Intramolecular, Nucleophile-Catalyzed Aldol-Lactonization (NCAL) Reactions: Catalytic, Asymmetric Synthesis of Bicyclic β-Lactones

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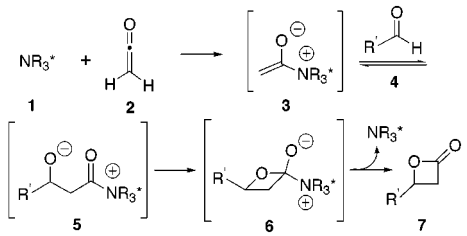
β-Lactones continue to be important targets for asymmetric methodology development due to their masked aldol functionality and their inherent reactivity.[1,2] The Wynberg β-lactone synthesis was one of the first practical, catalytic asymmetric reactions developed, and its utility was demonstrated by the fact that Lonza Ltd. employed this process for the large-scale synthesis of optically active malic and citramalic acids.[3] The proposed mechanism involves an aldol-lactonization process (Scheme 1).

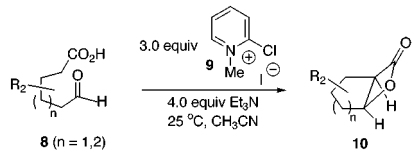
Limitations to the Wynberg procedure are the need for a ketene generator and the requirement of activated (i.e., typically α-dihalogenated) aldehyde substrates.[4] Our interest in developing concise, asymmetric routes to β-lactones[5] led us to begin addressing these limitations. In this regard, we recently described the development of a reaction protocol that allows the use of in situ generated ketene in the Wynberg β-lactone synthesis.[6] The more challenging hurdle for increasing the utility of this methodology would be to extend this reaction to nonactivated carbonyl compounds. We decided to investigate an intramolecular variant, which would minimize unfavorable entropic barriers.[7] We now report our initial studies of an intramolecular nucleophile-catalyzed aldol-lactonization (NCAL) process of aldehyde acids that leads to a variety of novel β-lactone-fused bicyclic systems. Significantly, we have found that this reaction is subject to asymmetric catalysis employing chiral amine nucleophiles. To the best of our knowledge, this represents the first example of a catalytic, asymmetric NCAL reaction with nonactivated aldehydes.

The intramolecular cyclization of ketenes and carbonyl compounds leading to β-lactones has been postulated once[8] and documented in two cases.[9] The mechanism of β-lactone formation under the reaction conditions reported could involve a thermal [2 + 2] cycloaddition or a NCAL process. We recognized that the use of a chiral amine would enable us to distinguish between these mechanisms and potentially lead to an asymmetric synthesis of β-lactones.

Scheme 1



We began our studies of the intramolecular NCAL reaction employing 6-oxo-hexanoic acid (**8a**)[10] with the idea of generating an ammonium enolate using conditions previously reported to generate ketenes in situ from carboxylic acids.[11] After several unsuccessful attempts with various activating agents and conditions, we were pleased to find that addition of aldehyde acid **8a** to a mixture of Mukaiyama's reagent[12] (3.0 equiv) and Et_3N (4.0 equiv) in CH_2Cl_2 at 25 °C gave the volatile bicyclic β-lactone **10a**[13] in 23% yield along with significant quantities of recovered starting material. Slow (syringe pump) addition of the aldehyde



acid over 10 h and, more importantly, use of acetonitrile as the solvent improved the yield of β-lactone **10a** to 55% presumably due to the increased solubility of Mukaiyama's reagent. In this manner, several β-lactone-fused bicyclic systems were prepared including those possessing five- and six-membered carbocycles (Table 1).[14] In all cases, only cis-substituted β-lactones are isolated as expected on the basis of ring-strain considerations. Geminal substitution[15] (cf. Table 1, entry 1 vs entries 2−5 and 6 vs 7) led to a slight increase in yield. The fact that similar yields are obtained with the α,α-dimethyl substrate **8e** suggests that neither aldehyde enolization nor sterics have a significant effect on reaction efficiency (cf. Table 1, entry 3 vs 5). Unsubstituted keto acids participate but only with very low conversion.[16]

We next studied the possibility of diastereoselectivity with a chiral substrate, aldehyde acid **12** derived from (*R*)-citronellic acid.[17] We anticipated that an all-cis-substituted bicycle would be thermodynamically disfavored[18] relative to the trans-diaste-

(1) (a) For a review describing routes to optically active β-lactones, see: Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *51*, 6403−6434. (b) For a recent excellent advance in this area, see: Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743.

(2) (a) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−459. (b) For more recent transformations, see: Yang, H. W.; Romo, D. *J. Org. Chem.* **1999**, *64*, 7657−7660 and references cited therein.

(3) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166−168. (b) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87−130.

(4) (a) In early studies by Wynberg, it was determined that at least two α-halogen atoms were required, see: Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977−1979. (b) For other activated carbonyl compounds that participate in this reaction, see: Ramiandrasoa, P.; Guerin, P.; Girault, J. P.; Bascou, P.; Hammouda, A.; Cammas, S.; Vert, M. *Polym. Bull.* **1993**, *30*, 501−508.

(5) Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197−1199 and references cited therein.

(6) Tennyson, R.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248−7252.

(7) For a recent report of intramolecular ketene−allene cycloadditions and a compilation of related cycloadditions, see: McCaleb, K. L.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2631−2634.

(8) Brady reported the preparation of benzofurans by the presumed decarboxylation of a nonisolable β-lactone intermediate, see: Brady, W. T.; Giang, Y. F. *J. Org. Chem.* **1986**, *51*, 2147−2148.

(9) For reports of intramolecular, diastereoselective, net [2 + 2] cycloadditions of ketones and presumed ketenes, see: (a) Kagan, H. B.; Jacques, J. *Bull. Soc. Chim. Fr.* **1958**, 1600−1602. (b) Rull, T.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1958**, 1581−1586.

(10) Floresca, R.; Kurihara, M.; Watt, D. S.; Demir, A. *J. Org. Chem.* **1993**, *58*, 2196−2200.

(11) Several methods have been developed for this purpose, see: Tidwell, T. T. *Ketenes*; John Wiley & Sons: New York, 1995.

(12) (a) For use of Mukaiyama's reagent for in situ ketene generation, see: Brady, W. T.; Giang, Y. F.; Marchand, A. P.; Wu, A. *Synthesis* **1987**, 395−396. (b) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett* **1989**, 36−37.

(13) Philp, R. P.; Robertson, A. V. *Aust. J. Chem.* **1977**, *30*, 123−130.

(14) The aldehyde acid substrates were prepared by oxidative cleavage of α-hydroxy ketones or ozonolysis of the corresponding alkene acids or cyclic silyl enol ethers. See the Supporting Information for details.

(15) For a lead reference, see: Jung, M. E. *Synlett* **1999**, 843−846.

(16) Use of 6-oxoheptanoic acid gave only a 3% yield of the corresponding bicyclic β-lactone (**10h**).

(17) Overberger, C. G. Kage, H. *J. Am. Chem. Soc.* **1967**, *22*, 5640−5645.

(18) Our working mechanistic hypothesis for the NCAL process involves an initial, thermodynamically controlled equilibrium of an aldolate (cf. **5**, Scheme 1) followed by a rate- and stereochemical-determining ring closure to an oxetane (cf. **6**, Scheme 1).

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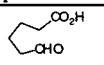
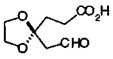
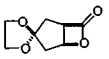
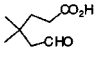
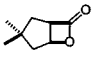
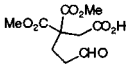
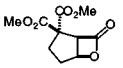
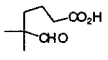
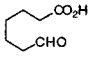
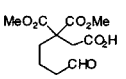
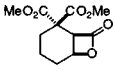
Table 1. Racemic Bicyclic β-lactones Obtained via the Intramolecular NCAL Reaction

entry	oxo-acid precursor	cmpd. no.	bicyclic-β-lactones	cmpd. no.	% yield[a]
1		**8a**		**10a**	55
2		**8b**		**10b**	66
3		**8c**		**10c**	68
4		**8d**		**10d**	62
5		**8e**		**10e**	62
6		**8f**		**10f**	36[b]
7		**8g**		**10g**	57

[a] Refers to isolated, purified yields. [b] Cyclohex-2-ene carboxylic acid (5%) was also isolated in this reaction.

Table 2. Catalytic, Asymmetric Intramolecular NCAL Reactions[a]

entry	bicyclic β-lactones	% yield	% ee[b]	config.
1	(+)-**10a**	54	92	1*R*,2*S*[c]
2	(−)-**10a**[d]	51	86	1*S*,2*R*
3	(+)-**10b**	37	92	3*R*,4*S*[e]
4	(+)-**10c**	45	90	1*R*,2*S*[f]

[a] Reactions were performed using 10 mol % catalyst, 3.0 equiv of **9**, and 4.0 equiv *i*-Pr_2NEt in CH_3CN at 25 °C for 108 h. [b] Enantiomeric excess was determined by chiral GC analysis. [c] Assigned by reduction to the known diol (ref 22) and comparison of optical rotations ($[\alpha]_D = -33.0$, lit. $[\alpha]_D = -37.7$). [d] 9-*O*-Acetylquinine was used as catalyst. [e] Assigned based on subsequent conversion to known cyclopentene (−)-**20**. [f] Determined by X-ray analysis of a derivative (see the Supporting Information for details).

reomer **13**. The latter compound was indeed the exclusive diastereomer produced employing Et_3N (Scheme 2).[19]

To determine if this process is subject to asymmetric catalysis and also differentiate between a thermal [2 + 2] cycloaddition and a NCAL reaction pathway, we next studied the use of a chiral amine catalyst. We were pleased to find that *slow addition of aldehyde acid* ***8a*** *to a mixture of O-acetyl quinidine*[20] *(O-AcQUIND, 10 mol %), Mukaiyama's reagent, and Hünig's base*[21] *in CH_3CN gave the bicyclic β-lactone* ***10a*** *in 92% ee* (54%, Table 2), providing evidence for a NCAL reaction mechanism and against a thermal [2 + 2] cycloaddition. The enantiomeric bicyclic β-lactone (−)-**10a** could also be obtained using *O*-acetylquinine (entry 2). β-Lactones **10b** and **10c** were also obtained with high enantioselectivity but also in modest yields.

Production of (1*R*, 2*S*)-(+)-**10a** with *O*-AcQUIND can be rationalized on the basis of previously proposed models[3b,23] modified for the intramolecular process (Figure 1). In this model,

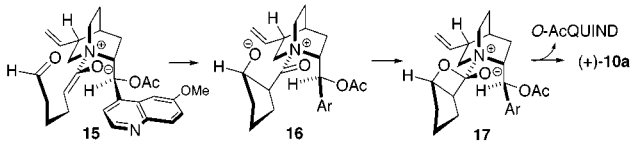
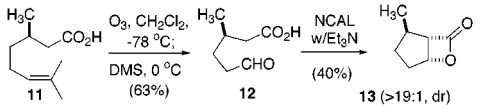
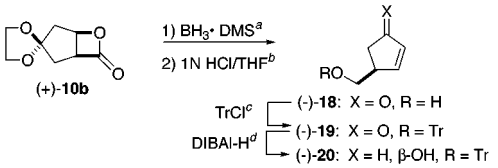


Figure 1. Proposed intermediates and transition-state arrangements leading to the 1*R*,2*S* enantiomer of bicyclic lactone (+)-**10a**. The (*E*)-(*O*)-ammonium enolate (not shown) is also possible.

Scheme 2



Scheme 3[a]



[a] (a) THF, 25 °C, 24 h; (b) 25 °C, 24 h, (51%, two steps); (c) CH_2Cl_2, 25 °C (90%); (d) THF, −78 °C (dr >19:1, 87%).

the aldehyde approaches the si face of the ammonium enolate **15**, opposite the quinoline ring, leading to aldolate **16**. The oxetane **17** is then formed from the *cis*-aldolate (vs trans, not shown) produced in this manner.

To demonstrate the utility of these bicyclic β-lactones, **10b** was transformed in four steps to cyclopentenol **20** with high diastereoselectivity (Scheme 3). The latter compound is a useful intermediate for the synthesis of antiviral carbocyclic nucleosides including (−)-aristeromycin.[24]

In summary, we have developed the first NCAL reactions with unactivated aldehydes, leading to novel bicyclic β-lactones. This structural motif is found in several natural products including spongiolactone and the triterpenes lueolactone and papyriogenin G.[25] More importantly, the presence of the β-lactone in these bicyclics allows for facile conversion to a variety of functional arrays,[2] and thus these bicyclics may serve as useful diversity scaffolds. Furthermore, the intramolecular NCAL is amenable to asymmetric catalysis and thus constitutes the first example of Wynberg's method applied to unactivated aldehydes. This methodology merges catalytic, asymmetric β-lactone synthesis with carbocycle construction employing an organic catalyst. Optimization and exploration of the scope of the asymmetric process including applications to heterocycle and natural product synthesis are currently underway.

Acknowledgment. This paper is dedicated to my mentor and friend Professor Albert I. Meyers, a father of asymmetric synthesis, on the occasion of his retirement. We thank the NSF (CAREER Award, CHE-9624532), the Welch Foundation (A-1280), the NIH (Postdoctoral Supplement to G.S.C., GM-52964-06) and Zeneca Pharmaceuticals for support of these investigations. D.R. is an Alfred P. Sloan Fellow and a Camille-Henry Dreyfus Teacher-Scholar. We thank Mr. Yingcai Wang for helpful discussions. We thank Dr. Joe Reibenspies (TAMU) for X-ray support obtained on NSF-funded instruments (CHE-9807975).

Supporting Information Available: General procedures for the intramolecular NCAL reactions and characterization data (including ^1H and ^{13}C NMR spectra) for bicyclic β-lactones **10a**−**10h**, **13**, and cyclopentenes **19** and **20** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016134+

(19) The stereochemistry of bicycle **13** was determined by coupling constant analysis and GOESY experiments: Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc*. **1994**, *116*, 6037−6038.

(20) (a) Waddell, T. G.; Woods, L. A.; Harrison, W.; Meyer, G. M. *J. Tennessee Acad. Sci.* **1984**, *59*, 48−50. (b) For a lead reference to superb uses of cinchona alkaloids as nucleophilic catalysts, see: Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(21) In our previous studies (ref 6), we determined that Hünig's base catalyzes the NCAL reaction only very slowly (<5% after 24 h).

(22) Inoguchi, K.; Fujie, N.; Yoshikawa, K.; Achiwa, K. *Chem. Pharm. Bull.* **1992**, *40*, 2921−2926.

(23) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121−6131.

(24) Alcohol (+)-**20** was employed in the synthesis of (+)-aristeromycin, the enantiomer of the natural product, see: Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2605−2607.

(25) For reviews of naturally occurring β-lactones and their synthesis, see: (a) Lowe, C.; Vederas, J. C. *Org. Prep. Proced. Int.* **1995**, *27*, 305−346. (b) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729−744.