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Communications

Synthesis of Carbocyclic Systems via Radical-Induced Epoxide Fragmentation

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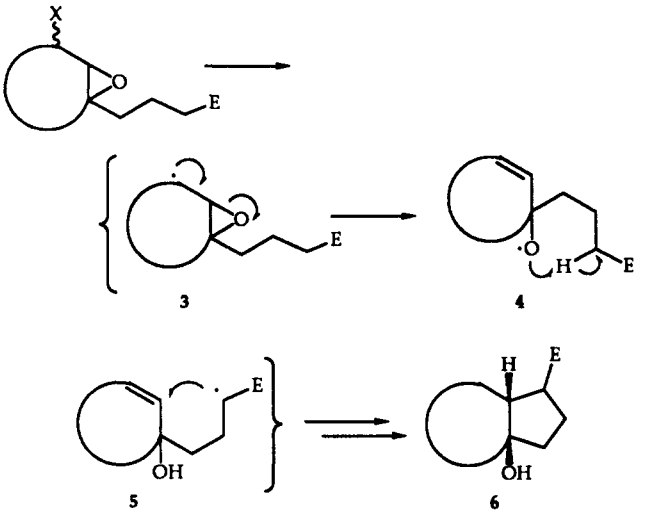
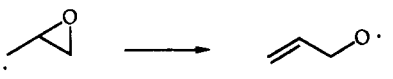
Summary: Cis-fused bicyclic compounds are synthesized from simple monocyclic enone precursors. The key step involves a tandem radical-mediated epoxide fragmentation, radical translocation, and cyclization.

In 1963 Sabatino and Gritter[1] reported the first example of an epoxide C–O bond fragmentation (**1** → **2**) caused by a radical on the α-carbon, a process that resembles the cyclopropylcarbinyl[2] radical rearrangement.[3] The salient feature of the epoxide fragmentation reaction is the formation of a highly reactive oxygen-centered radical from a carbon-centered one,[4] precisely the reverse of the more common process.[5] This is a fast rearrangement[6] and is undoubtedly propelled by the relief of ring strain (ca. 27.5 kcal).[7] Despite the relative ease with which an alkoxy radical is produced, this rearrangement appears to have received relatively little attention,[8] especially from the synthetic viewpoint.[9] We have looked into the synthetic potential of the epoxide fragmentation reaction and report here a powerful reaction sequence which uses this reaction to generate cis-fused bicyclic systems.

Scheme I





(1) Sabatino, E. C.; Gritter, R. J. *J. Org. Chem.* **1963**, *28*, 3437.
(2) Beckwith, A. L. J.; Ingold, K. U. In *Free Radical Rearrangements*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 161–310.
(3) For general reviews on free radical chemistry, see, inter alia: (a) Hart, D. J. *Science (Washington, DC)* **1984**, *223*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of C-C Bonds*; Pergamon Press: New York, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Curran, D. P. *Synthesis* **1988**, *417*, 489.
(4) Fragmentation of the C–C bond is observed in systems that lead to a stabilized radical, see: (a) Stogryn, E. L.; Gianni, M. H. *Tetrahedron Lett.* **1970**, 3025. (b) Cook, M.; Hares, O.; Johns, A.; Murphy, J. A.; Patterson, C. W. *J. Chem. Soc., Chem. Commun.* **1986**, 1419. (c) Johns, A.; Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1987**, 1238. (d) Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1988**, 294.
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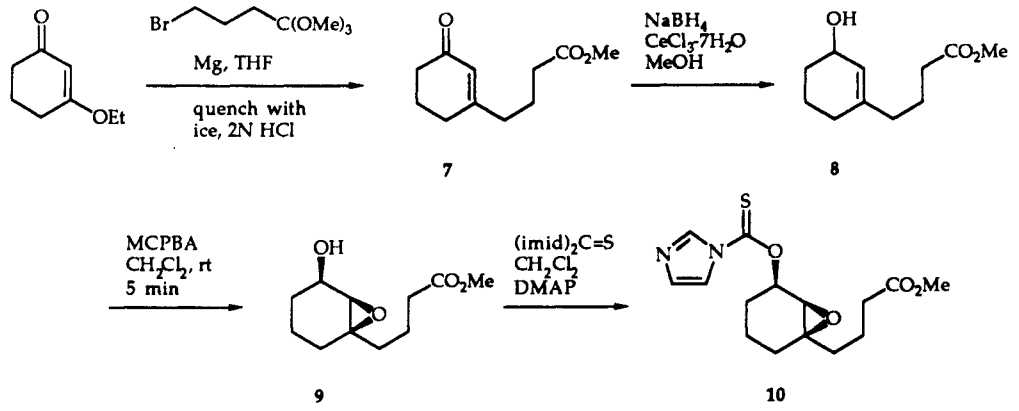
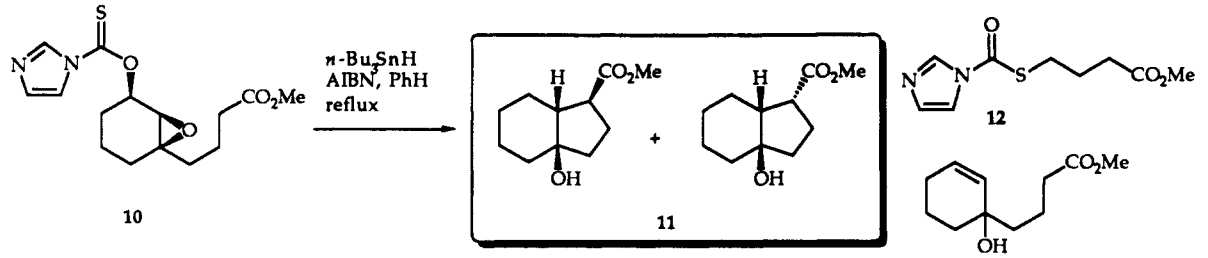
Scheme II



7 8 9 10

Scheme III



10 11 12 13

The general reaction design is outlined in Scheme I. The initially formed radical (**3**) was expected to rearrange rapidly to the alkoxy radical. This oxygen centered radical (**4**), like other highly reactive radicals,[2,5] was expected then to abstract an H• from the δ-carbon.[5b] The resulting stabilized radical (**5**) was then set up for cyclization onto the olefin produced from the fragmentation, to generate a bicyclic system (**6**).[10,11]

Scheme II outlines the preparation of the precursor for testing this reaction sequence. Addition of the Grignard salt of trimethyl 4-bromoorthobutyrate[12] to 3-ethoxycyclohexenone followed by an acid quench gave enone–ester **7** in 69% yield. Reduction of the enone under the Luche conditions,[13] followed by epoxidation, yielded epoxy alcohol **9** in quantitative yield. Reaction of the epoxy alcohol with thiocarbonyldiimidazole, in the presence of a catalytic amount of DMAP,[14] produced a >90% overall yield of thionoimidazolide **10**, the key precursor for the fragmentation–cyclization sequence.[15]

The cyclization sequence was triggered under standard radical generation conditions (*n*-Bu_3SnH, AIBN, PhH, reflux) and afforded the expected product, **11**, in 69% yield (Scheme III). The rings were expected to be cis-fused for stereoelectronic and geometric reasons, and literature precedent.[16] The product was, however, a mixture of two epimeric esters, as evidenced by the presence of two methyl peaks in the proton NMR spectrum, in a ratio of approximately 2.7:1. The epimer balance can be tilted further to one side, to 9:1, by stirring the mixture with a catalytic amount of *t*-BuOK. The ester group of the major product was assigned exo (β) orientation.[17]

An unexpected side product of the reaction was **12**, the imidazolide of methyl 4-mercaptobutyrate (5–10%). This substance is believed to arise from fragmentation of the intermediate alkoxy radical (such as **4**) to the ketone by expulsion of the butyrate side chain. Attack of the thionoimidazolide by the butyrate radical then generates a new oxiranylcarbinyl radical (**3**), which continues the chain. A very small amount of the simple epoxide fragmentation–reduction product (**13**) was also isolated (<3%). The proportion of **13** increased when the reaction temperature was lowered. It is important to note that the radical cyclization sequence produces a cis ring juncture containing a tertiary hydroxyl group, a substitution pattern found in many biologically important natural products, such as the toxic lactone picrotoxinin[18] (**14**), furan-con-

(10) For other examples of 1,5-hydrogen translocation–cyclization processes, see: (na) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772 and references cited therein; (b) Kalvoda, J.; Crob, J. *CNRS International Colloquium on Organic Free Radicals*; Aix-en Provence, 1978, CNRS, Paris, pp 507–514. (c) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409. (d) Gilbert, B. C.; Parry, D. J. *J. Chem. Soc., Perkin Trans. 2*, **1988**, *875*. (e) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. (f) Cekovic, Z.; Ilijev, D. *Tetrahedron Lett.* **1988**, *29*, 1441. (g) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900.

(11) Murphy et al. recently observed, as an unexpected side reaction, a similar process in which abstraction of an allylic hydrogen was followed by cyclization (9c).

(12) (a) Casy, G.; Patterson, J. W.; Taylor, R. J. K. *Org. Synth.* **1988**, *67*, 193. This compound is now available from Aldrich Chemical Company, Inc. (b) For preparation of an analogous cyclopropane-containing system, see: Harling, J. D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1380.

(13) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(14) This small variation of Barton's procedure (see ref 8b) gives excellent yields and obviates the need to heat the reaction mixture to reflux.

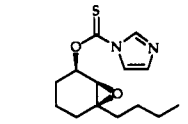
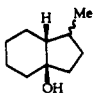
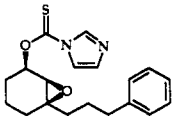
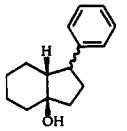
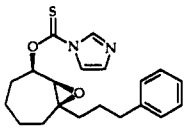
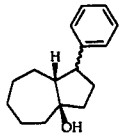
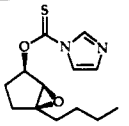
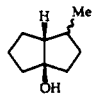
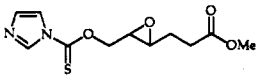
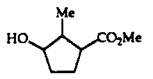
(15) All new compounds are homogeneous (TLC, NMR) and their structure assignments are consistent with spectroscopic data (250-, 300-, or 500-MHz ^1H NMR, IR, HRMS).

(16) (a) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: New York, 1983; p 359. (b) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (c) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1987**, *109*, 2829.

(17) The stereochemical assignment was confirmed with the aid of $Eu(fod)_3$ shift reagent. In the presence of 30 mol % shift reagent, the methyl group in the minor fraction (faster moving by chromatography) was shifted downfield by 0.18 ppm. Under the same conditions the methyl group of the major component exhibited a much larger downfield shift (1.09 ppm), presumably because of intramolecular coordination of the Eu with the hydroxyl group and the β-oriented ester carbonyl.

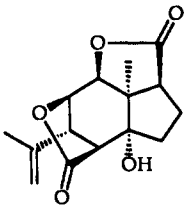
(18) de Mayo, P.; Williams, R. E. *J. Am. Chem. Soc.* **1965**, *87*, 3275. Synthesis: Corey, E. J.; Pearce, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 5841.

Table I. Fragmentation–Cyclization of Epoxythionoimidazolides

entry	substrate	product	ratio	% yield
1			2.7:1	68
2			2.7:1	47
3			1:1	58
4			1.3:1	52
5			*a*	50

[a] Complex mixture of diastereomers.

taining terpene furoscrobiculin D (**15**),[19] *Botrytis* derived plant growth regulator (**16**),[20] as well as a whole class of steroids, many of which exhibit potent cardiotonic (e.g., **17**)[21] or cytotoxic[22] properties.



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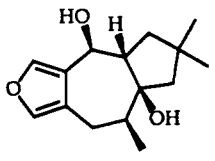
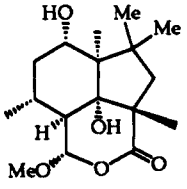
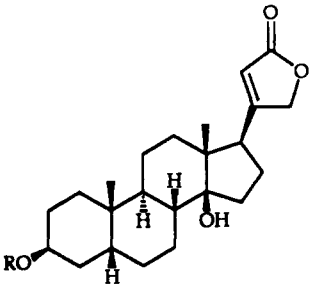


15



16



17

To better understand the scope and limitation of the fragmentation–cyclization methodlogy, we have examined the reaction of a number of related systems, shown in Table I. The substrates for entries 1 and 2 were prepared along parallel lines to that used to synthesize **10**. Precursors for entries 3 and 4 were prepared by the reaction of the appropriate Grignard reagent with cycloheptenone and cyclopentenone, respectively. The resulting tertiary allylic alcohols were oxidized with PDC[23] to the three-substituted enones, which were then converted to the cyclization precursor by the steps described above. The cyclizations were carried out under the standard tin hydride conditions and afforded the products as a mixture of isomers. The first entry, which represents a simple model for natural products such as **15** and **16**, is particularly interesting since it does not contain a radical-stabilizing group on the side chain. The oxygen-centered radical intermediate is highly reactive and the H• abstraction–cyclization sequence proceeds efficiently. The second example illustrates the formation and cyclization of a benzylic radical, a system which normally does not cyclize well. A related unit, having a furan or pyrone terminus, would be required for the synthesis of cardenolides. Bicyclo[5.3.0]decane and bicyclo[3.3.0]octane systems are generated in the third and fourth examples, demonstrating the flexibility of the strategy. The last example shows the application of the chemistry to acyclic systems.

These results demonstrate that the radical-induced epoxide fragmentation reaction can be taken advantage of for the synthesis of a variety of carbocyclic systems. We are also investigating analogous fragmentation–cyclization chemistry of azidirine and cyclopropane containing systems.

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(21) See, for example: (a) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959; pp 727–809. (b) Craig, C. R.; Stitzel, R. G.; Eds. *Modern Pharmacology*, 2nd ed.; Little, Brown & Co.: Boston, 1986; p 345. (c) Kupchan, S. M.; Hemingway, R. J.; Hemingway, J. C. *J. Org. Chem.* **1969**, *34*, 3894. (d) Vasina, O. E.; Maslennikova, V. A.; Abubakirov, N. K. *Chem. Nat. Compd.* **1986**, *22*, 243.

(22) Yamagishi, T.; Yan, X.-Z.; Wu, R.-Y.; McPhail, D. R.; McPhail, A. T.; Lee, K.-H. *Chem. Pharm. Bull.* **1988**, *36*, 1615.

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