"Anomalous" Ozonolysis of Cyclic Allylic Alcohols: Mechanism and Synthetic Utility

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The reaction of ozone with an olefin in which both the double bond and an adjacent single bond are cleaved is known as an "anomalous" ozonolysis.[1] The factors controlling this abnormal behavior have not been fully elucidated, and as a result, synthetic exploitation has been difficult. The presence of certain allylic substituents, alcohols in particular, often leads to anomalous products through a mechanism that has been the subject of debate.[1b,2] Provided herein are details of the anomalous ozonolysis of cyclic allylic alcohols which shed light on the mechanism as well as the factors controlling this transformation. The synthetic utility of this procedure for the introduction of isotopic carbon atoms as well as alkyl and aryl substituents at the α-position of enones is described.

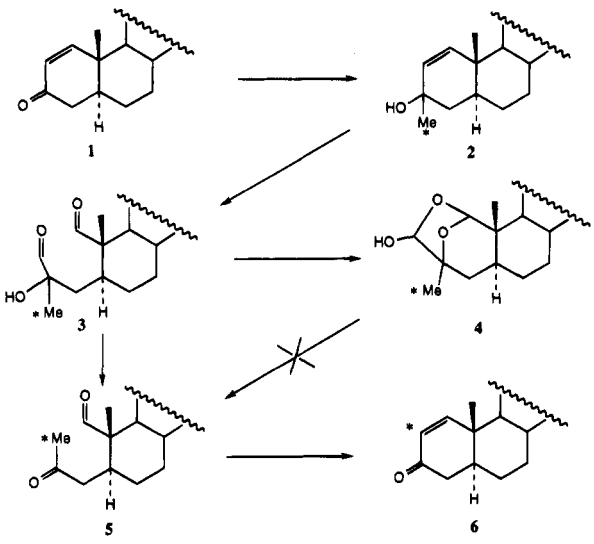
While examining methods for the ^{14}C radiolabeling of steroids, the route shown in Scheme 1 was explored. The conversion of ketoaldehydes such as **5** to enones of type **6** was well precedented, so compound **5** became the initial target. Osmylation of **2**, prepared by Grignard addition to **1**, followed by periodate treatment did lead to the structure type **3**, but it rapidly cyclized to the lactol **4**, which was resistant to further reaction. It was anticipated that ozonolysis of **2** might result in the formation of compound **5** if the anomalous pathway was operative.

The model olefin **7** was chosen to explore this chemistry (Scheme 2). When compound **7** was treated with ozone in dichloromethane at −78 °C, followed immediately by reductive workup (PPh_3), a high yield of the "normal" dialdehyde product was obtained (i.e., structure type **4**). However, if the unreduced reaction mixture was allowed to stir at room temperature, compound **11** was produced over several days with a concomitant production of formic acid.[3] Although the initial goal of preparing **11** was achieved, we became intrigued by the pathway by which it was formed and set out to identify the ozonolysis intermediate.

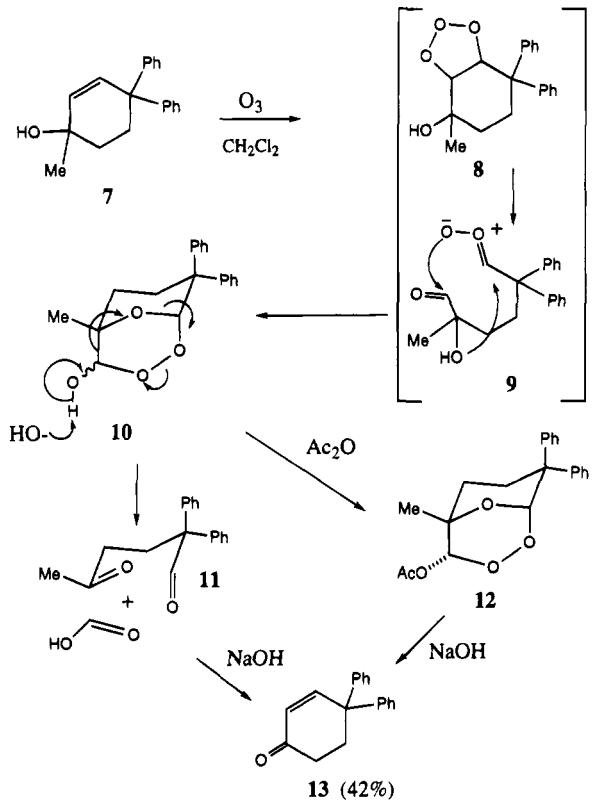
Purification of the crude ozonolysis reaction mixture was accomplished by silica gel chromatography, which produced a mixture of interconverting alcohol products[4] in ~50% yield. Since these compounds readily transformed to the ketoaldehyde **11**, they were acetylated, which improved their stability and allowed for a more thorough spectroscopic evaluation. The major product, **12**, could be purified and was stable in solution for several weeks. Unfortunately, NMR studies failed to give an unambiguous structure determination. Unequivocal structural assignment was ultimately secured through X-ray crystallographic analysis of a single crystal of **12**. The X-ray structure of **12** is as represented in Scheme 2.

With the structure of **12** established, it becomes clear that **10** is produced by intramolecular trapping of the carbonyl oxide intermediate **9**,[5] followed by cyclic acetal formation.[6,7] The spontaneous conversion of **10** to **11** appears to be driven by the formation of three carbonyl groups as well as the breaking of the O–O bond. This process is reminiscent of a Grob fragmentation,[8] which is often base catalyzed. This analogy prompted the exploration of basic workups of the ozonolysis reaction to accelerate the deformylation process. The use of

Scheme 1



Scheme 2



(1) (a) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic: New York, 1978; Vol. 1. (b) Bailey, P. S. *Chem. Rev.* **1958**, *58*, 925–1010.

(2) (a) Everest, D. J.; Grant, P. K.; Slim, G. C.; Yeo, I. K. L. *Aust. J. Chem.* **1988**, *41*, 1025–1035. (b) Cargill, R. L.; Wright, B. W. *J. Org. Chem.* **1975**, *40*, 120–122. (c) Wadt, W. R.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1975**, *97*, 3004–3021.

(3) As evidenced by a singlet produced at δ 8.01 in the ^1H NMR spectrum ($CDCl_3$).

(4) The presence of hydroxyl groups was supported by D_2O exchange experiments, and their interconversion was shown by a two-dimensional TLC analysis.

(5) Intramolecular trapping of a carbonyl oxide by an alcohol has been reported: See ref 2a and the following: (a) Paryzek, Z.; Martynow, J.; Swoboda, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1220–1221. (b) Schreiber, S. L.; Liew, W. F. *J. Am. Chem. Soc.* **1985**, *107*, 2980–2982 and references cited therein.

(6) The remaining 50% of the material not accounted for by **10** may have followed other pathways from **8**, perhaps through the alternate carbonyl oxide intermediate.

(7) This mechanism is consistent with the observation that no product **13** is observed if the starting allylic alcohol is protected as an acetate or trimethylsilyl ether.

(8) For a review, see: Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1–15.

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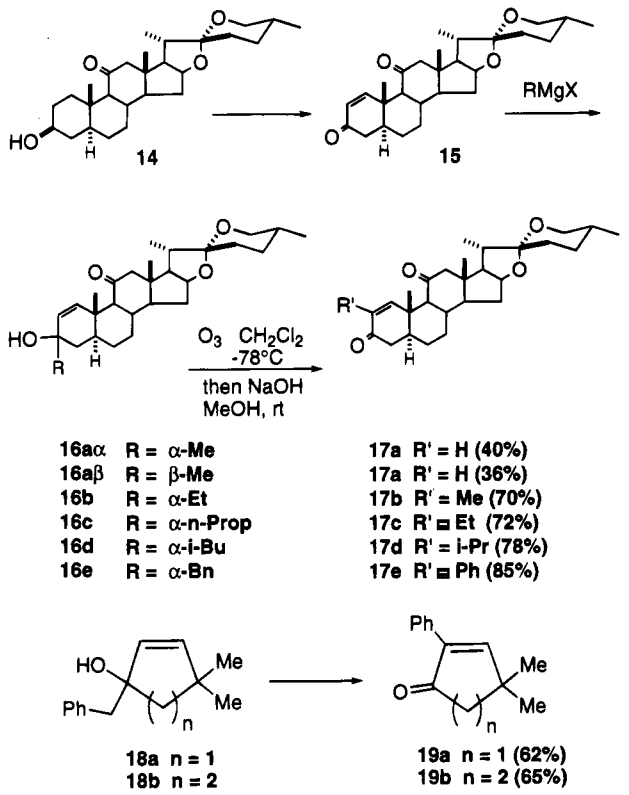
Scheme 3



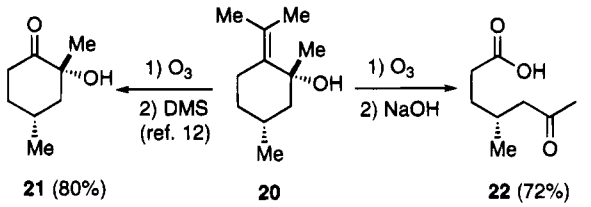
some bases (DBU, KOtBu) led to intractable byproducts; however, success was realized using methanolic sodium hydroxide solution,[9] which catalyzed not only the deformylation but the aldol and dehydration steps as well. Under these nontraditional workup conditions, the crude ozonolysis mixture was converted directly to **13** in 42% yield within a few hours. When the acetate **12** was treated under the same conditions (NaOH, MeOH), enone **13** was formed in high yield (90%). This result suggests that the low overall yield of the process is the result of the inefficient production of **10** from the decomposition of the primary ozonide **8**. It is important to note that in this mechanistic formulation, the α-carbon of the enone product **13** originated from the allylic methyl group in the starting material.

This method has been applied to the steroidal system **16** (Scheme 3). The epimeric alcohols **16aα** and **16aβ** reacted similarly to give the parent enone **17a** in 40 and 36% yields, respectively. The procedure has also been used to generate enones alternatively substituted at the α-carbon by elaborating the nucleophilic reagent. For example, when propyl- or benzyl-substituted allylic alcohols were utilized in the reaction, the α-ethyl and α-phenyl enones **17c** (72%) and **17e** (85%) were produced. The simple cyclopentenol **18a** and cyclohexenol **18b** also gave useful yields of products. The improved yields of the substituted enones were unexpected and difficult to rationalize. The introduction of substituents at the α-position of enones by this protocol complements the existing methods for achieving this transformation,[10] including the closely related Fujimoto–Belleau reaction.[10p]

The issue of controlling the anomalous versus normal ozonolysis was revisited. From the studies on the model system **7**, it became clear that it was the workup which dictated the outcome of the reaction. To demonstrate this idea, compounds **7**, **16aα**, and **16e** were each treated with ozone at −78 °C and then reduced with triphenylphosphine. In all of these cases, high yields (76–89%) of the normal ozonolysis products

(9) Similar hydroxide-catalyzed deformylations have been reported. See, for example: (a) Hoffman, J. *J. Am. Chem. Soc.* **1957**, *79*, 503–504. (b) Smith, D. C. C. *J. Chem. Soc.* **1957**, 2690–2697. (c) Hardegger, von E.; Schellenbaum, M.; Huwyler, R.; Zust, A. *Helv. Chim. Acta* **1957**, *40*, 1815–1857.

Scheme 4



(internally ketalized dialdehydes analogous to **4**) were isolated. The reduction of compound **10** also afforded a high yield of the dialdehyde product, supporting the possibility that the 1,2,4-trioxane is a common intermediate in both types of reactions. These studies serve to illustrate that both anomalous and normal ozonolysis products can be obtained from the same allylic alcohol with the appropriate choice of reaction conditions.[11] To illustrate the generality of this concept, an example was taken from the literature in which the normal product was obtained from an ozonolysis of the allylic alcohol **20** (Scheme 4).[12] Upon repeating this reaction, this time using sodium hydroxide as the workup reagent, a slow but clean fragmentation reaction occurred, and the acid **22** was isolated in 72% yield. While the reactions in this study, as well as others,[2b] appear to require added base to facilitate the fragmentation reaction, other examples[1] proceed uncatalyzed. This difference in reactivity may reflect the inherent stability of the proposed 1,2,4-trioxane intermediate.

In summary, the anomalous ozonolysis of cyclic allylic alcohols has been investigated. A distinct mechanistic pathway has been elucidated on the basis of the structure determination of the 1,2,4-trioxane intermediate. The reaction is the basis of a new and concise method for the incorporation of isotopic carbon atoms as well as alkyl and aryl substituents at the α-position of cyclic enones. The utility of this method for the incorporation of a radiolabel at the C-2 position of steroids was demonstrated by the preparation of ^{14}C-labeled 11-ketotigogenin **14**, a component of a cholesterol absorption inhibitor in clinical development. Details of this synthesis will be forthcoming.

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Supporting Information Available: Experimental procedures and spectral data for all reaction products and X-ray crystallographic data for compound **12** (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(11) For references dealing with unconventional ozonolysis workups, see ref 1a and the following: (a) Schreiber, S. L.; Claus R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867–3870. (b) Hon, Y.-S.; Lin, S.-W.; Chen, Y.-J. *Synth. Commun.* **1993**, *23*, 1543–1553. (c) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675–3680.

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