Allene Epoxidation. Oxidative Cyclizations of Allenyl Acids

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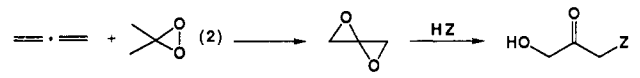
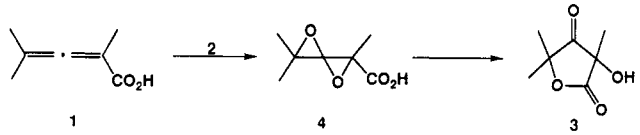
Summary: The dimethyldioxirane oxidation of a series of allenyl carboxylic acids with varying numbers (0–3) of carbons between the two functions leads to highly functionalized lactones derived from cyclization of intermediate diepoxides. The regiochemistry is generally controlled so as to give γ- and δ-lactones.

We have reported recently[1] that application of the dimethyldioxirane oxidation protocol[2] provides a general method for the conversion of allenes into their diepoxides, 1,4-dioxaspiro[2.2]pentanes.[3,4] Addition of nucleophiles to these spirodioxides completes a two-step process for the introduction of functionality at each of the three carbons of the original allene unit. This addition can occur with



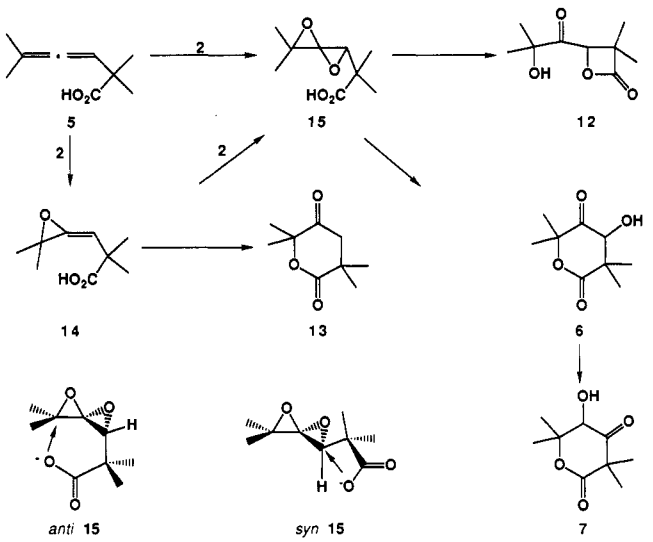
high regiochemical and stereochemical selectivities with appropriately substituted allenes. Subsequent work[5] has demonstrated that a variety of allenic alcohols are converted into oxygen heterocycles by this type of oxidation, presumably via intermediate diepoxides which undergo spontaneous cyclization to the observed tetrahydrofuran and tetrahydropyran products. We now disclose that oxidative cyclizations of allenic carboxylic acids proceed similarly to give highly functionalized lactones of considerable interest as synthetic intermediates.

Oxidation of the fully methylated α-allenyl acid **1**[6] with 10 equiv of dimethyldioxirane (**2**) in acetone yielded crystalline γ-lactone **3**[7] in 73% yield. This transformation

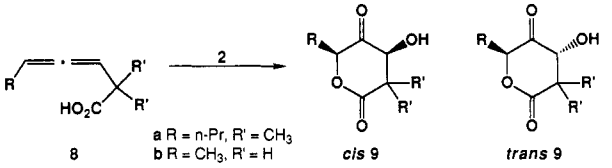


logically proceeds through the diepoxide species **4**, which cyclizes under the reaction conditions. Interestingly, trapping of the intermediate allene monoepoxide by the neighboring carboxylic acid group is not competitive with the second epoxidation step.

In a similar manner the β-allenyl acid **5**[8] was converted by **2** into the crystalline δ-lactone **6** (96% yield).[9] Early attempts to purify this material by chromatography on silica gel were unsuccessful owing to its propensity to undergo ketol transposition[10] to the isomeric lactone **7**.[11]



Essentially complete conversion of **6** to **7** could be effected by stirring with a slurry of silica gel in THF, indicating that **7** is significantly more stable than **6**. The disubstituted β-allenyl acid **8a**[12] was converted in 84% yield to a 2:3 mixture of diastereomeric lactones **9a**, which could be separated by HPLC into the major trans isomer and the minor cis isomer.[13] The minor isomer was assigned as cis



on the basis of a long-range coupling across the carbonyl (^4J = 1 Hz).[14] The analogous acid **8b**[15] gave a similar 2:3 mixture of the diastereomers of **9b** in 76% yield.[16] Finally, β-allenyl acid **10a**[17] was converted into δ-lactone **11**[18] (87%

(1) Crandall, J. K.; Batal, D. J. *J. Org. Chem.* **1988**, *53*, 1338.
(2) Murray, R. W.; Jeyaraman, R *J. Org. Chem.* **1985**, *50*, 2847. For reviews on dioxiranes, see: (a) Curci, R. *Advances In Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 2, Chapter 1. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205.
(3) Crandall, J. K.; Conover, W. W.; Komin, J. B.; Machleder, W. H. *J. Org. Chem.* **1974**, *39*, 1723.
(4) For reviews of allene oxide chemistry, see: (a) Stang, P. J. *The Chemistry of Functional Groups, Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Analogs*; Patai, S., Ed.; Wiley: New York, 1983; pp 859–879. (b) L'Abbe, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 276. (c) Smadja, W. *Chem. Rev.* **1983**, *83*, 263.
(5) Crandall, J. K.; Batal, D. J. *Tetrahedron Lett.* **1988**, *29*, 4791.
(6) Allenyl acid **1** was prepared by basic hydrolysis of the corresponding ester: Bestmann, H.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198. Bestmann, H.; Hartung, H. *Helv. Chim. Acta* **1979**, *62*, 1027.
(7) Lactone **3** shows: ^{13}C NMR δ 210.4, 173.9, 87.4, 69.7, 24.5, 24.4, 23.3; IR 3443, 1801, 1765 cm^{-1}; mp 99–100 °C.
(8) Bly, R. S.; Koock, S. U. *J. Am. Chem. Soc.* **1969**, *91*, 3292.
(9) Lactone **6** shows: ^{13}C NMR δ 209.0, 173.1, 85.4, 74.4, 45.2, 27.6, 25.4, 23.6, 19.0; IR 3520, 1760, 1745 cm^{-1}; mp 95–96 °C.
(10) The oxidation products of allenic alcohols displayed similar behavior: Batal, D. J., unpublished results.
(11) Lactone **7** shows; ^{13}C NMR δ 211.2, 177.7, 88.3, 72.1, 44.4, 26.5, 24.9, 22.2, 19.3; IR 3570, 1753, 1738 cm^{-1}.
(12) Allenyl acid **8a** was prepared by Tollen's oxidation of the corresponding aldehyde.[8]
(13) The trans lactone shows: ^{13}C NMR δ 207.7, 173.2, 81.9, 75.8, 44.4, 34.7, 22.8, 17.9, 17.6, 13.5; IR 3511, 1753, 1736 cm^{-1}. The cis lacone shows: ^{13}C NMR δ 206.1, 173.1, 82.5, 76.1, 44.5, 34.5, 23.3, 19.4, 18.7, 13.4; ^{1}H NMR δ 4.81 (ddd, 1, J = 6, 3, 1 Hz), 4.42 (d, 1, J = 1 Hz), 3.38 (br s, 1), 2.09 (m, 1), 1.62 (m, 3), 1.46 (s, 3), 1.08 (s, 3), 0.97 (t, 3); IR 3507, 1751, 1734 cm^{-1}.
(14) Laslo, P.; Musher, J. I. *Bull. Soc. Chim. Fr.* **1965**, 2558.
(15) Crandall, J. K.; Mayer, C. F. *Org. Photochem. Synth.* **1971**, *1*, 58.
(16) The mixture of diastereomers **9b** shows: IR 3510, 1753, 1726 cm^{-1}. One diastereomer shows: ^{13}C NMR δ 205.2, 170.9, 79.3, 68.2, 37.5, 16.7. The other diastereomer shows: ^{13}C NMR δ 204.8, 170.7, 79.0, 68.5, 37.0, 17.8.
(17) We gratefully thank Dr. Gerard Gil for this sample.
(18) Lactone **11** shows: ^{13}C NMR δ 209.2, 166.8, 85.7, 67.6, 36.4, 26.9, 25.9; IR 1770, 1745 cm^{-1}.

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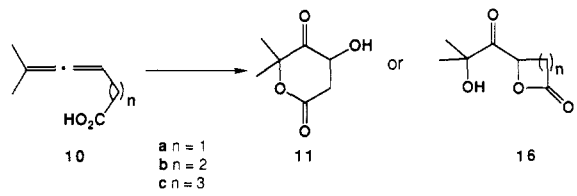
yield).



A dramatic change occurred when acid **5** was converted to its salt with $NaHCO_3$ prior to the addition of **2**. In this case the oxidation product consisted of a mixture of δ-lactone **6** (44% isolated yield), the isomeric β-lactone **12** (11%),[19] and the nonhydroxylated δ-lactone **13** (11%).[20] Treatment of **12** with triethylamine in $CDCl_3$ resulted in its disappearance with the formation of considerable amounts of **6**.[21] Lactone **13** undoubtedly arises from carboxylate anion trapping of monoepoxide **14**. Indeed, lactone **13** was the only product observed (76% yield) when oxidation was performed by adding **5** to an in situ preparation of dioxirane **2** (Oxone, acetone, aqueous $NaHCO_3$). Small amounts of **13** (<5%) were also observed in the reaction of the free acid **5** described above. Thus, intramolecular cyclization of intermediate **14** can be competitive with further epoxidation under the appropriate conditions.

Interestingly, the oxidation of **5** in the presence of *p*-toluenesulfonic acid or either cesium or potassium carbonate gave **6** containing a small amount of **13**. In a control experiment the reaction mixture of **6**, **12**, and **13** was found to be unchanged upon stirring with acetic acid in wet acetone-d_6. On the other hand, the same mixture in the presence of potassium carbonate in wet acetone-d_6 showed a decrease in the ratio of **12**:**6**, suggesting preferential decomposition of β-lactone **12** under these more basic conditions.

The overall regiochemistry of the intramolecular reaction of spirodioxide **15** depends on the reaction conditions in a subtle manner. In the experiments using $NaHCO_3$ to buffer the reaction conditions, the presence of the carboxylate anion appears to be the important feature. Although the stereoselectivity of spirodioxide formation may be changed by this difference at the neighboring acid group, the main influence is surely in the cyclization process itself. Under the $NaHCO_3$-buffered conditions, the intramolecular addition probably takes place via an S_N2 mechanism and, consequently, only the diastereomeric spirodioxide with the acid side chain situated anti to the oxygen of the remote ring is able to give δ-lactone **6**. The β-lactone is, however, accessible by the alternate mode of exo ring closure from either spirodioxide geometry. Under acidic conditions, the cyclization may well take place by a carbocationic mechanism which permits δ-lactone formation from either diastereomer of the spirodioxide.

As anticipated, allenes with more remote carboxylic acid functions cyclize in an exo fashion. Thus, the γ-allenyl acid **10b**[22] was transformed by **2** into γ-lactone **16b**[24] in 82% yield. Similarly, δ-lactone **16c**[25] (71% yield) was generated by the oxidation of δ-allenyl acid **10c**.[26]

In conclusion, oxidations of allenyl acids by dimethyldioxirane provide an interesting synthetic route to highly functionalized lactones. The lactones should prove to be useful synthetic intermediates; for example, in the preparation of unusual monosaccharides.

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Supplementary Material Available: Experimental procedures for the preparation of substances **3**, **6**, **7**, **9a,b**, **11–13**, and **16b,c** (5 pages). Ordering information is given on any current masthead page.

(19) Lactone **12** shows: ^{13}C NMR δ 207.5, 173.2, 81.2, 77.1, 58.6, 27.6, 25.9, 21.7, 18.1; IR 3620, 1840, 1740 cm^{-1}; mp 92–93.5 °C.

(20) Lactone **13** shows: ^{13}C NMR δ 207.9, 174.4, 87.9, 46.9, 39.6, 26.5, 26.4; IR 1737, 1726 cm^{-1}; mp 94–95 °C.

(21) Lactone **6** comprised about half of the product, but was accompanied by other unidentified compounds.

(22) Allenyl acid **10b** was prepared by basic hydrolysis of the corresponding nitrile.[23]

(23) Delair, T.; Doutheau, A.; Gore, J. *Bull. Soc. Chim. Fr.* **1988**, *1*, 125.

(24) Lactone **16b** shows: ^{13}C NMR δ 209.6, 176.6, 77.9, 76.8, 26.8, 26.7, 25.1; IR 3508, 1784, 1730 cm^{-1}.

(25) Lactone **16c** shows: ^{13}C NMR δ 210.0, 170.2, 79.5, 77.2, 29.5, 27.1, 26.9, 24.1, 17.2; IR 3477, 1742, 1728 cm^{-1}.

(26) Allenyl acid **10c** was prepared by oxidation of the corresponding alcohol[27] with pyridinium dichromate: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(27) Crandall, J. K.; Mualla, M. *Tetrahedron Lett.* **1986**, *27*, 2243.