Cyclobutenedione-Based Method for the Synthesis of Substituted 2-Pyridinones and Dihydro-2-pyridinones

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1,2-Addition of *N*-Boc-protected α-amino carbanions to cyclobutenediones followed by methylation of the resulting alkoxides generated 4-(1-*N*-Boc-aminoalkyl)-4-methoxy-3-cyclobutenones. Removal of the Boc protecting group and thermal ring expansion gave dihydro-2-pyridinones in good yields. Treatment of the dihydro-2-pyridinones with NBS/pyridine led to the formation of the corresponding 2-pyridinones. This methodology proved general with regard to both the cyclobutenediones and α-amino carbanions.

Introduction

The 2-pyridinone substructure is found in many biologically active natural and synthetic compounds that possess medicinal properties. These range from antibacterial[1−3] and antifungal[4] agents to free radical scavengers,[5] the latter of which play a role in a variety of diseases including cardiovascular disease, connective tissue damage, inflammatory disorder, and CNS injury.[6] Huperzine A, isolated from the Chinese drug *Huperzia serrata*, is a potent inhibitor of acetylcholinesterase and is effective in the treatment of memory impairment, myasthenia gravis, and multi-infarct dementia, with minimal side effects. It is also a promising drug candidate for senile dementia diseases, including Alzheimer's.[7] *N*-Substituted 2-pyridinones have been employed as active ingredients in drugs for the therapy of fibrotic disease[8] and have been evaluated as inhibitors of human leukocyte elastase.[9] Some synthetic 2-pyridinones have also demonstrated high hypotensive activity[10] or cardiotropic activity.[11] For these reasons, the synthesis of compounds containing a 2-pyridinone substructure has become increasingly important in a variety of medical applications.

Numerous methods for the preparation of substituted 2-pyridinones have been reported in the literature.[12,13] A century ago, Decker investigated the oxidation of pyridinium salts to the corresponding 2-pyridinones with ferricyanide under basic conditions.[14] This method provides easy access to a variety of 2-pyridinones as long as the starting pyridinium salts are available. Other oxidants such as H_2O_2, $KMnO_4$, and Ag(I) salts have also been used in the transformation of pyridinium salts to the corresponding 2-pyridinones.[15]

Substituted 2-pyridinones are commonly synthesized from acyclic starting materials. Chung's synthesis of 2-pyridinones involves an intramolecular Dieckmann-like condensation,[16] and many 2-pyridinone synthetic methodologies incorporate the Michael addition as a key step in the formation of the six-membered rings. Representative synthetic routes have been developed by Junjappa,[17,18] Chuit,[19] and Cainelli.[20] 2-Pyridinones have also been synthesized through a variety of cycloaddition procedures.[13,21−24] Although a variety of methods for the preparation of substituted 2-pyridinones have been reported, new, concise, regioselective, and functional-group-tolerant methods are continuously being sought.

Background

In 1994, a route to ring-fused 2-pyridinones by an intramolecular regioselective vinylketene cyclization was reported (Scheme 1).[25] The precursors of the key vinylketene intermediates are 4-heteroaromatic substituted cyclobutenones, which are obtained either through

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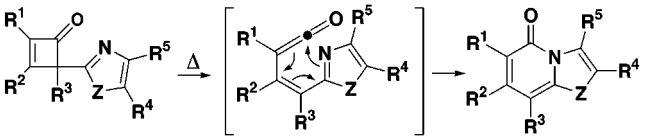
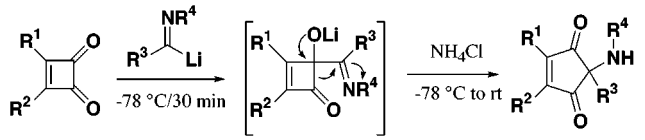
Scheme 1[a]

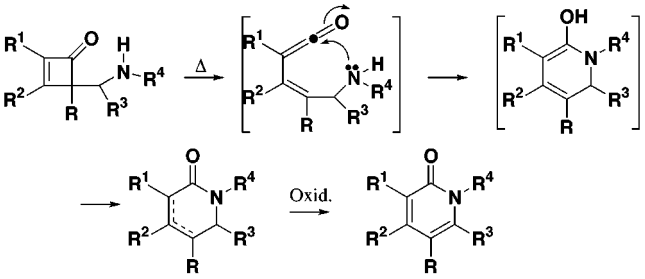


[a] Z = CH=CH, C(OMe)=CH, S, *N*−Me, *N*-MOM; R^1 = aryl, alkyl; R^2 = alkyl, aryl, alkoxy, amino; R^3 = H, OH, OAc; R^4, R^5 = H or benzo.

Scheme 2



Scheme 3



Stille cross-coupling of 4-chlorocyclobutenones with 2-heteroaromatic stannanes or through nucleophilic addition of 2-lithiated heteroaromatics to substituted cyclobutenediones. This methodology proved quite general and allowed the construction of 2-pyridinone-based azaheteroaromatics bearing various substituents in moderate to good yields.

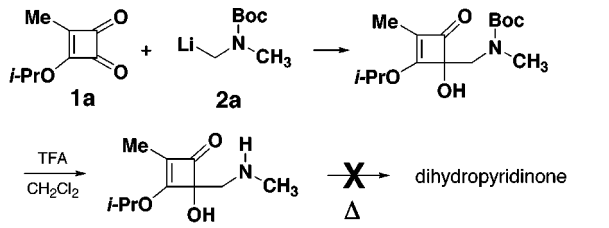
In an effort to extend the cyclobutenone-based method for the synthesis of 2-pyridinones to nonfused heteroaromatic systems, lithiated imines were added to substituted cyclobutenediones.[26] However, the ring-expansion process did not provide the expected 2-pyridinones through cyclization of vinylketene intermediates; rather, a 1,2-shift led to the formation of substituted 2-amino-4-cyclopentene-1,3-diones (Scheme 2).

To circumvent this process, a dihydropyridinone synthesis was attempted through ring expansion of cyclobutenones bearing an aminoalkyl substituent at the 4-position, as shown in Scheme 3. Oxidation of the resulting dihydropyridinones would then generate the corresponding pyridinones. The results of that study are described herein.

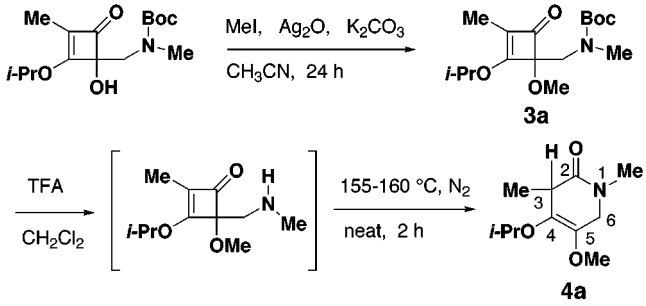
Results and Discussion

In contrast to the inefficient direct deprotonation of *N*-*tert*-butoxycarbonyl dimethylamine (*sec*-BuLi in Et_2O at −78 °C for 10 h),[27] the readily available tri-*n*-butylstannylated *N*-Boc-dimethylamine effectively produced the corresponding lithiate **2a** by tin−lithium exchange.[28] Low-temperature reaction of this α-amino anion with 3-isopropoxy-4-methylcyclobutene-1,2-dione **1a** followed by aqueous $NaHCO_3$ quench and deprotection of the amine with anhydrous TFA at room temperature[29] gave

Scheme 4



Scheme 5



the 1,2-addition product in 51% yield (Scheme 4). Unfortunately, under a variety of thermolytic reaction conditions, complicated mixtures were obtained, from which the desired dihydropyridinone could not be isolated.

To eliminate the possible interference of the hydroxyl group during the thermal ring-expansion process, which proceeds through a vinylketene intermediate, protection of the 4-hydroxyl group of the cyclobutenone product was carried out (Scheme 5). This tactic was successful. The *O*-methylated product **3a** was produced quantitatively by following a literature procedure.[30] Removal of the Boc protecting group followed by thermolysis of the crude product generated the 3,6-dihydro-2-pyridinone **4a** in 75% yield after chromatographic purification (Scheme 5). Spectroscopic data are consistent with the proposed structure. The assignment of the C=C bond at the indicated γ,δ-position for **4a** is based upon the chemical shifts of the C3 methyl group and the C3-H (δ 1.50 and 3.08 ppm) and the magnitude of the coupling constant between them (J = 7.2 Hz).

The MeI-based protection of the 4-hydroxyl group of other 4-hydroxycyclobutenones was problematic, but direct methylation of the alkoxide intermediate, produced upon the addition of the α-amino carbanion to a cyclobutenedione, with $MeOSO_2CF_3$ was effective in most cases. This allowed the generality of the cyclobutenedione-based approach to dihydropyridinones to be assayed. The results are summarized in Table 1. The regiochemistry of nucleophilic attack on the unsymmetrically substituted cyclobutenediones, which is well established to occur at the nonvinylogous ester or amide carbonyl group, dictates the substitution pattern in the resulting dihydropyridinone. Treatment of the reaction mixture generated from the addition of the α-amino carbanions **2** to cyclobutenediones **1** with 2.5 equiv of MeOTf at −78 °C for 20 min, followed by quenching of the reaction mixture with aqueous $NaHCO_3$ at −78 °C, gave the methylated products **3** in the indicated yields after chromatography. The low-temperature quench was essential; a complicated mixture was obtained when a

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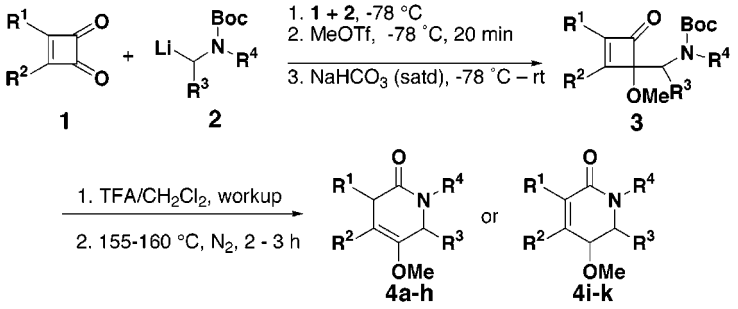
Table 1. Dihydro-2-pyridinone Synthesis



	cyclobutenedione, **1**		α-amino anion, **2**					
entry	R^1	R^2	R^3	R^4	**3**	yld %	**4**	yld %
1	Me	*i*-PrO	H	Me	**3a**	53	**4a**	75
2	*t*-Bu	*i*-PrO	H	Me	**3b**	73	**4b**	87
3	Ph	*i*-PrO	H	Me	**3c**	68	**4c**	86
4	Et	Et	H	Me	**3d**	55	**4d**	71
5	Ph	*i*-PrO	$-(CH_2)_4-$		**3e**	*a*	**4e**	68[b]
6	Et	Et	$-(CH_2)_3-$		**3f**	42	**4f**	80
7	Ph	*i*-PrO	EtO_2C	Me	**3g**	74[c]	**4g**	73
8	Et	Et	EtO_2C	Me	**3h**	64[c]	**4h**	32
9	Ph	NMe_2	H	Me	**3i**	85	**4i**	89
10	Ph	NMe_2			**3j**	*a*	**4j**	40[b]
11	Ph	NMe_2	Ph	Bn	**3k**	88	**4k**	83

[a] The crude products **3e** and **3j** displayed complex spectroscopic data due to diastereomers and rotamers and were not purified. [b] Overall yields for **4e** and **4j** were calculated from the corresponding cyclobutenedione **1**. [c] **3g** and **3h** were isolated as the 4-hydroxycyclobutenone, not the methyl ethers. The 4-methoxycyclobutenone was subsequently generated by using the Ag_2O/MeI protocol and was used without purification.

room-temperature quench was applied. The α-amino-carbanions used in entries 1−6 and 9 were generated by Sn−Li exchange, starting from the corresponding tri-*n*-butylstannyl derivatives.[31] The α-amino carbanions in entries 10 and 11 were generated directly from the Boc-protected amines by deprotonation with *sec*-BuLi; LDA was used to deprotonate *N*-*tert*-butoxycarbonyl-*N*-methyl glycine ethyl ester for entries 7 and 8.

The alkoxide produced by reaction of the LDA-generated enolate of *N*-*tert*-butoxycarbonyl-*N*-methyl glycine ethyl ester with a cyclobutenedione gave complicated mixtures when treated with MeOTf (entries 7 and 8). In these cases, methylation of the free alcohol was successfully achieved by using the MeI/Ag_2O protocol shown in Scheme 5.[30] Because mixtures of diastereomers were generated with the *N*-*tert*-butoxycarbonyl-*N*-methyl glycine ethyl ester system, the crude products were subjected to deprotection and thermal ring expansion without purification of the intermediates.

After *N*-Boc deprotection of **3b**−**k**, thermolysis gave dihydropyridones **4b**−**k**, whose structures were assigned by analogy to **4a** as described above. The structure assignments of **4b**−**h** in entries 2−8 were based upon the IR spectral data similar to those obtained for **4a** (C=O stretch 1635−1643 cm^{-1}) and, inter alia, the enol ether-like ^1H NMR chemical shift of the OMe group (δ 3.44−3.80) and the ^{13}C NMR spectroscopic data for the ring CHR^1 carbons (δ 37.9−53.9 ppm). The position of the double bond of **4i**−**k** in entries 9−11 is different from that in **4a**−**h**, perhaps a consequence of the greater double bond delocalization achievable in these three cases (β-(dimethylamino)-α,β-unsaturated amide). The structure assignment was based upon the exceptionally low IR absorption for the carbonyl groups of **4i**−**k** (1618 cm^{-1}), the downfield ^{13}C NMR absorptions for the ring CHOMe carbons (δ > 70 ppm), and the simple methyl ether-like ^1H NMR chemical shift of the OMe group (δ 3.01−3.18).

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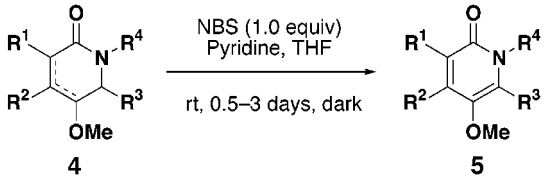
Table 2. Oxidation of Dihydro-2-pyridinones to 2-Pyridinones



entry	R^1	R^2	R^3	R^4	product	yld %
1	Me	*i*-PrO	H	Me	**5a**	86
2	*t*-Bu	*i*-PrO	H	Me	**5b**	77
3	Ph	*i*-PrO	H	Me	**5c**	88
4	Et	Et	H	Me	**5d**	85
5	Ph	*i*-PrO	$-(CH_2)_4-$		**5e**	82
6	Et	Et	$-(CH_2)_3-$		**5f**	60
7	Ph	*i*-PrO	EtO_2C	Me	**5g**	66
8	Et	Et	EtO_2C	Me	**5h**	85
9	Ph	NMe_2	H	Me	**5i**	99
10	Ph	NMe_2			**5j**	41
11	Ph	NMe_2	Ph	Bn	**5k**	71

Oxidation of some of the dihydro-2-pyridinones (**4a**−**d**) to 2-pyridinones **5** could be carried out with DDQ in refluxing benzene;[32] however, NBS/pyridine (1:3) in THF gave good to excellent yields of 2-pyridinones **5** from all of the dihydropyridinones prepared in this study. The results are summarized in Table 2. The oxidation was generally complete within 12 h, but longer reaction times were required for highly congested substrates.

Conclusions

A new method for the synthesis of dihydro-2-pyridinones, starting from substituted cyclobutenediones and α-aminoanions, has been established. The combination of NBS/pyridine was a versatile oxidizing reagent for transforming the dihydro-2-pyridinones into the corresponding 2-pyridinones. This methodology allows the synthesis of highly substituted 2-pyridinones, which would be difficult to obtain through other methods.

Experimental Section

Materials and Methods. Flash chromatographic purification was performed using 32−63 mm SiO_2 with compressed air as a source of positive pressure. All thin-layer chromatography was carried out using Merck Kieselgel 60 F_{254} plates with visualization by UV and phosphomolybdic acid or iodine stain. Melting points are uncorrected and were taken on a Thomas-Hoover melting point apparatus in open capillary tubes, using either recrystallized samples or samples that crystallized during concentration of the chromatography eluents. ^{1}H NMR spectra were recorded at 300 MHz and were internally referenced to $CHCl_3$ (7.26 ppm), C_6H_6 (7.15 ppm), or CH_2Cl_2 (5.32 ppm). ^{13}C NMR spectra were recorded at 75 MHz and were referenced to $CDCl_3$ (77.0 ppm) or C_6D_6 (128.0 ppm). IR spectra were recorded in CH_2Cl_2 solution using a KCl cell.

THF and CH_3CN were dried with 4 Å molecular sieves and then titrated for water content with a Fisher Coulomatic K−F Titrimeter. *n*-Butyllithium and *sec*-butyllithium solutions were obtained from Aldrich in Sure-Seal bottles and were titrated using diphenylacetic acid as titrant and indicator. MeI, TMEDA, and *i*-Pr_2NH were obtained from Aldrich and freshly distilled before use. Trifluoroacetic acid, tri-*n*-butyltin chloride, *N*-bromosuccinimide, and silver(I) oxide were purchased from Aldrich and used without purification. Lithium diisopropylamide (LDA) was freshly made from *i*-Pr_2NH (1.0 equiv) and *n*-butyllithium (1.0 equiv) in THF (0.5 M) under N_2 at 0 °C for 10 min.

The following compounds were prepared by literature methods: 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione,[33] 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione,[33] 4-*tert*-butyl-3-isopropoxy-3-cyclobutene-1,2-dione,[33] 3,4-diethyl-3-cyclobutene-1,2-dione,[25] *N*-Boc-dimethylamine,[31] *N*-Boc-piperidine,[31] *N*-Boc-pyrrolidine,[31] *N*-Boc-dibenzylamine,[31] *N*-Boc-isoquinoline,[31] *N*-Boc-sarcosine ethyl ester,[31] *N*-Boc-(tri-*n*-butylstannyl)dimethylamine,[31] *N*-Boc-2-(tri-*n*-butylstannyl)piperidine,[31] and *N*-Boc-2-(tri-*n*-butylstannyl)pyrrolidine.[31] 3-(*N*,*N*-Dimethylamino)-4-phenyl-3-cyclobutene-1,2-dione was prepared by a procedure similar to that described in the literature for the preparation of 3-methyl-4-(*N*,*N*-dibenzylamino)-3-cyclobutene-1,2-dione.[34]

General Procedure for Making 3a−f and 3i−k. A 0.25 M THF solution (1.10 molar equiv) of α-tri-*n*-butylstannyl-*N*-Boc-dialkylamine, *N*-Boc-isoquinoline, or *N*-Boc-dibenzylamine in a flame-dried round-bottomed flask was cooled to −78 °C under N_2, and 1.10 molar equiv of *n*-butyllithium (for **3a**−**f** and **3i**) or *sec*-butyllithium (for **3j**,**k**) was added dropwise via syringe. The reaction mixture was kept at −78 °C for 20 min and then transferred slowly to a 0.4 M THF solution of the cyclobutenedione **1**, which was precooled to −78 °C under N_2. The solution of the α-amino anion was kept at −78 °C during the transfer process to avoid decomposition. After 30 min of stirring at −78 °C, 2.50 molar equiv of MeOTf was added slowly, and stirring was continued at −78 °C for 15 min. The reaction mixture was then quenched with 10 mL of a saturated aqueous solution of $NaHCO_3$ and then warmed to room temperature over 30 min. Hexane (2 mL) was added to the solution, and the aqueous layer was diluted with 10 mL of H_2O and extracted with 3 × 20 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography using the solvents shown below. In the cases of **3a**−**f** and **3i**, the residue before chromatography was dissolved in 50 mL of CH_3CN and washed with 3 × 10 mL hexane to remove most of the *n*-Bu_4Sn byproduct. Collection of the CH_3CN layer and removal of the solvent gave the crude product, which was then purified by flash chromatography. For **3e** and **3j**, the crude products were carried on directly to the next step without chromatographic purification.

4-(*N*-Boc-*N*-methylaminomethyl)-3-isopropoxy-4-methoxy-2-methyl-2-cyclobuten-1-one, 3a. *N*-Boc-(tri-*n*-butylstannyl)dimethylamine (1.433 g, 3.300 mmol, 1.10 equiv), *n*-butyllithium (3.00 mL, 1.10 M, 3.30 mmol, 1.10 equiv), 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (0.462 g, 3.000 mmol, 1.00 equiv), and methyl triflate (1.230 g, 7.500 mmol, 2.50 equiv) yielded 0.500 g (1.600 mmol, 53%) of **3a** as a yellow oil after chromatography; TLC (silica gel, 30% EtOAc in hexane, R_f = 0.10); chromatographic purification (flash column, silica gel, 2 × 15 mm, 20% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1758 (s), 1691 (s), 1612 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.82 (sept, *J* = 6.0 Hz, 1 H), 3.79 (d, *J* = 14.7 Hz, 1 H), 3.36 (d, *J* = 14.7 Hz, 1 H), 3.29 (s, 3 H), 2.85 (s, 3 H), 1.77 (s, 3 H), 1.42 (s, 9 H), 1.42 (d, *J* = 6.0 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ190.6 (190.1), 179.8 (178.7), 155.2 (154.9), 122.4 (123.0), 95.9, 78.6 (79.1), 76.3 (76.1), 51.7, 49.2 (49.6), 35.9 (35.4), 27.8, 22.4, 6.4 (6.7) (absorptions due to rotamers are indicated in brackets). Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47; O, 25.53. Found: C, 61.18; H, 8.71; N, 4.42.

4-(*N*-Boc-*N*-methylaminomethyl)-2-*tert*-butyl-3-isopropoxy-4-methoxy-2-cyclobuten-1-one, 3b. *N*-Boc-(tri-*n*-butylstannyl)dimethylamine (1.433 g, 3.300 mmol, 1.10 equiv), *n*-butyllithium (3.00 mL, 1.10 M, 3.30 mmol, 1.10 equiv), 4-*tert*-butyl-3-isopropoxy-3-cyclobutene-1,2-dione (0.589 g, 3.000 mmol, 1.00 equiv), and methyl triflate (1.230 g, 7.500 mmol, 2.50 equiv) yielded 0.780 g (2.190 mmol, 73%) of **3b** as a white solid after chromatography; TLC (silica gel, 30% EtOAc in hexane, R_f = 0.44); chromatographic purification (flash column, silica gel, 2 × 15 mm, 10% EtOAc in hexane); mp 81.2−83.0 °C. IR (CH_2Cl_2, KCl, cm^{-1}): 1749 (s), 1690 (s), 1603 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.92 (sept, *J* = 6.0 Hz, 1 H), 4.02 (d, *J* = 14.7 Hz, 1 H), 3.27 (s, 3 H), 3.06 (d, *J* = 14.7 Hz, 1 H), 2.73 (s, 3 H), 1.35 (s, 9 H), 1.26 (d, *J* = 6.0 Hz, 6 H), 1.10 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 188.5, 178.6, 155.6, 138.0, 96.9, 79.2, 77.4, 51.8, 50.1, 36.4, 30.9, 28.2, 27.9, 22.8, 22.6. Anal. Calcd for $C_{19}H_{33}NO_5$: C, 64.20; H, 9.36; N, 3.94; O, 22.50. Found: C, 64.28; H, 9.43; N, 3.92.

4-(*N*-Boc-*N*-methylaminomethyl)-3-isopropoxy-4-methoxy-2-phenyl-2-cyclobuten-1-one, 3c. *N*-Boc-(tri-*n*-butylstannyl)dimethylamine (1.433 g, 3.300 mmol, 1.10 equiv), *n*-butyllithium (3.00 mL, 1.10 M, 3.30 mmol, 1.10 equiv), 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (0.649 g, 3.000 mmol, 1.00 equiv), and methyl triflate (1.230 g, 7.500 mmol, 2.50 equiv) yielded 0.770 g (2.050 mmol, 68%) of **3c** as a white solid after chromatography; TLC (silica gel, 30% EtOAc in hexane, R_f = 0.40); chromatographic purification (flash column, silica gel, 2 × 15 mm, 5% EtOAc in hexane); mp 83.0−84.6 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1749 (s), 1691 (s), 1623 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77 (d, *J* = 7.2 Hz, 2 H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 2 H), 7.26 (t, *J* = 7.2 Hz, 1 H), 5.16 (sept, *J* = 5.7 Hz, 1 H), 4.17 (d, *J* = 14.7 Hz, 1 H), 3.43 (s, 3 H), 3.30 (d, *J* = 14.7 Hz, 1 H), 2.84 (s, 3 H), 1.55 (d, *J* = 5.7 Hz, 3 H), 1.45 (d, *J* = 5.7 Hz, 3 H), 1.31 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 187.1, 179.1, 155.7, 128.4, 128.1, 127.6, 126.6, 125.7, 98.0, 79.3, 78.7, 52.4, 50.3, 36.3, 27.9, 22.8, 22.6. Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73; O, 21.31. Found: C, 67.26; H, 7.86; N, 3.67.

4-(*N*-Boc-*N*-methylaminomethyl)-2,3-diethyl-4-methoxy-2-cyclobuten-1-one, 3d. *N*-Boc-(tri-*n*-butylstannyl)dimethylamine (1.433 g, 3.300 mmol, 1.10 equiv), *n*-butyllithium (3.00 mL, 1.10 M, 3.30 mmol, 1.10 equiv), 3,4-diethyl-3-cyclobutene-1,2-dione (0.415 g, 3.00 mmol, 1.00 equiv), and methyl triflate (1.230 g, 7.500 mmol, 2.50 equiv) yielded 0.492 g (1.650 mmol,

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55%) of **3d** as a light yellow oil after chromatography; TLC (silica gel, 30% EtOAc in hexane, $R_f = 0.41$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 10% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1752 (s), 1689 (s), 1624 (w). ^1H NMR (C_6D_6, 300 MHz): δ 4.10 (d, $J = 14.4$ Hz, 1 H), 3.18 (d, $J = 14.4$ Hz, 1 H), 3.11 (s, 3 H), 2.72 (s, 3 H), 2.60 (m, 2 H), 1.97 (m, 2 H), 1.35 (s, 9 H), 1.09 (t, $J = 7.5$ Hz, 3 H), 0.99 (t, $J = 7.5$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.9, 180.6, 155.3, 154.0, 99.0, 78.8, 51.5, 49.6, 36.0, 27.8, 20.8, 16.3, 11.5, 10.4. Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71; O, 21.52. Found: C, 64.62; H, 9.19; N, 4.65.

4-(*N*-Boc-2-piperidinyl)-3-isopropoxy-4-methoxy-2-phenyl-2-cyclobuten-1-one, 3e. *N*-Boc-2-(tri-*n*-butylstannyl)piperidine (0.996 g, 2.100 mmol, 1.05 equiv), *n*-butyllithium (2.00 mL, 1.10 M, 2.20 mmol, 1.10 equiv), 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (0.433 g, 2.00 mmol, 1.00 equiv), and methyl triflate (0.820 g, 5.00 mmol, 2.50 equiv) yielded **3e** as a light yellow solid that displayed complex spectroscopic data due to diastereomers and rotamers. The crude product was carried on to the next step without purification.

4-(*N*-Boc-2-pyrrolidinyl)-2,3-diethyl-4-methoxy-2-cyclobuten-1-one, 3f. *N*-Boc-2-(tri-*n*-butylstannyl)pyrrolidine (2.030 g, 4.41 mmol, 1.10 equiv), *n*-butyllithium (4.00 mL, 1.10 M, 4.40 mmol, 1.10 equiv), 3,4-diethyl-3-cyclobutene-1,2-dione (0.553 g, 4.00 mmol, 1.00 equiv), and methyl triflate (1.640 g, 10.00 mmol, 2.50 equiv) yielded **3f** (0.540 g, 1.670 mmol, 42%) as a pale yellow oil after chromatography. The NMR spectra of the crude product depict a mixture of two diastereomers in a 3:4 ratio; TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.46$, 0.52); chromatographic purification (flash column, silica gel, 2 × 15 mm, 1st, 400 mL of 5% EtOAc in hexane; 2nd, 10% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1748 (s), 1688 (s), 1623 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.21−4.14 (m, 1 H), 3.46−3.02 (m, 2 H), 3.23 (s, major, δ 3.20, s, minor, 3 H), 2.92−1.68 (m, 8 H), 1.44 (s, 2 H), 1.39 (s, 9 H), 1.29 (t, $J = 7.8$ Hz, major, δ 1.20, t, $J = 7.8$ Hz, minor, 3 H), 1.10 (t, $J = 7.8$ Hz, major, δ 1.13, t, $J = 7.8$ Hz, minor, 3 H). Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33; O, 19.79. Found: C, 66.97; H, 8.99; N, 4.22.

(*N*-Boc-*N*-methylamino)-(1-hydroxy-2-isopropoxy-4-oxo-3-phenyl-cyclobut-2-enyl)-acetic acid ethyl ester, 3g. *N*-Boc-sarcosine ethyl ester (0.913 g, 4.200 mmol, 1.05 equiv) in 5 mL of THF was added slowly to a THF solution of LDA (4.400 mmol, 1.10 equiv) at −78 °C under nitrogen. After 30 min of stirring at −78 °C, the solution was transferred slowly to a solution of 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (0.865 g, 4.000 mmol, 1.00 equiv) in 5 mL of THF, which was precooled to −78 °C. After 30 min at −78 °C, the reaction was quenched with 10 mL of saturated aqueous $NaHCO_3$ and then warmed slowly to room temperature. H_2O (10 mL) was used to dilute the mixture, which was extracted with 3 × 20 mL of Et_2O. The combined Et_2O layers were dried over $MgSO_4$, concentrated, and purified by chromatography to yield **3g** (1.274 g, 2.940 mmol, 74%) as a light yellow viscous oil (NMR spectra of the crude product show a 1:3 ratio of two diastereomers); TLC (silica gel, 20% EtOAc in hexane, $R_f = 0.11$−0.15); chromatographic purification (flash column, silica gel, 2 × 15 mm, 10% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 3446 (br, s), 1755 (s), 1693 (s), 1628 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75−7.71 (m, 2 H), 7.40−7.26 (m, 3 H), 5.22 (sept, $J = 6.0$ Hz, major, δ 5.10, sept, $J = 6.0$ Hz, minor, 1 H), 4.84 (br s, major, δ 5.06, br s, minor, 1 H), 4.53 (s, major, δ 5.54, s, minor, 1 H), 4.38−4.12 (m, 2 H), 3.01 (s, major, δ 2.69, s, minor, 1 H), 1.50−1.36 (m, 15 H), 1.23 (t, $J = 7.2$ Hz, 3 H). Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23; O, 25.83. Found: C, 63.63; H, 7.27; N, 3.18.

(*N*-Boc-*N*-methylamino)-(2,3-diethyl-1-hydroxy-4-oxo-cyclobut-2-enyl)-acetic acid ethyl ester, 3h. *N*-Boc-sarcosine ethyl ester (0.913 g, 4.200 mmol, 1.05 equiv), LDA (4.400 mmol, 1.10 equiv), and 2,3-diethyl-3-cyclobutene-1,2-dione (0.553 g, 4.000 mmol, 1.00 equiv) yielded after purification by chromatography **3h** (0.912 g, 2.570 mmol, 64%) as a light yellow viscous oil (1:1 ratio of two diastereomers) following the procedure for **3g**; TLC (silica gel, 20% EtOAc in hexane, $R_f =$ 0.10−0.14); chromatographic purification (flash column, silica gel, 2 × 15 mm; 1st, 200 mL of 10% EtOAc in hexane; 2nd, 20% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 3500 (br, m), 1756 (s), 1691 (s), 1628 (w). ^1H NMR ($CDCl_3$, 300 MHz: δ 5.00 (s, diastereomer 1, δ 4.93 s, diastereomer 2, 1 H), 4.28−4.08 (m, 3 H), 2.91 (s, diastereomer 1, δ 2.68 s, diastereomer 2, 3 H), 2.65−2.53 (m, 2 H), 2.23−2.12 (m, 2 H), 1.40 (s, diastereomer 1, δ 1.37 s, diastereomer 2, 9 H), 1.28−1.17 (m, 6 H), 1.09−1.02 (m, 3 H). Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94; O, 27.01. Found: C, 60.72; H, 8.23; N, 3.85.

4-(*N*-Boc-*N*-methylaminomethyl)-3-(*N*, *N*-dimethylamino)-4-methoxy-2-phenyl-2-cyclobuten-1-one, 3i. *N*-Boc-(tri-*n*-butylstannyl)dimethylamine (0.945 g, 2.180 mmol, 1.09 equiv), *n*-butyllithium (2.00 mL, 1.10 M, 2.200 mmol, 1.10 equiv), 3-*N*,*N*-(dimethylamino)-4-phenyl-3-cyclobutene-1,2-dione (0.403 g, 2.000 mmol, 1.00 equiv), and methyl triflate (0.820 g, 5.000 mmol, 2.50 equiv) yielded 0.614 g (1.700 mmol, 85%) of **3i** as a pale yellow solid after chromatography; TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.22$); chromatographic purification (flash column, silica gel, 2 × 15 mm; 1st, 200 mL of 20% EtOAc in hexane; 2nd, 2% MeOH/$CHCl_3$); mp 118.0−120.0 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1741 (s), 1690 (s), 1614 (s), 1595 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38−7.20 (m, 5 H), 4.12 (d, $J = 14.7$ Hz, 1 H), 3.41 (s, 3 H), 3.26 (s, 3 H), 3.22 (d, $J = 14.7$ Hz, 1 H), 3.03 (s, 3 H), 2.83 (s, 3 H), 1.43 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 184.2, 166.9, 155.8, 129.7, 128.2, 128.0, 126.5, 119.3, 95.2, 79.0, 51.9, 50.0, 41.1, 39.9, 36.6, 28.1. HRMS (EI) calcd for $C_{20}H_{29}N_2O_4$ $(M + H)^+$: 361.2627, found 361.2141. Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77; O, 17.75. Found: C, 65.92; H, 7.62; N, 7.70.

4-(*N*-Boc-isoquinolino)-3-(*N*,*N*-dimethylamino)-4-methoxy-2-phenyl-2-cyclobuten-1-one, 3j. *N*-Boc-isoquinoline (0.770 g, 3.300 mmol, 1.10 equiv), *sec*-butyllithium (3.00 mL, 1.10 M, 3.300 mmol, 1.10 equiv), 3-*N*,*N*-(dimethylamino)-4-phenyl-3-cyclobutene-1,2-dione (0.604 g, 3.00 mmol, 1.00 equiv), and methyl triflate (1.230 g, 7.50 mmol, 2.50 equiv) yielded a yellow solid that displayed complex spectroscopic data due to diastereomers and rotamers. The crude product was carried on to the next step without purification.

4-(*N*-Boc-*N*-benzylaminobenzyl)-3-(*N*,*N*-dimethylamino)-4-methoxy-2-phenyl-2-cyclobuten-1-one, 3k. *N*-Boc-dibenzylamine (0.654 g, 2.200 mmol, 1.10 equiv), *sec*-butyllithium (2.00 mL, 1.10 M, 2.200 mmol, 1.10 equiv), 3-*N*,*N*-(dimethylamino)-4-phenyl-3-cyclobutene-1,2-dione (0.402 g, 2.00 mmol, 1.00 equiv), and methyl triflate (0.820 g, 5.00 mmol, 2.50 equiv) yielded 0.911 g (1.780 mmol, 88%) of **3k** as a mixture of two diastereomers (major diastereomer, 0.580 g, white solid; minor diastereomer, 0.331 g, light yellow foam) after chromatography; TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.48$ for the major diastereomer; $R_f = 0.37$ for the minor diastereomer); chromatographic purification (flash column, silica gel, 2 × 15 mm; 1st, 500 mL of 15% EtOAc in hexane; 2nd, 30% EtOAc in hexane). Data for the major diastereomer: mp 186−188 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1741 (m), 1683 (s), 1612 (s), 1596 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, $J = 7.5$ Hz, 2 H), 7.48 (d, $J = 7.5$ Hz, 2 H), 7.39 (t, $J = 7.5$ Hz, 2 H), 7.32−7.25 (m, 3 H), 7.18 (t, $J = 7.5$ Hz, 1 H), 6.96−6.92 (m, 3 H), 6.56−6.53 (m, 2 H), 6.19 (s, 1 H), 4.19 (d, $J = 15.9$ Hz, 1 H), 4.07 (d, $J = 15.9$ Hz, 1 H), 3.41 (s, 3 H), 3.35 (s, 3 H), 3.04 (s, 3 H), 1.21 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 182.8, 166.8, 156.0, 139.7, 136.1, 131.5, 130.1, 128.5, 128.3, 128.1, 127.5, 127.2, 127.0, 126.4, 125.7, 120.8, 98.6, 79.8, 62.4, 52.1, 47.5, 41.6, 39.6, 28.0. Anal. Calcd for $C_{32}H_{36}N_2O_4$: C, 74.97; H, 7.08; N, 5.46; O, 12.48. Found: C, 74.88; H, 7.08; N, 5.53. Data for the minor diastereomer. IR (CH_2Cl_2, KCl, cm^{-1}): 1743 (m), 1682 (s), 1614 (s), 1596 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28−6.83 (m, 15 H), 6.06 (br s, 1 H), 5.04 (br s, 2 H), 3.36 (s, 3 H), 3.33 (s, 3 H), 2.82 (s, 3 H), 1.25−1.19 (m, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 182.9, 166.4, 156.6, 140.8, 137.9, 129.2, 128.6, 128.3, 128.1, 127.9, 127.6, 127.3, 126.8, 126.3, 125.3, 121.2, 98.6, 79.7, 52.3, 49.7, 41.2, 39.6, 31.4, 28.0. Anal. Calcd for $C_{32}H_{36}N_2O_4$: C, 74.97; H, 7.08; N, 5.46; O, 12.48. Found: C, 75.05; H, 7.14; N, 5.48.

General Procedure for 4a−k. Compound **3** in 10 mL of CH_2Cl_2 was treated with 1−2 mL of TFA under N_2 at room

temperature for 2 h. The reaction mixture was neutralized with 2 M NaOH solution with stirring and then diluted with 20 mL of Et_2O. The aqueous layer was extracted with 3 × 20 mL of Et_2O, and the combined organic layers were dried over K_2CO_3. Removal of solvent gave the crude amine, which was directly subjected to thermolysis at 155−160 °C under N_2 for 2.5 h. The resulting compound was purified by chromatography.

Before thermolysis to generate **4g** and **4h**, 1.00 equiv of the 4-hydroxycyclobutenones **3g** and **3h** were methylated following a literature procedure,[29] using 2.00 equiv of Ag_2O, 4.00 equiv of MeI, and 5.00 equiv of K_2CO_3 in 10 mL of CH_3CN for 3 days. The crude methyl ethers **3g** and **3h** were then subjected to thermolysis after removal of the Boc protecting group.

4-Isopropoxy-5-methoxy-1,3-dimethyl-3,6-dihydro-2-pyridone, 4a. 4-(*N*-Boc-*N*-methylaminomethyl)-3-isopropoxy-4-methoxy-2-methyl-2-cyclobuten-1-one **3a** (0.470 g, 1.500 mmol, 1.00 equiv) in 2.0 mL of TFA and thermolysis yielded 0.240 g (1.130 mmol, 75%) of **4a** as a light yellow oil after chromatography; TLC (silica gel, EtOAc, $R_f = 0.32$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 50% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1715 (w), 1642 (s). ^1H NMR (C_6D_6, 300 MHz): δ 4.02 (sept, $J = 6.0$ Hz, 1 H), 3.36 (s, 3 H), 3.29 (dd, $J = 15.6$, 3.9 Hz, 1 H), 3.17 (dd, $J = 15.6$, 3.0 Hz, 1 H), 3.08 (ddq, $J = 7.2$, 3.9, 3.0 Hz, 1 H), 2.59 (s, 3 H), 1.50 (d, $J = 7.2$ Hz, 3 H), 1.04 (d, $J = 6.0$ Hz, 3 H), 1.02 (d, $J = 6.0$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.4, 134.8, 131.7, 70.5, 58.5, 48.3, 37.9, 33.5, 22.6, 22.0, 17.4. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57; O, 22.50. Found: C, 61.65; H, 8.92; N, 6.41.

3-*tert*-Butyl-4-isopropoxy-5-methoxy-1-methyl-3,6-dihydro-2-pyridone, 4b. 2-*tert*-Butyl-4-(*N*-Boc-*N*-methylaminomethyl)-3-isopropoxy-4-methoxy-2-cyclobuten-1-one (0.640 g, 1.800 mmol, 1.00 equiv) **3b** in 1.5 mL of TFA and thermolysis yielded 0.400 g (1.570 mmol, 87%) of **4b** as a light yellow oil after chromatography; TLC (silica gel, EtOAc, $R_f = 0.46$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 40% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1704 (m), 1642 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.13 (sept, $J = 6.0$ Hz, 1 H), 3.92 (dd, $J = 16.5$, 2.1 Hz, 1 H), 3.76 (s, 3 H), 3.47 (d, $J = 16.5$ Hz, 1 H), 2.95 (s, 3 H), 2.70 (d, $J = 2.1$ Hz, 1 H), 1.19 (d, $J = 6.0$ Hz, 3 H), 1.17 (d, $J = 6.0$ Hz, 3 H), 1.01 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 169.1, 136.8, 132.9, 70.9, 59.0, 53.9, 49.4, 37.9, 33.4, 28.1, 22.4, 21.9. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.85; H, 9.87; N, 5.49; O, 18.80. Found: C, 65.71; H, 9.83; N, 5.41.

4-Isopropoxy-5-methoxy-1-methyl-3-phenyl-3,6-dihydro-2-pyridone, 4c. 4-(*N*-Boc-*N*-methylaminomethyl)-3-isopropoxy-4-methoxy-2-phenyl-2-cyclobuten-1-one **3c** (0.720 g, 1.920 mmol, 1.00 equiv) in 2.0 mL of TFA and thermolysis yielded 0.453 g (1.650 mmol, 86%) of **4c** as a yellow solid after chromatography; TLC (silica gel, EtOAc, $R_f = 0.45$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 50% EtOAc in hexane); mp 58.5−60.1 °C (hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1714 (w), 1650 (s). ^1H NMR (C_6D_6, 300 MHz): δ 7.47 (br d, $J = 7.5$ Hz, 2 H), 7.12 (dd, $J = 7.5$, 7.5 Hz, 2 H), 7.03 (br t, $J = 7.5$ Hz, 1 H), 4.29 (br d, $J = 2.1$ Hz, 1 H), 3.97 (sept, $J = 6.0$ Hz, 1 H), 3.48 (dd, $J = 16.2$, 3.6 Hz, 1 H), 3.44 (s, 3 H), 3.16 (dd, $J = 16.2$, 2.1 Hz, 1 H), 2.46 (s, 3 H), 0.87 (d, $J = 6.0$ Hz, 3 H), 0.86 (d, $J = 6.0$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 167.5, 138.3, 133.2, 132.6, 128.0, 127.5, 126.7, 70.4, 58.4, 49.7, 48.3, 33.3, 22.2, 21.6. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09; O, 17.43. Found: C, 69.89; H, 7.66; N, 5.10.

3,4-Diethyl-5-methoxy-1-methyl-3,6-dihydro-2-pyridone, 4d. 4-(*N*-Boc-*N*-methylaminomethyl)-2,3-diethyl-4-methoxy-2-cyclobuten-1-one **3d** (0.745 g, 2.500 mmol, 1.00 equiv) in 2.0 mL of TFA and thermolysis yielded 0.350 g (1.770 mmol, 71%) of **4d** as a light brown oil after chromatography; TLC (silica gel, EtOAc, $R_f = 0.27$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 50% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1710 (w), 1642 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.97 (br d, $J = 16.2$ Hz, 1 H), 3.72 (br d, $J = 16.2$ Hz, 1 H), 3.56 (s, 3 H), 3.03 (br m, 1 H), 2.97 (s, 3 H), 2.47 (dq, $J = 13.8$, 7.5 Hz, 1 H), 2.02 (m, 1 H), 1.78 (m, 1 H), 1.65 (m, 1 H), 0.97 (br t, $J = 7.5$ Hz, 3 H), 0.76 (br t, $J = 7.5$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 170.0, 141.8, 119.4, 57.6, 48.2, 42.7, 33.3, 23.8, 18.7, 11.7, 8.5. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10; O, 16.22. Found: C, 67.08; H, 9.69; N, 7.01.

3,6,7,8,9,9*a*-Hexahydro-2-isopropoxy-1-methoxy-3-phenyl-quinolizin-4-one, 4e. 4-(*N*-Boc-2-piperidino)-3-isopropoxy-4-methoxy-2-phenyl-2-cyclobuten-1-one **3e** (crude product) in 2.0 mL of TFA and thermolysis yielded 0.430 g (1.360 mmol, 68% from **1e**) of **4e** as a light brown viscous oil after chromatography. The product was a mixture of two diastereomers in a 0.6:1 ratio. TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.35$−0.40); chromatographic purification (flash column, silica gel, 2 × 15 mm, 20% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1760 (w), 1711 (w), 1643 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37−7.14 (m, 5 H), 4.58−4.52 (m, 1 H), 4.16−3.84 (m, 3 H), 3.72 (s, major, δ 3.69, s, minor, 3 H), 3.67−3.65 (m, 1 H), 2.45−1.15 (m, 6 H), 1.05−0.98 (m, 6 H). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44; O, 15.22. Found: C, 72.18; H, 7.98; N, 4.37.

6,7-Diethyl-8-methoxy-2,3,6,8*a*-tetrahydro-1*H*-indolizin-5-one, 4f. 4-(*N*-Boc-2-pyrrolidino)-2,3-diethyl-4-methoxy-2-cyclobuten-1-one **3f** (0.362 g, 1.120 mmol, 1.00 equiv) in 1.5 mL of TFA and thermolysis yielded 0.200 g (0.900 mmol, 80%) of **4f** as a light yellow oil after chromatography. The product was a mixture of two diastereomers in a 2:3 ratio; TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.08$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 60% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1635 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.19−3.69 (m, 2 H), 3.60 (s, major, δ 3.61, s, minor, 3 H), 3.44−2.93 (m, 2 H), 2.63−2.38 (m, 1 H), 2.24−1.40 (m, 7 H), 0.98 (t, $J = 7.8$ Hz, major, δ 0.99, t, $J = 7.8$ Hz, minor, 3 H), 0.88 (t, $J = 7.5$ Hz major, δ 0.63, t, $J = 7.5$ Hz, minor, 3 H). HRMS (EI) calcd for $C_{13}H_{21}NO_2Li$ $(M+Li)^+$: 230.1732, found 230.1735.

6-Carboethoxy-4-isopropoxy-5-methoxy-1-methyl-3-phenyl-3,6-dihydro-2-pyridone, 4g. (*N*-Boc-*N*-methylamino)-(1-hydroxy-2-isopropoxy-4-oxo-3-phenyl-cyclobut-2-enyl)-acetic acid ethyl ester **3g** (1.185 g, 2.730 mmol, 1.00 equiv), methyl iodide (1.552 g, 10.930 mmol, 4.00 equiv), silver(I) oxide (1.267 g, 5.470 mmol, 2.00 equiv), and potassium carbonate (1.889 g, 13.670 mmol, 5.01 equiv) followed by deprotection with 2.0 mL of TFA and thermolysis yielded 0.690 g (1.990 mmol, 73%) of **4g** as a light brown viscous oil after chromatography. The product was a mixture of two diastereomers in a 1:3 ratio: TLC (silica gel, 30% EtOAc in hexane, $R_f = 0.10$−0.14); chromatographic purification (flash column, silica gel, 2 × 15 mm; 1st, 400 mL of 20% EtOAc in hexane; 2nd, 30% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1742 (s), 1655 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.24 (m, 3 H), 7.49 (app d, $J = 6.9$ Hz, 2 H), 4.48 (d, $J = 2.1$ Hz, major, δ 4.64, d, $J = 3.3$ Hz, minor, 1 H), 4.28−4.17 (m, 4 H), 3.80 (s, major, δ 3.79 s, minor, 3 H), 2.95 (s, major, δ 2.88, s, minor, 3 H), 1.26 (t, $J = 7.2$ Hz, major, δ 1.31, t, $J = 7.2$ Hz, minor, 1 H), 1.13−1.04 (m, 6 H). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03; O, 23.03. Found: C, 65.56; H, 7.18; N, 3.97.

6-Carboethoxy-3,4-diethyl-5-methoxy-1-methyl-3,6-dihydro-2-pyridone, 4h. (*N*-Boc-*N*-methylamino)-(2,3-diethyl-1-hydroxy-4-oxo-cyclobut-2-enyl)-acetic acid ethyl ester **3h** (0.853 g, 2.400 mmol, 1.00 equiv), methyl iodide (1.363 g, 9.600 mmol, 4.00 equiv), silver(I) oxide (1.112 g, 4.800 mmol, 2.00 equiv), and potassium carbonate (1.659 g, 12.000 mmol, 5.00 equiv) and followed by deprotection with 2.0 mL of TFA and thermolysis yielded 0.211 g (0.780 mmol, 32%) of **4h** as a light brown viscous oil after chromatography. The product was a mixture of two diastereomers in a 1:4 ratio; TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.30$−0.36); chromatographic purification (flash column, silica gel, 2 × 15 mm, 30% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1740 (s), 1648 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.50 (br s, major, δ 4.63, br s, minor, 1 H), 3.64 (s, major, δ 3.62 s, minor, 3 H), 2.98−2.90 (m, 4 H), 2.58−1.62 (m, 6 H), 1.42−0.68 (m, 9 H). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20; O, 23.76. Found: C, 62.21; H, 8.51; N, 5.08.

4-(*N*,*N*-Dimethylamino)-5-methoxy-1-methyl-3-phenyl-5,6-dihydro-2-pyridone, 4i. 4-(*N*-Boc-*N*-methylaminomethyl)-3-(*N*,*N*-dimethylamino)-4-methoxy-2-phenyl-2-cyclobuten-1-one **3i** (0.600 g, 1.660 mmol, 1.00 equiv) in 1.5 mL of TFA and thermolysis yielded 0.382 g (1.470 mmol, 89%) of **4i** as a light brown solid after chromatography; TLC (silica gel, EtOAc, R_f = 0.07); chromatographic purification (flash column, silica gel, 2 × 15 mm, EtOAc); mp 116−118 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1618 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.21−7.14 (m, 4 H), 7.09−7.03 (m, 1 H), 4.10 (app t, J = 3.0 Hz, 1 H), 3.58 (app t, J = 3.0 Hz, 2 H), 3.44 (s, 3 H), 3.02 (s, 3 H), 2.59 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.4, 151.2, 137.8, 131.4, 126.8, 125.3, 107.7, 71.3, 54.9, 48.3, 41.2, 34.3. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76; O, 12.29. Found: C, 68.96; H, 7.72; N, 10.71.

8,9-Benzo-2-(*N*,*N*-dimethylamino)-1-methoxy-3-phenyl-1,6,7,9*a*-tetrahydro-quinolizin-4-one, 4j. 4-(*N*-Boc-isoquinolino)-3-(*N*,*N*-dimethylamino)-4-methoxy-2-phenyl-2-cyclobuten-1-one **3j** (crude product) in 2.0 mL of TFA and thermolysis yielded 0.420 g (1.210 mmol, 40% from **1j**) of **4j** as a yellow solid after chromatography. Only one diastereomer was formed. TLC (silica gel, 60% EtOAc in hexane, R_f = 0.25); chromatographic purification (flash column, silica gel, 2 × 15 mm, 30% EtOAc in hexane); mp 175−177 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1616 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37−7.16 (m, 9 H), 4.94 (br d, J = 2.7 Hz, 1 H), 4.85 (ddd, J = 12.3, 4.2, 2.1 Hz, 1 H), 4.50 (d, J = 2.7 Hz, 1 H), 3.05−2.99 (m, 1 H), 3.01 (s, 3 H), 2.91 (dd, J = 12.3, 2.1 Hz, 1 H), 2.82−2.77 (m, 1 H), 2.67 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.6, 152.5, 137.9, 137.2, 133.0, 131.5, 128.7, 127.0, 126.6, 126.2, 126.1, 125.6, 108.2, 76.8, 58.0, 57.2, 41.7, 38.0, 29.4. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04; O, 9.18. Found: C, 75.71; H, 6.94; N, 7.99.

1-Benzyl-4-(*N*,*N*-dimethylamino)-5-methoxy-1-methyl-3,6-diphenyl-5,6-dihydro-2-pyridone, 4k. 4-(*N*-Boc-*N*-benzylaminobenzyl)-3-(*N*,*N*-dimethylamino)-4-methoxy-2-phenyl-2-cyclobuten-1-one **3k** (0.677 g, 1.320 mmol, 1.00 equiv) in 1.5 mL of TFA and thermolysis yielded 0.455 g (1.100 mmol, 83%) of **4k** as a light yellow solid after chromatography. Only one diastereomer was formed. TLC (silica gel, 60% EtOAc in hexane, R_f = 0.45); chromatographic purification (flash column, silica gel, 2 × 15 mm, 20% EtOAc in hexane); mp 222−224 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1615 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38−7.20 (m, 15 H), 5.77 (d, J = 15.0 Hz, 1 H), 4.64 (br d, J = 1.5 Hz, 1 H), 3.90 (d, J = 2.1 Hz, 1 H), 3.51 (d, J = 15.0 Hz, 1 H), 3.18 (s, 3 H), 2.42 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 166.2, 149.1, 138.2, 137.9, 137.2, 131.6, 128.7, 128.4, 128.3, 127.8, 127.2, 127.0, 126.8, 125.9, 108.1, 78.4, 57.4, 55.2, 47.6, 41.2. Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79; O, 7.76. Found: C, 78.50; H, 6.87; N, 6.81.

General Procedure for the Preparation of 2-Pyridinone 5a−k. Compound **4** in 10 mL of THF was treated with 1.10 molar equiv of NBS and 3.00 molar equiv of pyridine at room temperature in the dark for 3 days. The reaction mixture was then diluted with 20 mL of Et_2O and washed with 3 × 5 mL of 2 M NaOH solution to remove the succinimide formed during the reaction. The NaOH wash was not used for the more sensitive pyridones **5g**,**h** and **5j**,**k**. The aqueous layer was extracted with 3 × 20 mL of Et_2O, and the combined extracts were washed once with 5 mL of 2 M NaOH. The combined organic layers were dried over $MgSO_4$. Removal of solvent gave crude pyridinone **5**, which was purified by chromatography or recrystallization.

4-Isopropoxy-5-methoxy-1,3-dimethyl-2-pyridone, 5a. 4-Isopropoxy-5-methoxy-1,3-dimethyl-3,6-dihydropyridone **4a** (0.180 g, 0.840 mmol, 1.00 equiv), NBS (0.165 g, 0.930 mmol, 1.11 equiv), and pyridine (0.199 g, 2.52 mmol, 3.00 equiv) yielded 0.152 g (0.720 mmol, 86%) of **5a** as a white solid after recrystallization; TLC (silica gel, EtOAc, R_f = 0.07); mp 93−95 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1659 (s), 1590 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.63 (s, 1 H), 4.50 (sept, J = Hz, 1 H), 3.62 (s, 3 H), 3.42 (s, 3 H), 1.98 (s, 3 H), 1.20 (d, J = 6.0 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 162.0, 155.6, 139.3, 119.7, 117.7, 75.3, 57.1, 37.0, 22.4, 10.7. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63; O, 22.72. Found: C, 62.61; H, 8.13; N, 6.60.

3-*tert*-Butyl-4-isopropoxy-5-methoxy-1-methyl-2-pyridone, 5b. 3-*tert*-Butyl-4-isopropoxy-5-methoxy-1-methyl-3,6-dihydropyridone **4b** (0.383 g, 1.50 mmol, 1.00 equiv), NBS (0.294 g, 1.65 mmol, 1.10 equiv), and pyridine (0.356 g, 4.500 mmol, 3.00 equiv) yielded 0.295 g (1.160 mmol, 77%) of **5b** as a white solid after recrystallization; TLC (silica gel, EtOAc, R_f = 0.32); mp 119−121 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1658 (s), 1589 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.71 (s, 1 H), 4.74 (sept, J = 6.0 Hz, 1 H), 3.68 (s, 3 H), 3.44 (s, 3 H), 1.46 (s, 9 H), 1.27 (d, J = 6.0 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.6, 155.8, 139.1, 128.9, 118.4, 74.6, 57.3, 37.3, 36.3, 30.5, 22.1. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53; O, 18.95. Found: C, 66.45; H, 9.14; N, 5.51.

4-Isopropoxy-5-methoxy-1-methyl-3-phenyl-2-pyridone, 5c. 4-Isopropoxy-5-methoxy-1-methyl-3-phenyl-3,6-dihydropyridone **4c** (0.248 g, 0.900 mmol, 1.00 equiv), NBS (0.176 g, 0.990 mmol, 1.10 equiv), and pyridine (0.214 g, 2.71 mmol, 3.01 equiv) yielded 0.215 g (0.790 mmol, 88%) of **5c** as a white solid after recrystallization; TLC (silica gel, EtOAc, R_f = 0.17); mp 173−175 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1655 (s), 1593 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37 (d, J = 6.9 Hz, 2 H), 7.27 (dd, J = 6.9, 6.9 Hz, 2 H), 7.18 (t, J = 6.9 Hz, 1 H), 6.17 (s, 1 H), 4.12 (sept, J = 6.0 Hz, 1 H), 3.63 (s, 3 H), 3.42 (s, 3 H), 0.92 (d, J = 6.0 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 160.8, 156.2, 139.3, 133.4, 130.4, 127.2, 126.8, 122.6, 119.7, 75.5, 57.2, 37.1, 21.9. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12; O, 17.56. Found: C, 70.31; H, 7.05; N, 5.18.

3,4-Diethyl-5-methoxy-1-methyl-2-pyridone, 5d. 3,4-Diethyl-5-methoxy-1-methyl-3,6-dihydro-2-pyridone **4d** (0.160 g, 0.810 mmol, 1.00 equiv), NBS (0.159 g, 0.890 mmol, 1.10 equiv), and pyridine (0.192 g, 2.430 mmol, 3.00 equiv) yielded 0.135 g (0.690 mmol, 85%) of **5d** as a light brown solid after recrystallization; TLC (silica gel, EtOAc, R_f = 0.08); mp 86−87 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1657 (s), 1590 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 6.55 (s, 1 H), 3.66 (s, 3 H), 3.50 (s, 3 H), 2.60 (q, J = 7.5 Hz, 2 H), 2.54 (q, J = 7.5 Hz, 2 H), 1.10 (t, J = 7.5 Hz, 3 H), 1.08 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 160.2, 145.0, 142.0, 131.9, 114.6, 55.7, 37.2, 20.1, 19.9, 13.5, 13.3. Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17; O, 16.39. Found: C, 67.63; H, 8.75; N, 7.18.

2-Isopropoxy-1-methoxy-3-phenyl-6,7,8,9-tetrahydro-quinolizin-4-one, 5e. 3,6,7,8,9,9*a*-Hexahydro-2-isopropoxy-1-methoxy-3-phenyl-quinolizin-4-one **4e** (0.315 g, 1.000 mmol, 1.00 equiv), NBS (0.196 g, 1.100 mmol, 1.10 equiv), and pyridine (0.237 g, 3.00 mmol, 3.00 equiv) yielded 0.256 g (0.820 mmol, 82%) of **5e** as a light yellow semisolid after chromatography; TLC (silica gel, 60% EtOAc in hexane, R_f = 0.19); chromatographic purification (flash column, silica gel, 2 × 15 mm, 24% EtOAc/56% hexane/20% CH_2Cl_2). IR (CH_2Cl_2, KCl, cm^{-1}): 1636 (s), 1575 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (app d, J = 7.2 Hz, 2 H), 7.23 (app t, J = 7.2 Hz, 2 H), 7.13 (app t, J = 7.2 Hz, 1 H), 4.11 (sept, J = 6.0 Hz, 1 H), 3.85 (t, J = 6.3 Hz, 2 H), 3.64 (s, 3 H), 2.76 (t, J = 6.6 Hz, 2 H), 1.81 (m, 2 H), 1.68 (m, 2 H), 0.90 (d, J = 6.0 Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.3, 158.0, 138.3, 135.1, 133.7, 130.5, 127.1, 126.4, 118.7, 75.1, 60.5, 42.4, 22.4, 22.0, 21.8, 18.2. HRMS (EI) calcd for $C_{19}H_{24}NO_3$ $(M + H)^+$ 314.1757, found 314.1769.

6,7-Diethyl-2,3-dihydro-8-methoxy-1*H*-indolizin-5-one, 5f. 6,7-Diethyl-8-methoxy-2,3,6,8*a*-tetrahydro-1*H*-indolizin-5-one **4f** (0.200 g, 0.900 mmol, 1.00 equiv), NBS (0.175 g, 0.980 mmol, 1.09 equiv), and pyridine (0.214 g, 2.71 mmol, 3.01 equiv) yielded 0.12 g (0.540 mmol, 60%) of **5f** as a deep blue viscous oil after chromatography; TLC (silica gel, EtOAc, R_f = 0.06); chromatographic purification (flash column, silica gel, 2 × 15 mm, 1% Et_3N in EtOAc). IR (CH_2Cl_2, KCl, cm^{-1}): 1653 (s), 1575 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.12 (t, J = 7.5 Hz, 2 H), 3.69 (s, 3 H), 3.10 (t, J = 7.5 Hz, 2 H), 2.54 (pent, J = 7.5 Hz, 4 H), 2.16 (pent, J = 7.5 Hz, 2 H), 1.14 (t, J = 7.5 Hz, 3 H), 1.12 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 160.0, 148.3, 137.6, 136.9, 129.2, 61.2, 48.8, 28.7, 21.5,

20.2, 20.1, 14.5, 13.5. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33; O, 14.46. Found: C, 70.62; H, 8.74; N, 6.32. The deep blue color of compound **5f** was caused by an impurity that formed during column separation and the subsequent concentration process. A second chromatographic purification left a blue band at the top of the column, but the final compound was still deeply colored with no obvious improvement. Nevertheless, clean NMR spectra were obtained, and the compound passed elemental analysis.

6-Carboethoxy-4-isopropoxy-5-methoxy-1-methyl-3-phenyl-2-pyridone, 5g. 6-Carboethoxy-4-isopropoxy-5-methoxy-1-methyl-3-phenyl-3,6-dihydro-2-pyridone **4g** (0.539 g, 1.550 mmol, 1.00 equiv), NBS (0.303 g, 1.700 mmol, 1.10 equiv), and pyridine (0.368 g, 4.650 mmol, 3.00 equiv) yielded 0.352 g (1.020 mmol, 66%) of **5g** as a light brown viscous oil after chromatography; TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.36$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 30% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1768 (w), 1736 (s), 1644 (s), 1596 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39−7.19 (m, 5 H), 4.39 (q, $J = 7.2$ Hz, 2 H), 4.13 (sept, $J = 6.0$ Hz, 1 H), 3.76 (s, 3 H), 3.39 (s, 3 H), 1.35 (t, $J = 7.2$ Hz, 3 H), 0.94 (d, $J = 6.0$ Hz, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.8, 160.9, 158.1, 136.4, 132.9, 132.4, 130.3, 127.4, 127.3, 123.8, 75.9, 62.4, 62.1, 33.0, 22.1, 13.9. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06; O, 23.16. Found: C, 65.90; H, 6.74; N, 4.02.

6-Carboethoxy-3,4-diethyl-5-methoxy-1-methyl-2-pyridone, 5h. 6-Carboethoxy-3,4-diethyl-5-methoxy-1-methyl-3,6-dihydro-2-pyridone **4h** (0.090 g, 0.330 mmol, 1.00 equiv), NBS (0.065 g, 0.370 mmol, 1.12 equiv), and pyridine (0.079 g, 1.000 mmol, 3.03 equiv) yielded 0.075 g (0.280 mmol, 85%) of **5h** as a light yellow viscous oil after chromatography; TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.32$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 30% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1734 (s), 1646 (s), 1591 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.40 (q, $J = 7.2$ Hz, 2 H), 3.69 (s, 3 H), 3.40 (s, 3 H), 2.58 (q, $J = 7.2$ Hz, 2 H), 2.52 (q, $J = 7.2$ Hz, 2 H), 1.38 (t, $J = 7.2$ Hz, 3 H), 1.14 (t, $J = 7.2$ Hz, 3 H), 1.09 (H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 162.4, 160.3, 147.6, 139.8, 134.4, 130.6, 63.5, 62.4, 33.2, 20.9, 20.3, 14.3, 14.0, 13.2. HRMS (EI) calcd for $C_{14}H_{22}NO_4$ $(M + H)^+$: 268.1549, found: 268.1559. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24; O, 23.94. Found: C, 62.27; H, 7.95; N, 5.24.

4-(*N*,*N*-Dimethylamino)-5-methoxy-1-methyl-3-phenyl-2-pyridone, 5i. 4-(*N*,*N*-Dimethylamino)-5-methoxy-1-methyl-3-phenyl-5,6-dihydro-2-pyridone **4i** (0.182 g, 0.700 mmol, 1.00 equiv), NBS (0.137 g, 0.770 mmol, 1.10 equiv), and pyridine (0.166 g, 2.100 mmol, 3.00 equiv) yielded 0.178 g (0.690 mmol, 99%) of **5i** as a light yellow solid after recrystallization; TLC (silica gel, 2% MeOH in $CHCl_3$, $R_f = 0.04$); mp 148−150 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1650 (s), 1602 (s), 1585 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33−7.17 (m, 5 H), 6.69 (s, 1 H), 3.66 (s, 3 H), 3.42 (s, 3 H), 2.48 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.1, 151.5, 140.2, 136.8, 130.7, 127.5, 126.3, 119.4, 119.3, 57.2, 42.7, 36.8. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84; O, 12.39. Found: C, 69.65; H, 7.00; N, 10.92.

8,9-Benzo-6,7-dihydro-2-(*N*,*N*-dimethylamino)-1-methoxy-3-phenyl-quinolizin-4-one, 5j. 8,9-Benzo-2-(*N*,*N*-dimethylamino)-1-methoxy-3-phenyl-1,6,7,9*a*-tetrahydro-quinolizin-4-one **4j** (0.296 g, 0.850 mmol, 1.00 equiv), NBS (0.166 g, 0.930 mmol, 1.09 equiv), and pyridine (0.202 g, 2.550 mmol, 3.00 equiv) yielded 0.120 g (0.350 mmol, 41%) of **5j** as a yellow solid after chromatography; TLC (silica gel, EtOAc, $R_f = 0.36$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 30% EtOAc in hexane); mp 215−216 °C (CH_2Cl_2/hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1620 (s), 1600 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.41−8.38 (m, 1 H), 7.39−7.20 (m, 8 H), 4.20 (br t, $J = 6.0$ Hz, 2 H), 3.43 (s, 3 H), 2.90 (t, $J = 6.0$ Hz, 2 H), 2.59 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 160.8, 153.8, 138.3, 137.1, 133.3, 130.7, 129.6, 129.0, 128.0, 127.8, 127.3, 126.7, 126.4, 118.4, 60.0, 42.8, 39.6, 29.1. HRMS (EI) calcd for $C_{22}H_{23}N_2O_2$ $(M + H)^+$: 347.1760, found 347.1750.

1-Benzyl-4-(*N*,*N*-dimethylamino)-5-methoxy-1-methyl-3,6-diphenyl-2-pyridone, 5k. 1-Benzyl-4-(*N*,*N*-dimethylamino)-5-methoxy-1-methyl-3,6-diphenyl-5,6-dihydro-2-pyridone **4k** (0.256 g, 0.620 mmol, 1.00 equiv), NBS (0.121 g, 0.680 mmol, 1.10 equiv), and pyridine (0.147 g, 1.860 mmol, 3.00 equiv) yielded 0.182 g (0.440 mmol, 71%) of **5k** as a light yellow foam after chromatography; TLC (silica gel, 60% EtOAc in hexane, $R_f = 0.50$); chromatographic purification (flash column, silica gel, 2 × 15 mm, 25% EtOAc in hexane). IR (CH_2Cl_2, KCl, cm^{-1}): 1626 (s), 1600 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.50−7.15 (m, 13 H), 6.91 (t, $J = 3.6$ Hz, 2 H), 5.08 (br s, 2 H), 3.31 (s, 3 H), 2.63 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 161.9, 153.0, 140.2, 137.8, 137.0, 131.7, 130.8, 129.5, 128.6, 127.9, 127.8, 127.6, 127.1, 126.5, 126.3, 117.8, 60.0, 48.4, 42.4. HRMS (EI) calcd for $C_{27}H_{27}N_2O_2$ $(M + H)^+$: 411.2073, found 411.2072.

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