$ = +170.5 (c = 1.38 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1692 (s, C═O), 1668 (s, C═O); δ_H(500 MHz, $CDCl_3$) 7.66 (d, J = 8.2 Hz, 2H, ArH), 7.31−7.45 (m, 8H, ArH), 7.17 (t, J = 5.0 Hz, 1H, −NH−), 6.24 (s, 1H, H-2), 4.16 (dd, J = 6.3, 7.9 Hz, 1H, H-4), 4.01−4.07 (m, 1H, H-5), 3.52 (septet, J = 6.3 Hz, 1H, H-13), 3.39−3.43 (m, 2H, H-12), 3.28−3.35 (m, 4H, H-4′, H-6, H-10), 2.13 (dd, J = 3.8, 15.1 Hz, 1H, H-6′), 1.66−1.71 (m, 2H, H-11), 1.14 (d, J = 6.0 Hz, 6H, H-14); δ_C (125 MHz, $CDCl_3$) 174.8 (C-8), 167.3 (C-9), 138.1, 137.2, 130.0, 129.3, 128.8, 128.5, 127.2, 125.9 (ArC), 87.9 (C-2), 71.7 (C-13), 71.1 (C-4), 65.7 (C-12), 56.0 (C-7), 54.8 (C-5), 37.2 (C-10), 36.1 (C-6), 29.7 (C-11), 22.1, 22.1 (C-14); m/z (ESI+) 525.17 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{25}H_{30}N_2O_4SeNa$ ([M + Na]$^+$), 525.1264; found, 525.1259.

*(2R,5S,7S)-1-Aza-7-(3′-isopropoxypropylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7S)-**4d**.* Scale of reaction 190 mg, 0.548 mmol, yield (216 mg, 78%), R_f = 0.18 (1:1 PE/EtOAc); pale yellow oil; $[\alpha]_D^{20}$ = +102.8 (c = 1.44 in $CHCl_3$);

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ν_{max}/cm^{-1} (film) 1696 (s, C═O), 1662 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.72 (t, J = 5.0 Hz, 1H, −NH−), 7.57 (t, J = 8.2 Hz, 2H, ArH), 7.35−7.42 (m, 6H, ArH), 7.18 (t, J = 7.6 Hz, 2H, ArH), 6.21 (s, 1H, H-2), 4.23 (dd, J = 6.3, 8.5 Hz, 1H, H-4), 3.73−3.79 (m, 1H, H-5), 3.55 (septet, J = 6.0 Hz, 1H, H-13), 3.49 (d, J = 8.2 Hz, 1H, H-4′), 3.43 (t, J = 6.3 Hz, 2H, H-12), 3.30- 3.38 (m, 2H, H-10), 2.71 (dd, J = 6.9, 14.8 Hz, 1H, H-6), 2.64 (dd, J = 6.9, 14.8 Hz, 1H, H-6′), 1.70−1.77 (m, 2H, H-11), 1.16 (d, J = 1.9 Hz, 3H, H-14), 1.15 (d, J = 1.9 Hz, 3H, H-14′); δ_C (125 MHz, $CDCl_3$) 173.6 (C-8), 168.2 (C-9), 137.9, 137.9, 137.7, 130.1, 129.0, 128.9, 128.5, 126.4, 126.0 (ArC), 86.8 (C-2), 72.0 (C-4), 71.6 (C-13), 65.6 (C-12), 54.8 (C-5), 53.8 (C-7), 37.2 (C-10), 36.1 (C-6), 29.7 (C-11), 22.09, 22.06 (C-14); m/z (ESI+) 525.15 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{25}H_{30}N_2O_4SeNa$ ([M + Na]$^+$), 525.1264; found, 525.1249.

*(2R,5S,7R)-1-Aza-7-(cyclohexylmethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7R)-**4e**.* Scale of reaction 200 mg, 0.584 mmol, yield (253 mg, 87%), R_f = 0.65 (1:1 PE/EtOAc); colorless oil; $[\alpha]_D^{20}$ = +176.8 (c = 1.44 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1693 (s, C═O) with broad shoulder; δ_H (500 MHz, $CDCl_3$) 7.65−7.67 (m, 2H, ArH), 7.32−7.46 (m, 8H, ArH), 6.95 (t, J = 5.7 Hz, 1H, −NH−), 6.25 (s, 1H, H-2), 4.17 (dd, J = 6.3, 7.9 Hz, 1H, H-4), 4.02−4.07 (m, 1H, H-5), 3.33 (dd, J = 8.2, 8.8 Hz, 1H, H-4′ and dd, J = 8.2, 14.8 Hz, 1H, H-6), 2.97−3.09 (m, 2H, H-10), 2.13 (dd, J = 3.8, 14.8 Hz, 1H, H-6′), 1.62−1.70 (m, 5H, H-12, H-13, one of H-14), 1.34−1.42 (m, 1H, H-11), 1.07−1.28 (m, 3H, H-13′, and one of H-14), 0.83−0.91 (m, 2H, H-12′); δ_C (125 MHz, $CDCl_3$) 175.0 (C-8), 167.2 (C-9), 138.0, 137.2, 130.0, 129.3, 128.8, 128.5, 127.2, 125.9 (ArC), 87.9 (C-2), 71.0 (C-4), 55.8 (C-7), 55.8 (C-5), 46.2 (C-10), 37.7 (C-11), 31.5 (C-6), 30.7 (C-12), 26.3 (C-14), 25.8 (C-13); m/z (ESI−) 497.14 ([M−H]$^-$, 57%); HRMS (ESI+): calcd for $C_{26}H_{30}N_2O_3SeNa$ ([M + Na]$^+$), 521.1315; found, 521.1309.

*(2R,5S,7S)-1-Aza-7-(cyclohexylmethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7S)-**4e**.* Scale of reaction 200 mg, 0.584 mmol, yield (253 mg, 87%), R_f = 0.44 (1:1 PE/EtOAc); colorless solid; mp = 121−124 °C; $[\alpha]_D^{20}$ = +91.9 (c = 0.72 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1694 (s, C═O), 1662 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.65 (t, J = 5.0 Hz, 1H, −NH−), 7.57 (d, J = 8.2 Hz, 2H, ArH), 7.36−7.43 (m, 6H, ArH), 7.18 (t, J = 7.9 Hz, 2H, ArH), 6.22 (s, 1H, H-2), 4.25 (dd, J = 6.3, 8.2 Hz, 1H, H-4), 3.74−3.80 (m, 1H, H-5), 3.51 (t, J = 8.2 Hz, 1H, H-4′), 3.01−3.13 (m, 2H, H-10), 2.62−2.72 (m, 2H, H-6 and H-6′), 1.65−1.73 (m, 5H, H-12, H-13, one of H-14), 1.37−1.44 (m, 1H, H-11), 1.11−1.27 (m, 3H, H-13′, and one of H-14), 0.86−0.95 (m, 2H, H-12′); δ_C (125 MHz, $CDCl_3$) 173.7 (C-8), 168.2 (C-9), 137.9, 137.6, 130.1, 129.0, 128.9, 128.5, 126.4, 126.0 (ArC), 86.7 (C-2), 72.0 (C-4), 54.9 (C-5), 53.8 (C-7), 45.9 (C-10), 37.62 (C-11), 36.1 (C-6), 30.8 (C-12), 26.3 (C-14), 25.8 (C-13); m/z (ESI−) 497.2 ([M−H]$^-$, 96%); HRMS (ESI+): calcd for $C_{26}H_{30}N_2O_3SeNa$ ([M + Na]$^+$), 521.1315; found, 521.1315.

*(2R,5S,7S)-1-Aza-6,7-epoxy-7-(4′-morpholino-N-oxidephenylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, **6a**.* H_2O_2 (35% wt in H_2O) (75 μL, 0.848 mmol, 6 equiv) was added at rt to a solution of the selenyl amide **4a** (80 mg, 0.142 mmol, 1.0 equiv) in CH_2Cl_2, and the biphasic reaction mixture was stirred vigorously for 1 h. The reaction was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product. The crude was then purified via flash column chromatography on silica gel (eluent = MeOH/EtOAc, 1−5%) to give 30 mg (50% yield) of **6a** as a white waxy solid. R_f = 0.15 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ = +188.5 (c = 1.2857 in $CHCl_3$); white waxy solid; δ_H (500 MHz, $CDCl_3$) 10.26 (br s, 1H, −NH−), 8.00 (d, J = 8.5 Hz, 2H, morpholinoaniline ArH), 7.77 (d, J = 8.5 Hz, 2H, morpholinoaniline ArH), 7.31−7.46 (m, 5H, PhH), 6.38 (s, 1H, H-2), 4.70 (apparent t, J = 11.3 Hz, 2H, morpholine −CH_2−, H-11), 4.58 (s, 1H, H-6), 4.25−4.29 (m, 2H, H-5, and H-4), 3.86−3.94 (m, 4H, morpholine −CH_2−, H-11, and H-10), 3.67 (t, J = 11.3 Hz, 1H, H-4′), 3.11 (apparent d, J = 11.0 Hz, 2H, morpholine −CH_2−, H-10); δ_C (125 MHz, $CDCl_3$) 172.2 (C-8), 159.1 (C-9), 150.2, 136.6, 136.1, 128.1, 127.7, 124.8, 120.3, 119.6 (ArC), 87.1 (C-2), 66.7 (C-11), 64.6 (C-4), 62.4 (C-6), 61.3 (C-10), 57.2 (C-5), 56.1 (C-7); m/z (ESI−) 436.17 ([M−H]$^-$, 94%); HRMS (ESI+): calcd for $C_{23}H_{24}N_3O_6$ ([M + H]$^+$), 438.1660; found, 438.1648.

General Procedure for Oxidative Elimination of 4b−f. H_2O_2 (35% wt in H_2O) (6 equiv) was added at rt to a solution of the selenyl amides **4b−f** (1.0 equiv) in CH_2Cl_2, and the biphasic reaction mixture was stirred vigorously for 1 h. The reaction was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product.

*(2R,5S)-1-Aza-3-oxa-8-oxo-2-phenyl-7-(phenylcarbamoyl)-bicyclo[3.3.0]oct-6-ene, **5b**.* Scale of reaction 230 mg, 0.482 mmol, yield (148 mg, 96%), R_f = 0.26 (2:1 PE/EtOAc); yellow oil; $[\alpha]_D^{20}$ = +231.0 (c = 0.98 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1702 (s, C═O), 1672 (s, C═O); δ_H (500 MHz, $CDCl_3$) 10.20 (br s, 1H, −NH−), 8.14 (d, J = 1.9 Hz, 1H, H-6), 7.70 (d, J = 8.2 Hz, 2H, ArH), 7.55−7.57 (m, 2H, ArH), 7.35−7.46 (m, 5H, ArH), 7.16 (t, J = 7.3 Hz, 1H, ArH), 6.26 (s, 1H, H-2), 4.73 (dt, J = 1.6, 7.6 Hz, 1H, H-5), 4.41 (t, J = 7.6 Hz, 1H, H-4), 3.51 (t, J = 8.8 Hz, 1H, H-4′); δ_C (125 MHz, $CDCl_3$) 174.3 (C-8), 157.5 (C-9), 152.2 (C-6), 137.6, 137.3 (ArC), 133.4 (C-7), 129.1, 129.07, 128.7, 126.1, 124.9, 120.2 (ArC), 87.7 (C-2), 67.84 (C-4), 62.7 (C-5); m/z (ESI+) 343.13 ([M + Na]$^+$, 83%); HRMS (FI+), calcd for $C_{19}H_{16}N_2O_3$ ([M]$^+$), 320.1161; found, 320.1163.

*(2R,5S)-1-Aza-7-(4′-bromophenylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]oct-6-ene, **5c**.* Scale of reaction 100 mg, 0.180 mmol, yield (66 mg, 92%), R_f = 0.24 (2:1 PE/EtOAc); yellow oil; $[\alpha]_D^{20}$ = +240.6 (c = 0.56 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1701 (s, C═O), 1672 (s, C═O); δ_H (500 MHz, $CDCl_3$) 10.24 (s, 1H, −NH−), 8.15 (d, J = 1.6 Hz, 1H, H-6), 7.40−7.62 (m, 9H, ArH), 6.25 (s, 1H, H-2), 4.74 (dt, J = 1.6, 7.9 Hz, 1H, H-5), 4.42 (t, J = 7.3 Hz, 1H, H-4), 3.52 (t, J = 8.5 Hz, 1H, H-4′); δ_C (125 MHz, $CDCl_3$) 174.2 (C-8), 157.5 (C-9), 152.4 (C-6), 137.4, 136.4 (ArC), 133.2 (C-7), 132.1, 129.2, 128.7, 126.1, 121.7, 117.5 (ArC), 87.7 (C-2), 67.8 (C-4), 62.7 (C-5); m/z (ESI+) 421.05 ([M + Na]$^+$, 100%), (ESI−) 397.04 ([M−H]$^-$, 100%); HRMS (FI+): calcd for $C_{19}H_{15}BrN_2O_3$ ([M]$^+$), 398.0266; found, 398.0266.

*(2R,5S)-1-Aza-7-(3′-isopropoxypropylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]oct-6-ene, **5d**.* Scale of reaction 120 mg, 0.239 mmol, yield (85 mg, quantitative), R_f = 0.50 (EtOAc); colorless oil; $[\alpha]_D^{20}$ = +163.6 (c = 1.15 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1698 (s, C═O), 1662 (s, C═O); δ_H (500 MHz, $CDCl_3$) 8.35 (br s, 1H, −NH−), 8.01 (d, J = 1.9 Hz, 1H, H-6), 7.52 (d, J = 6.9 Hz, 2H, ArH), 7.36−7.43 (m, 3H, ArH), 6.21 (s, 1H, H-2), 4.65 (dt, J = 1.6, 7.9 Hz, 1H, H-5), 4.35 (t, J = 7.6 Hz, 1H, H-4), 3.57 (quintet, J = 6.1 Hz, 1H, H-13), 3.49−3.53 (m, 4H, H-10, and H-12), 3.47 (t, J = 8.5 Hz, 1H, H-4′), 1.82−1.87 (m, 2H, H-11), 1.17 (d, J = 6.0 Hz, 6H, H-14); δ_C (125 MHz, $CDCl_3$) 174.3 (C-8), 159.8 (C-9), 151.2 (C-6), 137.8 (ArC), 133.3 (C-7), 128.9, 128.6, 126.1 (ArC), 87.6 (C-2), 71.7 (C-13), 67.74 (C-4), 65.7 (C-12), 62.5 (C-5), 36.9 (C-10), 29.7 (C-11), 22.0 (C-14); m/z (ESI+) 367.17 ([M + Na]$^+$, 97%); HRMS (FI+): calcd for $C_{19}H_{24}N_2O_4$ ([M]$^+$), 344.1736; found, 344.1739.

*(2R,5S)-1-Aza-7-(cyclohexylmethylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]oct-6-ene, **5e**.* Scale of reaction 35 mg, 0.704 mmol, yield (24 mg, quantitative), R_f = 0.16 (1:1 PE/EtOAc); colorless oil; $[\alpha]_D^{20}$ = +159.4 (c = 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1698 (s, C═O), 1663 (s, C═O); δ_H (500 MHz, $CDCl_3$) 8.28 (br s, 1H, −NH−), 8.02 (d, J = 1.9 Hz, 1H, H-6), 7.52−7.54 (m, 2H, ArH), 7.36−7.43 (m, 3H, ArH), 6.21 (s, 1H, H-2), 4.67 (dt, J = 1.6, 6.9 Hz, 1H, H-5), 4.37 (t, J = 7.6 Hz, 1H, H-4), 3.47 (t, J = 8.5 Hz, 1H, H-4′), 3.25 (t, J = 6.5 Hz, 2H, H-10), 1.66−1.79 (m, 5H, H-12, H-13, and one of H-14), 1.51−1.60 (m, 1H, H-11), 1.12−1.28 (m, 3H, H-13′, and one of H-14), 0.96−1.03 (m, 2H, H-12′); δ_C (125 MHz, $CDCl_3$) 174.5 (C-8), 159.8 (C-9), 151.1 (C-6), 137.7 (ArC), 133.4 (C-7), 129.0, 128.6, 126.1 (ArC), 87.6 (C-2), 67.8 (C-4), 62.6 (C-5), 45.3 (C-10), 37.8 (C-11), 30.8 (C-12), 26.3 (C-14), 25.8 (C-13); m/z (ESI−) 339.19 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{20}H_{24}N_2O_3Na$ ([M + Na]$^+$), 363.1679; found, 363.1666.

Procedure for Epoxidation of α,β-Unsaturated Lactam 5b to 6b Using Other Tertiary Amine or Pyridine. H_2O_2 (35% wt in H_2O) (6 equiv) was added to a solution of the α,β-unsaturated lactam **5b** (1.0 equiv) and tertiary amine—Et_3N or DABCO—or pyridine

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(1.0 equiv) at rt. The biphasic mixture was then stirred vigorously at rt for 1 h. (In the case with pyridine, 1.0 equiv of pyridine and 6 equiv of 35% (wt in H_2O) H_2O_2 was added after each hour until the reaction was observed to be completed via TLC analysis after 3 h). The reaction was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product. The crude was then purified via flash column chromatography on silica gel (eluent = EtOAc/PE) to afford the epoxide.

General Procedure for Epoxidation of α,β-Unsaturated Lactams 5b−e. The α,β-unsaturated lactams **5b−e** used in this reaction were the crude obtained from the oxidative−elimination step. H_2O_2 (35% wt in H_2O) (6 equiv), followed by 4-methylmorpholine (1.0 equiv), was added to a solution of the α,β-unsaturated lactams **5b−e** (1.0 equiv) at rt. The biphasic mixture was then stirred vigorously at rt for 1 h. The reaction was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product. The crude was then purified via flash column chromatography on silica gel (eluent = EtOAc/PE) to afford the epoxides.

(2R,5R,6R,7S)-1-Aza-6,7-epoxy-3-oxa-8-oxo-2-phenyl-7-(phenylcarbamoyl)bicyclo[3.3.0]octane, ***6b.*** Scale of reaction 148 mg, 0.462 mmol, yield (115 mg, 74%), R_f = 0.56 (1:1 PE/EtOAc); pale yellow solid; mp = 202−206 °C; $[\alpha]_D^{20}$ = +258.8 (*c* = 1.30 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1716 (s, C═O), 1685 (s, C═O); δ_H(500 MHz, $CDCl_3$) 10.05 (s, 1H, −NH−), 7.65 (d, *J* = 7.9 Hz, 2H, ArH), 7.35−7.41 (m, 7H, ArH), 7.19 (t, *J* = 7.3 Hz, 1H, ArH), 6.40 (s, 1H, H-2), 4.57 (s, 1H, H-6), 4.25−4.31 (m, 2H, H-5, and H-4), 3.67 (t, *J* = 11.3 Hz, 1H, H-4′); δ_C (125 MHz, $CDCl_3$) 173.5 (C-8), 159.7 (C-9), 137.3, 137.0, 129.2, 130.0, 128.7, 125.8, 125.4, 120.20 (ArC), 88.17 (C-2), 65.67 (C-4), 63.22 (C-6), 58.21 (C-5), 57.16 (C-7); *m/z* (ESI−) 335.12 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{19}H_{17}N_2O_4$ ([M + H]$^+$), 337.1183; found, 337.1178.

(2R,5R,6R,7S)- 1-Aza-7-(4′-bromophenylcarbamoyl)-6,7-epoxy-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***6c.*** Scale of reaction 29 mg, 0.073 mmol, yield (27 mg, 87%), R_f = 0.42 (2:1 PE/EtOAc); white solid; mp = 195−198 °C; $[\alpha]_D^{20}$ = +213.9 (*c* = 1.08 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1718 (s, C═O), 1687 (s, C═O); δ_H (500 MHz, $CDCl_3$) 10.11 (s, 1H, −NH−), 7.55 (d, *J* = 8.8 Hz, 2H, ArH), 7.49 (d, *J* = 8.8 Hz, 2H, ArH), 7.36−7.41 (m, 5H, ArH), 6.39 (s, 1H, H-2), 4.57 (s, 1H, H-6), 4.25−4.30 (m, 2H, H-5, and H-4), 3.67 (t, *J* = 11.3 Hz, 1H, H-4′); δ_C (125 MHz, $CDCl_3$) 173.3 (C-8), 159.7 (C-9), 137.0, 136.0, 132.2, 129.1, 128.7, 125.8, 121.4, 118.0 (ArC), 88.1 (C-2), 65.6 (C-4), 63.2 (C-6), 58.1 (C-5), 57.0 (C-7); *m/z* (ESI−) 413.03 ([M−H]$^-$, 17%); HRMS (ESI+): calcd for $C_{19}H_{15}BrN_2NaO_4$ ([M + Na]$^+$), 437.0107; found, 437.0108.

(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(3′-isopropoxypropylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***6d.*** Scale of reaction 37 mg, 0.107 mmol, yield (31 mg, 80%), R_f = 0.39 (EtOAc); white solid; mp = 132−136 °C; $[\alpha]_D^{20}$ = +233.5 (*c* = 1.24 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1726 (s, C═O), 1656 (s, C═O); δ_H (500 MHz, $CDCl_3$) 8.29 (br s, 1H, −NH−), 7.32−7.39 (m, 5H, ArH), 6.36 (s, 1H, H-2), 4.42 (s, 1H, H-6), 4.18−4.24 (m, 2H, H-5, and H-4), 3.57−3.63 (m, 2H, H-4′, and H-13), 3.47−3.55 (m, 4H, H-12, and H-10), 1.84 (quintet, *J* = 6.0 Hz, 2H, H-11), 1.20 (d, *J* = 6.3 Hz, 6H, H-14); δ_C (125 MHz, $CDCl_3$) 172.9 (C-8), 161.6 (C-9), 137.5, 128.9, 128.5, 125.8 (ArC), 88.0 (C-2), 71.9 (C-13), 66.4 (C-12), 65.6 (C-4), 62.7 (C-6), 58.1 (C-5), 57.0 (C-7), 38.2 (C-10), 29.2 (C-11), 22.0, 22.0 (C-14 and C-14′); *m/z* (ESI−) 359.18 ([M−H]$^-$, 98%); HRMS (ESI+): calcd for $C_{19}H_{25}N_2O_5$ ([M + H]$^+$), 361.1758; found, 361.1760.

(2R,5R,6R,7S)-1-Aza-7-(cyclohexylmethylcarbamoyl)-6,7-epoxy-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***6e.*** Scale of reaction 55 mg, 0.162 mmol, yield (42 mg, 73%), R_f = 0.59 (1:2 PE/EtOAc); white solid; mp = 182−186 °C; $[\alpha]_D^{20}$ = +268.0 (*c* = 1.20 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1713 (s, C═O), 1678 (s, C═O); δ_H (500 MHz, $CDCl_3$) 8.20 (br s, 1H, −NH−), 7.33−7.40 (m, 5H, ArH), 6.36 (s, 1H, H-2), 4.47 (s, 1H, H-6), 4.20−4.26 (m, 2H, H-5, and H-4), 3.62 (t, *J* = 7.3 Hz, 1H, H-4′), 3.26−3.32 (m, 1H, H-10), 3.17−3.22 (m, 1H, H-10′), 1.68−1.79 (m, 5H, H-12, H-13, and one of H-14), 1.53−1.61 (m, 1H, H-11), 1.14−1.31 (m, 3H, H-13′, and one of H-14), 0.96−1.04 (m, 2H, H-12′); δ_C (125 MHz, $CDCl_3$) 173.4 (C-8), 161.7 (C-9), 137.3, 129.0, 128.6, 125.7 (ArC), 88.0 (C-2), 65.6 (C-4), 62.7 (C-6), 58.1 (C-5), 56.9 (C-7), 46.0 (C-10), 37.6 (C-11), 30.8 (C-12), 26.3 (C-14), 25.7 (C-14); *m/z* (ESI−) 355.18 ([M−H]$^-$, 97%); HRMS (ESI+): calcd for $C_{20}H_{25}N_2O_4$ ([M + H]$^+$), 357.1809; found, 357.1801.

Procedure for Synthesis of Weinreb Amide 10a. LiOH (95.7 mg, 3.996 mmol, 1.1 equiv) was added to a solution of **2a** (1 g, 3.632 mmol, 1.0 equiv) in THF/H_2O (1:1). The reaction mixture was stirred at rt for 6 h, and an additional 0.3 equiv of LiOH was added. After a total reaction time of 8.5 h, the reaction mixture was acidified with 10% aq HCl dropwise (to about pH 1) and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated to give the crude. The crude was used for the next step. For the purpose of characterization, **2b** was isolated once via column chromatography on silica gel (eluent = 30−100% EtOAc/PE, then 5% MeOH/EtOAc). CDI (1,1′-carbonyldiimidazole) (647.8 mg, 3.995 mmol, 1.1 equiv) was added to a dry MeCN (15 mL) solution of crude **2b** (assumed complete conversion for previous step), and the reaction mixture was stirred at rt for 1 h. *N,O*-dimethylhydroxylamine hydrochloride (389.7 mg, 3.995 mmol, 1.1 equiv) was then added and stirred at rt for another 18 h. The reaction mixture was diluted with deionized water (pH 7−8), acidified with aq 10% HCl dropwise (until pH 1−2), extracted with EtOAc, dried with $MgSO_4$, filtered, and evaporated to give the crude. The crude was purified via flash column chromatography on silica gel (eluent = 10−60% EtOAc/PE) to give the product (944 mg) as a colorless oil in 90% yield.

*(2R,5S,7S)- and (2R,5S,7R)-1-Aza-7-(carboxyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, (7RS)-***2b.** R_f = 0.08 (5% MeOH/EtOAc), tailing from baseline of TLC; colorless oil; ν_{max}/cm^{-1} (film) 3429 (br,−OH), 1688 (br with a shoulder, C═O); δ_H (500 MHz, acetone-d_6) 7.34−7.49 (m, 5H, Ph−H), 6.22 (s, 0.5H, H-2_a), 6.19 (s, 0.5H, H-2_b), 4.25−4.34 (m, 2H, H-4_a, H-4_b, H-5_a, H-5_b), 4.03 (t, *J* = 9.6 Hz, 0.5H, H-7_a), 3.69−3.73 (m, 2H, H-$4'_a$, H-7_b), 3.61 (t, *J* = 7.9 Hz, 0.5H, H-$4'_b$), 2.67−2.75 (m, 1H, H-6_a, H-6_b), 2.32−2.39 (m, 1H, H-$6'_a$, H-$6'_b$); δ_C (125 MHz, acetone-d_6) major diastereoisomer (a): 174.0 (C-8), 170.7 (C-9), 88.0 (C-2), 72.7 (C-4), 58.2 (C-5), 51.8 (C-7), 28.6 (C-6). Minor diastereoisomer (b): 173.7 (C-8), 170.9 (C-9), 88.2 (C-2), 72.3 (C-4), 59.0 (C-5), 52.5 (C-7), 27.6 (C-6). Unable to assign the following aromatic carbons to the individual diastereomer: 140.3, 140.0, 129.5, 129.4, 129.3, 129.2, 127.1, 127.0. *m/z* (ESI−) 246.07 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{13}H_{13}NNaO_4$ ([M + Na]$^+$), 270.0737; found, 270.0740.

*(2R,5S,7S)- and (2R,5S,7R)-1-Aza-7-(N,O-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, (7RS)-***10a.** R_f = 0.44 (EtOAc); colorless oil; ν_{max}/cm^{-1} (film) 1703 (s, C═O), 1654 (s, C═O); diastereomer A (7*R*), diastereomer B (7*S*); δ_H (500 MHz, $CDCl_3$) 7.43−7.47 (m, Ph−H), 7.30−7.39 (m, Ph−H), 6.31 (s, 1H, H-2_A), 6.28 (s, 1H, H-2_B), 4.53 (t, *J* = 9.3 Hz, 1H, H-7_B), 4.38−4.44 (m, 1H, H-5_A), 4.28−4.31 (m, 1H, H-4_B), 4.28−4.31 (m, 1H, H-7_A), 4.25 (dd, *J* = 6.5, 8.0 Hz, 1H, H-4_A), 4.13−4.18 (m, 1H, H-5_B), 3.88 (s, 3H, −O$\underline{Me}_A$), 3.84 (s, 3H, −O$\underline{Me}_B$), 3.75 (t, *J* = 8.2 Hz, 1H, H-$4'_B$), 3.51 (t, *J* = 8.2 Hz, 1H, H-$4'_A$), 3.28 (s, 3H, −N$\underline{Me}_B$), 3.24 (s, 3H, −N$\underline{Me}_A$), 2.67−2.71 (m, 1H, H-6_A), 2.44−2.53 (m, 2H, H-6_B, and H-$6'_B$), 2.09−2.15 (m, 1H, H-$6'_A$); δ_C (125 MHz, $CDCl_3$) 173.5 (C-8_B), 173.4 (C-8_A), 170.0 (C-9_A), 169.2 (C-9_B), 138.6, 138.0, 128.6, 128.5, 128.4, 126.0, 126.0, 87.3 (C-2_A), 87.2 (C-2_B), 71.9 (C-4_B), 71.7 (C-4_A), 62.1 (−O$\underline{Me}_A$), 61.9 (−O$\underline{Me}_B$), 58.4 (C-5_A), 57.2 (C-5_B), 48.4 (C-7_A), 47.7 (C-7_B), 32.4 (−N$\underline{Me}_A$), 32.3 (−N$\underline{Me}_B$), 27.9 (C-6_A), 26.8 (C-6_B); *m/z* (ESI+) 313.11 ([M + Na]$^+$, 31%); HRMS (ESI+): calcd for $C_{15}H_{18}N_2NaO_4$ ([M + Na]$^+$), 313.1159; found, 313.1160.

Procedure for Synthesis of Selenyl Derivatives 10b from Weinreb Amide 10a. NaH was prewashed with dry Et_2O and used immediately for the reaction. **10a** (600 mg, 2.067 mmol, 1.0 equiv) in anhydrous THF (7 mL) was added dropwise to prewashed NaH (82.7 mg, 2.067 mmol, 1.0 equiv, in 60% mineral oil) at 0 °C, and the mixture was warmed to rt and stirred for 30 min. PhSeBr (487.7 mg, 2.067 mmol, 1.0 equiv) in anhydrous THF (2 mL) was then added

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dropwise to the mixture at rt and stirred at rt for a further 1 h. The reaction mixture was then quenched with saturated aq NH_4Cl and extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude. The crude was purified via flash column chromatography on silica gel (eluent = EtOAc/PE) to give the two separate diastereomers of **10b** as a colorless oil (combined yield 792 mg, 82%).

*(2R,5S,7R)-1-Aza-7-(N,O-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7R)-**10b**.* R_f = 0.56 (1:1 EtOAc/PE); colorless oil; $[\alpha]_D^{20}$ = +240.1 (c = 0.89 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1694 (s, C═O), 1646 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.44−7.76 (m, 2H, Ph−H), 7.42−7.45 (m, 3H, Ph−H), 7.29−7.39 (m, 5H, Ph−H), 6.13 (s, 1H, H-2), 3.93−4.01 (m, 2H, H-5, and H-4), 3.36 (s, 3H, −OMe), 3.25 (s, 3H, −NMe), 2.97 (dd, J = 7.3, 13.9 Hz, 1H, H-6), 2.72 (t, J = 7.7 Hz, 1H, H-4′), 2.27 (dd, J = 5.2, 14.0 Hz, 1H, H-6′); δ_C (125 MHz, $CDCl_3$) 171.7 (C-8), 168.3 (C-9, br), 138.4, 138.1, 129.8, 129.2, 128.7, 128.4, 126.7, 126.0 (Ph−C), 87.0 (C-2), 70.6 (C-4), 62.3 (C-7, br), 60.8 (−OMe), 56.4 (C-5), 36.9 (C-6, br), 34.0 (−NMe); m/z (ESI+) 447.07 ([M + H]$^+$, 18%), 915.13 ([2M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{21}H_{22}N_2NaO_4Se$ ([M + Na]$^+$), 469.0638; found, 469.0631.

*(2R,5S,7S)-1-Aza-7-(N,O-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenyl-7-(phenylselanyl)bicyclo[3.3.0]octane, (7S)-**10b**.* R_f = 0.36 (1:1 EtOAc/PE); colorless oil; $[\alpha]_D^{20}$ = −47.2 (c = 1.13 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1700 (s, C═O), 1649 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.65 (dd, J = 1.1, 8.0 Hz, 2H, Ph−H), 7.25−7.33 (m, 4H, Ph−H), 7.02−7.05 (m, 4H, Ph−H), 6.24 (s, 1H, H-2), 3.96 (t, J = 7.3 Hz, 1H, H-4), 3.72 (s, 3H, −OMe), 3.48 (t, J = 7.9 Hz, 1H, H-4′), 3.28 (s, 3H, −NMe), 3.05 (apparent quintet, J = 7.9 Hz, 1H, H-5), 2.86 (dd, J = 1.9, 6.3 Hz, 2H, H-6, and H-6′); δ_C (125 MHz, $CDCl_3$) 172.8 (C-8), 168.5 (C-9), 138.5, 137.7, 129.5, 128.9, 128.5, 128.2, 125.98, 125.94 (Ph−C), 86.9 (C-2), 71.7 (C-4), 63.0 (C-7), 60.1 (−OMe), 55.4 (C-5), 38.6 (C-6), 33.2 (−NMe); m/z (ESI+) 447.07 ([M + H]$^+$, 30%), 915.12 ([2M + Na]$^+$, 48%); HRMS (ESI+) calcd for $C_{21}H_{22}N_2NaO_4Se$ ([M + Na]$^+$), 469.0638; found, 469.0630.

*(2R,5S)-1-Aza-7-(N,O-dimethylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]oct-6-ene, **11**.* H_2O_2 35% (wt in H_2O) (837 μL, 9.43 mmol, 6 equiv) was added to a solution of the selenyl amide **10b** (705 mg, 1.58 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C, and the biphasic reaction mixture was stirred vigorously at 0 °C for 45 min. The reaction was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product as a colorless oil (460 mg) with quantitative crude yield. R_f = 0.24 (EtOAc); colorless oil; $[\alpha]_D^{20}$ = +107.6 (c = 1.03 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1704 (s, C═O), 1655 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.51−7.54 (m, 2H, Ph−H), 7.48 (br s, 1H, H-6), 7.34−7.42 (m, 3H, Ph−H), 6.22 (s, 1H, H-2), 4.64 (dt, J = 1.9, 7.3 Hz, 1H, H-5), 4.28 (t, J = 7.3 Hz, 1H, H-4), 3.73 (br s, 3H, −OMe), 3.53 (t, J = 8.4 Hz, 1H, H-4′), 3.29 (s, 3H, −NMe); δ_C (125 MHz, $CDCl_3$) 172.5 (C-8), 162.9 (C-9, br), 146.7 (C-6, br), 138.2 (Ph−C), 137.1 (C-7), 128.8, 128.5, 126.2 (Ph−C), 87.8 (C-2), 67.7 (C-4), 63.2 (C-5), 61.7 (−OMe, br), 32.00 (−NMe, br); m/z (ESI+) 311.09 ([M + Na]$^+$, 27%), 599.16 ([2M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{15}H_{16}N_2NaO_4$ ([M + Na]$^+$), 311.1002; found, 311.1003.

*(2R,5R,5R,7R)-1-Aza-7-(N,O-dimethylcarbamoyl)-6,7-epoxy-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, **12**.* Triethylamine (366 μL, 2.63 mmol, 1.0 equiv) was added dropwise to a solution of the α,β-unsaturated lactam **11** (760 mg, 2.63 mmol, 1.0 equiv) and 35% (wt in H_2O) H_2O_2 (1.39 mL, 15.67 mmol, 6 equiv) at 0 °C. The biphasic mixture was then stirred vigorously at 0 °C for 1 h. The reaction was quenched with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product. The crude was purified via flash column chromatography on silica gel (eluent = 10−60% EtOAc/petroleum ether) to give the epoxide **12** (744 mg) in 93% yield as white solid. dr ≈ 1:0.1; R_f = 0.53 (EtOAc); white solid; mp = 159−161 °C; $[\alpha]_D^{20}$ = +110.7 (c = 1.13 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1734 (s, C═O), 1673 (s, C═O); major Diastereomer δ_H (500 MHz, $CDCl_3$) 7.32−7.41 (m, 5H, Ph−H), 6.38 (s, 1H, H-2), 4.19−4.26 (m, 3H, H-4, H-5, and H-6), 3.78 (s, 3H, −OMe), 3.66 (t, J = 7.9 Hz, 1H, H-4′), 3.30 (s, 3H, −NMe); δ_C (125 MHz, $CDCl_3$) 171.8 (C-8), 162.4 (C-9), 137.7, 128.8, 128.5, 125.8 (Ph−C), 88.5 (C-2), 65.4 (C-4), 61.3 (−OMe), 61.2, 61.2 (C-6, C-7), 58.8 (C-5), 32.1 (−NMe); m/z (ESI+) 305.09 ([M + H]$^+$, 90%); HRMS (ESI+): calcd for $C_{15}H_{17}N_2O_5$ ([M + H]$^+$), 305.1132; found, 305.1133.

General Procedures for the Synthesis of Keto-α,β-epoxy-γ-lactams 13a−e. Magnesium flakes were washed with 1 M aq HCl, followed by EtOH and then Et_2O. The magnesium flakes were then dried under vacuum for 3 h at rt. The respective Grignard reagents were prepared in excess: magnesium flakes (100 mg, 4.114 mmol, 1.05 equiv) and I_2 (1 small crystal) were placed in a two-necked, round-bottomed flask attached with a condenser. A 0.5 mL solution of the bromide (1.0 equiv) in 10 mL THF was added to the magnesium first, followed by the remaining solution dropwise. Once addition of the reagent was completed, the mixture was heated at 45 °C for 1 h. The solution was then cooled to rt, and the required amount was used for the Grignard reaction directly. For compound **13d**, a commercially available 2 M Et_2O solution of isobutylmagnesium bromide was used instead. The Grignard reagent in THF (1.3 equiv based on amount of **12** used) was added to **12** (1.0 equiv) in THF at −15 °C. The reaction was stirred at −15 °C for 15−45 min (monitored via thin-layer chromatography of the reaction mixture), after which it was quenched with saturated aq NH_4Cl and extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product. The crude was purified via flash column chromatography on silica gel (eluent = EtOAc/PE) to give the product.

*(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(4′-methylphenylcarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, **13a**.* Scale of reaction 75 mg, 0.246 mmol, yield (71 mg, 86%), R_f = 0.56 (1:1 PE/EtOAc); colorless crystals, mp = 108−110 °C; $[\alpha]_D^{20}$ = +121.2 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1723 (s, C═O), 1679 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.96 (d, J = 8.5 Hz, 2H, Ar−H), 7.35−7.44 (m, 5H, Ph−H), 7.32 (d, J = 8.5 Hz, 2H, Ar−H), 6.43 (s, 1H, H-2), 4.27−4.32 (m, 3H, H-4, H-5, H-6), 3.77 (apparent quintet, J = 6.9 Hz, 1H, H-4′), 2.45 (s, 3H, −Ar−Me); δ_C (125 MHz, $CDCl_3$) 188.4 (C-9), 172.5 (C-8), 146.0, 137.8, 132.1, 129.7, 129.5, 128.9, 128.5, 125.9 (Ar−C, Ph−C), 88.5 (C-2), 65.7 (C-4), 63.7 (C-7), 61.7 (C-6), 58.8 (C-5), 21.9 (−Ar−Me); m/z (ESI+) 358.11 ([M + Na]$^+$, 29%), 693.23 ([2M + Na]$^+$, 81%); HRMS (ESI+): calcd for $C_{20}H_{17}NNaO_4$ ([M + Na]$^+$), 358.1050; found, 358.1045.

*(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(4′-methoxyphenylcarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, **13b**.* Scale of reaction 150 mg, 0.495 mmol, yield (131 mg, 76%), R_f = 0.45 (1:1 EtOAc/PE); colorless oil; $[\alpha]_D^{20}$ = +209.3 (c = 0.99 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 1720 (s, C═O), 1672 (s, C═O); δ_H (500 MHz, $CDCl_3$) 8.06 (d, J = 8.8 Hz, 2H, Ar−H), 7.38−7.44 (m, 5H, Ph−H), 6.99 (d, J = 8.8 Hz, 2H, Ar−H), 6.42 (s, 1H, H-2), 4.26−4.32 (m, 3H, H-4, H-5, H-6), 3.90 (s, 3H, Ar−OMe), 3.76 (ddd, J = 0.6, 6.6, 12.3 Hz, 1H, H-4′); δ_C (125 MHz, $CDCl_3$) 187.0 (C-9), 172.6 (C-8), 164.8 (ArC−OMe), 137.8 (PhC, no H), 132.2 (ArC), 128.8, 128.5 (PhC), 127.7 (ArC, no H), 125.9 (PhC), 114.1 (ArC), 88.46 (C-2), 65.8 (C-4), 63.7 (C-7), 61.6 (C-6), 58.8 (C-5), 55.6 (ArC−OMe); m/z (ESI+) 374.0 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{20}H_{17}NNaO_5$ ([M + Na]$^+$), 374.0999; found, 374.0988.

*(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(octylcarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, **13c**.* Scale of reaction 100 mg, 0.329 mmol, yield (91 mg, 77%), R_f = 0.53 (30% EtOAc/PE); colorless oil; $[\alpha]_D^{20}$ = +206.6 (c = 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1735 (br with shoulder, s, C═O); δ_H (500 MHz, $CDCl_3$) 7.32−7.41 (m, 5H, Ph−H), 6.39 (s, 1H, H-2), 4.19−4.24 (m, 3H, H-4, H-5, H-6), 3.56−3.61 (m, 1H, H-4′), 2.73 (t, J = 7.4 Hz, 2H, H-10), 1.56−1.67 (m, 2H, H-11), 1.25−1.35 (m, 10H, H-12, H-13, H-14, H-15, H-16), 0.89 (t, J = 6.9 Hz, 3H, H-17); δ_C (125 MHz, $CDCl_3$) 199.6 (C-9), 171.1 (C-8), 137.7, 128.8, 128.5, 125.8 (Ph−C), 88.3 (C-2), 65.6 (C-4), 62.9 (C-6), 61.9 (C-7), 58.3 (C-5), 40.8 (C-10), 31.8 (C-15), 29.3, 29.1, 29.0 (C-12, C-13, C-14), 22.8 (C-11), 22.6 (C-16), 14.1 (C-17); m/z (ESI+)

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380.18 ([M + Na]$^+$, 57%), 737.38 ([2M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{21}H_{27}NNaO_4$ ([M + Na]$^+$), 380.1832; found, 380.1837.

(2R,5R,6R,7S)-1-Aza-7-(butylcarbonyl)-6,7-epoxy-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***13d.*** Scale of reaction 150 mg, 0.493 mmol, yield (112 mg, 75%), R_f = 0.38 (30% EtOAc/PE); colorless solid, mp = 96−98 °C; $[\alpha]_D^{20}$ = +258.3 (c = 0.96 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 1735 (br with shoulder, s, C═O); δ_H (500 MHz, $CDCl_3$) 7.34−7.41 (m, 5H, Ph−H), 6.39 (s, 1H, H-2), 4.19−4.24 (m, 3H, H-4, H-5, H-6), 3.59 (ddd, J = 0.9, 7.6, 11.7 Hz, 1H, H-4′), 2.73 (t, J = 7.4 Hz, 2H, H-10), 1.61−1.66 (m, 2H, H-11), 1.33−1.40 (m, 2H, H-12), 0.93 (t, J = 7.4 Hz, 3H, H-13); δ_C (125 MHz, $CDCl_3$) 199.6 (C-9), 171.1 (C-8), 137.7, 128.8, 128.5, 125.8 (Ph−C), 88.3 (C-2), 65.6 (C-4), 62.9 (C-6), 61.9 (C-7), 58.3 (C-5), 40.4 (C-10), 24.9 (C-11), 22.1 (C-12), 13.8 (C-13); m/z (ESI+) 324.1 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{17}H_{19}NNaO_4$ ([M + Na]$^+$), 324.1206; found, 324.1200.

(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(isobutylcarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***13e.*** Scale of reaction 110 mg, 0.361 mmol, yield (68 mg, 62%), R_f = 0.61 (1:1 EtOAc/PE); colorless crystals, mp = 116−118 °C; $[\alpha]_D^{20}$ = +279.7 (c = 1.01 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 1732 (s, C═O, with shoulder toward shorter wavenumber); δ_H (500 MHz, $CDCl_3$) 7.32−7.40 (m, 5H, PhH), 6.38 (s, 1H, H-2), 4.18−4.24 (m, 3H, H-4, H-5, H-6), 3.58 (ddd, br, J = 0.9, 6.9, 12.3 Hz, 1H, H-4′), 2.65 (dd, J = 6.6, 17.0 Hz, 1H, H-10), 2.57 (dd, J = 6.6, 17.0 Hz, 1H, H-10′), 2.23 (doublet of septet, J = 6.8, 13.5 Hz, 1H, H-11), 0.98 (d, J = 6.6 Hz, 3H, H-12), 0.96 (d, J = 6.6 Hz, 3H, H-12′); δ_C (125 MHz, $CDCl_3$) 199.2 (C-9), 171.1 (C-8), 137.7, 128.8, 128.5, 125.8 (Ph−C), 88.3 (C-2), 65.7 (C-4), 62.8 (C-6), 62.0 (C-7), 58.3 (C-5), 49.3 (C-10), 24.0 (C-11), 22.6, 22.4 (C-12, C-12′); m/z (ESI+) 324.1 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{17}H_{19}NNaO_4$ ([M + Na]$^+$), 324.1206; found, 324.1195.

General Procedures for the Synthesis of Keto-α,β-epoxy-γ-lactams 13f,g. The respective alkynyl Grignard reagents were prepared in excess: a 2 M solution of isobutylmagnesium bromide in Et_2O (1.0 equiv) was added dropwise to a THF (5 mL) solution of the 1-bromoalkyne (1.05 equiv) at 0 °C. The yellow suspension was then warmed to rt and then heated at 40 °C for 1.25 h. The solution was used for the Grignard reaction directly at 40 °C. The alkynyl Grignard reagent in THF (1.2−1.3 equiv based on amount of **12** used) was added to **12** (1.0 equiv) in THF at −15 °C. The reaction was stirred at −15 °C for 0.5−1 h (monitored via thin-layer chromatography of the reaction mixture), after which it was quenched with saturated aq NH_4Cl and extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude product. The crude was purified via flash column chromatography on silica gel (eluent = EtOAc/PE) to give the product.

(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(phenylacetylenecarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***13f.*** Scale of reaction 152 mg, 0.500 mmol, yield (124 mg, 72%), R_f = 0.34 (30% EtOAc/PE); white solid, mp = 154−156 °C; $[\alpha]_D^{20}$ = +193.4 (c = 0.93 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2195 (s, alkyne), 1728 (s, C═O), 1659 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.64−7.65 (m, 2H, Ph−H), 7.50−7.54 (m, 1H, Ph−H), 7.33−7.44 (m, 7H, Ph−H), 6.44 (s, 1H, H-2), 4.43 (s, 1H, H-6), 4.23−4.27 (m, 2H, H-4, and H-5), 3.65 (dt, J = 2.8, 11.3 Hz, 1H, H-4′); δ_C (125 MHz, $CDCl_3$) 175.1 (C-9), 169.6 (C-8), 137.7, 133.6, 131.7, 128.9, 128.8, 128.5, 125.8, 119.0 (Ph−C), 97.2 (C-11), 88.4 (C-2), 85.8 (C-10), 65.6 (C-4), 63.7 (C-6), 62.2 (C-7), 58.1 (C-5); m/z (ESI+) 368.0 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{21}H_{15}NNaO_4$ ([M + Na]$^+$), 368.0893; found, 368.0882.

(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(butylacetylenecarbonyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***13g.*** Scale of reaction 152 mg, 0.500 mmol, yield (115 mg, 71%), R_f = 0.42 (30% EtOAc/PE); colorless oil; $[\alpha]_D^{20}$ = +246.7 (c = 0.99 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 2209 (s, alkyne), 1730 (s, C═O), 1666 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.32−7.40 (m, 5H, Ph−H), 6.39 (s, 1H, H-2), 4.33 (s, 1H, H-6), 4.19−4.25 (m, 2H, H-4, and H-5), 3.60 (dt, J = 6.9, 7.9 Hz, 1H, H-4′), 2.45 (t, J = 7.3 Hz, 2H, H-12), 1.58−1.63 (m, 2H, H-13), 1.42−1.49 (m, 2H, H-14), 0.94 (t, J = 7.3 Hz, 3H, H-15); δ_C (125 MHz, $CDCl_3$) 175.1 (C-9), 169.6 (C-8), 137.7, 128.8, 128.5, 125.8 (Ph−C), 101.3 (C-11), 88.3 (C-2), 78.6 (C-10), 65.6 (C-4), 63.4 (C-6), 62.2 (C-7), 58.1 (C-5), 29.4 (C-13), 21.9 (C-14), 19.0 (C-12), 13.4 (C-15); m/z (ESI+) 348.1 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{19}H_{19}NNaO_4$ ([M + Na]$^+$), 348.1206; found, 348.1195.

General Procedures for Acidic Oxazolidine Hydrolysis To Give 14a−h. TFA (0.4−0.6 mL) was added to a solution of **13a−g** or **12** in THF/H_2O (1:1) at rt. The reaction mixture was stirred at rt for 17−24 h, and the solvents were evaporated (toluene was used to azeotrope the water solvent under reduced pressure) to give the crude. The crude was purified via flash column chromatography on silica gel (eluent = EtOAc/PE, 50−100%, then 10% MeOH/EtOAc) to give the product.

(2R,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(N,O-dimethylcarbamoyl)-oxopyrrolidinone, ***14a.*** dr ≈ 1:0.1; R_f = 0.24 (10% MeOH/EtOAc); white needle-like crystals; mp = 193−198 °C; $[\alpha]_D^{20}$ = +14.2 (c = 0.48 in MeOH); ν_{max}/cm^{-1} (film) 3394 (br, lactam −NH−), 3239 (br, −OH), 1710 (s, C═O), 1659 (s, C═O); major diastereoisomer, at elevated temperature due to broad signals of rotamers; δ_H (400 MHz, acetonitrile-d_3, 338 K) 6.18 (br s, 1H, −NH), 4.17 (d, J = 2.4 Hz, 1H, H-3), 3.72−3.74 (m, 1H, H-4), 3.70 (s, 3H, −OMe), 3.63 (dd, J = 5.7, 11.2 Hz, 1H, H-5), 3.57 (dd, J = 6.6, 11.2 Hz, 1H, H-5′), 3.21 (s, 3H, −NMe); δ_C (100 MHz, acetonitrile-d_3, 338 K) 170.8 (C-1), 164.2 (C-6), 63.2 (C-5, br), 62.2 (−OMe, br), 61.8 (C-2), 61.4 (C-3, br), 57.5 (C-4), 33.1 (−NMe, br); m/z (ESI+) 239.05 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_8H_{12}N_2NaO_5$ ([M + Na]$^+$), 239.0638; found, 239.0638.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(4′-methylphenylcarbonyl)-1-oxopyrrolidinone, ***14b.*** Scale of reaction 71 mg, 0.212 mmol, yield (49 mg, 94%), R_f = 0.18 (EtOAc); white solid; mp = 182−186 °C; $[\alpha]_D^{20}$ = −38.4 (c = 0.625 in acetonitrile); ν_{max}/cm^{-1} (film) 3496 (br, lactam −NH−), 3324 (br, −OH), 1707 (s, C═O), 1678 (s, C═O); δ_H (500 MHz, acetonitrile-d_3) 8.00 (d, J = 8.2 Hz, 2H, Ar−H), 7.34 (d, J = 8.2 Hz, 2H, Ar−H), 6.38 (br s, 1H, −NH−), 4.31 (d, J = 2.5 Hz, 1H, H-3), 3.84 (dt, J = 1.4, 3.7 Hz, 1H, H-4), 3.72−3.80 (m, 2H, H-5), 3.41 (t, J = 5.7 Hz, 1H, −OH), 2.41 (s, 3H, Ar−Me); δ_C (125 MHz, acetonitrile-d_3) 190.5 (C-6), 171.7 (C-1), 146.7, 133.7, 130.4, 130.1 (Ar−C), 64.2 (C-2), 63.6 (C-3), 62.3 (C-5), 57.6 (C-4), 21.9 (Ar−Me); m/z (ESI+) 270.08 ([M + Na]$^+$, 25%), 517.15 ([2M + Na]$^+$, 97%); HRMS (ESI+): calcd for $C_{13}H_{13}NNaO_4$ ([M + Na]$^+$), 270.0737; found, 270.0739.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(4′-methoxyphenylcarbonyl)1-oxopyrrolidinone, ***14c.*** Scale of reaction 40 mg, 0.114 mmol, yield (26 mg, 87%), R_f = 0.25 (EtOAc); colorless solid, mp = 180−181 °C; $[\alpha]_D^{20}$ = −26.8 (c = 0.91 in MeOH); ν_{max}/cm^{-1} (film) 3439 (br), 3213 (br), 1709 (s, C═O), 1660 (s, C═O); δ_H (500 MHz, MeCN-d_3) 8.12 (d, J = 8.8 Hz, 2H, ArH), 7.05 (d, J = 8.8 Hz, 2H, ArH), 6.44 (br s, 1H, −NH−), 4.33 (d, J = 2.5 Hz, 1H, H-3), 3.90 (s, 3H, Ar−OMe), 3.87 (dt, J = 1.6, 3.6 Hz, 1H, H-4), 3.75−3.82 (m, 2H, H-5, and H-5′), 3.46 (br s, 1H, −OH); δ_C (125 MHz, MeCN-d_3) 188.03 (C-6), 170.80 (C-1), 164.5, 131.5, 128.1, 114.0 (Ar−C), 63.1 (C-2), 62.4 (C-3), 61.2 (C-5), 56.5 (C-4), 55.5 (Ar−OMe); m/z (ESI+) 286.1 ([M + Na]$^+$, 80%), (ESI−) 262.1 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{13}H_{13}NNaO_5$ ([M + Na]$^+$), 286.0686; found, 286.0682.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(octylcarbonyl)-1-oxopyrrolidinone, ***14d.*** Scale of reaction 71 mg, 0.199 mmol, yield (38 mg, 71%), R_f = 0.34 (EtOAc); white solid; mp = 78−80 °C; $[\alpha]_D^{20}$ = +115.7 (c = 0.98 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3424 (br, lactam −NH−), 3274 (br, −OH), 1718 (s, C═O), 1673 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.18 (br s, 1H, −NH−), 4.13 (d, J = 2.2 Hz, 1H, H-3), 3.89 (very br s, 1H, H-4), 3.83 (dd, J = 3.2, 12.3 Hz, 1H, H-5), 3.71 (dd, J = 3.5, 12.3 Hz, 1H, H-5′), 2.56 (ddd, J = 6.3, 8.5, 14.8 Hz, 1H, H-7), 2.47 (ddd, J = 6.3, 8.5, 14.8 Hz, 1H, H-7′), 1.50−1.60 (m, 2H, H-8), 1.26−1.32 (m, 10H, H-9, H-10, H-11, H-12, H-13), 0.88 (t, J = 6.9 Hz, 3H, H-14); δ_C (125 MHz, $CDCl_3$) 202.0 (C-6), 170.5 (C-1), 62.4 (C-3), 61.8 (C-5), 61.4 (C-2), 55.9 (C-4), 39.2 (C-7), 31.8 (C-13), 29.3, 29.1, 29.0, 22.6 (C9, C-10, C-11, C-12), 22.6 (C-8), 14.1 (C-14); m/z (ESI+) 292.15 ([M + Na]$^+$, 41%), 561.29 ([2M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{14}H_{23}NNaO_4$ ([M + Na]$^+$,) 292.1519; found, 292.1522.

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(2S,3R,4R)-2-(Butylcarbonyl)-2,3-epoxy-4-hydroxymethyl-1-oxopyrrolidinone, ***14e.*** Scale of reaction 112 mg, 0.372 mmol, yield (76 mg, 96%), R_f = 0.24 (EtOAc); colorless oil; $[\alpha]_D^{20}$ = +147.4 (c = 0.85 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3324 (br), 1720 (s, C═O), 1690 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.15 (br s, 1H, −NH−), 4.13 (d, J = 1.9 Hz, 1H, H-3), 3.89 (br t, J = 2.8 Hz, 1H, H-4), 3.83 (dd, J = 3.2, 12.3 Hz, 1H, H-5), 3.72 (dd, J = 12.0, 3.5 Hz, 1H, H-5′), 2.58 (ddd, J = 6.3, 8.5, 18.0 Hz, 1H, H-7), 2.48 (ddd, J = 6.5, 8.4, 17.9 Hz, 1H, H-7′), 1.50−1.60 (m, 2H, H-8), 1.31 (sextet, J = 7.4 Hz, 2H, H-9), 0.90 (t, J = 7.3 Hz, 3H, H-10); δ_C (125 MHz, $CDCl_3$) 201.9 (C-6), 170.5 (C-1), 62.5 (C-3), 61.8 (C-5), 61.4 (C-2), 55.9 (C-4), 38.9 (C-7), 24.6 (C-8), 22.1 (C-9), 13.8 (C-10); m/z (ESI+) 236.1 ([M + Na]$^+$, 100%), (ESI−) 212.1 ([M−H]$^-$, 65%); HRMS (ESI+): calcd for $C_{10}H_{15}NNaO_4$ ([M + Na]$^+$), 236.0893; found, 236.0893.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(isobutylcarbonyl)-1-oxopyrrolidinone, ***14f.*** Scale of reaction 60 mg, 0.199 mmol, yield (34 mg, 80%), R_f = 0.26 (EtOAc); colorless oil, which later solidifies to colorless solid, mp = 118−120 °C; $[\alpha]_D^{20}$ = +135.8 (c = 0.93 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3326 (br), 1719 (s, C═O), 1689 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.22 (br s, 1H, −NH−), 4.12 (d, J = 2.2 Hz, 1H, H-3), 3.89 (br t, J = 2.8 Hz, 1H, H-4), 3.82 (dd, J = 3.2, 12.3 Hz, 1H, H-5), 3.72 (dd, J = 3.5, 12.3 Hz, 1H, H-5′), 2.49 (dd, J = 6.5, 16.9 Hz, 1H, H-7), 2.32 (dd, J = 7.3, 16.7 Hz, 1H, H-7′), 2.16 (doublet of septet, J = 6.4, 13.4 Hz, 1H, H-8), 0.94 (d, J = 6.6 Hz, 3H, H-9), 0.91 (d, J = 6.6 Hz, 3H, H-9′); δ_C (125 MHz, $CDCl_3$) 201.7 (C-6), 170.5 (C-1), 62.3 (C-3), 61.8 (C-5), 61.5 (C-2), 55.9 (C-4), 47.6 (C-7), 23.9 (C-8), 22.6, 22.4 (C-9, C-9′); m/z (ESI) 212.1 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{10}H_{15}NNaO_4$ ([M + Na]$^+$), 236.0893; found, 236.0896.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(phenylacetylenecarbonyl)-1-oxopyrrolidinone, ***14g.*** Scale of reaction 108 mg, 0.313 mmol, yield (62 mg, 77%), R_f = 0.26 (EtOAc); colorless oil; $[\alpha]_D^{20}$ = +198.8 (c = 0.88 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3307 (br), 2192 (s, alkyne), 1702 (s, C═O), 1654 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.57 (d, J = 7.3 Hz, 2H, Ph−H), 7.44−7.47 (m, 2H, Ph−H, and −NH−), 7.36 (t, J = 7.9 Hz, 2H, Ph−H), 4.38 (d, J = 1.9 Hz, 1H, H-3), 4.16 (br t, J = 5.4 Hz, 1H, −OH), 3.96−3.97 (m, 1H, H-4), 3.87−3.91 (m, 1H, H-5), 3.75−3.80 (m, 1H, H-5′); δ_C (125 MHz, $CDCl_3$) 177.4 (C-6), 169.6 (C-1), 133.6, 131.5, 128.7, 119.0 (Ph−C), 96.1 (C-8), 85.1 (C-7), 63.2 (C-3), 61.7 (C-2), 61.6 (C-5), 55.9 (C-4); m/z (ESI+) 258.1 ([M + H]$^+$, 100%); HRMS (ESI+): calcd for $C_{14}H_{11}NNaO_4$ ([M + Na]$^+$), 280.0580; found, 280.0575.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(butylacetylenecarbonyl)-1-oxopyrrolidinone, ***14h.*** Scale of reaction 92 mg, 0.283 mmol, yield (58 mg, 86%), R_f = 0.30 (EtOAc); colorless oil; $[\alpha]_D^{20}$ = +172.7 (c = 0.96 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3325 (br) 2960, 2935 (w, −NH−), 2211 (s, alkyne), 1705 (s, C═O; with a shoulder on the shorter frequency side); δ_H (500 MHz, $CDCl_3$) 7.57 (br s, 1H, −NH−), 4.29 (d, J = 1.9 Hz, 1H, H-3), 3.91 (br t, J = 3.8 Hz, 1H, H-4), 3.86 (dd, J = 3.2, 12.3 Hz, 1H, H-5), 3.73 (dd, J = 3.2, 12.3 Hz, 1H, H-5′), 2.40 (t, J = 7.1 Hz, 2H, H-9), 1.54−1.59 (m, 2H, H-10), 1.38−1.46 (m, 2H, H-11), 0.92 (t, J = 7.4 Hz, 3H, H-12); δ_C (125 MHz, $CDCl_3$) 177.7 (C-6), 170.0 (C-1, br), 100.3 (C-8), 77.8 (C-7), 63.0 (C-3), 61.6 (C-5), 61.3 (C-2), 56.0 (C-4), 29.4 (C-10), 21.9 (C-11), 18.9 (C-9), 13.41 (C-12); m/z (ESI+) 236.1 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{12}H_{15}NNaO_4$ ([M + Na]$^+$), 260.0893; found, 260.0890.

Procedure for Synthesis of (*E*)-Enones 16a,b. *Reductive Hydrogenation with Lindlar's Catalyst, 5% Pd/CaCO$_3$ (Poisoned with Pb).* To a EtOAc solution (~0.02−0.05 M) of the ynone was added Lindlar's catalyst (10−15% wt of ynone). Quinoline (1 μL) was added for the reduction of all butylethynyl derivatives. The suspension was stirred at rt with H_2 gas (balloon) bubbled through the mixture, and the progress of the reaction was monitored using low-resolution mass spectrum (LRMS) analysis. The suspension was then filtered over Celite and rinsed with EtOAc, and the solvent was removed in vacuo to give the crude material **15a,b**.

Isomerization of Enones. The crude from the above reduction was dissolved in EtOAc (~0.02 M), with one drop of dilute I_2/EtOAc solution added. The solution was irradiated using a 500 W halogen lamp with stirring for 5−6 h. The reaction was quenched with aq $Na_2S_2O_3$ solution and extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude. Purification of the crude was done via reverse-phase preparative HPLC on an Agilent 1200 series system with Phenomenex Luna C18(2) column (10.0 × 100 mm, 5 μm) using the elution gradient with a MeCN−H_2O mobile phase at a flow rate of 5 mL/min and detection at λ210 and 254 nm.

For **15c** and **16a**, elution conditions are as follows: 2 min at 5% MeCN/H_2O, a gradient from 5% to 25% MeCN/H_2O in 18 min, 5 min at 25% MeCN/H_2O, a gradient from 25% to 80% MeCN/H_2O in 5 min, followed by 80% MeCN/H_2O for 5 min.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-[(E)-phenylvinylenecarbonyl]-1-oxopyrrolidinone, ***16a.*** Preparative HPLC retention time = 20.37 min; white solid, mp = 71−73 °C; $[\alpha]_D^{20}$ = +45.2 (c = 1.0 in MeOH); ν_{max}/cm^{-1} (film) 3330 (br, −OH), 1711 (s, C═O), 1671 (s, C═O); δ_H (400 MHz, MeCN-d_3) 7.84 (d, J = 16.2 Hz, 1H, H-8), 7.66−7.68 (m, 2H, PhH), 7.40−7.50 (m, 3H, PhH), 7.07 (d, J = 16.2 Hz, 1H, H-7), 6.36 (br s, 1H, −NH−), 4.25 (d, J = 2.4 Hz, 1H, H-3), 3.77−3.82 (m, 1H, H-4), 3.69 (dd, J = 3.7, 11.8 Hz, 1H, H-5), 3.64 (dd, J = 4.4, 11.8 Hz, 1H, H-5′), 3.28 (br s, 1H, −OH); δ_C (100 MHz, MeCN-d_3) 190.3 (C-6), 170.7 (C-1), 145.9 (C-8), 135.3, 132.2, 130.1, 129.8 (PhC), 123.0 (C-7), 63.5 (C-3), 62.9 (C-2), 62.5 (C-5), 56.8 (C-4); m/z (ESI+) 282.50 ([M + Na]$^+$, 90%); HRMS (ESI+): calcd for $C_{14}H_{13}NNaO_4$ ([M + Na]$^+$), 282.0737; found, 282.0746.

(2S,3R,4R)-2,3-Epoxy-2-(phenylethylcarbonyl)-4-hydroxymethyl-1-oxopyrrolidinone, ***15c.*** Preparative HPLC retention time = 22.21 min; colorless oil; $[\alpha]_D^{20}$ = +90.1 (c = 0.25 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3336 (br, −OH), 1724 (s, C═O), 1692 (s, C═O); δ_H (400 MHz, MeCN-d_3) 7.25−7.32 (m, 2H, PhH), 7.16−7.24 (m, 3H, PhH), 6.30 (br s, 1H, −NH−), 4.09 (d, J = 2.5 Hz, 1H, H-3), 3.70−3.73 (m, 1H, H-4), 3.61 (dd, J = 4.0, 11.7 Hz, 1H, H-5), 3.55 (dd, J = 4.7, 11.7 Hz, 1H, H-5′), 2.85−2.96 (m, 4H, H-7, and H-8); δ_C (100 MHz, MeCN-d_3) 201.0 (C-6), 170.2 (C-1), 142.0, 129.5, 129.3, 127.1 (PhC), 63.4 (C-3), 62.5 (C-5), 62.4 (C-2), 56.5 (C-4), 42.1, 29.4 (C-7 and C-8); m/z (ESI+) 284.51 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{14}H_{15}NNaO_4$ ([M + Na]$^+$), 284.0893; found, 284.0897.

For **14f**, **15a**, and **15b**, elution conditions are as follows: 2 min at 5% MeCN/H_2O, a gradient from 5% to 25% MeCN/H_2O in 18 min, 5 min at 25% MeCN/H_2O, a gradient from 25% to 80% MeCN/H_2O in 5 min, followed by 80% MeCN/H_2O for 5 min.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(isobutylcarbonyl)-1-oxopyrrolidinone, ***14f.*** Retention time = 13.97 min.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-[(E)-butylvinylenecarbonyl]-1-oxopyrrolidinone, ***16b.*** Retention time = 21.67 min; colorless oil; $[\alpha]_D^{20}$ = +127.3 (c = 0.83 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3318 (br, −OH), 1713 (br s, C═O; with shoulder toward smaller wavenumber); δ_H (400 MHz, MeCN-d_3) 7.12 (dt, J = 7.0, 15.8 Hz, 1H, H-8), 6.39 (dt, J = 1.6, 15.8 Hz, 1H, H-7), 6.31(br s, 1H, −NH−), 4.14 (d, J = 2.4 Hz, 1H, H-3), 3.73−3.76 (m, 1H, H-4), 3.65 (dd, J = 3.8, 11.7 Hz, 1H, H-5), 3.59 (dd, J = 4.5, 11.7 Hz, 1H, H-5′), 2.26 (apparent dq, J = 1.6, 7.1 Hz, 2H, H-9), 1.40−1.50 (m, 2H, H-10), 1.28−1.39 (m, 2H, H-11), 0.91 (t, J = 7.3 Hz, 3H, H-12); δ_C (100 MHz, MeCN-d_3) 190.2 (C-6), 170.7 (C-1), 152.4 (C-8), 126.8 (C-7), 63.2 (C-3), 62.7 (C-2), 62.4 (C-5), 56.8 (C-4), 33.0 (C-9), 30.8 (C-10), 23.0 (C-11), 14.1 (C-12); m/z (ESI+) 240.51 ([M + H]$^+$, 100%); HRMS (ESI+): calcd for $C_{12}H_{17}NNaO_4$ ([M + Na]$^+$), 262.1050; found, 262.1053.

(2S,3R,4R)-2-(Hexylcarbonyl)-2,3-epoxy-4-hydroxymethyl-1-oxopyrrolidinone, ***15d.*** Retention time = 27.61 min; colorless oil; $[\alpha]_D^{20}$ = +109.7 (c = 0.5 in CH_2Cl_2); ν_{max}/cm^{-1} (film) 3333 (br, −OH), 1723 (s, C═O), 1692 (s, C═O); δ_H (400 MHz, MeCN-d_3) 6.30 (br s, 1H, −NH−), 4.11 (d, J = 2.4 Hz, 1H, H-3), 3.70−3.73 (m, 1H, H-4), 3.62 (dd, J = 4.0, 11.7 Hz, 1H, H-5), 3.56 (dd, J = 4.7, 11.7 Hz, 1H, H-5′), 2.58 (apparent t, J = 7.4 Hz, 2H, H-7), 1.50−1.60 (m, 2H), 1.24−1.35 (m, 6H) (H-8, H-9, H10, H11), 0.88 (t, J = 7.3 Hz, 3H, H-12); δ_C (100 MHz, MeCN-d_3) 201.9 (C-6), 170.4 (C-1), 63.4 (C-3), 62.5 (C-5), 62.4 (C-2), 56.5 (C-4), 40.6 (C-7), 32.3, 29.4, 23.5, 23.2 (C-8, C-9, C-10, C-11), 14.0 (C-12); m/z (ESI+) 242.56 ([M + H]$^+$,

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100%); HRMS (ESI+): calcd for $C_{12}H_{19}NNaO_4$ ([M + Na]$^+$), 264.1206; found, 264.1209.

Procedure for Methylation of Secondary Amide 6b. A solution of **5c** (35 mg, 0.104 mmol, 1.0 equiv) in dry THF (3 mL) was added to NaH (60% in mineral oil) (4.2 mg, 0.104 mmol, 1.0 equiv) at 0 °C. The mixture was stirred at rt for 35 min. MeI (7 μL, 0.104 mmol, 1.0 equiv) was then added, and the reaction mixture was stirred at rt for 45 min. The reaction was quenched with water, acidified with 10% aq HCl dropwise, and extracted with EtOAc. The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo to give the crude. The crude was purified via flash column chromatography on eluent (eluent = EtOAc/PE, 0−40%) to give the product (20 mg) as colorless oil with an isolated yield of 55%.

(2R,5R,6R,7S)-1-Aza-6,7-epoxy-7-(N,N′-methylphenylcarbamoyl)-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane, ***8****.* R_f = 0.13 (1:1 EtOAc/PE); white solid, mp = 182−185 °C; $[\alpha]_D^{20}$ = +81.2 (*c* = 0.99 in $CHCl_3$); ν_{max}/cm^{-1} (film) 1720 (s, C═O), 1665 (s, C═O); δ_H (500 MHz, $CDCl_3$) 7.42−7.49 (m, 3H, Ph−H), 7.29−7.36 (m, 7H, Ph−H), 6.12 (s, 1H, H-2), 4.01 (s, 1H, H-6), 3.97 (dd, *J* = 6.9, 9.5 Hz, 1H, H-5), 3.90 (t, *J* = 6.9 Hz, 1H, H-4), 3.38 (s, 3H, −NMe−), 2.65 (dd, *J* = 8.2, 9.1 Hz, 1H, H-4′); δ_C (125 MHz, $CDCl_3$) 172.1 (C-8), 161.3 (C-9), 141.8, 137.7, 129.9, 128.7, 128.7, 128.4, 127.6, 125.8 (Ph−C), 88.2 (C-2), 64.9 (C-4), 63.5 (C-6), 61.9 (C-7), 58.5 (C-5), 37.9 (−NMe−); *m*/*z* (ESI+) 373.1 ([M + Na]$^+$, 100%); HRMS (ESI+): calcd for $C_{20}H_{18}N_2NaO_4$ ([M + Na]$^+$), 373.1159; found, 373.1150.

(2S,3R,4R)-2,3-Epoxy-4-hydroxymethyl-2-(N,N′-methylphenylcarbamoyl)-1-oxopyrrolidinone, ***9****.* R_f = 0.11 (EtOAc); white solid, mp = 208−210 °C; $[\alpha]_D^{20}$ = −20.6 (*c* = 0.53 in MeOH); ν_{max}/cm^{-1} (film) 3423 (br), 3195 (br), 1684 (s, C═O), 1651 (s, C═O); δ_H (500 MHz, MeOD-d_4) 7.47−7.52 (m, 3H, Ph−H), 7.37−7.39 (m, 2H, Ph−H), 4.13 (s, 1H, H-3), 3.48 (dd, *J* = 6.5, 8.0 Hz, 1H, H-4), 3.33 (s, 3H, −NMe−; overlapped with MeOD signal but shows the desired correlation in HSQC and HMBC), 2.91 (dd, *J* = 6.5, 10.9 Hz, 1H, H-5), 2.58 (dd, *J* = 8.0, 10.9 Hz, 1H, H-5′); δ_C (125 MHz, MeOD-d_4) 172.5 (C-1), 164.2 (C-6), 142.9, 131.2, 130.1, 129.4 (Ph−C), 63.1 (C-3), 62.1 (C-5), 61.7 (C-2), 57.6 (C-4), 38.4 (−NMe−);*m*/*z* (ESI+) 285.1 ([M + Na]$^+$, 100%), (ESI−) 261.0 ([M−H]$^-$, 100%); HRMS (ESI+): calcd for $C_{13}H_{14}N_2NaO_4$ ([M + Na]$^+$), 285.0846; found, 285.0842.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds, details of bioassay protocol, and X-ray crystallographic data for compound **6e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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