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Intramolecular 1,6-Addition to 2-Pyridones. Mechanism and Synthetic Scope.

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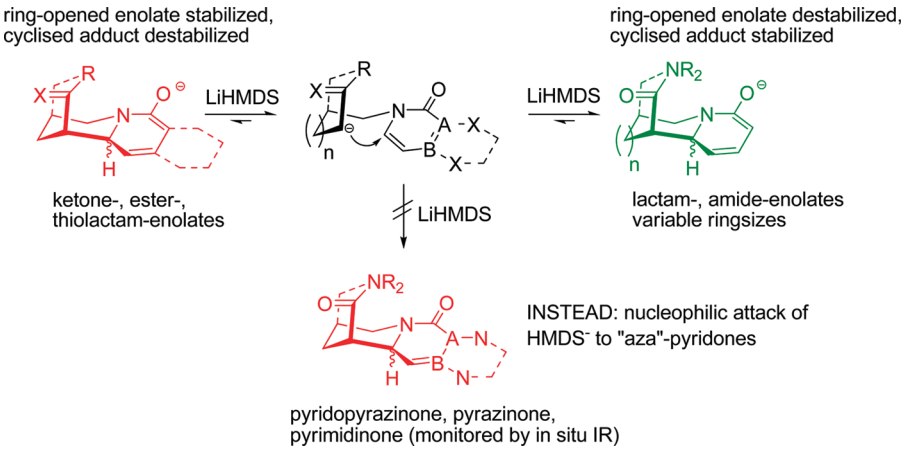

The scope and limitations of the intramolecular 1,6-addition of an enolate to a 2-pyridone moiety, a reaction that has found application in the synthesis of the lupin alkaloids, have been probed. This nucleophilic addition process has been shown to be reversible and favored in the case of (less stabilized) amide and lactam enolates, which readily form five- and six-membered bi-/tricyclic products. Alternative enolates (ketone, ester, thiolactam) and a variety of different acceptors (isoquinolinone, pyrimidinone, pyrazinone, pyridopyrazinone) have been evaluated, and a range of competing side reactions have been identified and characterized using various techniques, including in situ IR.

Introduction

Pyridones and pyridone-like heterocycles are key subunits in many biologically important molecules, so the development of novel methodologies to access this class of compounds is of value. Our interest has focused on the use of pyridones as electrophiles (Michael acceptor), and there have been very few examples of nucleophilic attack at the 6-position of 2-pyridones reported. In 1983, Tohda[1] described the addition of amine or enolate nucleophiles to highly activated 3,5-dinitro-2-pyridones. More recently, Hiroya[2] and co-workers have employed a carboxy ester to direct and control the Lewis acid catalyzed reaction of an ester-based silyl enol ether with 2-pyridones. Hiroya demonstrated a significant change of selectivity by repositioning the activating ester moiety; while 5-carboxy ester-2-pyridones were attacked predominantly at C(6), the corresponding 3-carboxy ester isomers reacted mainly at the 4-position. Given this background, it is perhaps more appropriate to rationalize these profiles as 1,4-additions with respect to the conjugated ester or nitro substituent rather than to focus on

(1) Tohda, Y.; Ariga, M.; Kawashima, T.; Matsumura, E. *Chem. Lett.* **1983**, *12*, 715–718.

(2) Hiroya, K.; Kawamoto, K.; Inamoto, K.; Sakamoto, T.; Doi, T. *Tetrahedron Lett.* **2009**, *50*, 2115–2118.

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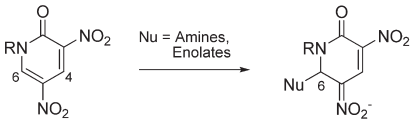
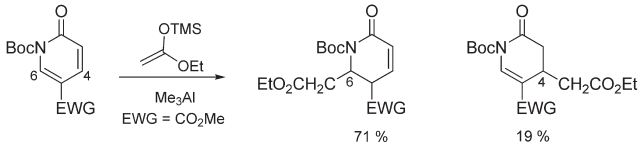
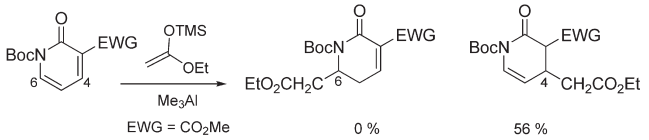
the pyridone carbonyl as the predominating electrophilic influence.

Tohda 1983



Hiroya 2009

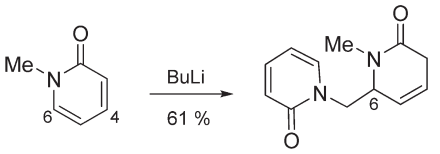




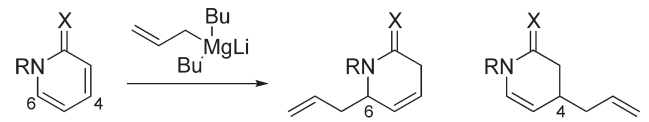
There are, however, pyridone addition processes that are more readily rationalized and recognizable as 1,6-addition reactions. Thomas[3] reported that 2-pyridone reacted with 2 equiv of butyllithium to give the 1,6-addition adduct in 55% yield; however, the use of other alkyllithium reagents was less successful. Joule[4] found that when *N*-methyl-2-pyridone was treated with butyllithium, formation of a dimer was observed, which can be attributed to the 1,6-addition of a *C*-lithiated *N*-methyl-2-pyridone to another mole of *N*-methyl-2-pyridone. Sośnicki[5] has described the addition of alkyllithium-modified Grignard reagents to unsubstituted (or alkyl substituted) *N*-alkyl-2-pyridones which led predominantly to attack at C(6), but C(4) adducts were also observed. The analogous thiopyridones, though more reactive, displayed a similar regioselectivity trend.

Thomas 1986

Joule 1988



Sośnicki 2005/6

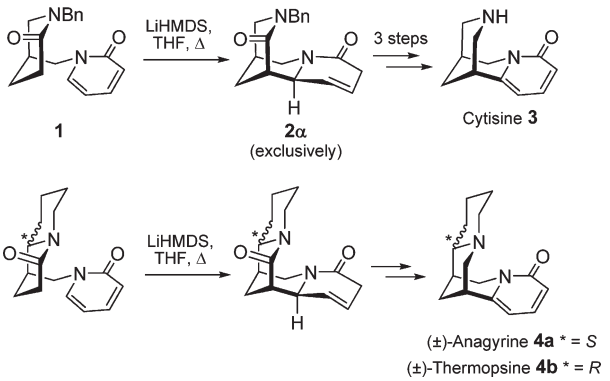


R = Li	X = O			
R = Me	X = O			
R = Li	X = S			
R = Me	X = S			
R = H	X = O	0 : 100	50 %	
R = Me	X = O	96 : 4	61 %	
R = H	X = S	0 : 100	84 %	
R = Me	X = S	84 : 16	80 %	

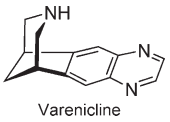
We recently reported the first examples of the intramolecular nucleophilic 1,6-addition to a 2-pyridone, which involved a lactam enolate, and this chemistry has been applied effectively to provide an efficient and convergent entry to representative lupin alkaloids,[6] including (+)-cytisine **3** (the unnatural enantiomer), (±)-anagyrine **4a**, and (±)-thermopsine **4b** (Scheme 1).

SCHEME 1. Lupin Alkaloid Synthesis via Intramolecular 1,6-Addition of Lactam Enolates

Gallagher 2004/2006



(−)-Cytisine **3** is a potent and selective partial agonist for the $\alpha4\beta2$ neuronal nicotinic acetylcholine receptor,[7] and while structural details of the receptor−ligand interaction have yet to be defined, cytisine nevertheless provided the inspiration for the design of varenicline (Chantix), Pfizer's smoking cessation agent.[8]

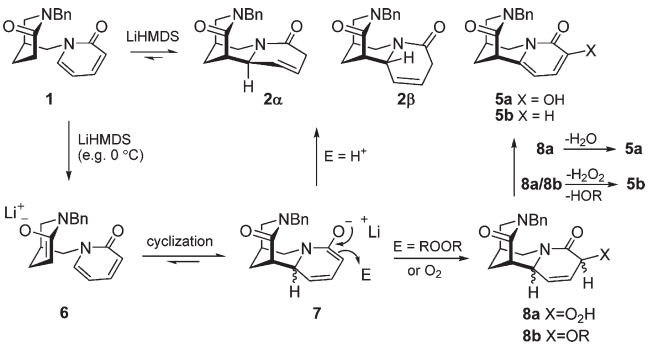


Access to novel structural variants of cytisine (and indeed other lupin alkaloids) offers an important and timely vehicle with which to probe both the nicotinic pharmacophore[9] and, of particular interest in terms of cytisine (vs other well-known full agonists such as nicotine), those structural characteristics that contribute to the partial agonist profile associated with cytisine.

This paper describes studies which have explored the scope of this intramolecular 1,6-enolate addition process and provided insights into the mechanistic detail of this process. This work was also pursued with a view to downstream

(3) Thomas, E. W. *J. Org. Chem.* **1986**, *51*, 2184–2191.
(4) Meghani, P.; Joule, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, *1*, 1–8.
(5) Sośnicki, J. G. *Tetrahedron Lett.* **2005**, *46*, 4295–4298. Sośnicki, J. G. *Tetrahedron Lett.* **2006**, *47*, 6809–6812.
(6) Gray, D.; Gallagher, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2419–2423. Botuha, C.; Galley, C. M. S.; Gallagher, T. *Org. Biomol. Chem.* **2004**, *2*, 1825–1826.
(7) Jensen, A. A.; Frølund, B.; Liljefors, T.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2005**, *48*, 4705–4745.
(8) (a) Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Wirtz, M. C.; Arnold, E. P.; Huang, J. H.; Sands, S. B.; Davis, T. I.; Lebel, L. A.; Fox, C. B.; Shrikhande, A.; Heym, J. H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R. S.; Chambers, L. K.; Rovetti, C. C.; Schulz, D. W.; Tingley, F. D.; O'Neill, B. T. *J. Med. Chem.* **2005**, *48*, 3474–3477. (b) Coe, J. W.; Brooks, P. R.; Wirtz, M. C.; Bashore, C. G.; Bianco, K. E.; Vetelino, M. G.; Arnold, E. P.; Lebel, L. A.; Fox, C. B.; Tingley, F. D.; Schulz, D. W.; Davis, T. I.; Sands, S. B.; Mansbach, R. S.; Rollema, H.; O'Neill, B. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4889–4897.
(9) Glennon, R. A.; Dukat, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1841–1844.

SCHEME 2. Cyclization Mechanism and Oxidation-Based Side Reactions



application of this chemistry to generate core variants of cytisine **3**.

Results and Discussion

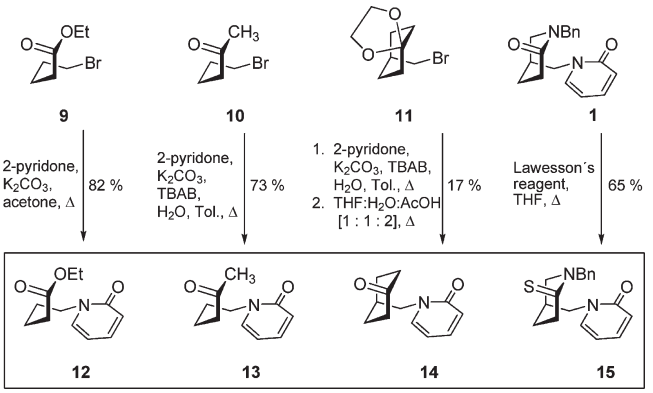
We previously reported that under thermodynamic (THF, reflux) conditions, intramolecular 1,6-addition of the enolate derived from **1** afforded tricyclic adduct **2α** exclusively and in high (94%) yield.[6] When lactam deprotonation/cyclization was carried out at lower temperatures (−78 °C, 0 °C, or rt) a mixture of diastereomeric adducts **2α** and **2*β*** were observed (Scheme 2).

Initially, the reproducibility of this sequence was an issue as varying amounts of adducts **2α** and **2*β***, which depended on the reaction conditions/solvent used, and several other products were observed. Conducting enolate formation and cyclization at lower temperatures (−78 °C, 2 h) produced a ∼1:1 ratio of **2α**/**2*β*** in excellent yield, but at higher temperatures (from rt to reflux) and longer reaction times, **2α** was obtained as either the predominant (at rt) or the exclusive (at reflux) product. These observations suggested that the 1,6-addition (enolate **6** → **7**) is a reversible process, and when pure **2*β*** was resubjected to these basic reaction conditions, isomerization occurred to afford **2α**/**2*β*** in a 7:10 ratio after 3 h at −78 °C. In addition, a small amount (5%) of the ring-opened lactam **1** was also obtained under these isomerization conditions which demonstrated (i) a thermodynamic and a kinetic preference for **2α** and **2*β***, respectively, and (ii) that (most reasonably) this equilibration involves ring-opening and reclosure, i.e., **2α/*β*** → **7** → ring-opened **6** (which is trapped on workup to give **1**) → **7** → **2α/*β***.

Minor reaction products, the yields of which depended on scale and other difficult-to-define variables, were identified as the tricyclic α-hydroxypyridone **5a** and pyridone **5b** which would be accounted for by the trapping of the initially formed adduct **7** by trace (but variable) levels of peroxides/oxygen present in alumina dried THF.[10] Fragmentation of adducts **8a/b** could occur via two different pathways leading to **5a** and **5b** with the driving force being restoration of the aromatic pyridone moiety. Oxidation products such as **5a** and **5b** were, however, completely suppressed by use of freshly distilled (from Na/benzophenone) THF, affording **2α** and **2*β*** cleanly, reproducibly, and in excellent yields (85−95%).

α-Hydroxypyridone **5a** is an attractive and potentially useful cytisine analogue, and the exploitation of this chemistry will be reported in due course. More importantly though, pyridone **5b** was a key intermediate in our previous route[6] to cytisine **3** and was obtained by MnO_2 oxidation of **2α**. Thus, the ability to generate **5b** *directly* without any need for isolation and conversion of **2α** was clearly advantageous, and once this pathway had been characterized, **5b** was obtained in 60% conversion (by ^{1}H NMR) when the tricyclic enolate **7** was trapped with bis(trimethylsilyl)peroxide (i.e., E = $Me_3SiOOSiMe_3$, Scheme 2) followed (effectively) by loss of $HOSiMe_3$.[11]

SCHEME 3. Non-Lactam Cyclization Precursors



Variation of the Nucleophilic Component

We have already demonstrated the versatility of the intramolecular 1,6-addition outlined in Scheme 1 in terms of related bicyclic lactam substrates which led to the synthesis of (±)-anagyrine **4a** and (±)-thermopsine **4b**, but the presence of a lactam/amide appears to be critical for successful 1,6-addition to a pendant 2-pyridone.

Using a simple model system, the ability of range of alternative enolate precursors to achieve 1,6-addition to a 2-pyridone has been evaluated (Scheme 3). Ester **12** and ketone **13** were prepared by N-alkylation of 2-pyridone with bromides **9** and **10**, respectively, and the "carbocytisine" keto-based precursor **14** was synthesized from the known acetal **11**.[12] A thioamide variant **15** was prepared from lactam **1** using Lawesson's reagent.[13]

Exposure of ester **12** to LiHMDS in THF resulted in formation of the corresponding intermolecular Claisen condensation adduct in 22% yield. Ketones **13** and **14** failed to cyclize, even when exposed to a range of different temperatures (−78 °C, 0 °C, refluxing THF), and thiolactam **15** also proved ineffective as a substrate for cyclization; in this latter case, a D_2O quench confirmed that thioenolate formation did occur. Given the equilibration process observed in the conversion of **1** to **2α**/**2*β***, our conclusion is that cyclization of **1** (Scheme 2) occurs because the product, the extended lactam enolate **7**, is more stable than the simple lactam enolate **6**. Therefore, the enhanced stability of enolates derived from **12**−**15** (compared to an extended lactam enolate) favors the ring-opened form.

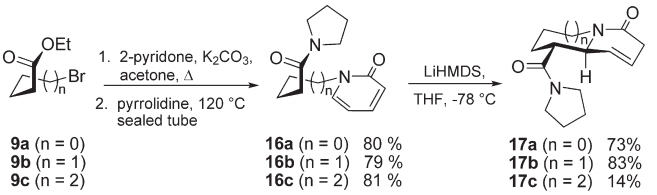
(10) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(11) Adam, W.; Korb, M. N. *Tetrahedron* **1996**, *52*, 5487–5494.

(12) De Loos, W. A. J.; van den Berg-Van Kuijk, A. J. W.; van Iersel, H.; de Haan, J.; Buck, H. *Recl. Trav. Chim. Pay. B.* **1980**, *99*, 53–57.

(13) Full details of the synthesis of these compounds is described in the Supporting Information.

SCHEME 4. Cyclization Precursors for 5-, 6-, and 7-Membered Ring Formation



Variation of Ring Size

Since the intramolecular 1,6-addition had only been used to make six-membered rings, the question remained as to whether other ring sizes (which provide the opportunity to access, for example, nor- or homobispidines) were accessible by this method. A series of amide-based precursors **16a**−**c** were synthesized by N-alkylation of 2-pyridone with the commercially available ω-bromoester and subsequent exposure to pyrrolidine (Scheme 4).[13]

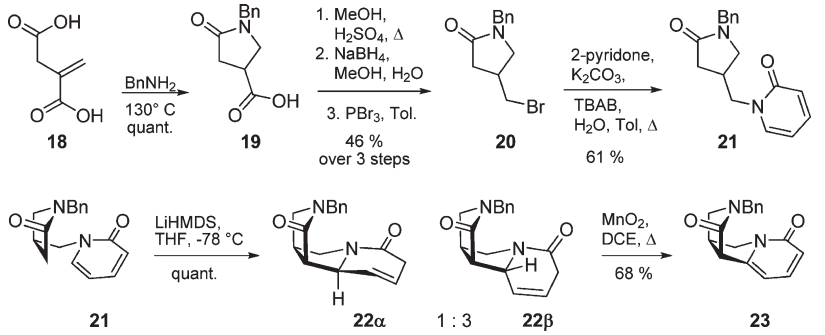
As expected, the six-membered cyclization product **17b** formed readily and in good yield. Differing from the cytisine analogues **2α/2β**, **17b** formed as a single diastereomer which was also resistant to subsequent oxidation (MnO_2) to form the corresponding pyridone. Five-ring formation was also facile, and **16a** cyclized readily upon treatment with LiHMDS to provide adduct **17a**. However, and as might be anticipated, formation of a seven-membered ring via this method, though achieved, was inefficient, and only small amounts of **17c** were observed, despite screening a range of bases and temperatures.[14]

Given the success of the formation of the 5-membered adduct **17a**, this method was extended to the synthesis of norbispidine **23** (Scheme 5). Following a procedure described by Stanetty,[15] reaction of itaconic acid **18** with benzylamine yielded lactam **19** in excellent yield. Subsequent esterification, reduction, and bromination yielded bromide **20**, which underwent N-alkylation with 2-pyridone, providing the cyclization precursor **21**. Conversion of **21** to diastereomers **22α** and **22β** (as a 1:3 ratio) occurred in essentially quantitative yield, and MnO_2 oxidation of this mixture yielded norbispidine **23** (seven steps, 19% overall yield). Analogous to the bispidine system (Scheme 2), a direct quench of the enolate resulting from cyclization of **21** with bis(trimethylsilyl)-peroxide led to the one-pot formation of pyridone **23** in 60% conversion (by ^{1}H NMR).

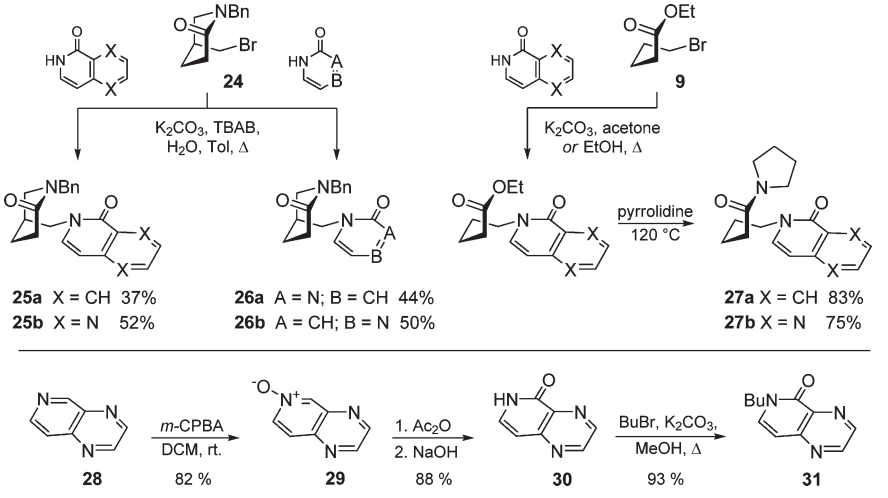
Variation of the Heterocyclic Acceptor

While lactam enolates added readily to pyridones to form five- or six-membered rings, 1,6-addition to other "acceptor" electrophiles, such as those shown in Scheme 6, have proven more challenging. The lactam-precursors **25a/b** and **26a/b** were synthesized directly by N-alkylation of the appropriate heterocycles with bromide **24**[6] and substrates **27a/b** were synthesized by N-alkylation with **9** and subsequent aminolysis with pyrrolidine. The requisite heterocyclic precursors were commercially available[16] except for pyridopyrazinone

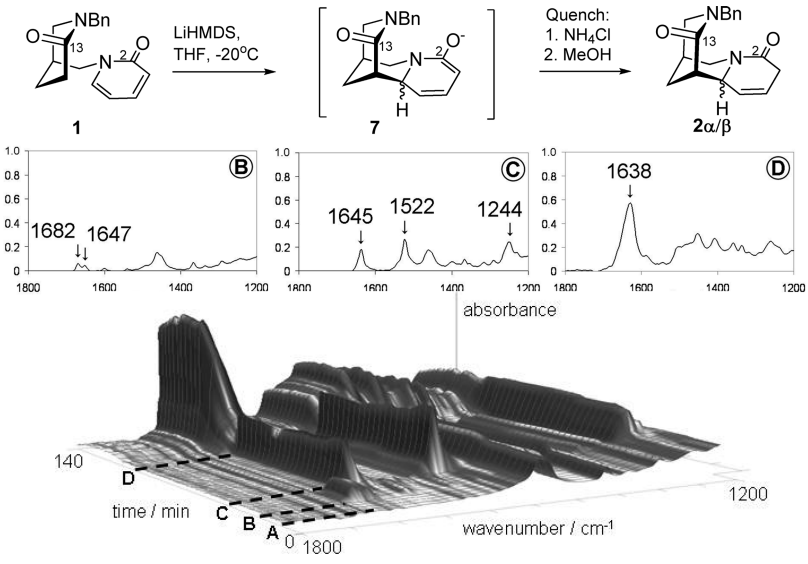
SCHEME 5. Application of a Five-Membered Cyclization to Nor-bispidine 23



SCHEME 6. Synthesis of Cyclization Precursors with Different "Acceptor" Heterocycles



SCHEME 7. In Situ IR Profile of the Cyclization of 1[a]



[a]Key: (A) solvent background (individual spectrum not shown); (B) lactam **1** in THF; (C) addition of LiHMDS; (D) quench NH_4Cl(s) then MeOH.

30, which was prepared from the literature known pyridopyrazine **28**.[17] N-Oxidation of **28** gave **29**[18] which, following acetylation and rearrangement, gave the target pyridopyrazinone **30** in good yield.[13]

Isoquinolone analogues **25a** and **27a** were unreactive toward cyclization at lower temperatures and decomposed under more forcing reflux conditions. Clearly, some disruption of aromaticity within the isoquinolone moiety would be associated with nucleophilic addition to these systems, which may have the effect of favoring the ring-open enolate (cf. **6** vs **7**, Scheme 2). This, again points to the 1,6-addition as a relatively finely balanced process that may require an additional factor(s) to stabilize/favor the cyclized product.[19]

More electron-deficient pyridone variants might be expected to promote cyclization; however, pyridopyrazinones **25b** and **27b** proved to be highly reactive and underwent rapid decomposition when exposed to basic conditions, even at low temperatures. To establish if this reactivity was associated with formation and reaction of a lactam enolate, the *n*-butyl analogue **31** was exposed to LiHMDS at −78 °C. This substrate also underwent rapid decomposition suggesting that these highly electron-deficient heterocycles are themselves excessively susceptible to nucleophilic attack.

More interestingly, because of the potential of this chemistry to provide access to fundamentally different core variants of cytisine, pyrimidinone **26a** and pyrazinone **26b** also proved problematic. In neither case was any reaction (apparently) observed at −78 °C, and at higher temperatures degradation of both **26a** and **26b** occurred according to ^{1}H NMR analysis of the crude reaction product.

This observation was, however, at odds with our rationale of the 1,6-addition equilibrium, since the more electron-deficient heterocycle was anticipated to stabilize the addition adduct (cf. the earlier work of Tohda[1] and Hiroya[2]). We suspected a competing and reversible reaction, for example, formation of an unstable (with respect to the protic quench) 1,2-addition, and in situ IR spectroscopy provided a flexible means by which to probe the nature of the enolate/cyclized species generated under these basic conditions.

To provide a baseline for the study of these problematic cases, initial spectroscopic studies focused on the conversion of **1** (via enolates **6** and **7**) to **2α/β** since these latter products had already been fully characterized. After addition of LiHMDS to a solution of **1** in THF, distinctive shifts for the carbonyl moieties were observed and assessed (a) as indicators of formation of the lactam enolate **6**, (b) as indicators that a reaction was occurring (via perturbation of the heteroarene carbonyl functionality), and (c) to support generation of the product lactam enolate **7**. In situ IR profiles of the cyclization of **1** were collected to compare the behavior of this well-understood substrate with that of pyrimidinone **26a** under the same reaction conditions. Due to instrument limitations, reactions involving both **1** and **26a** were carried out at −20 °C at which temperature formation of reaction

(14) LiHMDS/THF (−78 °C, 0 °C, rt, reflux), *n*-BuLi/THF (−78 °C), KO-*t*-Bu/DMF (110 °C).

(15) Stanetty, P.; Turner, M.; Mihovilovic, M. D. *Molecules* **2005**, *10*, 367–375.

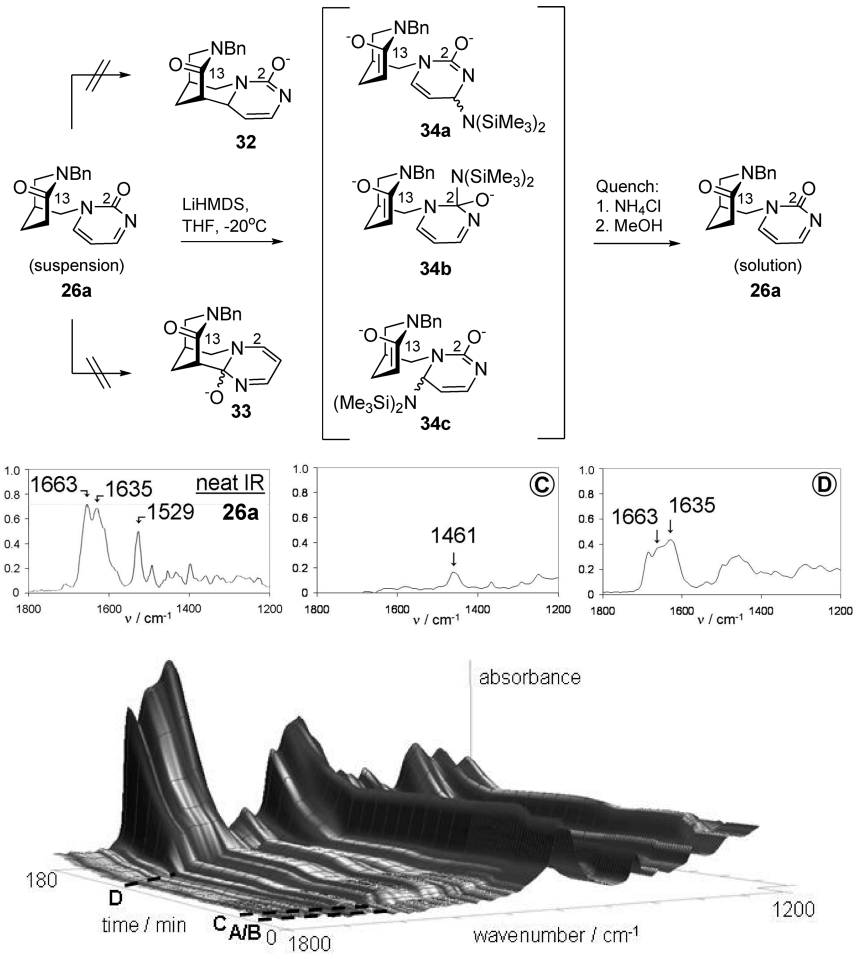
(16) 2-Pyrazinone, though commercially available, has been synthesized from serine ethyl ester by aminolysis with ammonia and subsequent condensation with glyoxal.

(17) Pyridopyrazine **28** was synthesized in two steps by (i) catalytic hydrogenation of 4-amino-3-nitropyridine and (ii) subsequent condensation with glyoxal as described by: (a) Clark-Lewis, J. W.; Singh, R. *J. Chem. Soc.* **1962**, 2379–2382. (b) Clark-Lewis, J. W.; Singh, R. *J. Chem. Soc.* **1962**, 3162–3167.

(18) Oxidation of pyridopyrazine **28** with *p*-nitroperbenzoic acid has been described in: Boutte, D.; Queguiner, G.; Pastour, P. *C. R. Seances Acad. Sci. C* **1971**, *273*, 1529–1532.

(19) A plausible alternative explanation for the apparent "lack of reaction" associated with **25a** is that this substrate undergoes preferentially 1,2-addition (to the isoquinolone C=O); see intermediate **33**, Scheme 8. This would not result in a disruption of the benzenoid aromaticity that would accompany 1,6-addition. Two experiments were carried out to probe possible fates of **25a**. Exposure of **25a** to LiHMDS followed by a D_2O quench showed no incorporation of D in recovered **25a**. Second, in the event that lactam enolate formation and cyclization were facile processes, we used $(TMSO)_2$ to trap the putative extended enolate (and cyclized) product (compare **7**→**8**→**5a/b**, Scheme 2). No evidence for an oxidized product analogous to **5a** (or a regioisomer) or **5b** was obtained, and only **25a** was recovered. It is difficult to understand why enolization should be particularly inhibited in the case of lactam **25a**, and these experiments cannot exclude the possibility that cyclization of **25a** does, nevertheless, occur (1,2- or 1,6-addition) but that the product is unstable with respect to ring opening on work up.

SCHEME 8. In Situ IR Profile of the Attempted Cyclization of 26a[a]



[a]Key: (A/B) solvent with undissolved **26a**; (C) addition of LiHMDS; (D) quench NH_4Cl(s) then MeOH.

intermediates occurred immediately. Schemes 7 and 8 outline the chemistry associated with **1** and **26a**, respectively, as well as the snapshot in situ IR spectra of the intermediates (as assigned) that formed during each reaction.[20]

Background spectra of the solvent provided a window (1500−1800 cm^{-1}) to monitor changes in the carbonyl functionalities during reaction. Lactam **1** displayed two carbonyl signals (1647 and 1682 cm^{-1}) which were identified as the piperidinone lactam [C(13)=O] and pyridone [C(2)=O][21] carbonyls, respectively (Scheme 7, Spectrum B).

After the system containing **1** had reached steady state, 2 equiv of LiHMDS was added over 1 min, and the initially colorless solution instantly turned bright yellow. Both carbonyl signals associated with **1** diminished to be replaced by new peaks that were assigned to **7**: 1645 cm^{-1} [C(13)=O], 1522 cm^{-1} [LiO-C(2)=C(3)],[22] and 1244 cm^{-1} (HMDS)[23] (Spectrum C). After 25 min, a slow quench was initiated with solid ammonium chloride, which was then accelerated by addition of methanol. At this point, IR signals associated with **7** were replaced by a broad peak at 1638 cm^{-1}, attributed to the two similar lactam carbonyls in **2** [C(13)=O] and [C(2)=O] (Spectrum D).[24] NMR analysis of the crude reaction mixture subsequently confirmed clean formation of a 3:1 mixture of **2α** and **1**. (The relatively larger amount of **1** isolated likely reflects the nature of the quench conditions used as compared to the more usual synthetic procedure).

The same reaction conditions were then applied to the pyrimidinone substrate **26a** (Scheme 8). No IR signals were observed for pyrimidinone **26a** prior to addition of base as this substrate was only sparingly soluble in THF at −20 °C. However, following addition of 2 equiv of LiHMDS, dissolution of **26a** occurred to give a bright yellow solution (as was observed with **1**), but and surprisingly, no sharp/strong IR signals were observed in the region of 1500−1800 cm^{-1}. The absence of C=O signals leads us to deduce that (a) an enolate derived from lactam **26a** had formed and (b) a

(20) **Instrumentation and Software.** The in situ IR reaction spectra were collected using a MCT (mercury cadmium telluride) detector; diamond composite probe connected via AgX 9.5 mm x 2 m fiber (silver halide); sampling 2000 to 650 at 8 cm^{-1} resolution. The MCT detector operates at liquid nitrogen temperature.

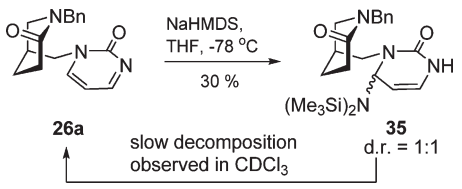
(21) These IR signals were consistent with the neat IR spectrum of lactam **1**.

(22) The frequencies for simple nonconjugated amide enolates have been reported as 1575, 1540, 1604 cm^{-1}. See: McWilliams, C.; Reamer, R. *Process Chemistry in the Pharmaceutical Industry*, 1st ed.; Gadamasetti, K., Braish, T., Eds.; CRC Press: Boca Raton, 2007; Vol. 2, Chapter 20, p 320.

(23) An IR spectrum of HMDS is available at http://www.Acros.com.

(24) These IR signals were consistent with the neat IR spectrum of lactam **2α**.

SCHEME 9. Isolation of the HMDS Adduct 35



reaction had occurred that involved the pyrimidinone C=O but (c) no new bispidine-like lactam, such as the expected intermediate **32** or the 1,2-addition-product **33**, was generated. After 40 min, the reaction was quenched (solid ammonium chloride followed by methanol) which led to rapid generation of a series of carbonyl signals, among which were those associated with **26a** (1663 cm^{-1} [C(13)=O] and 1635 cm^{-1} [C(2)=O]). NMR analysis of the crude reaction mixture confirmed the presence of **26a** as the major component as well as several unidentified but minor degradation products.

From these observations, we conclude that although deprotonation of the piperidinone lactam **26a** occurred, a competing process, involving nucleophilic addition of HMDS to the electron-deficient pyrimidinone, was preferred leading to adducts (some or all) of type **34**. Although most of the signals associated with these possible intermediates appear to be masked by the solvent background, an increased intensity of the broad solvent signal around 1461 cm^{-1} suggests the presence of more signals in this region. Based on recovery of **26a**, we suggest that adducts **34a**−**c** are unstable with respect to loss of HMDS upon protic quench.

Credible support for a process involving addition of HMDS to the pyrimidinone moiety was provided by the isolation of adduct **35** after reaction of **26a** with NaHMDS at −78 °C (Scheme 9). Adduct **35** was obtained as a 1:1 mixture of diastereomers in 30% yield and was characterized by $^1H/^{13}C$ NMR; this adduct proved to be relatively unstable with respect to reversion in solution to **26a**.

Conclusion

In conclusion, the intramolecular 1,6-addition of a lactam enolate to a pyridone, which is highly effective as the basis of a strategy for the synthesis of the lupin alkaloids, is a finely balanced process. Equilibration of adducts **2α/β** occurs via a reversible ring-opening/1,6-addition, and although this reaction will tolerate variation of the lactam unit,[25] other more stabilized enolates (derived from an ester, ketone, or thiolactam) shift this equilibrium toward the ring-opened form. Further, it has been shown that this chemistry is applicable in the synthesis of five-membered as well as six-membered rings, and this has been extended to the synthesis of a nor-bispidine core (**23**). Changes associated with the electrophilic heteroarene "acceptor" component have a major impact on the reaction outcome. Although attempts to promote cyclization by use of a more electron-deficient acceptor failed, alternative preferred pathways have been identified and validated by IR studies. The insights garnered from these studies, and with the scope and limitations of this 1,6-addition process now more clearly defined, open the way to tuning the process (via subtle changes to the precise structure of the heteroaromatic component) to broaden the applicability of this chemistry.

(25) In addition to the substrates shown, a series of 4-substituted pyridones variants of **1**, leading to the corresponding 4-substituted cytisine analogues, have also been successfully employed in this chemistry.

Experimental Section

General experimental procedures are described in the Supporting Information.

(±)-(2*R*,1*S*,9*S*)-11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridec-3-ene-6,12-dione (2*β*) and (±)-(2*S*,1*S*,9*S*)-11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridec-3-ene-6,12-dione (2α). To a solution of cyclization precursor **1** (130 mg, 0.44 mmol)[6] in THF (5 mL, freshly distilled from sodium and benzoquinone) at −78 °C was added LiHMDS (1.0 M THF solution, 0.84 mL, 0.84 mmol) dropwise. The reaction solution was stirred at −78 °C for 2 h and then quenched by the addition of saturated aq NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (5 mL) and CH_2Cl_2 (5 mL), and then the combined organic washings were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography [CH_2Cl_2/MeOH (99:1)] yielded **2*β*** (15 mg, 11%) as a colorless oil: R_f 0.45 [CH_2Cl_2/MeOH (10:1)]; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.21−7.46 (5H, m), 5.84 (1H, dtd, J = 10.0, 3.0, 2.0 Hz), 5.79 (1H, dtd, J = 10.0, 2.0, 1.5 Hz), 4.99 (1H, dd, J = 14.0, 10.5 Hz), 4.93 (1H, d, J = 14.0 Hz), 4.32 (1H, d, J = 14.0 Hz), 4.28 (1H, ddt, J = 7.5, 5.5, 2.0 Hz), 3.36 (1H, dd, J = 12.0, 3.5 Hz), 2.99−3.04 (2 H, m), 2.97 (1H, dt, J = 12.0, 2.0 Hz), 2.72 (1H, td, J = 3.5, 2.0 Hz), 2.43−2.52 (1H, m), 2.10 (1H, dd, J = 14.0, 6.0 Hz), 1.58−1.76 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.8, 167.2, 136.7, 128.7, 128.4, 127.7, 126.4, 122.8, 59.5, 51.8, 49.9, 43.3, 40.8, 31.6, 25.3, 21.2; IR ν_{max}/cm^{-1} (film) 2934 (s), 2239 (w), 1635 (s), 1454 (m), 1262 (s), 1075 (m), 726 (s); MS m/z ESI$^+$ 297 ([M + H]$^+$, 100), 319 ([M + Na]$^+$, 100); HRMS $C_{18}H_{21}N_2O_2$ requires 297.1598, found [M + H]$^+$ = 297.1597. NOE interactions outlined in the Supporting Information confirmed the relative stereochemistry of **2*β***.

Continued elution [CH_2Cl_2/MeOH (99:1)] yielded **2α** (30 mg, 22%) as a colorless oil: R_f 0.35 [CH_2Cl_2/MeOH (10:1)]; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.19−7.33 (5H, m), 5.75−5.84 (2H, m), 4.89 (1H, dt, J = 13.5, 2.5 Hz), 4.55 (1H, d, J = 14.5 Hz), 4.48 (1H, d, J = 14.5 Hz), 4.13−4.17 (1H, m), 3.35 (1H, dd, J = 13.0, 6.5 Hz), 3.24 (1H, d, J = 13.0), 2.84−2.93 (1H, m), 2.77−2.81 (2H, m), 2.72−2.75 (1H, m), 2.23−2.28 (1H, m), 2.18 (1H, ddd, J = 13.0, 5.5, 3.5 Hz), 2.00−2.05 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 167.9, 166.9, 136.7, 128.6, 128.2, 127.5, 123.6, 121.9, 60.2, 51.2, 50.0, 47.2, 43.9, 31.3, 28.9, 27.6. Spectroscopic data for this compound were consistent with those reported previously.[6] Intermediary fractions collected afforded a 1:1 mixture of diastereomers (~50% yield by mass). Complete separation of these isomers required multiple chromatography.

(±)-11-Benzyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridec-2,4-diene-6,12-dione (5b) via Tandem Cyclization−Oxidation. To a solution of cyclization precursor **1** (170 mg, 0.57 mmol)[6] in THF (10 mL, freshly distilled from sodium and benzoquinone) at −78 °C was added LiHMDS (1.0 M THF solution, 1.00 mL, 1.00 mmol) dropwise. The reaction solution was heated at reflux for 2 h and then cooled to rt. Freshly distilled bis(trimethylsilyl)peroxide (200 mg, 1.12 mmol, bp 42−44 °C/30 mmHg, lit.[11] bp 40 °C/30 mmHg) was then added via a glass pipet, and the reaction solution was stirred for 18 h at rt. After this time, the reaction was quenched by the addition of saturated aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL) and CH_2Cl_2 (10 mL). The combined organic washings were dried (Na_2SO_4) and concentrated in vacuo. The crude reaction mixture was analyzed by ^1H NMR to show ~60% conversion to **5b**: R_f 0.15 [CH_2Cl_2/MeOH (19:1)]; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.33 (1H, dd, J = 9.0, 7.0 Hz), 7.25−7.32 (3H, m), 7.10 (2H, dd, J = 7.5, 2.0 Hz),

6.52 (1H, dd, J = 9.0, 1.5 Hz), 6.36 (1H, dd, J = 7.0, 1.5 Hz), 4.64 (1H, d, J = 14.5 Hz), 4.41 (1H, d, J = 14.5 Hz), 4.07 (1H, dt, J = 15.5, 1.0 Hz), 3.97 (1H, ddd, J = 15.5, 6.5, 1.0 Hz), 3.77 (1H, dd, J = 4.5, 3.0 Hz), 3.56 (1H, ddd, J = 13.0, 6.0, 1.0 Hz), 3.20 (1H, dt, J = 13.0, 1.5 Hz), 2.75−2.83 (1H, m), 2.20−2.28 (1H, m), 2.06−2.16 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 167.3, 163.4, 144.0, 139.2, 136.1, 128.8, 127.9, 127.7, 118.3, 106.5, 52.9, 50.0, 49.7, 43.2, 25.7, 23.1. Spectroscopic data for this compound were consistent with those reported previously.[6]

(±)-(1*S*,8a*R*)-1-(Pyrrolidine-1-carbonyl)-1,2,3,8a-tetrahydroindolizin-5(6*H*)-one (17a). To a solution of cyclization precursor **16a** (300 mg, 1.27 mmol) in THF (15 mL, freshly distilled from sodium and benzoquinone) at −78 °C was added LiHMDS (1.0 M THF solution, 2.55 mL, 2.55 mmol). The reaction solution was stirred at −78 °C for 4 h and then quenched by the addition of saturated aq NH_4Cl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL), and then the combined organic washings were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography [CH_2Cl_2/MeOH (49:1−24:1)] yielded **17a** (219 mg, 73%) as a colorless oil: R_f 0.27 [CH_2Cl_2/MeOH (9:1)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.74−5.85 (2H, m), 4.41−4.50 (1H, m), 3.87 (1H, dt, J = 12.0, 9.0 Hz), 3.39−3.56 (5H, m), 2.94−3.03 (1H, m), 2.89 (1H, dt, 21.5, 4.0 Hz), 2.69 (1H, dt, J = 11.0, 7.5 Hz), 2.16−2.26 (1H, m), 2.02−2.12 (1H, m), 1.98 (2H, quin, J = 6.5 Hz), 1.89 (2H, quin, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.3, 166.0, 123.4, 123.0, 61.4, 48.2, 46.5, 45.9, 43.2, 32.5, 26.3, 25.9, 24.1; IR ν_{max}/cm^{-1} (film) 2972 (w), 2881 (w), 1632 (s), 1447 (m), 1411 (w), 1346 (w), 691 (w); MS m/z ESI$^+$ 257 ([M + Na]$^+$, 100); HRMS $C_{13}H_{18}N_2O_2Na$ requires 257.1260, found [M + Na]$^+$ = 257.1266. NOE interactions outlined in the Supporting Information confirmed the relative stereochemistry of **17a**.

(±)-(1*S*,9a*R*)-1-(Pyrrolidine-1-carbonyl)-3,4,7,9a-tetrahydro-1*H*-quinolizin-6(2*H*)-one (17b). To a solution of cyclization precursor **16b** (200 mg, 0.81 mmol) in THF (5.0 mL) at −78 °C was added LiHMDS (1.0 M THF solution, 1.61 mL, 1.61 mmol). The reaction solution was stirred at −78 °C for 1 h then quenched via the addition of saturated aq NH_4Cl solution (25 mL). The aqueous phase was extracted with EtOAc (4 × 25 mL) and CH_2Cl_2 (4 × 25 mL), and then the combined organic washings were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography [CH_2Cl_2/MeOH (49:1)] yielded **17b** (165 mg, 83%) as an off-white solid: R_f 0.27 [CH_2Cl_2/MeOH (19:1)]; mp 121 °C (benzene/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.62−5.78 (2H, m), 4.90 (1H, ddt, J = 13.0, 4.0, 2.0 Hz), 4.16−4.26 (1H, m), 3.44−3.54 (3H, m), 3.39 (1H, dt, J = 10.0, 6.5 Hz), 2.88−3.04 (2H, m), 2.56 (1H, td, J = 13.0, 3.0 Hz), 2.39 (1H, ddd, J = 12.0, 10.5, 4.0 Hz), 1.77 - 2.03 (7H, m), 1.50 (1H, qt, J = 13.0, 4.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.2, 166.0, 123.6, 122.4, 59.6, 49.1, 46.7, 45.7, 41.9, 31.7, 28.3, 26.0, 24.31, 24.30; IR ν_{max}/cm^{-1} (film) 2951 (m), 2885 (m), 1635 (s, br), 1478 (s), 1440 (s), 1407 (m), 1341 (m), 1322 (m), 1265 (m), 1092 (m); MS m/z EI$^+$ 150 ([$C_9H_{12}NO$]$^+$, 100), 248 ([M]$^+$, 50); HRMS $C_{14}H_{20}N_2O_2$ requires 248.1525, found [M]$^+$ = 248.1537. NOE interactions outlined in the Supporting Information confirmed the relative stereochemistry of **17b**.

(±)-(10*S*,10a*R*)-10-(Pyrrolidine-1-carbonyl)-6,7,8,9,10,10a-hexahydropyrido[1,2-*a*]azepin-4(3*H*)-one (17c). To a solution of cyclization precursor **16c** (112 mg, 0.42 mmol) in THF (5.0 mL) at −78 °C was added LiHMDS (1.0 M solution in THF, 850 μL, 0.85 mmol). The reaction solution was stirred at −78 °C for 5 h and then quenched via the addition of saturated aq NH_4Cl solution (40 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 40 mL), and then the combined organic washings were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography [CH_2Cl_2/MeOH (9:1)] followed by secondary purification by column chromatography [EtOAc/MeOH (19:1)] yielded **17c** (15 mg, 14%) as an off-white solid: R_f 0.23 [CH_2Cl_2/MeOH (19:1)]; mp 148−152 °C (benzene/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.83−5.89 (1H, m), 5.77 (1H, ddd, J = 10.0, 4.0, 3.0 Hz), 4.45 (1H, ddd, J = 14.0, 7.0, 2.5 Hz), 4.32 (1H, ddt, J = 9.5, 5.0, 2.5 Hz), 3.44 (4H, m), 2.96−3.02 (2H, m), 2.92 (1H, m, J = 14.0, 11.0, 6.0 Hz), 2.43 (1H, td, J = 9.5, 4.5 Hz), 2.12 (1H, dtt, J = 13.5, 11.0, 7.0 Hz), 1.74−2.01 (7H, m), 1.57−1.67 (1H, m), 1.38−1.49 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 171.7, 168.0, 126.8, 122.9, 62.8, 53.6, 46.8, 46.6, 45.7, 32.4, 29.3, 26.0, 25.5, 24.3, 24.0; IR ν_{max}/cm^{-1} (film) 2935 (w), 1635 (s), 1592 (m), 1539 (w), 1471 (m), 1432 (m), 1401 (w), 1345 (w), 1320 (w), 1257 (w), 1065 (w), 808 (w), 706 (w); MS m/z EI$^+$ 126 (100%), 262 ([M]$^+$, 60); HRMS $C_{15}H_{22}N_2O_2$ requires 262.1681, found [M]$^+$ = 262.1680. NOE interactions outlined in the Supporting Information confirmed the relative stereochemistry of **17c**.

(±)-1-Benzyl-4-bromomethylpyrrolidin-2-one (20). To a solution of 1-benzyl-4-(hydroxymethyl)pyrrolidin-2-one (6.11 g, 29.77 mmol)[15] in toluene (100 mL) at 0 °C was added PBr_3 (2.93 mL, 31.26 mmol) dropwise. The reaction mixture was heated at reflux for 5 h, cooled to 0 °C, and quenched by dropwise addition of H_2O (5 mL). Concentration in vacuo afforded an orange gum which was dissolved in EtOAc (50 mL) and sonicated to aid dissolution. The solution was then partitioned between H_2O (30 mL) and EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford bromide **20** (5.11 g, 64%) as a colorless oil: R_f 0.35 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.22−7.45 (5H, m), 4.52 (1H, d, J = 14.5 Hz), 4.44 (1H, d, J = 14.5 Hz), 3.46 (1H, dd, J = 10.0, 0.5 Hz), 3.44 (1H, dd, J = 10.0, 3.0 Hz), 3.37 (1H, dd, J = 10.0, 7.5 Hz), 3.11 (1H, dd, J = 10.0, 6.0 Hz), 2.73−2.86 (1H, m), 2.68 (1H, ddd, J = 17.0, 9.0, 0.5 Hz), 2.35 (1H, dd, J = 17.0, 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.9, 136.1, 128.8, 128.2, 127.7, 51.1, 46.6, 36.6, 35.7, 33.5; IR ν_{max}/cm^{-1} (film) 2922 (m), 1685 (s), 1496 (m), 1445 (m), 1420 (m), 1358 (w), 1296 (m); MS m/z ESI$^+$ 268 ([M{^{79}Br} + H]$^+$, 77), 270 ([M{^{81}Br} + H]$^+$, 80), 290 ([M{^{79}Br} + Na]$^+$, 100), 292 ([M{^{81}Br}+Na]$^+$, 90); HRMS $C_{12}H_{15}NO^{79}Br$ requires 268.0331, found [M + H]$^+$ = 268.0343.

(±)-1-((1-Benzyl-5-oxopyrrolidin-3-yl)methyl)pyridin-2(1*H*)-one (21). A stirred mixture of 2-pyridone (2.61 g, 27.40 mmol), bromide **20** (7.99 g, 30.14 mmol), K_2CO_3 (8.33 g, 60.30 mmol), and tetrabutylammonium bromide (0.89 g, 2.75 mmol) in water (1 mL) and toluene (100 mL) was heated at reflux overnight. After being cooled to rt, the reaction mixture was filtered and concentrated in vacuo. Flash chromatography [CH_2Cl/MeOH (19:1)] yielded **21** (5.15 g, 61%) as a colorless oil: R_f 0.40 [CH_2Cl_2/MeOH (19:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.20−7.41 (6H, m), 6.82 (1H, dd, J = 7.0, 1.5 Hz), 6.54 (1H, dd, J = 9.0, 0.5 Hz), 6.05 (1H, td, J = 7.0, 1.5 Hz), 4.54 (1H, d, J = 14.5 Hz), 4.36 (1H, d, J = 14.5 Hz), 3.87 (1H, dd, J = 13.0, 7.0 Hz), 3.79 (1H, dd, J = 13.0, 8.0 Hz), 3.33 (1H, dd, J = 10.0, 7.0 Hz), 2.93−3.06 (2H, m), 2.62 (1H, dd, J = 17.0, 8.0 Hz), 2.24 (1H, dd, J = 17.0, 5.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 179.0, 172.9, 139.7, 137.6, 136.4, 128.8, 128.4, 127.8, 121.3, 106.0, 53.1, 48.9, 46.5, 35.3, 30.8; IR ν_{max}/cm^{-1} (film) 2918 (s), 2851 (s), 1681 (s), 1657 (s), 1586 (s), 1541 (m), 1429 (s), 1255 (m), 1155 (m); MS m/z ESI$^+$ 283 ([M + H]$^+$, 10), 305 ([M + Na]$^+$, 100); HRMS $C_{17}H_{18}N_2O_2Na$ requires 305.1267, found [M+Na]$^+$ = 305.1260.

(±)-(3a*S*,9a*R*,9b*S*)-2-Benzyl-2,3,3a,7,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,6(4*H*)-dione (22β) and (±)-(3a*S*,9a*S*,9b*S*)-2-Benzyl-2,3,3a,7,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,6(4*H*)-dione (22α). To a solution of cyclization precursor **21** (786 mg, 2.78 mmol) in THF (30 mL, freshly distilled from sodium and benzoquinone) at −78 °C was added LiHMDS (1.0 M THF solution, 5.6 mL, 5.60 mmol) dropwise. The reaction solution was stirred at −78 °C for 2 h and then quenched by the addition of saturated aq NH_4Cl (10 mL). The aqueous phase was extracted with EtOAc (2 × 15 mL) and CH_2Cl_2 (15 mL), and

then the combined organic washings were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography [CH_2Cl_2/MeOH (19:1)] yielded adduct **22*β*** (200 mg, 28%) as a colorless oil: R_f 0.25 [CH_2Cl_2/MeOH (19:1)] ^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 7.28−7.38 (3H, m), 7.22−7.26 (2H, m), 6.09−6.13 (1H, m), 5.84−5.89 (1H, m), 4.58 (1H, dd, J = 12.0, 8.5 Hz), 4.54 (1H, d, J = 14.5 Hz), 4.41 (1H, d, J = 14.5 Hz), 4.24−4.31 (1H, m), 3.49 (1H, dd, J = 10.5, 8.0 Hz), 3.09 (1H, dd, J = 10.5, 3.5 Hz), 3.03 (1H, dd, J = 10.0, 7.5 Hz), 2.84−3.00 (3H, m), 2.79 (1H, dd, J = 12.0, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 172.9, 165.7, 135.7, 128.7, 128.0, 127.8, 124.8, 123.0, 60.1, 52.9, 49.6, 49.2, 46.6, 32.8, 32.1; IR ν_{max}/cm^{-1} (film) 2922 (m), 2851 (m), 1684 (s), 1646 (s), 1496 (m), 1446 (s), 1314 (m), 1261 (m), 729 (w); MS m/z ESI$^+$ 283.1 ([M + H]$^+$, 33), 305.1 ([M + Na]$^+$, 100); HRMS $C_{17}H_{18}N_2O_2Na$ requires 305.1260, found [M + Na]$^+$ = 305.1267, $C_{17}H_{19}N_2O_2$ requires 283.1441, found [M+H]$^+$ = 283.1449.

Continued elution [CH_2Cl_2/MeOH (9:1)] yielded diastereomer **22α** (100 mg, 14%) as a colorless oil: R_f 0.50 [CH_2Cl_2/MeOH (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.07−7.38 (5H, m), 6.30−6.36 (1H, m), 5.81−5.90 (1H, m), 4.44 (1H, d, J = 15.0 Hz), 4.35 (1H, d, J = 15.0 Hz), 4.08−4.17 (1H, m), 3.48 (1H, dd, J = 11.0, 9.0 Hz), 3.34 (1H, dd, J = 12.5, 7.5 Hz), 3.27 (1H, t, J = 8.0 Hz), 2.92−3.04 (4H, m), 2.66 (1H, q, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 171.4, 166.0, 135.7, 128.7, 128.3, 127.9, 127.8, 122.2, 60.0, 52.2, 50.1, 50.0, 46.6, 32.4, 32.1; IR ν_{max}/cm^{-1} (film) 3152 (m), 3055 (m), 2925 (m), 1684 (s), 1647 (s), 1585 (m), 1496 (m), 1447 (s), 1322 (m), 1279 (m), 1077 (w); MS m/z ESI$^+$ 283 ([M + H]$^+$, 100); HRMS $C_{17}H_{19}N_2O_2$ requires 283.1441, found [M + H]$^+$ = 283.1449. Note: Intermediary fractions collected afforded a 3:1 mixture of diastereomers **22*β*** and **22α** (∼60% yield by mass).

(±)-2-Benzyl-2,3,3a,9b-tetrahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,6(4*H*)-dione (23) via MnO_2 Oxidation. To adducts **22*β*** and **22α** (930 mg, 3.29 mmol, as a 3:1 mixture of **22*β*/α**) in DCE (50 mL) was added MnO_2 (2.86 g, 32.9 mmol). The reaction mixture was heated at 90 °C for 18 h and then cooled to rt, filtered through a plug of Celite, and concentrated in vacuo to afford pyridone **23** (627 mg, 68%) as a pale brown microcrystalline solid: R_f 0.35 [CH_2Cl_2/MeOH (19:1)]; mp 203−206 °C (toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.41 (1H, dd, J = 9.0, 7.0 Hz), 7.27−7.35 (3H, m), 7.17−7.20 (2H, m), 6.50 (1H, dt, J = 7.0, 1.0 Hz), 6.48 (1H, dt, J = 9.0, 1.0 Hz), 4.48 (1H, d, J = 14.5 Hz), 4.43 (1H, d, J = 14.5 Hz), 4.42 (1H, dd, J = 13.5, 8.5 Hz), 4.14 (1H, dt, J = 9.0, 1.0 Hz), 3.92 (1H, dd, J = 13.5, 5.0 Hz), 3.62 (1H, dd, J = 10.5, 8.0 Hz), 3.28−3.36 (1H, m), 3.15 (1H, dd, J = 10.5, 4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.2, 162.1, 147.9, 135.3, 128.8, 127.9, 127.7, 118.8, 102.6, 54.3, 52.4, 50.8, 47.3, 31.2; IR ν_{max}/cm^{-1} (film) 2924 (m), 1695 (s), 1662 (s), 1582 (s), 1543 (w), 1496 (w), 1447 (s), 1262 (m), 1154 (m); MS m/z ESI$^+$ 281 ([M+H]$^+$, 100); HRMS $C_{17}H_{17}N_2O_2$ requires 281.1284, found [M+H]$^+$ = 281.1290.

(±)-2-Benzyl-2,3,3a,9b-tetrahydro-1*H*-pyrrolo[3,4-*a*]indolizine-1,6(4*H*)-dione (23) via Tandem Cyclization Oxidation. To a solution of cyclization precursor **21** (116 mg, 0.41 mmol) in THF (10 mL, freshly distilled from sodium and benzoquinone) at −78 °C was added LiHMDS (1.0 M THF solution, 0.82 mL, 0.82 mmol) dropwise. The reaction solution was stirred at −78 °C for 2 h, and then freshly distilled bis(trimethylsilyl)peroxide (146 mg, 0.82 mmol, bp 42−44 °C/30 mmHg, lit.[11] bp 40 °C/30 mmHg) was added via a glass pipet. The reaction solution was stirred for a further 18 h at rt and then quenched by the addition of NH_4Cl (50 mg, 0.93 mmol) and MeOH (5 mL) and concentrated in vacuo. The crude reaction mixture was analyzed by ^{1}H NMR to show ∼60% conversion by comparison with starting material **21** and oxidized product **23**.

(±)-(*R*)-3-(((*R*)-1-Benzyl-6-oxopiperidin-3-yl)methyl)-4-(bis(trimethylsilyl)amino)-3,4-dihydropyrimidin-2(1*H*)-one and (±)-(*S*)-3-(((*R*)-1-Benzyl-6-oxopiperidin-3-yl)methyl)-4-(bis(trimethylsilyl)amino)-3,4-dihydropyrimidin-2(1*H*)-one (35). To a solution of NaHMDS (124 mg, 0.67 mmol) in THF (3 mL) at −78 °C was added a solution of **26a** (100 mg, 0.34 mmol) in THF (3 mL, freshly distilled from sodium and benzoquinone) dropwise. The reaction solution was stirred at −78 °C for 2 h, quenched by the addition of saturated aq NH_4Cl (0.5 mL), and further diluted with water (3 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL), and then the combined organic washings were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography [CH_2Cl_2/MeOH (49:1)] yielded adduct **35** (46 mg, 30%) as a 1:1 mixture of diastereomers and as a pale yellow oil: R_f 0.45 [CH_2Cl_2/MeOH (19:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 (1H, m), 7.23−7.34 (5H, m), 5.96 (1H, m), 5.23 (1H, dd, J = 19.0, 3.5 Hz), 4.79 (0.5H, d, J = 15.0 Hz), 4.60 (1H, m), 4.56 (1H, m), 4.42 (0.5H, d, J = 15.0 Hz), 3.53−3.66 (1H, m), 3.13−3.26 (1H, m), 2.94−3.09 (2H, m), 2.54−2.70 (1H, m), 2.36−2.50 (1H, m), 2.10−2.30 (1H, m), 1.84−1.94 (1H, m), 1.49−1.63 (1H, m), 0−0.25 (18H, br m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.7, 169.5, 153.1, 152.9, 137.1, 136.9, 128.6, 128.5, 128.0, 128.0, 127.3, 127.3, 122.8, 122.8, 102.8, 69.1, 68.8, 50.8, 50.6, 50.4, 50.1, 44.1, 43.7, 32.7, 32.5, 31.5, 31.3, 25.5, 25.3, 2.5−3.1 (br), 2.4, 1.3. This material was subjected to NMR analysis immediately after isolation, and was found to be unstable, undergoing slow decomposition to regenerate **26a** (as judged by ^{1}H NMR) over a period of hours.

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Supporting Information Available: Additional synthetic procedures for new compounds not described in the Experimental Section, characterization data and copies of ^{1}H and ^{13}C NMR spectra of new compounds, descriptions of NOE interactions for **2*β***, **17a**, **17b**, **17c** and **22*β***, as well as expanded versions of the in situ IR data shown in Schemes 4 and 5. This material is available free of charge via the Internet at http://pubs.acs.org.