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

Bing Wang,*,† Zheng Zhong,†,‡ and Guo-Qiang Lin†,‡,§

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China, Institutes of Biomedical Sciences, Fudan University, 138 Yixueyuan Road, Shanghai 200032, China, and Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

wangbing@fudan.edu.cn

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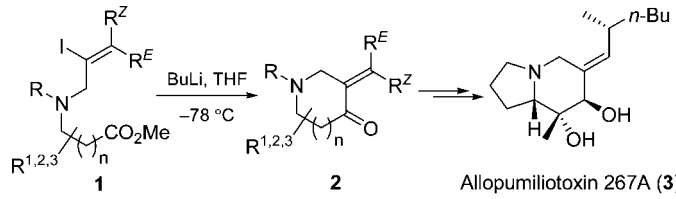
ABSTRACT



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 Julia[4] 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

† Department of Chemistry, Fudan University.
‡ Institutes of Biomedical Sciences, Fudan University.
§ Shanghai Institute of Organic Chemistry.

(1) (a) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (b) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (c) Xu, W.-Z.; Huang, Z.-T.; Zheng, Q.-Y. *J. Org. Chem.* **2008**, *73*, 5606. (d) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901. (e) Simpson, A. F.; Bodkin, C. D.; Butts, C. P.; Armitage, M. A.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3047. For selected overviews: (f) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1. (g) Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Elsevier: Oxford, 1991; Vol. 4, pp 69. (h) Kozlowski, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 169. (i) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(2) (a) Yee, S. W.; Jarno, L.; Gomaa, M. S.; Elford, C.; Ooi, L.-L.; Coogan, M. P.; McClelland, R.; Nicholson, R. I.; Evans, B. A. J.; Brancale, A.; Simons, C. *J. Med. Chem.* **2005**, *48*, 7123. (b) Anto, R. J.; Sukumaran, K.; Kuttan, G.; Rao, M. N. A.; Subbaraju, V.; Kutton, R. *Cancer Lett.* **1995**, *97*, 33.

(3) (a) House, H. O.; Babad, H. *J. Org. Chem.* **1963**, *28*, 90. For selected reviews, see: (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (c) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (d) Kolodiazhnyi, O. I. *Phosphorus Ylides*; Wiley-VCH: Weinheim, 1999.

(4) (a) Dumeunier, R.; Marko, I. E. In *Modern Carbonyl Olefination*; Gleiter, R., Hopf, H. Eds.; Wiley-VCH: Weinheim, 2004. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 729.

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

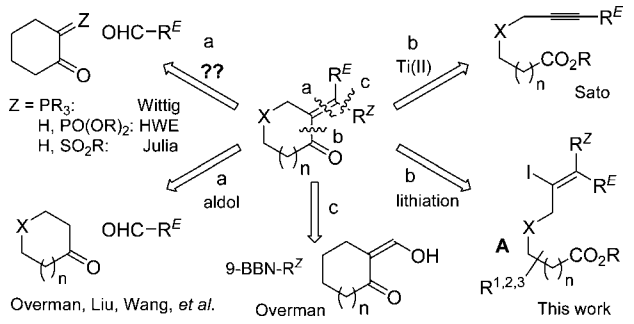
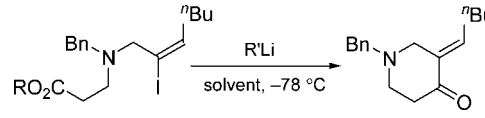


Figure 1. Approaches to α-alkylidene cycloketones.

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 were obtained by using 1.0 eq. ^{n}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 ^{n}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, ^{t}BuLi[14a,b] and MesLi[14c] were both inferior (entries 4, 5). With regard to the ester moiety, bulky ^{t}Bu was found to be detrimental (entry 7). The slightly electron-withdrawing CH_2CF_3 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

Table 1. Optimization of INAS Reaction of *β*-Amino-alkenyllithium[a]



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**, ^{t}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.

(5) For selected recent examples, see: (a) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179. (b) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652. (c) Wang, W.; Mei, Y.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 601. (d) Lian, J.-J.; Lin, C.-C.; Chang, H.-K.; Chen, P.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9661. (e) Kreher, U. P.; Rosamilia, A. E.; Raston, C. L.; Scott, J. L.; Strauss, C. R. *Org. Lett.* **2003**, *5*, 3107. (f) Yanagisawa, A.; Goudu, R.; Arai, T. *Org. Lett.* **2004**, *6*, 4281. (g) Ishihara, K.; Kurihara, H.; Yamamoto, H. *Synlett* **1997**, 597.

(6) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3315.

(7) (a) McElvain, S. M.; Rorig, K. *J. Am. Chem. Soc.* **1948**, *70*, 1820. (b) Walton, H. M. *J. Org. Chem.* **1957**, *22*, 1161. (c) Rosamilia, A. E.; Giarrusso, M. A.; Scott, J. L.; Strauss, C. R. *Green Chem.* **2006**, *8*, 1042.

(8) (a) Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984. (b) Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208. For an excellent overview, see: (c) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753.

(9) Falck, J. R.; He, A.; Reddy, L. M.; Kundu, A.; Barma, D. K.; Bandyopadhyay, A.; Kamila, S.; Akella, R.; Bejot, R.; Mioskowski, C. *Org. Lett.* **2006**, *8*, 4645.

(10) Overman, L. E.; Veltuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581.

(11) Taber, D. F.; Sikkander, M. I.; Berry, J. F.; Frankowski, K. J. *J. Org. Chem.* **2008**, *73*, 2029.

(12) (a) Nagaki, A.; Kim, H.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2008**, *47*, 7833. For a review of functionalized organometallic species, see: (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.

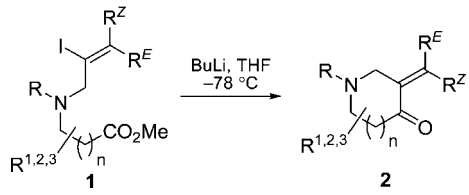
(13) (a) Yus, M.; Foubelo, F. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; pp 18−23. (b) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 553.

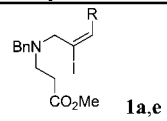
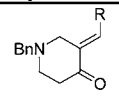
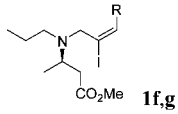
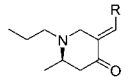
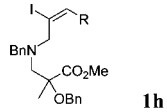
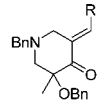
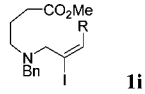
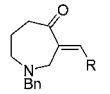
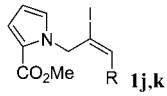
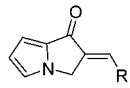
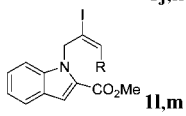
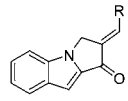
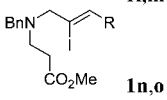
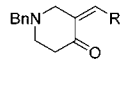
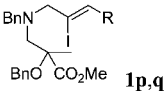
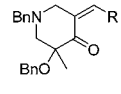
(14) (a) Paleo, M. R.; Lamas, C.; Castedo, C.; Domíngues, D. *J. Org. Chem.* **1992**, *57*, 2029. (b) Kim, D.; Kim, I. H. *Tetrahedron Lett.* **1997**, *38*, 415. (c) Kondo, Y.; Asai, M.; Miura, T.; Uchiyama, M.; Sakamoto, T. *Org. Lett.* **2001**, *3*, 13.

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 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 Information). 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 fused-cyclopentanone products were relatively more stable and thus isolable (entries 7−10).

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



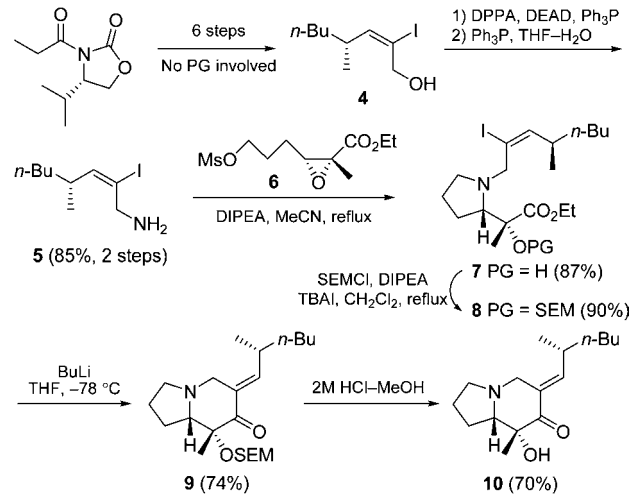
entry	alkenyl iodide **1**	product	R, **2**, yield (%)[b]
1	 **1a**,**e**		*n*-Bu, **2a**, 67
2			CH_2OTBS, **2e**, 56
3	 **1f**,**g**		*n*-Bu, **2f**, 64
4			CH_2OTBS, **2g**, 62
5	 **1h**		*n*-Bu, **2h**, 91
6	 **1i**		*n*-Bu, **2i**, 26
7	 **1j**,**k**		*n*-Bu, **2j**, 69
8			CH_2OTBS, **2k**, 52
9	 **1l**,**m**		*n*-Bu, **2l**, 50[c]
10			CH_2OTBS, **2m**, 16[c]
11	 **1n**,**o**		*n*-Bu, **2n**, 50
12			Ph, **2o**, 77
13	 **1p**,**q**		*n*-Bu, **2p**, 74
14			Ph, **2q**, 32[c]

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

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, Ph_3P) followed by Staudinger reaction[18] 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 SEM[20] 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 base-sensitivity of **9**.

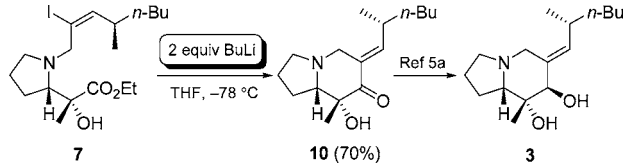
Scheme 1. Toward the Synthesis of Allopumiliotoxin 267A



As resorting to protection is both aesthetically and practically unappealing,[21] we further explored direct INAS reaction of unprotected **7** using 2 equiv of ^{n}BuLi (Scheme 2). Gratifyingly, the extra ^{n}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.

Scheme 2. Protection-Free Synthesis of Allopumiliotoxin 267A



(70%) of the desired intermediate **10** {$[\alpha]^{22}_D$ −6.8 (*c* 1.12, $CHCl_3$), lit.[8a] $[\alpha]^{25}_D$ −6.4 (*c* 0.96, $CHCl_3$)}. Notably, the formation of the bicyclic indolizidine skeleton and the stereospecific incorporation of the chiral side chain were integrated into only two steps, which is a significant improvement to our previous formal synthesis.[17c] Finally, substrate-directed[22] reduction using $Me_4NBH(OAc)_3$ completed the total synthesis of **3** {$[\alpha]^{22}_D$ +34.6 (*c* 1.15, MeOH), lit.[5a] $[\alpha]^{25}_D$ +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.

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(16) (a) Reference 5a. (b) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393. (c) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073. For an excellent review, see: (d) Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505, and references cited thereinFor recent progress, see: (e) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (f) Tan, C.-H.; Holmes, A. B. *Chem.−Eur. J.* **2001**, *7*, 1845. (g) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001**, *3*, 469.

(17) (a) Wang, B.; Liu, R.-H. *Eur. J. Org. Chem.* **2009**, DOI: 10.1002/ejoc.200900231. (b) Liu, R.-H.; Fang, K.; Wang, B.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2008**, *73*, 3307. (c) Wang, B.; Fang, K.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 7981. (d) Wang, B.; Yu, X.-M.; Lin, G.-Q. *Synlett* **2001**, 904. (e) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2000**, *65*, 9114.

(18) For reviews, see: (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.

(19) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(20) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15.

(21) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature (London)* **2007**, *446*, 404.

(22) For a review of substrate-directable reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.