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Functionalized Oxepines via Fragmentation of Highly Strained Epoxides

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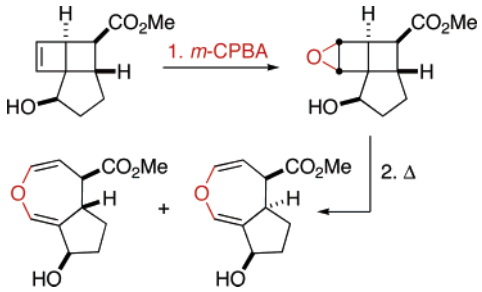
ABSTRACT

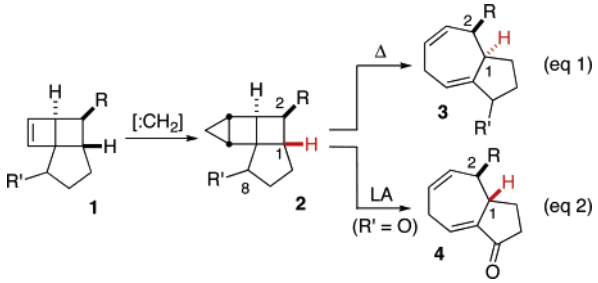


Epoxidation of highly strained cyclobutenes followed by thermal rearrangement provides a new entry into oxepine-containing bicyclo[5.3.0] ring systems. In contrast to the rearrangement of the corresponding cyclopropanated systems, the strained epoxides in this study are believed to fragment through two competing pathways leading to a mixture of diastereomeric 5-7 ring systems.

Recently, we described two methods for generating bicyclo-[5.3.0] ring systems (5-7 ring systems) from strained precursors.[1] As illustrated in Scheme 1, both strategies begin with a stereoselective cyclopropanation of the readily available cyclobutene **1**[2] to afford cyclopropane **2**. Thermal (eq 1) or Lewis acid mediated (eq 2) fragmentation of cyclopropane **2** affords either the 5-7 skeleton **3** or **4** with the complementary stereochemical outcome indicated. Building upon these findings, we sought to extend the fragmentation to heterocyclic variants of the 5-7 ring system. Herein, we report an epoxidation/thermal rearrangement that provides rapid access to functionalized oxepine-containing bicyclo[5.3.0] ring systems.[3]

Following known cyclobutene epoxidation procedures,[4] treatment of cyclobutene **5** with *m*-CPBA in CH_2Cl_2 afforded the desired epoxide **6** in high yield (Scheme 2). Epoxide **6** was isolated as a white solid, and X-ray analysis indicated that the epoxidation occurred selectively from the less-hindered face of the olefin providing the *anti*-tricyclo[3.2.0.0] ring system. The purity of *m*-CPBA affected the epoxidation

Scheme 1. Thermal and Lewis Acid Mediated Stereospecific Fragmentations Generating Bicyclo[5.3.0] Ring Systems



(1) Thermal: (a) Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152. Lewis acid: (b) Deak, H. L.; Williams, M. J.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 5785.

(2) (a) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196. (b) Limanto, J.; Snapper, M. L. *J. Org. Chem.* **1998**, *63*, 6440. (c) Limanto, J.; Tallarico, J. A.; Porter, J. R.; Khuong, S. K.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 14748−14758. (d) Limanto, J.; Khuong, S. K.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 16310−16321. (e) Seigal, B. A.; An, M. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4929.

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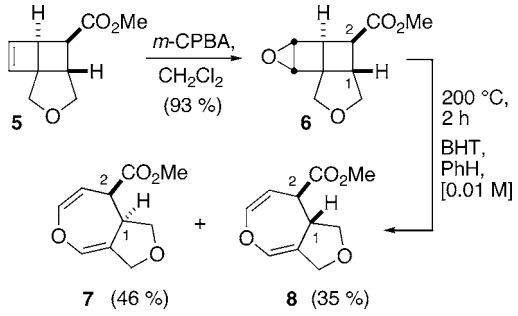
Scheme 2. Epoxidation of Cyclobutenes and Ring Expansion to Oxepines



as trace amounts of benzoic acid lowered the yield. Accordingly, the *m*-CPBA used in this study was pretreated with phosphate buffer (pH 8) to remove residual acid.[5]

With an efficient epoxidation in hand, we focused on implementing the thermal rearrangement. Using our cyclopropane fragmentation as a guide, we investigated the rearrangement of epoxide **6** in benzene at 200 °C in the presence of BHT. Under these conditions, the ring expansion was complete in 3 h and afforded two distinct oxepine products **7** and **8** in a combined yield of 81% (Scheme 2). An additive screen, involving bases and varying equivalents of BHT, showed no improvement in yield or change in product distribution. The fragmentation can be performed in the absence of BHT on a small scale (≤0.2 mmol); however, on larger-scale reactions (≥0.5 mmol), the BHT improved the yield, presumably through inhibition of post-fragmentation polymerization. Separation of the acid-sensitive products was achieved using medium-pressure liquid chromatography (MPLC) with base-washed columns.[6]

To explore the scope of the strategy, the epoxidation−thermolysis sequence was applied to the substrates shown in Table 1. Epoxidation of all cyclobutenes proceeded in ≥80% yield. In contrast to the cyclopropane fragmentations, the thermal rearrangement for each of these epoxides afforded two diastereomers in relatively similar amounts. Resubjecting the isolated oxepines individually to the fragmentation conditions indicated that these diastereomeric products were not equilibrating during the thermal ring opening.[7]

Entries 2−4 in Table 1 explore the electronic effects on the thermal rearrangement. Whereas the substituents on the

Table 1. Oxepine Synthesis via Epoxide Fragmentation

entry	epoxide (yield)	thermolysis product (yield)		
(1)	(93%) **6**	(46%) **7**		(35%) **8**
(2)	(98%) **9**	(53%) **10**		(15%) **11**
(3)	(97%) **12**	(52%) **13**		(18%) **14**
(4)	(97%) **15**	(48%) **16**		(23%) **17**
(5)	(80%) **18**	**19** (75%, 1:1)[a]		**20**
(6)	(99%) **21**	(32%) **22**		(23%) **23**
(7)	**24**	**25** (72% 1:3)[a]		**26**
(8)	(89%) **27**	(30%) **28**		(30%) **29**
(9)	(91%) **30**	(38%) **31**		(31%) **32**

[a] Not readily separable; product ratio determined by ^{1}H NMR.

(3) For examples of oxepine-containing natural products and related compounds, see: (a) Herz, W.; Subramaniam, P. S.; Santhanam, P. S.; Aota, A.; Hall, A. L. *J. Org. Chem.* **1970**, *35*, 1453. (b) Tomita, B.; Hirose, Y. *Tetrahedron Lett.* **1970**, *11*, 235. (c) Cox, P. J.; Sim, G. A. *J. Chem. Soc., Chem. Commun.* **1973**, 428. (d) Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 3516. (e) Neuss, N.; Nagarajan, R.; Molloy, B. B.; Huckstep, L. L. *Tetrahedron Lett.* **1968**, *9*, 4467. (f) Rastetter, W. H.; Chancellor, T.; Richard, T. J. *J. Org. Chem.* **1982**, *47*, 1509. (g) Seya, H.; Nozawa, K.; Nakajima, S.; Kawai, K. I.; Udagawa, S. I. *J. Chem. Soc., Perkin Trans. I* **1986**, 109. (h) Kawahara, N.; Nozawa, K.; Yamazaki, M.; Nakajima, S.; Kawai, K. I. *Heterocycles* **1990**, *30*, 507. (i) Zamorano, G.; Catalán, C. A. N.; Diaz, J. G.; Herz, W. *Phytochemistry* **1995**, *38*, 1257. (j) Zurcher, M.; Niggli, U. A.; Steck, A.; Pfander, H. *Tetrahedron Lett.* **1997**, *38*, 7853. (k) Ankisetty, S.; ElSohly, H. N.; Li, X.-C.; Khan, S. I.; Tekwani, B. L.; Smillie, T.; Walker, L. *J. Nat. Prod.* **2006**, *69*, 692.

(4) (a) Paquette, L. A.; Youssef, A. A.; Wise, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 5246 and references cited therein. (b) Garin, D. L. *J. Org. Chem.* **1969**, *34*, 2355.

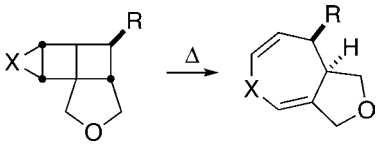
(5) (a) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976. (b) Bortolini, O.; Campestrini, S.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1987**, *52*, 5093. (c) Traylor, T. G.; Miksztal, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 2770.

(6) These oxepine products decomposed slowly on untreated silica gel.

(7) For a possible equilibration mechanism for these oxepines, see: Crandall, J. K.; Watkins, R. J. *Tetrahedron Lett.* **1967**, *18*, 1717.

cyclopropyl substrates influenced the minimal temperature for fragmentation,[1a] neither electron-rich nor electron-poor substituents changed the relative rate of ring opening for the epoxide substrates. The data illustrating this trend are shown in Table 2. Likewise, the similar product distribution and

Table 2. Electronic Substituent Effects on Minimum Fragmentation Temperatures for the Cyclopropyl and Epoxide Substrates

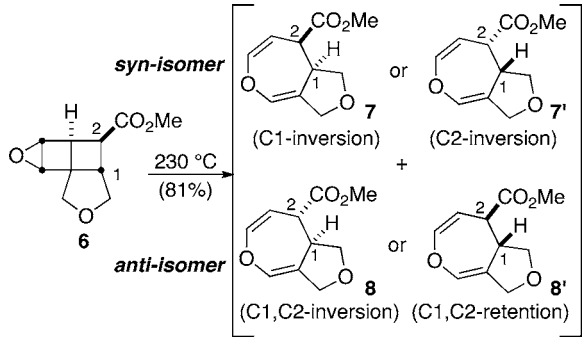


R	X = CH_2	X = O
C_6H_4-*p*-NO_2	190 °C	170 °C
Ph	150 °C	160 °C
C_6H_4-*o*-OMe	130 °C	160 °C

rate of rearrangement of epoxide **6** in either benzene or methylene chloride suggest that the fragmentation does not involve significant charge redistribution (i.e., polar intermediates), at least in the rate-determining step.[8]

At this point, the stereochemical identities of the oxepine products were not confirmed. ^{1}H NMR and X-ray analysis of the tetrahydrofuran-containing products (entries 1−4)[9] indicted that in one diastereomer the hydrogens at C1 and C2 were in a syn relationship (ie., **7**, **10**, **13**, and **16**), whereas in the other diastereomer (ie., **8**, **11**, **14**, and **17**), the hydrogens were oriented in an anti fashion. Because we were working with racemic materials, it was unclear whether the syn diastereomer arose from inversion at C1 to yield **7** or at C2 to provide **7′**. This aspect of the rearrangement is illustrated in Scheme 3. Likewise, the anti diastereomer could

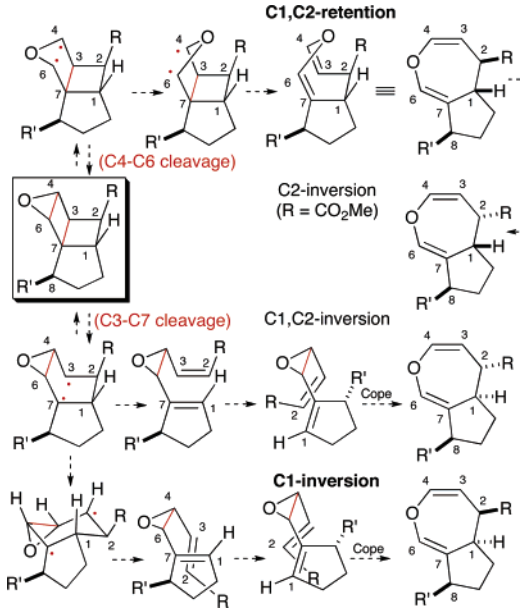
Scheme 3. Stereochemical Possibilities for Ring Opening



have been obtained from either retention or inversion at both C1 and C2. As illustrated in Scheme 4, fragmentation pathways could be envisioned for any of these scenarios.[10]

(8) *Solvents and Solvent Effects in Organic Chemistry*; Reichardt, C., Ed.; Wiley-VCH: New York, 2003; p 163.

Scheme 4. Possible Diradical Fragmentation Pathways to the Oxepines[a]



[a] Concerted and polar fragmentation pathways to generate these diastereomers are also possible.

Determining the absolute stereochemical outcome of these transformations should therefore provide useful insight into the mechanistic course of the ring expansion.

We chose to use a remote stereocenter that was not likely affected by the thermal rearrangement to determine the stereochemical outcome of the reaction. The C8 stereocenter located on the cyclopentane ring in epoxides **18**, **21**, **24**, **27**, and **30** (entries 5−9, Table 1) provided compounds with the appropriate reference substituents for comparison with the C1 and C2 stereocenters. NOE measurements on these substituted oxepines allowed for relative assignment of all the stereoisomers.[11] Figure 1 summarizes the results of these experiments. The findings indicated that the syn diastereomer (**28** and **31**) arose from an inversion at C1, and the anti diastereomer (**29** and **32**) resulted from retention of stereochemistry at both C1 and C2. These findings indicate that in addition to formation of the divinyl oxirane intermediate,

(9) ^{1}H NMR coupling constants associated with the α-proton in oxepine **7** provided the relative stereochemical identity of the syn diastereomer. X-ray crystal analysis of the 3,5-dinitrobenzoyl ester of oxepine **8** provided the relative stereochemical identity of the anti diastereomer.

(10) For a computational comparison of the Cope rearrangement of divinyl oxirane and cyclopropane, see: (a) Zora, M. *J. Org. Chem.* **2005**, *70*, 6018. For recent examples of these rearrangements, see: (b) Shimizu, M.; Fujimoto, T.; Liu, X.; Hiyama, T. *Chem. Lett.* **2004**, *33*, 438. (c) Aitken, R. A.; Cadogan, J. I. G.; Gosney, I.; Humphriese-Buchan, C. M.; McLaughlin, L. M.; Wyse, S. J. *J. Chem. Soc., Perkin Trans. 1: Org. Bio-Org. Chem.* **1999**, 605. (d) Chou, W. N.; White, J. B.; Smith, W. B. *J. Am. Chem. Soc.* **1992**, *114*, 4658. (e) Clark, D. L.; Chou, W. N.; White, J. B. *J. Org. Chem.* **1990**, *55*, 3975. (f) von Zezschwitz, P.; Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A. *J. Org. Chem.* **1999**, *64*, 3806. For representative oxidative entries into oxepines, see: (g) Sengul, M. E.; Balci, M. *J. Chem. Soc., Perkin Trans. 1: Org. Bio-Org. Chem.* **1997**, 2071. (h) Goodman, R. M.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 5125.

(11) Varian's NOESY1D (DPFGSE NOE) experiments for measurement of transient NOEs are generally lower in intensity than steady-state NOE values.

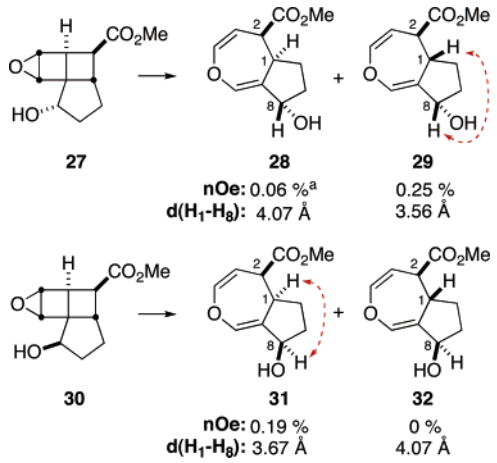


Figure 1. Results of transient 1D NOE experiments (NOESY1D)[11] and distances calculated at the AM1 level. [a]Value from overlapping peaks in spectra.

which as in the rearrangement of the cyclopropyl system leads to inversion of C1, these substrates also favor cleavage of the C4−C6 bond, which avoids formation of the dialkenyl oxirane and leads to the 5-7 ring system with retention of C1,C2 stereocenters (Scheme 4).[12]

In summary, epoxidation followed by thermal rearrangement of strained cyclobutenes is shown to provide rapid access to functionalized oxepine-containing 5-7 ring systems. Unlike fragmentations of the corresponding cyclopropane-containing ring systems, rearrangements of the epoxide substrates lead to a mixture diastereomers. Efforts to further explore the scope and to exploit the utility of these transformations are currently underway.

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Supporting Information Available: Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) In contrast to the systems with a methylene group, perhaps the epoxide oxygen allows for a more facile electrocyclic fragmentation of the C3−C4 bond in the C1−C2 retention pathway (Scheme 4).