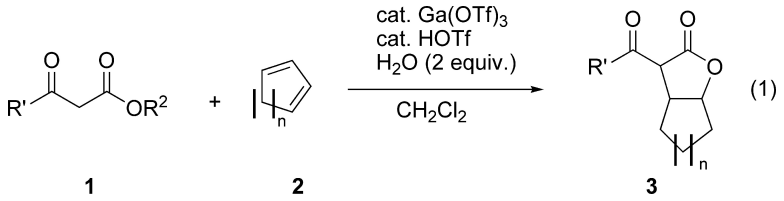
Communication

An Annulation toward Fused Bicyclolactones

Rene-Viet Nguyen, and Chao-Jun Li

J. Am. Chem. Soc., **2005**, 127 (49), 17184-17185• DOI: 10.1021/ja055883e • Publication Date (Web): 15 November 2005



1 **2** **3**

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 4 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 11/15/2005

An Annulation toward Fused Bicyclolactones

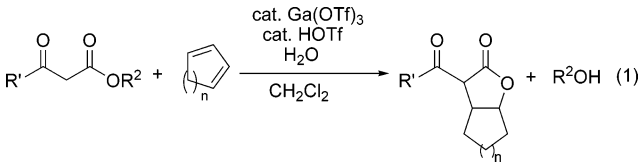
Rene-Viet Nguyen and Chao-Jun Li*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 2K6, Canada

Received September 5, 2005; E-mail: cj.li@mcgill.ca

Bicyclic lactones are found in many natural occurring products[1] and are potent enzyme inhibitors (Figure 1).[2] Halo[3]- and seleno-lactonization[4] are classical examples to form these molecules and entail the intramolecular addition of a carboxyl group to olefins. On the other hand, Backväll[5] has shown a similar process where the carboxylic group is added intramolecularly to a π-allyl palladium complex. Alternatively, formation of these lactones can be alkylated by a radical pathway.[6] The epoxide[7] and cyclopropane[8] route, oxymetalation,[9] and ring-closing metathesis[10] have also been useful for the construction of bicyclic lactones. However, multistep synthesis is usually required to construct these lactones.[11] Recent emphasis on green chemistry[12] has called for the development of methodologies in rapid syntheses of complex molecules in fewer steps. In an effort to develop reactions based on ''atom-economy",[13] we herein report a direct formation of bicyclic lactones.

Recently, we and others have reported the use of β-dicarbonyl for the hydroalkylation of alkenes[14] and dienes.[15,16] However, the addition was mainly limited to the use of dibenzoylmethane as the β-diketone. Indeed, a less activated methylene, 2,4-pentanedione, failed to add to cyclooctadiene when a combination of $AuCl_3$ and AgOTf were used as catalysts. However, a combination of $Ga(OTf)_3$ and HOTf successfully catalyzed the reaction and yielded the expected product. This result encouraged us to extend our system to β-ketoesters, which could lead to the formation of lactones (eq 1).



In our initial studies, ethyl benzoyl acetate was added to cyclooctadiene using various combinations of catalysts (Table 1). The combination of $AuCl_3$ and AgOTf did not lead to any conversion, while the use of $Ga(OTf)_3$ and HOTf converted the β-ketoester into the lactone with minimal side products (entries 1 and 2). $Ga(OTf)_3$ is more effective than $GaCl_3$ (entry 3), while other Lewis acids afford a lower yield of the product (entries 4−6). The use of $Ga(OTf)_3$ alone did not lead to any conversion (entry 7). The use of HOTf alone can also catalyze the reaction albeit in lower yield (entry 8). Increasing the amount of HOTf led mainly to dimerization of the diene (entry 9). Clearly, the role of $Ga(OTf)_3$ is important for this reaction. Among the various solvents tested, CH_2Cl_2 was found to be the preferred solvent.

Subsequently, various β-ketoesters were added to a range of cyclic dienes under the optimized conditions (Table 2, entries 1−10). The presence of an electron-withdrawing substituent on the aryl group seems to be more beneficial (entries 4, 6, 8) compared to an electron-donating substituent (entry 7). The position of the substituent is also important. A meta-substituted phenyl decreases the yield of the reaction (entry 9), whereas an ortho-substituted

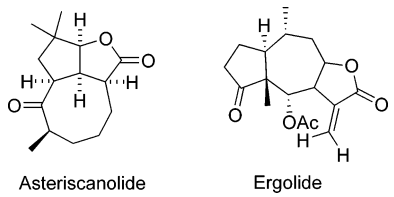
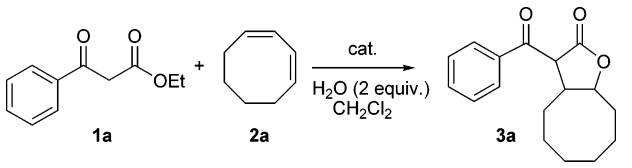


Figure 1. Natural products containing bicyclic lactones.

Table 1. Reaction of Cycloctadiene with Ethyl Benzoyl Acetate under Various Conditions[a]

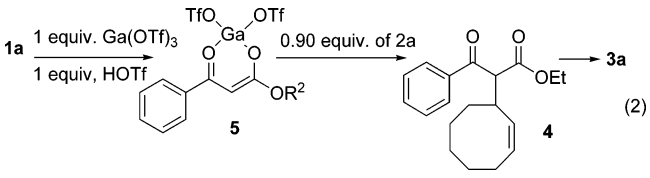


entry	catalysts[b]	conversion[c] (%)	isolated yield (%)
1	5% $AuCl_3$/15% AgOTf	0	0
2	$Ga(OTf)_3$/HOTf	75	64
3	$GaCl_3$/HOTf	0	0
4	$In(OTf)_3$/HOTf	60	53
5	$Zn(OTf)_2$/HOTf	45	32
6	$Cu(OTf)_2$/HOTf	low	trace
7	$Ga(OTf)_3$	0	0
8	HOTf	35	29
9	40% HOTf	84	10

[a] Conditions: 1.1 equiv. of **1a** under refluxing dichloromethane. [b] 15% mol of Lewis acid and 5% of HOTf were used, unless otherwise mentioned. [c] Based on **2a**.

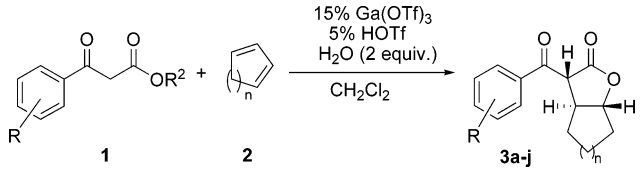
electron-withdrawing group on the phenyl lead to only a trace amount of desired product. Finally, a methyl ester seems to be more beneficial than the ethyl ester (entry 5). On the other hand, less activated β-ketoesters (such as acetoacetate) and malonates lead to very low conversions under the present conditions. Linear dienes were also effective but gave a complicated mixture that is still under investigation. Interestingly, only a single diastereoisomer is observed for these reactions, except in the case of product **3j**.

Mechanistically, **4** can be isolated during the course of the reaction. Subsequent treatment of this intermediate with a catalytic amount of $Ga(OTf)_3$ and HOTf affords the expected product **3a** in almost quantitative yield. This result suggests that the product is formed via a cascade addition of activated methylene to the diene followed by an in situ lactonization. To verify this hypothesis, when a stoichoimetric amount of $Ga(OTf)_3$ and HOTf is added to



10.1021/ja055883e CCC: $30.25

Table 2. Addition of Various β-Ketoesters to Dienes Catalyzed by Gallium and HOTf[a]

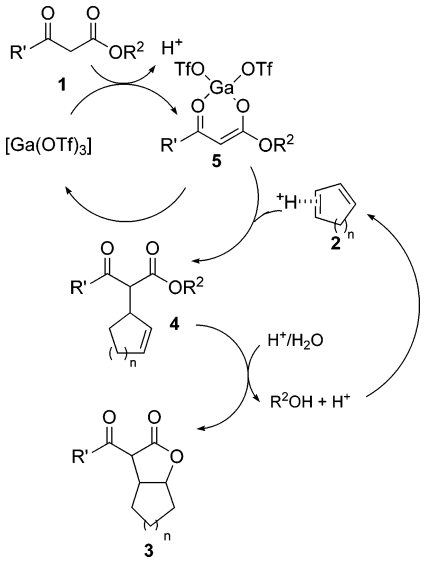


entry[b]	R	R^2	n	product	isolated yield (%)
1	4-H	Et	4	**3a**	64
2	4-H	Et	2	**3b**	66
3	4-Me	Et	4	**3c**	61
4	4-Cl	Et	4	**3d**	70
5	4-Cl	Me	4	**3e**	80
6	4-Br	Et	4	**3f**	71
7	4-OMe	Et	4	**3g**	37
8	4-CF_3	Et	4	**3h**	75
9	3-CF_3	Et	4	**3i**	42
10	4-Cl	Me	3	**3j**	78 (10:1)[c]

[a] The relative stereochemistry was determined by NOE. [b] 1.1 equiv of **1** under refluxing dichloromethane. [c] The ratio of diastereoisomers was determined by ^{1}H NMR.

β-ketoester **1a**, only the enolate form **5** of the β-ketoester is observed. This suggests a coordination of $Ga(OTf)_3$ to the dicarbonyl. Addition of **2a** led to the formation of **4** which was eventually transformed into **3a** (eq 2). A tentative mechanism is thus proposed in Scheme 1. β-ketoester **1** is activated by $Ga(OTf)_3$. Species **5** adds to the acid-activated diene **2** to afford intermediate **4**. Subsequent lactonization affords the fused lactone **3**. The acid is regenerated for further reaction.[17]

Scheme 1



In conclusion, we have developed a direct route to fused lactones. The scope, mechanism and synthetic applications of this reaction are currently under investigation in our laboratories.

Acknowledgment. We are grateful to the Canada Research Chair (Tier I) foundation (to C.J.L.), the CFI, NSERC, Merck Frosst, and McGill University for support of this research. R.V.N. thanks Dr. Xiaoquan Yao for his help with ^{13}C NMR.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA055883E

(1) For a recent review, see: Zhang, S.; Won, Y.-K.; Ong, C.-N.; Shen, H.-M. *Curr. Med. Chem.: Anti-Cancer Agents* **2005**, *5*, 239.
(2) Weir, M. P.; Bethell, S. S.; Cleasby, A.; Campbell, C. J.; Dennis, R. J.; Dix, C. J.; Finch, H.; Jhoti, H.; Mooney, C. J.; Patel, S.; Tang, C.-M.; Ward, M.; Wonacott, A. J.; Wharton, C. W. *Biochemistry* **1998**, *37*, 6645−6657.
(3) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.
(4) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Product Synthesis*; CIS, Inc.: Philadelphia, 1994.
(5) For a recent representative reference, see: Verboom, R. C.; Persson, B. A.; Backväll, J. E. *J. Org. Chem.* **2004**, *69*, 3102 and references therein.
(6) (a) Tin-mediated radical reaction: Chatgilialuglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991. (b) Copper-mediated radical reaction: Clark, A. T. *Chem. Soc. Rev.* **2002**, *31*, 1.
(7) (a) Madhushaw, R. J.; Li, C.-L.; Shen, K.-H.; Hu C.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2001**, *123*, 7427. (b) Madhushaw, R. J.; Li, C.-L.; Su, H. L.; Hu C.-C.; Lush, S. F.; Liu, R. S. *J. Org. Chem.* **2003**, *68*, 1872.
(8) (a) Singh, R. K.; Danishefsky, S. *J. Org. Chem.* **1976**, *41*, 1668. (b) Strekowski, L.; Battiste, M. *Tetrahedron Lett.* **1981**, *22*, 279.
(9) (a) Larock, R. C.; Harrison, L. W.; Su, M. H. *J. Org. Chem.* **1984**, *49*, 3662. (b) Pearson, A. J.; Role, S. L.; Ray, T. *J. Am. Chem. Soc.* **1984**, *106*, 6060.
(10) For reviews on ring-closing metathesis, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. For recent representative references, see: (a) Paquette, L. A.; Mendez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301. (b) Rodriguez, C. M.; Ravelo, J. L.; Martin, V. S. *Org. Lett.* **2004**, *25*, 4787.
(11) The addition of glyoxylic acid to cyclopentadiene leads to a bicylic lactone in a single step. See: Lubineau, A.; Auge, J.; Grand, E.; Lubin, N. *Tetrahedron* **1994**, *50*, 10265−10276.
(12) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.
(13) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
(14) Yao, X.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 6884.
(15) Nguyen, R. V.; Yao, X.; Bohle, D. S.; Li, C. J. *Org. Lett.* **2005**, *7*, 673.
(16) For similar reactions: (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002. (b) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (c) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (d) Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552.
(17) While the exact role of water is unclear at the moment, it presumebly helps to remove the corresponding alcohol.