Intramolecular Aza-[4+3] Cycloaddition Reactions of α-Halohydroxamates

Arjun Acharya, John A. Eickhoff, Christopher S. Jeffrey*

Department of Chemistry, University of Nevada, Reno, 1664 N. Virginia St. Mail Stop 0216, Reno, NV 89557, USA
Fax +1(775)7846804; E-mail: cjeffrey@unr.edu

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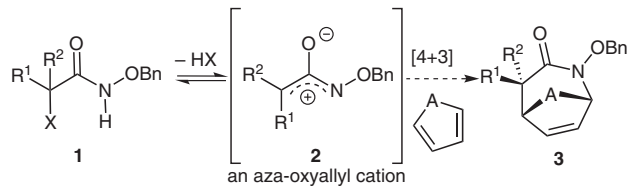
This article is dedicated in honor of Professor Scott Denmark's 60th birthday.

Abstract: Polyheterocyclic scaffolds were prepared by intramolecular aza-[4+3] cycloaddition reactions of aza-oxyallylic cations with cyclic dienes. The aza-oxyallylic cation was generated in situ by the dehydrohalogenation of α-halohydroxamates. The highly functionalized heterocyclic products undergo a variety of reactions that provide useful scaffolds for target-directed synthesis, including macrocyclic furans and polyhydroxylated azepanes.

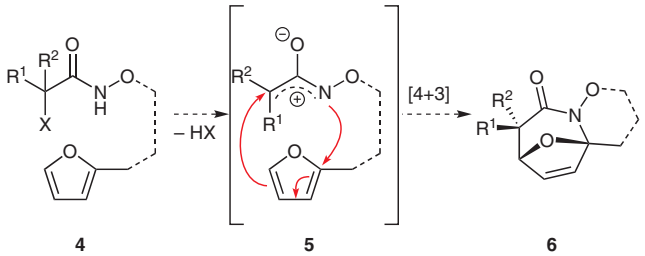
Key words: cycloaddition, nitrogen, azasugars, heterocycles, macrocycles

Polyheterocyclic compounds are an important class of small molecules used in drug discovery and natural product synthesis.[1] Our group has reported an efficient method for the synthesis of caprolactams and diazepanones using an aza-[4+3] cycloaddition of a transient aza-oxyallylic cation with a diene (Scheme 1, A).[2] The aza-allylic cation was formed in situ via dehydrohalogenation of α-halo benzylhydroxylamines or *N*-chlorourea derivatives. The oxygen donor group was essential for the success of this reaction, and was computationally identified to stabilize the proposed intermediate.[2a,3,4]

A. Established: the intermolecular [4+3] cycloaddition of aza-oxyallyl cations



B. This work: the intramolecular [4+3] cycloaddition of aza-oxyallyl cations



Scheme 1 The concept for the intramolecular aza-[4+3]-cycloaddition reaction of aza-oxyallylic cations

Intramolecular variants of the [4+3] cycloaddition of oxyallylic cations with dienes are established as powerful methods for target-directed synthesis.[5] Like the all-carbon [4+3] cycloadditions, we envisioned that analogous aza-[4+3] methods would provide access to new classes of polyheterocyclic scaffolds for target-directed synthesis and drug discovery (Scheme 1, B). Herein, we report our investigation of the intramolecular aza-[4+3] cycloaddition and its application to the synthesis of various polyheterocyclic scaffolds.

The intramolecular cycloaddition of oxyallylic cations has been categorized based upon the connectivity of the diene and dienophilic reactants.[5f,j] Type I [4+3]-cycloaddition reactions are the most commonly explored type and are characterized by the tethering of diene and dienophilic reactants through their termini. Two possible modes of type I cycloaddition reactions are available when considering the aza-[4+3] cycloaddition and are differentiated by whether the diene is tethered through the nitrogen or carbon terminus of the eventual aza-allylic cation. The type I′ aza-[4+3]-cycloaddition reaction, whereby the diene and dienophilic components are tethered through the N–O bond, was the subject of our initial studies (Scheme 1, B).

Difficulties associated with the incorporation and stability of haloketones into the cycloaddition precursors have limited the number of examples of all-carbon intramolecular [4+3] cycloaddition triggered by dehydrohalogenation.[6] In order to circumvent problems associated with incorporating this reactive and labile functional group, we have designed our approach such that a late stage amide couples with α-haloacid halides and a diene-tethered hydroxylamine **8**. To establish the feasibility of this strategy, the hydroxylamine **8** was synthesized from 2-furanpropanol (**7**) in two steps (Scheme 2). Acylation of the hydroxylamine with 2-bromo-2-propanoyl bromide provided the cycloaddition precursor **9** for our initial studies.

Treatment of the α-haloamide **9** under the Föhlisch conditions (Et_3N, CF_3CH_2OH)[7] provided the tricyclic product **10**, representing the first example of a type I′ intramolecular aza-[4+3]-cycloaddition reaction.[7] Further attempts at optimization of this reaction provided variable results, predominantly due to the competitive elimination or solvolysis of the haloamide functional group.[2a]

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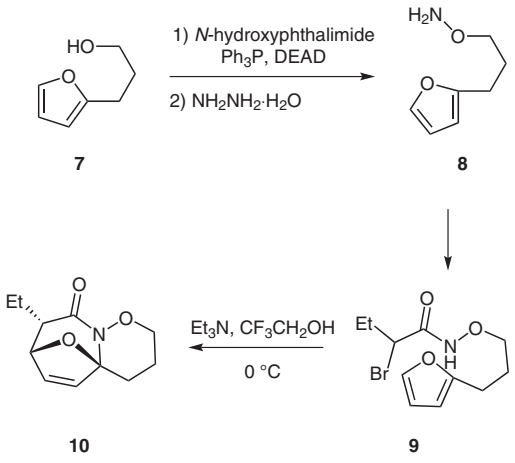
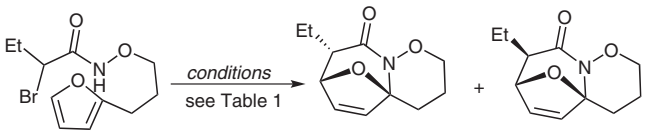


Scheme 2 The first example of an intramolecular aza-[4+3] cycloaddition of α-halohydroxamates with an appended furan

Overall, the best results were obtained when conducting the reaction at 0.25 M using triethylamine as the base (Table 1, entry 2). Running the reaction at concentrations lower than 0.25 M did not improve the yield of the cycloadduct and resulted in slow reaction rates (entry 1). Our previous studies of the intermolecular aza-[4+3]-cycloaddition reaction demonstrated that sodium carbonate was an effective base. However, in the intramolecular case, the use of sodium carbonate slowed the reaction rate (entry 3). Reaction of the halohydroxamate with $LiClO_4$ and triethylamine in anhydrous diethyl ether provided good yield of the cycloadduct **10** with diminished diastereoselectivity (entry 4).[8]

The scope of the aza-[4+3]-cycloaddition reaction of six-atom tethered substrates was evaluated with respect to diene, α-hydroxamate substitution, and tether substitution (Table 2). The cycloaddition precursors for these studies were easily prepared in three to five steps by homologation of various 2-substituted furan or pyrrole alcohols or by direct installation of the tethering unit from the parent heterocycle (see Supporting Information for details). In all cases, reactions under the standard conditions provided the cycloadducts in fair to good yield. The use of hexafluoroisopropanol (HFIP) as the solvent improved the overall yield of reactions of α,α′-dialkylhaloamide substrates (Table 2, entries 2, 4, 5, 11) by minimizing the competitive solvolysis with trifluoroethanol.[2a,9] Unlike the intermolecular analogues of this reaction, the monosubstituted haloamides provided only marginal diastereoselectivity for the *endo*-cycloadduct, which is consistent

Table 1 Evaluation of Effect of Reaction Conditions for the Cycloadduct Product **10**



9 *endo*-**10** *exo*-**10**

Entry	Conditions[a]	Concn (M)	Time	Yield (%)[b] (dr, *endo*/*exo*)[c]
1	Et_3N, TFE	0.025 M	2 d	46 (3:1)
2	Et_3N, TFE	0.25 M	40 h	68 (3:1)
3	Na_2CO_3, TFE	0.25 M	4 d	49 (2.5:1)
4	Et_3N, $LiClO_4$, Et_2O, reflux	0.25 M	2 d	68 (2:1)
5	Et_3N, HFIP	0.25 M	10 d	84 (2.1:1)

[a] All reactions were conducted by adding the base to a solution of the substrate in the specified solvent at 0 °C. After the addition, the mixture was allowed to warm to r.t. until complete consumption of starting material; TFE: CF_3CH_2OH; HFIP: $(CF_3)_2CHOH$.
[b] Reaction yields represent the combined yield of both the isolated diastereoisomeric cycloadducts.
[c] Diastereoisomeric ratio (dr) was determined via crude ^1H NMR analysis of the mixture after workup.

with the diastereoselectivity observed for other type I intramolecular [4+3]-cycloaddition reactions of haloketones with furans (entries 2, 3, 6, 7, and 9, 10). With respect to the diene reactant, *N*-Boc-pyrrole containing substrates underwent the cycloaddition in good yield and better diastereoselectivity compared with the furan substrates (entries 5–7). A 5-methyl-substituted furan substrate provided the tricyclic product in good yield (entry 10). Interestingly, the incorporation of a fused aryl group in the 6-atom tether provided the cycloadduct (entries 8, 9) with excellent diastereoselectivity (entry 9). The rigidity of the unsaturated system likely reduces the degrees of freedom in the side-chain resulting in the enhanced yield and diastereoselectivity. Finally, the effect of a side-chain stereogenic center on the diastereoselectivity of the cycloaddition reaction was studied. As shown, methyl substitution at the benzylic position had little effect on the diastereoselectivity of the reaction, resulting in only a ~2:1 ratio of diastereoisomers under a variety of conditions (entry 11).

Table 2 Evaluation of the Substrate Scope for the Intramolecular Aza-[4+3] Reactions of 6-Atom-Tethered Halogenated Hydroxamates with Various Dienes

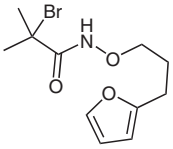
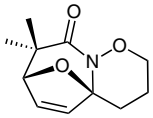
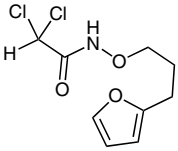
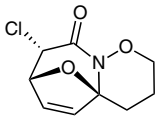
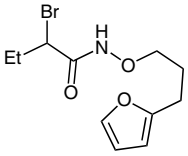
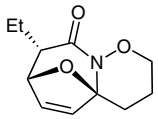
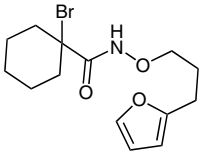
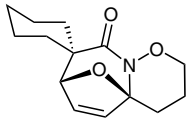
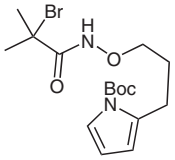
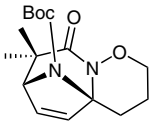
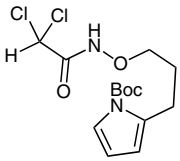
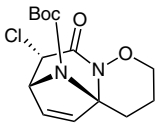
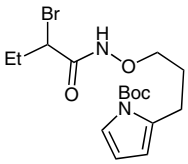
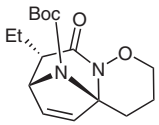
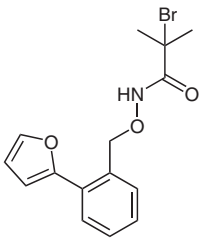
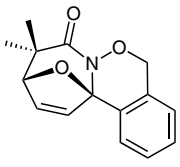
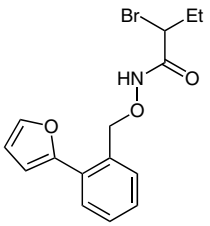
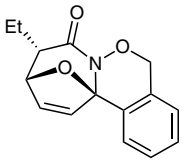
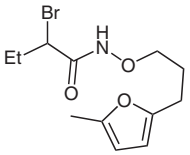
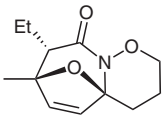
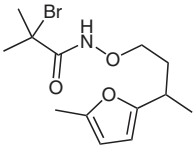
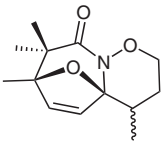
Entry	Substrate	Reaction conditions[a]	Product	Yield (%)[b] (dr, *endo*/*exo*)[c]
1		TFE, Et_3N, 3 h		47
2		TFE, Et_3N, 48 h HPIP, Et_3N, 72 h		68 (1:1) 79 (2.5:1)
3		see Table 1		see Table 1
4		Et_3N, HFIP, 20 h		74
5		Et_3N, TFE, 5 h Et_3N, HFIP, 24 h Na_2CO_3, TFE, 20 h		45 85 56
6		Et_3N, TFE, 40 h Et_3N, HFIP, 65 h Na_2CO_3, TFE, 72 h		66 (4:1) 61 (5:1) 60 (4.8:1)
7		Et_3N, TFE, 18 h Et_3N, HFIP, 12 d Na_2CO_3, TFE, 40 h		48 (4:1) 57 (3:1) 49 (4.1:1)
8		Et_3N, HFIP, 3 h		71
9		Et_3N, TFE, 12 h Et_3N, HFIP, 13 d		63 (≥ 19:1) 69 (≥ 19:1)

Table 2 Evaluation of the Substrate Scope for the Intramolecular Aza-[4+3] Reactions of 6-Atom-Tethered Halogenated Hydroxamates with Various Dienes (continued)

Entry	Substrate	Reaction conditions[a]	Product	Yield (%)[b] (dr, *endo*/*exo*)[c]
10		Et_3N, TFE, 18 h Et_3N, HFIP, 14 d		67 (2.2:1) 75 (3:1)
11		Et_3N, TFE, 16 h Et_3N, HFIP, 20 h Na_2CO_3, TFE, 30 h		65 (2.6:1; α/β) 95 (2:1; α/β) 60 (2.4:1; α/β)

[a] All reactions were conducted by adding the base to a solution of the substrate in the specified solvent at 0 °C. After the addition, the mixture was allowed to warm to r.t. until complete consumption of the starting material. HFIP = $(CF_3)_2CHOH$; TFE = CF_3CH_2OH.
[b] Reaction yields represent the combined yield of both isolated diastereoisomeric cycloadducts.
[c] Diastereoisomeric ratio (dr) was determined via crude ^1H NMR analysis of the mixture after workup.

Shortening the tether length to a five-atom tether provided better yields of the cycloadduct when compared with the six-atom tethered analogues with diminished diastereoselectivity (Table 3, entries 2–4). Interestingly, the ethyl-substituted substrate with the five-atom tether demonstrated a preference for the *exo*-cycloadduct (entry 4) The attempted cycloaddition reactions of a 2-furylmethanol tethered amide failed to close the strained four-membered oxazetidine and instead resulted in only elimination to the methacrylamide. Extension of the tether from 6 to 7 atoms provided the corresponding 1,2-oxazepane products in good yield in all cases (entries 5–7). Again, the diastereoselectivity in these examples remained close to identical to the six-membered analogues. Further extension to an eight-atom tether provided exclusive formation of a macrocyclic product, which was the subject of our following investigations (entry 8).

Table 3 Evaluation of the Effect of Variable Tether Length on the Yield of the Intramolecular Aza-[4+3] Reactions of Halohydroxamates

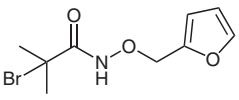
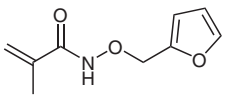
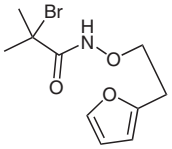
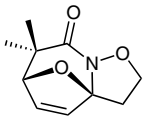
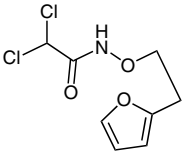
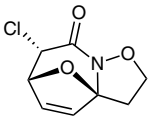
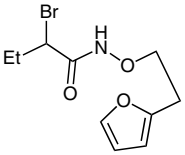
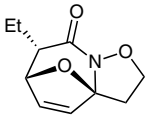
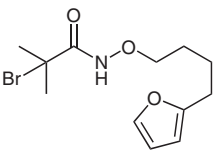
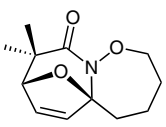
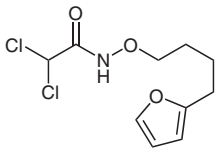
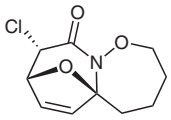
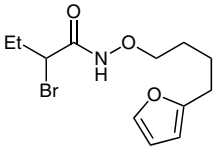
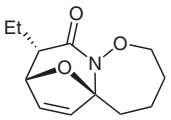
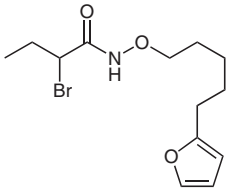
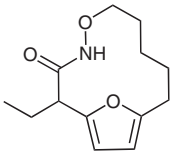
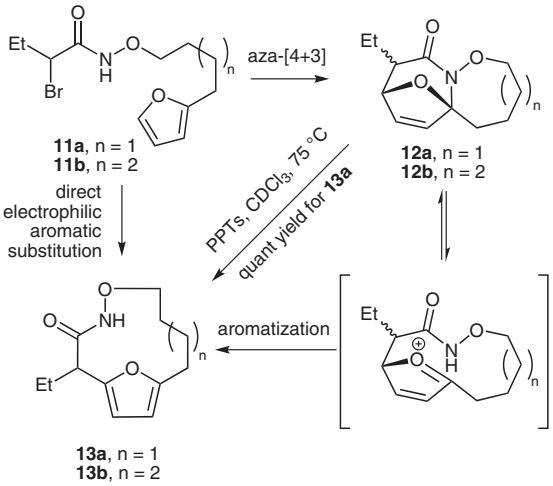
Entry	Substrate	Reaction conditions[a]	Product	Yield (%)[b] (dr, *endo*/*exo*)[c]
1		Et_3N, HFIP, reflux, 2 d		n.d.
2		Et_3N, HFIP, 1 h		82
3		Et_3N, HFIP, 30 h		91 (3:2)
4		Et_3N, TFE, 16 h Et_3N, HFIP, 12 d Na_2CO_3, TFE, 30 h		85 (1:2.8) 83 (1:2.3) 75 (1:2.5)
5		Et_3N, TFE, 1 h Et_3N, HFIP, 1 h		30 51

Table 3 Evaluation of the Effect of Variable Tether Length on the Yield of the Intramolecular Aza-[4+3] Reactions of Halohydroxamates (continued)

Entry	Substrate	Reaction conditions[a]	Product	Yield (%)[b] (dr, *endo*/*exo*)[c]
6		Et_3N, HFIP, 36 h		91 (1:1.1)
7		Et_3N,TFE, 18 h		67 (1:1.5)
8		Et_3N, HFIP, 18 h		50

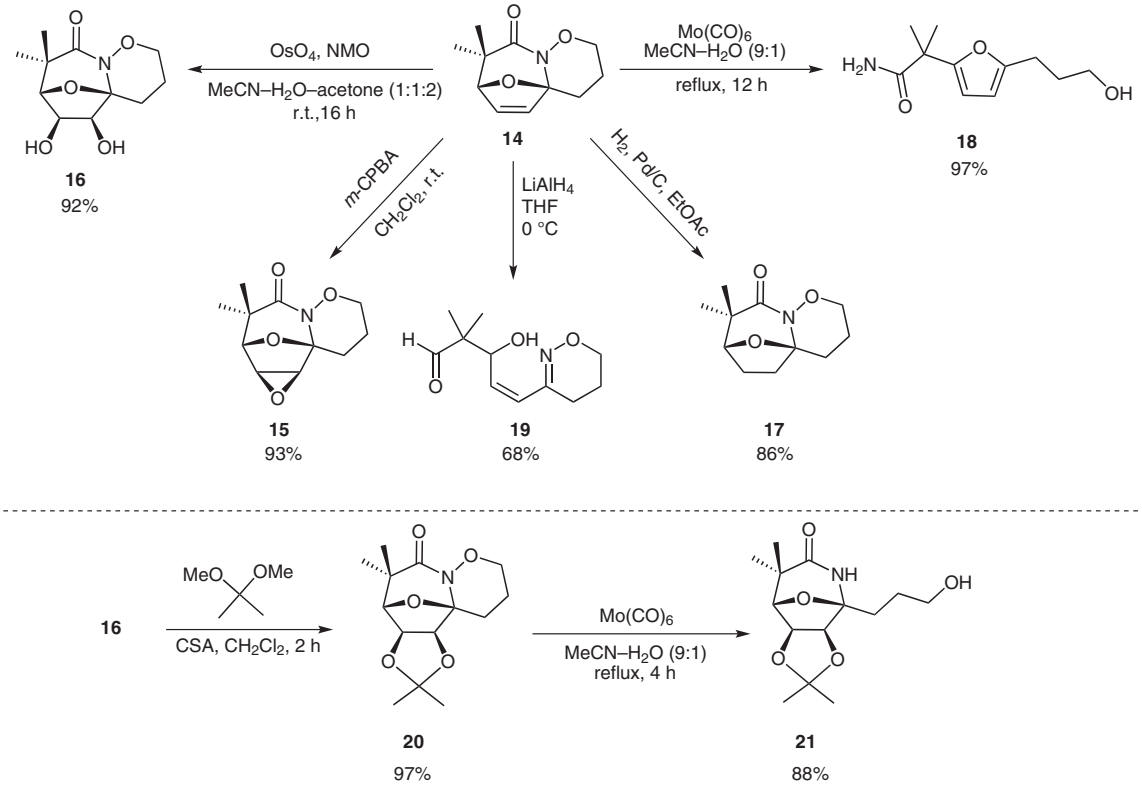
[a] All reactions were conducted by adding the base to a solution of the substrate in the specified solvent at 0 °C. After the addition, the mixture was allowed to warm to r.t. until complete consumption of starting material; n.d.: not detected.
[b] Reaction yields represent the combined yield of both isolated diastereoisomeric cycloadducts.
[c] Diastereoisomeric ratio (dr) was determined via crude ^{1}H NMR analysis of the mixture after workup.

Isolation of the interesting macrocyclic product led us to consider two mechanistic pathways for the formation of the heterocylophane **13b**: (1) direct electrophilic aromatic substitution at the electrophilic carbon atom of the aza-oxyallylic cation or (2) the [4+3] cycloaddition to provide **12b** followed by rearrangement to the furan **13b**. Given the exclusive selectivity for the 2,5-disubstituted macrocyclic product **13b**, we propose that the macrocyclic product is the result of the stepwise process that proceeds through **12b**. Indeed, isolation of the cycloadduct **12a** and treatment with acid provided quantitative conversion to the heterocyclophane **13a** in support of this two-step pathway (Scheme 3). Further investigations of the scope of this formal heteromacrocyclization are under way.



Scheme 3 Preliminary mechanistic studies of the origin of the macrocyclic products **13a** and **13b** (n = 1, 2)

The heterocyclic products formed via the intramolecular aza-[4+3] cycloaddition provide highly functionalized building blocks for organic synthesis. The array of orthogonal functional groups present in the tricyclic product provides ample opportunities for the synthesis of biologically active classes of heterocycles, including nucleoside mimics and polyhydroxylated azepanes.[10] The alkene moiety underwent diastereoselective oxidation from the concave face of the [3.2.1]-azabicyclooctane ring of **14** providing the epoxide **15** and diol **16** in good yield (Scheme 4). Catalytic hydrogenation of the alkene **14** using palladium on carbon selectively provided the saturated heterocycle **17** without cleavage of the weak N–O bond. Attempted cleavage of the 1,2-hydroxazine of the lactam **14** using $Mo(CO)_6$ provided the furan **18** in excellent yield.[11] Formation of the furan **18** presumably proceeds via Lewis acid catalyzed rupture of the aminal moiety to an oxocarbenium ion and aromatization. Reductive opening of the caprolactam **14** using lithium aluminum hydride occurred in good yield to provide the cyclic oxime **19**. The presence of the aldehyde in **19** suggests that half reduction occurs to form a stable tetrahedral intermediate that opens to the aldehyde upon workup. Protection of the dihydroxylated derivative **16** and treatment of the ketal **20** with $Mo(CO)_6$ provided the lactam **21** in excellent yield, demonstrating that the N–O bond in the [3.2.1]-bicyclo product can be cleaved in the absence of the dihydrofuran moiety (Scheme 4).



Scheme 4 Examples of derivatization reactions of the [3.2.1]-azabicyclononane **14**

In conclusion, intramolecular [4+3] cycloaddition reactions of α-halohydroxamates and cyclic aromatic dienes have been established as methods for the construction of polyheterocyclic caprolactams. Substrates containing furan and pyrrole dienes, a variety of α-substituents, and variable tether lengths provided the cycloadducts in fair to good yield. Attempts to close an eight-membered hydroxazocene **12b** resulted in the formation of a macrocyclic furan **13b**. The [3.2.1]-azabicyclononane core could be converted to a variety of highly substituted heterocyclic products, including macrocycles, polyhydroxylated caprolactams, and oxazines.

All reactions were carried out under an atmosphere of N_2 in oven-dried glassware with magnetic stirring, unless otherwise specified. CH_2Cl_2 was purified by passage through a bed of activated alumina. All other reagents and solvents were purchased from Sigma-Aldrich Chemical Company and used without any further purification. TLC information was recorded on Silicycle glass 60 F254 plates and developed by staining with $KMnO_4$ or ceric ammonium molybdate (CAM). Purification of reaction products was carried out by flash chromatography using Silicycle Siliaflash® P60 (230–400 mesh). ^{1}H NMR spectra were measured on Varian 400 (400 MHz), Varian MR400 (400 MHz), or Varian 500 (500 MHz) spectrometers and are reported in ppm. Standard abbreviations were used to denote signal multiplicities; coupling constant(s) are in Hz. TMS was used as an internal standard (TMS at 0.00 ppm) in $CDCl_3$. ^{13}C NMR spectra were recorded on V400 or V500 spectrometer and reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm and CD_3OD at 49.86 ppm). IR spectra were recorded on a Nicolet 6700 FT-IR with a diamond ATR and data are reported as cm^{-1}. High-resolution mass spectra were obtained using an Agilent 6230 TOF LC/MS with an (atmospheric pressure photoionization (APPI) or electrospray (ESI) source with purine and HP-0921 as an internal calibrants.

[4+3]-Cycloaddition Reactions; General Procedure

To a solution of haloamide (1 equiv) in TFE or HFIP (0.25 M with respect to haloamide) was added Et_3N or Na_2CO_3 (2 equiv) at 0 °C. The solution was allowed to warm to r.t. and the reaction was monitored to completion by TLC (3:1 or 2:1 hexanes–EtOAc). After the reaction was complete, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography (9:1 to 3:1, hexanes–EtOAc) to provide the respective cycloadduct.

(±)-(1*S*,9*S*,*Z*)-8,8-Dimethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one (Table 2, entry 1)

Prepared in 47% yield (33 mg, 0.16 mmol) as a white solid from 1-[*O*-3-(2-furyl)propyloxyamino]-2-bromo-2-methylpropan-1-one (100 mg, 0.34 mmol) via the general procedure; mp 115.1–116.6 °C; R_f = 0.22 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3080, 2945, 2870, 1676, 1456, 1445, 1385, 1357, 1331, 1316, 1304, 1279, 1261, 1224, 1176, 1104, 1062 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, J = 5.9 Hz, 1 H), 6.47 (ddd, J = 5.9, 2.0, 0.9 Hz, 1 H), 4.48 (d, J = 2.0 Hz, 1 H), 4.21 (dddd, J = 11.6, 4.6, 4.6, 1.7 Hz, 1 H), 3.92 (ddd, J = 11.7, 2.3, 2.3 Hz, 1 H), 2.04 (m, 3 H), 1.88 (m, 1 H), 1.50 (s, 3 H), 1.07 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.0, 136.2, 134.9, 97.3, 86.3, 70.5, 49.9, 29.1, 26.8, 23.6, 20.1.

HRMS (ESI): m/z calcd for $C_{11}H_{15}NO_3$ + Na (M + Na)$^+$: 232.0944; found: 232.0946.

(±)-(1*S*,8*S*,9*S*,*Z*)-8-Chloro-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one and (±)-(1*S*,8*R*,9*S*,*Z*)-8-Chloro-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one (Table 2, entry 2)
Prepared in 38% yield (32 mg, 0.15 mmol) as a white solid from 1-[*O*-3-(2-furyl)propyloxyamino]-2,2-dichloroethan-1-one (100 mg, 0.40 mmol) via the general procedure.

***endo*-Diastereoisomer**
Mp >116 °C (dec.); R_f = 0.32 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3098, 2967, 2937, 2919, 2855, 1701, 1591, 1435, 1358, 1348, 1338, 1279, 1261, 1226, 1190, 1147, 1096 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (d, *J* = 6.0 Hz, 1 H), 6.57 (dd, *J* = 6.0, 1.9 Hz, 1 H), 5.14 (dd, *J* = 5.1, 1.9 Hz, 1 H), 4.85 (d, *J* = 5.1 Hz, 1 H), 4.29–4.22 (m, 1 H), 3.96 (ddd *J* = 12.2, 2.6, 2.6 Hz, 1 H), 2.14–1.89 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.8, 137.8, 133.1, 98.2, 81.3, 70.8, 57.8, 28.8, 23.3.

HRMS (ESI): *m*/*z* calcd for $C_9H_{10}ClO_3$ + Na (M + Na)$^+$: 240.0215; found: 240.0198.

***exo*-Diastereoisomer**
Mp 115.3–116.8 °C; R_f = 0.21 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3095, 2992, 2963, 2922, 2856, 1683, 1591, 1440, 1361, 1346, 1330, 1289, 1262, 1236, 1211, 1195, 1145, 1094 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 5.8 Hz, 1 H), 6.42 (ddd, *J* = 5.9, 2.1, 1.0 Hz, 1 H), 5.02 (d, *J* = 2.2 Hz, 1 H), 4.25 (dddd, *J* = 11.6, 3.4, 3.4, 1.7 Hz, 1 H), 4.17 (d, *J* = 1.1 Hz, 1 H), 4.01 (ddd, *J* = 11.6, 2.6, 2.6 Hz, 1 H), 2.24 (ddd, *J* = 3.9, 5.3, 5.3 Hz, 1 H), 2.15–1.91 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.4, 138.8, 131.6, 97.6, 82.9, 70.8, 56.3, 28.4, 23.4.

HRMS (ESI): *m*/*z* calcd for $C_9H_{10}ClO_3$ + Na (M + Na)$^+$: 240.0215; found: 240.0212.

(±)-(1*S*,8*S*,9*S*,*Z*)-8-Ethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one and (±)-(1*S*,8*R*,9*S*,*Z*)-8-Ethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one (Table 2, entry 3)
Prepared in 68% yield (48 mg, 0.23 mmol) as a white solid from (±)-1-[*O*-3-(2-furyl)propyloxyamino]-2-bromobutan-1-one (100 mg, 0.34 mmol) via the general procedure.

***endo*-Diastereoisomer**
Mp 119.5–121.6 °C; R_f = 0.27 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3089, 2985, 2963, 2936, 2883, 2867, 2360, 2337, 2163, 1682, 1591, 1474, 1463, 1450, 1430, 1388, 1356, 1320, 1296, 1281, 1266, 1241, 1222, 1200, 1144, 1119, 1096 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 6.0 Hz, 1 H), 6.42 (ddd, *J* = 6.0, 1.9, 0.9 Hz, 1 H), 4.99 (dd, *J* = 5.0, 1.9 Hz, 1 H), 4.22 (dddd, *J* = 11.7, 4.7, 4.7, 1.5 Hz, 1 H), 3.93 (ddd, *J* = 11.8, 2.4, 2.4 Hz, 1 H), 3.04 (dt, *J* = 9.9, 5.1 Hz, 1 H), 2.15–1.95 (m, 4 H), 1.24–1.15 (m, 2 H), 1.04 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.4, 136.7, 133.8, 97.3, 80.5, 70.6, 52.5, 29.3, 23.7, 19.3, 12.1.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{16}NO_3$ (M + H)$^+$: 210.1125; found: 210.1128.

***exo*-Diastereoisomer**
Mp 108.4–110.9 °C; R_f = 0.20 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3083, 2963, 2933, 2867, 1686, 1590, 1553, 1442, 1358, 1321, 1286, 1272, 1234, 1145, 1199, 1094 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (d, *J* = 5.9 Hz, 1 H), 6.43 (dd, *J* = 5.9, 2.1 Hz, 1 H), 4.79 (d, *J* = 2.2 Hz, 1 H), 4.22 (dddd, *J* = 11.7, 4.6, 4.6, 1.7 Hz, 1 H), 3.94 (ddd, *J* = 11.8, 2.4, 2.4 Hz, 1 H), 2.36 (dd, *J* = 8.6, 6.2 Hz, 1 H), 2.16–1.97 (m, 4 H), 1.95–1.83 (m, 2 H), 1.08 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.4, 135.2, 134.8, 97.3, 80.1, 70.6, 53.3, 28.9, 25.0, 23.7, 11.9.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{15}NO_3$ + Na (M + Na)$^+$: 232.0944; found: 232.0933.

(±)-(1*S*,9*S*,*Z*)-5,12-Dioxa-4-azatetracyclo[7.2.1.5^{2,2}.0^{4,9}]heptadec-10-en-3-one (Table 2, entry 4)
Prepared in 74% yield (55 mg, 0.22 mmol) as a white solid from (±)-[*O*-3-(2-furyl)propyloxyamino](1-bromocyclohexyl)formaldehyde (100 mg, 0.30 mmol) via the general procedure; mp 139.4–141.2 °C; R_f = 0.33 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3091, 2936, 2849, 1678, 1595, 1453, 1355, 1324, 1290, 1275, 1262, 1222, 1206, 1185, 1146, 1103, 1089 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (d, *J* = 6.0 Hz, 1 H), 6.47 (dd, *J* = 5.9, 2.1 Hz, 1 H), 4.94 (d, *J* = 2.1 Hz, 1 H), 4.20 (dddd, *J* = 11.7, 4.6, 4.6, 1.6 Hz, 1 H), 3.91 (ddd, *J* = 11.7, 2.2, 2.2 Hz, 1 H), 2.14–1.74 (m, 8 H), 1.67–1.56 (m, 3 H), 1.49–1.23 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.1, 136.3, 134.8, 97.1, 82.1, 70.4, 53.8, 33.9, 29.1, 29.0, 25.4, 23.7, 21.5, 21.3.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{20}NO_3$ (M + H)$^+$: 250.1438; found: 250.1438.

***tert*-Butyl (±)-(1*R*,9*S*,*Z*)-8,8-Dimethyl-7-oxo-5-oxa-6,12-diazatricyclo[7.2.1.0^{1,6}]dodec-10-ene-12-carboxylate (Table 2, entry 5)**
Prepared in 85% yield (67 mg, 0.38 mmol) as a white solid from *tert*-butyl 2-{3-[*N*-2-bromo-2-methylpropionyl(aminooxy)]propyl}-1*H*-pyrrole-1-carboxylate (100 mg, 0.26 mmol) via the general procedure; mp 130.9–131.8 °C; R_f = 0.36 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 2994, 2975, 2932, 2863, 1703, 1683, 1603, 1468, 1461, 1441, 1385, 1375, 1366, 1351, 1341, 1331, 1306, 1283, 1253, 1272, 1219, 1233, 1196, 1168, 1148, 1111, 1082 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 6.1 Hz, 1 H), 6.43 (dd, *J* = 6.0, 2.7 Hz, 1 H), 4.56 (d, *J* = 2.7 Hz, 1 H), 4.23 (dddd, *J* = 11.4, 4.5, 2.7, 1.8 Hz, 1 H), 4.07 (ddd, *J* = 11.1, 3.4, 3.2 Hz, 1 H), 3.42 (ddd, *J* = 13.2, 5.2, 5.0 Hz, 1 H), 2.07 (dddd, *J* = 13.9, 3.9, 3.9, 1.7 Hz, 1 H), 2.03 (ddd, *J* = 14.0, 3.9, 3.9, 1.7 Hz, 1 H), 2.01–1.88 (m, 2 H), 1.49 (s, 9 H), 1.41 (s, 3 H), 1.13 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.2, 150.6, 139.0, 134.6, 82.4, 81.1, 70.5, 66.6, 51.3, 28.3, 26.7, 26.2, 22.9, 21.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{25}N_2O_4$ (M + H)$^+$: 309.1809; found: 309.1823.

***tert*-Butyl (±)-(1*R*,8*S*,9*S*,*Z*)-8-Chloro-7-oxo-5-oxa-6,12-diazatricyclo[7.2.1.0^{1,6}]dodec-10-ene-12-carboxylate and *tert*-Butyl (±)-(1*R*,8*R*,9*S*,*Z*)-8-Chloro-7-oxo-5-oxa-6,12-diazatricyclo[7.2.1.0^{1,6}]dodec-10-ene-12-carboxylate (Table 2, entry 6)**
Prepared in 61% yield (55 mg, 0.18 mmol) as a white solid from *tert*-butyl 2-{3-[*N*-2,2-dichloroacetyl(aminooxy)]propyl}-1*H*-pyrrole-1-carboxylate (100 mg, 0.29 mmol) via the general procedure.

***endo*-Diastereoisomer**
Mp 141.1–144.0 °C; R_f = 0.6 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3088, 2981, 2948, 2968, 2912, 2864, 1701, 1603, 1481, 1449, 1337, 1311, 1280, 1293, 1252, 1206, 1157, 1108, 1070 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81 (d, *J* = 6.2 Hz, 1 H), 6.46 (dd, *J* = 6.2, 2.7 Hz, 1 H), 4.93 (dd, *J* = 4.7, 2.7 Hz, 1 H), 4.88 (d, *J* = 4.7 Hz, 1 H), 4.25 (dddd, *J* = 11.6, 4.2, 2.1, 2.1 Hz, 1 H), 4.04 (dd, *J* = 11.5, 2.6, 2.6 Hz, 1 H), 3.50 (br s, 1 H), 2.05–1.88 (m, 3 H), 1.52 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.9, 151.4, 140.2, 131.3, 82.8, 82.5, 70.6, 63.7, 58.8, 28.3, 25.9, 22.8.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{19}ClN_2O_4$ + Na (M + Na)$^+$: 337.0926; found: 337.0948.

***exo*-Diastereoisomer**
Mp >138 °C (dec.); R_f = 0.40 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3090, 3005, 2980, 2932, 2868, 1713, 1695, 1523, 1477, 1454, 1444, 1383, 1368, 1355, 1343, 1329, 1313, 1282, 1246, 1267, 1190, 1214, 1156, 1170, 1111, 1083 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.90 (d, *J* = 6.0 Hz, 1 H), 6.34 (dd, *J* = 6.0, 2.8 Hz, 1 H), 5.10 (dd, *J* = 2.8, 1.2 Hz, 1 H), 4.25 (d, *J* = 1.3 Hz, 1 H), 4.26–4.21 (m, 1 H), 4.16–4.10 (m, 1 H), 3.61 (dt, *J* = 15.5, 9.5 Hz, 1 H), 2.00 (m, 3 H), 1.51 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.0, 150.6, 141.9, 130.7, 82.2, 81.9, 70.6, 63.5, 57.8, 28.2, 25.0, 22.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{19}ClN_2O_4$ + Na (M + Na)$^+$: 337.0926; found: 337.0937.

***tert*-Butyl (±)-(1*R*,8*S*,9*S*,*Z*)-8-Ethyl-7-oxo-5-oxa-6,12-diazatricyclo[7.2.1.0^{1,6}]dodec-10-ene-12-carboxylate and *tert*-Butyl (±)-(1*R*,8*R*,9*S*,*Z*)-8-Ethyl-7-oxo-5-oxa-6,12-diazatricyclo[7.2.1.0^{1,6}]dodec-10-ene-12-carboxylate (Table 2, entry 7)**
Prepared in 57% yield (46 mg, 0.15 mmol) as a white solid from *tert*-butyl 2-{3-[*N*-2-bromobutyryl(aminooxy)]propyl}-1*H*-pyrrole-1-carboxylate (100 mg, 0.26 mmol) via the general procedure.

***endo*-Diastereoisomer**
Mp 131.1–134.3 °C; R_f = 0.48 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3088, 2974, 2860, 1739, 1707, 1694, 1454, 1346, 1289, 1245, 1163, 1102 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, *J* = 6.2 Hz, 1 H), 6.29 (dd, *J* = 6.2, 2.7 Hz, 1 H), 4.72 (dd, *J* = 4.4, 2.8 Hz, 1 H), 4.21 (dddd, *J* = 11.5, 4.0, 1.9, 1.9 Hz, 1 H), 4.02 (ddd, *J* = 11.6, 2.5, 2.5 Hz, 1 H), 3.6 (br s, 1 H), 3.00 (dt, *J* = 10.1, 4.4 Hz, 1 H), 2.11 (dddd, *J* = 15.4, 7.7, 4.7, 4.7 Hz, 1 H), 2.05–1.83 (m, 4 H), 1.51 (s, 9 H), 1.30–1.16 (m, 2 H), 1.03 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 152.0, 139.0, 131.7, 81.9, 81.5, 70.4, 61.0, 52.6, 28.4, 26.2, 23.2, 20.1, 11.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{24}N_2O_4$ + Na (M + Na)$^+$: 331.1628; found: 331.1632.

***exo*-Diastereoisomer**
Mp 127.5–129.9 °C; R_f = 0.35 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 2978, 2938, 2881, 1682, 1700, 1443, 1456, 1476, 1379, 1367, 1362, 1352, 1344, 1326, 1303, 1284, 1269, 1248, 1171, 1152, 1114, 1075 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (d, *J* = 6.0 Hz, 1 H), 6.36 (dd, *J* = 6.0, 2.8 Hz, 1 H), 4.84 (d, *J* = 2.8 Hz, 1 H), 4.25–4.19 (m, 1 H), 4.05 (ddd, *J* = 11.1, 3.3, 3.3 Hz, 1 H), 3.47 (td *J* = 12.7, 4.7 Hz, 1 H), 2.43 (dd, *J* = 10.0, 5.3 Hz, 1 H), 2.07–1.90 (m, 5 H), 1.73 (ddq, *J* = 14.5, 10.0, 7.3 Hz, 1 H), 1.50 (s, 9 H), 1.11 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.8, 150.9, 137.7, 134.3, 82.3, 81.3, 70.6, 59.3, 55.0, 28.3, 26.0, 24.4, 23.0, 12.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{24}N_2O_4$ (M + Na)$^+$: 331.1628; found: 331.1634.

(±)-(1*S*,13*S*,14*Z*)-12,12-Dimethyl-9,16-dioxa-10-azatetracyclo[11.2.1.0^{1,10}.0^{2,7}]hexadeca-2(7),3,5,14-tetraen-11-one (Table 2, entry 8)
Prepared in 71% yield (54 mg, 0.20 mmol) as a white solid from 1-{*O*-[*o*-(2-furyl)phenyl]methyloxyamino}-2-bromo-2-methylpropan-1-one (100 mg, 0.29 mmol) via the general procedure; mp 151.2–152.6 °C; R_f = 0.36 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3095, 2994, 2979, 2963, 2938, 2907, 2865, 1681, 1493, 1471, 1382, 1363, 1336, 1287, 1269, 1204, 1183, 1125, 1102, 1068 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 3 H), 7.14–7.12 (m, 1 H), 6.70 (d, *J* = 6.0 Hz, 1 H), 6.43 (dd, *J* = 5.7, 1.9 Hz, 1 H), 5.30 (dd, *J* = 14.3, 0.6 Hz, 1 H), 5.00 (d, *J* = 14.4 Hz, 1 H), 4.70 (d, *J* = 1.9 Hz, 1 H), 1.53 (s, 3 H), 1.15 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 138.9, 134.7, 134.0, 131.0, 128.8, 127.7, 126.1, 124.0, 95.8, 87.3, 71.6, 49.6, 26.9, 20.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}NO_3$ + Na (M + Na)$^+$: 280.0944; found: 280.0954.

(±)-(1*S*,12*S*,13*S*,14*Z*)-12-Ethyl-9,16-dioxa-10-azatetracyclo[11.2.1.0^{1,10}.0^{2,7}]hexadeca-2(7),3,5,14-tetraen-11-one (Table 2, entry 9)
Prepared in 63% yield (48 mg, 0.18 mmol) as a light brown oil from (±)-1-{*O*-[*o*-(2-furyl)phenyl]methyloxyamino}-2-bromobutan-1-one (100 mg, 0.29 mmol) via the general procedure; R_f = 0.54 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3215, 3071, 2966, 2931, 2876, 2851, 1689, 1590, 1496, 1456, 1360, 1331, 1279, 1249, 1219, 1202, 1158, 1118, 1102, 1072 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.35 (m, 3 H), 7.15–7.10 (m, 1 H), 6.64 (d, *J* = 5.7 Hz, 1 H), 6.56 (dd, *J* = 5.7, 1.9 Hz, 1 H), 5.30 (d, *J* = 14.3 Hz, 1 H), 5.02 (d, *J* = 1.9 Hz, 1 H), 5.00 (d, *J* = 14.3 Hz, 1 H), 2.44 (ddd, *J* = 8.7, 6.0, 0.8 Hz, 1 H), 2.06 (ddq, *J* = 13.6, 7.6, 6.0 Hz, 1 H), 1.92 (ddq, 13.7, 8.8, 7.4 Hz, 1 H), 1.10 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5, 138.0, 134.6, 133.8, 130.7, 129.0, 127.8, 126.2, 124.1, 95.8, 80.9, 76.7, 71.5, 52.8, 25.1, 12.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}NO_3$ + Na (M + Na)$^+$: 280.0944; found: 280.0966.

(±)-(1*S*,8*S*,9*R*,*Z*)-8-Ethyl-9-methyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one and (±)-(1*S*,8*R*,9*R*,*Z*)-8-Ethyl-9-methyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one (Table 2, entry 10)
Prepared in 67% yield (44 mg, 0.22 mmol) as a white solid from (±)-1-[*O*-3-(5-methyl-2-furyl)propyloxyamino]-2-bromobutan-1-one (100 mg, 0.33 mmol) via the general procedure.

***endo*-Diastereoisomer**
Mp 94.8–97.1 °C; R_f = 0.46 (3:7 hexanes–EtOAc).

FT-IR (ATR, neat): 3089, 2965, 2947, 2932, 2879, 2854, 1743, 1684, 1596, 1530, 1502, 1460, 1445, 1377, 1355, 1338, 1317, 1303, 1277, 1252, 1231, 1209, 1194, 1163, 1133, 1096 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.63 (d, *J* = 5.8 Hz, 1 H), 6.20 (d, *J* = 5.8 Hz, 1 H), 4.21 (dddd, *J* = 11.6, 4.0, 4.0, 1.2 Hz, 1 H), 3.92 (ddd, *J* = 11.7, 2.5, 2.5 Hz, 1 H), 2.79 (dd, *J* = 7.0, 3.7 Hz, 1 H), 2.07–1.95 (m, 4 H), 1.90–1.84 (m, 1 H), 1.78–1.68 (m, 1 H), 1.52 (s, 3 H), 1.04 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.3, 137.6, 135.6, 97.1, 87.8, 70.5, 58.3, 29.8, 23.6, 21.9, 19.2, 14.0.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}NO_3$ + Na (M + Na)$^+$: 246.1101; found: 246.1112.

***exo*-Diastereoisomer**
Mp 95.2–98.4 °C; R_f = 0.3 (3:7 hexanes–EtOAc).

FT-IR (ATR, neat): 3091, 2968, 2926, 2870, 2857, 1743, 1668, 1598, 1446, 1381, 1360, 1293, 1274, 1261, 1246, 1226, 1217, 1189, 1159, 1137, 1099 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.64 (d, *J* = 5.7 Hz, 1 H), 6.24 (d, *J* = 5.7 Hz, 1 H), 4.21 (br dd, *J* = 12.0, 5 Hz, 1 H), 3.92 (ddd, *J* = 11.6, 2.1, 2.1 Hz, 1 H), 2.39 (dd, *J* = 8.7, 5.1 Hz, 1 H), 2.10–1.77 (m, 6 H), 1.42 (s, 3 H), 1.08 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.7, 139.8, 134.8, 97.7, 86.2, 70.4, 56.2, 29.2, 23.7, 21.7, 18.7, 12.3.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}NO_3$ + Na (M + Na)$^+$: 246.1101; found: 246.1121.

(±)-(1*S*,2*S*,9*R*,*Z*)-2,8,8,9-Tetramethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one and (±)-(1*S*,2*R*,9*R*,*Z*)-2,8,8,9-Tetramethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one (Table 2, entry 11)

Prepared in 91% yield (66 mg, 0.30 mmol) as a white solid from (±)-1-[*O*-3-(5-methyl-2-furyl)butyloxyamino]-2-bromo-2-methylpropan-1-one (100 mg, 0.33 mmol) via the general procedure.

(±)-(1*S*,2*S*,9*R*,*Z*)-2,8,8,9-Tetramethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one

Mp 123.9–126.8 °C; R_f = 0.54 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3091, 2973, 2940, 2869, 1678, 1598, 1468, 1440, 1368, 1286, 1327, 1255, 1227, 1155, 1120 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.59 (d, *J* = 5.9 Hz, 1 H), 6.28 (dd, *J* = 6.0, 0.9 Hz, 1 H), 4.17 (ddd, *J* = 11.6, 4.7, 1.5 Hz, 1 H), 3.96 (ddd, *J* = 14.0, 11.8, 4.7, 2.3 Hz, 1 H), 2.26–2.12 (m, 1 H), 1.62 (ddd, *J* = 13.3, 4.3, 2.0 Hz, 1 H), 1.87–1.80 (m, 1 H), 1.78–1.65 (m, 1 H), 1.40 (d, *J* = 1.1 Hz, 6 H), 1.10 (s, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.4, 139.6, 133.5, 101.0, 88.8, 70.3, 52.7, 33.8, 32.2, 23.3, 20.16, 16.4, 14.9.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}NO_3$ + Na (M + Na)$^+$: 260.1257; found: 260.1260.

(±)-(1*S*,2*R*,9*R*,*Z*)-2,8,8,9-Tetramethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one

Mp 120.0–124.1 °C; R_f = 0.54 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 2972, 2938, 2875, 2360, 2340, 1677, 1465, 1439, 1369, 1328, 1289, 1255, 1121 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.70 (d, *J* = 5.8 Hz, 1 H), 6.27 (d, *J* = 5.8 Hz, 1 H), 4.20–4.15 (m, 1 H), 4.04–4.00 (m, 1 H), 2.25–2.14 (m, 2 H), 1.38 (s, 6 H), 1.09 (s, 3 H), 1.09 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.2, 139.0, 136.6, 99.4, 88.9, 65.8, 53.4, 52.6, 52.6, 31.1, 30.4, 23.2, 16.6, 12.5.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{19}NO_3$ + Na (M + Na)$^+$: 260.1257; found: 260.1283.

(±)-(1*S*,8*S*,*Z*)-7,7-Dimethyl-4,11-dioxa-5-azatricyclo[6.2.1.0^{1,5}]undec-9-en-6-one (Table 3, entry 2)

Prepared in 82% yield (57 mg, 0.29 mmol) as a white solid from (±)-1-[*O*-2-(2-furyl)ethyloxyamino]-2-bromo-2-methylpropan-1-one (100 mg, 0.36 mmol) via the general procedure; mp 110.9–112.1 °C; R_f = 0.44 (2:8 hexanes–EtOAc).

FT-IR (ATR, neat): 3081, 2979, 2894, 1662, 1595, 1472, 1460, 1436, 1390, 1371, 1362, 1332, 1319, 1305, 1287, 1225, 1210, 1148, 1183, 1112, 1085 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.51 (dd, *J* = 5.7, 2.0 Hz, 1 H), 6.44 (d, *J* = 5.7 Hz, 1 H), 4.56 (d, *J* = 2.0 Hz, 1 H), 4.25 (ddd, *J* = 8.3, 7.3, 6.7 Hz, 1 H), 4.18 (ddd, *J* = 8.6, 8.3, 6.7 Hz, 1 H), 2.69 (ddd, *J* = 13.2, 9.0, 7.4 Hz, 1 H), 2.64 (ddd, *J* = 13.2, 6.6, 3.8 Hz, 1 H), 1.46 (s, 3 H), 1.12 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.1, 135.3, 134.7, 99.1, 88.0, 68.9, 47.3, 34.6, 27.1, 20.5.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{13}NO_3$ + Na (M + Na)$^+$: 218.0788; found: 218.0807.

(±)-(1*S*,7*S*,8*S*,*Z*)-7-Chloro-4,11-dioxa-5-azatricyclo[6.2.1.0^{1,5}]undec-9-en-6-one and (±)-(1*S*,7*R*,8*S*,*Z*)-7-Chloro-4,11-dioxa-5-azatricyclo[6.2.1.0^{1,5}]undec-9-en-6-one (Table 3, entry 3)

Prepared in 91% yield (84 mg, 0.38 mmol) as a white solid from 1-[*O*-2-(2-furyl)ethyloxyamino]-2,2-dichloroethan-1-one (100 mg, 0.42 mmol) via the general procedure.

***endo*-Diastereoisomer**

Mp 134.2–137.3 °C; R_f = 0.67 (2:8 hexanes–EtOAc).

FT-IR (ATR, neat): 3115, 3010, 2966, 2901, 1678, 1601, 1469, 1431, 1378, 1334, 1323, 1307, 1291, 1205, 1248, 1225, 1147, 1108, 1077 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.57 (d, *J* = 5.7 Hz, 1 H), 6.53 (dd, *J* = 5.7, 2.0 Hz, 1 H), 5.14 (d, *J* = 2.0 Hz, 1 H), 4.34–4.26 (m, 2 H), 4.22 (s, 1 H), 2.78–2.74 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 136.0, 134.1, 100.0, 81.3, 69.6, 54.0, 34.5.

HRMS (ESI): *m*/*z* calcd for $C_8H_8ClNO_3$ + Na (M + Na)$^+$: 224.0085; found: 224.0072.

***exo*-Diastereoisomer**

Mp 132.8–133.6 °C; R_f = 0.58 (2:8 hexanes–EtOAc).

FT-IR (ATR, neat): 3081, 2979, 2894, 1662, 1595, 1472, 1436, 1371, 1362, 1332, 1319, 1305, 1287, 1225, 1210, 1148, 1112, 1085 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.68 (dd, *J* = 5.7, 1.9 Hz, 1 H), 6.54 (d, *J* = 5.7 Hz, 1 H), 5.18 (dd, *J* = 6.1, 2.0 Hz, 1 H), 4.65 (d, *J* = 6.1 Hz, 1 H), 4.32 (ddd, *J* = 8.4, 7.5, 3.2 Hz, 1 H), 4.21 (ddd, *J* = 9.6, 8.4, 6.4 Hz, 1 H), 2.77 (ddd, *J* = 13.5, 9.6, 7.5 Hz, 1 H), 2.67 (ddd, *J* = 13.6, 6.4, 3.2 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.7, 137.77, 132.7, 99.9, 86.1, 69.5, 55.3, 34.0.

HRMS (ESI): *m*/*z* calcd for $C_8H_8ClNO_3$ + Na (M + Na)$^+$: 224.0085; found: 224.0092.

(±)-(1*S*,7*R*,8*S*,*Z*)-7-Ethyl-4,11-dioxa-5-azatricyclo[6.2.1.0^{1,5}]undec-9-en-6-one and (1*S*,7*S*,8*S*,*Z*)-7-Ethyl-4,11-dioxa-5-azatricyclo[6.2.1.0^{1,5}]undec-9-en-6-one (Table 3, entry 4)

Prepared in 85% yield (63 mg, 0.32 mmol) as a white solid from (±)-1-[*O*-2-(2-furyl)ethyloxyamino]-2-bromobutan-1-one (100 mg, 0.36 mmol) via the general procedure.

***endo*-Diastereoisomer**

Mp 108.9–111.2 °C, R_f = 0.37 (2:8 hexanes–EtOAc).

FT-IR (ATR, neat): 3080, 2963, 2877, 2340, 2360, 1662, 1463, 1436, 1364, 1229, 1148, 1115 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.51 (dd, *J* = 5.7, 2.0 Hz, 1 H), 6.36 (d, *J* = 5.7 Hz, 1 H), 4.82 (d, *J* = 2.0 Hz, 1 H), 4.23 (ddd, *J* = 8.4, 7.3, 3.7 Hz, 1 H), 4.17 (ddd, *J* = 8.3, 7.4, 3.8 Hz, 1 H), 2.71 (ddd, *J* = 13.2, 9.5, 7.5 Hz, 1 H), 2.64 (ddd, *J* = 13.1, 6.5, 3.7 Hz, 1 H), 2.29 (dd, *J* = 8.4, 4.1 Hz, 1 H), 2.05 (dddd, *J* = 14.8, 7.6, 7.6, 7.6, 4.0 Hz, 2 H), 1.93–1.83 (m, 2 H), 1.05 (t, *J* = 7.5 Hz, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.1, 136.0, 134.2, 99.3, 81.7, 68.9, 48.8, 34.7, 23.90, 11.3.

***exo*-Diastereoisomer**

Mp 106.1–110.3 °C; R_f = 0.37.

FT-IR (ATR, neat): 3078, 2963, 2935, 2877, 1664, 1595, 1464, 1436, 1364, 1340, 1326, 1308, 1295, 1228, 1148, 1083, 1049, 1028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.53 (dd, *J* = 5.8, 2.0 Hz, 1 H), 6.43 (d, *J* = 5.8 Hz, 1 H), 5.01 (dd *J* = 6.3, 1.9 Hz, 1 H), 4.23 (m, 1 H), 4.17 (m, 1 H), 2.94 (ddd, *J* = 11.1, 6.2, 2.94 Hz, 1 H), 2.71 (m, 1 H), 1.92 (m, 1 H), 1.38 (m, 1 H), 1.04 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.6, 135.4, 134.4, 105.0, 99.5, 80.9, 69.0, 51.0, 35.1, 21.5, 12.2.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{14}NO_3$ (M + H)$^+$: 196.0968; found: 196.0960.

(±)-(1*S*,10*S*,*Z*)-9,9-Dimethyl-6,13-dioxa-7-azatricyclo[8.2.1.0^{1,7}]tridec-11-en-8-one (Table 3, entry 5)
Prepared in 51% yield (37 mg, 0.17 mmol) from (±)-1-[*O*-4-(2-furyl)butyloxyamino]-2-bromo-2-methylpropan-1-one (100 mg, 0.33 mmol) via the general procedure; white solid; mp 96.1–98.7 °C; R_f = 0.38 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3097, 3086, 2984, 2974, 2958, 2928, 2866, 1672, 1596, 1506, 1472, 1449, 1436,1383, 1373, 1359, 1343, 1329, 1290, 1281, 1262, 1221, 1202, 1144, 1117, 1077 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.47 (dt, *J* = 5.8, 0.6 Hz, 1 H), 6.36 (dd, *J* = 5.8, 1.8 Hz, 1 H), 4.49 (d, *J* = 1.8 Hz, 1 H), 4.33 (dddd, *J* = 12.5, 4.2, 3.5, 1.3 Hz, 1 H), 3.79–3.72 (m, 1 H), 2.26 (ddd, *J* = 15.1, 11.3, 1.1 Hz, 1 H), 2.12 (dddd, *J* = 15.2, 7.4, 1.3, 0.6 Hz, 1 H), 2.05–1.92 (m, 1 H), 1.92–1.83 (m, 1 H), 1.83–1.76 (m, 2 H), 1.49 (s, 3 H), 1.05 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.8, 138.6, 133.7, 101.2, 87.6, 78.4, 48.2, 34.5, 31.3, 27.2, 21.7, 19.5.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{18}NO_3$ (M + H)$^+$: 224.1281; found: 224.1279.

(±)-(1*S*,9*S*,10*S*,*Z*)-9-Chloro-6,13-dioxa-7-azatricyclo[8.2.1.0^{1,7}]tridec-11-en-8-one and (±)-(1*S*,9*R*,10*S*,*Z*)-9-Chloro-6,13-dioxa-7-azatricyclo[8.2.1.0^{1,7}]tridec-11-en-8-one (Table 3, entry 6)
Prepared in 38% yield (32 mg, 0.14 mmol) as a white sticky liquid from 1-[*O*-4-(2-furyl)butyloxyamino]-2,2-dichloroethan-1-one (100 mg, 0.38 mmol) via the general procedure.

***endo*-Diastereoisomer**
R_f = 0.58 (4:6 hexanes–EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.56 (d, *J* = 5.8 Hz, 1 H), 6.48 (dd, *J* = 5.8, 1.8 Hz, 1 H), 5.14 (dd, *J* = 5.4, 1.8 Hz, 1 H), 4.76 (d, *J* = 5.4 Hz, 1 H), 4.38 (ddd, *J* = 12.6, 3.2, 1.2 Hz, 1 H), 3.86–3.22 (m, 1 H), 2.28 (ddd, *J* = 15.3, 10.7, 1.8 Hz, 1 H), 2.17 (ddd, *J* = 15.4, 6.8, 2.2 Hz, 1 H), 1.99–1.79 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.2, 139.8, 132.3, 102.2, 82.0, 78.8, 56.2, 34.2, 31.2, 21.5.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{12}ClNO_3$ + Na (M + Na)$^+$: 252.0398; found: 252.0401.

***exo*-Diastereoisomer**
R_f = 0.46 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat; characterized as a mixture): 2938, 2864, 1693, 1595, 1439, 1380, 1346, 1327, 1283, 1270, 1249, 1221, 1201, 1143, 1125, 1078 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (d, *J* = 5.7 Hz, 1 H), 6.31 (dd, *J* = 5.7, 2.0 Hz, 1 H), 5.03 (d, *J* = 2.0 Hz, 1 H), 4.40 (dddd, *J* = 12.5, 6.8, 1.7, 1.7 Hz, 1 H), 4.13 (s, 1 H), 3.85 (m, 1 H), 2.30 (ddd, *J* = 15.2, 11.0, 1.8 Hz, 1 H), 2.21 (m, 1 H), 2.13–2.00 (m, 1 H), 1.98–1.79 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.1, 141.2, 130.5, 101.8, 84.4, 79.0, 56.0, 33.8, 31.2, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{12}ClNO_3$ + Na (M + Na)$^+$: 252.0398; found: 252.0402.

(±)-(1*S*,9*S*,10*S*,*Z*)-9-Ethyl-6,13-dioxa-7-azatricyclo[8.2.1.0^{1,7}]tridec-11-en-8-one and (±)-(1*S*,9*R*,10*S*,*Z*)-9-Ethyl-6,13-dioxa-7-azatricyclo[8.2.1.0^{1,7}]tridec-11-en-8-one (Table 3, entry 7)
Prepared in 67% yield (49 mg, 0.22 mmol) as a white solid from 1-[*O*-4-(2-furyl)butyloxyamino]-2-bromobutan-1-one (100 mg, 0.33 mmol) via the general procedure.

***endo*-Diastereoisomer**
Mp 78.5–81.2 °C; R_f = 0.56 (3:7 hexanes–EtOAc).

FT-IR (ATR, neat): 3080, 2935, 2875, 1678, 1594, 1452, 1439, 1380, 1346, 1304, 1276, 1261, 1220, 1201, 1147, 1130, 1111, 1076 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.47 (d, *J* = 5.8 Hz, 1 H), 6.32 (dd, *J* = 5.8, 1.7 Hz, 1 H), 4.98 (dd, *J* = 5.3, 1.7 Hz, 1 H), 4.33 (ddd, *J* = 11.9, 3.5, 3.5 Hz, 1 H), 3.80 (ddd, *J* = 12.4, 8.8, 5.9 Hz, 1 H), 2.96 (ddd, *J* = 10.4, 5.1, 5.1 Hz, 1 H), 2.26 (ddd, *J* = 15.0, 11.0, 1.6 Hz, 1 H), 2.13 (ddd, *J* = 15.1, 7.2, 1.6 Hz, 1 H), 2.08–1.91 (m, 2 H), 1.89–1.84 (m, 1 H), 1.81–1.76 (m, 2 H), 1.27–1.15 (m, 1 H), 1.03 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.9, 139.1, 132.7, 100.93, 81.4, 78.4, 51.0, 34.5, 31.3, 21.1, 19.4, 12.1.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}NO_3$ + Na (M + Na)$^+$: 246.1101; found: 246.1108.

***exo*-Diastereoisomer**
Mp 75.2–76.9 °C; R_f = 0.42 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3082, 2963, 2932, 2874, 1662, 1595, 1456, 1439, 1381, 1346, 1331, 1304, 1277, 1245, 1222, 1202, 1145, 1128, 1075 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.40 (d, *J* = 5.8 Hz, 1 H), 6.31 (dd, *J* = 5.7, 1.9 Hz, 1 H), 4.80 (d, *J* = 1.9 Hz, 1 H), 4.36 (dddd, *J* = 12.6, 3.7, 3.7, 1.3 Hz, 1 H), 3.78–3.71 (m, 1 H), 2.28 (ddd, *J* = 15.5, 11.2, 1.5 Hz, 1 H), 2.25 (dd, *J* = 8.6, 5.0 Hz, 2 H), 2.15 (ddd, *J* = 15.1, 7.2, 1.5 Hz, 2 H), 2.04–1.90 (m, 4 H), 1.81 (ddd, *J* = 9.9, 4.6, 4.2 Hz, 3 H), 1.09 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.4, 137.5, 133.9, 101.1, 81.2, 78.6, 51.01, 34.40, 31.40, 25.09, 21.71, 11.75.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}NO_3$ + Na (M + Na)$^+$: 246.1101; found: 246.1105.

(±)-2-Ethyl-5,14-dioxa-4-azabicyclo[9.2.1]tetradeca-1(13),11-dien-3-one (Table 3, entry 8; 13b)
Prepared in 50% yield (38 mg, 0.0.16 mmol) as a white solid from 1-[*O*-5-(2-furyl)pentyloxyamino]-2-bromobutan-1-one (100 mg, 0.31 mmol) via the general procedure; mp 122.2–124.5 °C; R_f = 0.52 (2:8 hexanes–EtOAc).

FT-IR (ATR, neat): 3176, 3022, 2960, 2922, 2864, 2353, 2322, 1686, 1655, 1552, 1457, 1225, 1189, 1072 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 6.11 (d, *J* = 3.0 Hz, 1 H), 5.95 (d, *J* = 3.1 Hz, 1 H), 4.00 (br s, 1 H), 3.84 (br s, 1 H), 3.45 (br s, 1 H), 2.67 (ddd, *J* = 21.5, 8.0, 4.0 Hz, 2 H), 2.15–1.97 (m, 1 H), 1.87 (m, 1 H), 1.77–1.76 (m, 1 H), 1.64–1.60 (m, 1 H), 1.48–1.45 (m, 2 H), 1.26–1.19 (m, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, CD_3OD): δ = 171.5, 157.5, 153.6, 109.0, 107.9, 48.1, 28.9, 27.0, 26.7, 26.5, 22.2, 13.07, 13.1.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{20}NO_3$ (M + H)$^+$: 238.1438; found: 238.1436.

(±)-(1*S*,11*S*,*Z*)-2-Ethyl-5,14-dioxa-4-azabicyclo[9.2.1]tetradec-12-en-3-one (13a)
To a solution of (±)-(1*S*,9*S*,10*S*,*Z*)-9-ethyl-6.13-dioxa-7-azatricyclo[8.2.1.0^{1,7}]tridec-11-en-8-one (8.0 mg, 0.04 mmol) in $CDCl_3$ (0.4 mL) was added pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol) and the NMR tube was tightly sealed. The reaction mixture was heated at 75 °C and monitored to completion by NMR analysis. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (1:9 to 4:1 hexanes–EtOAc) to provide **13b** with quantitative yield (8.0 mg, 0.04 mmol) as a white solid; mp 157.4–158.5 °C; R_f = 0.54 (4:6 hexanes–EtOAc).

FT-IR (ATR, neat): 3157, 2952, 2929, 2881, 1657, 1612, 1545, 1492, 1467, 1448, 1376, 1261, 1158, 1088 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 6.14 (d, *J* = 3.0 Hz, 1 H), 5.97 (d, *J* = 2.9 Hz, 1 H), 3.78 (t, *J* = 7.2 Hz, 2 H), 3.06 (br s,

1 H), 2.76–2.64 (m, 2 H), 2.43 (br s, 1 H), 2.21–2.08 (m, 1 H), 2.07–1.96 (m, 1 H), 1.94–1.72 (m, 3 H), 1.02 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.6, 155.1, 150.0, 108.0, 106.3, 77.91, 46.9, 27.4, 26.8, 26.0, 21.6, 12.1.

HRMS (ESI): m/z calcd for $C_{12}H_{17}NO_3$ + Na $(M + Na)^+$: 246.1101; found: 246.1079.

(±)-(1*S*,9*R*,10*S*,12*S*)-8,8-Dimethyl-5,11,13-trioxa-6-azatetracyclo[7.3.1.0^{1,6}.0^{10,12}]tridecan-7-one (15)

To a solution of **14** (50 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was added *m*-CPBA (82 mg, 0.48 mmol) and the reaction mixture was stirred for 3 d. The complete consumption of **14** was confirmed by TLC (1:1 hexanes–EtOAc). The white precipitate was filtered, the filtrate was washed with aq $NaHCO_3$ (5 mL) and brine (5 mL), and then the organic layer was dried (Na_2SO_4). The volatiles were removed under reduced pressure and purified by flash column chromatography (4:1 to 3:2 hexanes–EtOAc) to afford the product **15** in 93% yield as a white solid (50.2 mg, 0.22 mmol); mp 177.1–179.6 °C; R_f = 0.57 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3062, 2980, 2928, 2868, 2361, 2339, 1675, 1492, 1474, 1438, 1396, 1386, 1366, 1349, 1321, 1280, 1266, 1237, 1217, 1175, 1160, 1149, 1129, 1097 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.24 (dddd, J = 11.6, 4.6, 4.6, 1.6 Hz, 1 H), 4.12 (d, J = 3.0 Hz, 1 H), 4.0 (s, 1 H), 3.88 (ddd, J = 11.7, 11.7, 2.2 Hz, 1 H), 3.71 (d, J = 3.0 Hz, 1 H), 2.17–2.13 (m, 1 H), 2.11–1.98 (m, 2 H), 1.93–1.88 (m, 1 H), 1.42 (s, 3 H), 1.21 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.4, 92.2, 79.5, 70.8, 54.2, 51.3, 46.3, 26.8, 26.0, 23.0, 19.3.

HRMS (ESI): m/z calcd for $C_{11}H_{15}NO_4$ + Na $(M + Na)^+$: 248.0893; found: 248.0888.

(±)-(1*S*,9*R*,10*S*,11*S*)-10,11-Dihydroxy-8,8-dimethyl-5.12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodecan-7-one (16)

To a solution **14** (100 mg, 0.48 mmol) in MeCN–H_2O–acetone (1 mL:1 mL:2 mL) was added NMO (112 mg, 0.98 mmol) and OsO_4 (0.65 mL, 1% in H_2O), and the mixture was stirred at r.t. for overnight. The complete consumption of **14** was confirmed by TLC (1:1 hexanes–EtOAc). To the reaction mixture was added $NaHSO_3$ (0.50 g) and stirred for 1 h. The mixture was filtered and the filtrate was neutralized to pH 7 with aq 1 N H_2SO_4 and the solvents were removed by rotary evaporation and the pH was further adjusted to 2. The solution was extracted with EtOAc (100 mL), the organic layer dried (Na_2SO_4), and concentrated under rotary vapor to obtain product **16** in 92% yield as a pale yellow crystalline solid (107 mg, 0.44 mmol); mp 151.2–153.3 °C; R_f = 0.5 (1:9 MeOH–$CHCl_3$).

FT-IR (ATR, neat): 3364, 2964, 2948, 2925, 2874, 2852, 1650, 1453, 1441, 1387, 1362, 1333, 1314, 1282, 1269, 1238, 1223, 1157, 1124, 1092 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.43 (t, J = 6.1 Hz, 1 H), 4.36 (t, J = 6.5 Hz, 1 H), 4.18 (dddd, J = 11.3, 4.7, 4.7, 1.6 Hz, 1 H), 3.87 (s, 1 H), 3.85 (ddd, J = 12.0, 2.3 Hz, 1 H), 3.44 (d, J = 6.8 Hz, 1 H), 3.26 (d, J = 6.0 Hz, 1 H), 2.41–2.37 (m, 1 H), 1.98 (dddd, J = 12.4, 4.5, 4.5, 3.4 Hz, 1 H), 1.87 (dd, J = 13.0, 4.5 Hz, 1 H), 1.80 (dtd, J = 11.5, 4.2, 2.1 Hz, 1 H), 1.40 (s, 3 H), 1.20 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.6, 98.2, 89.9, 72.1, 71.2, 71.1, 44.7, 27.0, 25.5, 22.7, 19.8.

HRMS (ESI): m/z calcd for $C_{11}H_{18}NO_5$ $(M + H)^+$: 244.1179; found: 244.1161.

(±)-(1*S*,9*S*,*Z*)-8,8-Dimethyl-5,12-dioxa-6-azatricyclo[7.2.1.0^{1,6}]dodec-10-en-7-one (17)

To a solution of **14** (50 mg, 0.24 mmol) in EtOAc (2 mL) was added 10% Pd/C (15 mg) and evacuated with house vacuum (water aspirator) and flushed with H_2 gas through a balloon. The reaction mixture was stirred under H_2 gas balloon at r.t. for 5 h. The complete consumption of **14** was confirmed by TLC (1:1 hexanes–EtOAc). The mixture was passed through a Celite bed and washed with EtOAc (20 mL). The collected filtrate was concentrated under reduced pressure. Purification by flash column chromatography (4:1 to 3:2 hexanes–EtOAc) afforded the product **17** in 86% yield as a white solid (21 mg, 0.20 mmol); mp 57.1–59.7 °C; R_f = 0.60 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 2957, 2982, 2937, 2865, 1679, 1459, 1447, 1387, 1358, 1311, 1290, 1273, 1249, 1214, 1194, 1155, 1126, 1080 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.20 (dddd, J = 11.4, 4.6, 4.6, 1.7 Hz, 1 H), 4.07 (dd, J = 7.9, 1.5 Hz, 1 H), 3.85 (ddd, J = 11.6, 2.7 Hz, 1 H), 2.61 (ddd, J = 9.5, 3.8, 3.8 Hz, 1 H), 2.17–2.08 (m, 1 H), 2.02–1.78 (m, 2 H), 1.67 (ddd, J = 12.3, 5.9 Hz, 1 H), 1.40 (s, 1 H), 1.10 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.2, 97.0, 83.0, 71.1, 46.9, 33.3, 31.0, 27.1, 24.5, 23.7, 20.2.

HRMS (ESI): m/z calcd for $C_{11}H_{17}NO_3$ + K $(M + K)^+$: 250.0840; found: 250.0856.

(±)-2-[5-(3-Hydroxypropyl)-2-furyl]-2-methylpropionamide (18)

Prepared in 96% yield (61 mg, 0.23 mmol) as a white solid from **14** (50 mg, 0.24 mmol) via general procedure E (Supporting Information); mp 90.2–92.9 °C; R_f = 0.50 (2:8 hexanes–EtOAc).

FT-IR (ATR, neat): 3391, 3286, 3190, 2985, 2937, 2891, 1651, 1619, 1557, 1478, 1463, 1446, 1400, 1366, 1344, 1324, 1256, 1237, 1215, 1179 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.11 (d, J = 3.2 Hz, 1 H), 6.02–5.92 (m, 1 H), 5.58 (s, 1 H), 5.33 (s, 1 H), 3.70 (t, J = 6.2 Hz, 2 H), 2.73 (t, J = 7.4 Hz, 2 H), 1.95–1.83 (m, 2 H), 1.53 (s, 7 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.7, 156.3, 155.4, 106.4, 105.7, 62.0, 43.5, 31.0, 24.6, 24.5.

HRMS (ESI): m/z calcd for $C_{11}H_{17}NO_3$ + Na $(M + Na)^+$: 234.1101; found: 234.1093.

(*Z*)-3-Hydroxy-2,2-dimethyl-5-(3,4,5,6-tetrahydropyrid-2-yl)penten-4-al (19)

To a solution **14** (50 mg, 0.24 mmol) in anhyd Et_2O (1.5 mL) was added a solution of $LiAlH_4$ (2 M solution in THF, 0.12 mL, 0.26 mmol) at 0 °C and the reaction at room temperature was stirred for 1 h. The complete consumption of **14** was confirmed by TLC (1:1 hexanes–EtOAc). The crude product was purified by flash column chromatography (3:2 to 1:1 hexanes–EtOAc) to provide the product **19** in 68% yield as a pale yellow oil (34 mg, 0.16 mmol); R_f = 0.45 (1:1 hexanes–EtOAc).

FT-IR (ATR, neat): 3327, 2971, 2928, 1717, 1465, 1364, 1053 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.94 (dd, J = 11.8, 7.2 Hz, 1 H), 5.86 (ddt, J = 11.8, 1.2, 0.6, 0.6 Hz, 1 H), 4.48 (d, J = 7.2 Hz, 1 H), 4.09–4.04 (m, 1 H), 3.99–3.94 (m, 1 H), 2.27 (ddd, J = 11.8, 1.2, 0.6 Hz, 2 H), 2.05–1.85 (m, 2 H), 1.14 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 206.2, 154.8, 135.4, 128.5, 71.0, 65.8, 49.6, 23.85, 19.1, 18.9, 16.9.

HRMS (ESI): m/z calcd for $C_{11}H_{18}NO_3$ $(M + H)^+$: 212.1281; found: 212.1302.

(±)-(1*S*,9*R*,10*S*,14*S*)-8,8,12,12-Tetramethyl-5,11,13,15-tetroxa-6-azatetracyclo[7.5.1.0^{1,6}.0^{10,14}]pentadecan-7-one (20)

To a solution **16** (80 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) were added camphorsulfonic acid (1 mg, 2 mol%) and 2,2-dimethoxypropane (0.06 mL, 0.49 mmol) and the mixture was stirred at r.t. for 2 h. The complete consumption of **16** was confirmed by TLC (1:1 hexanes–EtOAc). To the reaction mixture was added sat. aq $NaHCO_3$ (1 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under

reduced pressure to obtain product **20** in 97% yield as a white solid (102 mg, 0.32 mmol); mp 188.0–192.0 °C; R_f = 0.68 (1:9 MeOH–$CHCl_3$).

FT-IR (ATR, neat): 2987, 2960, 2942, 2873, 1680, 1475, 1456, 1444, 1389, 1359, 1325, 1379, 1295, 1277, 1266, 1233, 1208, 1255, 1093, 1167, 1147 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (s, 1 H), 4.80 (d, *J* = 7.2 Hz, 1 H), 4.79 (d, *J* = 7.2 Hz, 1 H), 4.20 (dddd, *J* = 11.5, 4.6, 1.6, 1.6 Hz, 1 H), 3.95 (s, 1 H), 3.84 (td, *J* = 11.6, 2.6 Hz, 1 H), 2.34–2.32 (m, 1 H), 2.32–2.30 (m, 1 H), 1.99–1.84 (m, 1 H), 1.82–1.77 (m, 1 H), 1.49 (s, 3 H), 1.42 (s, 3 H), 1.33 (s, 3 H), 1.20 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.6, 112.9, 97.1, 87.2, 80.7, 80.1, 70.9, 44.1, 27.2, 26.0, 25.3, 25.1, 22.8, 19.8.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{21}NO_5$ + Na $(M + Na)^+$: 306.1312; found: 306.1308.

(±)-(1*R*,2*S*,6*S*,7*S*)-7-(3-Hydroxypropyl)-4,4,10,10-tetramethyl-3,5,11-trioxa-8-azatricyclo[5.3.1.$0^{2,6}$]undecan-9-one (21)
Prepared in 88% yield (46 mg, 0.16 mmol) as a white solid from **20** (52 mg, 0.18 mmol) via general procedure E (Supporting Information); mp 167.7–170.0 °C; R_f = 0.50 (1: 9 MeOH–$CHCl_3$).

FT-IR (ATR, neat): 3380, 3199, 3084, 2982, 2957, 2937, 2869, 1644, 1451, 1402, 1476, 1369, 1317, 1273, 1342, 1231, 1192, 1154, 1104, 1081 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 4.84 (d, *J* = 5.6 Hz, 1 H), 4.48 (d, *J* = 5.6 Hz, 1 H), 3.98 (s, 1 H), 3.70 (t, *J* = 8.2 Hz, 2 H), 2.84 (s, 1 H), 2.06 (m, 1 H), 1.94 (m, 1 H), 1.86–1.73 (m, 2 H), 1.48 (s, 3 H), 1.35 (s, 3 H), 1.31 (s, 3 H), 1.18 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.0, 112.8, 93.4, 88.2, 86.0, 79.8, 61.9, 40.8, 28.0, 27.2, 26.2, 25.6, 25.2, 19.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{23}NO_5$ + Na $(M + Na)^+$: 308.1468; found: 308.1478.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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