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Intramolecular Cyclization Manifolds of 4-Alkylpyridines Bearing Ambiphilic Side Chains: Construction of Spirodihydropyridines or Benzylic Cyclization via Anhydrobase Intermediates

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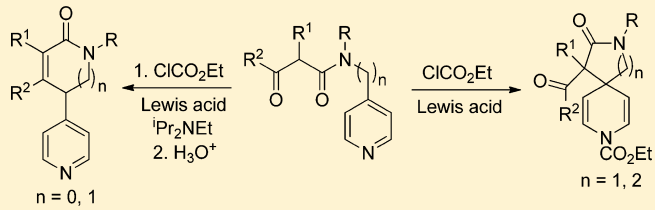
Supporting Information

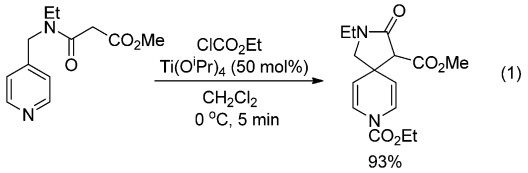
ABSTRACT: 4-Alkylpyridines possessing nucleophilic β-dicarbonyl side chains have been converted to spirodihydropyridines upon treatment with ethyl chloroformate and sub-stoichiometric amounts of $Ti(O^iPr)_4$. Alternatively, inclusion of mild base in the reaction medium was found to facilitate generation of anhydrobase intermediates. Subsequent aldol-like condensations with electrophilic side chain moieties followed by hydrolysis delivered benzylically cyclized pyridines in good yield. In situ hydrogenation of cyclized anhydrobase intermediates afforded 4-substituted piperidines.



INTRODUCTION

Pyridines and pyridine derivatives are ubiquitous heterocyclic motifs that are encountered in numerous natural products, pharmaceutical agents, and functional materials.[1−4] Developing preparative methods suitable for construction of substituted pyridines[5−7] and further defining synthetic approaches for manipulation of preformed pyridine substrates[8−12] are important objectives. Continued success in research along these lines has potential to significantly impact many diverse areas within the field of contemporary organic chemistry.

A convenient and well-established means of functionalizing simple pyridine derivatives entails activation of the pyridine ring system via N-alkylation or N-acylation followed by regioselective nucleophilic addition to either the α or γ pyridine carbon.[8,13−15] The resulting dihydropyridine products can then be further processed to afford substituted piperidines or rearomatized to yield substituted pyridines. Intramolecular variants of this strategy, however, have not been extensively developed despite their potential to deliver concise entry to a variety of polycyclic heterocyclic frameworks.[16−22] In this context we recently reported efficient spirocyclization reactions of 4-alkylpyridines possessing β-amido ester groups in the side chain (e.g., eq 1).[23] In this manner several diazaspiro[4.5]-



(1)

decane and diazaspiro[5.5]undecane derivatives were obtained from 4-aminomethyl and 4-aminoethyl pyridine precursors via acylation of the pyridine ring followed by Ti-mediated nucleophilic addition of the dicarbonyl side chain.

The spirocyclization protocol described above proved to be effective when β-amido ester groups served as pro-nucleophilic components. We have subsequently attempted to expand the scope of this transformation to include 4-alkylpyridines possessing substituted β-keto amide and β-keto ester side chains. During the course of these investigations a second intramolecular cyclization reaction manifold available to these pyridine substrates was uncovered that appears to proceed via generation of nucleophilic anhydrobase intermediates. Under these modified reaction conditions, cyclization between the benzylic position of the pyridine and an electrophilic carbonyl group of the side chain occurs to afford new pyridyl-substituted hetero- and carbocyclic ring systems. Thus, judicious choice of reaction conditions allows structurally similar pyridine derivatives to be converted to either spirodihydropyridines or polycyclic pyridyl lactams in good yield. Notably, each of these heterocyclic frameworks possesses pharmacological significance.[24,25]

RESULTS AND DISCUSSION

We previously reported that exposure of simple β-keto amide-substituted pyridines **1** and **3** to the reaction conditions illustrated in eq 1 gave the corresponding spirocyclic products **2** and **4** in greatly diminished yields as compared to reactions involving closely related β-amido ester analogues (Scheme 1).[23] The reactivity of several additional 4-alkylpyridines with β-keto amide side chains was screened under these conditions, and the results are depicted in Table 1. The reaction was found to be sensitive to the nature of the amide N-substituent (allyl and benzyl amides returned dihydropyridine products in significantly lower yield, entries 1 and 2) as well as substitution at the

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Scheme 1

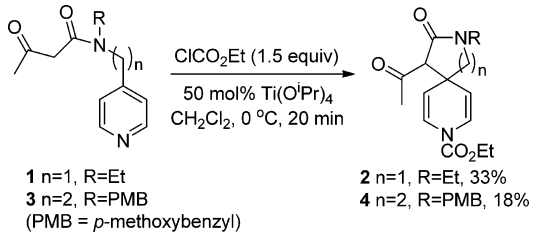
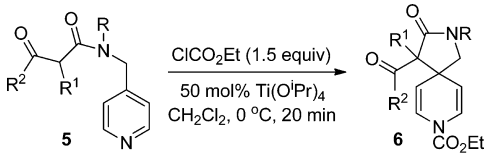


Table 1. Spirocyclization of 4-Alkylpyridines with β-Keto Amide Side Chains



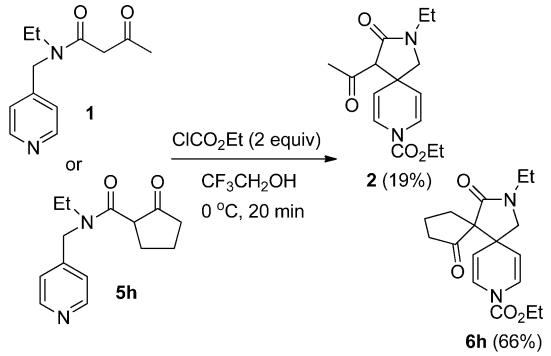
entry	substrate	R	R^1	R^2	product (% yield)[a]
1	**5a**	allyl	H	Me	**6a** (12)
2	**5b**	Bn	H	Me	**6b** (18)
3	**5c**	Et	H	Et	**6c** (53)
4	**5d**	Et	H	Ph	**6d** (43)
5	**5e**	Et	F	Me	**6e** (10)
6	**5f**	Et	allyl	Me	np[b]
7	**5g**	Et	propargyl	Me	np[b]
8	**5h**	Et	$-CH_2CH_2CH_2-$		**6h** (51)

[a]Isolated yield. [b]No product.

activated methylene group of the β-dicarbonyl moiety (entries 5−7). An exception to this trend was observed in cyclizations involving an oxoamide cyclopentanone side chain (entry 8). Notably, cyclizations of analogous cyclopentanone amides derived from 4-aminoethyl pyridine precursors were also much more efficient compared to simpler acyclic β-keto amide congeners.[23b] In all cases, however, pyridines with β-amido ester side chains (as in eq 1) proved to be superior substrates for this transformation.

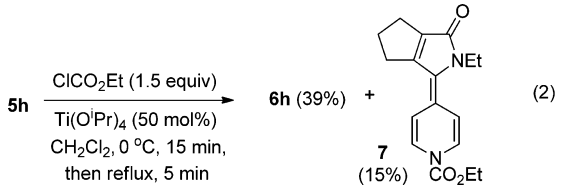
Some effort was briefly directed toward enhancing the reactivity of β-keto amide substrates by variation of reaction conditions. For example, reactions of **1** were performed in several other solvents (DMF, THF, acetone, toluene), but no cyclized products were observed. In addition, the ability of different Lewis acids to mediate the cyclization of **1** in the presence of ethyl chloroformate was probed. Of the acids examined ($InCl_3$, $Mg(OTf)_2$, $Cu(OTf)_2$, TMSOTf), only $InCl_3$ proved effective but was still inferior to the action of $Ti(O^iPr)_4$. Likewise, the reactivity of pyridine **5h** was also examined in the presence of alternative Lewis acids. Once again $Ti(O^iPr)_4$ proved to be the additive of choice, although spirocyclization was also observed in comparable yield using $MgBr_2$. Other Lewis acids ($CuSO_4$, $SnCl_4$, $TiCl_4$) were ineffective. Interestingly, both **1** and **5h** were found to undergo spontaneous spirocyclization when treated with $ClCO_2Et$ in trifluoroethanol (TFE) solvent. While the isolated yield of **2** under these conditions was modest, tricyclic dihydropyridine **6h** was obtained in higher yield compared to reactions performed in the presence of Lewis acid (Scheme 2). We speculate that the strong hydrogen bonding ability of TFE helps to promote enolization of the dicarbonyl side chain, thereby facilitating spirocyclization. The effect was not universal, however, as other

Scheme 2



substrates (Table 1) were not efficiently cyclized under these conditions.

An interesting observation was recorded when a crude CH_2Cl_2 reaction mixture (Scheme 1 conditions) of **5h** was briefly heated to reflux. In this instance, the expected spirocycle **6h** was obtained in 39% along with a byproduct identified as the relatively stable anhydrobase **7** in 15% yield (eq 2).The



formation of **7** is attributed to facile benzylic deprotonation of **5h** upon acylation of the pyridine, perhaps assisted by the presence of dissociated $^iPrO^-$ ligands. Condensation with the pendant ketone carbonyl and elimination of water give rise to the observed lactam ring. While anhydrobases of pyridine are certainly well-established species,[26] their use as synthetic intermediates is relatively rare.[27] Recent reports, however, have described the ability of 2-picolines to participate in intermolecular condensation reactions with activated electrophiles catalyzed by Lewis acids,[28] Brønsted acids,[29] or simply upon thermal activation[30] via anhydrobase (enamine)-like intermediates. Accordingly, we became interested in further developing this second intramolecular reaction manifold potentially available to the 4-alkylpyridine derivatives in hand.

We began these studies by examining the effect of added base in established spirocyclization procedures. The inclusion of 1.5 equiv of $^iPr_2NEt$ along with the other reagents indicated in Scheme 1 to reaction mixtures of **1**, however, failed to produce any products emanating from anhydrobase intermediates (although the yield of spiro-adduct **2** was increased to 44%). Changing the solvent to DMF and heating to 100 °C further increased the yield of **2** to 49%, but again no products formed from benzylic deprotonation were detected. Better results were obtained with keto amide substrates **8** and **9**. Indeed, exposure of these pyridine derivatives to $ClCO_2Et/Ti(O^iPr)_4/^iPr_2NEt$ in DMF (100 °C) cleanly afforded cyclized anhydrobase products (**10** and **11**) in good yield (Scheme 3). These materials were isolated and spectroscopically characterized in crude form after aqueous workup of the reaction mixtures as both **10** and **11** proved to be unstable to silica gel, neutral alumina, and basic alumina flash column chromatography (EtOAc/hexane eluent). In considering procedures whereby a stable and tractable product may be obtained from this process, we reasoned that in

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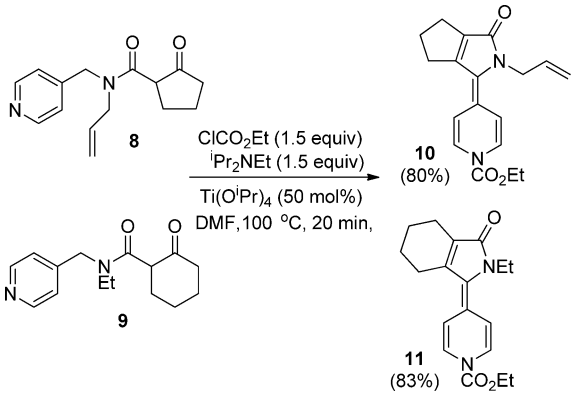
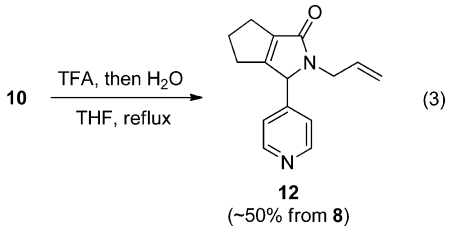
Scheme 3



situ protonation of **10**/**11** should generate an acyl pyridinium species that might be prone to subsequent hydrolysis to give a rearomatized pyridine moiety. To test this notion, crude **10** in THF was combined with excess TFA and heated to reflux for 5 min. Water was then added, and reflux was maintained for an additional ~10 min. Gratifyingly, stable pyridine derivative **12** was isolated from the reaction upon cooling in ~50% overall yield from **8** (eq 3).

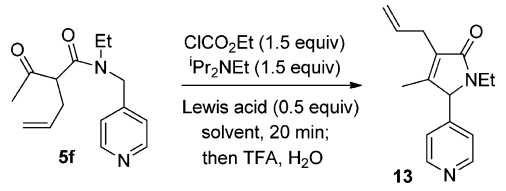


(3)

The conversion of **8** to **12** via **10** represents a potentially convenient means of assembling pyridyl-substituted lactams, especially if the sequence of transformations could be reduced to an efficient one-pot process. Toward this end, pyridine **5f** was selected as a substrate for screening of reaction conditions since, unlike **1**, **5f** fails to undergo potentially competing spirocyclization. Initially, **5f** was exposed to $ClCO_2Et$, Ti(O^iPr)$_4$, and $^iPr_2NEt$ in refluxing CH_2Cl_2. After 20 min TLC indicated disappearance of **5f**, and an excess (10 equiv) of TFA was added. After an additional 5 min water was added, and reflux was continued for another 5−10 min. After cooling the reaction mixture was neutralized with Na_2CO_3, followed by aqueous workup and chromatography to afford the anticipated pyridyl pyrrolidinone **13**, albeit in only 12% isolated yield (Table 2, entry 1). Control experiments established that chloroformate, Lewis acid (Ti(O^iPr)$_4$), and $^iPr_2NEt$ were all required for cyclization to be observed. Consequently, reaction conditions were screened in which the solvent and Lewis acid were varied to identify the optimal combination (Table 2). In each case TFA was added after 20 min, followed by H_2O in order to effect rearomatization of the pyridine group. These experiments revealed THF to be the best solvent for this transformation. Several Lewis acids were investigated (Table 2, entries 5−9), but Ti(O^iPr)$_4$ gave the highest yields of **13**. Optimized conditions for this transformation are indicated in Table 2 entry 4 and provided **13** in excellent 94% isolated yield.

A straightforward mechanistic rationale to account for the conversion of **5f** to **13** via a putative anhydrobase intermediate is illustrated in Scheme 4. Acylation of **5f** with $ClCO_2Et$ gives

Table 2. Benzylic Cyclization of 5f



entry	solvent	Lewis acid	T	% yield **13**[a]
1	CH_2Cl_2	Ti(O^iPr)$_4$	reflux	12
2	DMF	Ti(O^iPr)$_4$	100 °C	40
3	$PhCH_3$	Ti(O^iPr)$_4$	reflux	65
4	**THF**	**Ti(O^iPr)$_4$**	**reflux**	**94**
5	THF	$TiCl_4$	reflux	0
6	THF	$InCl_3$	reflux	22
7	THF	TMSOTf	reflux	48
8	THF	$BF_3{\cdot}OEt_2$	reflux	62
9	THF	Cu(OTf)$_2$	reflux	0

[a]Isolated yield.

pyridinium salt **14**. In the presence of Hünig's base **14** is converted to neutral anhydrobase **15**. Intramolecular cyclization of the anhydrobase with the ketone carbonyl (activated by the Lewis acid additive) then gives **16**. Loss of H_2O and a second benzylic deprotonation afford anhydrobase **17** (analogous to **10** and **11**, see Scheme 3). At this stage addition of TFA reprotonates **17**, and the resulting acyl pyridinium cation then suffers hydrolysis upon addition of H_2O to furnish the observed product.

With a reasonably efficient one-pot procedure in hand for conversion of **5f** to **13**, the generality of the reaction was next assayed using several 4-aminomethyl- and 4-aminoethyl-substituted pyridines. The results of this study are illustrated in Table 3. Each transformation was performed using the conditions indicated in entry 4 of Table 2. Substrates featuring activated methine groups in the β-dicarbonyl moiety were employed since **1** (with an unsubstituted β-dicarbonyl methylene group) was observed to undergo spirocyclization exclusively irrespective of reaction conditions. Pyridyl-substituted lactam products were obtained in each case in moderate to good isolated yield. Entries 1−7 show the successful construction of pyridyl-substituted pyrrolidinone derivatives from pyridines possessing acyclic and cyclic β-dicarbonyl side chains, including examples incorporating potentially removable N-amide protecting groups (allyl, benzyl, entries 6 and 7). Entries 8 and 9 illustrate the successful use of 4-aminoethyl pyridines as substrates to afford the corresponding pyridyl-substituted piperidinone products in good yield. The reaction depicted in entry 10 was performed in order to probe the possibility of diastereoselective cyclization. Pyridine (±)-**32** bearing an α-methyl-p-methoxybenzyl substitutent on the amide nitrogen was subjected to optimized benzylic cyclization conditions to give the expected pyridyl lactam **33** as a 2.7:1 mixture of inseparable diastereomers. Thus, the presence of a remote stereogenic center seems to have limited influence on reaction diastereoselectivity. Finally, allyl-substituted β-amido ester **34** was also found to undergo smooth benzylic cyclization under the optimized reaction conditions. In this case the initial tetramic acid product was isolated as the enol carbonate after acylation by excess ethyl chloroformate or by an acyl pyridinium intermediate analogous to **18** (see Scheme 4).

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Scheme 4

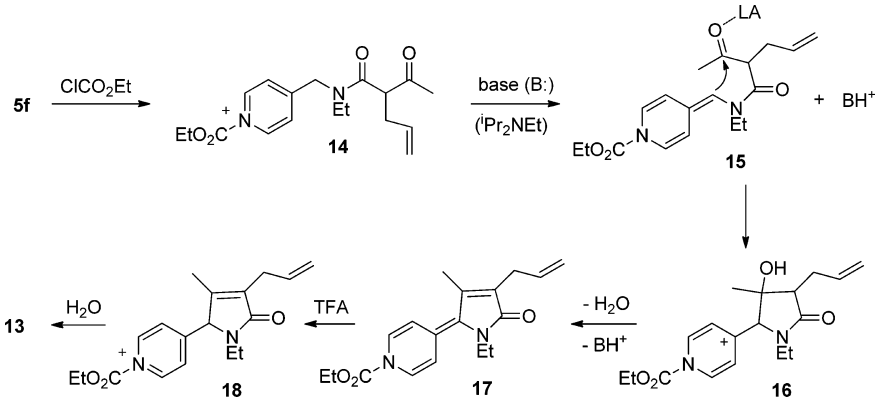
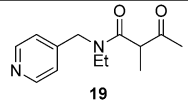
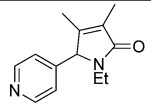
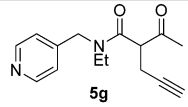
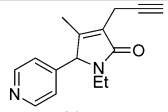
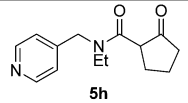
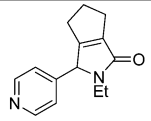
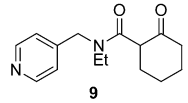
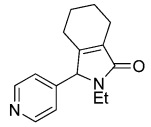
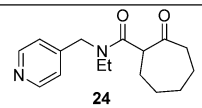
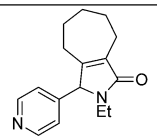
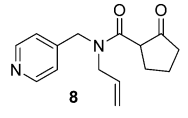
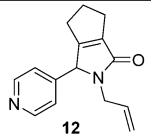
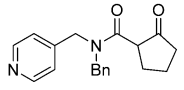
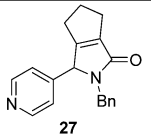
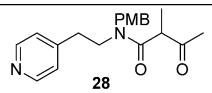
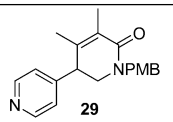
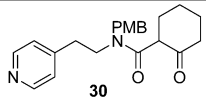
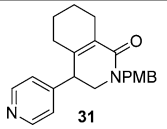
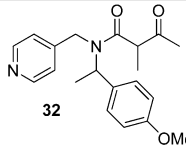
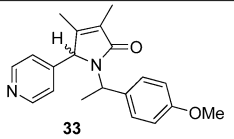
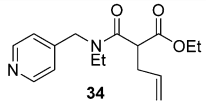
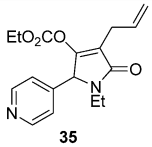


Table 3. Synthesis of Pyridyl-Substituted Lactams via Benzylic Cyclization[a]

Entry	Substrate	Product	Yield[b]
1	 19	 20	59%
2	 5g	 21	86%
3	 5h	 22	63%
4	 9	 23	68%
5	 24	 25	42%
6	 8	 12	44%

Entry	Substrate	Product	Yield[b]
7	 26	 27	48%
8	 28	 29	48%
9	 30	 31	68%
10	 32	 33	36%[c]
11	 34	 35	62%

[a]Reactions performed according to conditions given in Table 2, entry 4. [b]Isolated yield. [c]2.7:1 mixture of diastereomers.

We have also briefly examined the reactivity of substrates in which the amide linkage in the pyridine side chain has been replaced with an ester group or removed altogether. Exchange of the amide linkage for an ester group resulted in significantly altered reactivity. For example, **1** is a keto amide substrate that was observed to participate only in the spirocyclization reaction manifold.[23a] Exposure of the ester analogue (**36**) to the reaction conditions indicated in eq 4, however, produced the corresponding cyclized anydrobase product **37** in 77% crude yield. For reasons that remain obscure, **37** appears to be

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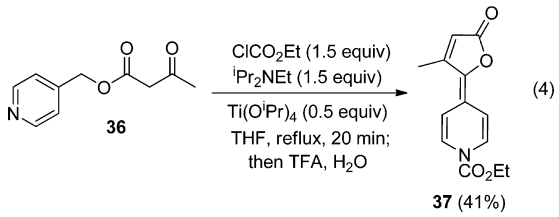
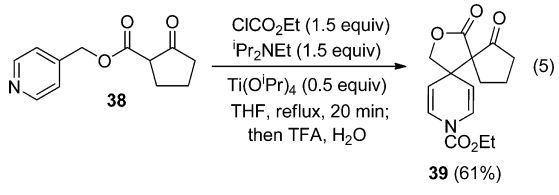
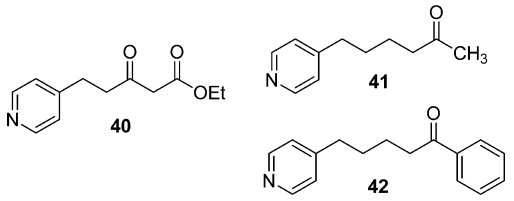


resistant to rearomatization via protonation/hydrolysis. Purification of **37** by chromatography resulted in some decomposition, but the anhydrobase was still isolated in 41% yield, and the structural assignment was confirmed by X-ray crystallography.[31] In contrast, **38** was converted to the spirodihydropyridine **39** in good yield under the same reaction conditions (eq 5).



Carbocyclic ring construction via anhydrobase intermediates was probed using substrates **40**–**42**. The *β*-keto ester **40**, previously found to be unreactive toward spirocyclization,[23a] was equally unreactive toward benzylic cyclization when exposed to the optimized conditions indicated in Table 2. We attribute this failure to inappropriate positioning of the electrophilic ketone carbonyl with respect to the benzylic carbon. Consequently, substrates **41** and **42** possessing an electrophilic center four carbons removed from the benzylic carbon were prepared using the route shown in Scheme 5. Treatment of these pyridines with $ClCO_2Et$ and Hünig's base in the presence of $Ti(O^iPr)_4$, however, gave only trace amounts of the expected product. Much better results were obtained when the Lewis acid additive was changed to TMSOTf, and the desired cyclopentene products were isolated in excellent yield. Perhaps $Ti(O^iPr)_4$ is better able to activate dicarbonyl side chains via formation of chelated structures, whereas TMSOTf is better suited to activate the monocarbonyl side chains encountered in **41** and **42**.

The manipulations above all involve rearomatization of putative anhydrobase intermediates via protonation, ultimately leading to restoration of a pyridine ring. In an effort to enhance the versatility of these cyclizations, we have also explored alternative methods for processing these intermediates. Specifically, hydrogenation of anhydrobases would offer a



direct route to piperidine-pyrrolidinone and piperidine-piperidinone ring systems. Notably, products exhibiting this latter framework may serve as precursors to bis(piperidine) derivatives, a structural motif encountered in numerous marine alkaloid natural products (Figure 1).[32] Toward this end,

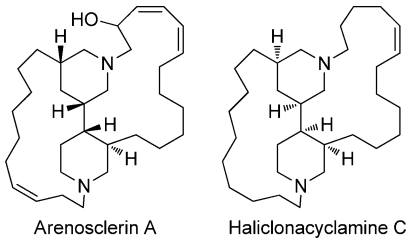
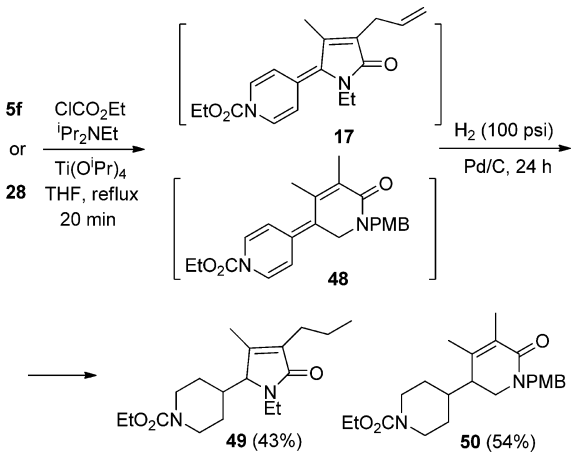


Figure 1. Representative bis(piperidine) alkaloids.

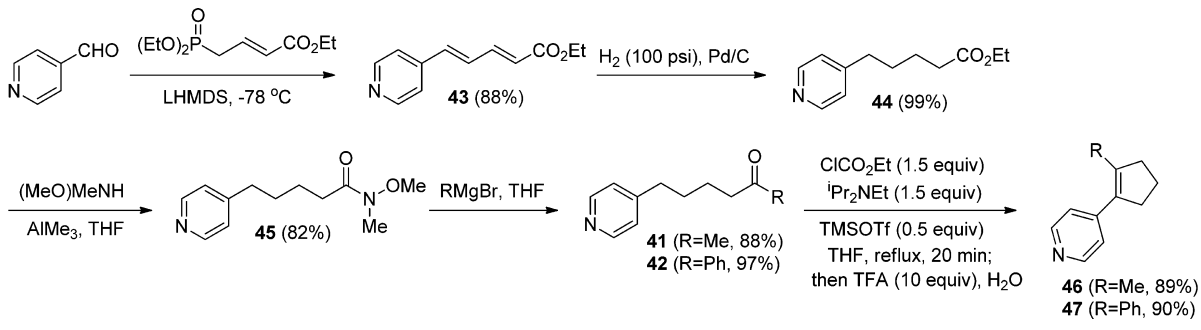
substrate **5f** was treated with $ClCO_2Et/Ti(O^iPr)_4/^iPr_2NEt$ in refluxing THF until TLC indicated complete conversion of the starting material to a highly colored and less polar material (presumably **17**, Scheme 6). The reaction mixture was then

Scheme 6



allowed to cool to room temperature and quickly filtered through a plug of basic alumina. Catalytic hydrogenation of the

Scheme 5. Carbocyclization of 4-Alkylpyridines



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filtrate (Pd/C, 100 psi H_2) then afforded **49**. Evidently, the tetrasubstituted conjugated olefin is resistant to hydrogenation under these conditions. In similar fashion, 4-aminoethyl pyridine **28** was converted to the corresponding anhydrobase **48**. In situ reduction of **48** then provided 3,4′-bis(piperidine) derivative **50** in reasonable overall yield.

CONCLUSIONS

This work demonstrates that simple 4-alkylpyridines imbued with ambiphilic (nucleophilic and electrophilic) side chains can be converted to either spiro(dihydropyridines) or pyridyl (or piperidine)-substituted lactams as a function of reaction conditions. In addition, benzylic cyclization of pyridines bearing ketone side chains has been shown to afford pyridyl-substituted cyclopentenes in good yield. These methods provide convenient and direct access to diverse heterocyclic structures of pharmacological relevance. In the future we hope to expand this general strategy to include catalytic transformations and alternative modes of cyclization involving additional electrophilic and nucleophilic components. We are also seeking reaction conditions suitable for manipulation of 2-substituted pyridines, substrates that have thus far been unwilling participants in these types of intramolecular transformations. Finally, applications of this chemistry in the stereoselective construction of bis(piperidine) alkaloids (Figure 1) is also under active investigation.

EXPERIMENTAL SECTION

General Information. All commercially available starting materials and reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina or activated molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane for NMR spectra obtained in $CDCl_3$ or residual undeuterated solvent for all other spectra not obtained in $CDCl_3$. IR spectra were recorded on a FT-IR spectrophometer as thin films on sodium chloride discs. High resolution mass spectra were obtained using electron spray ionization (ESI) on a double-focusing magnetic sector mass spectrometer. Melting points were recorded using a capillary melting point apparatus and are uncorrected.

Experimental Procedures and Characterization Data for 4-Alkyl Pyridine Substrates. General procedure for the preparation of 4-alkylpyridines with amide side chains: These substrates were prepared by treatment of an *N*-alkyl (aminomethyl)pyridine or *N*-alkyl (aminoethyl)pyridine (1.00 g) with the appropriate β-keto methyl ester in refluxing toluene (~20 mL) for 36 h. Crude products were purified by silica gel flash column chromatography using 50−70% EtOAc in hexanes as eluent. 4-Alkylpyridines **1**, **3**, and **34** have been previously reported.[23]

5a. Yield 0.88 g, 56%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 14.58−14.50 (m, 0.25H), 8.62−8.55 (m, 2H), 7.23−7.11 (m, 2H), 5.82−5.70 (m, 1H), 5.29−5.15 (m, 2H), 4.61 (s, 1.4H), 4.51−4.47 (m, 0.6H), 4.04−4.02 (m, 0.5H), 3.85−3.82 (m, 1.5H), 3.65 (s, 1H), 3.52 (s, 0.4H), 2.31−2.28 (m, 2.2H), 1.98−1.90 (m, 0.8H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 202.4, 167.6, 150.6, 150.2, 146.2, 132.2, 132.0, 122.6, 121.5, 118.5, 117.8, 86.9, 50.7, 50.0, 49.8, 48.6, 47.9, 30.7, 22.2. HRMS (ESI): calculated for $C_{13}H_{17}N_2O_2$ [M + H] $^+$, 233.1290; found 233.1308.

5b. Yield 1.01 g, 71%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 14.69−14.57 (m,0.3H), 8.61−8.53 (m, 2H), 7.41−7.07 (m, 7H), 5.29 (s, 0.2H), 5.03 (s, 0.1H), 4.64−4.60 (m, 2H), 4.44−4.41 (m, 2H), 3.71 (s, 0.9H), 3.58 (s, 0.5H), 2.30 (s, 2H), 1.96−1.92 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 202.3, 167.8, 167.4, 150.6, 150.3, 145.9, 145.5, 135.6, 129.4, 129.2, 129.0, 128.3, 128.0, 126.8, 126.6, 122.7, 121.5, 86.8, 51.5, 50.6, 50.0, 49.9, 48.9, 47.9, 30.7, 22.3. HRMS (ESI): calculated for $C_{17}H_{19}N_2O_2$ [M + H]$^+$, 283.1447; found 283.1462.

5c. Yield 1.01 g, 59%, yellow-brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 14.71−14.62 (m,0.2H), 8.62−8.55 (m, 2H), 7.23−7.13 (m, 2H), 4.61−4.50 (m, 2H), 3.66 (s, 1.2H), 3.48−3.41 (m, 1.1H), 3.33−3.26 (m, 1.5H), 2.67−2.55 (m, 1.6H), 2.31−2.24 (m, 0.4H), 1.20−1.03 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 205.1, 180.6, 167.2, 150.6, 150.2, 146.6, 122.5, 121.5, 85.1, 50.5, 49.0, 48.5, 47.4, 43.3, 41.7, 36.8, 29.2, 14.0, 12.7, 7.8. HRMS (ESI): calculated for $C_{13}H_{19}N_2O_2$ [M + H] $^+$, 235.1447; found 235.1460.

5d. Yield 1.24 g, 60%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 15.27−15.18 (m, 0.5H), 8.61−8.54 (m, 2H), 8.05−7.95 (m, 1H), 7.82−7.37 (m, 4H), 7.25−7.13 (m, 2H), 5.86 (s, 0.3H), 5.58 (s, 0.1H), 4.68−4.61 (m, 2H), 4.23 (s, 0.8H), 4.04 (s, 0.3H), 3.57−3.31 (m, 2H), 1.27−1.13 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers/tautomers) δ: 194.2, 172.5, 167.5, 150.6, 150.2, 147.1, 146.6, 136.3, 135.0, 134.1, 131.1, 129.04, 129.0, 128.8, 128.7, 126.2, 122.6, 122.5, 121.6, 84.8, 84.5, 50.6, 50.2, 47.9, 47.5, 46.1, 45.8, 43.4, 43.0, 41.7, 14.0, 12.6. IR (film): 1683, 1638 cm^{-1}. HRMS (ESI): calculated for $C_{17}H_{19}N_2O_2$ [M + H] $^+$, 283.1447; found 283.1462.

5e. A reaction mixture containing **1** (0.30 g, 1.36 mmol, 1 equiv) in acetonitrile (10 mL) was cooled to 0 °C, and Selectfluor (0.48 g, 1.36 mmol, 1 equiv) was added. The resulting mixture was warmed to room temperature, stirred for 18 h, quenched with satd aq $NaHCO_3$ solution (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The crude product was purified by silica gel column chromatography using 50−90% ethyl acetate in hexanes to obtain **5e** as a brown oil (0.23 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.63−8.55 (m, 2H), 7.16−7.12 (m, 2H), 5.65 (s, 0.3H), 5.50−5.48 (m, 0.4H), 5.33−5.31 (m, 0.3H), 4.73−4.50 (m, 2H), 3.58−3.30 (m, 2H), 2.44−2.36 (m, 3H), 1.22 (t, J = 7.2 Hz, 2.1H), 1.13 (t, J = 7.2 Hz, 0.9H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 202.5 (d, $^2J_{C-F}$ = 24.9 Hz), 164.5 (d, $^2J_{C-F}$ = 20.2 Hz), 150.6, 150.3, 145.7, 145.5, 122.4, 121.7, 92.1 (d, J^1_{C-F} = 196.2 Hz), 91.4 (d, $^1J_{C-F}$ = 194.7 Hz), 53.6, 49.3, 48.1, 47.8, 42.6, 42.0, 26.5, 26.4, 14.1, 12.3. HRMS (ESI): calculated for $C_{12}H_{16}N_2O_2F$ [M + H] $^+$, 239.1196; found 239.1206.

5f. Yield 1.13 g, 59%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotomers) δ: 8.60 (d, J = 6.1 Hz, 0.5H), 8.54 (d, J = 6.0 Hz, 1.5H), 7.15−7.11 (m, 2H), 5.85−5.59 (m, 1H), 5.20−5.02 (m, 2H), 4.80−4.42 (m, 2H), 3.77−3.72 (m, 0.7H), 3.65−3.42 (m, 1.3H), 3.37−3.24 (m, 1H), 2.83−2.59 (m, 2H), 2.23 (s, 2.2H), 2.17 (s, 0.8H), 1.19 (t, J = 7.2 Hz, 2.2H), 1.13 (t, J = 7.1 Hz, 0.8H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotomers) δ: 204.7, 204.5, 169.0, 168.5, 150.4, 150.1, 146.6, 146.1, 134.5, 134.3, 122.5, 121.4, 118.0, 58.2, 57.6, 49.8, 48.0, 42.8, 42.0, 33.8, 33.6, 27.5, 27.1, 14.3, 12.6. HRMS (ESI): calculated for $C_{15}H_{21}N_2O_2$ [M + H] $^+$, 261.1603; found 261.1612.

5g. Yield 1.19 g, 63%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.61 (d, J = 6.1 Hz, 0.5H), 8.55 (d, J = 6.0 Hz, 1.5H), 7.18 (d, J = 6.1 Hz, 2H), 4.83−4.56 (m, 2H), 3.96−3.91 (m, 0.7H), 3.69−3.35 (m, 2.3H), 2.89−2.79 (m, 2H), 2.25 (s, 2.2H), 2.17 (s, 0.8H), 2.08 (t, J = 2.7 Hz, 0.7H), 2.06−2.04 (m, 0.3H), 1.26 (t, J = 7.2 Hz, 2.2H), 1.15 (t, J = 7.1 Hz, 0.8H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 202.4, 168.6, 167.9, 150.5, 150.1, 146.4, 146.0, 122.6, 121.5, 80.8, 71.1, 56.5, 55.8, 50.0, 48.1, 43.1, 42.2, 27.6, 27.1, 19.0, 14.3, 12.5. HRMS (ESI): calculated for $C_{15}H_{19}N_2O_2$ [M + H] $^+$, 259.1447; found 259.1454.

5h. Yield 1.65 g, 91%, yellow-brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.64−8.52 (m, 2H), 7.19−7.14 (m, 2H), 5.05−4.95 (m, 1H), 4.47 (d, J = 18.4 Hz, 0.3H), 4.26 (d, J = 16.1 Hz, 0.7H), 3.81−3.67 (m, 1H), 3.57−3.51 (m, 0.7H), 3.31−3.11 (m, 1.3H), 2.62−2.49 (m, 1H), 2.39−2.04 (m, 4H), 1.96−1.83 (m, 1H), 1.22−1.11 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 214.7, 169.3, 150.5, 150.1, 146.9, 122.3, 121.5, 52.3, 52.0, 49.9, 47.9, 42.9, 42.1, 38.7, 27.7, 21.3, 14.3, 12.8. IR (film): 1735, 1628 cm^{-1}.

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HRMS (ESI): calculated for $C_{14}H_{19}N_2O_2$ $[M + H]^+$, 247.1447; found 237.1462.

8. Yield 1.10 g, 63%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.61−8.54 (m, 2H), 7.19−7.12 (m, 2H), 5.88−5.70 (m, 1H), 5.27−4.99 (m, 3H), 4.49−4.37 (m, 1.3H), 4.14−4.09 (m, 0.7H), 3.80−3.72 (m, 0.7H), 3.66−3.59 (m, 0.3H), 3.52−3.46 (m, 0.7H), 3.31−3.25 (m, 0.3H), 2.63−2.38 (m, 1H), 2.36−2.14 (m, 4H), 1.96−1.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 214.8, 169.6, 150.6, 150.2, 146.4, 132.8, 132.2, 122.3, 121.4, 117.9, 117.1, 52.3, 50.0, 49.5, 48.9, 48.3, 38.7, 27.5, 21.2. IR (film): 1735, 1641 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{19}N_2O_2$ $[M + H]^+$, 259.1447; found 259.1461.

9. Yield 1.45 g, 76%, yellow-brown oil ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.61−8.54 (m, 2H), 7.30−7.29 (m, 1.6H), 7.13−7.11 (m, 0.4H), 5.04 (d, J = 16.5 Hz, 0.8H), 4.52 (d, J = 18.1 Hz, 0.2H), 4.36 (d, J = 18.1 Hz, 0.2H), 4.23 (d, J = 16.2 Hz, 0.8H), 3.68−3.61 (m, 1H), 3.36−3.04 (m, 2H), 2.64−1.69 (m, 8H), 1.15 (t, J = 7.2 H, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 207.6, 169.9, 150.5, 150.1, 146.8, 146.6, 122.4, 121.5, 54.6, 54.5, 49.9, 47.5, 42.4, 42.2, 41.9, 41.7, 30.6, 30.4, 27.1, 26.9, 23.9, 23.5, 14.3, 12.6. HRMS (ESI): calculated for $C_{15}H_{21}N_2O_2$ $[M + H]^+$, 261.1603; found 261.1616.

19. Yield 1.10 g, 64%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.63−8.54 (m, 2H), 7.17−7.12 (m, 2H), 4.78−4.70 (m, 1H), 4.49−4.42 (m, 1H), 3.77−3.70 (q, J = 7.0 Hz, 0.7H), 3.67−3.60.(m, 0.3H), 3.50−3.38 (m, 1H), 3.34−3.22 (m, 1H), 2.24−2.13 (m, 3H), 1.47 (d, J = 7.0 Hz, 2.1H), 1.37 (d, J = 7.0 Hz, 0.9H), 1.21 (t, J = 7.1 Hz, 2.1H), 1.15 (t, J = 7.1 Hz, 0.9H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 205.4, 170.7, 170.4, 150.6, 150.2, 146.7, 146.3, 122.5, 121.3, 52.2, 51.5, 50.0, 47.7, 42.8, 42.0, 27.5, 27.1, 14.3, 12.6. IR (film): 1722, 1637 cm^{-1}. HRMS (ESI): calculated for $C_{13}H_{19}N_2O_2$ $[M + H]^+$, 235.1447; found 235.1471.

24. Yield 1.39 g, 69%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.62−8.53 (m, 2H), 7.18−7.14 (m, 2H), 4.92−4.80 (m, 1H), 4.46−4.32 (m, 1H), 3.78−3.73 (m, 0.7H), 3.59−3.44 (m, 1.3H), 3.27−3.17 (m, 1H), 2.89−2.80 (m, 1H), 2.61−2.42 (m, 1H), 2.24−1.90 (m, 6H), 1.57−1.37 (m, 3H), 1.22−1.09 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 211.1, 170.8, 170.2, 150.4, 150.1, 146.9, 146.6, 122.3, 121.5, 57.2, 56.5, 50.0, 47.7, 43.3, 42.9, 41.9, 30.4, 28.5, 28.4, 27.8, 25.8, 25.5, 14.4, 12.7. IR (film): 1699, 1642 cm^{-1}. HRMS (ESI): calculated for $C_{16}H_{23}N_2O_2$ $[M + H]^+$, 275.1760; found 275.1776.

26. Yield 1.18 g, 76%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.60−8.54 (m, 2H), 7.41−7.08 (m, 7H), 5.26−4.94 (m, 2H), 4.42−4.33 (m, 1H), 4.18−4.01 (m, 1H), 3.56−3.51 (m, 0.7H), 3.36−3.31 (m, 0.3H), 2.66−2.54 (m, 1H), 2.39−2.33 (m, 2H), 2.26−2.15 (m, 2H), 1.92−1.79 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 214.8, 169.9, 150.6, 150.3, 146.2, 136.5, 136.2, 129.3, 129.0, 128.1, 128.0, 126.4, 122.4, 121.4, 52.4, 51.0, 49.5, 48.4, 38.8, 27.5, 21.2. IR (film): 1739, 1646 cm^{-1}. HRMS (ESI): calculated for $C_{19}H_{21}N_2O_2$ $[M + H]^+$, 309.1614; found 309.1615.

28. Yield 1.22 g, 87%, yellow-brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.55−8.48 (m, 2H), 7.19−7.04 (m, 4H), 6.91−6.85 (m, 2H), 4.73−4.68 (m, 0.3H), 4.52−4.44 (m, 1H), 4.31−4.26 (m, 0.7H), 3.80−3.78 (m, 3H), 3.76−3.71.(m, 0.6H), 3.63 (q, J = 6.9 Hz, 0.7H), 3.57−3.44 (m, 1.7H), 2.87−2.77.(m, 2H), 2.12−2.11 (m, 3H), 1.37 (d, J = 7.0 Hz, 2H), 1.32 (d, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 205.1, 171.0, 170.4, 159.6, 150.4, 150.1, 148.0, 146.9, 129.6, 129.3, 128.2, 127.8, 124.4, 124.2, 114.7, 114.4, 55.5, 52.1, 51.9, 51.6, 48.2, 47.5, 34.5, 33.4, 27.4, 27.0, 14.2. IR (film): 1726, 1633 cm^{-1}. HRMS (ESI): calculated for $C_{20}H_{25}N_2O_3$ $[M + H]^+$, 341.1865; found 341.1858.

30. Yield 0.64 g, 42%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.54−8.48 (m, 2H), 7.28−7.24 (m, 2H), 7.04−7.01 (m, 2H), 6.89−6.86 (m, 2H), 4.96−4.91 (m, 0.3H), 4.37−4.29 (m, 1H), 4.11−4.05 (m, 0.7H), 3.94−3.87 (m, 0.7H), 3.80−3.79. (m, 3H), 3.56−3.47 (m, 0.7H), 3.38−3.18 (m, 1.6H), 2.91−2.73 (m, 2H), 2.57−2.52 (m, 1H), 2.35−1.98 (m, 5H), 1.83−1.76 (m, 1H), 1.65−1.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 207.6, 170.3, 169.9, 159.4, 159.2, 150.3, 150.0, 148.5, 147.5, 129.3, 128.3, 127.8, 124.5, 124.3, 114.6, 114.2, 55.5, 54.7, 54.5, 51.5, 47.8, 47.6, 47.4, 42.1, 42.0, 34.4, 33.4, 30.5, 27.1, 23.8. IR (film): 1704, 1642 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{27}N_2O_3$ $[M + H]^+$, 367.2022; found 367.2040.

32. Yield 0.88 g, 66%, brown oil. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 8.56−8.39 (m, 2H), 7.25−7.02 (m, 3H), 6.96−6.78 (m, 3H), 6.21−6.08 (m, 0.4H), 5.30−5.19 (m, 0.6H), 4.79−3.90 (m, 2.6H), 3.81−3.76 (m, 3H), 3.33−3.22 (m, 0.4H), 2.25 (d, J = 9.4 Hz, 1.7H), 2.15 (d, J = 6.0 Hz, 1.3H), 1.54−1.48 (m, 4H), 1.42−1.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 205.7, 204.9, 171.3, 171.0, 159.5, 150.4, 150.2, 149.9, 149.8, 148.1, 148.0, 132.4, 131.9, 131.1, 129.2, 128.8, 128.6, 127.9, 122.2, 122.13, 121.1, 121.0, 114.5, 114.3, 114.2, 114.1, 55.7, 55.6, 55.5, 52.8, 52.4, 52.1, 51.8, 51.6, 46.1, 45.7, 45.4, 27.7, 27.6, 27.2, 19.2, 17.2, 17.1, 14.5, 14.1. IR (film): 1722, 1637 cm^{-1}. HRMS (ESI): calculated for $C_{20}H_{25}N_2O_3$ $[M + H]^+$, 341.1865; found 341.1883.

36. A reaction mixture containing 4-(hydroxymethyl) pyridine (2.20 g, 20.16 mmol, 1 equiv) and *tert*-butyl acetoacetate (4.78 g, 30.24 mmol, 1.5 equiv) in toluene (50 mL) was refluxed for 36 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by silica gel column chromatography using 70−100% ethyl acetate in hexanes to afford the desired β-keto ester **36** (2.10 g, 54%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of tautomers) δ: 11.89 (s, 0.1H), 8.62−8.59 (m, 2H), 7.29−7.24 (m, 2H), 5.20−5.19 (m, 2H), 5.11 (s, 0.1H), 3.58 (s, 1.8H), 2.29 (s, 2.7H), 2.00 (s, 0.3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of tautomers) δ: 200.1, 166.8, 150.3, 144.4, 122.1, 65.2, 50.0, 30.5. IR (film): 1744, 1708 cm^{-1}. HRMS (ESI): calculated for $C_{10}H_{12}NO_3$ $[M + H]^+$, 194.0817; found 194.0834.

38. Prepared from 4-hydroxymethylpyridine (2.00 g) and cyclopentanone-2-carboxylate methyl ester using the procedure given for **36**. Isolated yield (yellow oil) 1.84 g, 46%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (d, J = 6.1 Hz, 2H), 7.29 (d, J = 5.9 Hz, 2H), 5.28−5.14 (m, 2H), 3.29 (t, J = 9.3 Hz, 1H), 2.59−1.85 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.0, 169.0, 150.1, 144.7, 121.8, 65.0, 54.8, 38.2, 27.4, 21.1. IR (film): 1757, 1726 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{13}NO_3$ $[M + H]^+$, 220.0974; found 220.0995.

General Procedure for the Synthesis of Spiro-(dihydropyridine)s. The preparation of **2** is representative. Keto amide **1** (0.10 g, 0.45 mmol, 1 equiv) in ∼3 mL CH_2Cl_2 was cooled to 0 °C. $Ti(O^iPr)_4$ (61 μL, 0.23 mmol, 0.5 equiv) was added, and the reaction was stirred for 2 min. Ethyl chloroformate (83 μL, 0.68 mmol, 1.5 equiv) was then added, and the resulting mixture was stirred for ∼10−15 min. The reaction was then directly subjected to silica gel flash column chromatography eluting with 70−80% EtOAc in hexanes. Dihydropyridine **2** was obtained as a yellow oil (43 mg, 33%). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of tautomers) δ: 12.32 (s, 0.3H), 6.99−6.88 (m, 2H), 4.94−4.89 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.48−3.29 (m, 3.3H), 3.23−3.15 (m, 1.4H), 2.26 (s, 2H), 1.83 (s, 1H), 1.37−1.31 (m, 3H), 1.16−1.11 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.0, 171.4, 168.8, 167.4, 151.4, 151.2, 124.9, 122.9, 121.3, 110.2, 105.9, 69.8, 63.3, 63.2, 61.0, 39.7, 37.4, 36.6, 33.4, 17.5, 14.6, 12.6, 12.5. IR (film): 3435, 1659, 1632 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{21}N_2O_4$ $[M + H]^+$, 293.1501; found 293.1492.

Using the procedure given above the spiro(dihydropyridine)s **4**, **6a−e**, and **6h** were prepared starting from 100 mg of **2**, **5a−e**, and **5h**, respectively.

Spiro(dihydropyridine) 4. Pale yellow liquid, 22 mg, 18%. ^{1}H NMR (300 MHz, $CDCl_3$) δ mixture of tautomers: 16.0 (s, 0.2H), 7.27−7.18 (m, 2H), 6.95−6.82 (m, 4H), 4.77−4.49 (m, 4H), 4.30−4.22 (m, 2H), 3.81−3.80 (m, 3H), 3.59 (s, 0.8H), 3.32−3.12 (m, 2H), 2.31 (s, 2.4H), 2.26−2.17 (m, 1H), 2.00 (s, 0.6H), 1.77−1.62 (m, 1H), 1.35−1.29 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of tautomers) δ: 205.5, 176.7, 165.3, 159.3, 151.3, 129.6, 129.4, 129.2, 128.9, 123.9, 123.1, 120.9, 114.3, 109.6, 107.9, 67.1, 63.2, 55.5, 49.8, 41.7, 41.1, 40.4, 37.0, 35.4, 34.7, 33.8, 21.5, 14.6. IR (film): 1722, 1686, 1628 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{27}N_2O_5$ $[M + H]^+$, 399.1920; found 399.1934.

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Spiro(dihydropyridine) 6a. Brown liquid, 16 mg, 12%. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of tautomers) δ: 12.27 (s, 0.3H), 7.00−6.88 (m, 2H), 5.78−5.70 (m, 1H), 5.28−5.19 (m, 2H), 4.97−4.81 (m, 2H), 4.30 (q, J = 7.0 Hz, 2H), 4.00−3.89 (m, 2H), 3.47−3.45 (m, 1.3H), 3.21 (s, 0.7H), 3.16−3.14 (m, 0.7H), 2.28 (s, 2H), 1.86 (s, 1H), 1.37−1.33 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of tautomers) δ: 203.9, 171.6, 167.9, 151.2, 132.2, 131.9, 118.8, 118.5, 109.9, 69.8, 63.7, 63.4, 63.2, 61.3, 45.4, 44.7, 39.8, 36.7, 33.4, 29.9, 17.6, 14.6. HRMS (ESI): calculated for $C_{16}H_{21}N_2O_4$ $[M + H]^+$, 305.1501; found 305.1511.

Spiro(dihydropyridine) 6b. Yellow liquid, 23 mg, 18%. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of tautomers) δ: 12.32 (s, 0.4H), 7.38−7.22 (m, 5H), 6.95−6.83 (m, 2H), 4.82−4.75 (m, 2H), 4.51−4.48 (m, 1H), 4.44 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.49 (s, 0.6H), 3.33 (d, J = 9.9 Hz, 0.6H), 3.11 (s, 0.8H), 3.02 (d, J = 9.9 Hz, 0.6H), 2.28 (s, 2H), 1.85 (s, 1H), 1.35−1.29 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of tautomers) δ: 203.9, 171.7, 168.1, 151.4, 151.1, 136.2, 135.9, 129.0, 128.33, 128.3, 128.0, 127.9, 122.9, 110.0, 69.7, 63.3, 63.2, 60.1, 46.8, 46.1, 39.7, 36.6, 33.5, 17.6, 14.6. HRMS (ESI): calculated for $C_{20}H_{23}N_2O_4$ $[M + H]^+$, 355.1658; found 355.1675.

Spiro(dihydropyridine) 6c. Yellow liquid, 69 mg, 53%. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of tautomers) δ: 12.40 (s, 0.2H), 6.95 (br s, 2H), 4.90 (br s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.51 (d, J = 9.7 Hz, 0.8H), 3.44−3.28 (m, 2.8H), 3.21 (s, 0.4H), 3.14 (d, J = 9.7 Hz, 0.8H), 2.72−2.43 (m, 1.6H), 2.16 (q, J = 7.4 Hz, 0.4H), 1.37−1.31 (m, 3H), 1.16−1.08 (m, 3H), 1.06−1.00 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of tautomers) δ: 206.4, 171.7, 169.1, 151.2, 124.7, 122.5, 121.1, 110.5, 105.8, 69.5, 63.5, 63.3, 63.2, 61.1, 39.6, 37.5, 36.7, 24.4, 14.6, 12.5, 11.0, 7.1. HRMS (ESI): calculated for $C_{16}H_{23}N_2O_4$ $[M + H]^+$, 307.1658; found 307.1675.

Spiro(dihydropyridine) 6d. Brown liquid, 54 mg, 43%. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 7.93−7.91 (m, 2H), 7.59−7.54 (m, 1H), 7.48−7.43 (m, 2H), 6.97−6.76 (m, 2H), 5.08 (br s, 2H), 4.88 (br s, 1H), 4.30 (s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.65 (d, J = 9.7 Hz, 1H), 3.53−3.33 (m, 2H), 3.23 (d, J = 9.8 Hz, 1H), 1.31−1.26 (m, 3H), 1.19 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 196.0, 169.6, 151.1, 137.6, 133.7, 129.1, 128.7, 124.6, 122.3, 110.5, 106.1, 65.4, 63.2, 61.4, 40.2, 37.5, 14.5, 12.5. IR (film): 1723, 1678, 1669 cm^{-1}. HRMS (ESI): calculated for $C_{20}H_{23}N_2O_4$ $[M + H]^+$, 355.1658; found 355.1679.

Spiro(dihydropyridine) 6e. Pale yellow liquid, 13 mg, 10%. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ: 7.11−7.01 (m, 2H), 4.88−4.79 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.50 (d, J = 9.5 Hz, 1 H), 3.48−3.30 (m, 2H), 3.12 (d, J = 9.6 Hz, 1H), 2.30 (d, J_{HF} = 5.8 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H). 1.16 (t, J = 7.3 Hz, 3H). Insufficient sample for ^{13}C NMR spectrum. HRMS (ESI): calculated for $C_{15}H_{20}FN_2O_4$ $[M + H]^+$, 311.1407; found 311.1415.

Spiro(dihydropyridine) 6h. Pale yellow oil, 66 mg, 51%. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 6.98 (br s, 2H), 4.85 (br s, 1H), 4.66 (br s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.76 (d, J = 9.5 Hz, 1H), 3.44−3.28 (m, 2H), 3.02 (d, J = 9.5 Hz, 1H), 2.37−2.24 (m, 2H), 2.12−2.06 (m, 3H), 0.1.90−1.87 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 216.0, 171.0, 151.1, 125.9, 123.2, 108.2, 105.1, 69.0, 63.2, 59.1, 43.8, 39.8, 37.6, 28.6, 19.9, 14.5, 12.5. HRMS (ESI): calculated for $C_{17}H_{22}N_2O_4Na$ $[M + Na]^+$, 341.1477; found 341.1459.

Procedure for Spirocyclization in Trifluoroethanol (TFE). Ethyl chloroformate (78 μL, 0.81 mmol, 2 equiv) was added to a solution of **5h** (0.10 g, 0.41 mmol, 1 equiv) in TFE (2 mL) at room temperature. The resulting mixture was stirred for 15−20 min and then directly loaded onto a silica gel column and purified using 70−80% ethyl acetate in hexanes to give **6h** (85 mg, 66%). In a similar fashion **1** (0.10 g) was converted to **2** (yellow oil, 25 mg, 19% isolated yield).

Anhydrobase 7. This compound was obtained as a minor byproduct when pyridine **5h** was subjected to the spirocyclization reaction conditions described previously except that the CH_2Cl_2 reaction mixture was heated to reflux before purification by flash column chromatography. From 100 mg of **5h**, the expected spirocycle **6h** was obtained (50 mg, 39% isolated yield) accompanied by **7** as a brown oil (18 mg, 15% isolated yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 (d, J = 8.2 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 6.32 (d, J = 9.0 Hz, 1H), 6.29 (d, J = 9.0 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.88 (q, J = 7.2 Hz, 2H), 2.86−2.81 (m, 2H), 2.59−2.54 (m, 2H), 2.41−2.34 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9, 152.4, 150.4, 137.4, 127.5, 125.0, 112.7, 109.6, 64.3, 37.2, 31.8, 28.3, 25.4, 15.9, 14.5. HRMS (ESI): calculated for $C_{17}H_{21}N_2O_3$ $[M + H]^+$, 301.1552; found 301.1569.

Procedure for the Preparation of Anhydrobases 10 and 11. The preparation of **11** is representative. Titanium isopropoxide (58 μL, 0.2 mmol, 0.5 equiv) and diisopropylethylamine (95 μL, 0.58 mmol, 1.5 equiv) were added to a solution of **9** (0.10 g, 0.38 mmol, 1 equiv) in DMF (3 mL) and the reaction was placed in a preheated 100 °C oil bath for 2 min. Ethyl chloroformate (55 μL, 0.58 mmol, 1.5 equiv) was added to the warm reaction mixture, causing the reaction to immediately turn dark brown. Heating was maintained for 20 min, after which time the reaction was allowed to cool to room temperature. The reaction was made basic by addition of satd aq Na_2CO_3 solution and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with water (10 mL) and brine (5 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to yield the crude anhydrobase product **11** (0.10 g, 83%, crude yield). Attempted purification by flash column chromatography resulted in decomposition. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 6.36 (d, J = 8.6 Hz, 1H), 6.30 (d, J = 8.3 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.84 (q, J = 7.1 Hz, 2H), 2.56−2.54 (m, 2H), 2.36−2.34 (m, 2H), 1.77−1.65 (m, 4H), 1.38 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 150.4, 141.9, 128.2, 127.6, 126.4, 125.0, 116.8, 112.4, 110.7, 64.1, 37.7, 27.0, 23.6, 21.8, 21.3, 15.2, 14.5. IR (film): 1731, 1642 cm^{-1}. HRMS (ESI): calculated for $C_{18}H_{23}N_2O_3$ $[M + H]^+$, 315.1709; found 315.1731. Using the same procedure **8** (0.10 g) was converted to **10** (isolated as a brown oil, 97 mg, 80% crude yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16−7.12 (m, 2H), 6.35−6.27 (m, 2H), 6.01−5.89 (m, 1H), 5.23−5.11 (m, 2H), 4.44−4.42 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 2.89−2.84 (m, 2H), 2.62−2.58 (m, 2H), 2.43−2.36 (m, 4H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8, 152.6, 150.3, 136.8, 135.0, 127.2, 125.3, 124.1, 117.6, 116.1, 112.5, 109.6, 64.2, 44.7, 31.7, 28.3, 25.5, 14.5. HRMS (ESI): calculated for $C_{18}H_{21}N_2O_3$ $[M + H]^+$, 313.1552; found 313.1566.

General Procedure for the Preparation of Pyridyl-Substituted Lactams (Tables 2 and 3). The preparation of **13** is representative. Titanium isopropoxide (57 μL, 0.19 mmol, 0.5 equiv) and diisopropylethylamine (0.10 mL, 0.58 mmol, 1.5 equiv) were added to a solution of **5f** (0.10 g, 0.38 mmol, 1 equiv) in THF (2 mL) and heated to reflux in a preheated 80 °C oil bath for 2 min. Ethyl chloroformate (55 μL, 0.58 mmol, 1.5 equiv) was added to the refluxing reaction mixture, which immediately turned dark brown. Reflux was maintained for 20 min, then TFA (10 equiv) was added, and reflux was continued for an additional 5 min. Water (2 mL) was then added and reflux continued for 10−15 min before allowing the reaction to cool to room temperature. The mixture was made basic by addition of satd aq Na_2CO_3 solution and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with water (10 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a residue that was purified via flash column chromatography (70−90% EtOAc in hexanes) to afford **13** as a brown oil (87 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.62 (d, J = 5.9 Hz, 2H), 7.1 (d, J = 6 Hz, 2H), 5.96−5.82 (m, 1H), 5.09−5.02 (m, 2H), 4.78 (s, 1H), 3.87−3.75 (m, 1H), 3.09 (d, J = 6.2 Hz, 2H), 2.88−2.76 (m, 1H), 1.74 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7, 150.5, 150.1, 145.9, 134.3, 131.0, 122.5, 115.8, 66.6, 35.3, 27.9, 13.8, 12.1. IR (film): 1681 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{19}N_2O$ $[M + H]^+$, 243.1497; found 243.1520. Substituted pyridines shown in Table 3 were prepared starting from 0.10 g of the corresponding 4-alkyl pyridine.

Pyridyl-dehydropyrrolidinone 20. Brown oil, 54 mg, 59%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.62 (d, J = 5.5 Hz, 2H), 7.08 (d, J = 5.9

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Hz, 2H), 4.73 (s, 1H), 3.88−3.76 (m, 1H), 2.86−2.74 (m, 1H), 1.87 (s, 3H), 1.72 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.5, 150.6, 148.5, 146.0, 129.3, 122.6, 66.5, 35.3, 13.9, 12.1, 8.9. IR (film): 1685 cm^{-1}. HRMS (ESI): calculated for $C_{13}H_{17}N_2O$ [M + H] $^+$, 217.1341; found 217.1371.

Pyridyl-dehydropyrrolidinone 21. Brown oil, 80 mg, 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.64 (d, J = 5.9 Hz, 2H), 7.1 (d, J = 6.1 Hz, 2H), 4.78 (s, 1H), 3.87−3.75 (m, 1H), 3.29−3.28 (m, 2H), 2.88−2.76 (m, 1H), 2.04 (t, J = 2.8 Hz, 1H), 1.88 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 151.1, 150.7, 145.2, 127.9, 122.5, 79.9, 69.2, 66.6, 35.3, 13.8, 13.5, 12.2. IR (film): 1681 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{17}N_2O$ [M + H] $^+$, 241.1341; found 241.1361.

Pyridyl-dehydropyrrolidinone 22. Brown oil, 58 mg, 63%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.62 (d, J = 5.9 Hz, 2H), 7.11 (d, J = 6.0 Hz, 2H), 4.97 (s, 1H), 3.88−3.76 (m, 1H), 2.90−2.79 (m, 1H), 2.61−2.12 (m, 6H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.6, 164.3, 150.6, 145.1, 142.3, 122.0, 62.2, 35.6, 28.2, 27.5, 26.0, 14.0. IR (film): 1685 cm^{-1}. HRMS (ESI): calculated for $C_{14}H_{17}N_2O$ [M + H] $^+$, 229.1341; found 229.1368.

Pyridyl-dehydropyrolidinone 23. Brown oil, 63 mg, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (d, J = 5.9 Hz, 2H), 7.08 (d, J = 6.0 Hz, 2H), 4.80 (s, 1H), 3.89−3.77 (m, 1H), 2.89−2.78 (m, 1H), 2.30−2.11 (m, 3H), 1.82−1.59 (m, 5H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8, 152.9, 150.7, 145.9, 132.2, 122.3, 65.7, 35.1, 23.0, 22.2, 21.8, 20.4, 14.0. IR (film): 1681 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{19}N_2O$ [M + H] $^+$, 243.1497; found 243.1515.

Pyridyl-dehydropyrrolidinone 25. Brown oil, 39 mg, 42%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (d, J = 5.1 Hz, 2H), 7.09 (d, J = 5.9 Hz, 2H), 4.73 (s, 1H), 3.83−3.72 (m, 1H), 2.83−2.72 (m, 1H), 2.57−2.50 (m, 2H), 2.28 (m, 2.20 9 m, 1H), 2.05−1.94 (m, 1H), 1.76−1.71 (m, 2H), 1.64−1.61 (m, 3H), 1.43−1.35 (m, 1H), 1.04 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.2, 154.8, 150.5, 145.7, 135.2, 122.8, 66.1, 35.3, 30.9, 28.7, 27.2, 27.1, 25.0, 13.9. IR (film): 1681 cm^{-1}. HRMS (ESI): calculated for $C_{16}H_{21}N_2O$ [M + H] $^+$, 257.1654; found 257.1661.

Pyridyl-dehydropyrrolidinone 12. Brown oil, 41 mg, 44%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (d, J = 6.1 Hz, 2H), 7.07 (d, J = 6.0 Hz, 2H), 5.80−5.67 (m, 1H), 5.14−4.93 (m, 3H), 4.56−4.49 (m, 1H), 3.22 (dd, J = 15.6, 7.7 Hz, 1H), 2.62−2.14 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.7, 164.9, 150.7, 145.1, 142.3, 133.6, 122.3, 118.1, 62.3, 43.5, 28.4, 27.6, 26.2. IR (film): 1685 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{17}N_2O$ [M + H] $^+$, 241.1341; found 241.1362.

Pyridyl-dehydropyrrolidinone 27. Brown oil, 45 mg, 48%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (d, J = 5.9 Hz, 2H), 7.29−7.25 (m, 3H), 7.12−7.09 (m, 2H), 7.01 (d, J = 6.1 Hz, 2H), 5.20 (d, J = 15 Hz, 1H), 4.70 (s, 1H), 3.65 (d, J = 15.1 Hz, 1H), 2.65−2.58 (m, 2H), 2.46−2.26 (m, 3H), 2.19−2.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 165.0, 150.8, 144.8, 142.1, 137.5, 128.9, 128.4, 127.7, 122.3, 61.9, 44.5, 28.4, 27.6, 26.2. IR (film): 1690 cm^{-1}. HRMS (ESI): calculated for $C_{19}H_{19}N_2O$ [M + H] $^+$, 291.1497; found 291.1494.

Pyridyl-dehydropiperidinone 29. Brown oil, 45 mg, 48%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (d, J = 5.9 Hz, 2H), 6.96 (d, J = 6.1 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 4.61 (d, J = 14.5 Hz, 1H), 4.22 (d, J = 14.5 Hz, 1H), 3.81−3.68 (m, 4H), 3.28 (s, br, 1H), 3.14 (dd, J = 12.4, 2.8 Hz, 1H), 2.04 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5, 159.1, 150.2, 149.0, 141.5, 129.6, 128.9, 128.4, 123.3, 113.9, 55.4, 50.4, 49.6, 45.4, 19.5, 12.9. IR (film): 1659 cm^{-1}. HRMS (ESI): calculated for $C_{20}H_{23}N_2O_2$ [M + H] $^+$, 323.1760; found 323.1760.

Pyridyl-dehydropiperidinone 31. Brown oil, 65 mg, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (d, J = 5.9 Hz, 2H), 6.98 (d, J = 6.0 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 4.62 (d, J = 14.5 Hz, 1H), 4.23 (d, J = 14.5 Hz, 1H), 3.78−3.72 (m, 4H), 3.23−3.22 (m, 1H), 3.16 (dd, J = 12.3, 2.9 Hz, 1H), 2.66−2.58 (m, 1H), 2.44−2.31 (m, 1H), 2.11−2.05 (m, 1H), 1.95−1.88 (m, 1H), 1.76−1.53 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ:165.3, 158.9, 150.1, 149.2, 143.8, 129.9, 129.5, 128.8, 123.2, 113.8, 55.4, 50.5, 49.3, 44.1, 29.4, 23.8, 22.4, 22. IR (film): 1659 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{25}N_2O_2$ [M + H] $^+$, 349.1916; found 349.1923.

Pyridyl-dehydropyrrolidinone 33. Brown oil, 34 mg, 36%, 2.7:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ Major diastereomer: 8.56 (d, J = 5.7 Hz, 2H), 7.08−7.00 (m, 2H), 6.95 (d, J = 6.0 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.54 (q, J = 7.3 Hz, 1H), 4.26 (s, 1H), 3.82 (s, 3H), 1.88−1.86 (m, 3H), 1.52 (s, 3H), 1.17 (d, J = 7.3 Hz, 3H). Minor diastereomer: 8.35 (d, J = 5.7 Hz, 2H), 7.08−7.00 (m, 2H), 6.78 (d, J = 5.8 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 5.08 (q, J = 7.2 Hz, 1H), 4.64 (s, 1H), 3.71 (s, 3H), 1.88−1.86 (m, 3H), 1.66 (d, J = 7.2 Hz, 3H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ mixture of diastereomers: 173.4, 173.2, 159.2, 159.0, 150.4, 150.0, 149.6, 149.1, 147.8, 146.5, 133.4, 132.8, 129.4, 128.9, 128.8, 122.9, 122.7, 114.0, 113.6, 66.3, 65.5, 55.5, 51.4, 50.6, 18.8, 18.3, 12.1, 12.0, 9.0, 8.96. IR (film): 1668 cm^{-1}. HRMS (ESI): calculated for $C_{20}H_{23}N_2O_2$ [M + H] $^+$, 323.1760; found 323.1780.

Pyridyl-dehydropyrrolidinone 35. Brown oil, 68 mg, 62%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.63 (d, J = 6.0 Hz, 2H), 7.14 (d, J = 6.1 Hz, 2H), 5.95−5.82 (m, 1H), 5.36 (m, 1H), 5.17−5.06 (m, 2H), 4.2 (q, J = 7.2 Hz, 2H),3.85−3.73 (m, 1H), 3.10−3.07 (m, 2H), 2.91−2.79 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.6, 158.5, 151.1, 150.8, 143.5, 133.1, 122.9, 120.4, 116.9, 66.0, 61.9, 35.3, 27.0, 14.1, 13.8. IR (film): 1766, 1690 cm^{-1}. HRMS (ESI): calculated for $C_{17}H_{21}N_2O_4$ [M + H] $^+$, 317.1501; found 317.1501.

Anhydrobase 37. Using the procedure given for the preparation of **13**, **37** (52 mg) was isolated from 0.10 g of **36** as an orange-brown crystalline solid (41%, 77% crude yield). Mp 157−162 °C (dec), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (d, J = 6.5 Hz, 1H), 7.35 (d, J = 6.4 Hz, 1H), 6.54 (dd, J = 8.4, 2.2 Hz, 1H), 6.34 (dd, J = 8.5, 2.2 Hz. 1H), 5.70 (d, J = 1.08 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 2.3 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.7, 151.4, 150.2, 137.4, 128.2, 127.8, 119.8, 113.0, 110.4, 108.2, 64.7, 15.9, 14.4. IR (film): 1717, 1650 cm^{-1}. HRMS (ESI): calculated for $C_{13}H_{14}NO_4$ [M + H] $^+$, 248.0923; found 248.0931.

Spiro(dihydropyridine) 39. Using the procedure given for the preparation of **13**, **39** was obtained from 0.10 g of **38** as pale yellow oil (81 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ: 7.05 (br s, 2H), 4.80−4.72 (m, 2H), 4.52 (d, J = 8.7 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.07 (d, J = 8.7 Hz, 1H), 2.45−2.33 (m, 2H), 2.26−2.06 (m, 3H), 1.97−1.88 (m, 1H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ: 212.8, 173.8, 151.0, 127.2, 124.2, 106.3, 102.4, 67.4, 63.6, 47.4, 39.8, 29.3, 19.9, 14.5. IR (film): 1775, 1734, 1685 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{17}NO_5$ Na [M + Na] $^+$, 314.1004; found 314.1022.

Ethyl 5-(4-Pyridyl)-pentadienoate 43. LHMDS (1.0 M solution, 26.4 mL, 1.1 equiv) was added to a solution of triethyl 4-phosphonocrotonate (6.00 g, 24.0 mmol, 1 equiv) in THF at 0 °C and stirred for 45 min. 4-Pyridine carboxaldehyde (2.57 g, 24.0 mmol, 1 equiv) was added, and the reaction mixture was allowed to warm to room temperature and maintained overnight. The reaction was quenched with satd aq NH_4Cl and extracted with EtOAc (3 × 50 mL), and the combined organic layer was washed with water (50 mL) and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using 50−70% EtOAc in hexanes to yield **43** as a brown liquid, (4.3 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.60 (d, J = 4.6 Hz, 2H), 7.43 (dd, J = 15.3, 11.0 Hz, 1H), 7.31 (d, J = 4.5 Hz, 2H), 7.03 (dd, J = 15.6, 10.9 Hz, 1H), 6.81 (d, J = 15.6 Hz, 1H), 6.09 (d, J = 15.2 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.7, 150.6, 143.3, 143.2, 137.3, 130.6, 124.3, 121.3, 60.8, 14.5. IR (film): 1694 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{14}NO_2$ [M + H] $^+$, 204.1025; found 204.1050.

Ethyl 5-(4-Pyridyl)-pentanoate 44. Substrate **43** (4.0 g) was dissolved in ethanol (5 mL), and 10% Pd/C was added (10 mg). The resulting mixture was hydrogenated at 100 psi for 14 h and then filtered through a bed of Celite. The filtrate was evaporated in vacuo and dried to afford **44** as a brown liquid (4.0 g, 99%), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.49 (d, J = 6.1 Hz, 2H), 7.10 (d, J = 5.9 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.65−2.61 (m, 2H), 2.35−2.31 (m, 2H), 1.70−1.65 (m,

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4H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.6, 151.2, 149.9, 124.0, 60.5, 35.1, 34.2, 29.8, 24.6, 14.4. IR (film): 1654 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{18}NO_2$ [M + H]$^+$, 208.1338; found 208.1366.

Weinreb Amide 45. $AlMe_3$ (2.80 mL, 56 mmol, 4 equiv) was added dropwise to a reaction mixture containing *N*,*O*-dimethyl hydroxylamine hydrochloride (5.46 g, 56 mmol, 4 equiv) in THF at −78 °C, and the resulting mixture was stirred for 45 min. Substrate **44** (2.90 g, 14 mmol, 1 equiv) was added, and the reaction mixture was stirred for 16 h. The reaction was quenched with satd aq NH_4Cl and then extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water (100 mL) and brine (50 mL). The organic layer was dried over anhydrous $NaSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using 50−70% EtOAc in hexanes to yield **45** as a brown oil (2.6 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48 (d, J = 6.0 Hz, 2H), 7.12 (d, J = 6.0 Hz, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 2.66−2.62 (m, 2H), 2.47−2.44 (m, 2H), 1.69 (quintet, J = 3.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.3, 151.3, 149.8, 124.0, 61.3, 35.2, 32.3, 31.7, 30.1, 24.3. IR (film): 1654 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{19}N_2O_2$ [M + H]$^+$, 223.1447; found 223.1470.

6-(4-Pyridyl)-2-hexanone 41. Methyl magnesium bromide (3.0 M solution in THF, 1.1 mL, 3.3 mmol, 1.5 equiv) was added dropwise to a reaction mixture containing Weinreb amide **45** (0.50 g, 2.2 mmol, 1 equiv) in THF (25 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with satd aq NH_4Cl solution and then extracted with EtOAc (3 × 15 mL), and the combined organic layer was washed with water (10 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by silica gel flash column chromatography using 50−70% EtOAc in hexanes to give **41** as a brown oil (0.34 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48 (d, J = 5.8 Hz, 2H), 7.10 (d, J = 5.8 Hz, 2H), 2.62 (t, J = 7.0 Hz, 2H), 2.46 (t, J = 6.6 Hz, 2H), 2.13 (s, 3H), 1.63 (quintet, J = 3.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.7, 151.2, 149.9, 124.0, 43.5, 35.2, 30.1, 29.9, 23.4. IR (film): 1708 cm^{-1}. HRMS (ESI): calculated for $C_{11}H_{16}NO$ [M + H]$^+$, 178.1232; found 178.1262.

1-Phenyl-5-(pyridin-4-yl)-pentan-1-one 42. Weinreb amide **45** (0.60 g, 2.7 mmol) was treated with phenyl magnesium bromide according the procedure given above to afford **42** (0.63 g, 97%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.48 (d, J = 6.3 Hz, 2H), 7.97−7.94 (m, 2H),7.59−7.54 (m, 1H), 7.49−7.44 (m, 2H), 7.12 (d, J = 6.3 Hz, 2H), 3.01 (t, J = 6.7 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 21.83−1.69 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.1, 151.2, 149.9, 137.0, 133.2, 128.8, 128.2, 124.0, 38.3, 35.3, 30.1, 23.9. IR (film): 1681 cm^{-1}. HRMS (ESI): calculated for $C_{16}H_{18}NO$ [M + H]$^+$, 240.1388; found 240.1415.

1-Methyl-2-(pyridin-4-yl)-cyclopentene 46. TMSOTf (52 μL, 0.28 mmol, 0.5 equiv) and diisopropylethylamine (0.14 mL, 0.85 mmol, 1.5 equiv) were added to a solution of **46** (0.10 g, 0.56 mmol, 1 equiv) in THF (2 mL). The reaction mixture was placed in an oil bath preheated to 80 °C for 2 min. Ethyl chloroformate (81 μL, 0.85 mmol, 1.5 equiv) was added to the refluxing reaction mixture, which immediately turned dark brown. The reaction was refluxed for 20 min, after which time TFA (10 equiv) was added. The reaction was refluxed for an additional 10 min and then H_2O (2 mL) was added. After 5 min the reaction was removed from the oil bath and allowed to cool to room temperature. The mixture was made basic by addition of satd aq Na_2CO_3 and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with water (10 mL) and brine (5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent gave a residue that was purified using silica gel flash column chromatography using 70−90% EtOAc in hexanes to afford **46** (80 mg, 89%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.54 (d, J = 4.9 Hz, 2H), 7.18 (d, J = 6.0 Hz, 2H), 2.78−2.69 (m, 2H), 2.55−2.50 (m, 2H), 1.96−1.86 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.7, 146.2, 140.3, 132.7, 122.4, 40.6, 36.5, 21.9, 15.8. HRMS (ESI): calculated for $C_{11}H_{14}N$ [M + H]$^+$, 160.1126; found 160.1148.

1-Phenyl-2-(pyridin-4-yl)-cyclopentene 47. Using the procedure given above, **42** (0.10 g) was converted to **47** (brown oil, 83 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.39 (d, J = 5.9 Hz, 2H), 7.27−7.19 (m, 3H), 7.17−7.13 (m, 3H), 7.02 (d, J = 6.2 Hz, 2H), 2.93−2.88 (m, 4H), 2.07 (p, J = 6.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.1, 149.7, 146.0, 142.6, 137.8, 134.7, 128.6, 128.1, 127.5, 122.9, 40.0, 38.1, 22.2. HRMS (ESI): calculated for $C_{16}H_{16}N$ [M + H]$^+$, 222.1283; found 222.1291.

Piperidine-dehydropyrrolidinone 49. Titanium isopropoxide (57 μL, 0.19 mmol, 0.5 equiv) and diisopropylethylamine (99 μL, 0.57 mmol, 1.5 equiv) were added to a solution of **5f** (0.10 g, 0.38 mmol, 1 equiv) in THF (5 mL), and the reaction was placed in a preheated 80 °C oil bath for 2 min. Ethyl chloroformate (54 μL, 0.57 mmol, 1.5 equiv) was added to the refluxing reaction mixture, causing the color to immediately turn dark brown. The mixture was refluxed for 20 min and then removed from the oil bath and allowed to cool to room temperature. The mixture was then passed through a short plug of basic alumina. Ten milligrams of 10% Pd/C was added to the filtrate, and the mixture was placed under H_2 (100 psi) for 24 h. The reaction was then filtered through a bed of Celite and concentrated in vacuo. The crude product was purified by silica gel flash column chromatography using 70% EtOAc in hexanes to afford **49** as a brown oil (53 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.25−4.17 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.91−3.84 (m, 1H), 3.82 (s, 1H), 3.15−3.03 (m, 1H), 2.70−2.62 (m, 2H), 2.29−2.12 (m, 2H), 2.02−1.91 (m, 4H), 1.52−1.45 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.2, 155.6, 148.1, 134.6, 66.1, 61.5, 44.7, 44.5, 37.9, 35.5, 27.4, 25.7, 22.0, 14.8, 14.1, 13.9. HRMS (ESI): calculated for $C_{18}H_{31}N_2O_3$ [M + H]$^+$, 323.2335; found 323.2350.

Piperidine-dehydropiperidinone 50. Using the procedure given above, **28** (0.10 g, 0.29 mmol) was converted to **50** (brown oil, 64 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25−7.12 (m, 2H), 6.88−6.78 (m, 2H), 4.94−4.88 (m, 1H), 4.21−4.01 (m, 4H), 3.94−3.92 (m, 1.4H), 3.81−3.72 (m, 3.6H), 3.40 (dd, J = 12.9, 4.7 Hz, 1H), 3.12 (dd, J = 12.8, 1.4 Hz, 1H), 2.54−2.45 (m, 1H), 2.28−2.20 (m, 1H), 2.00 (s, 0.4H), 1.90 (s, 2.6H), 1.86 (s, 3H), 1.72−1.69 (m, 1H), 1.46−1.39 (m, 2H), 1.29−1.10 (m, 4H), 0.91−0.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5, 159.3, 155.5, 144.3, 130.4, 129.8, 126.5, 114.1, 61.3, 55.5, 49.5, 45.3, 45.1, 44.3, 44.1, 37.6, 30.7, 29.7, 21.6, 14.9, 13.0. IR (film): 1690, 1655 cm^{-1}. HRMS (ESI): calculated for $C_{23}H_{33}N_2O_4$ [M + H]$^+$, 401.2440; found 401.2438.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H/^{13}C NMR spectra and X-ray crystal structure of **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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