ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Versatile Approaches for the Synthesis of Fused-Ring γ-Lactones Utilizing Cyclopropane Intermediates

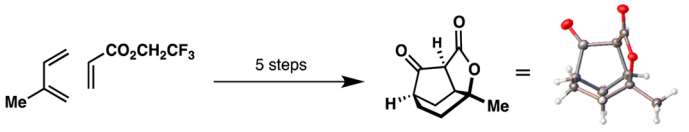
Timothy R. Newhouse, Philip S. J. Kaib, Andrew W. Gross, and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

corey@chemistry.harvard.edu

Received February 7, 2013

ABSTRACT



A highly effective acid-catalyzed cyclopropyl ester to γ-lactone skeletal rearrangement has been demonstrated and applied to the synthesis of a variety of bi- and tricyclic functionalized lactones, rigid and highly compact structures for use as biological probes.

γ-Lactones have served as versatile intermediates in countless syntheses of complex molecules, and as a consequence, many studies have been directed at increasing synthetic access to this structural subunit. As a result, there is now a large repetoire of methods for γ-lactone synthesis.[1,2] The most generally useful processes are those which allow stereocontrol by internal delivery or catalytic entantioselective access to complex chiral structures. Such processes include the following: (1) intramolecular Diels–Alder reactions of acrylate esters,[3] (2) intramolecular addition of diazo esters to carbon–carbon double bonds,[4] (3) addition of acrylate esters to ketonic carbonyls induced by SmI_2,[5] (4) intramolecular or intermolecular cycloaddition of ketenes to carbon–carbon double bonds followed by Baeyer–Villiger oxidation,[6] (5) intramolecular or intermolecular cycloaddition of β-keto acids to carbon–carbon double bonds induced by $Mn_3O(OAc)_7$,[7] (6) intramolecular halo- and hydroxylactonization,[8] and (7) intramolecular addition of radicals to carbon–carbon double bonds.[9]

This paper reports new and short routes to a variety of chiral γ-lactones using tactical combinations of a cyclopropyl ester to γ-lactone skeletal rearrangement[10] and a range of enantioselective processes.

We provide as the first illustration of our approach the enantioselective synthesis of the tricyclic keto-lactone (**1**) shown in Scheme 1. The starting point was the *R*-ester **3**, which was prepared enantioselectively as previously described, using the chiral oxazaborolidinium ion **2** as catalyst.[11] The β-ketoester **4** was accessed from **3** by Claisen condensation and then transformed into the corresponding α-diazoketone using tosyl azide and triethylamine.

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, 1988.

(2) (a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Mechanisms, Reactions, and Structure*, 5th ed.; John Wiley: New York, 2001. (b) Ogliaruso, M. A.; Waefe, J. F. *Synthesis of Lactones and Lactams*: John Wiley: New York, 2010; online.

(3) For an early example with a δ-lactone, see: Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031–8034.

(4) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423–1424.

(5) (a) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763–5764. (b) See also: Corey, E. J.; Zheng, G. Z. *Tetrahedron Lett.* **1997**, *38*, 2045–2048.

(6) (a) Corey, E. J.; Kang, M.-c.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649–651. (b) Corey, E. J.; Weinschenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677.

(7) (a) Heiba, E. I.; Dessau, R. M.; Koehl, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 5905–5906. (b) Corey, E. J.; Kang, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 5384–5385.

(8) (a) Ma, S.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 8306–8308. (b) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407–6410.

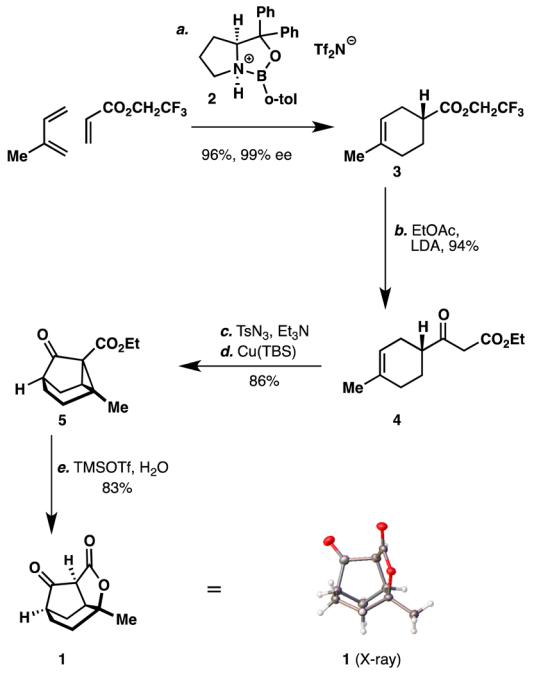
(9) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187–6189.

(10) This work was initiated by A.W.G. at Harvard in 1982 and completed recently by T.R.N. and P.S.J.K. For a related example, see: Kolsaker, P.; Jensen, A. K. *Acta Chem. Scand.* **1988**, *B 42*, 345–353.

(11) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390.

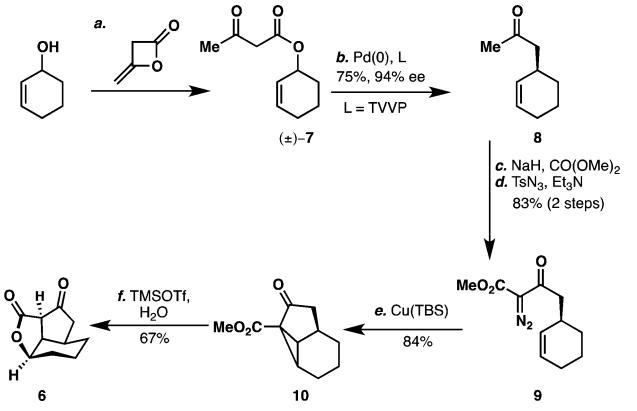
10.1021/ol400362t

Scheme 1. Synthesis of Ketolactone **1**[a]



[a] Reagents and conditions: (a) isoprene (5.0 equiv), cat. **2** (0.20 equiv), PhMe (1.0 M), −5 °C, 15 h, 96%, 99% ee; (b) EtOAc (2.5 equiv), LDA (2.5 equiv), THF, −78 to −45 °C, 3.5 h, 94%; (c) TsN_3 (1.1 equiv), Et_3N (0.5 M), 23 °C, 39 h, 99%; (d) Cu(TBS) (0.06 equiv), PhMe (0.02 M), 111 °C, 6 h, 87%; (e) TMSOTf (3.0 equiv), H_2O (1.5 equiv), *i*-$PrNO_2$ (20 mM), 23 °C, 17 h, 83%.

Scheme 2. Synthesis of Ketolactone **6**[a]



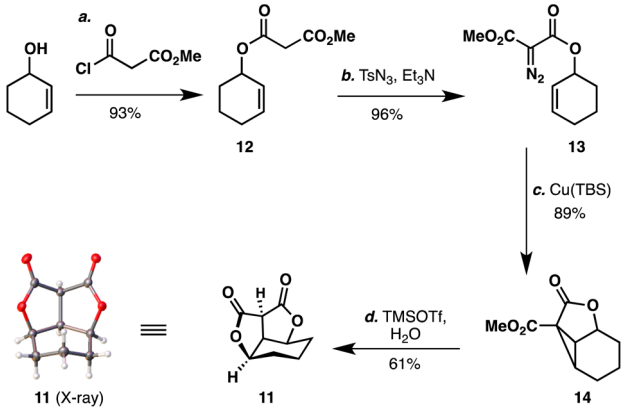
[a] Reagents and conditions: (a) and (b) ref 12; (c) NaH (6.0 equiv), $CO(OMe)_2$ (2.1 equiv), 1,4-dioxane (0.5 M), 101 °C, 3 h, 87%; (d) TsN_3 (1.1 equiv), Et_3N (1.0 M), 23 °C, 2 h, 95%; (e) Cu(TBS) (0.06 equiv), PhMe (0.05 M), 111 °C, 15 h, 84%; (f) TMSOTf (3.0 equiv), H_2O (1.5 equiv), *i*-$PrNO_2$ (20 mM), 110 °C, 3 h, 67%.

Internal [2 + 1]-cycloaddition to the C−C double bond of the diazo substrate was promoted by bis-(*N*-*t*-butylsalicylaldiminato)copper(II) (Cu(TBS)) as catalyst to form the tricyclic β-keto ester **5**. Finally, treatment of **5** with trimethylsilyl triflate and a small amount of water (to generate some triflic acid) in *i*-$PrNO_2$ at 23 °C produced the keto lactone **1** in 83% yield (X-ray structure as shown in Scheme 1).

A direct and efficient route to the chiral tricyclic keto lactone **6** is summarized in Scheme 2. The acetoacetate ester of (±)-2-cyclohexenol was converted into (*R*)-3-acetonylcyclohexene by the method of Burger and Tunge[12] via the π-allyl Pd complex with the C_2-symmetric Trost−Van Vranken bisphosphine (TVVP).[13] The desired chiral tricyclic keto lactone **6** was readily obtained from **8** via the sequence α-methoxycarbonylation, Regitz diazo transfer, Cu(TBS)-catalyzed internal [2 + 1] cycloaddition, and acid-catalyzed cyclopropane to lactone rearrangement via the intermediates **9** and **10**.

The prochiral tricyclic bis-lactone corresponding to **6** (**11**) could also be accessed rapidly using the cyclopropyl ester to γ-lactone rearrangement (see Scheme 3). Methyl 2-cyclohexenylmalonate (**12**) was transformed via the corresponding diazoester **13** to the cyclopropyl ester lactone **14**, rearrangement of which proceeded at 45 °C to afford bis-lactone **11**.

Scheme 3. Synthesis of Bislactone **11**[a]



[a] Reagents and conditions: (a) $ClCOCH_2CO_2Me$, Et_3N, CH_2Cl_2, 0−23 °C, 93%; (b) TsN_3 (1.2 equiv), Et_3N (1.0 M), 23 °C, 0.5 h, 96%; (c) Cu(TBS) (0.06 equiv), PhMe (0.02 M), 111 °C, 15 h, 89%; (d) TMSOTf (3.0 equiv), H_2O (1.5 equiv), *i*-$PrNO_2$ (20 mM), 45 °C, 5 h, 61%.

In a similar fashion, the bicyclic bis-lactone **15** (Scheme 4) was synthesized from methyl cinnamyl malonate (**16**) and diazoester **17**.[14] Cyclopropyl to γ-lactone rearrangement converted **17** to **15** and a minor diastereomer (ratio 5:1) in 83% yield. The structure of **15** was demonstrated by single-crystal X-ray diffraction analysis.

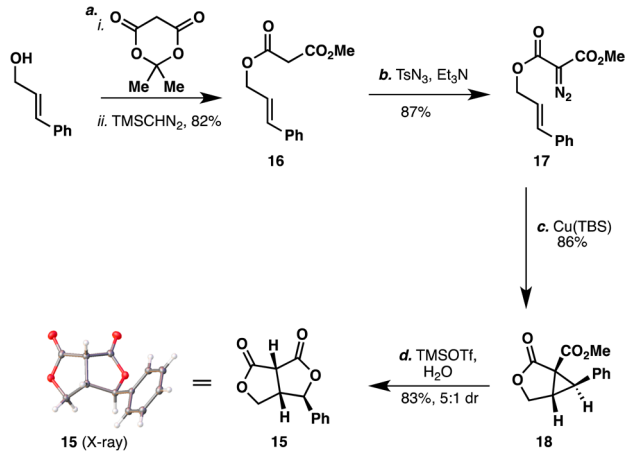
A final example of the application of our methodology to a short synthesis of a bicyclic keto lactone (**19**) is outlined in Scheme 5. 6-Methyl-5-hepten-2-one (**20**) was transformed first into the α-diazo-β-keto ester **21**, which

(12) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113–4115.

(13) (a) Van Vranken, D. L.; Trost, B. M. *Chem. Rev.* **1996**, *96*, 395–422. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944.

(14) The corresponding ethyl ester of **18** has been prepared by the method of: Xu, X.; Lu, H.; Ruppel, J. V.; Cui, X.; de Mesa, S. L.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 15292–15295. The conversion of the methyl ester **17** to **18** proceeds in 95% yield and 92% ee (personal communication with Xue Xu and X. Peter Zhang).

Scheme 4. Synthesis of Bislactone **15**[a]



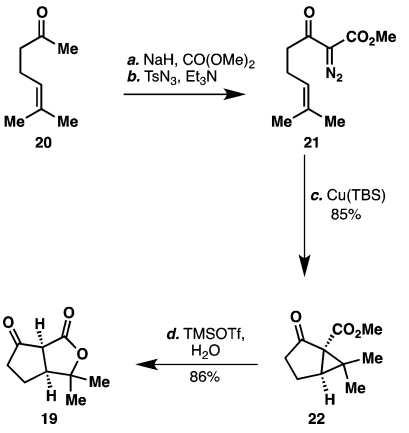
[a] Reagents and conditions: (a) (i) cinnamyl alcohol (1.0 equiv), Meldrum's acid (1.0 equiv), PhMe (3 M), 90 °C, 12 h, (ii) $TMSCHN_2$ (1.5 equiv), C_6H_6/MeOH (4:1), 23 °C, 10 min, 82%; (b) TsN_3 (1.1 equiv), Et_3N (1.0 M), 23 °C, 2 h, 87%; (c) Cu(TBS) (0.06 equiv), PhMe (0.05 M), 111 °C, 15 h, 86%; (d) TMSOTf (3.0 equiv), H_2O (1.5 equiv), *i*-$PrNO_2$ (20 mM), 40 °C, 24 h, 83% (5:1 dr).

by internal [2 + 1]-cycloaddition provided the bicyclic keto ester **22**. Acid catalyzed rearrangement of **22** produced (+)-**19** in good overall yield from **20**. Although our experiments employed racemic **22** to generate (±)-**19**, a catalytic enantioselective preparation of chiral **22** from **21** has been reported,[15] the use of which would lead to chiral ketolactone **19**.

(15) Cho, D.-J.; Jeon, S.-J.; Kim, H.-S.; Cho, C.-S.; Shim, S.-C.; Kim, T.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 3833–3848.

(16) General procedure for the cyclopropyl ester to γ-lactone rearrangement: To a solution of TMSOTf (54 μL, 0.30 mmol, 3.0 equiv) in *i*-$PrNO_2$ (4 mL) was added H_2O (2.7 μL, 0.15 mmol, 1.5 equiv) by dropwise addition. After stirring at ambient temperature for 10 min, the cyclopropane (0.1 mmol, 1.0 equiv) as a solution in *i*-$PrNO_2$ (1 mL) was added. After being stirred for the appropriate time and temperature, the reaction mixture was treated with aq phosphate buffer (pH = 7, 25 mL) and the organic phase was separated. The aqueous phase was extracted with EtOAc (5 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography provided the product.

Scheme 5. Synthesis of Ketolactone **19**[a]



[a] Reagents and conditions: (a) $CO(OMe)_2$ (2.1 equiv), NaH (6.0 equiv), 1,4-dioxane (0.5 M), 101 °C, 3 h; (b) TsN_3 (1.2 equiv), Et_3N (1.0 M), 23 °C, 0.5 h; (c) Cu(TBS) (0.06 equiv), PhMe (0.02 M), 111 °C, 13 h, 85%; (d) TMSOTf (3.0 equiv), H_2O (1.5 equiv), *i*-$PrNO_2$ (20 mM), 23 °C, 3 h, 86%.

In conclusion, the five sequences reported above and summarized in Schemes 1−5 demonstrate a useful methodology for the construction of a range of bi- to polycyclic lactones with control of stereochemistry and a minimum of synthetic steps.[16] These rigid and compact structues could be of value as small, ligand-efficient probes for screening purposes in medicinal research.

Acknowledgment. Dr. Shao-Zhen Liang is gratefully acknowledged for acquisition of all X-ray crystal structures. This work was supported by Bristol-Myers Squibb through a Postdoctoral Fellowship to T.R.N. The Fritz und Maria Hofmann-Stiftung and the Richard-Winter-Stiftung is acknowledged for financial support to P.S.J.K.

Supporting Information Available. Procedures, full characterization, spectra, and X-ray data (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.