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Two-Component Domino Reactions Initiated from Ketenes: Serendipitous Synthesis of Quinolizidinones Analogous to Chelated Lobeline's Conformation

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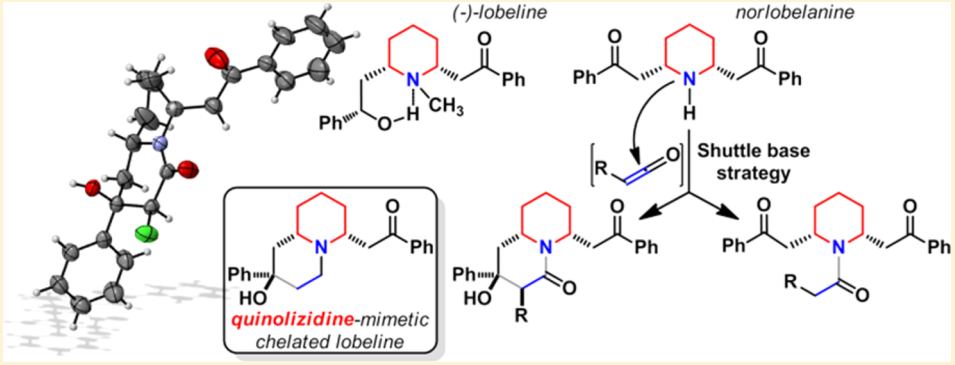
Supporting Information



ABSTRACT: An original and efficient synthesis of quinolizidinones through a one-pot two-component cascade reaction of norlobelanine with *in situ* generated ketenes is reported. Functionalized fused azabicyclic scaffolds bearing multiple stereogenic centers were prepared with excellent diastereoselectivities. Mild optimized conditions involving a key "shuttle base" deprotonation strategy was applied to the synthesis, in a short sequence, of a constrained mimetic of the privileged H-bonded conformation of (−)-lobeline.

INTRODUCTION

Lobelia is a large genus belonging to the Campanulaceae family. With more than 20 different alkaloids, *Lobelia inflata* is one of the most intensively investigated species.[1] Interest in *Lobelia* alkaloids has increased in recent years because of their biological activities. Among the most active of them, (−)-lobeline **1** (Scheme 1) currently arouses a renewed interest as a result of its activity on the central nervous system (CNS),[2] albeit it has persistently inspired the medicinal chemist for the preparation of structurally modified derivatives for treating drug abuse and CNS disorders.[2,3] In particular, (−)-lobeline **1** was recently proved to be a relevant template in a fragment growing hit optimization strategy in the nicotinic acetylcholine receptor (nAChR) subtype-selective lead discovery.[4] Among natural alkaloid ligands of high-affinity for nAChRs, (−)-lobeline **1** occupies a particular place due to its complex pharmacological profile: it was presented as a nAChR-subtype unselective ($\alpha4\beta2$ and $\alpha7$ partial agonist and $\alpha4\beta4$ full agonist) and either as a partial agonist or an antagonist of nicotine and epibatidine toward nAChRs.[5]

The pseudo-symmetrical structure of lobeline is constituted of a *N*-methylpiperidine backbone disubstituted in C_2 and C_6 positions, by two flexible carbonylated and hydroxylated arms respectively, authorizing a wide variability of rotational conformers (Scheme 1). Nonetheless, it is clearly established that the hydroxyl group provides an intramolecular strong hydrogen bonding in both neutral and protonated forms allowing the formation of chelated conformations such as **1b**.[6] Thus, the trifunctional character of lobeline and the possible existence of chelated and extended species render the rationalization of its binding affinity, agonistic and antagonistic activities extremely complex.[5a,7]

As a part of a fundamental research program aiming at studying nAChRs allosteric rearrangement, we pay particular attention to design and synthesize nAChR conformation-selective ligands. Since the concept of sustainability is from now on at the heart of the drug discovery efforts,[8] we are interested in the rational diversity-oriented synthesis of *Lobelia* alkaloids

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Scheme 1. (−)-Lobeline's Conformation Mimic

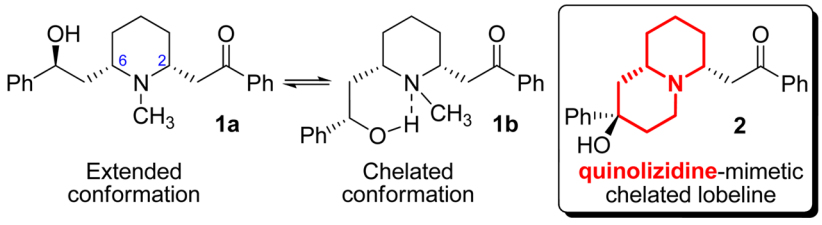
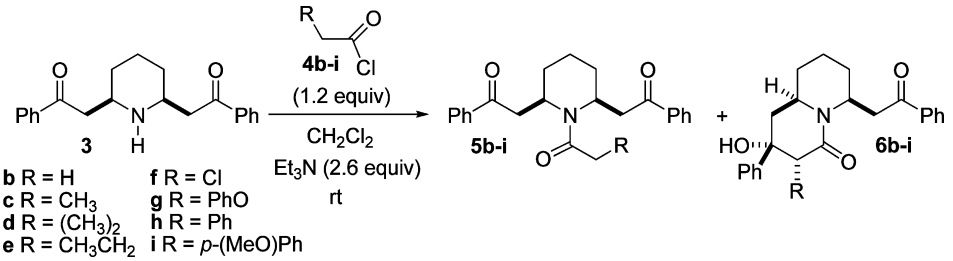


Table 1. Reaction of Norlobelanine with α-Substituted Ketenes



				yield (%)[b]	
entry	R	time (min)	**5b−i**:**6b−i** ratio[a]	**5b−i**	**6b−i**
1	H	15	1:1	45	42
2	CH_3	15	0:1	–	91
3	$(CH_3)_2$	60	2:3	40	57
4	CH_3CH_2	45	0:1	–	90
5	Cl	15	3:2	52	32
6	PhO	120	2:3	31	50
7	Ph	60	2:1	70[c,d]	
8	*p*-(MeO)Ph	10	7:3	80[c,d]	

[a]Ratio determined by ^{1}H NMR from the crude reaction mixture. [b]Isolated yield. [c]The starting material **3** was recovered in 20% yield. [d]Products inseparable by standard flash chromatography on alumina or silica gel.

analogues dealing with environmentally friendly considerations.[9] We recently studied the phenomenon of mutarotation exhibited by mimics of the "opened" lobeline geometry **1a** bearing a β-aminoketone pattern.[9a] We demonstrated that fine structural tuning allowed the formation of configurationally stable compounds which constitute good candidates for the stereoselective synthesis of lobeline analogues. With this objective, we tried to acetylate the norlobelanine **3** by condensing acetyl chloride in the presence of Et_3N. Unexpectedly, the reaction furnished an equimolar mixture of two compounds, the anticipated *N*-acetylated piperidine **5b** and the serendipitous quinolizidine fused azabicycle **6b**. The latter appears to us as an ideal framework able to mimic the chelated conformation **1b** of (−)-lobeline (Table 1). This premise was reinforced by the recently isolated quinolizidine alkaloid, epiquinamide, which was initially presumed selective of nAChR β2-subunit.[10] Moreover, to the best of our knowledge, structurally constrained lobeline analogues have never been studied.

From a synthetic point of view, stereocontrolled construction of aza-fused-ring systems in a limited number of steps constitutes a real challenge for the chemists' community. Consequently, novel synthetic strategies have received considerable attention in the past decades.[11] Among them, several monocyclisation approaches using appropriately substituted piperidines have been reported in the literature to accede in multistep sequence to functionalized quinolizidines.[12] Domino reactions have also demonstrated their synthetic efficiency to allow the rapid synthesis of a wide range of structurally diverse molecules, including azabicycle-containing natural products.[13] Therefore, developing novel multicomponent domino processes constantly contributes to the advancement of the medicinal chemistry field and the improvement of the eco-friendly practices.

In this present work, we thus envisaged to exploit our unanticipated desymmetrizing cascade reaction of norlobelanine **3** for the construction of a quinolizidine core. With the aim of developing a novel step-economical and divergent synthetic method of lobeline rigid analogues, we hypothesized that the condensation of the N-nucleophile **3** to ketene as C2 building block could provide a direct access to quinolizidinone scaffolds through a domino ketene amination/intramolecular aldol reaction. This original approach is presented herein.

RESULTS AND DISCUSSION

Preliminary studies were performed condensing to norlobelanine **3**, the TMS-ketene[14] **4a**, which seemed to be more appropriate in view of its easy handling, large scale preparation, and long-term storable stability.[15] The *meso*-piperidine **3** can be diastereoselectively synthesized according to our recently published procedure coupling a ring-closing double aza-Michael reaction with a crystallization-induced dynamic resolution.[3a] The two-component reaction was carried out in the presence of triethylamine under various reaction temperatures (from room temperature to reflux of 1,2-dichloroethane). After completion of the reaction, attested by TLC, usual workup and purification only afforded the amide **5a** resulting from the kinetically

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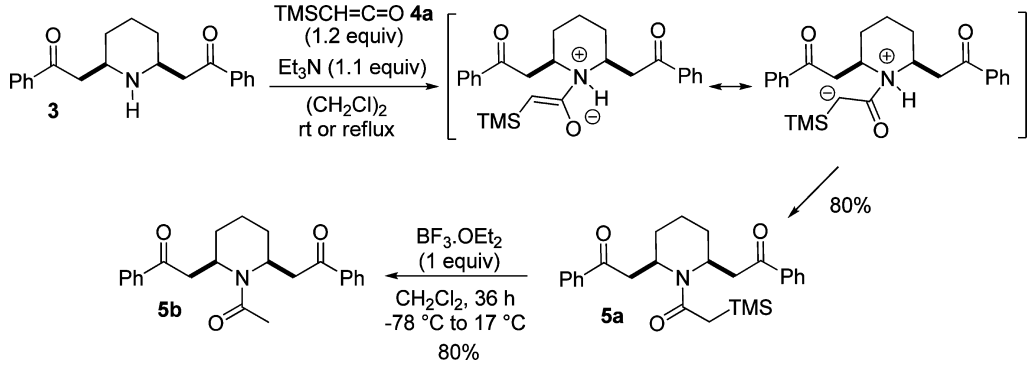
Scheme 2. Reaction of Norlobelanine with TMS-Ketene

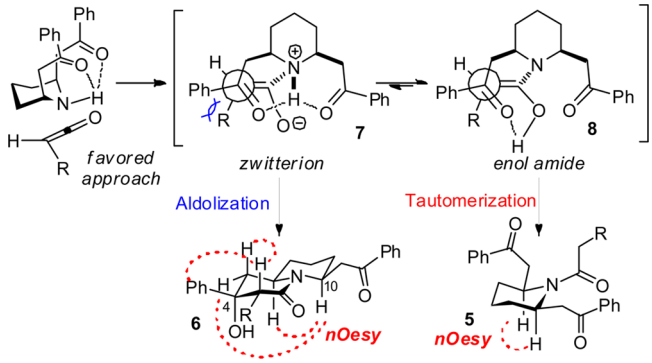


favored tautomeric reprotonation of the zwitterionic intermediate (Scheme 2). The targeted azabicycle was never observed. The chemoselective formation of the amide **5a** may be explained by both disfavored steric effects and electronic properties induced by the presence of the silylated group. The bulkiness induced by both the TMS group and the phenyl ketone may hamper the approach required to the intramolecular aldolization favoring the tautomeric reprotonation of the silicium-stabilized carbanionic species. As Lewis acids were reported to promote aldol reaction of α-TMS-ketenes with carbonyl compounds,[16] the amide **5a** was treated with a stoichiometric amount of $BF_3{\cdot}OEt_2$. Unfortunately, only the desilylated acetamide **5b** was isolated showing the difficulty to promote the intramolecular aldol reaction under mild conditions.

In order to determine the critical factor influencing the ketene amination/intramolecular aldolization cascade, the condensation of norlobelanine **3** with different α-substituted ketenes was investigated. Aliphatic and aromatic ketenes were prepared *in situ* from the corresponding acyl chlorides **4b**−**i** through a tertiary amine-induced dehydrohalogenation reaction (Table 1).[17] As aforementioned, reaction of norlobelanine **3** with acetyl chloride **4b** in the presence of Et_3N produced a separable mixture of both the formal cycloadduct **6b** and the acetylated piperidine **5b** (Table 1, entry 1). They were isolated in 42% and 45% yields, respectively. Delightfully, homologation of the acetyl chloride to propionyl and butyryl chloride exclusively afforded the corresponding quinolizidin-2-ones **6c** and **6e** in nearly 90% yield (Table 1, entries 2 and 4). In contrast, the presence of a bulkier α-substituent upturned the ratio in favor of the acylated product **5**, confirming the deleterious effect of the steric constraint on the cyclizing aldolization (Table 1, entries 3 and 6−8). For a ketene-stabilizing phenyl substituent, the corresponding constitutional isomers **5** and **6** were isolated as an inseparable mixture by standard flash chromatography on alumina or silica gel. If the presence of an electron-donating group accelerated the reaction completion, the ratio in favor of the piperidine **5** remained almost unmodified (Table 1, entries 7 vs 8). Similarly, π-donor heteroatomic α-substituents disfavored the cyclocondensation in benefit of the acylation process (Table 1, entries 5 and 6). These results reflect the crucial role played by both electronic and steric properties of the ketene α-substituent in controlling the switch of the reaction pathway.

Except for **6g** (R = OPh), quinolizidin-2-one derivatives **6** were obtained with total diastereoselectivity. The relative configuration was unambiguously determined by virtue of two-dimensional nOesy correlations showing the *syn*-configuration retention of the starting norlobelanine **3** and the *syn*-configuration between the C_4 phenyl group and the C_{10} phenacyl arm (Scheme 3). As the quinolizidin-2-ones **6b** and **6f** crystallized, single crystal X-ray analysis confirmed this relative configuration (see Supporting Information).

Scheme 3. Plausible Mechanism for the Cyclizing Cascade



Mechanistically, the excellent diastereocontrol could be explained by the retention of the stabilized intramolecularly H-bonded conformation adopted by the starting crystalline norlobelanine **3** (Scheme 3).[9a] The N-nucleophilic attack of ketenes by the norlobelanine **3** may operate in *anti* of the phenacyl arms on the less hindered piperidine side leading to the transient zwitterionic intermediate **7**. The latter can evolve through two switchable competitive pathways: (i) the intramolecular aldolization promoting the final ring closure into quinolizidin-2-ones **6**; or (ii) the tautomeric reprotonation affording the N-acylated *cis*-piperidine **5** (Scheme 3). Conspicuously, steric congestion induced by the ketene α-substituent could disfavor the compact approach required for the subsequent intramolecular aldolization and enhance the stability of the transient zwitterionic ylide **7**. Consequently, its reprotonation into ketene *N*,*O*-acetal **8** which tautomerizes in the amide **5** is preferred.[18]

The excellent diastereoselectivity observed for the ring-closing cascade may result from the preservation of six-membered H-bonded conformations throughout the reaction pathway.

In this context, we searched for optimal reaction conditions to preferentially reach quinolizidine framework. We studied the model reaction of the norlobelanine **3** with ethenone for which an equimolar ratio of aldol **6b** and amide **5b** was obtained when triethylamine was used in excess (Table 1, entry 1). We clearly demonstrated that reaction is dependent on the addition order

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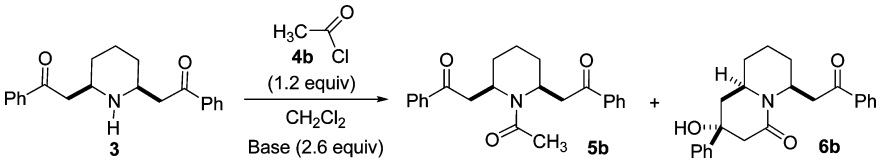
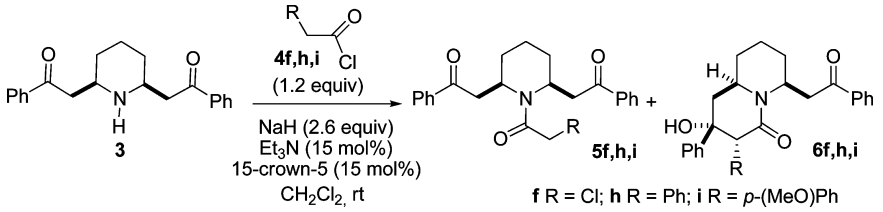
Table 2. Optimization of Reaction Conditions



entry	base	temp. (°C)	time	conv. (%)[b]	ratio (%)[b] 5b:6b
1[a]	Et_3N	rt	15 min	>98	35:65
2[a]	Et_3N	0	6 h	>98	80:20
3[a]	*i*-Pr_2NH	rt	24 h	45	35:10
4[a]	2,6-di-*tert*-butylpyridine	rt	24 h	30	20:10
5[a]	DBU	rt	24 h	50	35:15
6[a]	2,3,6-collidine	rt	24 h	55	35:20
7[a]	DABCO	rt	24 h	>98	90:10
8[a]	proton sponge, Et_3N (15 mol %)	rt	24 h	>98	35:65
9	NaH	rt	24 h	50	30:20
10	NaH, Et_3N (15 mol %)	rt	24 h	75	15:55
11	NaH, Et_3N (15 mol %) 15-crown-5 (15 mol %)	rt	24 h	>98	15:85(65)[c]

[a]Acetyl chloride **4b** (1.2 equiv) was added to a solution of norlobelanine **3**, base (2.6 equiv), and 3 Å molecular sieves in DCM (0.25 M). [b]Conversion and ratio determined by ^{1}H NMR. [c]Isolated yield.

Table 3. "Shuttle Base" Route Extension



				yield (%)	
entry	R	time (h)	conv. (%) (5:6 ratio)[a]	5f,h,i	6f,h,i
1	Cl	24	75 (33:67)	20[c]	55[b]
2	Ph	24	>98 (45:55)	39[d]	50[d]
3	*p*-(MeO)Ph	24	>98 (40:60)	30[d]	52[d]

[a]Ratio determined by ^{1}H NMR on the crude reaction mixture. [b]Crystallized from ether. [c]The starting material **3** was recovered in 15% yield. [d]Isolated after purification by reverse-phase preparative HPLC.

of the reagents, the reaction temperature, and the nature of the base employed. Indeed, quinolizidinone **6b** is only formed when the acyl chloride was added in end stage.[19] This could be explained by the short lifespan of the reactive ketene which must be rapidly trapped to overcome its known self-dimerization.[17] Interestingly, co-addition of molecular sieves increased the proportion of azabicycle **6b** clearly showing that the presence of a proton source favored the equilibrium shifts toward the tautomeric reprotonation of the zwitterionic common intermediate **7** (Table 2, entry 1). Concerning reaction temperature, low temperatures dramatically lengthened the reaction and reduced the formation of the azabicycle **6b** (Table 2, entry 2). This **6b**:**5b** ratio inversion observed at 0 °C suggested that the N- to O-prototropy/tautomerization sequence is kinetically favored. At −78 °C, starting piperidine is completely recovered even after 24 h of reaction.

Besides, ketenes formed *in situ* are invariably stirred with partially dissolved ammonium salts. The latter can act as external Brønsted acid and kinetically favors the tautomeric reprotonation of the intermediates **7** at the expense of the intramolecular aldolization. We thus studied the replacement of triethylamine by bulkier amines such as diisopropylamine, 2,6-di-*tert*-butylpyridine, DBU or collidine in order to sterically disfavor the reprotonation step. In all cases, the reaction rate is considerably diminished without tremendously increasing the proportion of aldol compound **6b** (Table 2, entries 3−6). In opposite, the use of the less encumbered DABCO gave the *N*-acetyl piperidine **5b** as the single *cis*-isomer (d.r. > 95%) (Table 2, entry 7). These results may be rationalized by the ability of amine base to act as a proton shuttle in the tautomeric reprotonation step of the reversible long-lived zwitterionic ylides.[20] The more the facade of the amine-base nitrogen is unencumbered, the more the proton transfer, and thus the amide formation are privileged.

At this point, the necessity for finding alternative methods became apparent. Thus, we turned our attention to the elegant work reported by Leckta and co-workers, dealing with the mild generation of monosubstituted ketenes though a "shuttle base" strategy.[20] Encouragingly, using a stoichiometric amount of a "kinetic base" (triethylamine) and an insoluble "thermodynamic base" (proton sponge) permitted the recovery of the initial proportion of the aldol compound **6b** obtained with triethylamine only (Table 2, entry 8). After a brief exploration of insoluble bases, sodium hydride emerged as the optimal one

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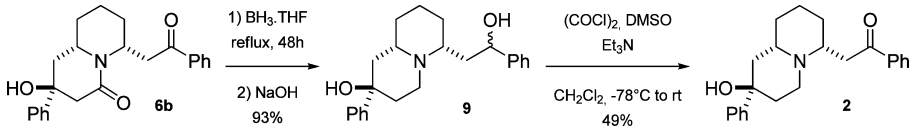
Scheme 4. Synthesis of Quinolizidine-Mimetic Chelated (−)-Lobeline



when compared to carbonates (Table 2, entry 9). Indeed, if similar conversions are obtained, carbonates (K_2CO_3 or $NaHCO_3$) induced the formation of the azabicycle in a marginal yield (inferior to 5%) showing that irreversible deprotonation benefited the cyclocondensation. More interestingly, the bicyclic compound **6b** could be mainly obtained when the reaction occurred in the presence of an excess of NaH (2.6 equiv) and a catalytic amount of triethylamine (15 mol %) (Table 2, entry 10). The addition of 15-crown-5 as a phase transfer co-catalyst helping the solubilization of NaH, significantly increased the yield of compound **6b** (Table 2, entry 11). Under these conditions, the expected quinolizidine **6b** was isolated as a single diastereomer in a 65% yield.

With these results in hand, we applied the optimized reaction conditions to the reluctant acyl chlorides for which standard conditions favored the ketene amination (Table 1, entries 5, 7−8). Satisfyingly, the **6**:**5** ratio was able to be switched to mostly produce the bicyclic compounds **6f** and **6h−i** without wholly offsetting the negative effect of the steric bulkiness (Table 3).

Finally, the quinolizidinone **6b** was afterward transformed in order to design a new family of constrained bicyclic nAChRs ligands mimicking the H-bonded conformation of (−)-lobeline (Scheme 4). In this context, considerable efforts have been made to develop a satisfactory reductive procedure to remove the lactam function of **6b**. The main difficulties remained in the selective reduction of the lactam function at the expense of the benzylic alcohol hydrogenolysis. Indeed, standard lactam reduction by using LAH in THF was unsuccessful. At room temperature, the starting quinolizidinone **6b** was recovered; in refluxing solvent, complete reduction was observed giving the 2-phenethylquinolizidine derivative as side-product. The best results were obtained by using BH_3·THF at reflux providing quantitatively the reduced quinolizidinediol **9**. Attempts to regenerate the carbonyl group of the phenacyl arm by MnO_2, PCC, PDC, or IBX failed. Only the Swern oxidation gave the desired mimetic **2**, isolated in a 45% yield over two steps.

■ CONCLUSION

We have developed a straightforward and diastereoselective method to synthesize highly substituted quinolizidinones through a desymmetrizing cascade reaction of norlobelanine with ketenes *in situ* generated. The cyclocondensation proceeds via a domino ketene amination/intramolecular aldol reaction. Preservation throughout the reaction pathway of six-membered H-bonded conformations is evoked to explain the excellent diastereocontrol of the cascade. In the particular case of sterically hindered ketenes, the generation of ketenes according to a "shuttle base" strategy improved the formation of the azabicyclic scaffolds at the expense of the *N*-acylpiperidine side products. Eventually, this methodology was successfully applied to the concise total synthesis of a stable constrained mimetic of the intramolecularly H-bonded conformers of (−)-lobeline.

■ EXPERIMENTAL SECTION

General and Materials. Commercially available reagents were used throughout without further purification other than those detailed below. Prior to use, CH_2Cl_2 was dried by means of a solvent purifier system. All anhydrous reactions were carried out under argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on 60F-254 precoated silica (0.2 mm) on glass and was revealed by UV light or Kägi-Misher or Dragendorf reagent. Flash chromatography separations were carried out on silica gel (40−63 μm). Preparative HPLC separations were achieved at 25 °C on an apparatus equipped with a binary pump and a UV−vis diode array detector (190−600 nm) using a C18 column (5 μm, 19 mm × 150 mm). Gradient elution procedure is mentioned below for each concerned product. Infrared (IR) spectra were obtained as neat films. ^1H and ^{13}C NMR spectra were recorded respectively at 300 or 400 MHz and 75 or 100 MHz unless otherwise specified. The chemical shifts for ^1H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the chloroform resonance as the internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. NMR peak has been assigned on the basis of HMBC, HMQC, nOesy, and $^1H-^1H$ COSY experiments. HRMS (ESI) analyses realized with a time-of-flight mass spectrometer yielded ion mass/charge (*m*/*z*) ratios in atomic mass units. The atmospheric pressure chemical ionization (APCI) mass spectra were recorded on a quadrupole time-of-flight mass spectrometer. Diastereomeric excesses (de) were determined by ^1H NMR spectroscopy. The X-ray crystallographic data were measured at ambient temperature (293 K) with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) or copper (λ = 1.54187 Å) rotating-anode generator equipped with confocal optics and a curved large-area Imaging-Plate detector.

Norlobelanine (**3**) was synthesized according to the procedure reported in the literature in 84% yield. Physical data are in accordance with the literature.[3a]

Experimental Procedures. *2,2′-(N-Acetylpiperidine-2,6-cis-diyl)-bis(1-phenylethanone) **5b**.* A mixture of norlobelanine **3** (100 mg, 0.31 mmol, 1 equiv), Et_3N (50 μL, 0.34 mmol, 1.1 equiv) and trimethylsilylketene[21] (88 mg, 0.77 mmol, 2.5 equiv) in $(CH_2Cl)_2$ (4.0 mL) was refluxed for 3 h, then allowed to cool to room temperature and directly concentrated. The residue was purified by silica gel column chromatography (Et_2O-EtOAc, 1:1) to afford the TMS-amide **5a** (108 mg, 80%) which is engaged in the following step. To a dichloromethane solution (3.3 mL) of **5a** was added dropwise BF_3·OEt_2 (54 μL, 0.25 mmol, 1eq). The mixture was stirred for 1 h at −78 °C and was allowed to warm slowly to room temperature for 2 h. The reaction mixture was quenched with saturated aqueous NaCl and washed with Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give yellow oil. The latter was purified by flash chromatography on silica gel using a DCM/Et_2O eluting mixture (90/10) to afford 72 mg (yield = 80%) of the corresponding acetylated compound **5b**.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, *J* = 7.5 Hz, 2H), 7.97 (d, *J* = 7.5 Hz, 2H), 7.61−7.45 (m, 6H), 5.16 (br s, 1H), 4.77 (br s, 1H), 3.71 (dd, *J* = 17.2, 10.3 Hz, 1H), 3.36 (dd, *J* = 13.0, 4.2 Hz, 1H), 3.07−3.02 (m, 2H), 2.15 (s, 3H), 1.80−1.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.6, 197.2, 170.7, 136.4, 136.3, 133.6, 133.2, 128.7, 128.6, 128.0, 48.5, 45.7, 43.2, 28.5, 27.0, 22.1, 13.8; IR (neat) υ_{max}/cm^{-1} 2944, 1716, 1683, 1671, 1580, 1286; HRMS calcd for $C_{23}H_{26}NO_3$ ($[M + H]^+$) 364.1907, found 364.1913.

*General Procedure for the Reaction of Norlobelanine **3** with Acyl Chlorides. Procedure A.* To a solution of norlobelanine **3** (321 mg, 1 mmol, 1 equiv) in dry CH_2Cl_2 (0.25M) at room temperature was added Et_3N (375 μL, 2.6 mmol, 2.6 equiv). The required acyl chloride **4** (1.2 mmol, 1.2 equiv) was then added dropwise. The mixture was

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stirred at room temperature. After completion of the reaction, followed by TLC on silica gel, the mixture was quenched with a 1 N HCl solution and extracted with DCM (3 × 15 mL). Combined organic layers were washed with $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (DCM/Et_2O = 90/10 or 80/20) or by preparative HPLC to yield the desired compounds.

Procedure B. To a solution of norlobelanine **3** (321 mg, 1 mmol, 1 equiv) in dry CH_2Cl_2 (4 mL, 0.25M) at room temperature were added Et_3N (22 μL, 0.15 mmol, 15 mol %), 15-crown-5 (30 μL, 0.15 mmol, 15 mol %), and NaH (63 mg, 2.6 mmol, 1 equiv). The required acyl chloride **4** (1.2 mmol, 1.2 equiv) was then added dropwise, and the mixture was stirred at room temperature. The reaction course was monitored by TLC (DCM/Et_2O = 9/1) until completion. The reaction was quenched with a 1 N HCl solution and extracted with DCM (3 × 15 mL). Combined organic layers were washed with $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (DCM/Et_2O = 90/10 or 80/20) or by preparative HPLC to yield the desired compounds.

With acetyl chloride (86 μL, 1.2 mmol, 1.2 equiv), the general procedure A gave the compound **5b** as a yellow oil (164 mg, 45%), and the compound **6b** was isolated as a white solid (153 mg, 42%). Similarly, the general procedure B gave **6b** in 65% yield (236 mg).

(2S,6R*,9aS*)-2-Hydroxy-6-(2-oxo-2-phenylethyl)-2-phenylquinolizidin-4-one* ***6b***. Mp 78−79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (br d, *J* = 7.2 Hz, 2H), 7.58−7.54 (m, 1H), 7.49−7.45 (m, 4H), 7.37−7.33 (m, 2H), 7.30−7.28 (m, 1H), 4.69−4.65 (m, 1H), 4.07−4.00 (m, 1H), 3.87 (dd, *J* = 13.8, 10.4 Hz, 1H), 2.87 (d, *J* = 17.7 Hz, 1H), 2.82 (s, 1H), 2.79 (dd, *J* = 13.8, 10.4 Hz, 1H), 2.68 (dd, *J* = 17.7, 3.0 Hz, 1H), 2.08 (dt, *J* = 10.0, 3.6 Hz, 1H), 1.91−1.81 (m, 4H), 1.77−1.61 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.9, 168.5, 146.1, 136.5, 133.2, 128.8, 128.7, 128.6, 127.5, 124.3, 71.2, 49.7, 48.7, 46.4, 43.0, 42.8, 28.7, 22.7, 15.4; IR (neat) υ_{max}/cm^{-1} 3025, 2289, 1725, 1678, 1607, 1580, 1294; HRMS calcd for $C_{23}H_{26}NO_3$ ([M + H]$^+$) 364.1907, found 364.1917.

With propionyl chloride (105 μL, 1.2 mmol, 1.2 equiv), the general procedure A afforded the compound **6c** as a white solid (344 mg, 91%).

(2S,3S*,6R*,9aS*)-2-Hydroxy-3-methyl-6-(2-oxo-2-phenylethyl)-2-phenylquinolizidin-4-one* ***6c***. Mp 216−218 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (br d, *J* = 7.2 Hz, 2H), 7.57−7.54 (m, 1H), 7.50−7.47 (m, 2H), 7.44−7.36 (m, 4H), 7.30−7.26 (m, 1H), 4.69−4.66 (m, 1H), 4.02−4.00 (m, 1H), 3.94 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.86 (q, *J* = 7.2 Hz, 1H), 2.80 (dd, *J* = 14.0, 10.3 Hz, 1H), 2.10 (s, 1H), 2.04 (dd, *J* = 13.8, 4.3 Hz, 1H), 1.95−1.59 (m, 7H), 1.07 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.9, 171.3, 145.6, 136.5, 133.1, 128.7, 128.6, 127.2, 124.4, 73.9, 50.1, 48.6, 46.4, 44.9, 42.8, 29.1, 23.0, 15.5, 9.8; IR (neat) υ_{max}/cm^{-1} 3382, 2238, 1681, 1603, 1580, 1287; Anal. calcd for $C_{24}H_{27}NO_3$: C, 76.37; H, 7.21; N, 3.71. Found: C, 76.32; H, 7.13; N, 3.65.

With isobutyryl chloride (125 μL, 1.2 mmol, 1.2 equiv), the general procedure A afforded the compound **5d** as a pale yellow oil (156 mg, 40%) and the compound **6d** as a white solid (223 mg, 57%).

2,2′-(N-Isobutyrylpiperidine-2,6-cis-diyl)bis(1-phenylethanone) ***5d***. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, *J* = 7.4 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.61−7.57 (m, 1H), 7.55−7.44 (m, 5H), 5.18 (m, 1H), 4.89 (m, 1H), 3.74 (dd, *J* = 17.3, 10.3 Hz, 1H), 3.35 (dd, *J* = 13.0, 4.9 Hz, 1H), 3.10−3.02 (m, 2H), 2.85 (sp, *J* = 6.7 Hz, 1H), 1.80−1.66 (m, 4H), 1.60−1.52 (m, 2H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.7, 197.3, 177.4, 136.5, 136.3, 133.6, 133.1, 128.7, 128.6, 128.5, 127.9, 47.2, 45.8, 43.7, 43.4, 30.4, 28.7, 27.3, 20.5, 19.2, 14.1; IR (neat) υ_{max}/cm^{-1} 2866, 1730, 1688, 1672, 1580, 1283; HRMS calcd for $C_{25}H_{30}NO_3$ ([M + H]$^+$) 392.2220, found 392.2228.

(2R,6R*,9aS*)-2-Hydroxy-3,3-dimethyl-6-(2-oxo-2-phenylethyl)-2-phenylquinolizidin-4-one* ***6d***. Mp 163−164 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, *J* = 7.5 Hz, 2H), 7.57−7.54 (m, 1H), 7.51−7.47 (m, 4H), 7.36 (m, 2H), 7.31−7.28 (m, 1H), 4.60 (m, 1H), 4.01−3.95 (m, 2H), 2.77 (dd, *J* = 14.1, 9.8 Hz, 1H), 2.58 (dd, *J* = 13.8, 10.9 Hz, 1H), 2.13 (s, 1H), 1.95−1.88 (m, 4H), 1.77−1.68 (m, 3H), 1.19 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 175.1, 143.4, 136.5, 133.1, 128.7, 127.7, 127.4, 126.7, 76.0, 50.8, 48.7, 47.7, 42.7, 39.00, 29.8, 26.7, 23.5, 18.8, 16.3; IR (neat) υ_{max}/cm^{-1} 3382, 2983, 2357, 1682, 1596, 1426; HRMS calcd for $C_{25}H_{30}NO_3$ ([M + H]$^+$) 392.2220, found 392.2201.

With butyryl chloride (125 μL, 1.2 mmol, 1.2 equiv), the compound **6e** was isolated through the general procedure A as a pale yellow solid (352 mg, 90%).

(2S,3S*,6R*,9aS*)-3-Ethyl-2-hydroxy-6-(2-oxo-2-phenylethyl)-2-phenylquinolizidin-4-one* ***6e***. Mp 82−84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, *J* = 7.3 Hz, 2H), 7.58−7.54 (m, 1H), 7.50−7.44 (m, 4H), 7.38 (m, 2H), 7.30−7.27 (m, 1H), 4.66 (m, 1H), 3.98−3.93 (m, 2H), 2.84 (dd, *J* = 14.5, 9.9 Hz, 1H), 2.64 (dd, *J* = 6.3, 4.1 Hz, 1H), 2.32 (s, 1H), 2.00−1.56 (m, 9H), 1.43−1.33 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.0, 171.5, 146.0, 136.6, 133.0, 128.6, 128.5, 127.0, 124.4, 74.7, 53.1, 50.1, 48.8, 45.3, 42.7, 29.4, 23.4, 19.7, 15.9, 14.9; IR (neat) υ_{max}/cm^{-1} 3395, 2958, 1686, 1610, 1580, 1495; HRMS calcd for $C_{25}H_{29}NNaO_3$ ([M + Na]$^+$) 414.2040, found 414.2054.

With chloroacetyl chloride (96 μL, 1.2 mmol, 1.2 equiv), the general procedure A or B provided the compound **5f** as a pale yellow oil (procedure A: 207 mg, 52%; procedure B: 119 mg, 30%) and the compound **6f** as a white solid (procedure A: 127 mg, 32%; procedure B: 219 mg, 55%).

2,2′-[N-(2-Chloroacetyl)-2,6-cis-diyl]bis(1-phenylethanone) ***5f***. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.65−7.63 (m, 1H), 7.56−7.44 (m, 5H), 5.13 (br s, 1H), 4.82 (br s, 1H), 4.40 (d, *J* = 2.4 Hz, 1H), 4.18 (d, *J* = 2.4 Hz, 1H), 3.58 (dd, *J* = 17.4, 8.8 Hz, 1H), 3.37−3.32 (m, 2H), 3.07 (br t, *J* = 12.0 Hz, 1H), 1.84−1.62 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1, 197.1, 167.1, 136.5, 136.2, 133.8, 133.3, 128.9, 128.7, 128.5, 128.0, 48.4, 46.7, 43.3, 43.0, 42.0, 28.8, 27.0, 14.2; IR (neat) υ_{max}/cm^{-1} 2862, 2242, 1688, 1678, 1580, 1289; HRMS calcd for $C_{23}H_{25}NO_3Cl$ ([M + H]$^+$) 398.1517, found 398.1525.

(2R,3S*,6R*,9aS*)-3-Chloro-2-hydroxy-6-(2-oxo-2-phenylethyl)-2-phenylquinolizidin-4-one* ***6f***. mp 230−231 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (d, *J* = 7.4 Hz, 2H), 7.59−7.55 (m, 1H), 7.52−7.48 (m, 2H), 7.45−7.39 (m, 4H), 7.34−7.31 (m, 1H), 5.01 (s, 1H), 4.79 (m, 1H), 4.07 (m, 1H), 3.88 (dd, *J* = 13.3, 4.0 Hz, 1H), 3.07 (s, 1H), 2.77 (dd, *J* = 13.4, 10.9 Hz, 1H), 2.26 (dd, *J* = 14.3, 3.7 Hz, 1H), 1.95−1.62 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.6, 164.5, 143.5, 136.3, 133.3, 128.8, 128.7, 127.9, 124.3, 73.9, 65.8, 50.4, 48.2, 43.7, 42.5, 28.1, 22.2, 14.6; IR (neat) υ_{max}/cm^{-1} 3397, 2984, 2355, 1701, 1610, 1411; HRMS calcd for $C_{23}H_{25}NO_3Cl$ ([M + H]$^+$) 398.1517, found 398.1525.

With phenoxylacetyl chloride (166 μL, 1.2 mmol, 1.2 equiv), the general procedure A allowed the isolation of the compound **5g** as a pale yellow viscous oil (141 mg, 31%) and a mixture of two separable diastereomers **6g** and **6′g** in a 50% overall yield (228 mg).

2,2′-[N-(2-Phenoxyacetyl)-2,6-cis-diyl]bis(1-phenylethanone) ***5g***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.54−7.39 (m, 6H), 7.18−7.11 (m, 2H), 6.88−6.78 (m, 3H), 5.12 (m, 1H), 4.82−4.69 (m, 3H), 3.52 (dd, *J* = 17.5, 9.3 Hz, 1H), 3.31 (dd, *J* = 15.0, 3.1 Hz, 1H), 3.20 (dd, *J* = 17.5, 3.6 Hz, 1H), 3.00 (dd, *J* = 13.5, 10.8 Hz, 1H), 1.75−1.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.2, 197.1, 168.2, 158.0, 136.5, 136.2, 133.6, 133.3, 129.4, 128.8, 128.7, 128.6, 128.0, 121.5, 114.7, 67.9, 47.6, 46.31, 43.5, 43.1, 28.7, 27.1, 14.2; IR (neat) υ_{max}/cm^{-1} 2366, 1683, 1678, 1580, 1288; HRMS calcd for $C_{29}H_{29}NO_4Na$ ([M + Na]$^+$) 478.1989, found 478.1992.

(2R,3S*,6R*,9aS*)-2-Hydroxy-6-(2-oxo-2-phenylethyl)-3-phenoxy-2-phenylquinolizidin-4-one* ***6g*** *and (2S*,3S*,6R*,9aS*)-2-Hydroxy-6-(2-oxo-2-phenylethyl)-3-phenoxy-2-phenylquinolizidin-4-one* ***6′g***. IR (neat) υ_{max}/cm^{-1} 3397, 2984, 2355, 1701, 1610, 1411; HRMS calcd for $C_{29}H_{29}NNaO_4$ ([M + Na]$^+$) 478.1989, found 478.1992.

Major diastereomer **6g** was isolated as a white solid (205 mg, 45%). Mp 222−223 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.57−7.54 (m, 1H), 7.49−7.45 (m, 2H), 7.42−7.40 (m, 2H),

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7.33−7.22 (m, 3H), 7.13−7.11 (m, 2H), 6.91−6.88 (m, 1H), 6.83−6.80 (m, 2H), 4.95 (s, 1H), 4.87−4.83 (m, 1H), 4.13−4.06 (m, 1H), 3.81 (dd, J = 14.1, 4.0 Hz, 1H), 3.39 (br s,1H), 2.89 (dd, J = 14.0, 10.4 Hz, 1H), 2.22−2.17 (m, 1H), 1.98−1.61 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.6, 168.1, 159.4, 143.9, 136.5, 133.2, 129.2, 128.5, 127.1, 124.6, 122.1, 117.1, 80.6, 74.2, 49.5, 48.3, 42.7, 42.5, 28.5, 22.7, 15.0.

Minor diastereomer **6′g** was isolated as semitransparent oil (23 mg, 5%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, J = 7.0 Hz, 2H), 7.57−7.53 (m, 1H), 7.47−7.44 (m, 2H), 7.41−7.39 (m, 2H), 7.35−7.31 (m, 2H), 7.28−7.27 (m, 1H), 7.14 (dd, J = 8.6, 7.3 Hz, 2H), 6.93−6.89 (m, 1H), 6.87−6.85 (m, 2H), 5.01 (s, 1H), 4.30 (m, 1H), 4.02 (dd, J = 16.1, 5.4 Hz, 1H), 3.52−3.46 (m, 1H), 3.17 (br s, 1H), 3.11 (dd, J = 16.0, 8.7 Hz, 1H), 2.40 (dd, J = 14.2, 5.9 Hz, 1H), 2.18 (dd, J = 14.2, 6.4 Hz, 1H), 2.14−2.05 (m, 1H), 1.96−1.88 (m, 1H), 1.83−1.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.5, 167.8, 158.9, 143.5, 136.8, 133.0, 129.2, 128.5, 128.4, 127.6, 124.8, 122.1, 116.7, 80.6, 75.2, 54.2, 53.6, 42.7, 42.0, 31.1, 26.5, 20.4.

With phenylacetyl chloride (159 μL, 1.2 mmol, 1.2 equiv), the general procedure B gave the compound **5h** as a semitransparent oil (171 mg, 39%) and the compound **6h** as a white solid (220 mg, 50%). They have been separated by preparative HPLC with a 17 mL/min flow rate. The mobile phase is a mixture of water and methanol. A gradient elution procedure was used: 0−20 min, 75% aq. MeOH; 20−30 min, 100% MeOH.

2,2′-[N-(2-Phenylacetyl)-2,6-cis-diyl]bis(1-phenylethanone) ***5h***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.15 (d, J = 7.1 Hz, 2H), 7.86 (d, J = 7.5 Hz, 2H), 7.62−7.45 (m, 6H), 7.28−7.18 (m, 4H), 7.09−7.05 (m, 1H), 5.24 (m, 1H), 4.89−4.84 (m, 1H), 3.85 (d, J = 14.5 Hz, 1H), 3.78 (d, J = 14.5 Hz, 1H), 3.54 (dd, J = 17.5, 10.3 Hz, 1H), 3.38 (dd, J = 12.1, 4.7 Hz, 1H), 3.02 (dd, J = 12.7, 10.8 Hz, 1H), 2.78 (d, J = 17.3 Hz, 1H), 1.75−1.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.7, 197.3, 171.4, 136.5, 136.3, 134.9, 133.5, 133.3, 128.7, 128.6, 127.9, 126.8, 48.2, 46.1, 43.3, 41.8, 28.4, 27.2, 14.0; IR (neat) υ_{max}/cm^{-1} 2855, 1683, 1676, 1580, 1286; HRMS calcd for $C_{29}H_{30}NO_3$ ([M + H]$^+$) 440.2220, found 440.2224.

(2S,3S*,6R*,9aS*)-2-Hydroxy-6-(2-oxo-2-phenylethyl)-2,3-diphenylquinolizidin-4-one* ***6h***. mp 117−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 7.5 Hz, 2H), 7.56−7.52 (m, 1H), 7.48−7.44 (m, 2H), 7.32−7.13 (m, 8H), 6.81−6.79 (m, 2H), 4.84 (m, 1H), 4.22 (s, 1H), 4.21−4.16 (m, 1H), 4.02 (dd, J = 13.4, 3.4 Hz, 1H), 2.82 (dd, J = 12.8, 11.1 Hz, 1H), 2.14 (d, J = 7.2 Hz, 2H), 2.01−1.74 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 169.5, 145.3, 136.4, 135.0, 133.1, 130.5, 128.8, 128.7, 128.3, 128.2, 127.3, 127.1, 124.5, 73.4, 60.0, 49.8, 48.2, 44.0, 42.9, 28.6, 22.8, 15.0; IR (neat) υ_{max}/cm^{-1} 3390, 2953, 2364, 1683, 1610, 1427; HRMS calcd for $C_{29}H_{29}NO_3Na$ ([M + Na]$^+$) 462.2040, found 462.2043.

With 4-methoxyphenylacetyl chloride (183 μL, 1.2 mmol, 1.2 equiv), the general procedure B afforded the compound **5i** as a semitransparent oil (141 mg, 30%) and the compound **6i** as a white solid (244 mg, 52%). They have been separated by preparative HPLC with a 17 mL/min flow rate. The mobile phase is a mixture of water and methanol. A gradient elution procedure was used: 0−20 min, 75% aq. MeOH; 20−30 min, 100% MeOH.

2,2′-{N-[2-(4-Methoxyphenyl)acetyl]-2,6-cis-diyl}bis(1-phenylethanone) ***5i***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.62−7.44 (m, 6H), 7.17 (d, J = 8.6 Hz, 2H), 6.70 (d, J = 8.3 Hz, 2H), 5.23 (m, 1H), 4.83 (m, 1H), 3.76 (m, 2H), 3.54 (s, 3H), 3.48 (dd, J = 17.7, 10.5 Hz, 1H), 3.38 (dd, J = 12.9, 4.7 Hz, 1H), 3.02 (dd, J = 12.7, 10.8 Hz, 1H), 2.71 (br d, J = 17.6 Hz, 1H), 1.80−1.47 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.7, 197.3, 171.6, 158.3, 136.6, 136.3, 133.3, 129.6, 128.7, 127.9, 126.7, 114.1, 54.9, 48.2, 46.0, 43.2, 41.1, 28.4, 27.2, 14.0; IR (neat) υ_{max}/cm^{-1} 2863, 1683, 1677, 1580, 1287; HRMS calcd for $C_{30}H_{31}NO_4Na$ ([M + Na]$^+$) 492.2145, found 492.2155.

(2S,3S*,6R*,9aS*)-2-Hydroxy-3-(4-methoxyphenyl)-6-(2-oxo-2-phenylethyl)-2-phenylquinolizidin-4-one* ***6i***. Mp 115−117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 8.5 Hz, 2H), 7.56−7.52 (m, 1H), 7.48−7.44 (m, 2H), 7.33−7.29 (m, 2H), 7.26−7.22 (m, 3H), 6.73−6.68 (m, 4H), 4.85−4.81 (m, 1H), 4.19 (s, 1H), 4.16−4.14 (m, 1H), 4.02 (dd, J = 13.5, 4.0 Hz, 1H), 3.72 (s, 3H), 2.80 (dd, J = 13.4, 10.8 Hz, 1H), 2.16−2.02 (m, 2H), 2.02−1.60 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.1, 169.7, 158.7, 145.5, 136.4, 133.2, 131.5, 128.8, 128.7, 128.3, 127.1, 127.0, 124.6, 113.8, 73.5, 59.2, 55.2, 49.8, 48.1, 43.9, 43.0, 28.6, 22.8, 14.9; IR (neat) υ_{max}/cm^{-1} 3390, 2950, 2362, 1677, 1618, 1439; HRMS calcd for $C_{30}H_{31}NO_4Na$ ([M + Na]$^+$) 492.2145, found 492.2158.

(2R,6R*,9aS*)-6-(2-Hydroxy-2-phenylethyl)-2-phenyl-quinolizidin-2-ol* ***9***. BH_3·THF (1 M in THF, 2.65 mL, 2.65 mmol) was added to the quinolizidinone **6b** (100 mg, 0.26 mmol), and the resulting solution was heated at reflux for 48h. The reaction was cooled at room temperature and quenched with H_2O (1.2 mL) followed by NaOH 1 M (3.5 mL). The mixture was then extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the diol **9** as a white solid (85 mg, 93%), which was subjected to the following reaction without purification.

Mp 182−183 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.2 Hz, 2H), 7.35−7.19 (m, 6H), 5.22 (dd, J = 11.4, 3.5 Hz, 1H), 3.85−3.61 (m, 3H), 3.25 (td, J = 10.9, 4.2 Hz, 1H), 2.40 (ddd, J = 13.7, 10.7, 3.5 Hz, 1H), 2.35−2.27 (m, 1H), 2.12 (ddd, J = 12.6, 10.3, 5.6 Hz, 1H), 1.93−1.45 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.5, 145.0, 128.1, 127.9, 126.7, 126.5, 125.7, 124.8, 71.8, 70.9, 59.4. 55.5, 42.1, 37.6, 35.3, 33.2, 26.9, 24.4, 23.3; IR (neat) υ_{max}/cm^{-1} 3390, 2926, 1683, 1494, 1284; HRMS calcd for $C_{23}H_{30}NO_2$ ([M + H]$^+$) 352.2271, found 352.2279.

2-[(4R,8R*,9aS*)-8-Hydroxy-8-phenyl-quinolizin-4-yl]-1-phenylethanone* ***2***. Under an inert atmosphere at −78 °C, DMSO (55 μL, 0.75 mmol) was added dropwise to a solution of oxalyl chloride (41 μL, 0.47 mmol) in dichloromethane (1.4 mL). After stirring for 10 min, a solution of **9** (120 mg, 0.34 mol) in dichloromethane (1 mL) was added dropwise. After stirring for 25 min, triethylamine (245 μL, 1.7 mmol) was added, and the reaction was stirred at −78 °C for an additional 45 min. The cooling bath was removed, and the reaction mixture was allowed to reach 0 °C. After completion (monitored by TLC), the reaction mixture was warmed to room temperature, quenched with HCl 3 M (1 mL) and water (1 mL), and extracted with dichloromethane. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give the crude product which was purified by flash column chromatography (DCM/Et_2O = 70/30) to afford **2** as brown oil (50 mg, 49%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.98 (br s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.63−7.60 (m, 1H), 7.52−7.47 (m, 4H), 7.35−7.26 (m, 3H), 4.23 (dd, J = 19.1, 5.8 Hz, 1H), 3.81 (m, 1H), 3.56−3.48 (m, 1H), 3.32−3.21 (m, 3H), 2.61 (dd, J = 14.5, 12.1 Hz, 1H), 2.40−2.29 (m, 1H), 2.09−2.05 (m, 1H), 1.97−1.64 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.3, 145.6, 135.5, 134.2, 128.9, 128.5, 127.7, 124.4, 70.3, 60.8, 60.3, 47.8, 43.2, 41.2, 35.4, 31.1, 30.0, 22.9; IR (neat) υ (cm^{-1}) 3394, 2922, 1672, 1607, 1447; HRMS calcd for $C_{23}H_{28}NO_2$ ([M + H]$^+$) 350.2115, found 350.2120.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01727.

X-ray crystallographic data of compounds **6a** and **6e** (CIF)

^{1}H and ^{13}C NMR spectra of the compounds **2**, **5b**, **5d**, **5f−i**, **6b−i**, and **9** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kursinszki, L.; Szőke, É *J. Mass Spectrom.* **2015**, *50*, 727−733. (b) Kesting, J. R.; Tolderlund, I.-L.; Pedersen, A. F.; Witt, M.; Jaroszewski, J. W.; Staerk, D. *J. Nat. Prod.* **2009**, *72*, 312−315.

(2) Szőke, É.; Lemberkovics, É.; Kursinszki. L. Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics andTerpenes. In *Natural Products*; Ramawat, K. G., Mérillon, J.-M., Eds; Springer-Verlag: Berlin, Heidelberg, 2013; pp 303−341.

(3) Willyard, C. *Nature* **2015**, *522*, S53−S55.

(4) Edink, E.; Rucktooa, P.; Retra, K.; Akdemir, A.; Nahar, T.; Zuiderveld, O.; van Elk, R.; Janssen, E.; van Nierop, P.; van Muijlwijk-Koezen, J.; Smit, A. B.; Sixma, T. K.; Leurs, R.; de Esch, I. J. P. *J. Am. Chem. Soc.* **2011**, *133*, 5363−5371.

(5) (a) Arias, H. R.; Feuerbach, D.; Ortells, M. *Int. J. Biochem. Cell Biol.* **2015**, *64*, 15−24. (b) Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Norrholm, S. D.; Crooks, P. A. *J. Med. Chem.* **2005**, *48*, 5551−5556. (c) Zheng, G.; Dwoskin, L. P.; Crooks, P. A. *J. Org. Chem.* **2004**, *69*, 8514−8517.

(6) Locati, A.; Berthelot, M.; Evain, M.; Lebreton, J.; Le Questel, J.-Y.; Mathé-Allainmat, M.; Planchat, A.; Renault, E.; Graton, J. *J. Phys. Chem. A* **2007**, *111*, 6397−6405.

(7) Spurny, R.; Debaveye, S.; Farinha, A.; Veys, K.; Vos, A. M.; Gossas, T.; Atack, J.; Bertrand, S.; Bertrand, D.; Danielson, U. H.; Tresadern, G.; Ulens, C. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, E2543−E2552.

(8) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourashraf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F. *J. Med. Chem.* **2013**, *56*, 6007−6021.

(9) (a) Amara, Z.; Bernadat, G.; Venot, P.-E.; Retailleau, P.; Troufflard, C.; Drege, E.; Le Bideau, F.; Joseph, D. *Org. Biomol. Chem.* **2014**, *12*, 9797−9810. (b) Amara, Z.; Drege, E.; Troufflard, C.; Retailleau, P.; Huu-Dau, M.-E. T.; Joseph, D. *Chem. - Eur. J.* **2014**, *20*, 15840−15848. (c) Amara, Z.; Drège, E.; Troufflard, C.; Retailleau, P.; Joseph, D. *Org. Biomol. Chem.* **2012**, *10*, 7148−7157. (d) Cabral dos Santos, L.; Bahlaouan, Z.; el Kassimi, K.; Troufflard, C.; Hendra, F.; Delarue-Cochin, S.; Zahouily, M.; Cavé, C.; Joseph, D. *Heterocycles* **2007**, *73*, 751−768.

(10) (a) Fitch, R. W.; Sturgeon, G. D.; Patel, S. R.; Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Blaauw, R. H. *J. Nat. Prod.* **2009**, *72*, 243−247. (b) Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345−1350.

(11) For reviews see: (a) Burtoloso, A. C. B.; Dias, R. M. P.; Bernardim, B. *Acc. Chem. Res.* **2015**, *48*, 921−934. (b) Amara, Z.; Caron, J.; Joseph, D. *Nat. Prod. Rep.* **2013**, *30*, 1211−1225.

(12) For few examples see: (a) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T. T.; Roberts, P. M.; Schofield, T. M.; Thomson, J. E. *Chem. Commun.* **2014**, *50*, 8309−8311. (b) Gobé, V.; Guinchard, X. *Org. Lett.* **2014**, *16*, 1924−1927. (c) Pansar, S. V.; Dyapa, R. *Org. Biomol. Chem.* **2012**, *10*, 6776−6784. (d) Ying, Y.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 796−799. (e) Saha, N.; Biswas, T.; Chattopadhyay, S. K. *Org. Lett.* **2011**, *13*, 5128−5131. (f) Airiau, E.; Girard, N.; Pizzeti, M.; Salvadori, J.; Taddei, M.; Mann, A. *J. Org. Chem.* **2010**, *75*, 8670−8673. (g) Ammat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosh, J. *J. Org. Chem.* **2003**, *68*, 1919−1928. (h) Pearson, W. H.; Suga, H. *J. Org. Chem.* **1998**, *63*, 9910−9918.

(13) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442−524.

(14) For preparation of TMS-ketene: Black, T. H.; Farrell, J. R.; Probst, D. A.; Zotz, M. C. *Synth. Commun.* **2002**, *32*, 2083−2088.

(15) (a) Pons, J. M.; Kocienski, P. J.; Dymock, B. W. *Chem. Commun.* **1996**, 1053−1054. (b) Romo, D.; Yang, H. W. *Tetrahedron Lett.* **1998**, *39*, 2877−2880. (c) Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125−2128.

(16) Inoue, T.; Sato, T.; Kuwajima, I. *J. Org. Chem.* **1984**, *49*, 4671−4674.

(17) (a) Wilsmore, N. T. M. *J. Chem. Soc., Trans.* **1907**, *91*, 1938−1941. (b) Chick, F.; Wilsmore, N. T. M. *J. Chem. Soc., Trans.* **1908**, *93*, 946−950. (c) Woodward, R. B.; Hofmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781−853.

(18) (a) Badal, M. M. R.; Zhang, M.; Kobayaski, S.; Mishima, M. *J. Phys. Org. Chem.* **2013**, *26*, 1071−1076. (b) Allen, A. D.; Andraos, J.; Tidwell, T. T.; Vukovic, S. *J. Org. Chem.* **2013**, *79*, 679−685.

(19) When norlobelanine is added to the solution of the preformed ketene, the starting norlobelanine **3** is recovered unchanged.

(20) (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832. (b) Taggi, A. E.; Wack, H.; Hafez, A. M.; France, S.; Lectka, T. *Org. Lett.* **2002**, *4*, 627−629.

(21) Black, T. H.; Farrell, J. R.; Probst, D. A.; Zotz, M. C. *Synth. Commun.* **2002**, *32*, 2083−2088.

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