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A Novel Bicyclic Ketal Fragmentation Reaction

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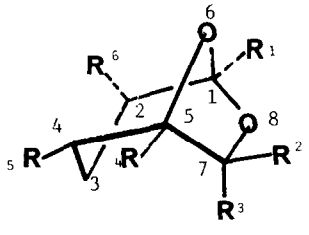
Abstract: Bicyclic ketals of the 6,8-dioxabicyclo[3.2.1]octane series are specifically cleaved to give δ,ε-unsaturated ketones by treatment of the ketal with acetyl iodide.

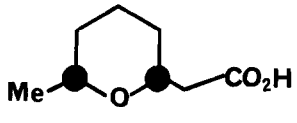
Bicyclic ketals of the 6,8-dioxabicyclo[3.2.1]octane series, (**1**), well-represented by the insect pheromones frontalin,(**2**), brevicomin, (**3**), and multistriatin, (**4**), have been found to be generally resistant to hydrolysis. Because methodologies are available to gain access to a host of substitution patterns having specific stereochemistries, it seemed that a useful endeavor should be directed towards the chemical modification of these readily-available, robust ketals. We have already demonstrated a specific utility in the stereospecific conversion of **5** to **6**, a component of the glandular secretion of the civet cat[1]. We now show a potentially useful entry into δ,ε -unsaturated ketones.



1. All R-groups are H, unless indicated.

2. $R_1 = R_4 = Me$ **4.** $R_1 = Et$; $R_5 = R_6 = Me$

3. $R_1 = Me$; $R_2 = Et$ **5.** $R_1 = R_2 = Me$

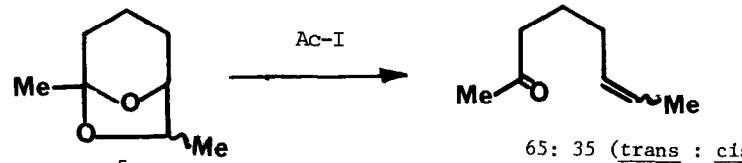


6

All of our previous experience had been specifically directed towards the O-8 - C-1 bond as a way to prepare pyran rings from the bicyclic ketals. The specificity for this cleavage can be found in our reductive cleavage of **5** with $AlClH_2$[1], and with Pd/C[2]. It has been established that O-8 is the preferred site of lanthanide interaction during lanthanide-induced shift studies[3]. The specificity does not seem to have its origins in electronic factors, since CNDO/2 calculations suggest that the electron density around the two oxygen atoms is comparable. A reasonable explanation for reaction preference may reside not in the site of initial attack; but, rather in the notion that the anomeric effects of the O-6 oxygen may help the displacement of the O-8 oxygen considerably better than the O-6.

In an attempt to find a reagent that would specifically fragment the O-6 bond to carbon, with the expectation of creating a new approach to oxepin derivatives, we reacted **5** with acetyl

iodide[4]. To our surprise, we obtained the elimination of both bridging oxygens (**Eq. 1**). We now report the further studies towards the generalization of this fragmentation procedure.



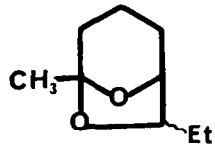
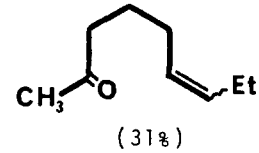
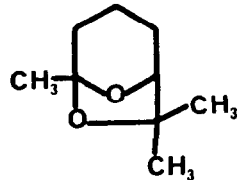
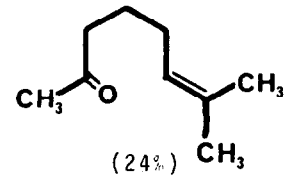
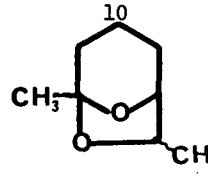
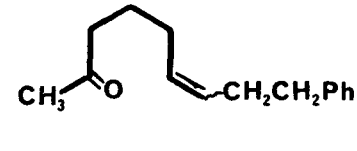
Eq. 1

5
60: 40 (exo : endo)

65: 35 (trans : cis)
7

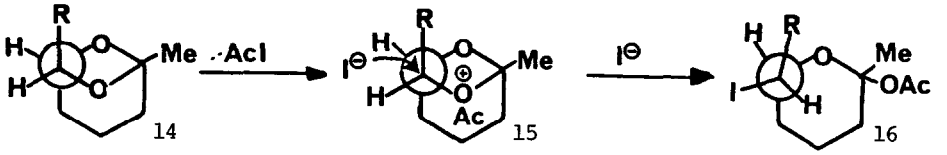
The results for a number of fragmentations of different substrates are given in Table I.

Table I
Acetyl iodide fragmentation of bicyclic ketals

Ketal	(% Unsaturated ketone)	
 8	60 exo 40 endo	 (31%) 9 — 71 trans 29 cis
 10		 (24%) 11
 12	60 exo 40 endo	 13 — 70 trans 30 cis

This study has demonstrated an interesting cleavage reaction that provides a general entry into δ,ε-enones. Although we have been unable to develop the chemistry to obtain high yields of the fragmentation products, the simplicity of the reaction and the ease of generating precursor ketals more than compensates for this. A useful mechanistic interpretation was generated from the observation that there appeared to be a relationship that **endo-** ketals gave **cis-** alkenes and **exo-** ketals gave **trans** alkenes. It has been an observation that Grignard additions or hydride reductions used in the synthesis of the bicyclic ketals always results in the predominance of **exo** products. In the simplest, and most often repeated experiment, the **exo-** to **endo-** ratio of **5** is 60:40. Cleavage of this ketal with NaI/AcCl gave a 65 : 35 ratio of **trans** to **cis** alkenes. In all of the other cases studied to date we find that the **trans** alkene is the major product, just

as the **exo** orientation prevails in the ketal. Although there are several possible ways to interpret these results, we suggest that a mechanism similar to that used by Goldsmith[5] for ether cleavage may find application (**Scheme 1**).



To test this hypothesis, we chose a reaction substrate that would not be influenced by the differences in "bulk" of the **exo** and **endo** substituents. The addition of deuteriomethyl Grignard to the dimer of methyl vinyl ketone gave the isomeric deuterio 5,7,7-trimethyl-6,8-dioxabicyclo-[3.2.1]octane derivatives,(**19**). The ratio of the **exo** and **endo** deuteriomethyl substitution (2:1) is easily derived from the proton NMR spectrum. Cleavage of this ketal (which should experience no steric biases) gave an alkene mixture of **19** and **20** as shown in Figure 1.

Scheme 1. A Mechanism for Ketal Cleavage

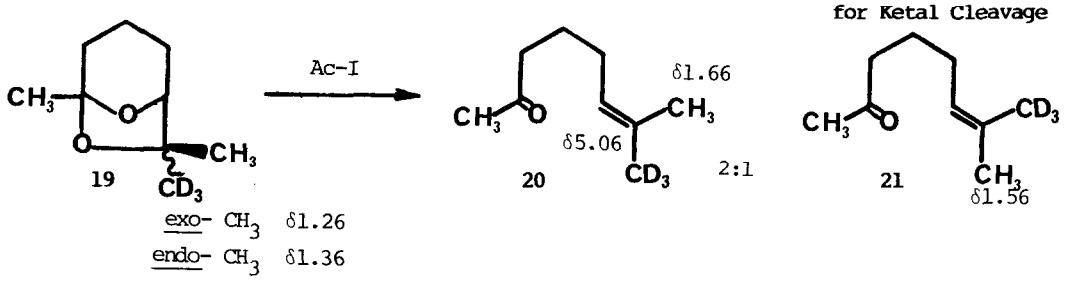
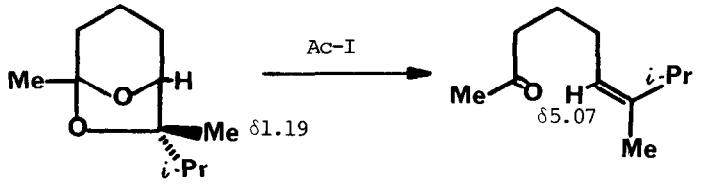


Figure 1. Evidence for Fragmentation Specificity

As a last test of this mechanistic interpretation, we were able to prepare pure endo 7-isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane, [**21**], in 65% yield by the addition of isopropylmagnesium chloride to the dimer of methyl vinyl ketone. Fragmentation gave only the Z-isomer of 7,8-dimethyl-6-nonen-2-one, [**23**]; however, in only 13% yield. Other fragmentation products from this particular reaction have not yet been identified.



This work seems to suggest that our mechanistic interpretation has experimental validity, and we note that the synthetic possibilities may find interesting application to a variety of endeavors. For example, only a cursory examination of structures of insect pheromones demonstrates that a number of these compounds may be made available by application of this methodology. We are currently working towards the completion of some of these interesting molecules.

ACKNOWLEDGMENTS

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2. K.B. Lipkowitz, B.P. Mundy and T.H. Matsko, **J. Org. Chem.**,(1976) 41 371

3. B.P. Mundy, G.W. Dirks, R.M. Larter, A.C. Craig, K.B, Lipkowitz and J. Carter,**J. Org. Chem.**, (1981) 46 4005.

4.a. For examples of the use of acetyl iodide, see: A. Oku, T. Harada, and K. Kita, **Tetrahedron Letters**, (1982), 681, and other literature cited.

b. For other means of fragmenting ketals, see: (1) R.J. Borders and T.A. Bryson, **Chemistry Letters**, (1984), 9, (2) S. Takano, M. Akiyama, S. Sato, and K. Ogasawara, **Ibid**, (1983), 1593, (3) R. Baker, R.H.O. Boyes, D.M.P. Broom, J.A. Devlin and C.J. Swain, **J. Chem. Soc., Chem. Commun.**, (1983), 829.

5. D.J. Goldsmith, E. Kennedy and R.G. Campbell, **J. Org. Chem.**,(1975), 40, 3571.

EXPERIMENTAL

General cleavage reaction: The **exo/endo** ketal mixture was stirred with two equivalents of NaI in 25 mL CH_3CN at 0°C. To this mixture was added two equivalents of acetyl chloride in 10 mL CH_3CN over a period of about 1 hr. The reaction mixture was then stirred for an additional hr. at 0°, and then at room temperature for 24 hr. After this time 15 mL of $NaHSO_3$ was added and the reaction mixture was stirred for 2 hr. The reaction mixture was extracted with three 50-mL portions of ether. The combined extracts were washed with dilute bicarbonate, brine, and then water. After drying over $MgSO_4$, the solvent was removed by rotary evaporation. The crude product was then run through a column (25 mm diameter) containing 150 mm hight of silica gel topped with 15 mm of Florisil, using as an elutant, petroleum ether:ethyl acetate (7:3). It was observed that attempting to directly distill the crude product resulted in extensive decomposition and formation of polymeric material.

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