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Bicyclic- and Tricyclic-β-lactones via Organonucleophile-Promoted Bis-Cyclizations of Keto Acids: Enantioselective Synthesis of (+)-Dihydroplakevulin

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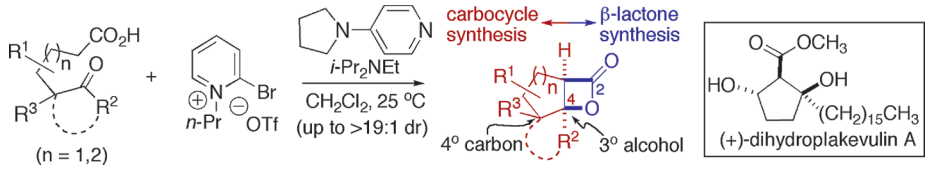
ABSTRACT



A highly diastereoselective, nucleophile-promoted bis-cyclization process, employing readily available and tractable keto acid substrates, is described. This methodology provides concise access to bicyclic- and tricyclic-β-lactones bearing tertiary carbinol centers and quaternary carbons, greatly extending the scope of previous routes to bicyclic-β-lactones from aldehyde acid substrates. The utility of the method was demonstrated by application to an enantioselective synthesis of (+)-dihydroplakevulin A. This and related processes may be revealing a subtle interplay between [2+2] cycloaddition and nucleophile-catalyzed aldol lactonization (NCAL) reaction manifolds.

In recent years, the asymmetric synthesis of β-lactones has become an area of active research[1] because these heterocycles are useful synthetic intermediates for natural product synthesis,[2] are found in a growing number of bioactive natural products,[3] and have continued potential as enzyme inhibitors[4] and as monomers for polymer synthesis.[5] The Wynberg catalytic, asymmetric β-lactone synthesis, involving an alkaloid-promoted reaction of ketene with highly electrophilic aldehydes (e.g., α-chlorinated), stands as a benchmark for further developments in this area.[6] We recently developed an intramolecular version of this nucleophile-catalyzed aldol lactonization (NCAL) process building on the work of Wynberg, which provided the first strategy to circumvent the limitation of highly electrophilic substrates (Scheme 1). This process employed aldehyde acid substrates **1** (R^2 = H), *O*-acetylquinidine (AcQUIN) as nucleophilic catalyst, and modified Mukaiyama's reagents (**2a**, **2b**), as carboxylic acid activators, and effectively merged catalytic, asymmetric β-lactone synthesis with carbocycle synthesis.[7] Recent studies employing Lewis acid additives further extend the utility of the intermolecular Wynberg process.[1d,f] The primary mechanistic pathway for this process with aldehyde acid substrates enables catalytic, asymmetric organocatalysis via ammonium

(1) For reviews, see: (a) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441. (b) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403. For more recent advances, see: (c) Kramer, J. W.; Lobkovsky, E. B.; Coates, G. W. *Org. Lett.* **2006**, *8*, 3709 and references cited therein. (d) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352. (e) Wilson, J. E.; Fu, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358. (f) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809.

(2) Wang, Y.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605.

(3) Lowe, C.; Vederas, J. C. *Org. Prep. Proced. Int.* **1995**, *27*, 305.

(4) (a) For lead references, see: Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536. (b) Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem.* **2006**, *71*, 4549.

(5) For a lead reference, see: Rieth, L. R.; Moore, D. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 15239.

(6) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166.

(7) (a) Cortez, G. S.; Tennyson, R.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945. (b) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, *11*, 1731. (c) Oh, S. H.; Cortez, G. C.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.

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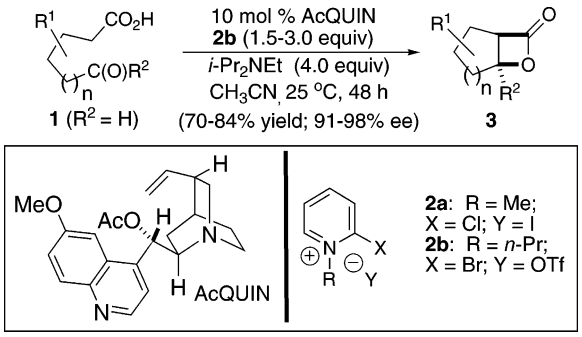
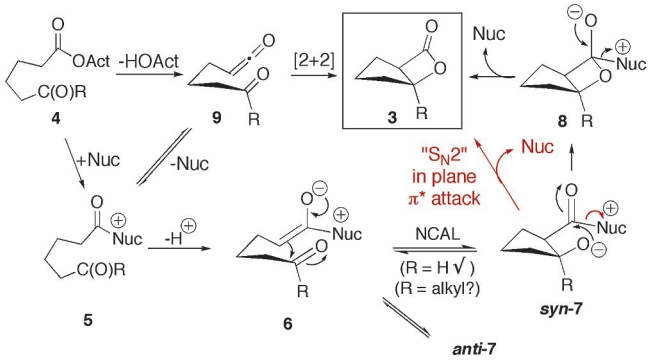
Published on Web 08/23/2006

Scheme 1. Catalytic, Asymmetric, Intramolecular NCAL Process with Aldehyde Acid Substrates



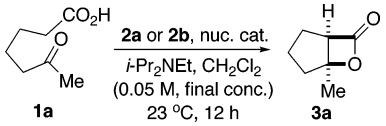
enolate **6**, a process not possible via a [2+2] cycloaddition pathway via ketene **9** (Scheme 2). We now report a facile, ambient temperature, nucleophile-promoted process that enables the use of more tractable keto acid substrates **1** (R^2 = alkyl), opening possibilities for asymmetric organocatalysis in these processes previously thought to proceed via [2+2] cycloaddition pathways. This significantly expands the scope of this process by allowing access to bicyclic and tricyclic systems bearing masked tertiary alcohols and a reactive β-lactone moiety.[8]

Scheme 2. Possible Mechanistic Pathways for Intramolecular Nucleophile-Catalyzed Bis-Cyclization Processes of Aldehyde Acids (R = H) and Keto Acids (R = Alkyl)



In our earlier studies, we reported that use of 6-oxoheptanoic acid (**1a**)[9] as a substrate led to only 3% isolated yield of the corresponding bicyclic-β-lactone using Et_3N as both the base and the nucleophilic promoter (Table 1, entry 1).[7a] Because of the lower electrophilicity of ketones and our interest in promoting a NCAL pathway, we reasoned that

Table 1. Optimization of the Bis-Cyclization with Keto Acid **1a**



entry	pyridinium salt (equiv)	*i*-Pr_2NEt (equiv)	nucleophile (equiv)	% yield **3a**
1	**2a** (3.0)	0	Et_3N (4.0)	3[a]
2	**2b** (3.0)	4.0	Py (1.0)	0
3	**2b** (3.0)	4.0	DMAP[a] (1.0)	19[b]
4	**2b** (3.0)	4.0	PPY (1.0)	48[b]
5	**2b** (3.0)	4.0	none	0

[a] Previously reported (see ref 7a). [b] Yield was estimated by ^1H NMR of the crude reaction mixture relative to the pyridone byproduct due to the volatility of **3a**.

increasing the nucleophilicity of the intermediate ammonium enolate (cf. **6**, Scheme 2) by increasing electron density on the nitrogen might promote this process with ketones. This might alter the equilibrium in favor of the aldolate intermediates **7**, promoting rate-limiting formation of tetrahedral intermediate **8**. Our attention was drawn to highly nucleophilic pyridine derivatives given their well-known ability to catalyze acylation reactions.[10] Initial studies with dimethylamino pyridine (DMAP) (1.0 equiv) using previously described conditions (slow addition of substrate over 1 h via syringe pump, 0.05 M final concentration, 25 °C) and the modified Mukaiyama reagent **2b** led to a >5-fold increase in conversion of β-lactone **3a** (19%, Table 1, entry 3). Further conversion (48%) was observed with the more nucleophilic promoter, 4-pyrrolidino pyridine (PPY) (1.0 equiv, Table 1, entry 4). However, under the same conditions, pyridine, diazabicyclooctane, DABCO, diazabicycloundecane (DBU), and phosphorus nucleophiles (PPh_3 and PBu_3) gave no β-lactone. Importantly, use of only Hünig's base gave no β-lactone, suggestive of a nucleophile-promoted process (entry 5).

Because of the volatility of β-lactone **3a**, further optimization was performed with dioxolane keto acid **1b**. Under optimized conditions, β-lactone **3b** could be obtained in 78% isolated yield, employing 0.7 equiv of PPY (1.0 equiv of **2b**/2.0 equiv of Hünig's base, Table 2, entry 1). The amount of PPY could be lowered to 0.25 equiv; however, an increase in reaction time (~118 h) and activating agent **2b** (2.0 equiv) was required to achieve yields in the range of 48−61%. Subsequently, it was determined that use of 1.5 equiv of both PPY and **2b** provided a practical compromise between reaction rate and reagent stoichiometry.

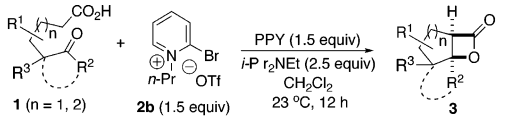
With these optimized conditions, the scope of this bis-cyclization process was explored using various keto acids **1c**−**j** (Table 2). As expected, only *cis*-cyclopentyl-fused

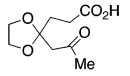
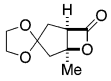
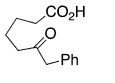
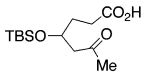
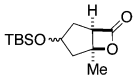
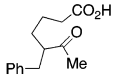
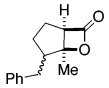
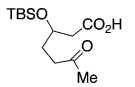
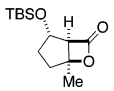
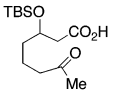
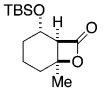
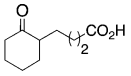
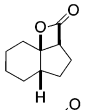
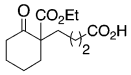
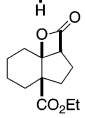
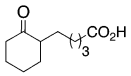
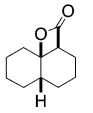
(8) For previous reports of β-lactones from keto acid derivatives with nucleophilic promoters via proposed [2+2] mechanisms, see: (a) Boswell, G. A.; Dauben, W. G.; Ourisson, G.; Rull, T. *Bull. Soc. Chim. Fr.* **1958**, 1598. (b) Kagan, H. B.; Jacques, J. *Bull. Soc. Chim. Fr.* **1958**, 1600. (c) Brady, W. T.; Gu, Y. Q. *J. Org. Chem.* **1988**, *53*, 1353. (d) Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 1717. For an anionic version, see: (d) Shindo, M.; Matsumoto, K.; Sato, Y.; Shishido, K. *Org. Lett.* **2001**, *3*, 2029.

(9) This keto acid substrate is commercially available. Other substrates were prepared by standard procedures (see Supporting Information for details).

(10) For lead references, see: (a) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436. (b) Heinrich, M. R.; Klisa, S. H.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4826. (c) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

Table 2. Bicyclic- and Tricyclic-β-lactones **3b**−**j** via Organonucleophile-Promoted Bis-Cyclization of Keto Acids **1b**−**j**



entry	keto acid	cmpd. no.	β-lactone[a]	cmpd. no.	% yield[b]	dr[d]
1		**1b**		**3b**	78[c]	-
2		**1c**		**3c**	58	-
3		**1d**		**3d**	51	2:1
4		**1e**		**3e**	75[c]	~1:1
5		**1f**		**3f**	67	>19:1
6		**1g**		**3g**	40	>19:1
7		**1h**		**3h**	61	>19:1
8		**1i**		**3i**	70	>19:1
9		**1j**		**3j**	57	>19:1

[a] Relative stereochemistry is based on strain arguments (**3a**−**c**), X-ray analysis (**3h**, **3i** (hydroxy acid derivative)), coupling constant analysis of derivatives (**3g**), or analogy to dihydroplakevulin (**3f**). See Supporting Information for details. [b] Yields refer to isolated (silica gel), purified product. [c] 0.7 equiv of PPY, 1.0 equiv of **2b**, and 2.0 equiv of Hünig's base were employed. [d] Only *cis*-β-lactones are formed (entries 1 and 2; dr refers to relative stereochemistry between the β-lactone and the ring stereocenter). Ratios were determined by 500 MHz ^{1}H NMR on crude reaction mixtures, and a dr of >19:1 indicates that minor diastereomers could not be detected.

β-lactones are obtained because of ring strain considerations leading to high diastereoselectivity (Table 2, entries 1 and 2). Keto acids bearing β- but not γ- or δ-stereocenters relative to the carboxylic acid provided excellent diastereoselectivities (cf. β-lactones **3f**,**g** vs **3d**,**e**). High diastereoselectivity was also observed in reactions leading to tricyclic products **3h**−**j** (Table 2, entries 7−9; Figure 1).

The utility of this process was demonstrated by the enantioselective synthesis of (1*S*,4*S*,5*R*)-dihydroplakevulin A, a known derivative of the DNA polymerase inhibitor plakevulin A.[11] Bis-cyclization of keto acid **12**, obtained from known β-silyloxy ester (+)-**10**, gave bicyclic-β-lactone **13** in moderate yield with high diastereoselectivity (>19:1, ^{1}H NMR, Scheme 3). Subsequent methanolysis and deprotection provided dihydroplakevulin, which correlated with published

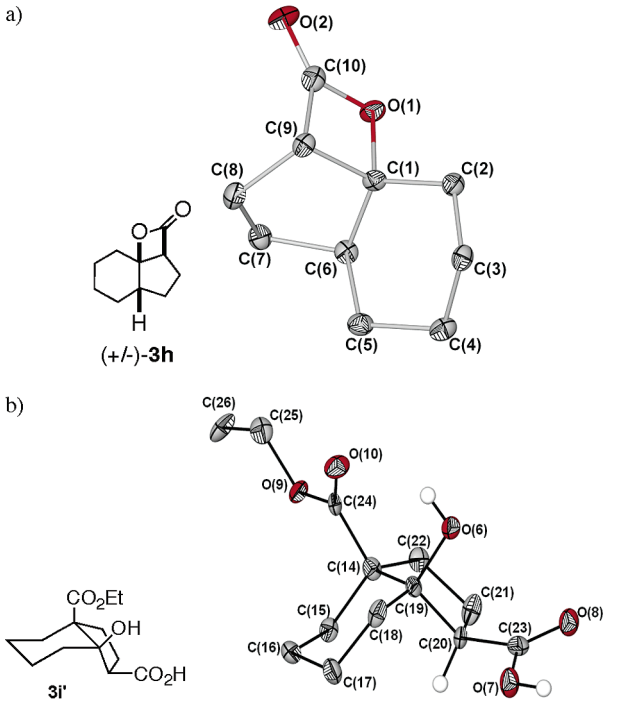
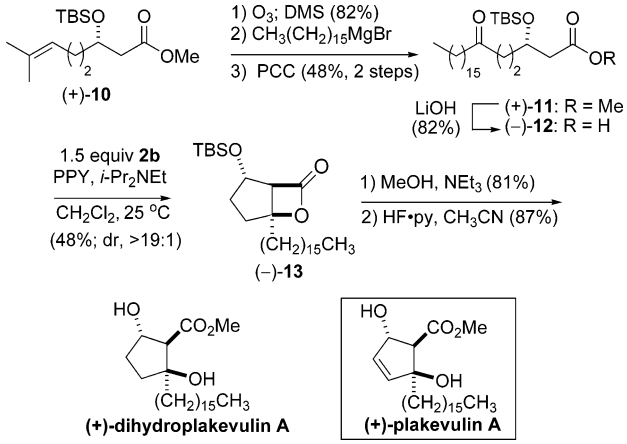


Figure 1. X-ray crystallographic analysis of (a) tricyclic-β-lactone **3h** and (b) hydroxy acid **3i′** derived from hydrolysis (pH 7.0 buffer) of tricyclic-β-lactone **3i**.

data and confirmed the relative stereochemistry of precursor bicyclic-β-lactone **13** and, by analogy, β-lactone **3f**.[11]

Scheme 3. Enantioselective Synthesis of (+)-Dihydroplakevulin A



Regarding the mechanism of this bis-cyclization process, at this time, we have not distinguished between a NCAL or a [2+2] cycloaddition pathway. However, our studies suggest

(11) (a) Tsuda, M.; Endo, T.; Perpelescu, M.; Yoshida, S.; Watanabe, K.; Fromont, J.; Mikami, Y.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1137. (b) Mizutani, H.; Watanabe, M.; Honda, T. *Synlett* **2005**, *5*, 793. (c) Kuramochi, K.; Saito, F.; Takeuchi, R.; Era, T.; Takemura, M.; Kobayashi, J.; Sakaguchi, K.; Kobayashi, S.; Sugawara, F. *Tetrahedron* **2006**, *62*, 8006.

nucleophile involvement prior to or during the rate-determining step on the basis of improved efficiency with increasingly nucleophilic promoters. Although ketene intermediates have not been observed by *in situ* IR spectroscopy, this does not exclude short-lived ketene intermediates. Calculations (B3LYP/6−31+G**+zpe) indicate lower-energy intermediates in a NCAL vs a [2+2] pathway with keto acid **1a**. These calculations suggest a possible direct S_N2-type substitution to deliver β-lactone **3** (Scheme 2, red arrows, **7→3**) as we were unable to locate a transition state for conversion of **8→3**.[12] Our current mechanistic hypothesis invokes establishment of an initial, steady-state equilibrium between *syn*- and *anti*-aldolates **7** and the keto ammonium enolate **6**. This is followed by rate-determining cyclization to the β-lactone via a direct S_N2-type substitution or typical addition−elimination mechanism. Further insights into the principal mechanistic pathway followed will be ascertained by use of suitable chiral nucleophilic promoters and further mechanistic studies. Overall, these and related processes may be revealing a subtle interplay between NCAL and [2+2] cycloaddition mechanisms.[7,8]

In summary, we have developed a mild and facile biscyclization process that employs tractable keto acid substrates. This process leads to highly versatile bicyclic- and tricyclic-β-lactones possessing up to three stereocenters including a masked tertiary carbinol center and a reactive β-lactone moiety. These systems should be of broad interest for natural product synthesis and scaffolds for diversity-oriented synthesis. The process expands the scope and utility of the intramolecular NCAL process of aldehyde acid substrates.[7] Although currently limited to a diastereoselective process, these studies open the possibility of asymmetric, nucleophilic organocatalysis if a NCAL pathway can be enforced and can be made competitive with possible [2+2] reaction manifolds. Studies toward this goal are underway.

Acknowledgment. We thank the NSF (CHE-0416260) and the Welch Foundation (A-1280) for funding this work. We thank Gang Liu (TAMU) and Andrea Matla (TAMU) for technical assistance and Chris Dalrympyle (TAMU undergraduate) for initially identifying the applicability of this process to plakevulin A. We thank Prof. Dan Singleton (TAMU) for helpful discussions and Dr. Nattamai Bhuvanesh (TAMU) for X-ray analysis.

Supporting Information Available: General procedures with characterization data (including ^1H and ^{13}C NMR spectra) for β-lactones **3b−j**, intermediates **11−13**, and dihydroplakevulin A. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061816T

(12) For lead references to this mechanistic possibility, see: (a) Adler, M.; Adler, S.; Boche, G. *J. Phys. Org. Chem.* **2005**, *18*, 193. (b) Fox, J. M.; Dmitrenko, O.; Liao, L.; Bach, R. D. *J. Org. Chem.* **2004**, *69*, 7317.