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Stereoselective Synthesis of Amido and Phenyl Azabicyclic Derivatives via a Tandem Aza Prins-Ritter/Friedel–Crafts Type Reaction of Endocyclic *N*-Acyliminium Ions

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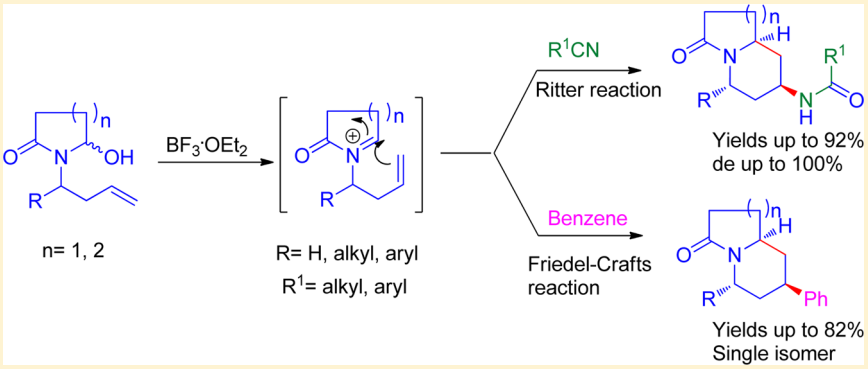
Supporting Information



ABSTRACT: A simple protocol is described for the synthesis of amido and phenyl hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one, and 1,3,4,10*b*-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one derivatives via endo-trig (aza-Prins type) cyclization followed by an intermolecular Ritter/Friedel–Crafts reaction of cyclic *N*-acyliminium ions, which are derived from the boron trifluoride etherate treatment of regioselectively reduced *N*-homoallyl imides. The reactions are highly diastereoselective with excellent yields.

INTRODUCTION

Azabicyclic alkaloids are present as core units of several highly significant natural products,[1] which have been shown to exhibit broad biological activity and a diverse pharmacological profile. For example, polyhydroxylated indolizidines, such as swainsonine (**1**; Figure 1) and castanospermine (**2**), exhibit potent glycosidase inhibitory activities[2] and show activity against carcinogenic cells and human immunodeficiency virus.[3] Similarly, a marine alkaloid in this class, lepadiformine (**3**), shows moderate cytotoxic activity[4] against various tumor cell lines in vitro and shows high in vivo and in vitro cardiovascular effects.[5] The quinolizidine alkaloid vertine (**4**) shows anti-inflammatory, sedative, and antispasmodic properties.[6] Similarly in this class, pictamine, clavepictamines A and B (**5**) act as potent blockers for two neuronal nicotinic acetylcholine receptors, possessing significant cytotoxicity against murine leukemia and human solid tumor cell lines (P-388, A-549, U-251, and SN12K1).[7] More recently, tetrahydropyrido[1,2-*a*]isoindolone derivatives (valmerins) **6** have been reported as potent cyclin-dependent kinase/glycogen synthase kinase-3 inhibitors and also show antitumor properties.[8] Because of their remarkably rich biological activity, the search and development of newer methodologies to construct substituted azabicycles is desirable. Cyclic *N*-acyliminium ions are versatile reaction intermediates[9] for the construction of various azabicyclic scaffolds. Pioneering work on *N*-acyliminium ions as electrophiles for C–C bond formation was explored by several groups through intra- and intermolecular nucleophilic substitution,[10] cationic polycyclizations,[11] and ring expansions of β-lactams toward γ-lactams.[12] *N*-acyliminium ions are also used for the synthesis of azabicyclic compounds via intramolecular Friedel–Crafts,[13] aza-Cope rearrangement,[14] intramolecular ene,[15] aza-Nazarov cyclization cascade,[16] and endo-trig cyclization reactions (aza-Prins type) on alkene, alkyne, and allene with various nucleophiles such as formate, hydroxyl, and halo groups.[17,18] A small number of biologically active natural products[19] have also been synthesized to date by using these intermediates. In addition to *N*-acyliminium ion chemistry, other methods have also been utilized for synthesizing azabicycles such as titanium-mediated cyclizations of ω-vinyl tethered imides,[20] fluoride-catalyzed difluoro(phenylsulfanyl)-methylations followed by radical cyclizations of cyclic imides,[21] intramolecular Schmidt reactions,[22] [4 + 2] cycloaddition reactions,[23] aza-Prins cyclizations of 2-allylpyrrolidines,[24] radical cyclization reactions,[25] amide/amine directed carbonylations/hydrocarbonylations,[26] criss-cross annulations,[27] intramolecular cyclizations of lactums,[28] and others.[29] Nevertheless, Prins type reactions followed by intermolecular trapping of nitrile/arene via a Ritter/Friedel–Crafts sequence on cyclic *N*-

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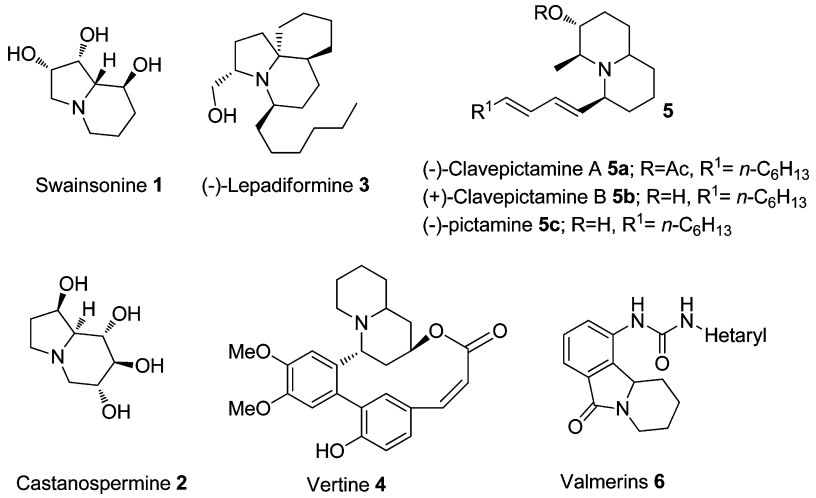


Figure 1. Some biologically active azabicyclic compounds.

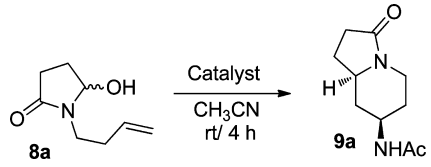
acyliminium ions for the synthesis of azabicyclic compounds have not been explored. Recently, our group and others have reported different methodologies for constructing substituted oxygen and nitrogen heterocycles by using Prins and aza-Prins strategies.[30] In a continuation of our research on nitrogen heterocyclic compounds,[31] we were interested in designing newer methodologies for the synthesis of azabicyclic compounds. Herein we wish to report a simple protocol for the synthesis of amido/phenyl substituted hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one, and 1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one derivatives via boron trifluoride etherate mediated tandem aza-Prins-Ritter/Friedel–Crafts reactions by using *N*-acyliminium ions as key intermediates.

RESULTS AND DISCUSSION

Although there are several methodologies for the construction of azabicyclic rings, many of them encounter some drawbacks such as harsh reaction conditions,[23d,26] use of an excess amount of reagent,[14a,16,17a,g,22h,i] generation of more than one product,[14b,17a,25b] lack of stereoselectivity,[15b,17b,c,25e] low yield,[13d,17a,25c,d,29f] and tedious starting material synthesis.[27,28] Most importantly, many methodologies provide halo,[17a,g] formate[17b–f] and acetate[17c,f] groups at the 4-position of the piperidine ring of the azabicyclic compounds. In our previous work we have demonstrated the synthesis of 4-amido- and 4-aryltetrahydropyrans[30a–e] using Prins–Ritter and Prins–Friedel–Crafts cyclization reactions. Inspired by this and taking cues from the literature that *N*-acyliminium ions can be used for the synthesis of azabicyclic compounds, we envisioned that amido and aryl azabicyclic compounds could be synthesized via endo-trig (aza-Prins type) cyclization followed by intermolecular Ritter/Friedel–Crafts reaction of cyclic *N*-acyliminium ions.

To start with, 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one was treated with 1.2 equiv of boron trifluoride etherate in acetonitrile at ambient temperature and the reaction proceeded smoothly to afford 7-(2-oxopropyl)hexahydroindolizin-3(2*H*)-one in 81% yield as a single isomer with two hydrogens at stereocenters cis to each other. With this result in hand, we started optimization of the reaction as depicted in Table 1 with a variety of Lewis acids such as $FeCl_3$, $SnCl_4$, $InCl_3$, $Sc(OTf)_3$, $In(OTf)_3$, TMSOTf, $Zn(OTf)_2$, $Cu(OTf)_2$, AgOTf, and montmorillonite K10 and Brønsted acids such as TsOH and camphorsulfonic acid. Among the screened reagents, boron trifluoride etherate was found to be efficient in terms of yields and diastereoselectivity. Chlorinated Lewis acids such as $FeCl_3$, $SnCl_4$, and $InCl_3$ afforded the product in 25%, 17%, and 53% yields with 80% de, respectively, without producing any halogenated products and 60%, 75% and 35% of starting material was recovered, respectively. Triflates such as $Sc(OTf)_3$, $In(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, AgOTf, and TMSOTf proved to be quite less effective, and montmorollonite K10 did not produce the desired product; starting material was recovered from the reaction mixture after prolonged reaction for 24 h. Similarly, the Bronsted acids TsOH and CSA also did not show any notable effect on yield and selectivity; instead, some decomposed product was observed.

Table 1. Optimization of the Reaction



entry	catalyst	amt of catalyst (mmol)	dr[a]	yield[b] (%)
1	$BF_3{\cdot}OEt_2$	1.2	100:0	81
2	$FeCl_3$	1.0	80:20	25[c,d]
3	$SnCl_4$	1.0	80:20	17[c,d]
4	$InCl_3$	1.2	80:20	53[c,d]
5	$In(OTf)_3$	0.2	90:10	<10[c,d]
6	TMSOTf	1.2	100:0	64
7	$Sc(OTf)_3$	0.2	90:10	12[c,d]
8	$Zn(OTf)_2$	1.0		n.d[c,d]
9	$Cu(OTf)_2$	1.2	80:20	38[c]
10	AgOTf	0.2		n.d[c,d]
11	montmorillonite K10			n.d[c,d]
12	TsOH	1.2	90:10	48[e]
13	CSA	1.2	90:10	29[e]

[a]The ratio was determined by ^{1}H NMR. [b]Yield refers to isolated yield. [c]Reaction continued for 24 h. [d]Starting material was recovered. n.d. = not detected. [e]Decomposed product was also observed. Montmorillonite K10 was used in milligrams.

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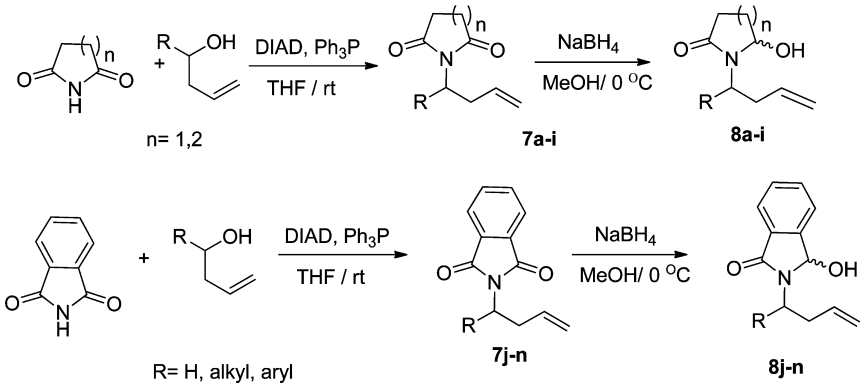
Scheme 1. Synthesis of Starting Materials



With the best conditions in hand, the scope of the reaction was investigated with a variety of substrates **8a−n**, which were synthesized according to literature methods (Scheme 1).[32] The tandem reaction with substrates **8a−n** produced moderate to excellent yields having de values ranging from 80 to 100, as determined from ^{1}H and ^{13}C NMR analysis of crude compounds (Table 2).

It was observed that the yield of the product depends on the nature of the substituent R of homoallylic side chain. In the case of hydrogen- or alkyl-substituted substrates (Table 2, entries 1, 3, 5−7, 10, and 13), the reaction gave higher yields in comparison to aryl-substituted substrates. On the other hand, substrates having electron-withdrawing aromatic substituents (entries 2, 9, and 11) generally gave higher yields in comparison to simple phenyl (entry 12) and electron-donating aromatic substituents (entries 4 and 14), probably due to electronic effects. 5-Hydroxy-1-(1-phenylpent-4-en-2-yl)-pyrrolidin-2-one (entry 3) afforded the desired product in 76% yield, without producing any intramolecular Friedel−Crafts product.[13] Similarly, substrates derived from succinimide and glutarimide (entries 1−4 and 6−9) gave single isomers. On the other hand, 5-hydroxy-1-(3-methylbut-3-en-1-yl)pyrrolidin-2-one (entry 5) yielded two inseparable diastereomers with a ratio of 60:40. Notably, substituted *N*-homoallyl-3-hydroxyisoindolin-1-ones (entries 10, 11, 13, and 14) gave diastereomeric mixture with dr values of 80:20 to 90:10, but phenyl-substituted *N*-homoallyl-3-hydroxyisoindolin-1-one (entry 12) produced a single isomer. The reaction is highly diastereoselective and produced exclusively single diastereomers having a cis relationship between the H_{10} hydrogen at C-10 of the piperidine ring and the H_{12} hydrogen at C-12 of the ring junction. On the other hand, substituents at C-8 and C-10 are trans to each other. A strong NOE between C−H_{12} and C−H_{10} and a weak NOE between C−H_8 and −NH− were observed in compound **9c**, which was also confirmed from X-ray crystallographic analysis (Figure 2).[33]

The reaction was further studied with other nitriles such as benzonitrile, allylnitrile, and dichloroacetonitrile, and the results are outlined in Table 3. The endo-trig cyclization followed by Ritter reaction of 3-hydroxy-2-(phenylbut-3-en-1-yl)isoindolin-1-one with benzonitrile produced a single diastereomer of **9o** in 65% yield. Similarly, allylnitrile and dichloroacetonitrile also produced single isomers of **9p,q** exclusively in 78% and 73% yields, respectively.

From these results of the endo-trig cyclization−Ritter sequence and previous reports on Prins−Friedel−Crafts reactions,[30] we envisaged that arene would trap the carbocation generated during an aza-Prins type cyclization of the endocyclic *N*-acyliminium ion (mechanism) via a Friedel−Crafts reaction. To check this hypothesis, 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one was treated with 1.2 equiv of boron trifluoride etherate in benzene and, as expected, the desired product was obtained as a single isomer in 73% yield (Scheme 2). The scope of the reaction was studied with various reduced *N*-homoallyl imides, as shown in Scheme 2. All the substrates worked well and produced the desired Friedel−Crafts products in moderate to good yields. The reaction is diastereoselective and produced exclusively single diastereomers. As discussed in the endo-trig cyclization−Ritter sequence, substrates having aliphatic substitutions at positions α to *N*-acyliminium ions provided products **10a−e,h** in higher yields than for aromatic substitution at the α position. The reaction is highly diastereoselective and produced exclusively single diastereomers having a trans relationship between the H_{10} hydrogen at C-10 of the piperidine ring and the H_{12} hydrogen at C-12 of the ring junction. On the other hand, the H_8 hydrogen at C-8 and H_{10} hydrogen at C-10 are cis to each other. This was confirmed from NOE and X-ray crystallographic analysis of compound **10i** (see the Supporting Information).[33] The reaction with other activated arenes such as toluene gave an inseparable mixture of ortho and para isomeric Friedel−Crafts products along with corresponding eliminated products in 45% overall yield (see the Supporting Information).[34] On the other hand, mesitylene failed to produce the desired products but gave only eliminated products.[34] This might be due to the steric effects of the comparatively bulky nature of toluene and mesitylene.

The diastereoselectivity of the reaction can be explained as follows. The reduced *N*-homoallyl imide under Lewis acidic conditions gives the corresponding *N*-acyliminium ion intermediate **A**, which undergoes 6-endo-trig cyclization to give the more favorable chairlike carbocation intermediate **B** with axial R substitution, due to strong (1,3) strain and less steric hindrance between the substituent R and the carbonyl group of the *N*-acyliminium ion intermediate (Scheme 3).[17e,35] The carbocation **B** thus formed is trapped by nitrile from an equatorial position to generate intermediate **C**, which after hydrolysis gives the corresponding amido azabicyclic compounds **9**. Similarly, the chairlike carbocation **B** undergoes a Friedel−Crafts reaction in the presence of benzene nucleophile to give the intermediate **D**, which after deprotonation gives the corresponding phenyl-substituted azabicyclic compounds **10**.

In order to address the observed diastereoselectivity of the reaction, DFT calculations at the B3LYP level were carried out.

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Table 2. Synthesis of Amido Azabicyclic Compounds via an Endo-trig Cyclization−Ritter Reaction

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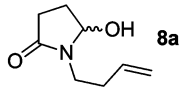
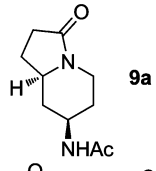
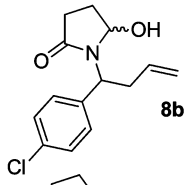
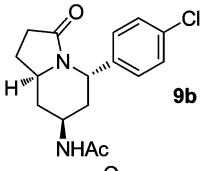
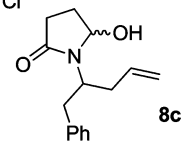
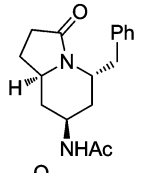
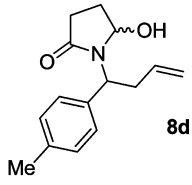
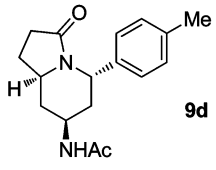
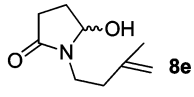
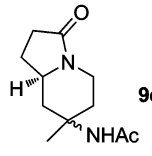
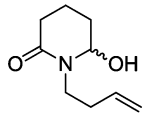
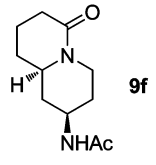
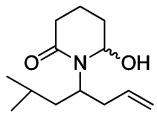
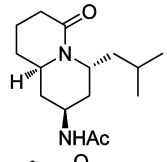
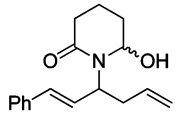
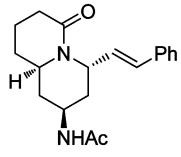
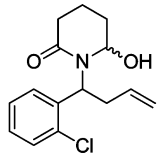
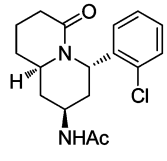
1	 **8a**	 **9a**	100:0	81
2	 **8b**	 **9b**	100:0	72
3	 **8c**	 **9c**	100:0	76
4	 **8d**	 **9d**	100:0	69
5	 **8e**	 **9e**	60:40	86
6	 **8f**	 **9f**	100:0	92
7	 **8g**	 **9g**	100:0	88
8	 **8h**	 **9h**	100:0	71
9	 **8i**	 **9i**	100:0	80

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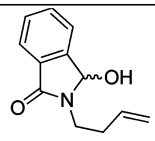
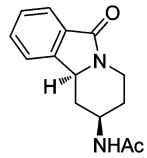
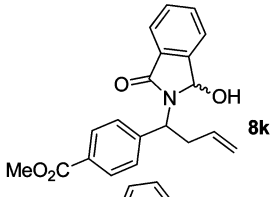
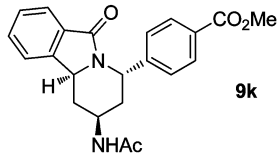
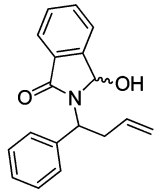
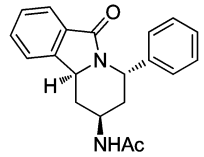
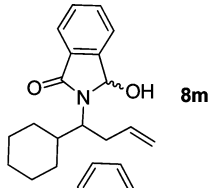
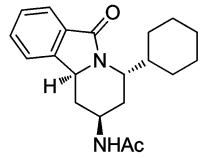
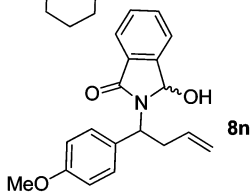
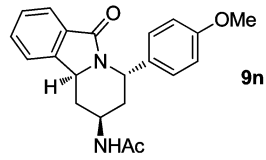
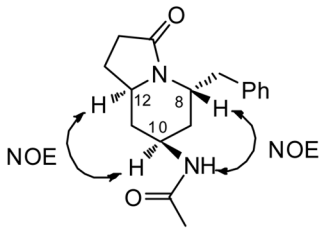
Table 2. continued

S.No.	Substrate **8**	Product **9**	dr[a]	(%) Yield[a]
10	 **8j**	 **9j**	90:10	78
11	 **8k**	 **9k**	90:10	72
12	 **8l**	 **9l**	100:0	70
13	 **8m**	 **9m**	80:20	85
14	 **8n**	 **9n**	90:10	66

[a]The ratio was determined by ^{1}H NMR. [b]Yield refers to isolated yield.



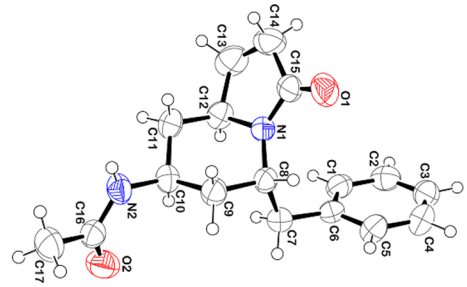


Figure 2. Correlation between NOE and X-ray crystallographic structure of **9c**.

The B3LYP/6-31G(d, p)-optimized carbocation intermediates **B** and **B′** of compound **8c** showed a preference for formation of **B** over **B′** by an energy of 46.304 kJ/mol (see the Supporting Information).

The importance of this methodology toward the synthesis of corresponding unnatural alkaloids is shown in Scheme 4. The reduction of compound **10d** with $LiAlH_4$ gave (2*R**,4*S**,9a*S**)-4-isobutyl-2-phenyloctahydro-1*H*-quinolizine (**11**) in 68% yield.[13a]

CONCLUSIONS

In conclusion, we have developed a methodology for the stereoselective synthesis of amido/phenyl substituted hexahydroindolizin-3(2*H*)-one, hexahydro-1*H*-quinolizin-4(6*H*)-one, and 1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one derivatives through tandem endo-trig cyclization (aza-Prins type) reactions and intermolecular Ritter/Friedel−Crafts reactions via *N*-acyliminium ions. The reaction is atom economical, and single diastereomers can be obtained in most of the cases. The present methodology should gain importance over the existing methods, as it provides a route for the synthesis of phenyl and amido/amino derivatives of azabicyclic compounds which are considered as important moieties for the biological activity of a molecule. This methodology could be useful for the synthesis of other substituted azabicyclic alkaloids and in natural product synthesis. The biological activity of synthesized compounds is under investigation.

EXPERIMENTAL SECTION

General Information. All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. BF_3·Et_2O was distilled over CaH_2 prior to use. Silica gel (60−120 mesh

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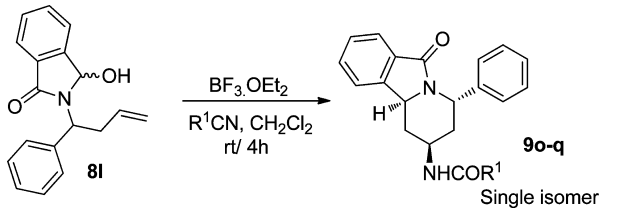
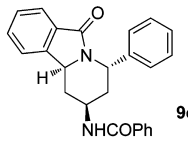
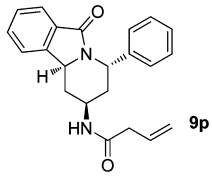
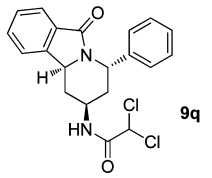
Table 3. Endo-trig Cyclization−Ritter Sequence with Different Nitriles



S.No.	nitrile	Product (**9**)	Yield (%)[a]
1		 **9o**	65
2		 **9p**	78
3		 **9q**	73

[a]Yield refers to isolated yield. The compounds were characterized by IR, NMR, and mass spectromentry.

size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in open capillary tubes and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as a neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (400 MHz, 300 MHz) or ^{13}C (100 MHz, 75 MHz). Chemical shifts (δ) are reported in ppm, and spin−spin coupling constants (J) are given in Hz. HRMS spectra were recorded using a Q-TOF mass spectrometer.

Synthesis of Starting Materials. The homoallyl imides and carbinol imides were synthesized as per literature procedures, and the structure and purity of the known compounds **7a,c,f,j** and **8a,c,f** were confirmed by comparison of their spectral data (^1H NMR and ^{13}C NMR) with those reported in the literature.[32]

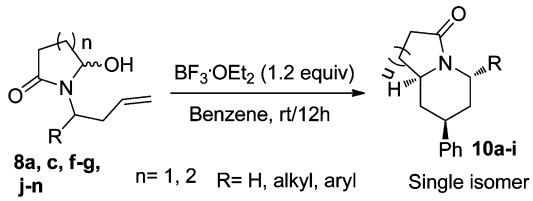
*1-(1-(4-Chlorophenyl)but-3-en-1-yl)pyrrolidine-2,5-dione (**7b**):* colorless liquid; yield 1.08 g, 82%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 4 H), 2.81−2.88 (m, 1 H), 3.23−3.31 (m, 1 H), 5.05 (d, J = 10.0 Hz, 1 H), 5.14 (d, J = 17.2 Hz, 1 H), 5.26 (dd, J = 10.4 and 6.0 Hz, 1 H), 5.64−5.74 (m, 1 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.42 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (2C), 44.0, 54.3, 118.6, 127.4, 128.6, 128.8 (2C), 129.9 (2C), 134.1, 177.2 (2C); IR (KBr, neat) 1702, 1641, 1493, 1386, 1238, 1179, 1104, 828 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}NO_2Cl$ $(M + H)^+$ 264.0786, found 264.0786.

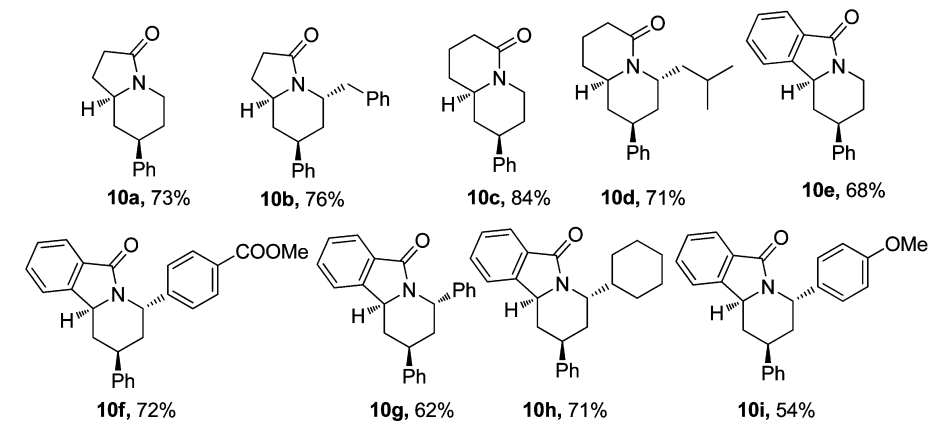
*1-(1-(p-Tolyl)but-3-en-1-yl)pyrrolidine-2,5-dione (**7d**):* pale yellow liquid; yield 0.95 g, 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.59 (s, 2 H), 2.60 (s, 2 H), 2.81−2.88 (m, 1 H), 3.25−3.34 (m, 1 H), 5.04 (d, J = 10.0 Hz, 1 H), 5.12 (d, J = 17.2 Hz, 1 H), 5.26 (dd, J = 10.4 and 5.6 Hz, 1 H), 5.65−5.75 (m, 1 H), 7.12 (d, J = 7.2 Hz, 2 H), 7.37 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 28.0 (2C), 34.5, 54.6, 118.1, 125.9, 128.3 (2C), 129.2 (2C), 134.6, 135.6, 177.3 (2C); IR (KBr, neat) 1724, 1640, 1459, 1377, 1254, 1176, 997, 840 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}NO_2$ $(M + H)^+$ 244.1332, found 244.1333.

*1-(3-Methylbut-3-en-1-yl)pyrrolidine-2,5-dione (**7e**):* colorless liquid; yield 0.78 g, 93%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 2.29 (t, J = 7.2 Hz, 2 H), 2.69 (s, 4 H), 3.64 (t, J = 7.6 Hz, 2 H), 4.66 (s, 1 H), 4.76 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 27.7 (2C), 35.0, 36.4, 112.1, 141.8, 176.9 (2C); IR (KBr, neat) 2914, 1731, 1669, 1450, 1362, 1218, 1110, 925 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}NO_2$ $(M + H)^+$ 168.1019, found 168.0981.

*1-(6-Methylhept-1-en-4-yl)piperidine-2,6-dione (**7g**):* colorless liquid; yield 0.80 g, 72%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, J

Scheme 2. Tandem Endo-trig Cyclization and Friedel−Crafts Reaction





[a]The ratio was determined from ^1H NMR. [b]Yield refers to isolated yield.

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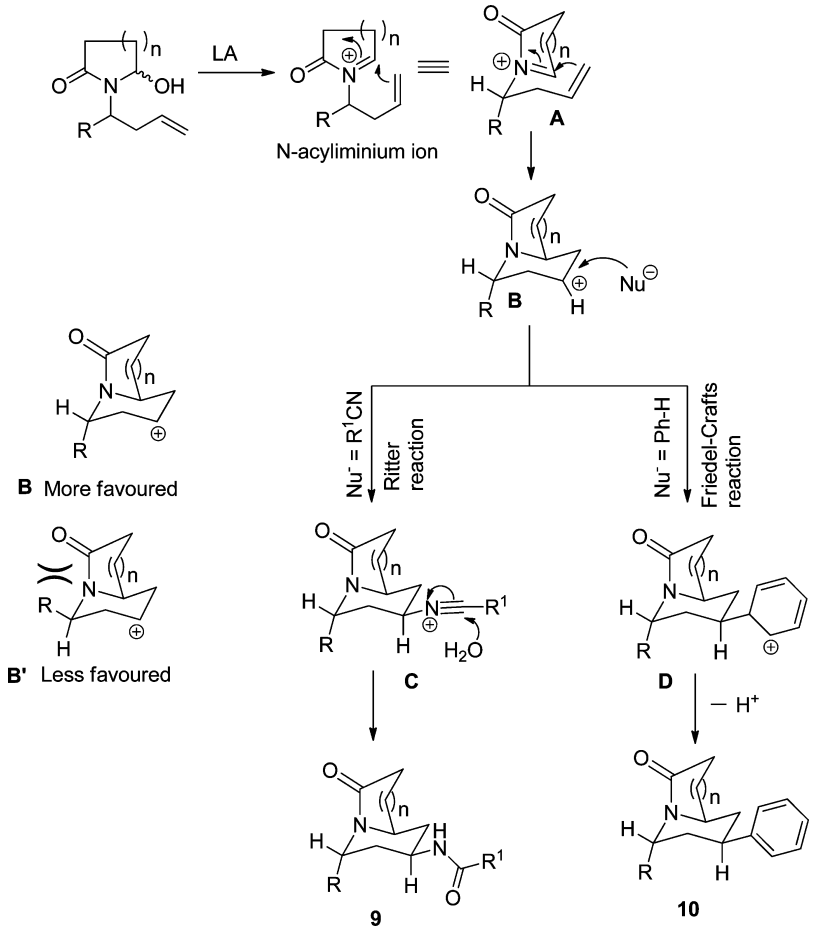
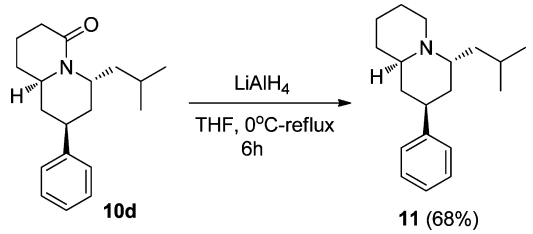
Scheme 3. Plausible Mechanism of the Reaction



Scheme 4. Synthesis of an Unnatural Alkaloid



= 6.4 Hz, 3 H), 0.81 (d, *J* = 6.4 Hz, 3 H), 1.30−1.39 (m, 2 H), 1.76−1.83 (m, 2 H), 1.92 (t, *J* = 8.8 Hz, 1 H), 2.23−2.30 (m, 1 H), 2.52 (t, *J* = 6.0 Hz, 4 H), 2.59−2.67 (m, 1 H), 4.76−4.84 (m, 1 H), 4.86−4.92 (m, 2 H), 5.53−5.63 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 21.8 (2C), 22.8, 25.1 (2C), 36.6, 40.6, 50.0, 116.4, 135.2, 172.7 (2C); IR (KBr, neat) 2928, 1724, 1672, 1464, 1384, 1237, 1177, 1125, 918, 738 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{21}NO_2$ $(M + H)^+$ 224.1645, found 224.1654.

(E)-1-(1-Phenylhexa-1,5-dien-3-yl)piperidine-2,6-dione (**7h**): colorless gum; yield 1.03 g, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85−1.92 (m, 2 H), 2.62 (t, *J* = 6.8 Hz, 4 H), 2.83−2.89 (m, 2 H), 4.94−5.06 (m, 2 H), 5.45−5.65 (m, 1 H), 5.66−5.80 (m, 1 H), 6.27 (d, *J* = 16.0 Hz,1 H), 6.63 (dd, *J* = 16.0 and 8.0 Hz,1 H), 7.19−7.30 (m, 4 H), 7.36−7.38 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 33.3 (2C), 36.6, 53.6, 117.4, 126.4 (2C), 127.6, 128.0, 128.5 (2C), 132.8, 134.7, 136.6, 172.7 (2C); IR (KBr, neat) 2979, 1725, 1678, 1494, 1384, 1239, 1173, 1108, 971, 918, 754, 695 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}NO_2$ $(M + H)^+$ 270.1489, found 270.1495.

1-(1-(2-Chlorophenyl)but-3-en-1-yl)piperidine-2,6-dione (**7i**): colorless gum; yield 1.12 g, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82−1.89 (m, 2 H), 2.51−2.63 (m, 4 H), 2.88−2.95 (m, 1 H), 3.08−3.16 (m, 1 H), 5.03−5.12 (m, 2 H), 5.77−5.88 (m, 1 H), 6.03 (dd, *J* = 10.0 and 6.0 Hz,1 H), 7.17−7.38 (m, 3 H), 7.67 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 33.2 (2C), 34.6, 51.1, 117.6, 125.8, 128.4, 129.3, 131.1, 133.6, 134.7, 135.9, 172.3 (2C); IR (KBr, neat) 2979, 1725, 1675, 1466, 1377, 1239, 1173, 1146, 998, 840 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NO_2Cl$ $(M + H)^+$ 278.0942, found 278.0949.

Methyl 4-(1-(1,3-dioxoisoindolin-2-yl)but-3-en-1-yl)benzoate (**7k**): colorless gum; yield 1.62 g, 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95−3.02 (m, 1 H), 3.35−3.44 (m, 1 H), 3.89 (s, 3 H), 5.02 (d, *J* = 10.0 Hz, 1 H), 5.14 (d, *J* = 16.8 Hz, 1 H), 5.49 (dd, *J* = 10.0 and 6.0 Hz, 1 H), 5.71−5.81 (m, 1 H), 7.60 (d, *J* = 7.2 Hz, 2 H), 7.68−7.71 (m, 2 H), 7.79−7.82 (m, 2 H), 8.00 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2, 52.2, 54.0, 118.7, 123.4 (2C), 128.1 (2C), 129.7, 129.9 (2C), 131.7, 134.0 (2C), 134.2 (2C), 144.1, 166.7, 168.2 (2C); IR (KBr, neat) 1771, 1707, 1641, 1436, 1384, 1279, 1110, 723 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{17}NO_4$ $(M + H)^+$ 336.1230, found 336.1229.

2-(1-Phenylbut-3-en-1-yl)isoindoline-1,3-dione (**7l**): pale yellow liquid; yield 1.30 g, 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93−3.00 (m, 1 H), 3.37−3.46 (m, 1 H), 4.99 (d, *J* = 10.8 Hz, 1 H), 5.13 (d, *J* = 16.0 Hz, 1 H), 5.44 (dd, *J* = 10.8 and 5.6 Hz, 1 H), 5.72−5.83 (m, 1 H), 7.24−7.28 (m, 1 H), 7.31−7.36 (m, 2 H), 7.54 (d, *J* = 7.6 Hz, 2 H), 7.67 (dd, *J* = 5.2 and 2.8 Hz, 2 H), 7.78 (dd, *J* = 5.2 and 3.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.2, 54.3, 118.1, 123.0 (2C), 127.8, 127.9 (2C), 128.5 (2C), 131.6, 133.8 (2C), 134.3 (2C), 139.2, 168.1 (2C); IR (KBr, neat) 1770, 1710, 1641, 1493, 1387, 1335, 1077, 922, 720, 698 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}NO_2$ $(M + H)^+$ 278.1176, found 278.1178.

2-(1-Cyclohexylbut-3-en-1-yl)isoindoline-1,3-dione (**7m**): colorless liquid; yield 1.00 g, 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91−

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1.37 (m, 6 H), 1.54−1.96 (m, 4 H), 2.06−2.17 (m, 2 H), 2.77−2.85 (m, 1 H), 3.97−4.02 (m, 1 H), 4.88 (d, J = 10.4 Hz, 1 H), 4.98 (d, J = 16.8 Hz, 1 H), 5.60−5.70 (m, 1 H), 7.68−7.71 (m, 2 H), 7.79−7.82 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 25.9, 26.3, 30.3, 30.8, 33.9, 39.3, 56.9, 117.6, 123.1 (2C), 131.7, 133.9 (2C), 135.2 (2C), 168.9 (2C); IR (KBr, neat) 2927, 2850, 1770, 1706, 1641, 1449, 1373, 1171, 840, 721 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NO_2$ (M + H)$^+$ 284.1645, found 284.1657.

*2-(1-(4-Methoxyphenyl)but-3-en-1-yl)isoindoline-1,3-dione (**7n**):* colorless liquid; yield 1.06 g, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91−2.98 (m, 1 H), 3.32−3.41 (m, 1 H), 3.77 (s, 3 H), 5.99 (d, J = 10.4 Hz, 1 H), 5.13 (d, J = 16.8 Hz, 1 H), 5.39 (dd, J = 10.4 and 6.0 Hz, 1 H), 5.70−5.83 (m, 1 H), 6.85 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.8 Hz, 2 H), 7.65−7.67 (m, 2 H), 7.76−7.79 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 54.0, 55.4, 114.0 (2C), 118.3, 123.3 (2C), 127.3, 129.5 (2C), 131.5, 132.0, 134.0 (2C), 134.6 (2C), 168.5 (2C); IR (KBr, neat) 2837, 1734, 1638, 1459, 1377, 1253, 1161, 972, 840 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{17}NO_3$ (M + H)$^+$ 308.1281, found 308.1294.

*1-(1-(4-Chlorophenyl)but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (**8b**):* 60:40 mixture of isomers; pale yellow liquid; yield 0.60 g, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71−1.79 (m, 1 H), 1.99−2.16 (m, 2 H), 2.41−2.55 (m, 1 H), 2.70−2.91 (m, 2 H), 4.84 (d, J = 5.2 Hz, 0.6 H), 4.95−5.11 (m, 3 H), 5.25 (d, J = 5.6 Hz, 0.4 H), 5.58−5.73 (m, 1 H), 7.18−7.34 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 29.0, 29.2, 29.8, 35.3, 36.9, 54.4, 54.9, 82.4, 83.0, 117.9 (2C), 128.8 (2C), 128.9 (2C), 129.5 (2C), 129.9 (2C), 133.6, 133.8, 134.7, 135.1, 137.2, 139.2, 175.0, 175.6; IR (KBr, neat) 2925, 1662, 1450, 1376, 1258, 1169, 1091, 996, 838 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}NO_2Cl$ (M + H)$^+$ 266.0942, found 266.0943.

*5-Hydroxy-1-(1-(p-tolyl)but-3-en-1-yl)pyrrolidin-2-one (**8d**):* 50:50 mixture of isomers; colorless liquid; yield 0.53 g, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76−1.87 (m, 1 H), 2.06−2.18 (m, 1 H), 2.25−2.32 (m, 1 H), 2.34 (s, 3 H), 2.56−2.67 (m, 1 H), 2.76−2.87 (m, 1 H), 2.87−2.98 (m, 1 H), 4.92 (t, J = 6.4 Hz, 0.5 H), 5.07 (d, J = 10.4 Hz, 1 H), 5.10−5.17 (m, 1 H), 5.23−5.31 (m, 1 H), 5.34 (t, J = 4.8 Hz, 0.5 H), 5.68−5.87 (m, 1 H), 7.16 (dd, J = 8.0 and 4.4 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (2C), 28.5, 28.9, 29.2 (2C), 35.5, 37.0, 54.5, 55.0, 82.2, 82.6, 117.4, 117.6, 127.9 (2C), 128.3 (2C), 129.3 (2C), 129.5 (2C), 135.0, 135.5, 135.6, 137.2, 137.5, 137.7, 175.0, 175.6; IR (KBr, neat) 2923, 1665, 1449, 1279, 1171, 1064, 993, 916, 841 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}NO_2$ (M + H)$^+$ 246.1489, found 246.1494.

*5-Hydroxy-1-(3-methylbut-3-en-1-yl)pyrrolidin-2-one (**8e**):* pale yellow liquid; yield 0.47 g, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 1.84−1.93 (m, 1 H), 2.25−2.35 (m, 4 H), 2.49−2.57 (m, 1 H), 3.26−3.33 (m, 1 H), 3.59−3.67 (m, 1 H), 3.87 (d, J = 7.6 Hz, 1 H), 4.72 (s, 1 H), 4.78 (s, 1 H), 5.21 (t, J = 5.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 27.9, 28.9, 35.3, 37.8, 82.7, 111.7, 142.6, 175.1; IR (KBr, neat) 2884, 1631, 1450, 1297, 1158, 1061, 987, 741 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}NO_2$ (M + H)$^+$ 170.1176, found 170.1170.

*6-Hydroxy-1-(6-methylhept-1-en-4-yl)piperidin-2-one (**8g**):* 60:40 mixture of isomers; colorless liquid; yield 0.57 g, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J = 5.6 Hz, 3 H), 0.90 (d, J = 6.4 Hz, 3 H), 1.31−1.50 (m, 2 H), 1.56−1.76 (m, 3 H), 1.92−1.96 (m, 1 H), 2.09−2.39 (m, 3 H), 2.49 (t, J = 8.0 Hz, 2 H), 4.53 (brs, 0.6 H), 4.78 (brs, 0.4 H), 5.01−5.12 (m, 3 H), 5.64−5.77 (m, 1 H), 5.78−5.89 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.2, 22.7, 23.1, 23.3, 23.4, 24.9, 25.2, 30.9, 31.0, 31.8, 32.3, 37.6 (2C), 38.7, 38.8, 41.4, 41.8, 107.1 (2C), 116.8, 117.0, 136.3, 136.7, 169.8, 171.3; IR (KBr, neat) 2955, 1618, 1467, 1330, 1181, 1085, 996, 752 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{23}NO_2$ (M + H)$^+$ 226.1802, found 226.1806.

*(E)-6-Hydroxy-1-(1-phenylhexa-1,5-dien-3-yl)piperidin-2-one (**8h**):* 60:40 mixture of isomers; colorless gum; yield 0.52 g, 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−1.64 (m, 0.8 H), 1.69−1.77 (m, 1.2 H), 1.84−1.93 (m, 1.2 H), 1.98−2.08 (m, 0.8 H), 2.21−2.45 (m, 1 H), 2.45−2.50 (m, 1.2 H), 2.55−2.65 (m, 0.8 H), 2.75−2.83 (m, 0.6 H), 2.85−2.88 (m, 0.4 H), 5.03−5.15 (m, 4 H), 5.71−5.84 (m, 1 H), 6.40−6.59 (m, 2 H), 7.19−7.23 (m, 1 H), 7.26−7.30 (m, 2 H), 7.32−7.37 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 15.3, 30.8, 31.2, 32.6, 32.7, 36.5, 37.6, 56.0, 58.0, 77.6,78.9, 117.5 (2C), 126.6 (2C), 126.7 (2C), 127.8, 127.9, 128.6, 128.7 (2C), 128.8 (2C), 129.1, 132.3, 132.6, 135.1, 135.7, 136.7, 136.8, 170.7, 171.0; IR (KBr, neat) 2923, 1628, 1459, 1377, 1265, 1182, 971, 840, 749 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}NO_2$ (M + H)$^+$ 272.1645, found 272.1646.

*1-(1-(2-Chlorophenyl)but-3-en-1-yl)-6-hydroxypiperidin-2-one (**8i**):* 50:50 mixture of isomer; pale yellow liquid; yield 0.61 g, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92−2.04 (m, 2 H), 2.23−2.28 (m, 2 H), 2.49−2.55 (m, 2 H), 2.64−2.78 (m, 2 H), 5.07−5.15 (m, 3 H), 5.67−5.77 (m, 0.5 H), 5.79−5.95 (m, 1 H), 6.01 (t, J = 6.4 Hz, 0.5 H), 7.18−7.45 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 20.0, 29.8, 31.9, 35.2, 36.3, 39.2, 43.0, 50.6, 52.3, 106.9 (2C), 118.0, 118.5, 125.9, 126.7, 127.1, 127.8, 128.8, 129.2, 130.2, 130.4, 132.9, 134.0, 134.2, 135.0, 136.6, 139.2, 169.2, 171.5; IR (KBr, neat) 2929, 1654, 1441, 1387, 1260, 1194, 917, 754,699 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{18}NO_2Cl$ (M + H)$^+$ 280.1099, found 280.1107.

*2-(But-3-en-1-yl)-3-hydroxyisoindolin-1-one (**8j**):* white solid; mp 62−64 °C; yield 0.55 g, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29−2.35 (m, 2 H), 3.23−3.30 (m, 1 H), 3.42−3.50 (m, 1 H), 4.92−5.04 (m, 3 H), 5.68−5.77 (m, 2 H), 7.38 (d, J = 7.2 Hz, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.50−7.57 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4, 38.3, 81.5, 116.8, 122.7, 123.1, 129.3, 131.2, 131.9, 135.0, 144.0, 167.5; IR (KBr, neat) 2902, 1665, 1430, 1215, 1148, 909, 745 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{13}NO_2$ (M + H)$^+$ 204.1019, found 204.1009.

*Methyl 4-(1-(1-hydroxy-3-oxoisoindolin-2-yl)but-3-en-1-yl)-benzoate (**8k**):* 50:50 mixture of isomers; colorless gum; yield 0.70 g, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93−3.00 (m, 1 H), 3.15−3.28 (m, 1 H), 3.80 (s, 1.5 H), 3.85 (s, 1.5 H), 4.23 (brs, 1 H), 5.02 (d, J = 9.6 Hz, 1 H), 5.10−5.20 (m, 1 H), 5.27 (dd, J = 10.0 and 6.4 Hz, 0.5 H), 5.43 (t, J = 8.0 Hz, 0.5 H), 5.52 (d, J = 11.6 Hz, 0.5 H), 5.72−5.87 (m, 1 H), 5.90 (d, J = 11.6 Hz, 0.5 H), 7.41−7.48 (m, 2 H), 7.53 (t, J = 8.8 Hz, 3 H), 7.66 (d, J = 7.2 Hz, 1 H), 7.81 (d, J = 7.2 Hz, 1 H), 7.92 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl3) δ 35.6, 36.3, 51.9, 52.0, 55.1, 55.4, 81.5, 82.2, 117.7, 117.8, 123.0 (2C), 123.1 (2C), 127.9 (2C), 128.3 (2C), 128.6 (2C), 129.1 (2C), 129.5 (4C), 129.7 (2C), 131.1, 131.3, 132.2 (2C), 134.6, 134.7, 144.0, 144.3, 166.8, 166.9, 167.3, 167.7; IR (KBr, neat) 1721, 1679, 1436, 1282, 1111, 1057, 920, 748 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{19}NO_4$ (M + H)$^+$ 338.1387, found 338.1395.

*3-Hydroxy-2-(1-phenylbut-3-en-1-yl)isoindolin-1-one (**8l**):* 60:40 mixture of isomers; white solid, mp 78−80 °C; yield 0.60 g, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92−3.00 (m, 1 H), 3.12−3.17 (m, 0.6 H), 3.24−3.32 (m, 0.4 H), 3.64 (brs, 1 H), 4.99 (d, J = 10.0 Hz, 1 H), 5.09- 5.17 (m, 1 H), 5.45−5.53 (m, 1 H), 5.73−5.90 (m, 2 H), 7.26 (t, J = 5.2 Hz, 2 H), 7.33 (t, J = 7.2 Hz, 1 H), 7.40−7.52 (m, 5 H), 7.63−7.66 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1, 36.7, 55.3, 56.0, 81.6, 81.7, 117.4, 117.5, 123.0, 123.2, 127.4, 127.8, 127.9 (2C), 128.4 (4C), 128.6 (2C), 129.4 (2C), 131.2, 131.6, 132.1, 132.2, 135.3, 135.4, 138.9 (2C), 141.0 (2C), 143.9, 144.1, 167.4, 167.8; IR (KBr, neat) 1665, 1407, 1208, 1104, 1057, 746 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}NO_2$ (M + H)$^+$ 280.1332, found 280.1334.

*2-(1-Cyclohexylbut-3-en-1-yl)-3-hydroxyisoindolin-1-one (**8m**):* 60:40 mixture of isomers; colorless liquid; yield 0.59 g, 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−1.28 (m, 6 H), 1.49−1.77 (m, 4 H), 1.93−1.95 (m, 1 H), 2.60−2.73 (m, 2 H), 3.73−3.76 (m, 0.4 H), 3.86−3.89 (m, 0.6 H), 4.93 (d, J = 8.4 Hz 1 H), 5.01−5.10 (m, 1 H), 5.67−5.85 (m, 2 H), 7.47−7.56 (m, 3 H), 7.57−7.76 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.8, 25.9, 26.1, 26.2, 26.5, 28.0 (2C), 29.0 (2C), 33.7, 33.9, 39.1, 39.5, 56.8, 57.6, 82.1, 82.8, 116.6, 116.9, 123.0 (2C), 129.4 (2C), 131.5, 131.7, 131.8 (2C), 133.8 (2C), 135.0, 135.4, 136.3, 136.5, 167.8, 168.1; IR (KBr, neat) 2925, 2852, 1672, 1448, 1208, 1161, 914, 747 cm^{-1}; HRMS (ESI) calcd for$C_{18}H_{23}NO_2$ (M + H)$^+$ 286.1802, found 286.1817.

*3-Hydroxy-2-(1-(4-methoxyphenyl)but-3-en-1-yl)isoindolin-1-one (**8n**):* 60:40 mixture of isomers; colorless liquid; yield 0.59 g, 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90−2.96 (m, 1 H), 3.08−3.16 (m, 1 H), 3.77 (s, 1.2 H), 3.79 (s, 1.8 H), 5.00 (d, J = 9.6 Hz, 1 H), 5.10−5.24 (m, 2 H), 5.45−5.51 (m, 1 H), 5.72−5.89 (m, 1 H), 6.79−6.89

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(m, 2 H), 7.24−7.34 (m, 2 H), 7.39−7.53 (m, 3.5 H), 7.70 (d, J = 7.2 Hz, 0.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1, 40.7, 52.9, 54.7, 55.3 (2C), 81.5, 81.6, 113.8 (2C), 114.0 (2C), 118.0, 118.2, 123.1, 123.2, 127.2 (2C), 127.7 (2C), 128.2, 129.2, 129.6, 129.7, 130.7, 131.1, 131.2, 131.5, 132.1, 132.2, 134.7, 135.4, 135.6, 135.8, 158.9, 159.1, 169.1 (2C); IR (KBr, neat) 1666, 1509, 1405, 1244, 1172, 1031, 745 cm^{-1}; HRMS (ESI) calcd for$C_{19}H_{19}NO_3$ (M + H)$^+$ 310.1438, found 310.1438.

Typical Procedure for the Synthesis of *N*-((7*R,8a*R**)-3-Oxooctahydroindolizin-7-yl)acetamide (9a).** To 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (78 mg, 0.50 mmol) in acetonitrile (3 mL) was added freshly distilled boron trifluoride etherate (86 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC with ethyl acetate as eluent. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate, the product was extracted with dichloromethane and then the organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography using ethyl acetate as eluent over silica gel to give *N*-((7S*,8a*S**)-3-oxooctahydroindolizin-7-yl)acetamide in a yield of 80 mg (81%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (q, J = 12.4 Hz, 1 H), 1.23 (dq, J = 12.4 and 5.2 Hz, 1 H), 1.55−1.65 (m, 1 H), 1.97 (s, 3 H), 2.19−2.29 (m, 3 H), 2.36−2.43 (m, 2 H), 2.75 (dt, J = 13.2 and 2.8 Hz, 1 H), 3.54−3.62 (m, 1 H), 3.94−4.02 (m, 1 H), 4.15 (dd, J = 13.2 and 3.2 Hz, 1 H), 6.02 (d, J = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 24.3, 30.0, 30.4, 38.1, 39.4, 45.9, 55.7, 169.7, 173.3; IR (KBr, neat) 2936, 2887, 1658, 1559, 1451, 1376, 1259, 1150, 738, 609 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}N_2O_2$ (M + H)$^+$ 197.1285, found 197.1286.

N-((5S,7S*,8aR*)-5-(4-Chlorophenyl)-3-oxooctahydroindolizin-7-yl)acetamide (**9b**):* white solid; mp 76−77 °C; yield 110 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (q, J = 12.0 Hz, 1 H), 1.56−1.71 (m, 2 H), 1.97 (s, 3 H), 2.10−2.16 (m, 1 H), 2.22−2.32 (m, 1 H), 2.48−2.54 (m, 2 H), 2.58−2.64 (m, 1 H), 3.59−3.66 (m, 1 H), 3.99−4.08 (m, 1 H), 5.50 (d, J = 5.2 Hz, 1 H), 5.68 (d, J = 7.2 Hz, 1 H), 7.24 (d, J = 8.4 Hz, 2 H), 7.1 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 24.4, 29.9, 33.3, 39.5, 42.7, 49.2, 52.8, 127.8 (2C), 128.9 (2C), 133.0, 136.7, 169.8, 174.1; IR (KBr, neat) 3066, 2938, 1667, 1550, 1419, 1372, 1288, 1097, 1012, 839, 735, 607 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2Cl$ (M + H)$^+$ 307.1208, found 307.1208.

N-((5R,7S*,8aR*)-5-Benzyl-3-oxooctahydroindolizin-7-yl)-acetamide (**9c**).* white solid; mp 91−93 °C; yield 109 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (q, J = 12.8 Hz, 1 H), 1.24 (dq, J = 12.8 and 6.0 Hz, 1 H), 1.52−1.61 (m, 1 H), 1.84 (dd, J = 13.2 and 2.0 Hz, 1 H), 1.96 (s, 3 H), 2.17−2.33 (m, 4 H), 2.84 (d, J = 8.0 Hz, 2 H), 3.78−3.85 (m, 1 H), 4.27−4.35 (m, 1 H), 4.50 (dd, J = 13.6 and 7.6 Hz, 1 H), 5.76 (d, J = 7.6 Hz, 1 H), 7.19−7.31 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.6, 30.1, 32.0, 36.7, 39.8, 42.1, 49.0, 52.4, 126.4, 128.3 (2C), 129.0 (2C), 137.5, 169.7, 173.2; IR (KBr, neat) 3064, 2944, 1660, 1552, 1421, 1372, 1284, 1178, 751, 702 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}N_2O_2$ (M + H)$^+$ 287.1754, found 287.1762.

N-((5S,7S*,8aR*)-3-Oxo-5-(p-tolyl)octahydroindolizin-7-yl)-acetamide (**9d**):* white solid; mp 78−80 °C; yield 99 mg, 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (q, J = 12.0 Hz, 1 H), 1.55−1.67 (m, 2 H), 1.96 (s, 3 H), 2.11−2.20 (m, 1 H), 2.21−2.28 (m, 1 H), 2.31 (s, 3 H), 2.442−2.53 (m, 2 H), 2.55−2.61 (m, 1 H), 3.62−3.69 (m, 1 H), 4.00−4.11 (m, 1 H), 5.50 (d, J = 5.2 Hz, 1 H), 5.92 (d, J = 7.2 Hz, 1 H), 7.15 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 23.2, 24.5, 30.2, 33.5, 40.0, 42.9, 49.5, 52.8, 126.3 (2C), 129.6 (2C), 135.0, 136.9, 169.8, 174.1; IR (KBr, neat) 3058, 2932, 1664, 1550, 1420, 1372, 1288, 1187, 822, 735, 602 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}N_2O_2$ (M + H)$^+$ 287.1754, found 287.1754.

N-((7S,8aS*)-7-Methyl-3-oxooctahydroindolizin-7-yl)acetamide and N-((7R*,8aS*)-7-methyl-3-oxooctahydroindolizin-7-yl)-acetamide (**9e**):* 60:40 mixture of isomers; colorless liquid; yield 90 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, J = 12.0 Hz, 1 H), 1.19−1.37 (m, 1 H), 1.39 (s, 1.8 H), 1.49 (s, 1.2 H), 1.53−1.63 (m, 1 H), 1.72 (dq, J = 13.2 and 5.6 Hz, 1 H), 1.85−1.90 (m, 0.4 H), 1.93 (s, 1.2 H), 1.98 (s, 1.8 H), 2.07−2.12 (m, 0.6 H), 2.16−2.27 (m, 1 H), 2.34−2.39 (m, 2 H), 2.73−2.78 (m, 0.4 H), 2.80−2.91 (m, 0.6 H), 3.58−3.67 (m, 1 H), 3.97 (dd, J = 13.6 and 4.0 Hz, 0.6 H), 4.05 (dd, J = 13.2 and 3.6 Hz, 0.4 H), 5.90 (brs, 0.4 H), 6.07 (br s, 0.6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 23.5, 23.6, 24.3, 24.6, 26.9, 29.8, 29.9, 34.2, 34.3, 35.1, 35.7, 42.0, 42.7, 51.6, 51.9, 52.2, 52.9, 169.9, 170.6, 173.0, 173.1; IR (KBr, neat) 2930, 2875, 1673, 1549, 1455, 1375, 1277, 1170, 751, 606 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}N_2O_2$ (M + H)$^+$ 211.1441, found 211.1447.

N-((2R,9aR*)-6-Oxooctahydro-1H-quinolizin-2-yl)acetamide (**9f**):* white solid; mp 101−103 °C; yield 97 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (q, J = 12.0 Hz, 1 H), 1.24 (dq, J = 12.8 and 4.4 Hz, 1 H), 1.45−1.54 (m, 1 H), 1.64−1.74 (m, 1 H), 1.77−1.86 (m, 1 H), 1.92−1.96 (m, 1 H), 1.97 (s, 3 H), 2.00−2.04 (m, 1 H), 2.07−2.12 (m, 1 H), 2.24−2.33 (m, 1 H), 2.41 (dt, J = 17.2 and 5.2 Hz, 1 H), 2.53 (dt, J = 13.2 and 2.4 Hz, 1 H), 3.33−3.40 (m, 1 H), 3.93−4.04 (m, 1 H), 4.78−4.84 (m, 1 H), 6.18 (d, J = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 22.8, 29.6, 31.1, 32.6, 39.7, 40.6, 46.3, 54.8, 169.2, 169.7; IR (KBr, neat) 3079, 2947, 1661, 1451, 1373, 1268, 1162, 1120, 976, 737, 608 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}N_2O_2$ (M + H)$^+$ 211.1441, found 211.1441.

N-((2S,4R*,9aR*)-4-Isobutyl-6-oxooctahydro-1H-quinolizin-2-yl)acetamide (**9g**):* white solid; mp 96−98 °C; yield 117 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.04 (q, J = 12.0 Hz, 1 H), 1.31−1.39 (m, 1 H), 1.42−1.50 (m, 1 H), 1.53−1.65 (m, 2 H), 1.74−1.82 (m, 2 H), 1.97 (s, 3 H), 2.08−2.14 (m, 2 H), 2.24−2.33 (m, 2 H), 2.41 (dt, J = 17.2 and 4.8 Hz, 2 H), 3.49−3.54 (m, 1 H), 4.15−4.24 (m, 1 H), 5.07−5.12 (m, 1 H), 6.12 (d, J = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 22.7 (2C), 23.2, 25.0, 30.1, 33.3, 34.5, 39.4, 40.8, 42.3, 46.2, 49.6, 169.4, 169.8; IR (KBr, neat) 3073, 2952, 2869, 1618, 1554, 1463, 1367, 1273, 1172, 1127, 973, 736, 608 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{26}N_2O_2$ (M + H)$^+$ 267.2067, found 267.2073.

N-((2S,4S*,9aR*)-6-Oxo-4-((E)-styryl)octahydro-1H-quinolizin-2-yl)acetamide (**9h**):* white solid; mp 126−128 °C; yield 111 mg, 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (q, J = 12.0 Hz, 1 H), 1.42−1.58 (m, 2 H), 1.66−1.72 (m, 1 H), 1.78−1.85 (m, 1 H), 1.98 (s, 3 H), 2.00−2.12 (m, 1 H), 2.16−2.25 (m, 1 H), 2.31−2.40 (m, 1 H), 2.45−2.58 (m, 2 H), 3.56−3.63 (m, 1 H), 4.18−4.25 (m, 1 H), 5.77 (brs, 1 H), 5.90 (d, J = 7.6 Hz, 1 H), 6.14 (dd, J = 16.0 and 4.4 Hz, 1 H), 6.48 (d, J = 16.0 Hz, 1 H), 7.23 (d, J = 7.2 Hz, 1 H), 7.30 (t, J = 7.2 Hz, 2 H), 7.37 (d, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 23.3, 30.3, 33.2, 34.9, 40.5, 43.1, 49.4, 51.1, 126.5 (2C), 127.2, 127.8, 128.6 (2C), 132.2, 136.4, 169.9 (2C); IR (KBr, neat) 3058, 2930, 2857,1702, 1619, 1551, 1449, 1370, 1263, 1175, 1124, 970, 757, 700, 608 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}N_2O_2$ (M + H)$^+$ 313.1911, found 313.1911.

N-((2S,4S*,9aR*)-4-(2-Chlorophenyl)-6-oxooctahydro-1H-quinolizin-2-yl)acetamide (**9i**):* white solid; mp 88−90 °C; yield 128 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (q, J = 12.0 Hz, 1 H), 1.51−1.60 (m, 1 H), 1.69−1.75 (m, 1 H), 1.78−1.82 (m, 1 H), 1.89 (s, 3 H), 2.01−2.08 (m, 1 H), 2.14−2.18 (m, 1 H), 2.38−2.53 (m, 4 H), 3.79−3.84 (m, 1 H), 4.02−4.07 (m, 1 H), 6.14 (d, J = 6.0 Hz 1 H), 6.28 (brs, 1 H), 7.15−7.23 (m, 2 H), 7.29−7.36 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 23.3, 30.7, 33.2, 34.1, 40.0, 43.0, 50.3, 53.9, 127.0, 127.5, 128.5, 130.8, 133.1, 138.5, 170.0, 170.2; IR (KBr, neat) 3067, 2947, 2867, 1627, 1552, 1439, 1343, 1309, 1276, 1134, 1038, 974,762, 737, 605 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_2Cl$ (M + H)$^+$ 321.1364, found 321.1364.

N-((2R,10bS*)-6-Oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]-isoindol-2-yl)acetamide (**9j**):* white solid; mp 111−113 °C; yield 95 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (q, J = 12.0 Hz, 1 H), 1.18−1.33 (m, 1 H), 2.03 (s, 3 H), 2.15 (d, J = 7.6 Hz,1 H), 2.61 (d, J = 7.6 Hz,1 H), 3.03−3.10 (m, 1 H), 4.19−4.25 (m, 1 H), 4.37−4.47 (m, 2 H), 6.29 (d, J = 7.6 Hz, 1 H), 7.36 (d, J = 7.2 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 1 H), 7.77 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 31.4, 37.7, 37.8, 46.1, 57.6, 121.8, 123.5, 128.4, 131.6, 131.7, 144.9, 166.3, 170.0; IR (KBr, neat) 3068, 2929, 2863, 1669, 1552, 1431, 1371, 1288, 1099, 971, 738, 612 cm^{-1};

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HRMS (ESI) calcd for $C_{14}H_{16}N_2O_2$ (M + H)$^+$ 245.1285, found 245.1285.

Methyl 4-((2R,4S*,10bS*)-2-acetamido-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-4-yl)benzoate (**9k**):* white solid; mp 135−137 °C; yield 136 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (q, J = 12.0 Hz, 1 H), 1.71 (dq, J = 12.8 and 5.6 Hz, 1 H), 2.02 (s, 3 H), 2.58−2.64 (m, 1 H), 2.74−2.80 (m, 1 H), 3.90 (s, 3 H), 4.25−4.32 (m, 1 H), 4.45 (dd, J = 11.6 and 3.6 Hz, 1 H), 5.82−5.90 (m, 2 H), 7.34−7.41 (m, 3 H), 7.49−7.59 (m, 2 H), 7.91 (d, J = 7.2 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 33.9, 37.9, 43.4, 49.3, 52.3, 55.1, 122.2, 124.1, 126.7 (2C), 128.7, 129.4, 130.3 (2C), 131.3, 132.1, 144.0, 145.2, 166.8, 167.3, 170.1; IR (KBr, neat) 2950, 2723, 1720, 1678, 1549, 1413, 1372, 1282, 1112, 1018, 963, 736, 697, 607 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{22}N_2O_4$ (M + H)$^+$ 379.1652, found 379.1659.

N-((2R,4S*,10bS*)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)acetamide (**9l**):* white solid; mp 128−130 °C; yield 112 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (q, J = 12.0 Hz, 1 H), 1.63−1.72 (m, 1 H), 2.02 (s, 3 H), 2.61 (d, J = 12.0 Hz,1 H), 2.75 (d, J = 12.0 Hz, 1 H), 4.32−4.39 (m, 1 H), 4.47 (dd, J = 12.0 and 3.6 Hz, 1 H), 5.74 (d, J = 7.6 Hz, 1 H), 5.87 (d, J = 5.6 Hz, 1 H), 7.23−7.26 (m, 1 H), 7.32−7.36 (m, 5 H), 7.48−7.57 (m, 2 H), 7.90 (d, J = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 33.8, 38.0, 43.2, 49.2, 55.0, 122.1, 123.9, 126.5 (2C), 127.5, 128.6, 129.0 (2C), 131.4, 132.0, 138.5, 145.3, 167.3, 170.1; IR (KBr, neat) 3058, 2930, 1678, 1549, 1413, 1374, 1279, 1116, 962, 738, 699, 606 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}N_2O_2$ (M + H)$^+$ 321.1598, found 321.1598.

N-((2R,4S*,10bS*)-4-Cyclohexyl-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)acetamide (**9m**):* white solid; mp 89−91 °C; yield 138 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (q, J = 12.0 Hz, 1 H), 0.96−1.14 (m, 4 H), 1.17−1.27 (m, 1 H), 1.45−1.50 (m, 1 H), 1.65−1.77 (m, 5 H), 1.84−1.89 (m, 1 H), 2.04 (s, 3 H), 2.12−2.17 (m, 1 H), 2.61−2.68 (m, 1 H), 4.19 (dd, J = 10.8 and 5.6 Hz, 1 H), 4.32−4.40 (m, 1 H), 4.44 (dd, J = 12.0 and 3.6 Hz, 1 H), 5.94 (d, J = 8.0 Hz, 1 H), 7.35 (d, J = 7.2 Hz, 1 H), 7.43−7.55 (m, 2 H), 7.78 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 25.9 (2C), 26.1, 29.7, 30.4, 32.0, 38.0, 38.3, 42.7, 52.7, 54.8, 121.9, 123.7, 128.4, 131.6 (2C), 145.2, 167.1, 170.1; IR (KBr, neat) 3068, 2927, 2851, 1671, 1549, 1417, 1370, 1232, 1110, 762, 737, 604 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{26}N_2O_2$ (M + H)$^+$ 327.2067, found 327.2067.

N-((2R,4S*,10bS*)-4-(4-Methoxyphenyl)-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)acetamide (**9n**):* white solid; mp 119−121 °C; yield 115 mg, 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (q, J = 12.0 Hz, 1 H), 1.57−1.66 (m, 1 H), 2.03 (s, 3 H), 2.55−2.60 (m, 1 H), 2.65−2.70 (m, 1 H), 3.77 (s, 3 H), 4.33−4.40 (m, 1 H), 4.42 (dd, J = 12.4 and 4.0 Hz, 1 H), 5.79 (d, J = 5.6 Hz, 1 H), 6.13 (d, J = 8.0 Hz, 1 H), 6.86 (d, J = 8.8 Hz, 2 H), 7.23 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 7.2 Hz, 1 H), 7.46−7.55 (m, 2 H), 7.87 (d, J = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 33.8, 37.9, 43.2, 48.7, 54.9, 55.3, 114.3 (2C), 122.1, 123.8, 127.7 (2C), 128.5, 130.5, 131.5, 131.9, 145.2, 158.8, 167.1, 170.1; IR (KBr, neat) 3058, 2932, 2836, 1674, 1512, 1415, 1374, 1252, 1181, 1033, 835, 737, 607 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_3$ (M + H)$^+$ 351.1703, found 351.1703.

Typical Procedure for the Synthesis of *N*-((2*R,4*S**,10b*S**)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)benzamide (9o).** To a mixture of 3-hydroxy-2-(1-phenylbut-3-en-1-yl)isoindolin-1-one (140 mg, 0.50 mmol) and benzonitrile (160 mg, 1.50 mmol) in dichloromethane (3 mL) was added freshly distilled boron trifluoride etherate (86 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate, the product was extracted with dichloromethane, and then the organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography over silica gel to give *N*-((2*R**,4*S**,10b*S**)-6-oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-*a*]isoindol-2-yl)benzamide (**9o**) in a yield of 124 mg (65%) as a white solid: mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (q, J = 12.0 Hz, 1 H), 1.71−1.81 (m, 1 H), 2.63−2.68 (m, 1 H), 2.81−2.86 (m, 1 H), 4.50 (dd, J = 12.0 and 3.6 Hz, 1 H), 4.56−4.62 (m, 1 H), 5.88 (d, J = 5.6 Hz, 1 H), 6.83 (d, J = 7.6 Hz, 1 H), 7.24−7.27 (m, 1 H), 7.31−7.35 (m, 5 H), 7.40−7.47 (m, 3 H), 7.48−7.50 (m, 3 H), 7.81 (d, J = 7.6 Hz, 1 H), 7.92 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.0, 38.2, 44.0, 49.4, 55.1, 122.2, 124.2, 126.7 (2C), 127.3 (2C), 127.6, 128.7, 128.8 (2C), 129.2 (2C), 131.7, 131.9, 132.0, 134.3, 138.7, 145.4, 167.3, 167.4; IR (KBr, neat) 2927, 1676, 1536, 1412, 1325, 1226, 1153, 1028, 908, 733, 695, 606 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{22}N_2O_2$ (M + H)$^+$ 383.1754, found 383.1757.

N-((2R,4S*,10bS*)-6-Oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)but-3-enamide (**9p**):* white solid; mp 101−103 °C; yield 135 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (q, J = 12.0 Hz, 1 H), 1.60 (dq, J = 13.2 and 5.6 Hz,1 H), 2.48−2.53 (m, 1 H), 2.66−2.70 (m, 1 H), 2.97 (d, J = 7.2 Hz, 2 H), 4.23−4.31 (m, 1 H), 4.38 (dd, J = 12.0 and 2.8 Hz, 1 H), 5.12−5.17 (m, 2 H), 5.79 (d, J = 4.8 Hz, 1 H), 5.81−5.92 (m, 2 H), 7.16−7.20 (m, 1 H), 7.24 (brs, 5 H), 7.40−7.49 (m, 2 H), 7.83 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 37.9, 41.7, 43.5, 49.2, 55.0, 119.7, 122.1, 124.1, 126.6 (2C), 127.5, 128.6, 129.1 (2C), 131.4, 131.6, 131.9, 138.7, 145.3, 167.2, 170.6; IR (KBr, neat) 3058, 2925, 2854, 1685, 1546, 1468, 1412, 1347, 1301, 1226, 1096, 1030, 920, 800, 748,696, 610 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{22}N_2O_2$ (M + H)$^+$ 347.1754, found 347.1758.

2,2-Dichloro-N-((2R,4S*,10bS*)-6-oxo-4-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-2-yl)acetamide (**9q**):* white solid; mp 115−117 °C; yield 142 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (q, J = 12.0 Hz, 1 H), 1.77 (dq, J = 13.2 and 6.0 Hz,1 H), 2.57−2.61 (m, 1 H), 2.76−2.81 (m, 1 H), 4.28−4.36 (m, 1 H), 4.47 (dd, J = 12.0 and 3.6 Hz, 1 H), 5.86 (d, J = 5.2 Hz, 1 H), 6.01 (s, 1 H), 7.24 (d, J = 7.2 Hz, 1 H), 7.28−7.36 (m, 6 H), 7.46−7.59 (m, 2 H), 7.89 (d, J = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 37.3, 44.7, 49.2, 54.8, 66.5, 122.2, 124.3, 126.5 (2C), 127.6, 128.8, 129.2 (2C), 131.6, 132.1, 138.3, 145.0, 164.1, 167.3; IR (KBr, neat) 2925, 1673, 1412, 1267, 1210, 1090, 1018, 911, 746, 697 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{18}N_2O_2Cl_2$ (M + H)$^+$ 398.0818, found 398.0814.

Typical Procedure for the Synthesis of (7*S,8a*S**)-7-Phenylhexahydroindolizin-3(2*H*)-one (10a).** To 1-(but-3-en-1-yl)-5-hydroxypyrrolidin-2-one (78 mg, 0.50 mmol) in benzene (3 mL) was added freshly distilled boron trifluoride etherate (86 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for a specified time. The progress of the reaction was monitored by TLC with ethyl acetate and hexane (3:7) as eluents. After completion of the reaction, the reaction mixture was treated with aqueous sodium bicarbonate, the product was extracted with dichloromethane, and then the organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and evaporated to leave the crude product, which was purified by column chromatography over silica gel to give (7*S**,8a*S**)-7-phenylhexahydroindolizin-3(2*H*)-one (**10a**; yield 79 mg, 73%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (q, J = 12.0 Hz, 1 H), 1.51−1.70 (m, 2 H), 1.85−1.92 (m, 1 H), 2.04−2.10 (m, 1 H), 2.21−2.30 (m, 1 H), 2.38−2.44 (m, 2 H), 2.70−2.83 (m, 2 H), 3.56−3.63 (m, 1 H), 4.26 (dd, J = 13.6 and 4.8 Hz, 1 H), 7.18−7.24 (m, 3 H), 7.27−7.35 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 30.4, 32.0, 40.0, 41.0, 42.0, 57.3, 126.6, 126.7 (2C), 128.6 (2C), 145.0, 173.6; IR (KBr, neat) 3027, 2930, 2853, 1686, 1452, 1375, 1267, 1188, 759, 701 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}NO$ (M + H)$^+$ 216.1383, found 216.1383.

(5S,7S*,8aR*)-5-Benzyl-7-phenylhexahydroindolizin-3(2H)-one (**10b**):* pale yellow solid; mp 72−74 °C; yield 116 mg, 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (q, J = 12.0 Hz, 1 H), 1.54−1.69 (m, 2 H), 1.75−1.81 (m, 1 H), 2.08−2.14 (m, 1 H), 2.21−2.30 (m, 1 H), 2.33−2.44 (m, 2 H), 2.87−2.98 (m, 2 H), 3.03−3.10 (m, 1 H), 3.84−3.90 (m, 1 H), 4.56−4.62 (m, 1 H), 7.16−7.23 (m, 4 H), 7.25−7.32 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 30.6, 33.6, 36.7, 36.8, 41.1, 49.6, 53.9, 126.7, 126.8 (2C), 128.7, 128.8 (4C), 129.3 (2C), 138.3, 145.0, 173.7; IR (KBr, neat) 2930, 1660, 1492, 1388, 1264, 1103, 753,

695 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{23}NO$ $(M + H)^+$ 306.1852, found 306.1853.

(8R,9aR*)-8-Phenylhexahydro-1H-quinolizin-4(6H)-one* (**10c**): colorless liquid; yield 96 mg, 84%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48−1.55 (m, 1 H), 1.56−1.59 (m, 1 H), 1.60−1.65 (m, 1 H), 1.66−1.74 (m, 1 H), 1.81−1.94 (m, 3 H), 1.99−2.04 (m, 1 H), 2.31−2.48 (m, 2 H), 2.58 (dt, J = 13.2 and 3.2 Hz, 1 H), 2.72−2.80 (m, 1 H), 3.36−3.43 (m, 1 H), 4.89−4.94 (m, 1 H), 7.18−7.23 (m, 3 H), 7.27−7.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 30.4, 32.7, 33.1, 41.7, 42.3, 42.7, 56.7, 126.6, 126.8 (2C), 128.7 (2C), 145.2, 169.5; IR (KBr, neat) 2933, 2859, 1629, 1452, 1341, 1268, 1169, 1088, 756 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}NO$ $(M + H)^+$ 230.1539, found 230.1546.

(6S,8R*,9aS*)-6-Isobutyl-8-phenylhexahydro-1H-quinolizin-4(6H)-one* (**10d**): pale yellow liquid; yield 101 mg, 71%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (q, J = 12.0 Hz, 1 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.39−1.57 (m, 3 H), 1.60−1.69 (m, 2 H), 1.77−1.85 (m, 2 H), 1.86−1.92 (m, 1 H), 1.97−2.04 (m, 1 H), 2.32−2.46 (m, 3 H), 2.96−3.04 (m, 1 H), 3.56−3.63 (m, 1 H), 5.12−5.18 (m, 1 H), 7.19−7.23 (m, 3 H), 7.29−7.33 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 22.8, 23.1, 25.3, 30.5, 33.3, 35.6, 36.8, 39.3, 41.9, 46.6, 51.1, 126.5, 126.8 (2C), 128.6 (2C), 145.3, 169.7; IR (KBr, neat) 2952, 2868, 1636, 1459, 1416, 1332, 1274, 1171, 1017, 758, 700 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{27}NO$ $(M + H)^+$ 286.2165, found 286.2169.

(2R,10bS*)-2-Phenyl-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-6(2H)-one* (**10e**): pale yellow solid; mp 86−88 °C; yield 89 mg, 68%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (q, J = 12.0 Hz, 1 H), 1.64 (dq, J = 12.4 and 4.8 Hz, 1 H), 1.96−2.06 (m, 1 H), 2.47−2.58 (m, 1 H), 2.96−3.04 (m, 1 H), 3.16 (dt, J = 13.2 and 3.2 Hz, 1 H), 4.46 (dd, J = 11.6 and 3.2 Hz,1 H), 4.60 (dd, J = 13.2 and 3.6 Hz, 1 H), 7.18 (d, J = 6.8 Hz, 2 H), 7.25 (d, J = 7.2 Hz, 1 H), 7.31 (t, J = 7.6 Hz, 2 H), 7.39 (d, J = 6.8 Hz, 1 H), 7.44−7.54 (m, 2 H), 7.87 (d, J = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9, 38.9, 39.3, 42.0, 58.8, 121.7, 123.8, 126.8 (2C), 128.3 (2C), 128.7 (2C), 131.2, 132.4, 144.6, 145.3, 166.2; IR (KBr, neat) 3026, 2920, 2859, 1688, 1451, 1359, 1289, 1240 1146, 1094, 973, 760, 735, 692 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}NO$ $(M + H)^+$ 264.1383, found 264.1383.

Methyl 4-((2R,4S*,10bS*)-6-oxo-2-phenyl-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindol-4-yl)benzoate* (**10f**): pale yellow solid; mp 131−133 °C; yield 143 mg, 72%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (q, J = 12.0 Hz, 1 H), 2.12 (dq, J = 13.2 and 5.6 Hz, 1 H), 2.44−2.50 (m, 1 H), 2.68−2.74 (m, 1 H), 2.97−3.04 (m, 1 H), 3.91 (s, 3 H), 4.59 (dd, J = 12.0 and 4.0 Hz, 1 H), 5.98 (d, J = 5.2 Hz, 1 H), 7.17 (d, J = 7.2 Hz, 2 H), 7.24 (d, J = 7.6 Hz, 1 H), 7.32 (t, J = 7.6 Hz, 2 H), 7.37−7.45 (m, 3 H), 7.51−7.58 (m, 2 H), 7.97 (d, J = 7.2 Hz, 1 H), 8.03 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 37.4, 38.8, 49.8, 52.1, 56.1, 121.9, 124.0, 126.5 (2C), 126.6 (2C), 126.8, 128.4, 128.7 (2C), 128.9, 130.0 (2C), 131.5, 131.6, 144.0, 144.8, 145.5, 166.6, 167.2; IR (KBr, neat) 3055, 2951, 2924, 1720, 1692, 1612, 1453, 1280, 1111, 1018, 930, 856, 736, 697 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{23}NO_3$ $(M + H)^+$ 398.1751, found 398.1752.

(2R,4S*,10bS*)-2,4-Diphenyl-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-6(2H)-one* (**10g**): pale yellow liquid; yield 105 mg, 62%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (q, J = 12.0 Hz, 1 H), 2.08 (ddd, J = 5.6, 13.2, and 18.8 Hz, 1 H), 2.44 (d, J = 12.4 Hz, 1 H), 2.69 (d, J = 12.4 Hz, 1 H), 3.06−3.12 (m, 1 H), 4.58 (dd, J = 3.6 and 12.0 Hz, 1 H), 5.95 (d, J = 5.2 Hz, 1 H), 7.18 (d, J = 7.6 Hz, 2 H), 7.23−7.43 (m, 8 H), 7.49−7.58 (m, 3 H), 7.97 (d, J = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 37.4, 39.0, 49.8, 56.0, 121.9, 124.1, 126.2, 126.5 (2C), 126.8 (2), 126.9, 127.1, 128.4, 128.8 (2C), 128.9 (2C), 129.0, 131.6, 139.4, 144.5, 167.2; IR (KBr, neat) 3057, 3028, 2923, 1699, 1616, 1494, 1468, 1409, 1234, 1161, 1029, 934, 764, 700 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}NO$ $(M + H)^+$ 340.1696, found 340.1697.

(2R,4S*,10bS*)-4-Cyclohexyl-2-phenyl-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-6(2H)-one* (**10h**): white solid; mp 76−78 °C; yield 122 mg, 71%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05−1.21 (m, 4 H), 1.33 (q, J = 12.0 Hz, 1 H), 1.60−1.91 (m, 8 H), 2.18−2.24 (m, 1 H), 2.45−2.52 (m, 1 H), 3.13−3.21 (m, 1 H), 4.32 (dd, J = 10.0 and 5.2 Hz, 1 H), 4.53 (d, J = 12.0 and 3.6 Hz, 1 H), 7.19−7.24 (m, 3 H), 7.31 (t, J = 7.8 Hz, 1 H), 7.39 (d, J = 7.2 Hz, 1 H), 7.45−7.54 (m, 3 H), 7.88 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 26.1, 29.7, 30.3, 33.3, 37.3, 37.8, 38.8, 39.2, 52.9, 55.8, 121.6, 123.9, 124.1, 126.8 (2C), 128.2, 128.7 (2C), 131.1, 131.5, 144.7, 145.5, 166.8; IR (KBr, neat) 3029, 2926, 2851, 1696, 1616, 1449, 1411, 1265, 1164, 1095, 1017, 950, 760, 737, 696 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{27}NO$ $(M + H)^+$ 346.2165, found 346.2164.

(2R,4S*,10bS*)-4-(4-Methoxyphenyl)-2-phenyl-1,3,4,10b-tetrahydropyrido[2,1-a]isoindol-6(2H)-one* (**10i**): white solid; mp 71−73 °C; yield 100 mg, 54%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (q, J = 12.0 Hz, 1 H), 2.02−2.10 (m, 1 H), 2.42−2.47 (m, 1 H), 2.63−2.68 (m, 1 H), 3.08−3.15 (m, 1 H), 3.80 (s, 3 H), 4.56 (dd, J = 12.0 and 4.0 Hz, 1 H), 5.90 (d, J = 4.4 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.19−7.26 (m, 3 H), 7.33 (t, J = 7.6 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.49−7.56 (m, 3 H), 7.96 (d, J = 6.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5, 37.4, 39.1, 49.3, 55.3, 55.9, 114.2 (2C), 121.8, 124.0, 126.7 (2C), 127.4 (2C), 127.7, 128.3 (2C), 128.7, 131.4, 131.5, 131.9, 144.5, 145.7, 158.5, 167.1; IR (KBr, neat) 2931, 2857, 1686, 1612, 1512, 1468, 1410, 1298, 1250, 1179, 1032, 835, 763, 737, 696 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}NO_2$ $(M + H)^+$ 370.1802, found 370.1801.

Procedure for the Synthesis of (2*R,4*S**,9a*S**)-4-Isobutyl-2-phenyloctahydro-1*H*-quinolizine (11).** To a stirred suspension of $LiAlH_4$ (38 mg, 1 mmol) in dry THF (5 mL) was added compound **10d** (86 mg, 0.3 mmol) in an ice bath, and the mixture was refluxed for 6 h. The solution was cooled in an ice bath and quenched by the addition of EtOAc. The precipitate was filtered off through Celite and washed with EtOAc. The combined filtrate was concentrated and purified by column chromatography using ethyl acetate and hexane (1:4) as eluents, giving (2*R**,4*S**,9a*S**)-4-isobutyl-2-phenyloctahydro-1*H*-quinolizine (55 mg, 68%) as a colorless liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J = 6.4 Hz, 3 H), 0.94 (d, J = 6.4 Hz, 3 H), 1.44−1.50 (m, 2 H), 1.52−1.71 (m, 4 H), 1.73−1.78 (m, 1 H), 1.81−1.86 (m, 1 H), 1.96 (dt, J = 12.8 and 4.4 Hz, 1 H), 2.41−2.48 (m, 2 H), 2.53 (dt, J = 11.2 and 3.2 Hz, 2 H), 2.63−2.70 (m, 2 H), 2.77−2.85 (m, 2 H), 2.98−3.04 (m, 1 H), 7.15−7.32 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 24.5, 26.4, 26.6, 32.1, 32.4, 34.3, 36.4, 36.5, 41.8, 51.8, 54.0, 58.6, 126.3, 127.1 (2C), 128.6 (2C), 146.6; IR (KBr, neat) 2924, 2852, 1465, 1261, 1086, 800 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{29}N$ $(M + H)^+$ 273.2373, found 273.2371.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, tables, and CIF files giving ^1H and ^{13}C NMR and HRMS spectra of all new compounds and crystal parameters and ORTEP diagrams of compounds **9c** and **10i**. 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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