Efficient Construction of Stereodefined α -Alkylidene Aza-cycloketones via β -Amino-alkenyllithium: Straightforward and Protection-Free Synthesis of Allopumiliotoxin 267A

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Received March 4, 2009

LETTERS 2009 Vol. 11, No. 9 2011–2014

ORGANIC



Intramolecular nucleophilic acyl substitution of highly functionalized β -amino-alkenyllithium species provided facile access to α -alkylidene aza-cycloketones with defined olefin geometry and rich structural diversity. A concise total synthesis of allopumiliotoxin 267A has been accomplished in 5 steps from 4 featuring this key transformation.

 α -Alkylidene cycloketones are versatile building blocks in organic synthesis,¹ as well as common structural features of many biologically active compounds.² Conventional methods such as Wittig,³ Horner–Wadsworth–Emmons^{3b,c} and Julia⁴ reactions are not effective ways to construct the exocyclic

olefin due to the difficulty in preparing the corresponding ylides or sulfones, and the intrinsic low reactivity of these species. Catalyzed or noncatalyzed aldol-dehydration sequences are alternative approaches with varying degrees of success.⁵ Unfortunately, the olefin geometry is often noncontrollable, ^{5a,b,6} or limited to the more stable *E*- isomers. Bis-condensation was also a serious side-reaction due to the

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higher reactivity of monocondensation product, even if the parent ketone was used in a large excess.⁷ Moreover, the issue of regioselectivity may arise for nonsymmetric ketones. Alternatively, Sato developed an alkyne-based intramolecular nucleophilic acyl substitution (INAS) reaction using a Ti(II) reagent, which afforded exclusively *E*- product.⁸ Falck and co-workers devised an interesting homologation—condensation cascade involving *tert*-trihalomethylcarbinols.⁹ On the other hand, only one recent report by Overman provided access to α -*Z*-alkylidene cycloketones, using a two-step sequence (R^{*Z*} = alkyl).¹⁰ Herein we report a convenient, flexible and stereospecific approach via highly functionalized alkenyl-lithium, offering a wider choice of alkene substitutions (R^{*Z*} = alkyl, aryl).

We envisaged that α -alkylidene aza-cycloketones were accessible from sequential I–Li exchange of vinyl iodide **A** (Figure 1, X = NR) and cyclization of the β -amino-



alkenyllithium species onto the ester. Since the alkene geometry of **A** could be readily established by known methods,¹¹ this route is amenable to both E- and Z- products with firm control of stereochemistry. Moreover, the site of

the cyclization is unambiguous, and double condensation

would not interfere. Nevertheless, in view of the high

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reactivity of organolithium species toward various functional groups including alkoxycarbonyl, this approach is non-trivial.¹²

Optimization of reaction parameters was carried out using substrates 1a-d to evaluate the effects of solvent, lithiating reagent, and the ester group (Table 1). The optimal results

Table 1. Optimization of INAS Reaction of β -Amino-alkenyllithium^{*a*}

	Bn N R'Li RO ₂ C Solvent, -78 °C		Bn N	
	1a-d		2a	
entry	1, R	R'Li (equiv)	solvent	2a (%) ^b
1	1a , Me	ⁿ BuLi (1.0)	THF	67
2	1a , Me	ⁿ BuLi (1.2)	THF	60
3^c	1a , Me	ⁿ BuLi (1.0)	THF	59
4	1a , Me	^t BuLi (2.0)	THF	29
5	1a , Me	MesLi (2.0)	THF	complex
6	1b, Et	ⁿ BuLi (1.0)	THF	65
7	1c , ^{<i>t</i>} Bu	ⁿ BuLi (1.0)	THF	29
8	$1d$, CH_2CF_3	ⁿ BuLi (1.0)	THF	53
9	1a , Me	ⁿ BuLi (1.0)	Et_2O	24
10	1a , Me	ⁿ BuLi (1.0)	Tol	20
11^d	1a , Me	ⁿ BuLi (1.0)	THF	56

^{*a*} Conditions: 0.5 mmol **1**, 5 mL THF, -78 °C, 10-30 min, unless noted otherwise. ^{*b*} Isolated yields. ^{*c*} Reaction run and quenched at -110 °C. ^{*d*} With 2 equiv TMEDA as the additive.

were obtained by using 1.0 eq. "BuLi in THF for methyl/ ethyl esters at -78 °C. Additional amount of this lithiating reagent or lower temperature (-110 °C) resulted in inferior yields (entries 2, 3). It is noteworthy that "BuLi metalated alkenyl iodide preferentially, instead of attacking the ester. In addition, β -elimination was not observed, even though the tertiary amine moiety of alkenyllithium intermediates cannot be stabilized by *N*-deprotonation.¹³ In contrast to some other reports, 'BuLi^{14a,b} and MesLi^{14c} were both inferior (entries 4, 5). With regard to the ester moiety, bulky 'Bu was found to be detrimental (entry 7). The slightly electronwithdrawing CH₂CF₃ group produced a moderate yield, although trifluoroethoxy anion is a better nucleofuge than ordinary alkoxides (entry 8). THF represented the most suitable solvent, shifting to ether or toluene lowered the yield considerably (entries 9, 10). Addition of TMEDA (2 equiv) offered no advantage (entry 11). The reaction time was also

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critical, prolonged exposure complicated the reaction, presumably due to the base-labile nature of the enone product.

With this protocol in hand, we examined its scope and limitations (Table 2). Substrates with various substitution

Table 2. Scope of the INAS Reaction of β -Amino-alkenyllithium



^a Conditions: See Table 1. ^b Isolated yields. ^c Unstable products.

patterns gave moderate to excellent yields of functionalized piperidin-4-ones. Oxygenated side chains including those at the allylic position were tolerated, allowing space for further modifications.¹⁵ Notably, additional α -substitutions to the ester enhanced the yields, which is a desirable characteristic for the synthesis of complex molecules. Importantly, α -*Z*-alkylidene cycloketones were accessible via this protocol (entries 11–14). The olefin geometry was unambiguously established by comparison with authentic samples of *E*-isomers and by NOE experiments (see Supporting Informa-

tion). Aliphatic and aryl esters were both suitable electrophiles for the INAS process. Seven- and five-membered ring systems can be obtained in fair to good yields (entries 6–10). Substrates derived from α -amino acids formed elusive products which decomposed during purification, while fusedcyclopentanone products were relatively more stable and thus isolable (entries 7–10).

Allopumiliotoxin 267A (**3**), a representative of amphibian alkaloids, has been the goal of multiple synthetic studies which stimulated the development of many elegant and useful synthetic methodologies.^{16,8a} As our continuing efforts in the synthesis of polyhydroxylated alkaloids,¹⁷ we initiated a novel total synthesis of **3** based on the present protocol, for which **1h** has served as an excellent model substrate with promising results.

Chiral *E*-2-iodoallylic alcohol 4^{16b} was conveniently prepared by the reported route, using Evans asymmetric alkylation as the key step to establish the stereogenic center. Azide displacement under Mitsunobu conditions (DPPA, DEAD, Ph₃P) followed by Staudinger reaction¹⁸ yielded amine 5. One-pot alkylation-epoxide opening with 6^{17c} assembled the pyrrolidine unit bearing a chiral quaternary side chain regio- and stereospecifically in high yield (87%). Conforming to Baldwin's rule,¹⁹ only the 5-exo-tet product was formed with complete inversion of configuration at C-3 of compound 6. Protection of the tertiary carbinol with SEM²⁰ and subsequent INAS reaction of the densely functionalized 8 smoothly afforded enone 9 (74%). Removal of SEM under acidic conditions (2 M HCl-MeOH) gave 10 in a moderate yield, while an attempted deprotection using TBAF resulted in complex mixtures due to the basesensitivity of 9.



As resorting to protection is both aesthetically and practically unappealing,²¹ we further explored direct INAS reaction of unprotected **7** using 2 equiv of "BuLi (Scheme 2). Gratifyingly, the extra "BuLi exchanged the acidic hydroxyl proton first, and the cyclization gave an equally good yield

⁽¹⁵⁾ See, for example, transformations via Negishi coupling: Hirashima, S.; Aoyagi, S.; Kibayashi, C. J. Am. Chem. Soc. **1999**, *121*, 9873.





(70%) of the desired intermediate **10** { $[\alpha]^{22}_{D}$ -6.8 (*c* 1.12, CHCl₃), lit.^{8a} $[\alpha]^{25}_{D}$ -6.4 (*c* 0.96, CHCl₃)}. Notably, the formation of the bicyclic indolizidine skeleton and the stereospecific incorporation of the chiral side chain were

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integrated into only two steps, which is a significant improvement to our previous formal synthesis.^{17c} Finally, substrate-directed²² reduction using Me₄NBH(OAc)₃ completed the total synthesis of **3** {[α]²²_D +34.6 (*c* 1.15, MeOH), lit.^{5a} [α]²⁵_D +31 (*c* 0.22, MeOH)}, in only 5 linear steps from the known compound **4**. To our knowledge, this is one of the most straightforward routes to **3**, and the only one without using protective groups.

In summary, an INAS reaction involving the highly functionalized β -amino-alkenyllithium species provided facile access to α -alkylidene aza-cycloketones with defined olefin geometry and rich structural diversity. Synthetically challenging α -Z-alkylidene cycloketones can be prepared efficiently in this manner. A concise total synthesis of Allopumiliotoxin 267A has been accomplished featuring this key transformation. Further synthetic applications of α -alkylidene cycloketones are currently under investigation in this laboratory.

Acknowledgment. Financial support from the NSFC (20832005, 20602008) is gratefully acknowledged.

Supporting Information Available: Characterization data and NMR spectra for compounds **2**, **5**, **7**, **10**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900452N

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