Selective Syntheses of $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ Butenolides from Allylic Cyclopropenecarboxylates via Tandem Ring Expansion/[3,3]-Sigmatropic Rearrangements

ORGANIC LETTERS 2013 Vol. 15, No. 7 1500–1503

Xiaocong Xie, Yi Li, and Joseph M. Fox*

Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States

jmfox@udel.edu

Received January 29, 2013

ABSTRACT



Allylic cyclopropenecarboxylates undergo ring expansion reactions to give 2-allyloxyfuran intermediates, which subsequently rearrange to $\Delta^{\beta,\gamma}$ butenolides via a Claisen rearrangement or to the corresponding $\Delta^{\alpha,\beta}$ butenolides via further Cope rearrangement. Also described are methods for chirality transfer in the rearrangement of nonracemic allylic esters.

Compounds with $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ butenolide substructures have received much interest for their utility in synthesis¹ and their prevalence in biologically active molecules and natural products.² A number of methods for preparing $\Delta^{\alpha,\beta}$ butenolides involve the reactivity of furan derivatives, including asymmetric variants based on the Michael,³ Mukaiyama–Michael,⁴ vinylogous Mannich,⁵ Morita– Baylis–Hillman,⁶ and aldol reactions⁷ that utilize siloxyfurans to provide enantiomerically enriched $\Delta^{\alpha,\beta}$ butenolides. There are also a number of enantiospecific syntheses of $\Delta^{\alpha,\beta}$ butenolides in which epoxides⁸ or allenoates⁹ are used as precursors.

Relative to methods for preparing $\Delta^{\alpha,\beta}$ butenolides,^{1d,10} the methods for accessing $\Delta^{\beta,\gamma}$ isomers are few, especially for butenolides that bear a quaternary α -stereocenter.

^{(1) (}a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (c) Hashem, A.; Senning, A. *Adv. Heterocycl. Chem.* **1999**, *73*, 275. (d) Hashem, A.; Kleinpeter, E. *Adv. Heterocycl. Chem.* **2001**, *81*, 107.

⁽²⁾ Ospina, C. A.; Rodríguez, A. D. Org. Lett. 2009, 11, 3786. (b) Yu, Z.-G.; Li, J.; Li, Z.-Y.; Guo, Y.-W. Chem. Biodiversity 2009, 6, 858.

⁽³⁾ Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. Chem. Commun. 2004, 1414.

^{(4) (}a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. J. Am. Chem. Soc. 2003, 125, 1192. (b) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. Tetrahedron 2001, 57, 10203. (c) Robichaud, J.; Tremblay, F. Org. Lett. 2006, 8, 597. (d) Ishihara, K.; Fushimi, M. Org. Lett. 2006, 8, 1921. (e) Yang, H.; Kim, S. Synlett 2008, 555.

^{(5) (}a) Martin, S. F.; Barr, K. J. J. Am. Chem. Soc. 1996, 118, 3299.
(b) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. J. Am. Chem. Soc. 2008, 130, 17961. (c) Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquotti, D.; Casiraghi, G. Eur. J. Org. Chem. 1999, 1395. (d) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. J. Am. Chem. Soc. 1999, 121, 6990. (e) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2006, 45, 7230. (f) González, A. S.; Arrayás, R. G.; Rivero, M. R.; Carretero, J. C. Org. Lett. 2008, 10, 4335. (g) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. J. Am. Chem. Soc. 2009, 131, 570. (h) Yuan, Z.-L.; Jiang, J.-J.; Shi, M. Tetrahedron 2009, 65, 6001.

⁽⁶⁾ Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. J. Am. Chem. Soc. 2008, 130, 7202.

^{(7) (}a) Szlosek, M.; Figadère, B. Angew. Chem., Int. Ed. 2000, 39, 1799. (b) Szlosek, M.; Franck, X.; Figadère, B.; Cavé, A. J. Org. Chem. 1998, 63, 5169. (c) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. J. Am. Chem. Soc. 1999, 121, 669. (d) Boeckman, R. K., Jr.; Pero, J. E.; Boehmler, D. J. J. Am. Chem. Soc. 2006, 128, 11032. (e) Nagao, H.; Yamane, Y.; Mukaiyama, T. Chem. Lett. 2007, 36, 8. (f) Fabra, M. J; Fraile, J. M.; Herrerias, C. I.; Lahoza, F. J.; Mayoral, J. A.; Pérez, I. Chem. Commun. 2008, 5402. (g) Frings, M.; Atodiresei, I.; Runsink, J.; Raabe, G.; Bolm, C. Chem. Zoc. 2009, 131, 1410.

⁽⁸⁾ Movassaghi, M.; Jacobsen, E. N. J. Am. Chem. Soc. 2002, 124, 2456.

Cycloisomerization and iodolactonization reactions have been used in the construction of $\Delta^{\beta,\gamma}$ butenolides that bear α -quaternary stereocenters.¹¹ Vedejs¹² and Smith¹³ have catalyzed carboxyl migration reactions of 5-arylfuran derived enol carbonates to give $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ butenolides.¹² Burger has demonstrated that allylic alkoxides can engage 2-fluoro-3-trifluoromethylfurans in tandem S_NAr/Claisen reactivity to produce $\Delta^{\beta,\gamma}$ butenolides.¹⁴ Recently, Ma described iodide catalyzed, regioselective alkylation of 2-methoxyfuran-3-carboxylic esters to give $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ butenolides.¹⁵

Very recently, Arseniyadis and Cossy have elegantly reported enantioselective Tsuji–Trost type reactions¹⁶ of allyl furan-2-yl carbonates.¹⁷ Quaternary centers were established in 69–90% ee to give $\Delta^{\beta,\gamma}$ butenolides via Claisen rearrangement and the corresponding $\Delta^{\alpha,\beta}$ butenolides via further Cope rearrangement.¹⁷





Cyclopropene carboxylic esters are attractive precursors for the preparation of butenolides,¹⁸ as they can be readily

(11) (a) Trost, B. M.; McClory, A. Angew. Chem., Int. Ed. 2007, 46, 2074. (b) Komeyama, K.; Takahashi, K.; Takaki, K. Chem. Lett. 2008, 37, 602. (c) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. J. Am. Chem. Soc. 2011, 133, 4778. (d) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-C.; Luo, T.; Yang, Z. J. Am. Chem. Soc. 2011, 133, 14944. (e) Wang, W.; Xu, B.; Hammond, G. B. Org. Lett. 2008, 10, 3713.

(12) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. J. Am. Chem. Soc. 2006, 128, 925.

(13) Joannesse, C.; Morrill, L.; Campbell, C.; Slawin, A.; Smith, A. Synthesis 2011, 2011, 1865.

(14) (a) Burger, K.; Fuchs, A.; Hennig, L.; Helmreich, B. *Tetrahedron Lett.* 2001, 1657. (b) Burger, K.; Hennig, L.; Fuchs, A.; Greif, D.; Spengler, J.; Albericio, F. *Monatsh. Chem.* 2005, *136*, 1763. (c) Burger, K.; Fuchs, A.; Hennig, L.; Helmreich, B.; Greif, D. *Monatsh. Chem.* 2001, *132*, 929.

(15) Chen, J.; Ni, S.; Ma, S. Adv. Synth. Catal. 2012, 354, 1114.

(16) (a) Behenna, D. C.; Stoltz, B. M. J. Am. Chem. Soc. **2004**, 126, 15044. (b) Burger, E. C.; Tunge, J. A. Org. Lett. **2004**, 6, 4113. (c) Trost, B. M.; Xu, J. J. Am. Chem. Soc. **2005**, 127, 2846.

(17) (a) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. Angew. Chem., Int. Ed. **2013**, *52*, 1257–1261. (b) Fournier, J.; Arseniyadis, S.; Cossy, J. Angew. Chem., Int. Ed. **2012**, *51*, 7562.

(18) Miege, F.; Meyer, C.; Cossy, J. Org. Lett. 2010, 12, 248.

(19) (a) Cho, S. H.; Liebeskind, L. S. J. Org. Chem. 1987, 52, 2631.
(b) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. J. Am. Chem. Soc. 2012, 134, 19981. (c) Davies, H. M. L.; Romines, K. R. Tetrahedron 1988, 44, 3343. (d) Müller, P.; Gränicher, C. Helv. Chim. Acta 1993, 76, 521. (e) Müller, P.; Nicole, P.; Doyle, M. P.; Bagheri, V. Helv. Chim. Acta 1990, 73, 1233. (f) Komendantov, M. I.; Domnin, I. N.; Bulucheva, E. V. Tetrahedron 1975, 31, 2495. (g) Ma, S.-M.; Zhang, J.-L. J. Am. Chem. Soc. 2003, 125, 12386. (h) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. Chem. Commun. 2008, 6405.

prepared by catalytic cyclopropenation of alkynes. The conversion of cyclopropene carboxylic esters to 2- alkoxyfurans is a well-known transformation that can be catalyzed by a variety of metals,¹⁹ and elegant studies have extended the scope of such reactions to the synthesis of fused heterocycles.¹⁸ Of the catalysts that promote ring expansion of cyclopropenes, Rh-based catalysts are among the most useful, and one-pot syntheses of furans from alkynes and diazo compounds have been achieved.^{19–21} Furthermore, Rh(I) and Rh(II) catalysts lead to distinct regioselectivities in the ring expansion. Liebeskind^{19a} and Padwa²² have proposed a mechanism that describes the differing regioselectivities induced by Rh(I) and Rh(II) catalysts.

We envisioned that readily prepared allylic cyclopropenecarboxylates (A) could engage in ring expansion reactions to give 2-allyloxyfuran intermediates (B) and that the resulting allyloxyfurans would subsequently rearrange to $\Delta^{\beta,\gamma}$ butenolides (C) via Claisen rearrangement or to the corresponding $\Delta^{\alpha,\beta}$ butenolides (**D**) via further Cope rearrangement (Scheme 1). Herein, we describe catalytic methods for realizing these processes and for selective formation of either $\Delta^{\beta,\gamma}$ or $\Delta^{\alpha,\beta}$ butenolides (C vs D). The procedure is not restricted to the reactivity of simple allyl esters, but it also functions for prenyl esters, progargyl esters, and esters derived from cyclic and acyclic secondary allylic alcohols. For more substituted analogs of A, we describe methods for controlling regioselectivity and chirality transfer from nonracemic allylic esters. Our work complements the very recent work of Arseniyadis and Cossy, where asymmetric catalysis is used to transfer unfunctionalized allyl groups.^{17a}

In general, allylic cycloprop-2-enecarboxylates could be prepared in good yields by alkylation of the corresponding acids with allylbromide/DBU or by Steglich esterification. The rearrangement to $\Delta^{\beta,\gamma}$ butenolides was first studied with allylic esters of cycloprop-2-enecarboxylates without vinylic substitution. A number of catalysts were surveyed, and Rh₂(OPiv)₄ was found to be highly effective. Allyl 3-phenylcycloprop-2-enecarboxylate (1a) gave butenolide 2a in 90% yield. Also rearrangements of

(22) Padwa, A.; Kassir, J. M.; Xu, S. L. J. Org. Chem. 1991, 56, 6971.

⁽⁹⁾ Liu, H.-J.; Leow, D.-S.; Huang, K.-W.; Tan, C.-H. J. Am. Chem. Soc. 2009, 131, 7212.

^{(10) (}a) Van den Hoven, B. G.; El Ali, B.; Alper, H. J. Org. Chem.
2000, 65, 4131. (b) Zhang, Q.; Cheng, M.; Hu, X.-Y.; Li, B.-G.; Ji, J.-X.
J. Am. Chem. Soc. 2010, 132, 7256. (c) Shi, Y.-L.; Roth, K. E.; Ramgren,
S. D.; Blum, S. A. J. Am. Chem. Soc. 2009, 131, 18022.

^{(20) (}a) Chuprakov, S.; Gevorgyan, V. Org. Lett. 2007, 9, 4463. (b) Sato, H.; Hiroi, K. Tetrahedron Lett. 2006, 47, 5793.

^{(21) (}a) Pang, W.; Zhu, S.-F.; Xin, Y.; Jiang, H.-F.; Zhu, S.-Z. *Tetrahedron* **2010**, *66*, 1261. (b) Li, H.-Y.; Hsung, R. P. *Org. Lett.* 2009, 11, 4462. (c) Peng, L.-L.; Zhang, X.; Ma, M.; Wang, J.-B. Angew. Chem., Int. Ed. 2007, 46, 1905. (d) Hamaguchi, M.; Tomida, N.; Iyama, Y. J. Org. Chem. 2007, 72, 1326. (e) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. Chem. Commun. 2006, 3296. (f) Ma, S.-M.; Lu, L.-H.; Lu, P. J. Org. Chem. 2005, 70, 1063. (g) Müller, P.; Allenbach, Y. F.; Bernardinelli, G. Helv. Chim. Acta 2003, 86, 3164. (h) Padwa, A.; Straub, C. S. J. Org. Chem. 2003, 68, 227. (i) Tollari, S.; Palmisano, G. Cenini, S.; Cravotto, G.; Giovenzana, G. B.; Penoni, A. Synthesis 2001, 735. (j) Lee, Y. R.; Suk, J. Y. Tetrahedron Lett. 2000, 41, 4795. (k) Lee, Y.-R.; Suk, J.-Y.; Kim, B.-S. Tetrahedron Lett. 1999, 40, 6603. (1) Padwa, A.: Hertzog, D. L.: Nadler, W. R.: Osterhout, M. H.: Price, A. T. J. Org. Chem. 1994, 59, 1418. (m) Padwa, A.; Hertzog, D. L. Tetrahedron 1993, 49, 2589. (n) Padwa, A.; Kinder, F. R. J. Org. Chem. 1993, 58, 21. (o) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. J. Org. Chem. 1991, 56, 820. (p) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. J. Org. Chem. 1990, 55 4518

3-phenylcycloprop-2-enecarboxylates (1b-e) derived from secondary allylic alcohols were studied. Successful rearrangements were realized with substrates with *n*-pentyl (1b,c), phenyl (1d), or *o*-tolyl (1e) substituents at the allylic position to give 2b-e in 58–81% yields.

As shown in Scheme 2, cyclohex-2-en-1-yl ester 1f rearranges to compound 2f in 87% yield and with >95:5 diastereoselectivity. Propargyl ether 1g also undergoes tandem ring expansion/Claisen rearrangement to give α -allenyl- α -phenyl- $\Delta\beta$, γ butenolide (2g) in 85% yield. Also successful was the rearrangement of a cyclopropene that is substituted at both the vinylic and allylic positions. Butenolide 2h was obtained in 48% yield by a two-step procedure, in which the intermediate ester was purified only by filtration through a plug of silica gel. The relatively low yield of 2h was a result of the difficulty of this particular Steglich esterification, and not the Rh-catalyzed rearrangement.





A model set forth in Scheme 3 predicts that the tandem ring expansion/Claisen rearrangements would be stereospecifically

1502

controlled by a chair transition state (F) with the allylic substituent in an equatorial position. This model predicts that the absolute configuration of the butenolides G is set by the absolute configuration of the ester side chain of cyclopropene E, which can be readily derived from enantiomerically enriched allylic alcohols. Chirality transfer was measured for the rearrangements of cyclopropenes 1b and 1c. For 1b. a high conversion of enantiomeric excess (96% cee) was indeed observed, and the absolute configuration was confirmed by conversion to (S)-3-allyl-3-methylfuran-2(3*H*)-one.¹⁷ Chirality transfer was also observed for the reaction of 1c to 2c (at 60 °C). albeit with a reduced conversion of enantiomeric excess (81% cee).²² The ready availability of nonracemic allylic alcohols makes the method presented in Scheme 2 an attractive method for the synthesis of enantiomerically enriched butenolides.





Rh(I) and Rh(II) catalysts lead to distinct regioselectivities in the ring expansion of cyclopropenecarboxylates.^{17a,20} We hypothesized that allylic cycloprop-2-enecarboxylates with C-2 substitution would undergo rearrangement to allyloxyfurans and subsequently to $\Delta^{\beta,\gamma}$ butenolides with catalyst-dependent regioselectivity (Scheme 4). Indeed, we found that treatment of 1i with Wilkinson's catalyst in refluxing benzene gave 4 in 92% yield via putative intermediate I. Conversely, treatment of 1i with Rh₂(OPiv)₄ leads to the complementary regioisomer 3 in 94% yield via putative H. Consistent with this mechanism,^{19a,22} nonracemic 1i (82% ee) gives racemic 4 in a reaction catalyzed by Wilkinson's catalyst.



Because compounds **2** are 1,5-dienes, it was anticipated that they could undergo a Cope rearrangement subsequent to the Claisen rearrangement at elevated temperature and that the sequence of ring expansion/Claisen/Cope rearrangement could take place in one flask. As displayed in

Scheme 5. Expansion/Claisen/Cope Rearrangements



Scheme 5, a number of allylic cycloprop-2-enecarboxylate derivatives undergo rearrangement to $\Delta^{\alpha,\beta}$ butenolides utilizing Rh₂(OPiv)₄ at 110 °C in toluene. Allyl 1-phenyl-cycloprop-2-enecarboxylate (1a), which rearranged to 2a at 60 °C, rearranges to 5a at 110 °C. Prenyl ester 1j undergoes spontaneous Claisen/Cope rearrangement to give $\Delta^{\alpha,\beta}$ butenolide 5j; the $\Delta^{\beta,\gamma}$ butenolide was not observed. We rationalize that the Thorpe–Ingold effect of the gem-dimethyl accelerates the rate of Cope rearrangement for the putative $\Delta^{\beta,\gamma}$ butenolide intermediate. For cycloprop-2-enecarboxylates derived from secondary allyl alcohols, sequential ring expansion/Claisen/Cope rearrangements can produce diastereomers. For such substrates (5c, 5d, 5f, 5k), the diastereoselectivity was high (\geq 93:7). The stereoselectivity of the tandem rearrangement is

rationalized via successive chair transition states, as shown at the bottom of Scheme 5. With enantiomerically enriched **1c**, compound **5c** was obtained with 83% ee. To see if the Cope rearrangement is Rh-catalyzed, the rate of the transformation of **2d** to **5d** was measured by ¹H NMR (0.04 M in toluene- d_6 , 100 °C). Without the catalyst, the rate was measured to be $6.0 \times 10^{-4} \text{ s}^{-1}$. For an identical experiment with 10 mol % Rh₂(OPiv)₄, the rate was measured as $5.9 \times 10^{-4} \text{ s}^{-1}$. These data suggest that the Cope rearrangement step is not catalyzed by Rh₂(OPiv)₄.

As was observed in the synthesis of $\Delta^{\beta,\gamma}$ butenolides, catalyst-dependent regioselectivity could be realized for $\Delta^{\alpha,\beta}$ butenolide synthesis via the rearrangement of cyclopropene **1i**, which is substituted at the vinylic position of the cyclopropene. Thus, **1i** rearranged to **6** in 94% yield utilizing Wilkinson's catalyst at 110 °C, whereas **7** was formed in 46% yield when Rh₂(OPiv)₄ was employed as the catalyst (Scheme 6).

In summary, we describe that allylic cyclopropenecarboxylates engage in Rh-catalyzed ring expansion reactions to give 2-allyloxyfuran intermediates and that the resulting allyloxyfurans would subsequently rearrange to $\Delta^{\beta,\gamma}$ butenolides via a Claisen rearrangement or to the corresponding $\Delta^{\alpha,\beta}$ butenolides via further Cope rearrangement. For allyloxycycloprop-2-enecarboxylates with C-2 substitution, the regioselectivity can be controlled through catalyst choice. Enantiomerically enriched butenolides can be prepared with good levels of stereospecificity with cyclopropenecarboxylates derived from enantiomerically enriched allylic alcohols. Propargyl cycloprop-2-enecarboxylates also participate in a tandem rearrangement to give $\Delta\beta,\gamma$ butenolides with allenic substitution.



Acknowledgment. For financial support we thank NIGMS (GM068650). For x-ray crystallography, we thank Glenn Yap (Delaware). NMR instrumention was supported by NSF CHE0840401 and NIH S10RR026962.

Supporting Information Available. Full experimental details, two cif files, and ¹H and ¹³C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.