

# Conclusive Evidence of the Trapping of Primary Ozonides

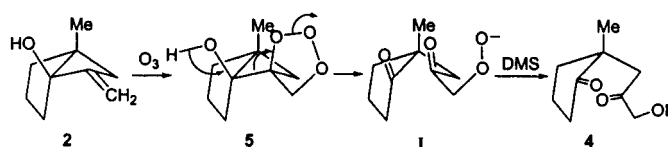
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Received January 9, 2001

## ABSTRACT



Anomalous ozonolysis of strained bicyclic allylic alcohols yields  $\alpha$ -hydroxymethyl ketones. The proposed mechanism involves an unusual trapping of the primary ozonide that undergoes a Grob-like fragmentation instead of dissociating into the Criegee intermediates.

In the course of a total synthesis of the cardioactive steroid ouabain,<sup>2</sup> we required a good method for the preparation of the  $\alpha$ -hydroxycyclobutanone **3**. An ideal approach would involve the ozonolysis of the  $\alpha$ -hydroxy methylenecyclobutane **2** or a hydroxyl-protected derivative. However, the ozonolysis of **2** did not proceed as expected and gave **4** instead of **3** (Scheme 1). We describe here the results of such anomalous ozonolyses, which furnish clear evidence for the trapping of a primary ozonide.

There have been many reports of the trapping of carbonyl

oxide with carbonyl compounds, alcohols, etc.<sup>3</sup> Primary ozonides have never been isolated and have only been observed in the gas phase,<sup>4</sup> in argon matrices,<sup>5</sup> or in low-temperature solutions.<sup>6</sup> Although there have been reports of the oxidation of other molecules by primary ozonides,<sup>7</sup> as far as we know, no unambiguous evidence for the trapping of the primary ozonide has been presented. We report here the first trapping of primary ozonides of strained allylic alcohols via a Grob-like fragmentation.<sup>8</sup>

Allylic alcohols<sup>9</sup> and methylenecyclobutanes<sup>10</sup> are known to undergo anomalous ozonolyses.<sup>11</sup> Several mechanisms have been proposed to explain the formation of the different

(1) 2000–2001 American Chemical Society Division of Organic Chemistry Graduate Fellow, sponsored by DuPont Pharmaceuticals, Inc.

(2) Fieser L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959; Chapter 20.

(3) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, 23, 3867–3870. (b) Criegee, R. *Angew. Chem.* **1975**, 87, 765–772; *Angew. Chem., Int. Ed. Engl.* **1975**, 14, 745–752. (c) Keul, H.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, 106, 3383.

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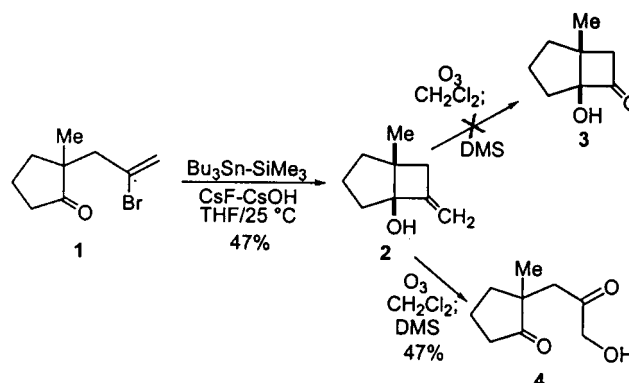
(6) (a) McGarrity, J. F.; Prodoliet, J. *J. Org. Chem.* **1984**, 49, 4465–4470. (b) Mile, B.; Morris, G. W.; Alcock, W. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1644–1652.

(7) (a) Criegee, R.; Schroder, G. *Chem. Ber.* **1960**, 93, 689–700. (b) Criegee, R.; Gunther, P. *Chem. Ber.* **1963**, 96, 1564–1567.

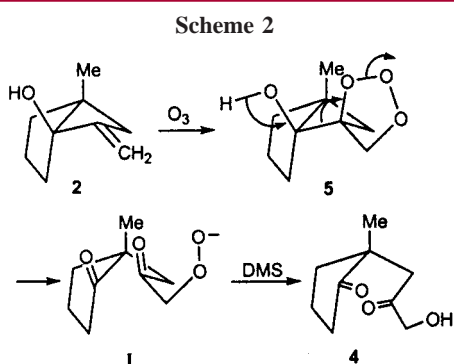
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Scheme 1

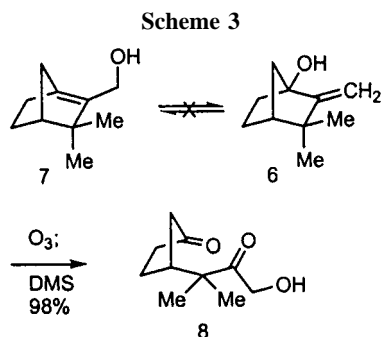


abnormal products, but few involve trapping of the primary ozonide.<sup>11b</sup> Subjecting the racemic allylic alcohol **2** to standard ozonolysis conditions ( $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ,  $\text{O}_3$ ;  $\text{Me}_2\text{S}$ ) surprisingly did not produce the ketone **3** but gave 2-(3-hydroxy-2-oxopropyl)cyclopentanone **4** in 47% yield. We have considered two possible mechanisms to account for the formation of **4**. The first one involves an initial allylic rearrangement that would yield the endocyclic olefin, which could lead directly to **4** through a normal ozonolysis pathway. Although this mechanism did not seem probable, since the cyclobutane would have significant additional strain and there was no acid catalyst for such rearrangement, we could not rule it out a priori. The second possible mechanism involves the formation of the primary ozonide **5**, which could undergo a Grob-like fragmentation to yield **4** via the  $\alpha$ -hydroperoxy-ketone intermediate **I** as shown in Scheme 2. The strain



energy release of the cyclobutane would be the driving force for this unusual rearrangement.

To test the first hypothesis, we decided to ozonize the allylic alcohol **6**, prepared in two steps from (+)-camphor (Scheme 3).<sup>12</sup> It cannot undergo an allylic rearrangement to



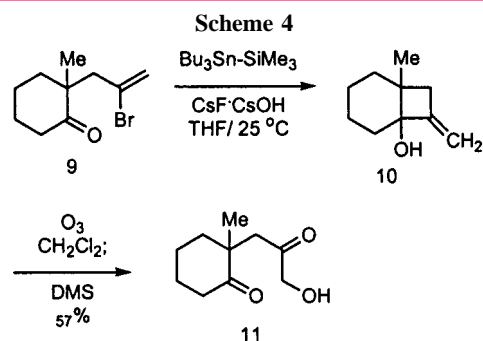
produce the highly strained bridged olefin **7** because that would violate Bredt's rule.<sup>13</sup> Thus, normal ozonolysis of **6**

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would suggest the allylic rearrangement as the preferred mechanism, while formation of the hydroxymethyl ketone **8** would argue for the intermediacy of the Grob-like fragmentation as the most likely mechanism. Treatment of the alcohol **6** in dichloromethane at  $-78^\circ\text{C}$  with ozone, followed by reductive workup with dimethyl sulfide, afforded the ketone **8** in 98%. Therefore, we believe that the mechanism of this anomalous ozonolysis involved a Grob-like fragmentation of the primary ozonide **5** as shown in Scheme 2. In addition, because the allylic alcohol **6** is derived from naturally occurring camphor, the ketone **8** is necessarily optically pure. This is an efficient and general method to synthesize 3-substituted homochiral cyclopentanones, a subunit commonly found in natural products.

The precursors for the cyclobutane formation were prepared by reacting 2,3-dibromopropene with the thermodynamic enolates of 2-methylcyclopentanone and -hexanone using Negishi's procedure.<sup>14</sup> The intramolecular four-membered ring formation, however, was problematic. The vinyl bromide moieties of **1** and **9** are surprisingly unreactive, being resistant to metal insertion reactions (Rieke zinc<sup>15</sup> and samarium(II) iodide<sup>16</sup>). The successful halogen–metal exchange and subsequent cyclization was based on a procedure of Mori et al.,<sup>17</sup> using the potent fused salt  $\text{CsF}\cdot\text{CsOH}$  as the fluoride source.<sup>18</sup> Thus, treatment of the vinyl bromides **1** and **9** with 3 equiv of  $\text{Bu}_3\text{SnSiMe}_3$  and 3 equiv of  $\text{CsF}\cdot\text{CsOH}$  in THF at ambient temperature generates the corresponding bicyclic compounds **2** and **10** in 47% and 43% isolated yields, respectively. The cyclohexyl analogue **10** also gave the anomalous ozonolysis product **11** in 57% yield. We



next considered the possibility that this primary ozonide fragmentation could be effected with electron-donating groups other than hydroxyl, ethereal oxygen and amide nitrogen. However, ozonolysis of both the benzyloxymethyl

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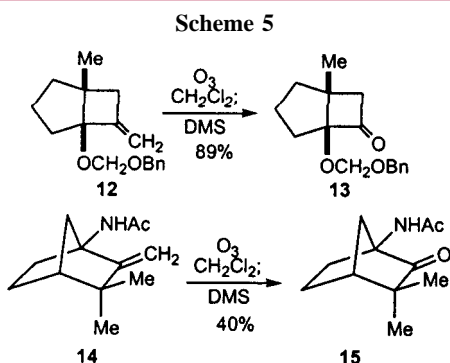
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ether **12**, prepared in 94% yield from **2**, and the bicyclic acetamide **14**, easily prepared in two steps from (+)-camphor,<sup>19,20</sup> afforded the normal products **13** and **15** in unoptimized yields of 89% and 40%, respectively. Thus, stronger electron donation than that offered by ethers and amides is required.

Finally, we have shown that one can control an additional stereocenter on the side chain by this ozonolysis process by using a trisubstituted alkene of known geometry. Thus the bromo-alkenyl ketone **16**, prepared in 80% yield by alkylation of the ketone with the *E*-allylic iodide, was converted



into the *E*-ethylidenecyclobutanol **17** using a modification of the stannyl anion procedure. Ozonolysis of this alkene occurred by addition of ozone on the more accessible exo

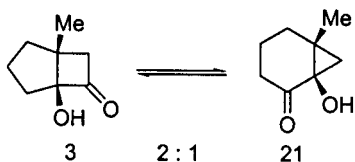
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(20) Ozonolysis of the hydrochloric salt of the corresponding free amine has been reported to proceed normally in quantitative yield. Martínez, A. G.; Teso, E.; García, A.; de la Moya, S.; Martínez, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2177–2180.

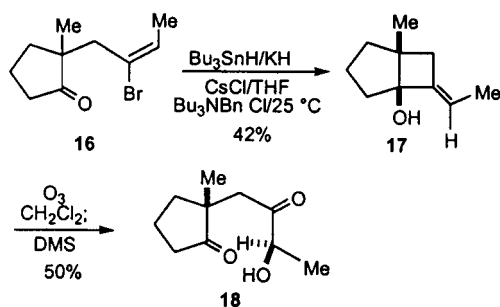
(21) The rest of the material (50%) is the hydroxycyclobutanone **3**.

(22) Prepared by isomerization of the *tert*-butyldimethylsilyl ether of the *E*-isomer with iodine and light (to give a 4:3 *E* to *Z* ratio) followed by desilylation and separation. It is interesting that Wittig olefination of the corresponding cyclobutanone (prepared from the silyl enol ether of 2-methylcyclopentanone by addition of ethyl propiolate, conversion of the ester to the aldehyde, Baeyer–Villiger oxidation, and hydrolysis) gave only the *E*-isomer of the alkene, even at high temperatures, in contrast to the work of Still. Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.

(23) It is interesting to note that the hydroxycyclobutanone **3** exists in solution as an equilibrium mixture of **3** and the hydroxyketone **21** in a 2:1 ratio. (a) Harding, K. E.; Trotter, J. W.; May, L. M. *J. Org. Chem.* **1977**, *42*, 2715–2719. (b) Paukstelis, J. V.; Kao, J.-L. *J. Am. Chem. Soc.* **1972**, *94*, 4783–4784.



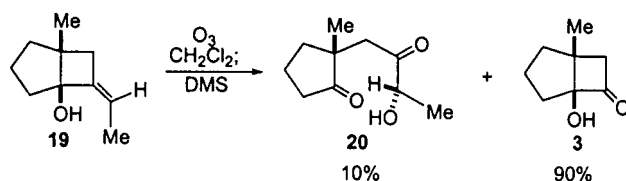
**Scheme 6**



face of the alkene to give after fragmentation only the single diastereomer **18** in 50% yield.<sup>21</sup>

Ozonolysis of the corresponding *Z* isomer **19**<sup>22</sup> afforded the opposite diastereomer **20** as the minor isomer in a 9:1 ratio with the hydroxycyclobutanone **3**.<sup>23</sup> Thus, one can control the stereochemistry of a secondary alcohol  $\alpha$  to the ketone of the side chain by this process.

**Scheme 7**



This rearrangement appears to be general for several strained bicyclic allylic alcohols, e.g., bicyclo[3.2.0]- and [2.2.1]heptanes and bicyclo[4.2.0]octanes. New conditions for producing strained methylenecyclobutanols in fair yield was also discovered. By combining (+)-camphor as a starting material with this primary ozonide fragmentation, we were able to produce an optically active  $\alpha$ -hydroxymethyl ketone building block efficiently in only three steps. Finally, one can control the stereochemistry of a secondary alcohol  $\alpha$  to the ketone of the side chain by this process.

**Acknowledgment.** P.D. thanks the NIH and UCLA for a Chemistry/Biology Interface Training Grant, USPHS National Research Service Award GM08496. This material is based upon work supported by the National Science Foundation under equipment grant no. CHE-9974928.

**Supporting Information Available:** Spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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