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Amine-Induced Michael/Conia-Ene Cascade Reaction: Application to a Formal Synthesis of (±)-Clavukerin A

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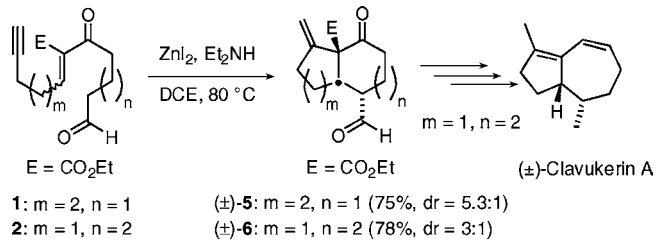
ABSTRACT



An efficient and versatile amine-induced Michael/Conia-ene cascade cyclization reaction has been developed for establishing 6,6- and 5,7-bicyclic fused carbocycles with simple acyclic *β*-ketoesters as the substrates in one-pot condition and this new cyclization method has been successfully utilized in a formal synthesis of (±)-Clavukerin A.

Developing efficient and versatile cascade cyclization methods for construction of various types of bicyclic fused carbocycles is an attractive approach in the synthesis of complex polycyclic molecules since they often enable the generation of the core ring structure with multiple stereogenic centers in a single synthetic operation.[1] We are particularly interested in developing the Michael reaction into a useful cascade cyclization method for establishing the core structure of polycyclic natural products. The Michael reaction is one of the most important organic transformations used in carbon−carbon bond formation.[2] Due to its reversible nature, the success of developing the intramolecular Michael reaction for ring closure relied on the studies of the geometric restraints associated with the ring formation, which included the ring size, the geometry at the reacting site, and the *endo* or *exo* nature of the cyclization.[3] In spite of these constraints, the intramolecular Michael reaction has been successfully demonstrated to be a useful method for carbocycle formations in natural product synthesis.[2b,4] Recently, amine-induced intramolecular Michael reaction of aldehyde substrates has been demonstrated to be a mild and powerful method for establishing 5-membered carbocycles stereoselectively.[5] How-

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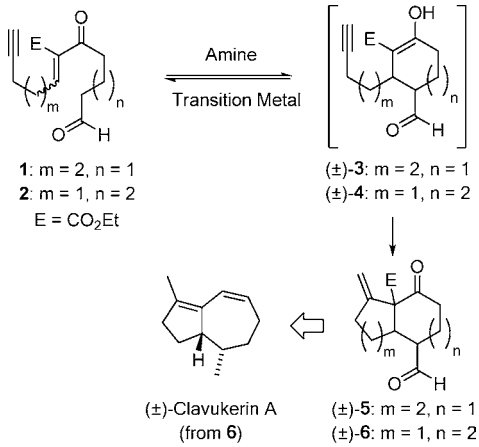
ever, its utility in establishing 6- and 7-membered carbocycles is still highly limited[6] probably due to the reversible nature of the Michael reaction. Our strategy is to couple the intramolecular amine-induced Michael reaction with an irreversible reaction, which is expected to provide the required driving force for the forward intramolecular Michael reaction. We herein report a novel amine-induced Michael/Conia-ene cascade cyclization reaction for establishing the 6,6- and 5,7-bicyclic fused carbocycles using simple acyclic β-ketoesters as the cyclization precursors and its application to a formal synthesis of (±)-Clavukerin A.

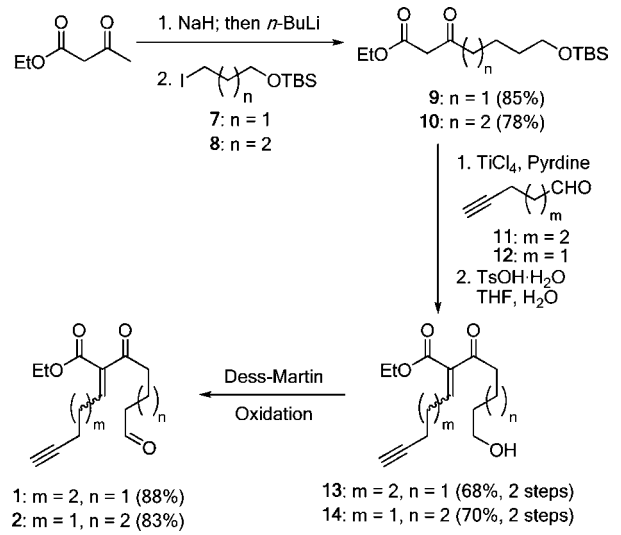
Scheme 1. Amine-Induced Michael/Conia-Ene Cascade Cyclization



As shown in Scheme 1, β-ketoesters **1** and **2** were anticipated to undergo the supposedly reversible 6- and 7-*endo*-trig intramolecular Michael addition to form equilibrium mixtures (**1** ⇌ **3** and **2** ⇌ **4**) upon treatment with an amine and a transition metal. The transition metal could activate the Michael acceptors by chelating with the β-keto ester moieties and facilitate the enamine formation.[7] Under the reaction condition, the Michael addition products (**3** and **4**) are expected to undergo Conia-ene reactions,[8] which should drive the equilibrium forward and furnish the 6,6- and 5,7-bicyclic products (**5** and **6**) in a one-pot manner. These highly functionalized 6,6- and 5,7-bicyclic products could be useful building blocks for natural product synthesis.

The cyclization precursors (**1** and **2**) were readily prepared from ethyl acetoacetate. As shown in Scheme 2, alkylation of the dianion of ethyl acetoacetate with the appropriate iodide (**7** and **8**) provided β-ketoester **9** and **10**, respectively. Subsequent Knoevenagel condensation with the appropriate alkynal (**11** and **12**) using $TiCl_4$ and pyridine[9] provided the condensation products as 1:1 *E*/*Z* mixtures of alkene isomers

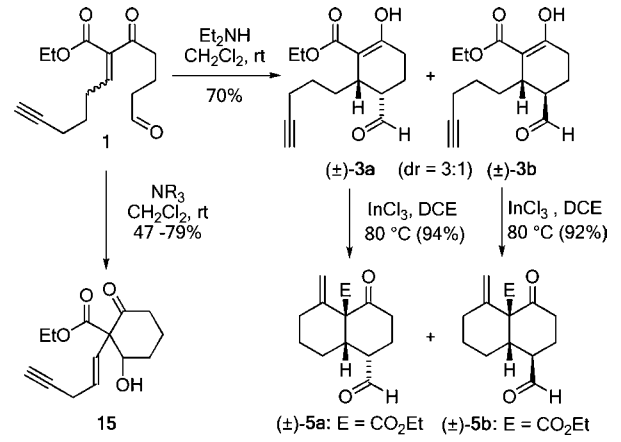
Scheme 2. Synthesis of the Amine-Induced Michael/Conia-Ene Cascade Cyclization Precursors



with the TBS protecting group being partially hydrolyzed. The mixtures were then submitted to TsOH·H_2O in THF/H_2O (10:1) to give **13** and **14**, which were oxidized to afford aldehyde **1** and **2**, respectively.

With the cyclization precursors prepared, the intramolecular Michael reaction of **1** was investigated with use of a variety of secondary amines. Cyclization of **1** went rapidly (0.5−1 h) with a stoichiometric amount of secondary amines in dichloromethane at room temperature and afforded the expected Michael product (**3**) in 36−70% yields (Scheme 3). Cyclic secondary amines, such as pyrrolidine and

Scheme 3. Stepwise Amine-Induced Michael/Conia-Ene Cascade Reaction



piperdine, afforded only modest yields (36−50%) of the Michael product. The optimal results were achieved by using diethylamine, which gave 70% of the Michael product in 1 h with **3a**:**3b** equaling 3:1. Reducing the amount of

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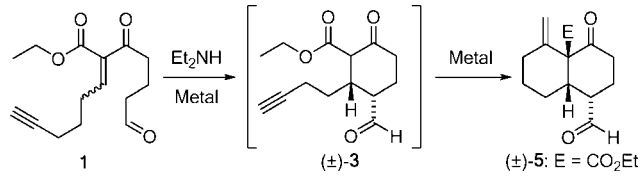
Table 1. Optimization of the Amine-Induced Michael/Conia-Ene Cascade Cyclization[a]



					yield[b] (%)	
entry	metal	solvent	temp (°C)	time (h)	**3** (dr)[c]	**5** (dr)[d]
1	$InCl_3$	DCE	80	3		60 (4:1)
2	$In(OTf)_3$	DCE	80	5		46 (1:1)
3	$TiCl_4$	THF	rt	12	decomposition	
4	$SnCl_4$	DCE	rt	12	decomposition	
5	$Ph_3PAuCl/AgOTf$	DCE	rt	2	decomposition	
6	$HgCl_2$	DCE	rt	3	undefined side-product	
7	$Ni(acac)_2$	dioxane	rt	3	45 (5:1)	
8	$Ni(acac)_2$	dioxane	80	10	38 (1:3)	trace
9	$Zn(OTf)_2$	DCE	rt	2	55 (5:1)	
10	$Zn(OTf)_2$	DCE	80	12	45 (1:1.3)	trace
11	ZnI_2	DCE	80	3		75 (5.3:1)
12	ZnI_2	toluene	80	10		56 (1:1)
13	ZnI_2	CH_3CN	reflux	6	55 (1:1)	trace
14	ZnI_2 (0.2 equiv)[e]	DCE	80	36	45 (1:1.2)	trace
15	ZnI_2 (1.1 equiv)[f]	DCE	80	24		32 (2:1)

[a] General condition: To a stirred solution of **1** (0.2 mmol) in the appropriate solvent (10 mL) was added diethylamine (1.1 equiv) and the metal (2.2 equiv) at room temperature. The reaction was stirred at the indicated temperature until TLC showed the consumption of **1**. [b] Isolated yields after silica column chromatography. [c] The dr value of **3a**/**3b** was determined by the ratio of δ_{3a} (9.83) to δ_{3b} (9.6) in ^{1}H NMR. [d] The dr value of **5a**/**5b** was determined by the ratio of δ_{5a} (5.07) to δ_{5b} (5.14) in ^{1}H NMR. [e] 0.1 equiv of Et_2NH was used. [f] 0.2 equiv of Et_2NH was used.

diethylamine to 0.2 equiv led to a slower and less efficient reaction. Since diethylamine could also induce the Michael reaction by acting as a base, the role of the amines was studied with use of a variety of tertiary amines including DBU, DIEA, and triethylamine. Surprisingly, no Michael product was observed and all tertiary amines gave 47−79% yields of an unexpected cyclization product (**15**), which could be produced via deprotonation followed by an intramolecular aldol reaction. These results suggested that diethylamine induced the Michael reaction via enamine formation instead of deprotonation. The intramolecular Michael reactions of **2** were also investigated by using a catalytic to a stoichiometric amount of diethylamine. However, neither the expected Michael addition product (**4**) nor the aldol side product was observed under these conditions. This result suggested that the forward 7-*endo*-trig cyclization may not be entropically favorable.

The initial amine-induced intramolecular Michael reaction of **1** afforded **3a** as the major product regardless of the geometry of the alkene moiety. However, **3a** was found to be able to equilibrate to **3b** under prolong treatment of diethylamine. Cyclization product **3b** became the major product when **1** was stirred with a stoichiometric amount of diethylamine for 12 h (50%, **3a**:**3b** = 1:3). The Michael products (**3a** and **3b**) were separated by silica gel column chromatography and submitted to $InCl_3$ in DCE at 80 °C for 2 h.[10] Both Michael products (**3a** and **3b**) underwent Conia-ene reaction and afforded the 6,6-bicyclic fused carbocycles (**5a** and **5b**, respectively) as a single diastereomer in very good yields (92−94%). The structures of the cyclization products were characterized unambiguously with NMR experiments.

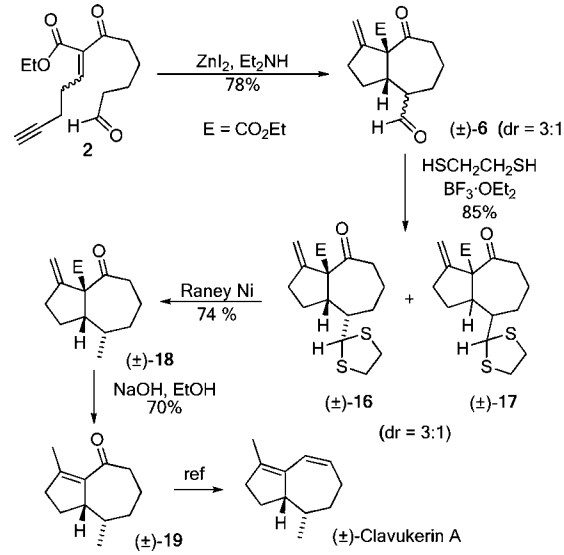
With these encouraging results in hand, the conditions of the one-pot Michael/Conia-ene cascade reaction were then investigated by using diethylamine with a variety of transition metal prompters. As shown in Table 1, the Michael/Conia-ene cascade reaction of **1** went smoothly with use of $InCl_3$ in DCE at 80 °C for 3 h. This one-pot procedure gave 60% yield of the cyclization product (**5**) with **5a**:**5b** equaling 4:1 (entry 1). Switching to $In(OTf)_3$[11a] led to a lower yield and a lower diastereoselectivity (entry 2). $TiCl_4$,[11b] $SnCl_4$,[11c] and $Ph_3AuCl/AgOTf$[11d] resulted in decomposition of the cyclization precursors (entry 3−5), and $HgCl_2$[11e] gave an unidentifiable side product after acid hydrolysis of the intermediate with use of NaI with aqueous HCl (entry 6). $Ni(acac)_2$ in dioxane[11f] and $Zn(OTf)_2$ in DCE[11g] gave the Michael adduct (**3**) in 45−55% yield (entry 7 and 9) at room temperature. However, increasing the reaction temperature led to only a trace amount of the bicyclic products and the Michael reaction intermediates decomposed gradually (entries 8 and 10). Finally, we found that the optimal yields and selectivity were achieved with ZnI_2 in DCE[11h] at 80 °C for 3 h. This condition provided 75% yield of the cyclization product with a dr value equaling 5.3:1 (entry 11). A brief survey of the solvent effects indicated that DCE provided the optimal results of the cascade reactions (entries 11−13). Reducing the amount of ZnI_2 and diethylamine to 0.2 and 0.1 equiv respectively led to a very slow reaction and gave only 45%

yield of the Michael product with very poor diastereoselectivity in 36 h (entry 14). Adjusting the ratio of ZnI_2/diethylamine to 1.1:0.2 can also provide the cyclization product but with low yield and poor selectivity (entry 15).

With the one-pot cyclization condition optimized, the Michael/Conia-ene cascade cyclization of **2** was then investigated. Upon treatment with ZnI_2/diethylamine in DCE at 60 °C, cyclization of **2** was completed in 2 h and gave the bicyclic product (**6**) in 78% with **6a**:**6b** equaling 3:1. During the course of reaction, the Michael adduct (**4**) was not observed. These results suggested that the Conia-ene reaction successfully drove the unfavorable 7-*endo*-trig intramolecular Michael reaction forward and furnished the 5,7-bicyclic product in one-pot condition. This encouraging result prompted us to explore the utility of the cyclization product (**6**) in a formal synthesis of (±)-Clavukerin A (a trinorguaiane sesquiterpene isolated from the Okinawan soft coral *Clavularai koellikeri* in 1983).[12] As shown in Scheme 4, the aldehyde moiety of **6** was selectively converted to dithane **16** and **17**, which can be separated by silica gel column chromatography. The dithane moieties were then reduced with Raney Nickel to afford **18**.[13] Finally, decarboxylation of **18** under basic conditions finished the synthesis of enone **19** (26%, 4 steps from **2**), which could lead to (±)-Clavukerin A according to literature procedures.[14a] To the best of our knowledge, this is the first example of establishing the 5,7-bicyclic core of (±)-Clavukerin A via a one-pot cascade cyclization method.[14]

In summary, we have successfully developed an efficient and versatile amine-induced Michael/Conia-ene cascade cyclization reaction for construction of the 6,6- and 5,7-bicyclic fused carbocycles using simple acyclic β-ketoesters as the substrates. With ZnI_2/Et_2NH in DCE at 60−80 °C for 2−3 h, both cyclization precursors (**1** and **2**) gave the bicyclic products (**5** and **6**) with yields up to 78% and dr values up to 5.3:1. Moreover, the 5,7-bicyclic product (**6**) has been successfully utilized for a formal synthesis of (±)-Clavukerin A. We are currently exploring the utilities of this new cascade cyclization method for the synthesis of other natural products bearing the 6,6- and 5,7-bicyclic carbocycle cores such as difuranofruticol[15] and thapsigargin.[16]

Scheme 4. Synthesis of (±)-Clavukerin A via the Amine-Induced Michael/Conia-Ene Cascade Cyclization Approach



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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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