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Synthesis of *cis*-Octahydroindoles via Intramolecular 1,3-Dipolar Cycloaddition of 2-Acyl-5-aminooxazolium Salts

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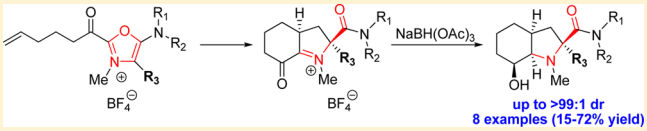
Supporting Information

ABSTRACT: A concise method for the diastereoselective synthesis of octahydroindoles is presented. The products contain 2-amido and 7-hydroxyl substituents. A series of 2-acyl-5-aminooxazoles were prepared in one step. Upon methylation of the oxazole nitrogen atom, the substrates underwent rapid intramolecular 1,3-dipolar cycloaddition with a tethered alkene and, after reduction with excess hydride, produced octahydroindoles with excellent diastereoselectivity. The method allows for the installation of α-quaternary stereogenic carbon atoms.



The prevalence of *cis*-octahydroindoles (OHIs) in biologically active natural products and constrained peptides has stimulated interest in synthetic methods for their construction.[1−11] The intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylides with alkenes provides a straightforward route to this valuable structural motif.[12,13] A variety of precursor compounds have been employed to generate the reactive azomethine ylide intermediate for intramolecular reactions.[12] Among them, azolium salts are valuable for their ease of preparation and mild reaction conditions in generation of the ylide. Nonetheless, methods introducing novel substitution patterns and functionality such as amides and quaternary stereogenic carbons remain underexplored. Efficient access to OHI ring systems would be advantageous to structure−activity studies of the medicinal properties of OHI analogues as well as applications to natural products synthesis. Herein we report a rapid diastereoselective preparation of *cis*-octahydroindoles, containing 2-amido and 7-hydroxyl substituents. 2-Amido-substituted OHIs are a common structural feature in the *aeruginosin* family of thrombin inhibitors,[6] whereas 7-hydroxyl substitution is found in such natural products as gliotoxin and epicoccin G.[14] This method also allows for synthesis of octahydroindoles containing α-quaternary stereogenic carbon atoms, a desirable aspect of various peptidomimetic compounds.[15]

During an investigation into the reactivity of oxazolium salts, we discovered that 2-acyl-5-aminooxazole **1a** underwent facile intramolecular 1,3-dipolar cycloaddition upon methylation of the oxazole nitrogen atom with methyl triflate (Scheme 1). The resultant iminium salt **2** was detected in the ^{1}H NMR spectrum of the crude reaction mixture as a single diastereomer (representative ^{1}H NMR shifts ($CDCl_3$): δ 5.28 (1H, dd, J = 10, 5.6 Hz, C2−H), 4.10 (1H, m, C3a-H), 3.44 (3H, s, $=NCH_3$).[16] Addition of excess sodium borohydride led to octahydroindole **3a** as a ∼3:1 mixture of diastereomers, differing at the configuration of the 7-hydroxyl group and containing a tertiary amide at the 2-position.

We found no examples in the literature of intramolecular 1,3-dipolar cycloadditions of aminooxazolium salts with alkenes. The related munchnone imines, a class of mesoionic compounds derived from Reissert salts, have been well studied by McEwen.[17] Munchnone imines are known to undergo intramolecular 1,3-dipolar cycloaddition with alkynes to produce fused-ring pyrroles as well as intermolecular reaction with alkenes to form pyridones.[18] A plausible mechanism for the cyclization observed in our study, shown in Scheme 2, is initiated by methylation of the oxazole nitrogen atom of **1a**, followed by resonance of the 5-amino lone pair electrons to produce a transient 1,3-dipole that is trapped by reaction with the alkene. Rearrangement of the cycloadduct leads to the observed iminium salt **2**.

The cycloaddition reaction could be initiated by methylation of the oxazole nitrogen by addition of 1 equiv of methyl triflate or trimethyloxonium tetrafluoroborate (Meerwein's salt). Both worked equally well, but Meerwein's salt was preferred for its longer shelf life and stability to air and moisture. The use of other activating groups will be investigated further, allowing flexibility in N-substitution; however, only methylating agents were tested in this study. Several solvents were screened to find the optimum conditions for dipolar cycloaddition (CH_2Cl_2, DCE, CH_3CN, CH_3NO_2). Reaction in nitromethane gave the highest and most consistent yields as well as the highest solubility for Meerwein's salt (solubility is poor in halogenated solvents). The maximum concentration of iminium ion **2** was observed after 2 h at room temperature as determined by decrease of alkene resonances in the ^{1}H NMR of the crude reaction solution.

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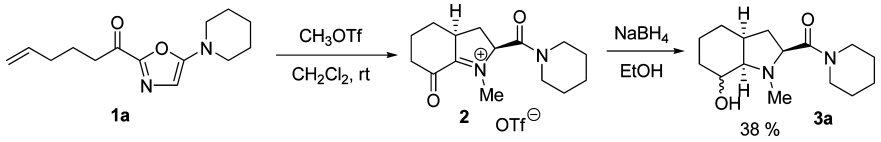
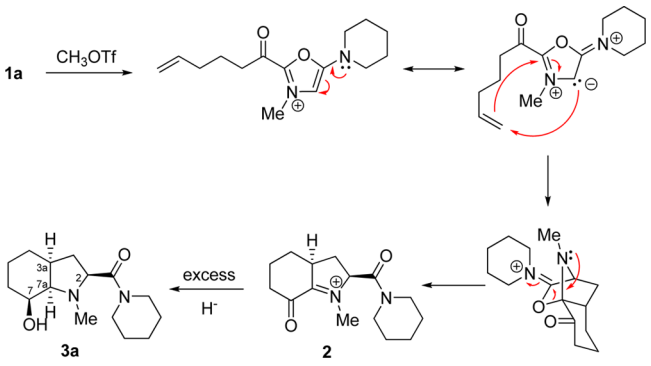
Scheme 1. Observed Cyclization of 2-Acyl-5-aminooxazole To Form an Octahydroindole



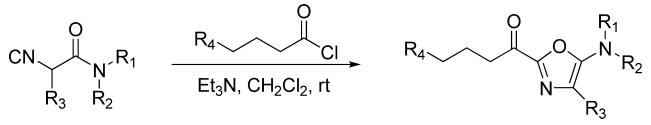
Scheme 2. Plausible Reaction Sequence of Cyclization/Reduction

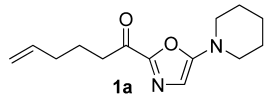
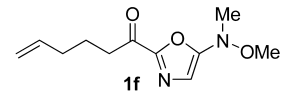
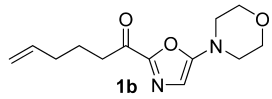
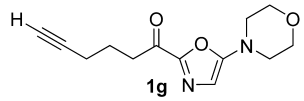
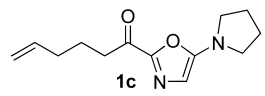
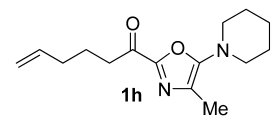
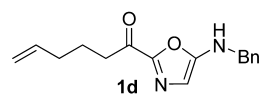
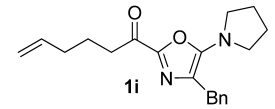
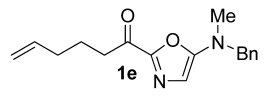
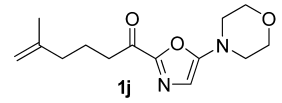


Subsequent reduction of the iminium ion **2** was accomplished initially by addition of excess sodium borohydride. This led to a ~3:1 mixture of diastereomeric products that were difficult to separate by flash column chromatography. After a bit of experimentation, we found that lowering the temperature to 0 °C followed by addition of sodium triacetoxyborohydride, $NaBH(OAc)_3$, and slow warming to room temperature yielded predominantly one major diastereomer product (92:8 dr). Coupling constant analysis of the C7a-H double doublet of **3a** suggested *cis*-ring fusion of the octahydroindole (J = 8.4 Hz) and a *cis*-orientation between the adjacent C7-H and C7a-H (J = 4.4 Hz). The X-ray structure of the tetrafluoroborate salt of octahydroindole **3a** confirmed the spectral interpretation and also revealed the relative configuration of the amido group at the 2-position of the ring. The *cis*-relationship between C2-H and C3a-H suggested that the allylic methylene carbon of the tether connected to the dipolarophile occupies an orientation *endo* to the bridged tricyclic intermediate of Scheme 2. This result is consistent with the general preference of intramolecular 1,3-dipolar cycloadditions with azomethine ylides.[12] A *trans* relationship between C2-H and C3a-H would be expected from the tether occupying an *exo* orientation. No diastereomer resulting from an *exo*-oriented tether was observed.

Encouraged by this optimized reaction sequence, several oxazole substrates (Table 1) were prepared to investigate the tolerance of the cyclization reaction to oxazole and dipolarophile substitution with different 5-amino groups and substituents at the 4-position of the oxazole, generating quaternary stereogenic carbon atoms at the OHI 2 −position. Oxazole substrates **1a**−**j** were synthesized in good to excellent yields (50−90%) using a one-step procedure developed by Mosetti and co-workers.[19] Isonitrile amide reactants (see Table

Table 1. Synthesis of 2-Acyl-5-aminooxazoles[a]



Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	 **1a**	82	6	 **1f**	50
2	 **1b**	69	7	 **1g**	73
3	 **1c**	74	8	 **1h**	90
4	 **1d**	66	9	 **1i**	56
5	 **1e**	87	10	 **1j**	64

[a]Isolated yields

[a]R_1, R_2 = 5-amino group of oxazoles. R_3 = H, Me, or Bn. R_4 = $CHCH_2$, CCH, or $C(CH_3)CH_2$.

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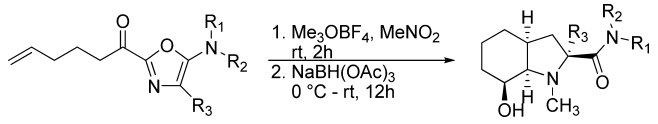
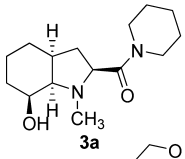
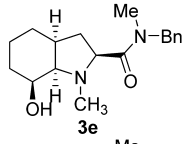
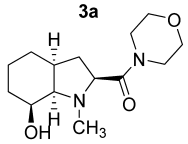
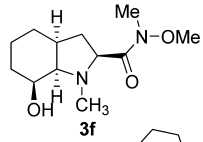
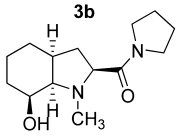
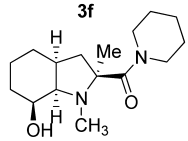
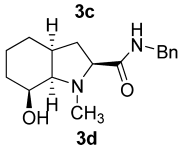
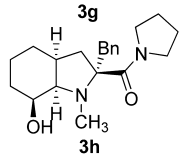
Table 2. Synthesis of Octahydroindoles from 2-Acyl-5-aminooxazoles



Product	Yield (%)	dr[a]	Product	Yield (%)	dr[a]
 **3a**	72	92:8	 **3e**	61	98:2
 **3b**	61	>99:1	 **3f**	15	nd
 **3c**	57	87:13	 **3g**	50	93:7[b]
 **3d**	45	88:12[b]	 **3h**	49	97:3

1) were obtained by reaction of commercially available methyl isocyanoacetate with primary or secondary amines in the absence of solvent. Most of the amides precipitated within a few minutes and were easily isolated by filtration. Those that did not were isolated in pure form by passing the crude amides through a pad of silica gel with ethyl acetate. Isocyano amides underwent cyclization to form oxazoles by treatment with an appropriate acid chloride in the presence of base. Hex-5-enoyl chloride[20] was used in most cases. Hex-5-ynoyl chloride was used to prepare oxazole **1h** and 5-methylhex-5-enoyl chloride was used to prepare oxazole **1j**.[21] Oxazoles **1h** and **1i** were synthesized from α-substituted isocyano amides (R_3 = Me and Bn), obtained by alkylation with methyl iodide or benzyl bromide and using CsOH as the base.[22] Oxazole **1f** was synthesized from a Weinreb amide (R_1 = Me, R_2 = OMe), prepared by the method of Greger and co-workers.[23]

The oxazole substrates **1a−e,h−i** underwent 1,3-dipolar cycloaddition with concomitant rearrangement of the cycloadduct to give iminium salts. Reduction of the iminium and keto groups with excess hydride led to *cis*-fused octahydroindoles **3a−e,g−h** with excellent diastereoselectivity in moderate to good yields (Table 2). In the cases where moderate yields were obtained, some uncyclized and reduced starting oxazole was detected in the crude reaction mixture. The minor diastereomer arises from variability in hydride addition to the top and bottom faces of the 7-keto group. In two cases (**3d** and **3g**), a trace amount (3% or less) of other minor diastereomers was detected in the HPLC−MS, presumably arising from some *trans*-fused octahydroindole formed during the iminium reduction step.

A variety of cyclic and acyclic tertiary 5-amino groups were well tolerated on the oxazole ring. Secondary amino groups were tolerated as well (e.g., 5-aminobenzyloxazole **1d** led to octahydroindole **3d**). Substitution at the 4-position of the oxazole did not seem to hinder cyclization, with no observable effect on reaction rate or isolated yields of products **3g** and **3h**.

In contrast, oxazole **1g**, containing a terminal alkyne, produced only the methylated oxazolium ion, with no cyclization observed at room temperature or after prolonged heating at reflux. There have been a few reports of problematic intramolecular dipolar cycloadditions of munchnones with terminal alkynes,[24] though others report some success.[25] Likewise, oxazole **1j** did not provide any cyclized product under similar conditions. Considering that azomethine ylides are known to be electron-rich species with relatively higher energy MOs, they may prefer to react with more electron deficient or unactivated alkenes.[26] Alternatively, the reaction may be hindered by the inability of the alkyne and methyl alkene to adopt a reactive conformation that allows sufficient orbital overlap in the transition state.

To better understand the mechanism of 1,3-dipole formation and subsequent cycloaddition, oxazole **1f** was prepared (Table 1, entry 6). For transient formation of the azomethine ylide it is necessary for the 5-amino lone pair electrons to be in conjugation with the double bond of the oxazolium ring (Scheme 2). Conjugation would be inhibited by the methoxy group in two possible ways. Inductive withdrawal of electron density from N by the more electronegative O and potential adoption of a conformation in which electron repulsion between an O lone pair and the developing p-orbital on N would both inhibit conjugation, leading to decreased partial negative charge on the 4-carbon of the oxazolium ring.[27] These effects are evident in the ^{1}H NMR spectra of the oxazole substrates. The chemical shift of the oxazole ring proton of compound **1f** was noticeably further downfield than all other oxazole substrates (6.59 ppm for **1f** vs ~6.1 ppm for all others). This downfield shifting suggests a smaller buildup of partial negative charge on C-4. As expected, after methylation, oxazole **1f** underwent sluggish cyclization and reduction to form octahydroindole **3f** in much lower yield, requiring longer reaction time at elevated temperature (20 h at 90 °C). This

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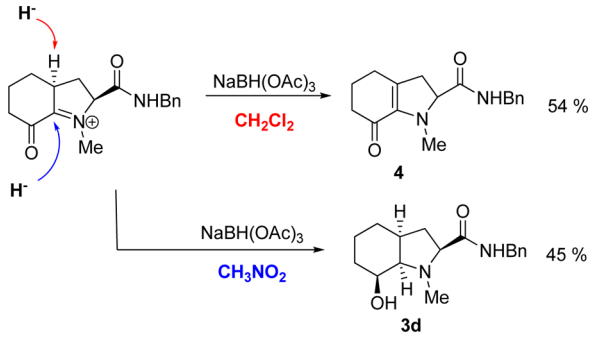
behavior establishes clearly the importance of conjugation of the enamine moiety for efficient reaction.

The hydride reduction reaction also plays a large role in overall yield of OHI synthesis. We found that the regioselectivity of the reduction was solvent polarity dependent. For example, when the cycloaddition/reduction sequence was performed on oxazole **1d** in CH_2Cl_2, the elimination product **4** was favored (Scheme 3). However, when the hydride reduction was performed in the more polar CH_3NO_2, **3d** was predominant.

Scheme 3. Competing Reduction/Elimination Pathways Are Solvent Dependent



In summary, we have developed an efficient two-step method for the production of *cis*-octahydroindoles containing a 2-amido and 7-hydroxyl group with excellent diastereoselectivity. We have presented a 1,3-dipolar cycloaddition reaction and proposed a plausible mechanism consistent with observed reactivity and product structural features. We have probed the generality of the cycloaddtion reaction to combinations of different oxazole and dipolarophile substitution. Further examination of the reaction sequence and application to target-directed synthesis is underway.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed under N_2 atmosphere in flame-dried glassware. Reaction solvents were dried using an automatic solvent purification system. Nitromethane was distilled from CaH_2. All other chemicals were used as obtained from the manufacturer. *CAUTION*: methyl isocyanoacetate has a very strong odor and should be used only in a fume hood. NMR spectra were obtained on a 400 MHz instrument: ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz). Chemical shifts are reported in ppm (δ units) relative to the solvent residual peak. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublet, dt = doublet of triplets, br = broad. For complex splitting patterns (i.e., dddd) the multiplicity is reported "as observed", recognizing that dddd ≈ p, dq, tt, or ddt where *J* value degeneracies are present.[28] HR-MS was obtained by ESI (positive ion mode) on TOF mass analyzer. FT-IR spectra were collected as cast films (from CH_2Cl_2 solutions) on NaCl plates. Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel plates coated at 0.25 mm thickness, and visualization was achieved by UV light (254 nm) and phosphomolybdic acid (PMA) staining. Flash column chromatography was performed on silica gel of 0.06−0.2 mm particle size. Samples of crude cyclization reaction mixtures were prepared for HPLC−MS analysis to a concentration of 0.1 mg/mL in a diluent of 15% MeCN/85% H_2O, except for sample **3d** which was prepared in 100% MeCN. Samples were filtered and injected (2 μL) on an HPLC−MS instrument and run with a flow rate of 2 mL/min through a Halo C-18 column (3.0 × 7.5 mm, 2.7 μm) at 40 °C. Gradient elution was performed (see the Supporting Information for the method) using water/acetonitrile mixtures with 0.1% formic acid. Mass spectra were acquired using electrospray ionization (ESI) and a time-of-flight (TOF) mass analyzer. Diastereomer ratios were estimated from peak integration of the extracted ion mass chromatogram (XIC).

Representative Procedure for Synthesis of 2-Keto-5-amino-oxazoles. *2-(Hex-5-enoyl)-5-(piperidin-1-yl)-1,3-oxazole (**1a**).* To a dried round-bottom flask under N_2 atm was added a solution of 2-isocyano-1-(piperidin-1-yl)acetamide[19] (0.694 g, 5.3 mmol) in CH_2Cl_2 (20 mL). Triethylamine (0.730 mL, 5.3 mmol) was then added. A solution of hex-5-enoyl chloride[20] (0.800 g, 5.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was monitored by TLC and was judged complete after 2 h at room temperature. The reaction was washed with 0.1 M Na_2CO_3 (aq), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (10−30% ethyl acetate/hexanes) to yield oxazole **1** as a yellow oil (1.07g, 82% yield): ^{1}H NMR ($CDCl_3$) δ 6.16 (s, 1H), 5.80 (dddd, 1H, *J* = 16.8, 10.0, 6.8, 6.8 Hz), 5.02 (dq, 1H, *J* = 17.6, 1.6 Hz), 4.97 (dq, 1H, *J* = 10.4, 1.2 Hz), 3.31 (m, 4H), 2.92 (t, 2H, *J* = 7.6 Hz), 2.13 (q, 2H, 7.2 Hz), 1.81 (p, 2H, *J* = 7.6 Hz), 1.64 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 185.8, 159.4, 150.1, 138.0, 115.2, 103.3, 47.5, 37.0, 33.3, 24.8, 24.0, 23.8; FT-IR (neat) 1674 cm^{-1}; HR-MS (ESI) for $C_{14}H_{20}N_2O_2$ (M + H) calcd 249.1598, found 249.1605.

*2-(Hex-5-enoyl)-5-morpholino-1,3-oxazole (**1b**).* Following the representative procedure above, the residue was purified by recrystallization from EtOAc/hexanes (3 crops) to yield a tan amorphous solid (0.562 g, 69%): mp (76−77 °C); ^{1}H NMR ($CDCl_3$) δ 6.19 (s, 1H), 5.80 (dddd, 1H, *J* = 16.8, 10.0, 6.4, 6.4 Hz), 5.03 (dq, 1H, *J* = 17.2, 1.6 Hz), 4.97 (dq, 1H, *J* = 10.4, 1.2 Hz), 3.81 (t, 4H, *J* = 4.8 Hz), 3.32 (t, 4H, *J* = 5.2 Hz), 2.94 (t, 2H, 7.2 Hz), 2.13 (q, 2H, *J* = 7.2 Hz), 1.82 (p, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 186.3, 158.9, 150.7, 137.9, 115.3, 103.8, 65.7, 46.6, 37.1, 33.2, 23.76; FT-IR (neat) 1685 cm^{-1}; HR-MS (ESI) for $C_{13}H_{18}N_2O_3$ (M + H) calcd 251.1390, found 251.1399.

*2-(Hex-5-enoyl)-5-(pyrrolidin-1-yl)-1,3-oxazole (**1c**).* Following the representative procedure above, the crude product was purified via flash column chromatography (10−30% EtOAc/hexanes) to yield an orange oil (1.00 g, 74% yield): ^{1}H NMR ($CDCl_3$) δ 7.30−7.33 (m, 2H), 7.20−7.24 (m, 3 H), 5.85 (dddd, 1H, *J* = 16.8, 10.4, 6.8, 6.8 Hz), 5.06 (dq, 1H, *J* = 17.2, 1.6 Hz), 5.00 (dq, 1H, *J* = 10.4, 1.2 Hz), 3.54 (t, 4H, *J* = 4.8 Hz), 2.96 (t, 2H, *J* = 7.6 Hz), 2.17 (q, 2H, *J* = 7.2 Hz), 1.95 (t, 4H, *J* = 6.4 Hz), 1.86 (p, 2H, *J* = 7.6); ^{13}C NMR ($CDCl_3$) δ 184.9, 154.5, 148.5, 140.7, 138.3, 128.7, 128.1, 126.4, 115.2, 114.2, 48.5, 37.0, 33.4, 32.6, 25.5, 24.3; FT-IR (neat) 1685 cm^{-1}; HR-MS (ESI) for $C_{13}H_{18}N_2O_3$ (M + H) calcd 251.1390, found 251.1399.

*5-(Benzylamino)-2-(hex-5-enoyl)-1,3-oxazole (**1d**).* Following the representative procedure above, the crude product was purified via flash column chromatography (10−30% EtOAc/hexanes) to yield an orange amorphous solid (2.45 g, 65% yield): ^{1}H NMR ($CDCl_3$) δ 7.27−7.39 (m, 5H), 6.12 (s, 1H), 5.79 (dddd, 1H, *J* = 17.2, 10.4, 6.8, 6.8 Hz), 5.27 (br s, 1H), 5.02 (dq, 1H, *J* = 17.2, 1.6 Hz), 4.97 (dq, 1H, *J* = 11.2, 1.2 Hz), 4.39 (d, 2H, *J* = 6.0 Hz), 2.91 (t, 2H, 7.6 Hz), 2.12 (q, 2H, *J* = 7.6 Hz), 1.80 (p, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 186.3, 158.0, 149.9, 137.9, 137.0, 128.9, 128.0, 127.3, 115.3, 102.9, 48.0, 37.0, 33.2, 33.8; FT-IR (neat) 3303, 1673 cm^{-1}; HR-MS (ESI) for $C_{16}H_{18}N_2O_2$ (M + H) calcd 271.1441, found 271.1446.

*5-(Benzyl(methyl)amino)-2-(hex-5-enoyl)-1,3-oxazole (**1e**).* Following the representative procedure above, the crude product was purified via flash column chromatography (10−40% EtOAc/hexanes) to yield a yellow oil (1.73 g, 87% yield): ^{1}H NMR ($CDCl_3$) δ 7.28−7.38 (m, 3H), 7.22−7.26 (m, 1H), 6.13 (s,1H), 5.81 (dddd, 1H, *J* = 16.8, 10.0, 6.4, 6.4 Hz), 5.04 (dq, 1H, *J* = 17.2, 1.6 Hz), 4.98 (dq, 1H, *J* = 10.4, 1.2 Hz), 4.50 (s, 2H), 2.95 (s, 3H), 2.94 (t, 2H, 7.6 Hz), 2.14 (q, 2H, *J* = 7.2 Hz), 1.83 (p, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ185.6, 159.3, 150.0, 138.0, 135.7, 128.9, 128.0, 127.7, 115.2, 102.6, 55.0, 37.0, 36.0, 33.3, 24.0; FT-IR (neat) 1674 cm^{-1}; HR-MS (ESI) for $C_{17}H_{20}N_2O_2$ (M + H) calcd 285.1598, found 285.1608.

*2-(Hex-5-enoyl)-5-(methoxy(methyl)amino)-1,3-oxazole (**1f**).* Following the representative procedure above, the crude product was

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purified via flash column chromatography (10% EtOAc/hexanes) to yield a red oil (0.282 g, 50% yield): ^{1}H NMR ($CDCl_3$) δ 6.59 (s, 1H), 5.80 (dddd, 1H, J = 16.8, 10.0, 6.4, 6.4 Hz), 5.04 (dq,1H, J = 17.2, 1.6 Hz), 4.99 (dq, 1H, J = 10.4, 1.2 Hz), 3.77 (s, 1H), 3.12 (s, 1H), 2.99 (t, 2H, J = 7.2 Hz), 2.14 (q, 2H, J = 7.2 Hz), 1.83 (p, 2H, 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ187.3, 159.4, 153.0, 137.9, 115.4., 109.7, 61.8, 40.9, 37.6, 33.1, 23.3; FT-IR (neat) 1693 cm^{-1}; HR-MS (ESI) for $C_{11}H_{16}N_2O_3Na$ (M + Na) calcd 247.1059, found 247.1060.

*2-(Hex-5-ynoyl)-5-morpholino-1,3-oxazole (**1g**).* Following the representative procedure above, the crude product was purified recrystallization from dichloromethane/hexanes to yield white crystals (1.05 g, 73%): mp (89−90 °C); ^{1}H NMR ($CDCl_3$) δ 6.20 (s, 1H), 3.81 (t, 4H, J = 4.8 Hz), 3.32 (t, 4H, J = 5.2 Hz), 3.07 (t, 2H, J = 7.2 Hz), 2.29 (dt, 2H, J = 7.2, 2.8 Hz), 1.97 (s, 1H), 1.95 (p, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 185.8, 159.3, 150.9, 104.3, 83.8, 69.4, 66.1, 47.0, 36.9, 23.4, 18.3; FT-IR (neat) 3300 cm^{-1}, 1685; HR-MS (ESI) for $C_{13}H_{16}N_2O_3Na$ (M + Na) calcd 271.1059, found 271.1055.

*2-(Hex-5-enoyl)-4-methyl-5-(piperidin-1-yl)-1,3-oxazole (**1h**).* Following the representative procedure above, the crude product was purified via flash column chromatography (10% EtOAc/hexanes) to yield a yellow oil (0.918 g, 90%): ^{1}H NMR ($CDCl_3$) δ 5.81 (dddd, 1H, J = 16.8, 10.0, 6.4, 6.4 Hz), 5.03 (dq, 1H, J = 17.2, 1.6 Hz), 4.97 (dq, 1H, J = 10.4, 1.2 Hz), 3.31 (t, 4H, J = 4.8 Hz), 2.92 (t, 4H, J = 7.6 Hz), 2.23 (s, 3H), 2.13 (q, 2H, J = 6.8 Hz), 1.57−1.70 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 186.3, 155.5, 149.5, 138.4, 116.5, 115.5, 49.6, 37.4, 33.6, 25.8, 24.2, 24.1, 13.3; FT-IR (neat) 1685 cm^{-1}; HR-MS (ESI) for $C_{15}H_{23}N_2O_2$ (M + H) calcd 263.1754, found 263.1764.

*4-Benzyl-2-(hex-5-enoyl)-5-(pyrrolidin-1-yl)-1,3-oxazole (**1i**).* Following the representative procedure above, the crude product was purified via flash column chromatography (10−20% EtOAc/hexanes) to yield a yellow oil (0.683 g, 56% yield): ^{1}H NMR ($CDCl_3$) δ 7.30−7.33 (m, 2H), 7.20−7.24 (m, 3 H), 5.85 (dddd, 1H, J = 16.8, 10.4, 6.8, 6.8 Hz), 5.06 (dq, 1H, J = 17.2, 1.6 Hz), 5.00 (dq, 1H, J = 10.4, 1.2 Hz), 3.54 (t, 4H, J = 4.8 Hz), 2.96 (t, 2H, J = 7.6 Hz), 2.17 (q, 2H, J = 7.2 Hz), 1.95 (t, 4H, J = 6.4 Hz), 1.86 (p, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 184.9, 154.5, 148.5, 140.7, 138.3, 128.7, 128.1, 126.4, 115.2, 114.2, 48.5, 37.0, 33.4, 32.6, 25.5, 24.3; FT-IR (neat) 1685, 1600, 1500 cm^{-1}; HR-MS (ESI) for $C_{20}H_{25}N_2O_2$ (M + H) calcd 325.1911, found 325.1919.

*2-(5-Methylhex-5-enoyl)-5-morpholino-1,3-oxazole (**1j**).* Following the representative procedure above, the crude product was purified via flash column chromatography (10−50% EtOAc/hexanes) to yield an orange oil (1.49 g, 64% yield): ^{1}H NMR ($CDCl_3$) δ 6.17 (s, 1H), 4.73 (d, 1H, J = 0.9 Hz), 4.69 (d, 1H, J = 0.9 Hz), 3.80 (t, 4H, J = 4.8 Hz), 3.31 (t, 4H, J = 5.2 Hz), 2.89 (t, 2H, J = 7.2 Hz), 2.09 (t, 2H, J = 7.6 Hz), 1.86 (p, 2H, J = 7.6 Hz), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 184.9, 159.3, 150.8, 144.6, 110.1, 104.3, 66.0, 46.5, 38.4, 38.3, 22.6, 22.5; FT-IR (neat) 1685 cm^{-1}; HR-MS (ESI) for $C_{14}H_{20}N_2O_3Na$ (M + Na) calcd 287.1372, found 287.1367.

Representative Procedure for Synthesis of Octahydroindoles. *Piperidin-1-yl 7-Hydroxy-1-methyl-cis-octahydroindole-2-carboxamide (**3a**).* To a dry flask under N_2 atmosphere was added a solution of trimethyloxonium tetrafluoroborate (0.732 g, 4.70 mmol) in nitromethane (10 mL). A solution of oxazole **1a** (1.00 g, 4.27 mmol) in nitromethane (10 mL) was added dropwise at room temperature. After 2 h, the reaction was cooled to 0 °C and solid $NaBH(OAc)_3$ (2.72 g, 12.81 mmol) was added in one portion. The mixture was slowly warmed to room temperature and stirred for 12 h. The reaction was quenched with satd $NaHCO_3$ (aq), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (6 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified via flash column chromatography (2.5−15% MeOH/CH_2Cl_2) to yield an orange oil (0.772 g, 72% yield): ^{1}H NMR (CD_3OD) δ 3.84 (ddd, 1H, J = 8.8, 4.4, 2.5 Hz), 3.68 (dd, 1H, J = 10, 6.4 Hz), 3.55 (m, 4H), 2.69 (dd, 1H, J = 8.4, 4.4 Hz), 2.42 (s, 3H), 2.38−2.29 (m, 1H), 2.06 (dt, 1H, J = 11.6, 6.8 Hz), 1.98−1.92 (m, 1H), 1.72−1.64 (m, 6H), 1.61−1.54 (m, 4H), 1.43−1.35 (m, 1H), 1.29−1.24 (m, 1H); ^{13}C NMR (CD_3OD) δ 173.1, 66.5, 66.3, 65.4, 45.9, 43.3, 39.7, 36.3, 36.1, 28.1, 26.6, 25.8, 25.5, 24.1, 15.1; FT-IR (neat) 3339, 1636 cm^{-1}; HR-MS (ESI) for $C_{15}H_{26}N_2O_2$ (M + H) calcd 267.2072, found 267.2072.

*Morpholinyl 7-Hydroxy-1-methyl-cis-octahydroindole-2-carboxamide (**3b**).* Following the representative procedure above, the crude material was purified via flash column chromatography (5−10% MeOH/CH_2Cl_2) to yield a yellow oil (0.065 g, 61% yield): ^{1}H NMR (CD_3OD) δ 3.85 (dd, 1H, J = 7.2, 4.4 Hz), 3.69−3.53 (m, 9H), 2.71 (dd, 1H, J = 8.0, 4.4 Hz), 2.43 (s, 3H), 2.64−2.38 (m, 1H), 2.08 (dt, 1H, J = 11.6, 6.8 Hz), 1.97−1.91 (m, 1H), 1.72−1.64 (m, 3H), 1.61−1.51 (m, 1H), 1.44−1.36 (m, 1H),1.28−1.21 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.7, 67.0, 66.3, 65.5, 65.2,45.5, 42.6, 36.5, 36.4, 29.2, 26.0, 14.1; FT-IR (neat) 3338, 1647 cm^{-1}; HR-MS (ESI) for $C_{14}H_{24}N_2O_3$ (M + H) calcd 269.1860, found 269.1858.

*Pyrrolidin-1-yl 7-Hydroxy-1-methyl-cis-octahydroindole-2-carboxamide (**3c**).* Following the representative procedure above, the crude material was purified via flash column chromatography (2.5−10% MeOH/CH_2Cl_2) to yield a yellow oil (0.618 g, 57% yield): ^{1}H NMR (CD_3OD) δ 3.85 (ddd, 1H, J = 7.2, 4.4, 3.2 Hz), 3.64 (dt, 1H, J = 10, 6.8 Hz), 3.57 (dd, 1H, J = 10, 6.4 Hz), 3.51−3.38 (m, 3H), 2.70 (dd, 1H, J = 8.4, 4.4 Hz), 2.45 (s, 3H), 2.38−2.29 (m, 1H), 2.11 (dt, 1H, J = 11.6, 6.8 Hz), 2.03−1.94 (m, 2H), 1.93−1.85 (m, 3H), 1.77−1.65 (m, 3H), 1.62−1.53 (m, 1H), 1.44−1.36 (m, 1H), 1.30−1.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.2, 67.1, 66.7, 65.4, 46.3, 46.0, 40.8, 36.5, 35.6, 29.2, 26.2, 26.0, 24.0, 14.5; FT-IR (neat) 3345, 1640 cm^{-1}; HR-MS (ESI) for $C_{14}H_{24}N_2O_2H$ (M + H) calcd 253.1916, found 253.1921.

*Benzyl 7-Hydroxy-1-methyl-cis-octahydroindole-2-carboxamide (**3d**).* Following the representative procedure above, the crude material was purified via flash column chromatography (80−90% EtOAc/hexanes) to yield a yellow oil (380 mg, 45% yield). ^{1}H NMR δ ($CDCl_3$) 7.61 (br s, 1 H), 7.29 (m, 5H), 4.49 (dd, 1H, J = 14.8, 6.0 Hz), 4.45 (dd, 1H, J = 14.8, 5.6 Hz), 3.85 (dt, 1H, J = 7.6, 3.6 Hz), 3.13 (dd, 1H, J = 9.2, 5.6 Hz), 2.78 (dd, 1H, J = 6.4, 3.6 Hz), 2.50 (s, 3H), 2.26 (ddd, 1H, J = 16.4, 9.6, 7.2 Hz), 2.10 (m, 1H), 1.74 (dt, 1H, J = 12.4, 5.2 Hz), 1.58−1.70 (m, 2H), 1.40−1.59 (m, 2H), 1.21−1.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.3, 138.5, 128.8, 127.7, 127.5, 70.6, 70.3, 68.9, 43.5, 43.1, 38.0, 35.9, 28.8, 27.2, 20.7; FT-IR (neat) 3311, 1652, 1521, 1454, 731, 699 cm^{-1}; HR-MS (ESI) for $C_{17}H_{24}N_2O_2Na$ (M + Na) calcd 311.1736, found 311.1738.

*N-Benzyl-N-methyl-7-hydroxy-1-methyl-cis-octahydroindole-2-carboxamide (**3e**).* Following the representative procedure above, the crude material was purified via flash column chromatography (2−10% MeOH/CH_2Cl_2) to yield a yellow oil (0.161 g, 61%): ^{1}H NMR (CD_3OD) (as a ∼3:2 mixture of amide rotamers at rt) 7.40−7.20 (m, 5H), 4.71 (AB, 0.4H, J = 17.2 Hz), 4.62 (AB, 0.6H, J = 14.8 Hz), 3.87 (dd, 0.6H, J = 7.2, 4.4 Hz), 3.84 (dd, 0.4H, J = 6.8, 4.0 Hz), 3.76 (dd, 0.6H, J = 10, 6.8 Hz), 3.69 (dd, 0.4H, J = 10, 6.4 Hz), 3.02 (s, 1.7H), 2.97 (s, 1.3H), 2.74 (dd, 0.6H, J = 8.0, 4.4 Hz), 2.66 (dd, 0.4H, J = 8.4, 4.4 Hz), 2.48 (s, 1.7H), 2.39 (s, 1.3H), 2.37−2.21 (m, 1H), 2.16 (dt, 0.7H, J = 11.6, 6.8 Hz), 2.02−1.91 (m, 1.4H), 1.81−1.50 (m, 4.3H), 1.46−1.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.9, 174.2, 137.1, 136.5, 128.9, 128.5, 127.9, 127.6, 127.3, 126.0, 66.3, 66.2, 65.4, 65.2, 52.33, 51.4, 40.63, 40.5, 36.8, 36.4, 36.0, 34.5, 33.9, 33.0, 29.6, 29.1, 25.9, 25.8, 14.1, 14.0; FT-IR (neat) 3350, 1645 cm^{-1}; HR-MS (ESI) for $C_{18}H_{26}N_2O_2H$ (M + H) calcd 303.2072, found 303.2066.

*N-Methoxy-N-methyl-7-hydroxy-1-methyl-cis-octahydroindole-2-carboxamide (**3f**).* Following the representative procedure above, however, the reaction was stirred for 20 h at 90 °C before all starting material was consumed as monitored by ^{1}H NMR. The crude material was purified via flash column chromatography (2.5−10% MeOH/CH_2Cl_2) to yield a yellow oil (0.015 g, 15% yield): ^{1}H NMR (CD_3OD, 50 °C) 3.87 (q, 1H, J = 4.4 Hz), 3.82 (dd, 1H, J = 9.6, 6.8 Hz), 3.74, (s, 3H) 3.22 (s, 3H), 2.79 (dd, 1H, J = 8.0, 4.4 Hz), 2.50 (s, 3H), 2.41−2.30 (m, 1H), 2.15 (dt, 1H, J = 11.6, 6.8 Hz), 1.97−1.91 (m, 1H), 1.76−1.64 (m, 3H), 1.61−1.52 (m, 1H), 1.44−1.34 (m, 1H), 1.29−1.22 (m, 2H); ^{13}C NMR ($CDCl_3$) 174.8*, 66.5, 65.4, 65.3, 61.6, 40.8, 36.4, 36.2, 32.6, 29.2, 25.9, 14.2 (*from HMBC correlation of amide **CON(Me)**(OMe)); FT-IR (neat) 3452, 1652 cm^{-1}; HR-MS (ESI) for $C_{12}H_{22}N_2O_3Na$ (M + H) calcd 265.1528, found 265.1528.

*Piperidin-1-yl 7-Hydroxy-1,2-dimethyl-cis-octahydroindole-2-carboxamide (**3g**).* Following the representative procedure above, the crude material was purified via flash column chromatography (5−10% MeOH/CH_2Cl_2) to yield a yellow oil (0.161 g, 50% yield): ^{1}H NMR (MeOD, 52 °C) δ 3.95 (q, 1H, J = 4.0 Hz), 3.67 (m, 4H), 2.79 (m, 1H), 2.49 (s, 3H), 2.45 (m, 1H), 2.05 (dd, 1H, J = 12.0, 7.6 Hz), 1.88−1.97 (m, 2H), 1.68−1.74 (m, 3H), 1.55−1.64 (m, 6H), 1.42−1.51 (m, 1H), 1.42 (s, 3H), 1.31−1.41 (m, 1H); ^{13}C NMR (CD_3CN) δ 184.9, 154.5, 148.5, 140.7, 138.3, 128.7, 128.1, 126.4, 115.2, 114.2, 48.5, 37.0, 33.4, 32.6, 25.5, 24.3; FT-IR (neat) 3400, 1625 cm^{-1}; HR-MS (ESI) for $C_{16}H_{28}N_2O_2H$ (M + H) calcd 281.2229, found 281.2233.

*Pyrrolidin-1-yl 2-Benzyl-7-hydroxy-1-methyl-cis-octahydroindole-2-carboxamide (**3h**).* Following the representative procedure above, the crude material was purified via flash column chromatography (2.5−5% MeOH/CH_2Cl_2) to yield a yellow oil (0.205 g, 49% yield): ^{1}H NMR (MeOD) δ 7.20−7.31 (m, 5 H), 3.84 (q, 1H, J = 4.0), 3.40−3.50 (m, 2H), 3.01 (dd, 2H, J = 13.6, 13.6), 2.84 (s, 3H), 2.74 (m, 1H); ^{13}C NMR (CD_3CN) δ 177.4, 139.3, 131.4, 128.8, 127.1, 73.2, 66.1, 65.3, 48.6, 39.3, 37.9, 34.1, 33.9, 29.3, 26.6, 14.9; FT-IR (neat) 3373, 1610 cm^{-1}; HR-MS (ESI) for $C_{21}H_{30}N_2O_2Na$ (M + Na) calcd 365.2205, found 365.2210.

*N-Benzyl-1-methyl-7-oxo-2,3,4,5,6,7-hexahydroindole-2-carboxamide (**4**).* Following the representative procedure above, except that the reaction was performed in CH_2Cl_2. The crude material was purified via flash column chromatography (50−90% EtOAc/hexanes) to yield a yellow oil (0.326 g, 54% yield): ^{1}H NMR ($CDCl_3$) δ 7.65 (br s, 1H), 7.22−7.38 (m, 5H), 4.50 (dd, 1H, J = 14.8, 6.4 Hz), 4.41 (dd, 1H, J = 14.8, 6.0 Hz), 3.59 (dd, 1H, J = 11.2, 9.2 Hz), 3.20 (ddt, 1H, J = 19.2, 11.5, 2.0, 2.0 Hz), 2.78 (s, 3H), 2.59 (ddt, 1H, J = 19.2, 9.6, 2.0, 2.0 Hz), 2.22−2.50 (m, 4H), 2.01 (p, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 193.0, 172.8, 143.3, 141.8, 138.2, 128.7, 127.7, 127.5, 69.3, 42.9, 40.7, 38.7, 38.6, 25.4, 23.3; FT-IR (neat) 3322, 1665, 1522 cm^{-1}; HR-MS (ESI) for $C_{17}H_{20}N_2O_2Na$ (M + Na) calcd 307.1422, found 307.1417.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds, HPLC−MS data, and X-ray crystallographic data for the BF_4 salt of compound **3**. 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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