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A Direct Method for the Conversion of Terminal Epoxides into  $\gamma$ -Butanolides

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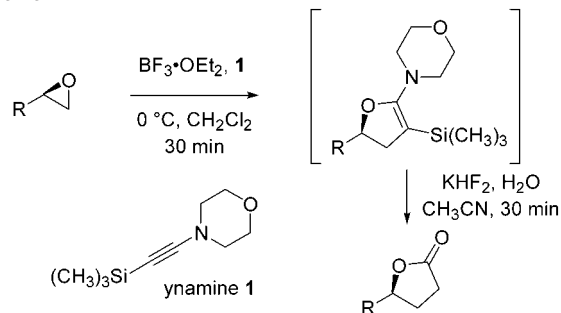
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Ring-opening of epoxides, particularly with carbon-based nucleophiles, is a highly valuable synthetic strategy for the stereo-specific elaboration of organic compounds.<sup>1–3</sup> Despite the venerable place held by enolates as carbon-based nucleophiles for organic synthesis,  $\gamma$ -hydroxy carboxylic acid derivatives are rarely accessed via epoxide ring opening by acetate enolates,<sup>3</sup> largely because of the paucity of reliable and efficient methodology for such transformations.<sup>4–6</sup> Herein we describe a new and efficient route to  $\gamma$ -butanolides in a single step and under mild reaction conditions from terminal epoxides (Scheme 1). Coupled with existing highly effective methods for the asymmetric synthesis of terminal epoxides,<sup>7,8</sup> this procedure provides ready access to a wide variety of  $\gamma$ -lactone derivatives in enantiopure form.

Our strategy was based on the expectation that a neutral, electron-rich carbon–carbon triple bond might serve as a functional equivalent of an enolate in epoxide additions. Specifically, we sought a reactive alkynyl nucleophile for a Lewis acid mediated opening of epoxides. Evaluation of a series of alkyne/Lewis acid combinations led to the discovery that use of 1-morpholino-2-trimethylsilyl acetylene<sup>9</sup> (**1**) and boron trifluoride diethyl etherate ( $\text{BF}_3 \cdot \text{OEt}_2$ ) allows the rapid and efficient conversion of terminal epoxides to the corresponding cyclic keteneaminals. Subsequent hydrolysis and protodesilylation affords the corresponding  $\gamma$ -butanolide (Scheme 1). The net transformation is equivalent to an acetate enolate opening of terminal epoxides that is compatible with a wide range of functional groups (Table 1). Enantiomerically enriched terminal epoxides led to  $\gamma$ -butanolides without loss of optical purity throughout the ring-opening, hydrolysis, protodesilylation sequence, thus establishing the applicability of this methodology toward the preparation of enantiopure  $\gamma$ -butanolide building blocks.<sup>10</sup>

Unambiguous evidence for the formation of a cyclic keteneaminal (Scheme 1) as the direct addition product between ynamine **1** and terminal epoxides was provided through a series of spectroscopic and reactivity studies. The addition of phenylglycidyl ether to a solution of **1** and  $\text{BF}_3 \cdot \text{OEt}_2$  in anhydrous dichloromethane was monitored at 0 °C by React-IR and solution-cell FTIR spectroscopy. Immediate loss of the ynamine absorption band<sup>9</sup> at  $2149 \text{ cm}^{-1}$  was detected, with concomitant appearance of a strong keteneaminal absorption band at  $1618 \text{ cm}^{-1}$ .<sup>11c,d</sup> Similarly,  $^{13}\text{C}$  NMR analysis of the reaction between ethylene oxide and ynamine **1**/ $\text{BF}_3 \cdot \text{OEt}_2$  in chloroform- $d_1$  at 0 °C revealed rapid formation of the corresponding keteneaminal with characteristic resonances at  $\delta$  165.1 and 82.1 ppm.<sup>11d</sup> A  $^{29}\text{Si}$  resonance due to the vinylic silane group was observed as a signal at  $\delta$  –10.5 in a variable-temperature  $^{29}\text{Si}$ - $^1\text{H}$  HMQC NMR experiment.<sup>11a,b</sup> Consistent with the intermediacy of a cyclic keteneaminal, the addition of trifluoroacetic acid- $d_1$  (5 equiv) to a solution of the keteneaminal derived from 1-epoxy-3-phenylpropane provided, after aqueous workup, the corresponding  $\gamma$ -butanolide in 90% isolated yield with >96% deuterium incor-

Scheme 1



poration at the  $\alpha$ -methylene position.<sup>12</sup> This new epoxide opening–keteneaminal cyclization sequence is thereby mechanistically distinct from metal acetylide ring-opening of epoxides, which involves formation of homopropargylic alcohols.<sup>2c,6</sup>

The intermediacy of cyclic keteneaminals in the ring-opening of epoxides with **1** is not only mechanistically significant but also provides an opportunity for the direct synthesis of more highly functionalized  $\gamma$ -butanolides by simply varying the method for reaction workup. Addition of *N*-bromosuccinimide (NBS) to a cold solution of the keteneaminal derived from (*R*)-1-epoxy-3-phenylpropane (>99% ee) led to the efficient synthesis of the corresponding  $\alpha,\alpha$ -dibromo- $\gamma$ -butanolide (96%, >99% ee, Scheme 2). Furthermore, treatment of the crude  $\alpha,\alpha$ -dibromo- $\gamma$ -butanolide with  $\text{LiCl}$  and  $\text{Li}_2\text{CO}_3$  in DMF at 70 °C rapidly afforded the  $\alpha$ -bromo- $\gamma$ -butanolide without loss of optical purity (82%, >99% ee).<sup>13</sup>

Both the regioselectivity and efficiency of the chemistry described above are compromised in the case of vinyl- and aryl-substituted epoxides. Styrene oxide undergoes  $\text{BF}_3 \cdot \text{OEt}_2$ -promoted rearrangement to phenylacetaldehyde faster than reaction with **1**.<sup>12,14</sup> Interestingly, the use of (*R*)-3-nitrostyrene oxide (>99% ee) led to a stereospecific epoxide ring-opening at the benzylic center to provide the corresponding  $\gamma$ -butanolide (62%, >99% ee).<sup>12</sup> More substituted epoxides and aziridine derivatives failed to provide the desired ring-opened products.<sup>12</sup>

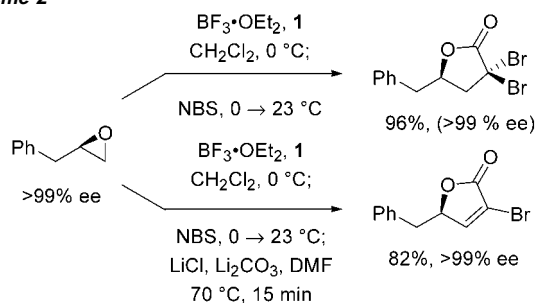
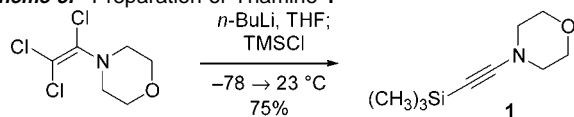
Ynamine **1** was found to possess superior reactivity for Lewis acid mediated ring-opening of epoxides as compared to a range of other electron-rich alkyne and keteneacetal derivatives.<sup>12</sup> While the amine component provides the necessary nucleophilicity for the Lewis acid-catalyzed epoxide ring-opening, the trimethylsilyl substituent inhibits the rapid decomposition of **1** in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ . Ynamine **1** is readily available in multigram quantities,<sup>12</sup> either by the sequential treatment of *N*-trichlorovinyl morpholine with *n*-BuLi followed by chlorotrimethylsilane (Scheme 3)<sup>9</sup> or by the addition of lithium morpholide to chlorotrimethylsilylacetylene,<sup>9b</sup> and is stable for months at 0 °C.

The present methodology provides a highly efficient and expedient new route to homoenolate aldols in the form of  $\gamma$ -butanolides. Furthermore, the interception of a cyclic keteneaminal intermediate

**Table 1.** Conversion of Terminal Epoxides to  $\gamma$ -Butanolides

Entry	Substrate	Product	Yield (%) <sup>a</sup>
1 <sup>b</sup>			89 <sup>c</sup>
2 <sup>b</sup>			92 <sup>c</sup>
3 <sup>b,d</sup>			84 <sup>c</sup>
4 <sup>e</sup>			71
5 <sup>b</sup>			84 <sup>c</sup>
6 <sup>e</sup>			95
7 <sup>e</sup>			86
8 <sup>e</sup>			69
9 <sup>b</sup>			65 <sup>c</sup>
10 <sup>b</sup>			96 <sup>c</sup>
11 <sup>e</sup>			86
12 <sup>b</sup>			91 <sup>c</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> Ee of substrate >99%. <sup>c</sup> Ee of product >99%.  
<sup>d</sup> Complete protodesilylation required 2 h at 23 °C. <sup>e</sup> Racemic substrate was used.

**Scheme 2****Scheme 3.** Preparation of Ynamine **1**

allows direct access to a variety of functionalized  $\gamma$ -lactones. The mild reaction conditions, wide functional group compatibility, overall efficiency, and ease of operation render this methodology a potentially powerful addition to the list of useful transformations

of epoxides. We anticipate that the building blocks rendered readily accessible by this chemistry will prove useful for the asymmetric synthesis of more complex targets.

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**Supporting Information Available:** Representative experimental procedures and analytical and spectroscopic characterization data for the products of Table 1 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.
- (2) (a) Klunder, J. M.; Posner, G. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 223–226. (b) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 262–266. (c) Garrat, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 277–280.
- (3) For an excellent review, see: Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149.
- (4) (a) Larchevêque, M.; Valette, G.; Cuvigny, T.; Normant, H. *Synthesis* **1975**, 256. (b) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028. (c) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242. (d) Grieco, P. A.; Ohfune, Y.; Majetich, G. J. *Org. Chem.* **1979**, *44*, 3092. (e) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163. (f) Sturm, T.-J.; Marolewski, A. E.; Rezenka, D. S.; Taylor, S. K. *J. Org. Chem.* **1989**, *54*, 2039. (g) Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett.* **1991**, *32*, 7583. (h) Ipaktschi, J.; Heydari, A. *Chem. Ber.* **1993**, *126*, 1905. (i) Myers, A. G.; McKinstry, L. J. *Org. Chem.* **1996**, *61*, 2428. (j) Lalic, G.; Petrovski, Z.; Galonic, D.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2001**, *57*, 583.
- (5) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509. (c) Taylor, S. K.; Atkinson, R. F.; Almli, E. P.; Carr, M. D.; Huis, T. J. V.; Whittaker, M. R. *Tetrahedron: Asymmetry* **1995**, *6*, 157.
- (6) (a) Danishefsky, S. J.; Kitahara, T.; Tsai, M.; Dynak, J. *J. Org. Chem.* **1976**, *41*, 1669. (b) Lipshutz, B. H.; Tirado, R. *J. Org. Chem.* **1994**, *59*, 8307.
- (7) Via hydrolytic kinetic resolution: (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* In press.
- (8) Via epoxidation of allylic alcohols: Katsuki, T. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Chapter 18.
- (9) (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1449. (b) Sato, Y.; Kobayashi, Y.; Sugiura, M.; Shirai, H. *J. Org. Chem.* **1978**, *43*, 199. (c) Berger, D.; Bartlome, A.; Neuenschwander, M. *Helv. Chim. Acta* **1996**, *79*, 179. (d) Himbert, G.; Nasshan, H.; Gerulat, O. *Synthesis* **1997**, 293. (e) Berger, D.; Wilhelm, P.; Neuenschwander, M. *Helv. Chim. Acta* **1999**, *82*, 326. (f) For a review, see: Zifcsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.
- (10) The following experimental procedure is illustrative: (*R*)-1-Epoxy-5-hexene (Table 1, entry 1, 1.10 g, 11.2 mmol, 1 equiv, >99% ee) was added to a clear and yellow solution of ynamine **1** (2.94 g, 16.0 mmol, 1.4 equiv) and  $\text{BF}_3 \cdot \text{OEt}_2$  (2.03 mL, 11.2 mmol, 1.4 equiv) in anhydrous dichloromethane (68 mL) at 0 °C. After 30 min, the yellow reaction solution was diluted sequentially with acetonitrile (15 mL) and an aqueous potassium hydrogen bifluoride solution (3.7 M, 15 mL) and the resulting mixture was warmed to 23 °C for 30 min. After extractive isolation and chromatography on silica gel, the corresponding  $\gamma$ -butanolide was obtained as a clear and colorless oil (1.4 g, 92%, >99% ee).
- (11) (a) Grignon-Dubois, M.; Laguerre, M. *Organometallics* **1988**, *7*, 1443. (b) Al-Hassan, M.; Al-Najjar, I. M.; Al-Oraifi, I. M. *Magn. Reson. Chem.* **1989**, *27*, 1112. (c) Himbert, G.; Kuhn, H.; Barz, M. *Liebigs Ann. Chem.* **1990**, 403. (d) Allen, A. D.; Huang, W.-w.; Moore, P. A.; Far, A. R.; Tidwell, T. T. *J. Org. Chem.* **2000**, *65*, 5676.
- (12) See the Supporting Information for details.
- (13) Forti, L.; Ghelfi, F.; Pagnoni, U. M. *Tetrahedron Lett.* **1995**, *36*, 3023.
- (14) Smith, J. G. *Synthesis* **1984**, 629.

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