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Synthesis of 6- and 7-membered cyclic enaminones: Scope and mechanism

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Abstract

Six- and seven-membered cyclic enaminones can be prepared using common, environmentally benign reagents. Amino acids are used as synthetic precursors allowing diversification and the incorporation of chirality. The key reaction in this multi-step process involves deprotection of Boc-aminoynones and subsequent treatment with methanolic K_2CO_3 to induce cyclization. A β-amino elimination side reaction was identified in a few labile substrates that led to either loss of stereochemical purity or degradation. This process can be mitigated in specific cases using mild deprotection conditions. NMR and deuterium labeling experiments provided valuable insight into the workings and limitations of this reaction. Although disguised as a 6-*endo*-dig cyclization, the reagents employed in the transformation play a direct role in bond-making and bond-breaking, thus changing the mode of addition to a 6-*endo*-trig cyclization. This method can be used to construct an array of monocyclic and bicyclic scaffolds, many of which are found in well-known natural products (*e.g*. indolizidine, quinolizidine and *Stemona* alkaloids).

Keywords

enaminone; vinylogous amide; ynone; 6-*endo*-trig; 6-*endo*-dig; 6-*exo*-trig; ®-amino elimination; *retro*-Michael; 2,3-dihydro-4-pyridone; azepine; Boc-deprotection

Introduction

Enaminones can best be described as β-acyl enamines or amides with an interpolated alkene. The reactivity and stability of these entities are much different than that of a conventional enamine which readily decomposes through hydrolytic or oxidative pathways.1 On the contrary, enaminones are quite stable and easily isolated. Although not quite as robust as the conventional amide, the conjugation of the enamine to a carbonyl attenuates its reactivity, endowing it with a unique and ambident nature. In addition to their distinct reactivity profile, enaminones have also attracted attention in pharmaceutical development, particularly as anti-convulsants and Pgp modulators.2 Their stability and favorable physicochemical properties are exemplified by their use as orally active medicinal agents.2d

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Supporting Information Paragraph: Representative experimental procedures; complete crystallographic data for compound **7a**; characterization data for all new compounds; spectra for compounds **1a–m, 2a–x, 3a–x, 7a, 14, 15, 16**; and NMR deuterium labeling study spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

A combination of the above factors became the impetus for developing a synthetic route to previously inaccessible or laboriously synthesized enaminone scaffolds.

Cyclic enaminones, particularly 6-membered enaminones (2,3-dihydro-4-pyridones), are extraordinarily versatile intermediates for the synthesis of piperidine-containing target molecules. Indeed, this heterocycle exists in numerous drugs and drug candidates as an indispensable binding element. Moreover, the piperidine moiety is prevalent in structural classes of bioactive natural products such as the indolizidines and quinolizidines.3 Considering the ubiquity of biologically active piperidine-containing compounds, practical methodologies for the synthesis of these structures, especially those bearing stereogenic centers, are of great value.

The synthetic utility of the enaminone is clear when considering the reactivity of each component moiety (amine, enamine, enone, and alkene) in isolation. The handles for modification of this core molecule include four nucleophilic sites and two electrophilic sites. As depicted in Figure 1, studies into reactivity of the 6-membered, cyclic enaminones have made possible a plethora of chemoselective transformations (*e.g. N*-functionalization,4 *O*-functionalization,5 C3,6 C4 [1,2-addition],7 C58 and C6 [1,4-addition] functionalization9 and [2+2] cylization10).

A number of approaches have been developed to construct the 6-membered enaminone core, yet only a few are capable of affording non-racemic products (Figure 2). Comins and co-workers have set precedent for the asymmetric synthesis of enaminones employing chiral *N*-acylpyridinium intermediates.11 This method has proven to be enormously effective in providing advanced intermediates in the synthesis of numerous natural products.12 More recent efforts have expanded the scope of this chemistry by using an assortment of chiral auxiliaries.5b›9f›13 Another approach which predates Comins' method is the asymmetric hetero Diels-Alder reaction of imines with Danishefsky's diene.14 In this reaction, the chirality can be derived from various chiral auxiliaries appended to the imine5b›5c›14a–f or through the use of chiral catalysts14g–m. A noteworthy corollary of this classic [4+2] approach has recently been reported by the Rovis group15 in which alkynes and alkenylisocyanates undergo [2+2+2] cycloaddition in the presence of a chiral rhodium catalyst. Although currently limited to the synthesis of the indolizidine enaminones, this method provides rapid access to these bicyclic molecules with impressive enantioselectivity. Despite the success of these asymmetric approaches, innate limiting factors, such as ring size and substituent constraints, warranted an exploration of new avenues for the construction of this useful scaffold.

In pursuit of this goal, we have developed a novel ring-forming reaction of amino acid-derived ynones to yield cyclic enaminones.16 Our route accesses the target molecules in high enantiomeric purity by utilizing the chiral pool strategy to take advantage of the chirality of readily available starting materials. A notable feature of this methodology is its power to generate previously unavailable or circuitously-constructed substrates, namely, bicylic enaminones, 2, 5-disubstituted enaminones, and enaminones with ⟨- and ®-stereocenters. Herein, we present a full disclosure of our investigations into the scope and mechanism of this reaction. This concise and operationally facile strategy gives ready access to novel 6- and 7-membered enaminones through a vinyl halide intermediate which allows cyclization to proceed through a highly-favored 6-*endo*-trig pathway.

Results and Discussion

Reaction Development

As previously mentioned, methods for the construction of non-racemic dihydropyridones are scarce, and the existing few, although highly contributive to this area, have left many structurally simple enaminones out of reach. Thus, we envisioned a complementary route to these coveted molecules using the chiral pool strategy (Figure 3). We first considered a direct-Michael addition of an amine into the linear ynone which would provide uninterrupted entry into our desired scaffold. It was reasoned that the necessary amino-ynone substrates could be obtained from β-amino acid precursors. This approach was attractive to us not only because it could potentially furnish pyridones with four distinct appendages and two stereogenic stereocenters, but also because it utilizes easily accessible chiral starting materials. The strategic use of ®-amino acids and their immediate precursors entrusts the chiral pool and established asymmetric chemistry17 to provide both diversity and asymmetry.

Despite the numerous examples of intermolecular 1,4-additions of amines to ynones, precedent for an intramolecular variant as proposed is scarce. The lack of literature precedent for such a 6-*endo*-dig transformation raised immediate concerns. Although this mode of cyclization is favored according to Baldwin's rules for ring-closing reactions,18 questions arose with regard to the feasibility of suitable amine/ynone orbital overlap and competitive intermolecular reactions. If direct addition to the ynone could not be achieved, however, the use of an appropriate ynone synthetic equivalent could direct this cyclization into well-explored mechanistic territory, providing a surer means to our desired target molecules.

In addition to our questions regarding the mode of addition, concerns arose about racemization and epimerization of the pre-established stereocenters also had to be investigated. Enolization processes leading to loss of ⟨-chiral centers are commonplace and would need to be avoided. We also considered the likelihood of β-amino ketone intermediates to undergo *retro*-Michael/*retro*-Mannich-type processes (Figure 4).19 This scenario would jeopardize the integrity both ⟨- and ®-stereocenters or lead to substrate decomposition, both of which would severely limit the utility of such a protocol. With these potential hurdles in mind, we ventured to construct the requisite ynone starting materials.

Three routes were devised to obtain ®-amino Weinreb amides, the immediate precursors of the desired ynone starting materials. In the cases where the Boc-®-amino acid was commercially available, an EDCI coupling with HN(OMe)Me•HCl in the presence of *N*-methylmorpholine (NMM) furnished the corresponding amide in a single step (Method A, Scheme 1). Alternatively, Boc-⟨-amino acids were converted to diazoketones which, in the presence of catalytic CF_3CO_2Ag, collapsed to the corresponding ketene. The ketene intermediate was trapped *in situ* with HN(OMe)Me, providing the desired Weinreb amides (Method B). Unsubstituted Weinreb amides were synthesized through a one-pot Michael-addition/Boc-protection sequence to afford Boc-®-aminomethylesters (Method C). Treatment of the methyl esters with HN(OMe)Me•HCl and *i*-PrMgCl afforded the desired amides.20 In the event that the Boc-protected amines required *N*-alkylation, this was accomplished subsequent to amide formation using NaH and an appropriate alkyl halide. In the final step, the desired ynones were obtained from the Weinreb amides through the addition of excess (5 equiv) alkynylmagnesium reagents. These simple steps could be conducted on multi-gram scale with minimal reduction in yield.

Due to our interest in indolizidine and quinolizidine natural products, we chose to synthesize ynones **2a–f** as potential precursors to these important heterocycles (entries 1–6, Table 1).

The isolated stereogenic center on the pyrrolidine ring of ynones **2g–k** was to be used to facilitate detection of the ®-epimerization (entries 7–11). Likewise, cyclohexyl systems **2m** and **2n** would allow ⟨-epimerization to be detected (entries 13 and 14). Finally, acyclic ynones **2o–t** were synthesized to obtain monocyclic enaminones (entries 15–21). Although the enaminones to be generated from ynones **2r–t** would be relatively unembellished, we were attracted to these targets because of a surprising lack of general routes to obtain them, in spite of their simplicity.

From the outset, we envisioned a protocol in which the Boc-protecting group would be removed to liberate a nucleophilic amine that would, in turn, react with the tethered ynone moiety. Our initial efforts found success in a two-tier deprotection/cyclization protocol to provide enaminone **3a** (Table 2).16 The use of 4N HCl (entries 5–9, Table 2) or TMS-I (entry 10) consistently gave higher yields than when TFA was used to deprotect (entries 1–4), regardless of the cyclization method. We were initially perplexed by this disparity. The putative ammonium salt intermediates of each method would seemingly only differ with respect to their counter ions (Cl^-, I^- or $CF_3CO_2^-$). Upon closer scrutiny, however, it became clear that HCl and TMS-I served another purpose. In addition to deprotecting the Boc-group, these reagents also promoted conjugate additions of their respective halides (Scheme 2). Isolation of the deprotected intermediates revealed that, prior to cyclization, the ynone **2a** had been converted by HCl and TMS-I to a mixture of vinyl halide **4** and dihaloketone **5**. Trifluoroacetic acid, however, left the ynone intact (**6**). The addition of chloride or iodide into the ynone prior to cyclization was evidently favoring ring-closure. This finding was good evidence that this reaction was not proceeding through a 6-*endo*-dig pathway as we first had thought (see below).

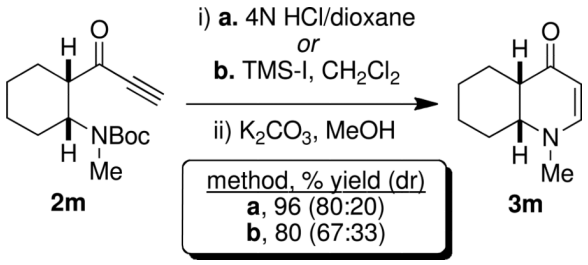
Another important observation that was made during these studies was the apparent dependency of the cyclization on water or MeOH. Regardless of the deprotection method, the enaminone would not form in THF or CH_2Cl_2 (entries 2, 3, 5 and 6; Table 2) unless water was used as a co-solvent (entries 4, 7 and 8). Although these wet solvents could affect cyclization, MeOH proved to be the best solvent and was chosen to further explore this reaction (entries 9 and 10). With these optimized conditions, we proceeded to establish the scope of this reaction.

Shortly after we embarked on our study of reaction scope, we encountered a formidable challenge. As we had feared, ynones bearing α- or β-stereocenters, when subjected to our one-pot procedure, yielded mixtures of diastereomers or partial racemates. We suspected enolization or ®-amino elimination or both processes were at hand; if not overcome, this would negate the principal advantage of the chiral pool approach. Although both acid- and base-induced epimerizations of this type are possible, we initially focused our attention on the acidic deprotection conditions. Since the most profound stereochemical damage was observed in proline-derived enaminones, hydroxylated ynone **2j** was employed as our model system to assess the extent of ®-epimerization under an array of deprotection conditions (Table 3).

Our previously optimized deprotection conditions had epimerized 15% of the isolated product (entry 1, Table 3). In neat and dilute TFA, the yields and diastereomeric ratios of enaminone **3j** showed no improvement (entries 2 and 3). Slow addition of HCl in ether until all the starting material was consumed also failed to give satisfactory results (entry 4). Positing an acid-induced mode of racemization we attempted to suppress the stereochemical deterioration using basic and neutral conditions (entries 5–7). Only TESOTf and 2,6-lutidine (entry 6) provided the desired product, albeit in 21% yield and with a dr of 83:17. When TMS-I was used to induce Boc-deprotection, we observed a marked reduction of epimerization and improvement in yields (entries 8–9). It should be noted that ynones have

been shown to react with TMS-I at −78 °C to form β-iodo-allenolates, which upon warming to 0 °C tautomerizes to afford a Danishefsky-type diene (Scheme 3).21 Although this would not directly compromise the integrity of the ®-stereocenter, substrates bearing α-stereocenters would be affected.

Subjecting enolizable substrate **2m** to the same conditions, epimerization was even more

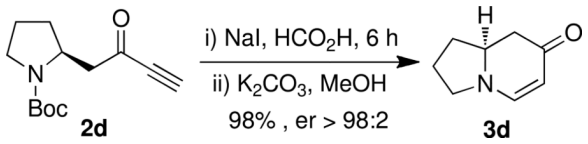


(1)

profound than when using HCl (eq 1). In addition to the detrimental stereochemical effects of TMS-I, the necessity of rigorously dried solvents, glassware, and cryogenic temperatures provoked a search for a new, simple protocol that would be suitable for epimerizable substrates.

With a wealth of known Boc-deprotection protocols to explore, we were attracted to the use of formic acid (HCO_2H) to avert epimerization.22 The simple technique of this method was attractive considering it could accomplish the desired deprotection at ambient temperature and in open air. Furthermore, we hoped that this relatively weak acid would lessen epimerization. Applying these conditions to ynone **2j**, the Boc-group could be easily removed, yet upon treatment with base, we did not observe any enaminone formation (entry 10, Table 3). As shown in earlier experiments, the success of this reaction is not only contingent on the removal of the Boc-group, but also on ynone "activation" with halides (Scheme 2). To this end, sodium iodide (NaI) was added as a nucleophilic halide source and the reaction was repeated (entry 11, Table 3). To our delight, the desired enaminone was formed in excellent yield (92%) and without any detectable epimerization. Conceivably, the remote hydroxy group could resist epimerization by directing the re-addition of the eliminated amine to the most favored *anti*-substituted product. We were encouraged to find that, in the absence of diasteromeric control, enaminones could be obtained in high enantiopurity (eq 2). When ynone **2d** was subjected to these deprotection conditions a crystalline solid formed in the reaction media and was determined by X-ray analysis to be the desired deprotected, vinyl iodide intermediate (**7a**, Figure 5). Upon treatment of this salt with base, enaminone **3d** was formed in less than 2 minutes. More importantly, the product was obtained with an enantiomeric ratio (er) of 98.5:1.5 showing that this protocol had effectively mitigated β-epimerization.

We next investigated these new conditions on enolizable ynone **2m** as a model for α-epimerization



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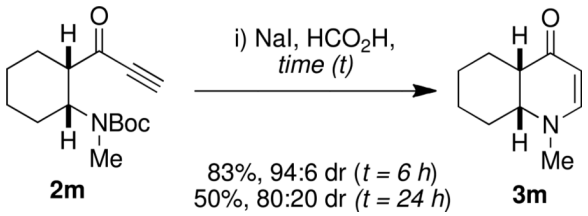

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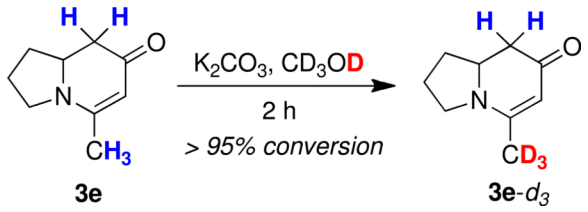
(eq 3). The new conditions yielded the desired product (**3m**) with a dr of 94:6. This was a considerable improvement over the previous method where the dr was 80:20. Interestingly, we also saw a time-dependent increase of epimerization indicating that the acid step was indeed responsible, at least in part, for ⟨-epimerization. Enolate formation during the basic step could also potentiate epimerization and was investigated further.

Vinyl iodides **7a**, **7b**, and **7c** were chosen as model substrates to examine enolization. These substrates were subjected to the cyclization conditions using deuterated methanol (CD_3OD) as a solvent and the extent of ⟨-deuteration was determined (Figure 6). Deuterium incorporation at the α-position is indicative of enolate formation revealing another potential source of epimerization. When intermediate **7a** was treated with methanol-d_4 and K_2CO_3, enaminone **3d** was immediately formed and no deuteration was observed. Once formed, this enaminone was resistant to deuterium incorporation for up to 24 h (*i.e.* to form enaminone **3d**-d_2). With the intent of slowing the cyclization we used substituted vinyl iodides **7b** and **7c**. For these cases, the cyclized products **3e**-d_5 and **3f**-d_2 were obtained with complete ⟨-deuteration. Furthermore, as observed before, enaminones **3e** and **3f**, which were formed in non-deuterated solvent, did not undergo α-deuteration under the prescribed conditions.

The point has already been made that enaminones are reluctant to undergo deuteration in the presence of K_2CO_3; however, an anomaly was noted when investigating enaminone **3e** (eq 4). This substrate underwent selective and complete ©-deuteration to provide enaminone **3e**-d_3 in 2 hours. Although it is out of the scope of this paper, this finding reveals another handle on this versatile scaffold for chemoselective modification.23

The collective data from the deuterium exchange reactions hinted at another liability in our



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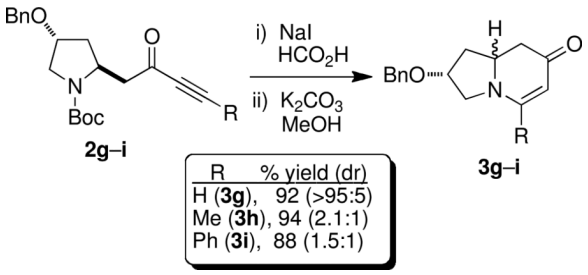

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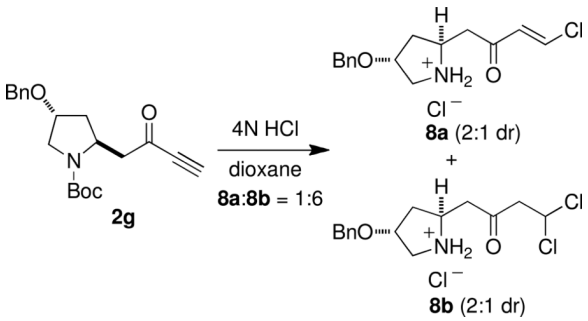
approach. We feared that the extent of α-deuteration might be diagnostic of pre-cyclized intermediates that would undergo β-amino elimination. Thus, ynones **2g**, **2h** and **2i** were subjected to the two-step procedure (eq 5). Terminal ynone **2g** cyclized with no observable epimerization whereas the methyl and phenyl substituted ynones, **2h** and **2i**, were obtained as diastereomeric mixtures.

In retrospect, these findings are not surprising. The principles of vinylogy would indeed predict an attenuated acidity of the enaminone α-position in relation to that of its ketone progenitor. Thus, α-epimerization or β-amino elimination is precluded by rapid formation of the vinylogous amide. When the rate of cyclization is retarded with substituted ynones there is a significant increase in epimerization, thus showing the vulnerability of the enaminone precursors in basic media. Despite the use of mild deprotection conditions, these new findings suggest that base-induced epimerization is predominant when cyclization is slow.

Suspicions immediately arose concerning the putative role of the acid in ®-amino elimination. Perhaps the discrepancies in the stereochemical outcome of each deprotection condition were attributable to the dissimilar haloketone intermediates and their particular reactivities under basic conditions. For instance, a conspicuous difference exists when considering the respective halides (Cl *vs.* I). Furthermore, double chloride addition into the ynone occurs in the presence of HCl whereas the diiodo congener is not formed in HCO_2H and NaI (Scheme 2). We were cognizant that these dissimilarities, rather than the strength of the acid used for deprotection, could dictate the extent of epimerization by governing the rate of cyclization. Fortunately, this could be directly investigated.

Experimental evidence suggests that the primary cause of ®-epimerization for *terminal ynones* is



(6)

the strongly acidic HCl conditions. When ynone **2g** was subjected to 4N HCl the resultant ammonium salts (**8a** and **8b**) were each generated as 2:1 diastereomeric mixtures (eq 6). From this we conclude that the acid is directly responsible for inducing amino-elimination. As such, this process can be mitigated when using a weaker acid such as HCO_2H. It is important to note that the use of HCO_2H and NaI does not assuage the stereochemical detriment in cases where cyclization is slow (*i.e.* substituted ynones). Thus, this mild protocol is most appropriate for terminal ynones. With these insights we next investigated the reaction scope to validate the utility and generality of this protocol.

Substrate Scope

As can be seen in Table 4, a diverse collection of enaminones can be constructed using the above methods. From this data set we intended to establish a basis for choosing appropriate deprotection conditions. Bicyclic enaminones are formed efficiently, providing a facile route to quinolizidine (entries 1–3) and indolizidine (entries 4–11) scaffolds. Synthesis of morpholino-enaminone **3l** was also feasible (entry 12). Pyrrolidine substrates were particularly susceptible to stereochemical erosion; however, this could be mitigated in terminal ynone substrates by using a HCO_2H and NaI during the deprotection step. Although the reason for this sensitivity has not been directly assessed, we believe this is due, in part, to the alleviation of pyrrolidine ring-strain. Not surprisingly, *anti*-substitued pyrrolidines were less prone to epimerization than their *syn*-counterparts (entries 10 and 11). Installation of aliphatic and aromatic substituents adjacent to the ring-fused nitrogen was also accomplished by employing terminally substituted ynones (entries 5, 6, 8 and 9). As expected, cyclization was relatively slow (15 min to 3 h) in these substrates but all proceeded in excellent yields. In these cases, however, the HCO_2H-based deprotection method was ineffective at preventing ®-epimerization.

Enolizable stereocenters were also a potential liability considering our protocol featured both an acidic and a basic step. As shown before, the use of HCl and TMS-I were destructive when attempting to establish the *cis*-fused enaminone **3m**. We were pleased to find that ⟨-epimerization could also be suppressed in this case under the milder conditions with HCO_2H and NaI (entry 13). It should be noted that since the *trans*-substituted product is expected to be more stable, epimerization is likely to be thermodynamically preferred. With this in mind, it was not surprising that *trans*-fused enaminone **3n** was more resistant to epimerization in both deprotection conditions and could be acquired in high diasteromeric purity (entry 14).

We next investigated the synthesis of monocyclic enaminones. These compounds would seemingly be more difficult to form, as they have no conformational constraints facilitating ring-closure. In this regard, acyclic β-aminoynones were found to be viable substrates (entries 15–22). Even sterically encumbered, internal ynones undergo cyclization to form monocyclic products (entry 18). In cases where the extruded amine is not tethered to the ynone, as in bicylic substrates **3a**–**3l**, the *retro*-Michael process leads to degradation instead of epimerization. Hence, it was observed that several monocyclic products were obtained in lower yields than their bicyclic analogues.

The observation that a subtle ring expansion had profound effects on the extent of β-racemization (entry 1 vs. 4) led us to attempt the construction of phenylglycine-derived enaminone **3o** (entry 15). We envisioned that this substrate would be particularly susceptible to β-amino elimination. Expecting to see a distinct improvement in yield when HCO_2H was used instead of HCl, we were surprised that both deprotection methods were equally suited for this sensitive substrate. By conducting this reaction in an NMR tube and carefully monitoring its progression, it became apparent that degradation (*i.e.* ®-amino elimination) occurred upon the addition of methanolic K_2CO_3 and not during deprotection. The complete

retention of stereochemistry suggests that this process was irreversible in contrast to cases where the extruded amine remains tethered to the resultant Michael acceptor (entries 1–12). From these results we suggest alternative methods be used to access enaminones of this type. Fortunately, this is well within the scope of both the Comins' *N*-acylpyridinium13 and the hetero Diels-Alder approach.14

In addition to introducing steric bulk, attenuating the nucleophilicity of the amine would seemingly impede an efficient ring closure. The synthesis of enaminone **3t** demonstrates that despite the use of a significantly less reactive anilino nitrogen, cyclization still occurs (entry 22), albeit in lower yields.

With success in constructing 6-membered enaminones, we next explored the feasibility of constructing 5- and 7-membered rings. This method lacks the strict confines of ring size for the alternative routes to cyclic enaminones. Our initial attempts to cyclize ⟨-amino ynones to form 5-membered enaminones were unsuccessful. This is consistent with our hypothesis that this reaction proceeds through an *endo*-trig mode of cyclization (5-*endo*-trig is disfavored). The synthesis of 5-membered enaminones remains a limitation of this methodology.

Previously reported methods for the construction of cyclic enaminones have not been amenable to the synthesis of 7-membered rings either. Furthermore, to our knowledge, there is no general method for their construction. Without any alteration of our protocol, γ-amino ynones **2u**–**2x** rendered four novel 7-membered enaminones (entries 1–4, Table 5). Indeed, pyrrolo[1,2-*a*]azepine **3u** bears resemblance to the core and distinguishing feature of the *Stemona* alkaloids.24 This unique molecule and its piperidino congener (**3v**) were both attainable in good yields (entries 1 and 2). Spirocyclic enaminone **3w** and baclofen-derived enaminone **3x** were also readily obtained via our deprotection/cyclization protocol (entries 3 and 4). Although all of these enaminones were constructed in racemic form and, hence, their stereochemical liabilities not investigated, we have no reason to believe that they are susceptible to the stereochemical deterioration seen in ®-amino ynones.

In summary, we have developed two complementary protocols for synthesizing 6- and 7-membered enaminones. The first method, using HCl, is rapid and able to activate and deprotect internal and terminal ynones in under 15 minutes. It is best suited for substrates without ⟨-stereocenters or those that are not sensitive to acid-induced ®-amino elimination. The second method, using HCO_2H and NaI, although requiring longer reaction times (6–24 h), is ideal for terminal ynones with sensitive ⟨- and ®-stereocenters. Both procedures are operationally facile and can be carried out in a single vessel. Furthermore, these experimentally simple and environmentally benign conditions are conducive to production of multi-gram quantities of these enaminone scaffolds.[25]

Mechanistic Insights

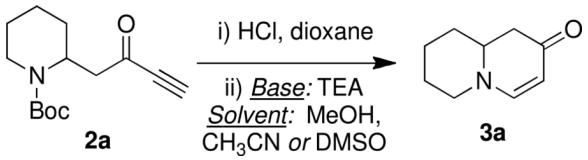
During the course of our investigation several observations have been made *en route* to optimization of this reaction using ynone **2a**. A couple of generalizations can be drawn from this data: 1) when using TFA or other deprotection methods (including basic or neutral conditions) which do not incorporate a halogen, the isolated yields were poor (Scheme 2); and 2) regardless of the deprotection protocol employed, no desired enaminone was obtained without the addition of water or MeOH (Table 2). These preliminary observations lay the groundwork for our mechanistic studies.

By isolating the pre-cyclized intermediates (**4** and **5**, Figure 7) and verifying a complete consumption of the ynone moiety, the first stipulation (*i.e.* the need for a halide source while deprotecting the Boc-group) became clear. In sufficiently acidic conditions, halides add into the ynone group forming a vinyl halide that readily undergoes ring closure to form the

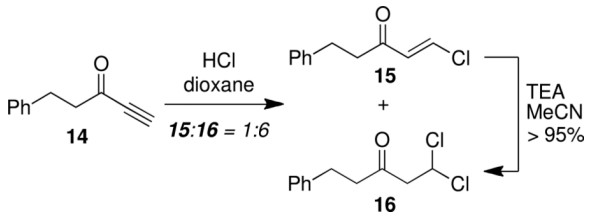
desired enaminone. When the ynone remains intact cyclization is not efficient and intermolecular processes (*i.e.* polymerization) predominate. Therefore, pre-activation is required for a successful reaction.

The discovery that the ynone group was transformed in the presence of halogenic acids demanded a reevaluation of our originally proposed 6-*endo*-dig mechanism. With direct evidence for the formation of halides **4** and **5**, a direct 1,4-addition 6-*endo*-trig cyclization/ halide elimination would be one plausible mechanism (Pathway A, Figure 7). We were initially impressed, however, by the strong solvent dependence of this reaction. When the reaction was carried out in bulky alcoholic (*s*-BuOH or *i*-PrOH) or non-nucleophilic solvents (CH_2Cl_2 or THF) the reaction was significantly impaired. On the other hand, the use of water or MeOH was highly beneficial and independent of the mode of deprotection. In our first disclosure of this reaction we proposed a mechanism in which an oxygen nucleophile plays a direct role in bond making and bond breaking.16 Therein, we suggested an addition of MeOH into vinyl chloride (**9**) which, upon extrusion of the chloride ion, the resultant oxonium intermediate **12** could undergo ring closure in a 6-*exo*-trig fashion (Figure 8, Pathway B).

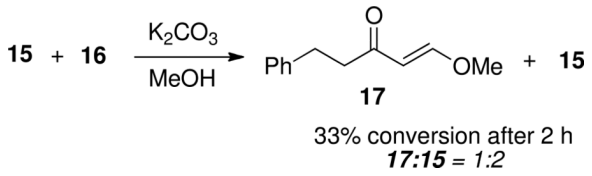
In an attempt to gain mechanistic insight through detecting transient intermediates, we dissolved the mixture of **4** and **5** in methanol-d_4 and monitored the reaction mixture via ^1H NMR after adding a solution of K_2CO_3 drop-wise. Dichloride **5** was first converted into vinyl chloride **9** and subsequent additions led to the formation of enaminone **3a** with no other detectible intermediates. When vinyl iodide analog of **4**, generated from NaI and HCO_2H, was subjected to these same conditions the product was also formed with no detectable intermediates. Although Pathway B provided a plausible explanation for the aforementioned solvent effects, dissimilarities in the solubilizing powers of each solvent would still need to be ascertained. Impaired yields would be expected if the protonated amine intermediates (**4** and **5**) or the base (K_2CO_3) were poorly soluble. Whether or not a nucleophilic solvent was necessary, however, was difficult to directly assess due the insolubility of the reaction constituents in most organic solvents. To answer this question, we explored alternative organic bases that we expected would allow the reaction to be carried out in non-nucleophilic solvents. Our first success demonstrated that triethylamine (TEA) could be used instead of K_2CO_3 (eq 7). As hoped, this base was not only compatible with MeOH but could be used with non-nucleophilic solvents, such as CH_3CN and DMSO, resulting in the formation of enaminone **3a**. Since these solvents are hygroscopic, adventitious water could potentially facilitate the cyclization in a catalytic manner. To rule out this possibility, we constructed ynone **14** to determine the fate of the electrophile in the absence of a tethered nitrogen nucleophile. Following treatment with 4N HCl the residue was dissolved in CH_3CN and TEA was added (eq 8). The NMR spectrum revealed vinyl chloride **15** as the sole product. Moreover, upon addition of excess D_2O, the vinyl chloride remained intact. Clearly, trace amounts of water were not facilitating the cyclization when the reaction was carried out in CH_3CN.



(7)



(8)



(9)

Delving further we examined the reactivity of intermediates **15** and **16** in the presence of methanolic K_2CO_3. If MeOH facilitates the cyclization through a conjugate addition it would be expected that the isolated vinyl halide (**15**) would be consumed more rapidly than the vinyl chloride **4** could form the enaminone. In other words, if the rate of amino cyclization is faster than the addition of MeOH, the former process would obviate the latter. To test this, a mixture of intermediates **15** and **16** were incubated in MeOH and K_2CO_3 (eq 9). After 2 hours the composition of the crude reaction mixture consisted of a 1:2 mixture of vinyl ether **17** and unreacted vinyl chloride **15** (33% conversion). Thus, the addition of MeOH to the vinyl chloride is much slower than the cyclization process which occurs in less than 5 minutes. From this data, it is reasonable to suggest that the addition of MeOH into a vinyl chloride should not be invoked in the reaction mechanism. Thus, we suggest that these results are strong evidence for a direct 6-*endo*-trig mode of cyclization (Pathway A, Figure 7).

Conclusions

We have developed a practical route to non-racemic 6- and 7-membered enaminones starting from amino acids, providing a complementary approach to preexisting methods. Using this approach, asymmetry can be derived from the rich supply of commercially available amino acids. The key reaction and final step in this sequence is a novel one-flask deprotection/cyclization reaction of Boc-aminoynones. Two methods were developed to achieve the Boc-deprotection that are suitable for different substrates. The use of 4N HCl in dioxane is most fitting for internal ynones or those without sensitivity to acid-mediated side reactions. Alternatively, for those substrates that have enolizable stereocenters or are susceptible to acid-promoted ®-amino elimination (*retro*-Michael) processes, NaI and HCO_2H are well-suited. The latter conditions provide a mild alternative and work best for terminal ynones. Both protocols are economic and operationally facile having no need for dry solvents/reagents and can be conducted at room temperature. Furthermore, both methods can be carried out on multi-gram scale with comparable yields.

The substrate scope of this reaction was also assessed. It appears that this reaction is general for the construction of 6- and 7-membered enaminones. When the deprotection conditions are judiciously chosen, monocyclic and bicyclic heterocycles can be obtained from amino-

ynones in high enantiomeric or diastereomeric purity. Many of the heterocyclic scaffolds reported here, though structurally simple, are unprecedented in the literature.

The mechanism of the final cyclization sequence has also been investigated. The success of this reaction relies on the conversion of the ynone moiety into a vinyl halide species and trapping of the protected amine as an ammonium salt following Boc-degradation. This pre-activation, allows for an efficient intramolecular 1,4-addition once the free amine is released upon the addition of base. Thus, this reaction is thought to proceed through a 6-*endo*-trig ring-closing process.

Experimental Section

(2*S**,4*R**)-*tert*-Butyl 4-(Benzyloxy)-2-(2-(methoxy(methyl)amino)-2-oxoethyl)-pyrrolidine-1-carboxylate (1c)

Warning: Large amounts of diazomethane were used for this transformation. Proper care should be taken when handling this highly explosive reagent. All glassware used was free of cracks, scratches or ground-glass joints and a blast shield was used. (2*S**,4*R**)-4-(Benzyloxy)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (4.41g, 13.8 mmol, 1.00 equiv) was taken into THF (80 mL) with stirring and cooled to 0 °C with an ice bath. The reaction solution was treated with TEA (2.09 mL, 15.1 mmol, 1.10 equiv) and allowed to react for 15 min to fully deprotonate the carboxylic acid. With the addition of ethyl chloroformate (1.31 mL, 13.8 mmol, 1.00 equiv), a thick white precipitate formed. Stirring was continued for 15 min then stopped. In a separate flask, an ice-cold ethereal solution of diazomethane was prepared and, without stirring, was carefully decanted into the freshly prepared anhydride reaction flask using a glass funnel. The reaction solution was lightly stirred for 4 seconds then stirring was stopped. The mixture was allowed to warm to room temperature and react overnight. Any additional diazomethane was carefully quenched with 0.5 N acetic acid (25 mL). The drop-wise addition of saturated sodium bicarbonate regulated the solution back to a basic pH 8–9 with gentle stirring. The organic and aqueous layers were separated. The organic phase was washed twice each with saturated sodium bicarbonate and brine then dried over sodium sulfate. The solvent was evaporated under reduced pressure and placed under high vacuum overnight. The diazoketone (3.71 g, 10.7 mmol, 1.00 equiv) was taken into THF (50 mL) and cooled to 0 °C. Foil was used to cover the reaction flask so as to exclude light from the reaction solution. To this was added freshly distilled *N*,*O*-dimethylhydroxylamine (1.96 g, 32.1 mmol, 3.00 equiv). In a separate foil covered flask, silver trifluoroacetate (240 mg, 1.07 mmol, 0.100 equiv) was dissolved in TEA (30 mL). This solution was added to the diazoketone mixture over 30 min. The reaction temperature was allowed to slowly warm to room temperature and the solution was stirred overnight. To the reaction mixture was added activated charcoal (~2 g) and the reaction mixture was stirred for 5 min and filtered. The filtrate was concentrated and the residue redissolved in EtOAc. To this was added activated charcoal (~2 g) and the process repeated. When the filtrate had been concentrated a second time the residue was purified via SiO_2 flash chromatography using 35% EtOAc/hexanes as eluent affording the title compound as a white solid (3.75 g, 72%): mp 69.5–70.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (1:1 mixture of rotamers) 1.46 (s, 18H), 1.95–2.03 (bm, 2H), 2.30–2.38 (bm, 2H), 2.44–2.54 (bm, 2H), 3.03–3.16 (m, 2H), 3.16 (s, 6H), 3.41–3.56 (m, 3H), 3.67 (s, 6H), 3.67–3.75 (m, 1H), 4.09–4.14 (bm, 2H), 4.27–4.34 (bm, 2H), 4.46–4.54 (m, 4H), 7.26–7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 32.0, 36.4, 36.9, 37.4, 38.1, 51.1, 51.9, 52.9, 61.2, 70.8, 75.7, 76.4, 79.3, 79.7, 127.6, 127.6, 128.4, 138.1, 154.5, 172.1, 172.4; IR (neat) 2974, 1693, 1665, 1397, 1160, 1118 cm^{-1}; HRMS (ESI^+) *m/e* calc'd for $[M+H]^+$ $C_{20}H_{31}N_2O_5$: 379.2233, found 379.2222.

tert-Butyl 3-(2-(Methoxy(methyl)amino)-2-oxoethyl)morpholine-4-carboxylate (1f)

2-(4-(*tert*-Butoxycarbonyl)morpholin-3-yl)acetic acid (980 mg, 4.0 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (100 mL) under an argon atmosphere and cooled to −15 °C. To this solution was added *N*,*O*-dimethylhydroxylamine•HCl (430 mg, 4.4 mmol, 1.1 equiv) and *N*-methylmorpholine (0.49 mL, 4.4 mmol, 1.1 equiv) followed by EDCI (840 mg, 4.4 mmol, 1.1 equiv). The reaction mixture was then allowed to come to room temperature. After 2 h, the reaction was again cooled to 0 °C and quenched by the addition of an ice cold 10% HCl solution (25 mL) and allowed to stir at this temperature for 5 min. The reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with saturated $NaHCO_3$ (x1), dried over Na_2SO_4, filtered and concentrated. Purification via SiO_2 flash chromatography using 80% EtOAc/hexanes as the eluent afforded the title compound as a white solid (1.14g, 99%): mp 71.9–72.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.54–2.64 (bm, 1H), 2.97–3.17 (bm, 2H), 3.17 (s, 3H), 3.45 (dt, *J* = 5.8, 2.8 Hz, 1H), 3.58 (dd, *J* = 11.7, 2.2 Hz, 1H), 3.71 (s, 3H), 3.71–3.88 (m, 3H), 4.41–4.46 (bm, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 31.1, 32.1, 39.2, 48.5, 61.3, 66.8, 69.1, 80.1, 154.5, 171.9; IR (neat) 2975, 1696, 1663, 1408, 1171, 1106 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{13}H_{25}N_2O_5$: 289.1763, found 289.1770.

tert-Butyl Benzyl(3-(methoxy(methyl)amino)-3-oxopropyl)carbamate (1l)

A round-bottomed flask was charged with benzylamine (8.00 mL, 73.1 mmol, 3.00 equiv) and cooled to –40 °C. Methyl acrylate (2.20 mL, 86.1 mmol, 1.00 equiv) was added dropwise over 5 min and the reaction was stirred at this temperature (–40 °C) for 24 h. Excess benzylamine was distilled off under reduced pressure. The remaining residue was dissolved in methanol (50 mL) and di-*tert*-butyldicarbonate (6.40 g, 29.2 mmol, 1.20 equiv) was added slowly. The reaction mixure was stirred for another 30 min and the solvent was removed *in vacuo*. The concentrated reaction mixture was redissolved in CH_2Cl_2 (300 mL) and washed with cold 10% HCl (100 mL × 2) and brine (100 mL × 2). The organic layer was dried with $MgSO_4$, concentrated and purified via SiO_2 flash chromatography (25% EtOAc in hexanes) to afford 6.62 g (88%) of the methyl ester as a clear viscous oil. This oil was converted to the corresponding Weinreb amide using the procedure reported by Williams *et al.*20 The methyl ester (6.62 g, 22.6 mmol, 1.00 equiv) and *N*,*O*-dimethylhydroxylamine•HCl (3.42 g, 35.0 mmol, 1.55 equiv) were dissolved in anhydrous THF (40 mL) at room temperature under N_2. This mixture was cooled to −20 °C and *iso*-propylmagnesium chloride (34 mL, 68 mmol, 3.0 equiv, 2.0 M in THF) was added dropwise over 10 minutes. The temperature was kept between −10 and −20 °C for 30 minutes. After the reaction was judged complete by TLC, it was quenched by the addition of a saturated solution of NH_4Cl (40 mL). The product was extracted with EtOAc (x3) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified via SiO_2 flash chromatography (40% EtOAc/hexanes) to give 6.29g (86%) of Weinreb amide **1l** as a clear viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (1:1 mixture of rotamers) 1.44 (s, 9H), 1.50 (s, 9H), 2.58–2.63 (bm, 2H), 2.67–2,72 (bm, 2H), 3.15 (s, 6H), 3.43–3.48 (bm, 2H), 3.51–3.55 (bm, 2H), 3.63 (bs, 6H), 4.48 (s, 4H), 7.22–7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 31.2, 32.1, 42.8, 43.1, 50.6, 51.6, 61.2, 61.3, 79.8, 127.2, 127.3, 127.8, 128.4, 138.4, 138.8, 155.5, 155.8, 172.5, 172.9; IR (neat) 2974, 1693, 1664, 1413, 1366, 1167 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+$ $C_{17}H_{27}N_2O_4$: 323.1971, found 323.1957.

(2*S**,4*R**)-*tert*-Butyl 4-(Benzyloxy)-2-(2-oxobut-3-ynyl)pyrrolidine-1-carboxylate (2g)

The Weinreb amide **1c** (604 mg, 1.60 mmol, 1.00 equiv) was dissolved in anhydrous THF (30 mL) under an argon atmosphere and cooled to 0 °C. To this reaction vessel, was added dropwise ethynyl magnesium bromide reagent (16.0 mL, 7.98 mmol, 5.00 equiv, 0.5 M in THF) and allowed to come to room temperature. After the reaction was judged complete by

TLC, it was quenched by the addition of an ice cold 10% HCl solution (15 mL) and allowed to stir at this temperature for 5 min. The reaction was diluted with water and extracted with EtOAc (x3). The combined organic layers were washed with saturated $NaHCO_3$ (x1), dried over Na_2SO_4, filtered and concentrated. The title compound was obtained as a colorless oil (503 mg, 92%) after flash chromatography (20% EtOAc/hexanes): ^{1}H NMR (400 MHz, $CDCl_3$) δ (1:1 mixture of rotamers) 1.46 (s, 9H), 1.48 (s, 9H), 1.77–1.87 (bm, 2H), 2.35 (dddd, *J* = 13.3, 7.7, 3.9, 1.0 Hz, 2H), 2.65–2.73 (bm, 2H), 3.16 (bd, *J* = 15.3 Hz, 1H), 3.26 (bd, *J* = 16.9 Hz, 2 H), 3.35–3.42 (m, 3H), 3.56 (bd, *J* = 11.3 Hz, 1H), 3.78 (bd, *J* = 11.6 Hz, 1H), 4.06–4.10 (m, 2H), 4.30–4.38 (bm, 2H), 4.44–4.55 (bm, 2H), 4.50 (bd, *J* = 10.2 Hz, 2H), 7.28–7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 36.9, 38.2, 49.7, 50.9, 51.1, 51.9, 52.2, 70.9, 75.6, 76.1, 78.8, 79.1, 79.7, 80.3, 81.5, 127.6, 127.7, 127.7, 128.5, 137.9, 154.4, 154.5, 185.0, 185.3; IR (neat) 2976, 2091, 1685, 1399, 1367, 1162 cm^{-1}; HRMS (ESI +) *m/e* calc'd for $[M+H]^+$ $C_{20}H_{26}NO_4$: 344.1862, found 344.1854

General procedures for cyclic enaminone formation

Deprotection—METHOD A: The Boc-aminoynone **2** (0.50 mmol) was dissolved in a 4N HCl-dioxane solution (1.5 mL) and allowed to react for 15 min. After this time the dioxane and excess HCl were allowed to evaporate while passing air over the reaction mixture. The remaining solid was placed under vacuum for 15 min and carried on to the cyclization step without further purification. METHOD B: The ynone (0.50 mmol, 1.0 equiv) was dissolved in 5 mL of 98% formic acid under a N_2 atmosphere and NaI (230 mg, 1.5 mmol, 3.0 equiv) was added. Note: For terminal ynones the reaction was left stirring for 6 h. When internal ynones were used the reaction was left for 24 h. The solvent was removed by passing N_2 over the reaction mixture. The remaining residue was placed under vacuum for 15 min and was carried on to the cyclization step without further purification.

Large Scale Modification—When using greater that 1.0 gram of ynone, the desired deprotected amine can be isolated as the ammonium salt by poring the reaction mixture into ether and collecting the precipitate via filtration. METHOD C: The ynone (0.50 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (10 mL) under an argon atmosphere and cooled to −78 °C. A solution of TMS-I (0.50 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (5 mL) was then added dropwise at this temperature. After 20 min at this temperature the reaction was allowed to warm to 0 °C and additional TMS-I (0.50–2.5 mmol) was added until all starting material was consumed (TLC, 25% EtOAc in hexanes). After 20 min the reaction was judged complete and this mixture was concentrated under reduced pressure and placed under vacuum for 15 min.

Cyclization—The deprotected intermediates from Methods A, B and C were dissolved in MeOH (50 mL) and excess K_2CO_3 (a minimum of 5.0 equiv) was added. The reaction times varied depending on the substrate (for enaminones **3d, 3g, 3j, 3k, 3m** and **3n** reactions were stirred for 1 h; for enaminones **3a, 3l, 3p, 3o, 3r** and **3s** reactions were stirred for 3 h; for enaminones **3b, 3c, 3e, 3f, 3h, 3i, 3q, 3t, 3u, 3v, 3w** and **3x** reactions were stirred for 6 h). After the allotted time, CH_2Cl_2 was added, the reaction suction filtered, and the organic solvents concentrated. To the solid residue was added more CH_2Cl_2 and the precipitates were once again filtered away. This residue was purified via flash chromatography to provide pure enaminone. *Large Scale Modification*: When the reaction was complete, the MeOH was removed *in vacuo* and the remaining residue redissolved in brine. The product was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4 and purified via SiO_2 flash chromatography. Note: Several of the enaminones (e.g. **3a, 3d, 3j, 3k**, etc.) were water soluble and could not be purified by this method.

(2*R**,8a*S**)-2-(Benzyloxy)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (3g)

The title compound was obtained as a colorless oil (*Method A, 94%; Method B, 92%)* after flash chromatography (100% acetone): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (ddd, *J* = 13.2, 11.2, 4.5 Hz, 1H), 2.35 (dd, *J* = 16.2, 16.2 Hz, 1H), 2.44–2.51 (m, 2H), 3.60 (d, *J* = 11.8 Hz, 1H), 3.70 (dd, *J* = 11.8, 4.9 Hz, 1H), 4.07 (dddd, *J* = 16.4, 10.9, 5.3, 5.3 Hz, 1H), 4.29 (dd, *J* = 4.5, 4.5 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.99 (d, *J* = 7.1 Hz, 1H), 7.17 (d, *J* = 7.1 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5, 41.4, 55.4, 56.2, 71.0, 77.1, 97.9, 127.6, 128.0, 128.6, 137.5, 149.9, 191.9; IR (neat) 2929, 1631, 1579, 1460, 1306, 1099 cm^{-1}; HRMS (ESI+) *m/e* calc'd for $[M+H]^+C_{15}H_{18}NO_2$: 244.1338, found 244.1332.

(*E*)-2-(4-Iodo-2-oxobut-3-enyl)pyrrolidinium Iodide (7a)

Ynone **2d** (0.50 mmol, 1.0 equiv) was dissolved in 98% formic acid (5.0 mL) under a N_2 atmosphere and NaI (230 mg, 1.5 mmol, 3.0 equiv) was added. After 6 h, Et_2O (200 mL) was slowly added to the reaction mixture allowing a precipitate to form. The precipitate was filtered and washed several times with Et_2O. The filtered precipitate was air dried and used without further purification. To obtain crystals for X-ray analysis, the precipitate was recrystallized from formic acid. See Supporting Information for X-ray crystal structure report. ^{1}H NMR (400 MHz, CD_3OD) δ 1.59–1.69 (m, 1H), 1.82–1.92 (m, 1H), 1.94–2.04 (m, 1H), 1.12–2.20 (m, 1H), 2.97 (dd, *J* = 18.9, 9.8 Hz, 1H), 3.13–3.24 (m, 3H), 3.76–3.83 (m, 1H), 7.16 (d, *J* = 15.2 Hz, 1H), 8.17 (d, *J* = 15.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) 24.6, 31.2, 42.6, 46.6, 56.8, 102.8, 145.2, 196.4; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 1.49–1.58 (m, 1H), 1.74–1.95 (m, 2H), 2.04–2.12 (m, 1H), 3.04 (dd, *J* = 18.7, 9.2 Hz, 1H), 3.04–3.17 (m, 2H), 3.17 (dd, *J* = 18.7, 4.3 Hz, 1H), 3.71–3.78 (m, 1H), 7.21 (d, *J* = 15.3 Hz, 1H), 8.26 (d, *J* = 15.3 Hz, 1H), 8.28 (bs, 1H), 8.85 (bs, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 23.1, 29.7, 41.4, 45.0, 54.3, 104.7, 143.7, 195.4.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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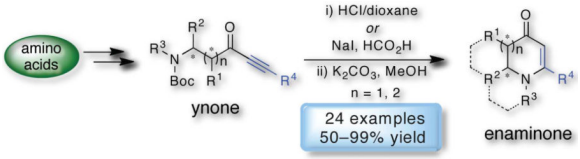


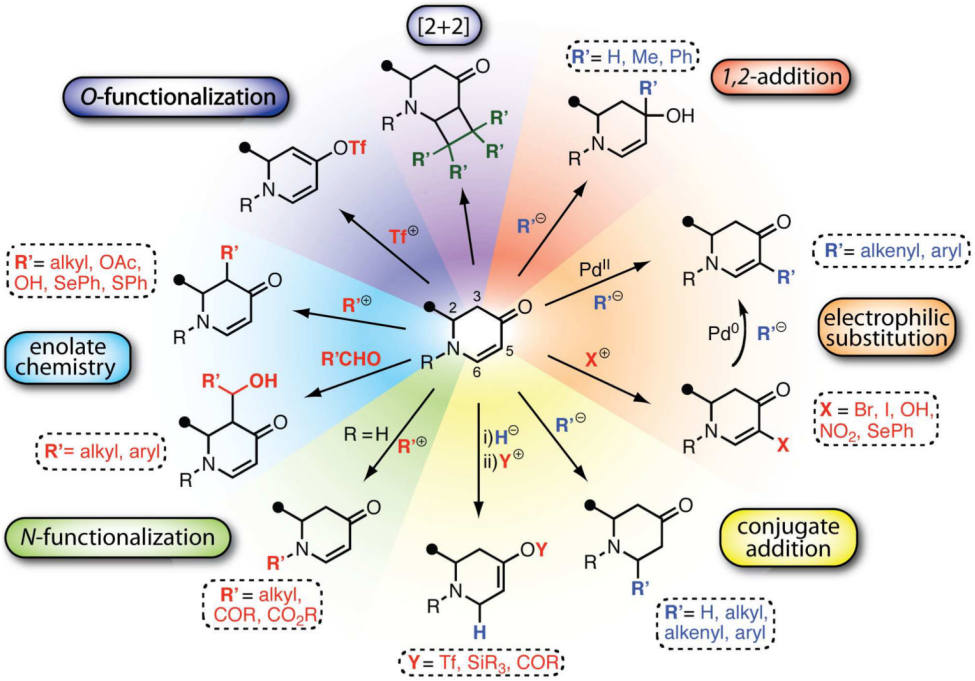


Figure 1.
Select synthetic transformations of the 6-membered cyclic enaminone.

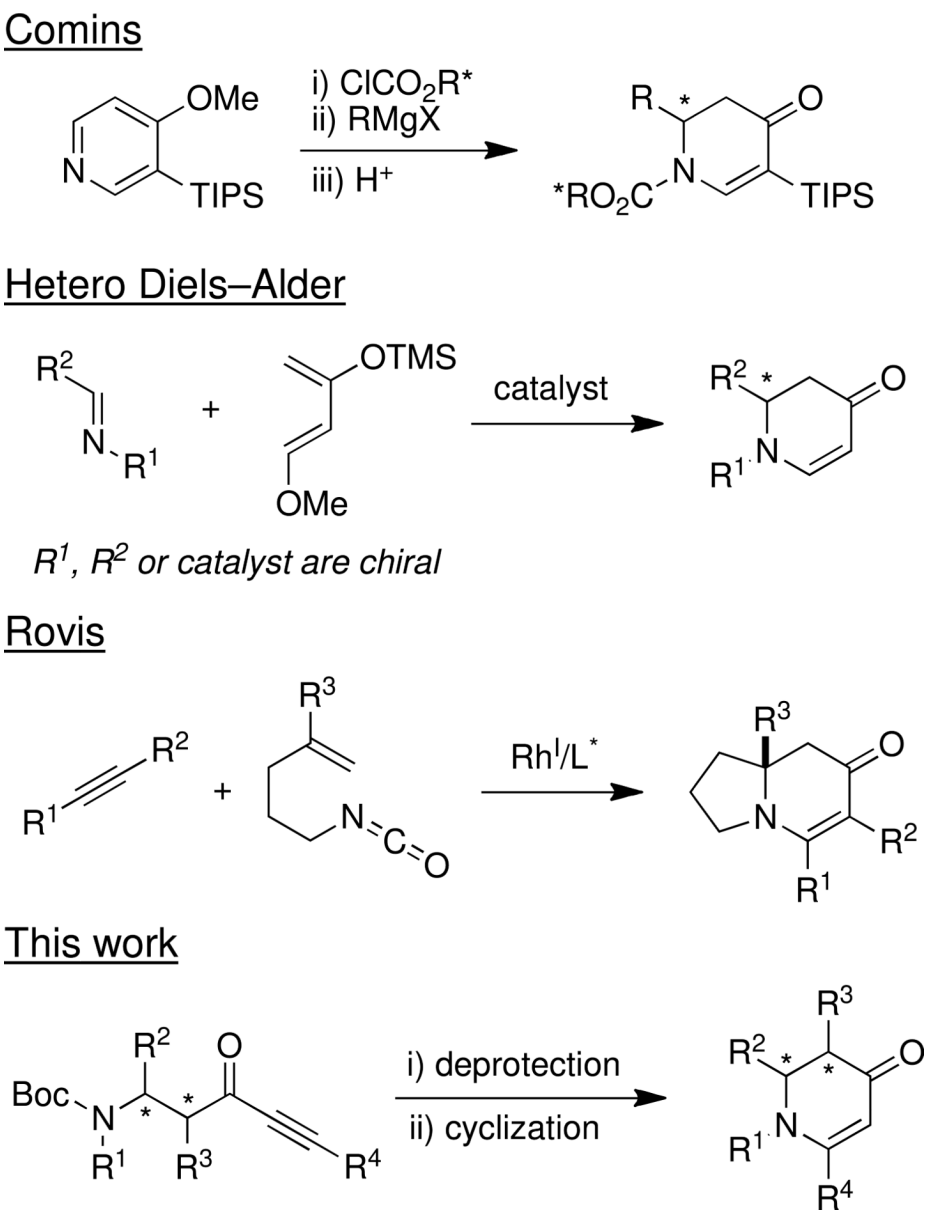


Figure 2.
General approaches to access non-racemic 6-membered enaminones.

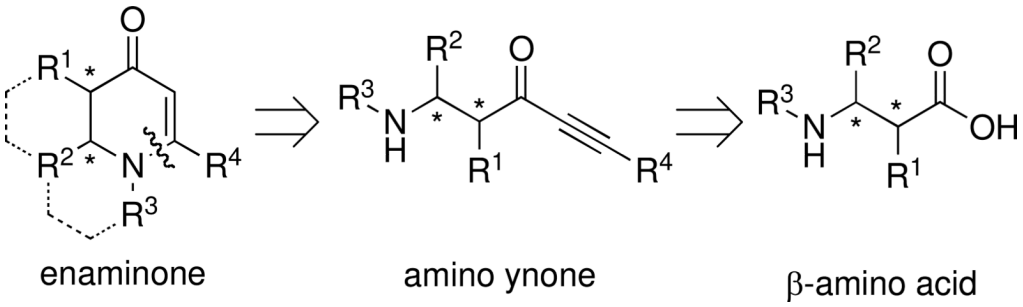


Figure 3.
Retrosynthetic analysis for enaminone construction.

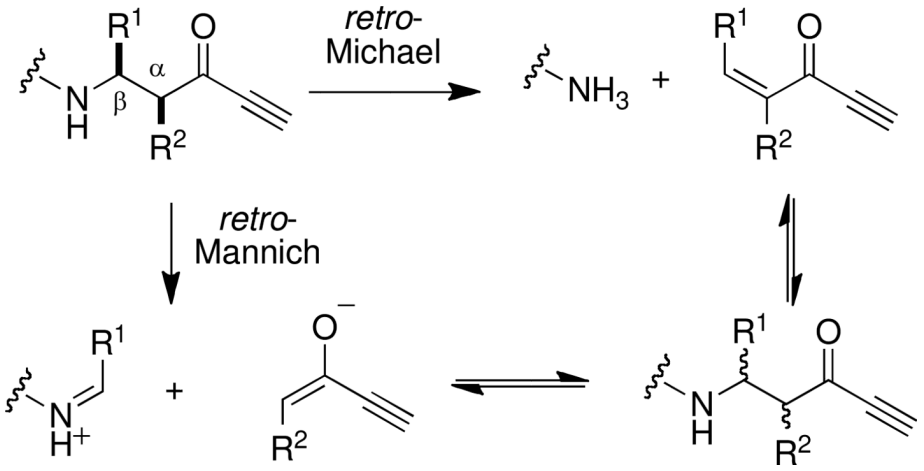


Figure 4.
Potential modes of racemization/epimerization.

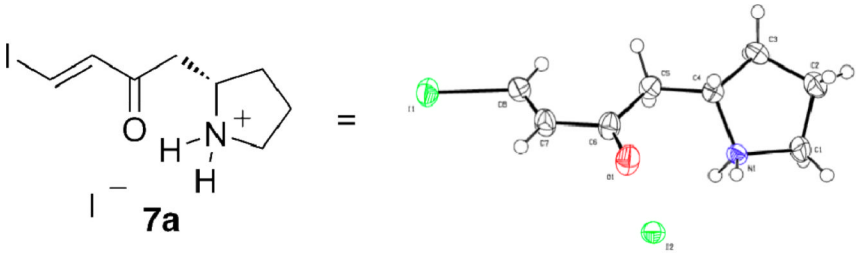


Figure 5.
X-ray crystal structure of vinyl iodide intermediate.

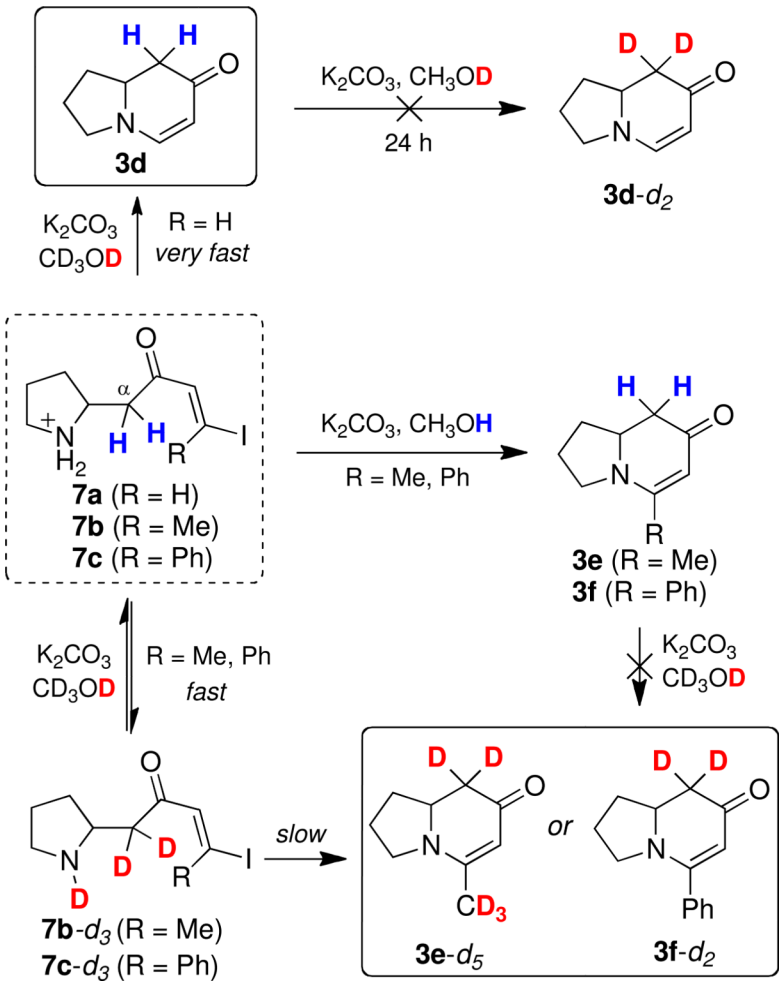


Figure 6.
Deuteration of cyclization intermediates and enaminone products.

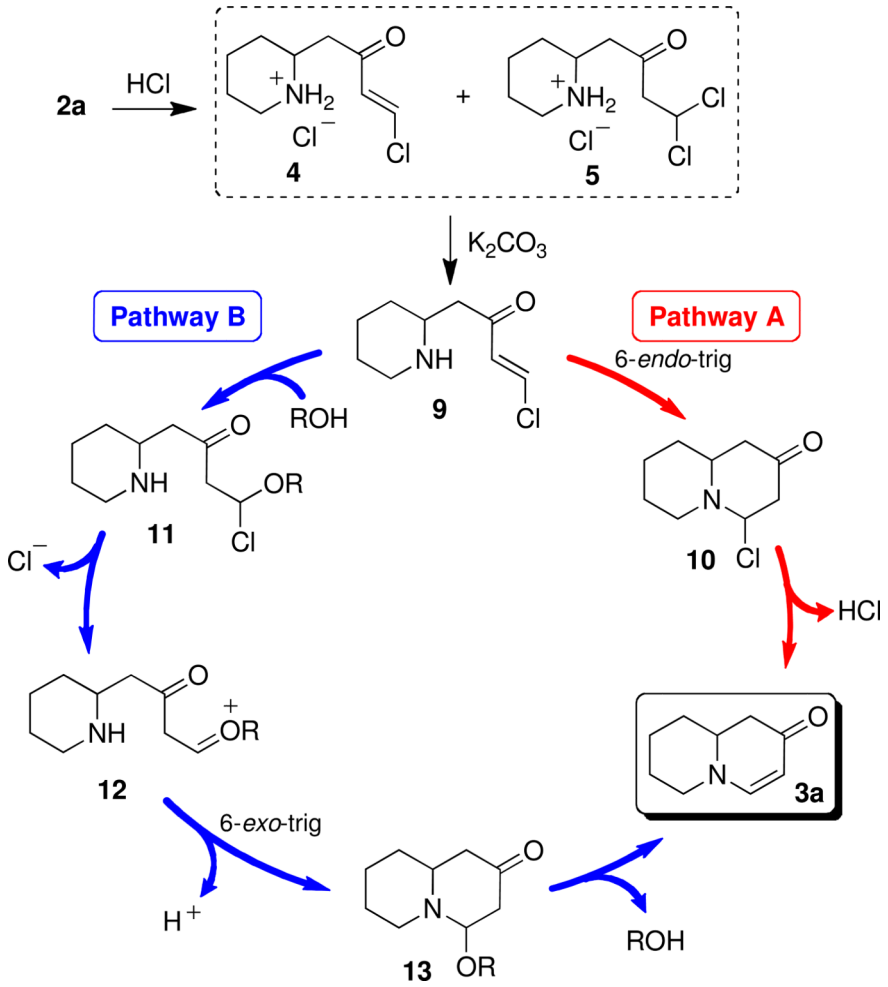
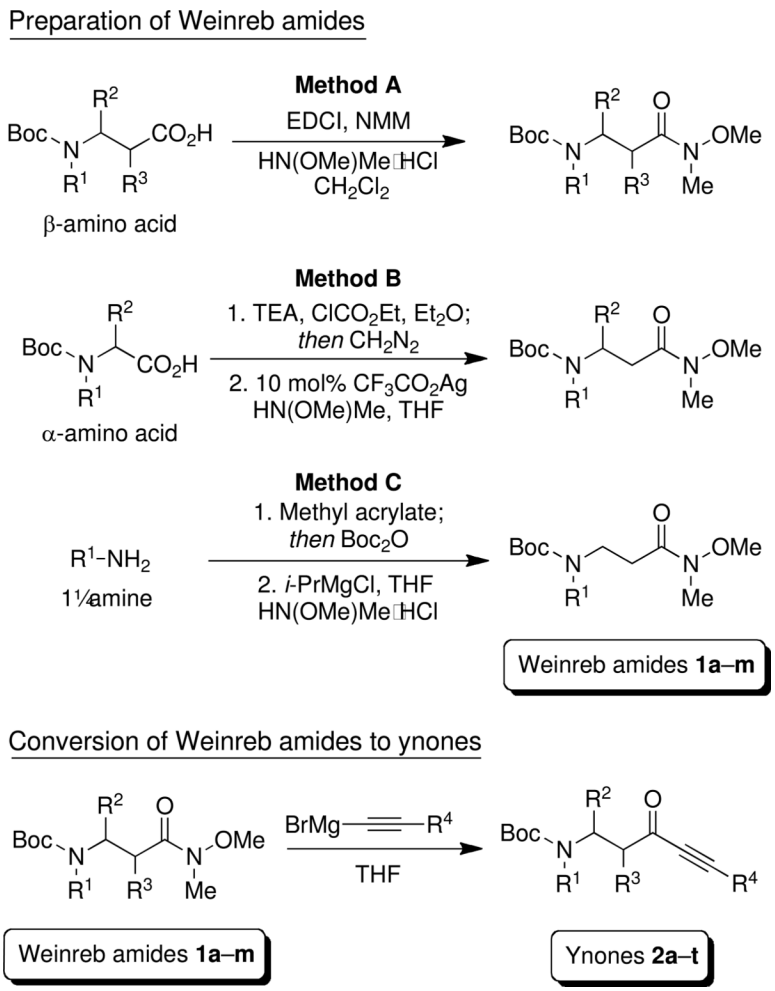
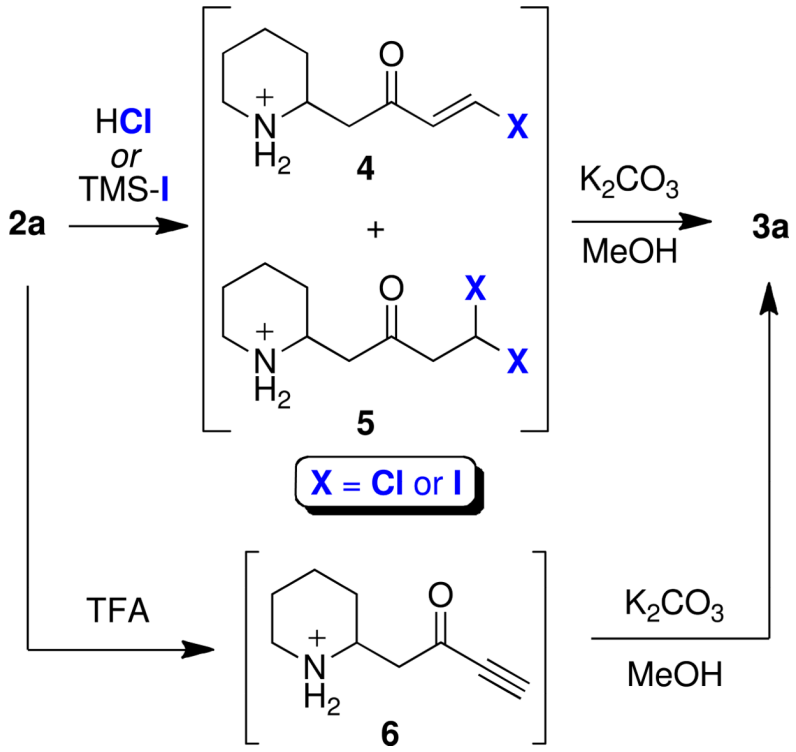


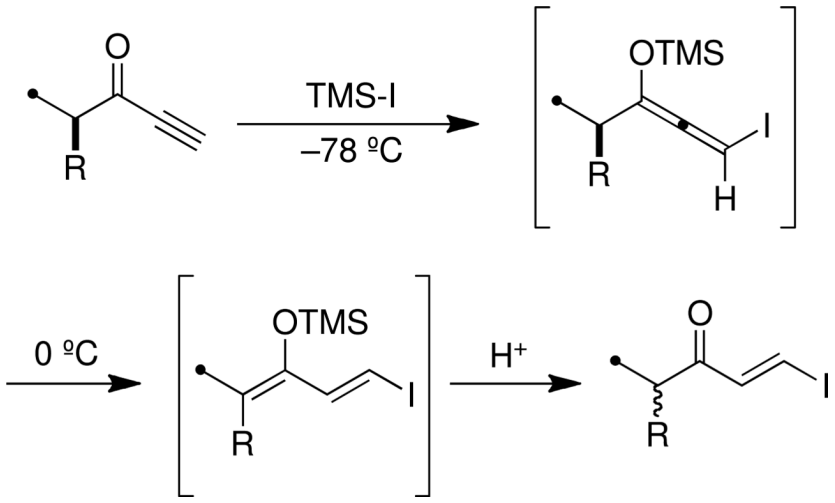
Figure 7.
Possible modes of cyclization.



Scheme 1.
Preparation of ynone intermediates



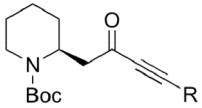
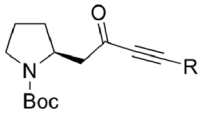
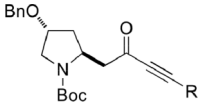
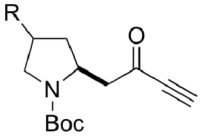
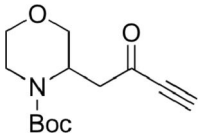
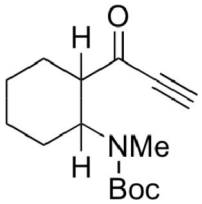
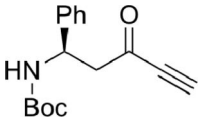
Scheme 2.
Fate of ynone upon Boc-deprotection with HCl, TMS-I and TFA



Scheme 3.
Plausible mechanism for TMS-I–induced α-epimerization of ynones

Table 1

Synthesized ynone substrates and multi-step yields for preparation using methods A, B or C (Scheme 1)

entry	ynone		R	method[a]	overall yield[b]
1		**2a**	H	B	60
2		**2b**	Me	B	62
3		**2c**	Ph	B	60
4		**2d**	H	A, B	95, 68
5		**2e**	Me	A, B	93, 66
6		**2f**	Ph	A, B	92, 66
7		**2g**	H	B	65
8		**2h**	Me	B	64
9		**2i**	Ph	B	60
10		**2j**	α-OH	B	52
11		**2k**	β-OH	B[c]	45
12		**2l**		A	94
13		**2m**	*cis*	A	87
14		**2n**	*trans*	A	87
15		**2o**		A	75

entry	ynone		R	method[a]	overall yield[b]
16		**2p**	H	B	30
17		**2q**	Me	B	39
19		**2r**	H	A	85
20		**2s**	$PhCH_2$	C	67
21		**2t**	Ph	C	46

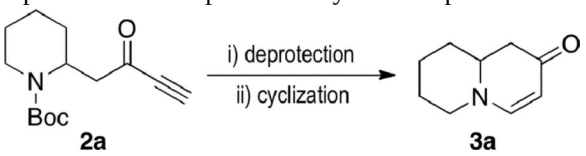
[a] See Scheme 1.

[b] Isolated multi-step yield from commercially available starting materials.

[c] Stereocenter was inverted from Weinreb amide arecursor using the Mitsunobu reaction.

Table 2

Optimization of deprotection/cyclization procedure for the preparation of cyclic enaminones



2a **3a**

entry	i) deprotection	ii) cyclization	time[a]	yield[b]
1	TFA, CH_2Cl_2	CH_2Cl_2, $NaHCO_3$[c]	na[d]	30
2	TFA, CH_2Cl_2	CH_2Cl_2, K_2CO_3	20 h	0
3	TFA, CH_2Cl_2	THF, K_2CO_3	20 h	0
4	TFA, CH_2Cl_2	CH_2Cl_2, H_2O, K_2CO_3	5 h	38
5	4N HCl/dioxane	CH_2Cl_2, K_2CO_3	20 h	0
6	4N HCl/dioxane	THF, K_2CO_3	20 h	0
7	4N HCl/dioxane	CH_2Cl_2, H_2O, K_2CO_3	1 h	74
8	4N HCl/dioxane	THF, H_2O, K_2CO_3	1 h	75
9	4N HCl/dioxane	MeOH, K_2CO_3	15 min	87
10	TMS-I, CH_2Cl_2	MeOH, K_2CO_3	30 min	95

[a] Reaction time of cyclization step.

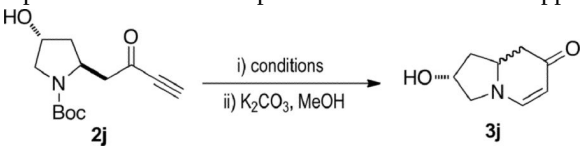
[b] Isolated yield.

[c] Sat. aqueous $NaHCO_3$.

[d] Reaction proceeded in a separatory funnel upon workup.

Table 3

Optimization of Boc-deprotection conditions to suppress β-epimerization



2j 3j

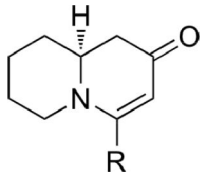
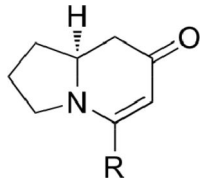
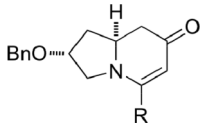
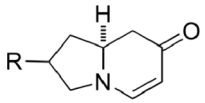
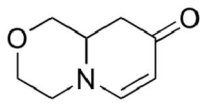
entry	conditions	yield %[a] (dr)[b]
1	4N HCl, dioxane	77 (85:15)
2	TFA (neat)	31 (67:33)
3	TFA/CH_2C1_2 (1:1)	18 (88:12)
4	1N HCl, ether	36 (67:33)
5	i) TBSOTf, 2,6-lutidine, CH_2Cl_2 ii) TBAF	0
6	TESOTf, 2,6-lutidine, CH_2Cl_2	21 (83:17)
7	CAN, CH_3CN, reflux	0
8	TMS-I (3 equiv), CH_2Cl_2, 0 °C	99 (75:25)
9	TMS-I (1 equiv), CH_2Cl_2, −78 to 0 °C; *then* TMS-I (2 equiv)	60 (94:6)
10	HCO_2H, rt	0
11	NaI (3 equiv), HCO_2H, rt	93 (>95:5)

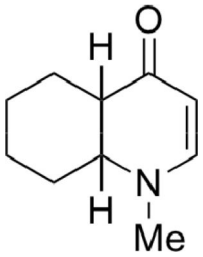
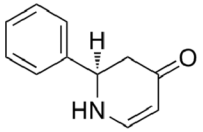
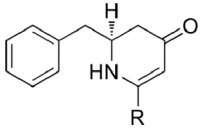
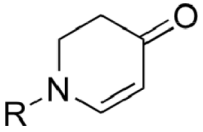
[a] Isolated yield.

[b] Diastereomeric ratio (dr) determined by ^{1}H NMR integration.

Table 4

Six-membered enaminone substrate scope

entry	enaminone		R	method[a]	yield[b]	er[c] or dr[d]
1		**3a**	H	A	87	97:3
				B	90	>98:2
2		**3b**	Me	A	87	73:27
				B	80	73:27
3		**3c**	Ph	A	91	58:42
				B	85	69:31
4		**3d**	H	A	89	70:30
				B	96	98:2
5		**3e**	Me	A	87	-
6		**3f**	Ph	A	89	-
7		**3g**	H	A	94	67:33
				B	92	>95:5
8		**3h**	Me	A	87	63:37
				B	94	68:32
9		**3i**	Ph	A	85	63:37
				B	88	60:40
10		**3j**	α-OH	A	77	85:15
				B	93	>95:5
				C	94	96:4
11		**3k**	β-OH	A	60	60:40
				B	95	92:8
				C	70	86:14
12		**3l**		A	80	-
				B	95	-

entry	enaminone		R	method[a]	yield[b]	er[c] or dr[d]
13		**3m**	cis	A	96	80:20
				B	83	94:6
				C	80	67:33
14		**3n**	trans	A	99	>95:5
				B	82	>95:5
15		**3o**		A	50	>99:1
				B	50	>99:1
17		**3p**	H	A	92	>95:5
18		**3q**	Me	A	96	>95:5
20		**3r**	H	A	70	-
				B	92	-
21		**3s**	$PhCH_2$	A	50	-
				B	86	-
22		**3t**	Ph	A	50	-
				B	70	-

[a] Method A: i) 4N HCl/dioxane. 15 min. ii) K_2CO_3, MeOH; Method B: i) NaI (3 equiv), formic acid. 6–24 h. ii) K_2CO_3, MeOH; Method C: i) TMS-I. CH_2Cl_2, −78 to 0 °C. ii) K_2CO_3, MeOH.

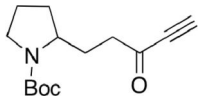
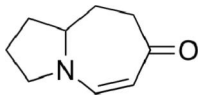
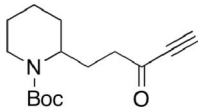
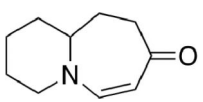
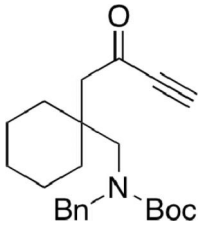
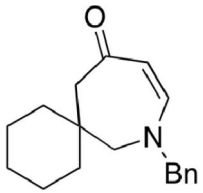
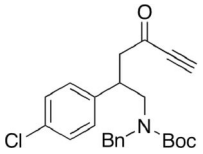
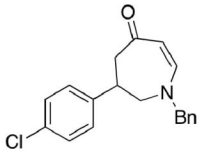
[b] Isolated yield.

[c] Chiral HPLC.

[d] ^{1}H NMR integration.

Table 5

Seven-membered enaminone preparation

entry	ynone[a]		enaminone		method[b]	yield[c]
1		**2u**		**3u**	A	60
					B	64
2		**2v**		**3v**	A	64
					B	63
3		**2w**		**3w**	A	81
					B	84
4		**2x**		**3x**	A	66
					B	65

[a] See Supporting Information for the synthesis of ynones **2u–2x**.

[b] Method A: i) 4N HCl/dioxane, 15 min. ii) K_2CO_3, MeOH; Method B: i) NaI (3 equiv), formic acid, 6–24 h. ii) K_2CO_3, MeOH;

[c] Isolated yield.