CHEMISTRY OF THE 6,8-DIOXABICYCLO[3.2.1]OCTANE SERIES
SOURCES, SYNTHESES, STRUCTURES AND REACTIONS

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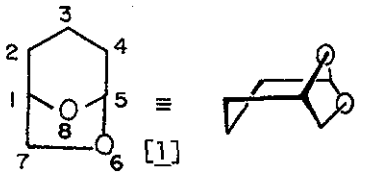
INTRODUCTION

The 6,8-dioxabicyclo[3.2.1]octane system [1] is a well-established structural unit in carbohydrate chemistry, and is occasionally found as the repeating unit in some synthetic polymers. However, the recent interest in this bicyclic ketal has surfaced primarily with the realization that this is a structural feature of several non-carbohydrate natural products.

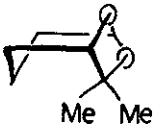
In this review we will identify some of the natural products, show the synthetic methodologies which are available to achieve this skeletal arrangement, and describe some of the novel chemistry associated with these systems. Carbohydrate chemistry will not be discussed in this review.



[1]

OCCURRENCE

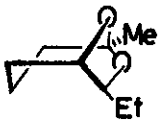
One of the earliest references to this bicyclic ketal concerned a constituent of Japanese hop oil from *Humulus lupulus* (1). Spectral analysis, coupled with a low-yield, but unambiguous synthesis, established the structure of the constituent to be [2].



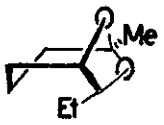
[2]

Real imputus towards a better understanding of the 6,8-dioxabicyclo-[3.2.1]octyl skeletal arrangement came with the structure determination and synthesis of brevicomin [3], the aggregating sex pheromone of the western pine bark beetle, *Dendroctonus brevicomis* (2). The *exo*-7-ethyl isomer, [3], is of more biological importance; however, [4] is a pheromone component and is normally found in most syntheses. Since powerful synergistic effects are noted in studies of insect pheromones (3), this isomer content may be significant. Frontalin [5] (4), and multistriatin [6] (5) have been dem-

onstrated to be the pheromones of the southern pine beetle, *D. frontalis* and the European elm bark beetle, *Scolytus multistriatus*, respectively.



[3]

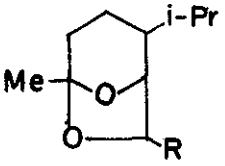


[4]

[5]

[6]

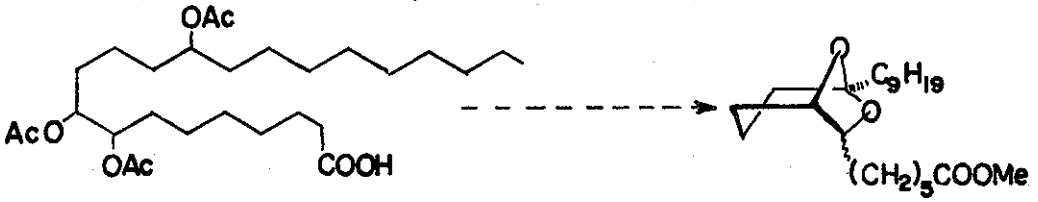
Several bicyclic ketals, including members from the 4,9-dioxabicyclo-[3.3.1]octane and 6,8-dioxabicyclo[3.2.1]octane series have been isolated from tobacco (6). In the latter series, ketals of the general structure [7] have been identified.



[7]

R = a. -COMe
b. -CH(OH)Me
c. -C(OH)Me_2

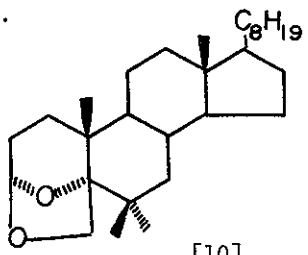
Recently it has been observed that a bicyclic ketal is formed during fatty acid metabolism in a yeast *(equation 1)* (7). This attractive biosynthetic route may warrant examination by those studying the orgin of insect pheromones of the bicyclic ketal constitution.



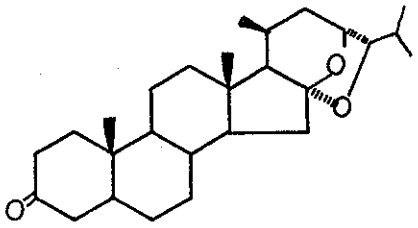
(1)

[8] [9]

Up to this point, the bicyclic ketal has been the major structural unit of the molecule. Two examples, [10] (8) and [11] (9), can be offered to demonstrate that the bicyclic ketal may be part of a larger structural type.



[10]



[11]

SYNTHESES

With the recent awareness of the 6,8-dioxabicyclo[3.2.1]octyl system, it is now pertinent to examine synthetic methodologies which can be utilized for its construction. In this section we will examine syntheses which have developed by both chance and design, in anticipation that the methodologies (or variations) may prove useful for future synthetic work.

Periodic acid cleavage of the triol [12] did not give the anticipated product [16], but rather the bicyclic ketal [15]. A rationalization for the observed product is given in figure 1 (10).

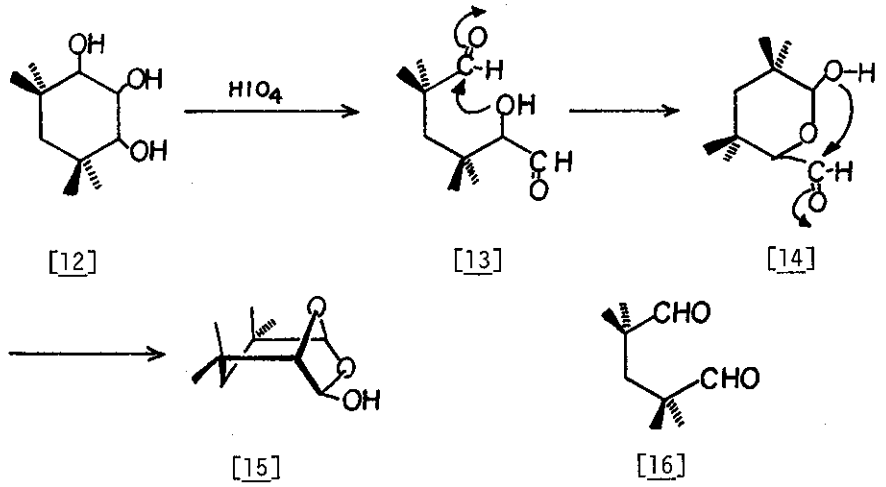
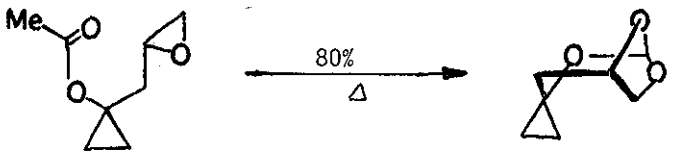


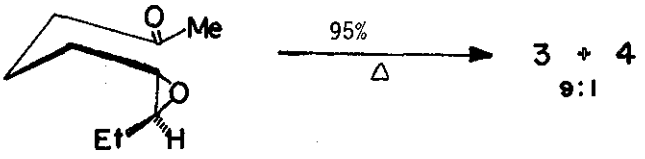
Figure 1. Periodic Acid Cleavage of a 1, 2, 3-Cyclohexane triol to a Dioxabicyclo[3.2.1]octane Derivative

As part of a study on the rearrangement of carbonyl-epoxides, Wasserman (11) noted the facile formation of bicyclic ketals, exemplified by the conversion of [17] to [18]. This prompted the use of the methodology for the synthesis of brevicomin *(equation 3)*.



(2)

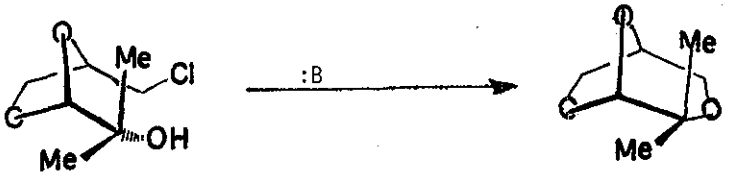
[17] [18]



(3)

[19]

There have not been many "oxa" bicyclic ketals discussed in the literature. Other than [18], seen in equation (2), another example [21], by a unique synthesis starting from a preformed ketal moiety has been reported *(equation 4)* (12).



[20] [21]

A low-yield cyclization of a pyranyl carbinol to [1] with lead tetraacetate has been postulated as taking place by a radical mechanism (figure 2) (13).

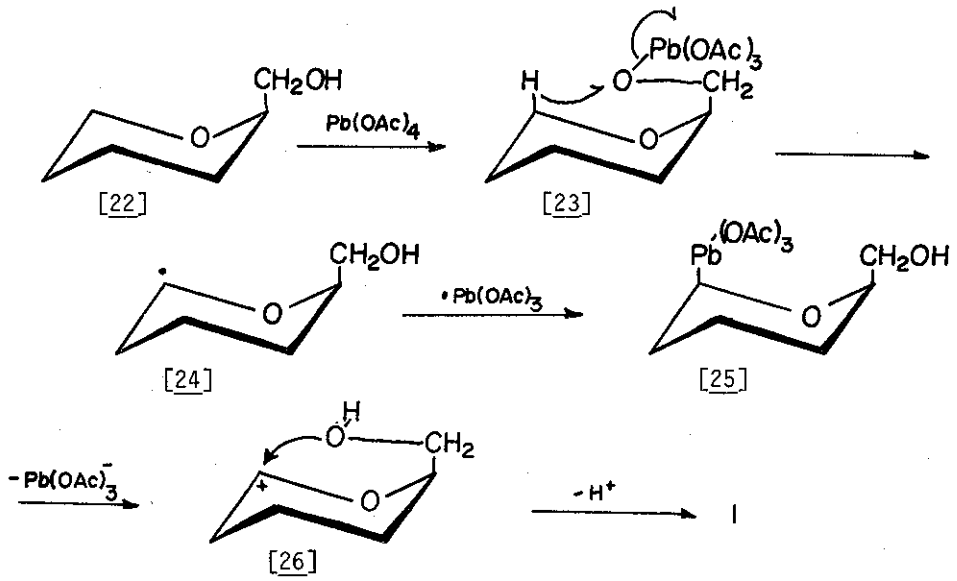


Figure 2. Lead tetraacetate Oxidation of a Pyranylcarbinol

If one examines the 6,8-dioxabicyclo[3.2.1]octane skeleton by an antithetic analysis (14), two rational pathways develop (figure 3). The approach in which the ketal is recognized as a

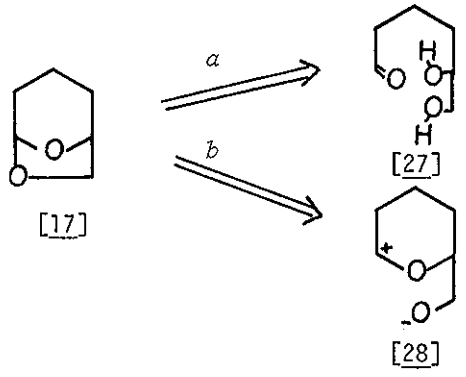


Figure 3. Antithetical Approach to 6,8-Dioxabicyclo[3.2.1]octane Derivatives

carbonyl and a glycol (path *a*) has, in a modified way, been utilized by Wasserman (11). Silverstein has developed three syntheses of brevicomin

utilizing this methodology (figure 4) (15). A recent, and very efficient, synthesis of brevicomin by a modification of the Silverstein route has been reported (figure 5) (16). A novel use of the Kolbe electrolysis technique

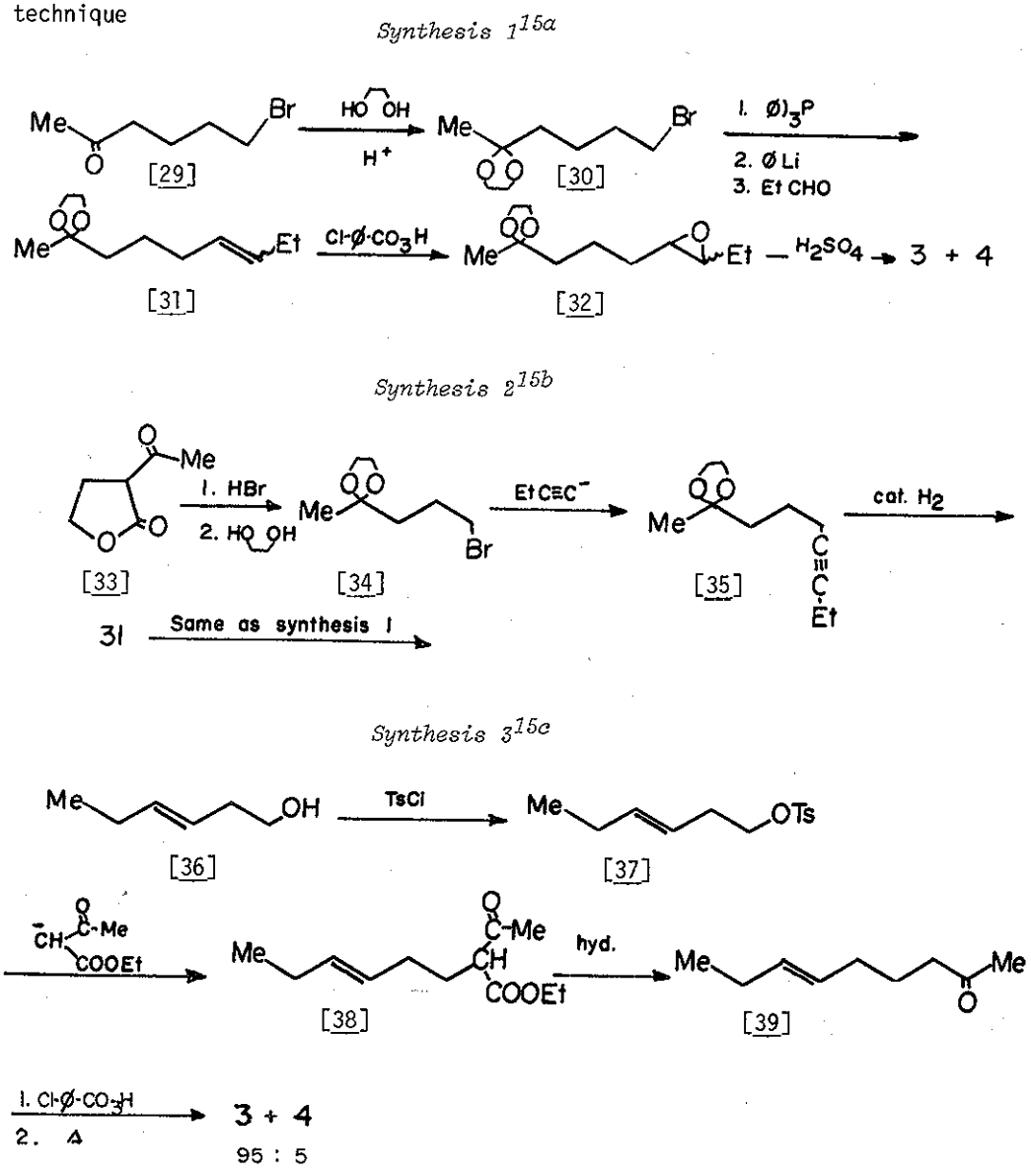


Figure 4. Silverstein Syntheses of Brevicomin

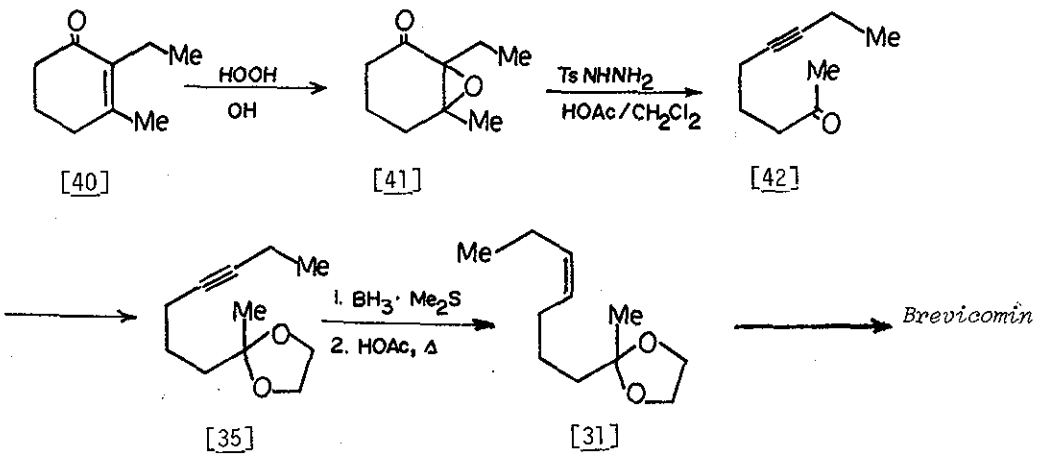
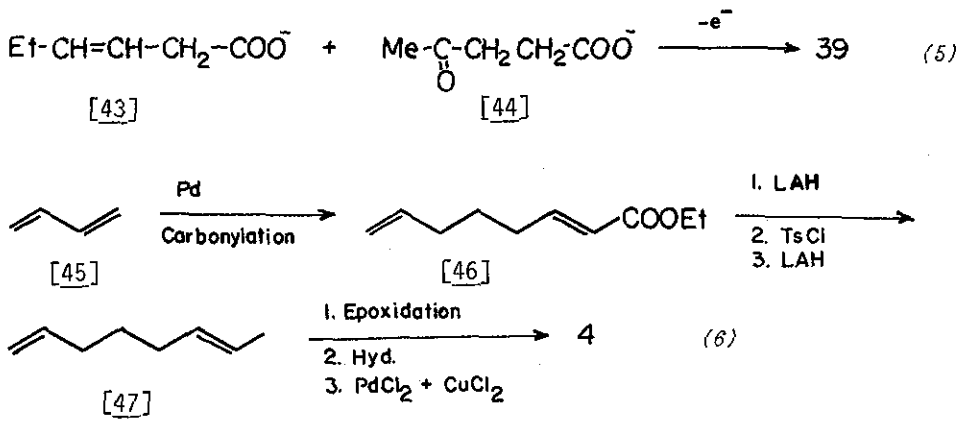


Figure 5. Cyclohexenone Approach to Brevicomin

has been shown to result in the requisite unsaturated ketone [39] for further elaboration to brevicomin by this methodology (*equation 5*) (17). *Endo* brevicomin has also recently been prepared from butadiene by a novel approach employing a modification of the keto-diol intermediate (*equation 6*) (18).



The synthesis of optically active frontalin was designed around the approach of forming a ketal from a carbonyl and a diol (figure 6) (19).

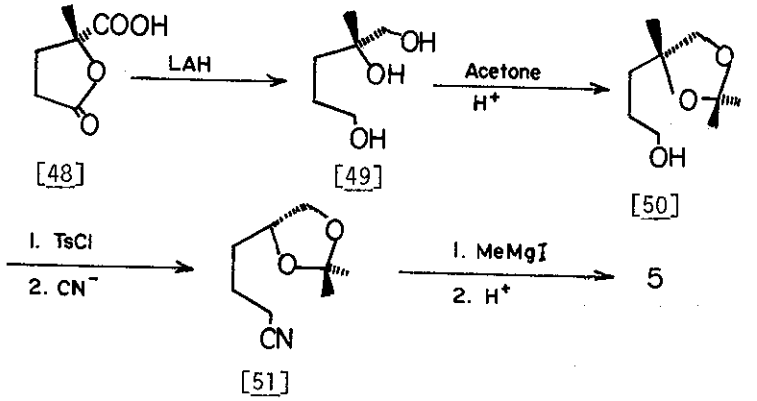
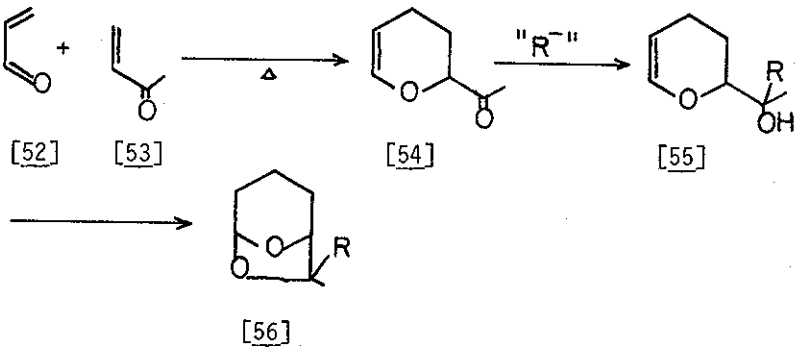


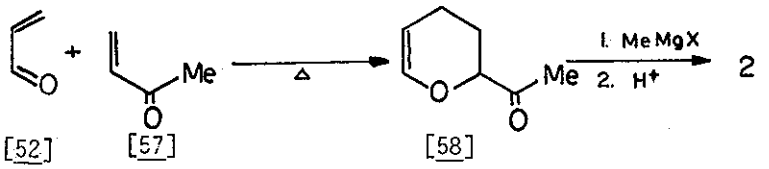
Figure 6. The Synthesis of Optically Active Frontalin

The methodology generated from antithetic route *b* can be generalized by *equation 7*.



(7)

This method was used to prepare [1] from acrolein (20), and was employed in the synthesis of the hop oil constituent [2] (1). The sequence, dilineated in *equation 8* resulted in a low-yield of [2].



(8)

It is of interest to note that the use of methyl vinyl ketone (*diene*) and acrolein (*dienophile*), a reversal of roles assigned in *equation 8*, was the basis of a quick, but also low-yield synthesis of brevicomin (figure 7) (21). By only a slight modification of the methodology, a synthesis of frontalin was also realized (figure 7) (21).

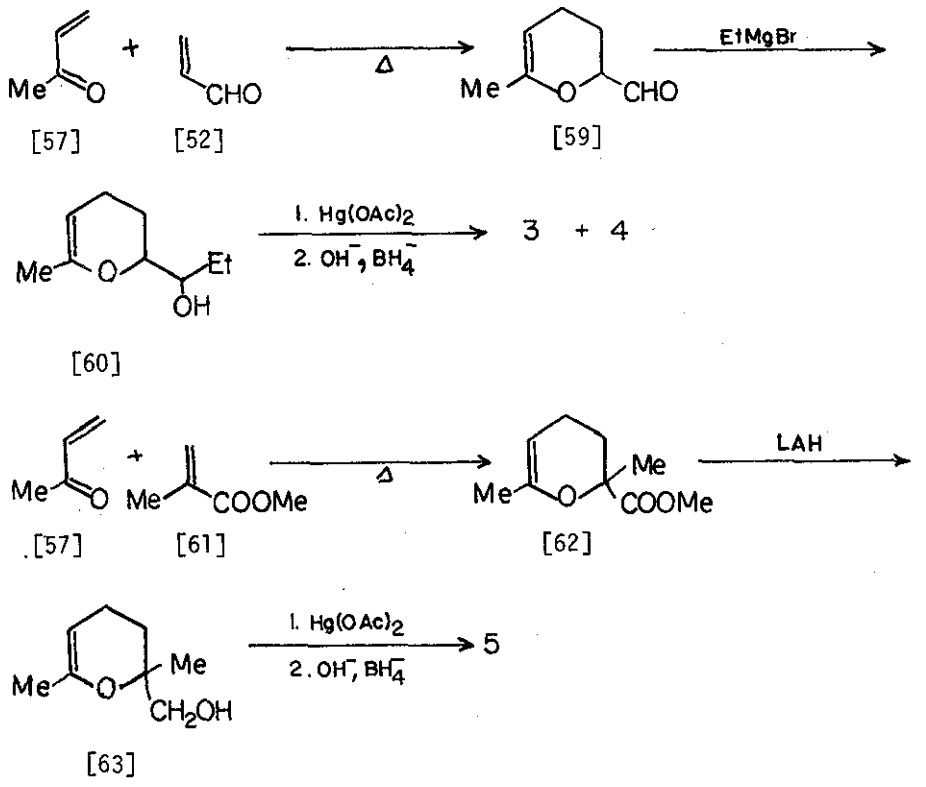


Figure 7. The Mundy Synthesis of Brevicomin and Frontalin

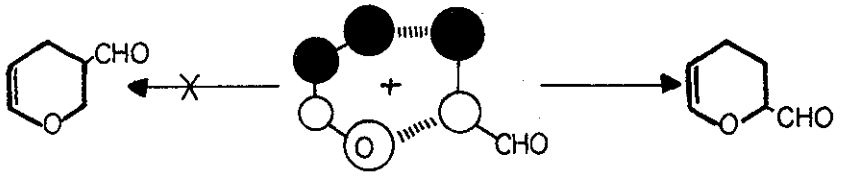
At this juncture it is of interest to examine the molecular orbital interpretation of these Diels-Alder reactions. If one compares the signs and magnitudes of the coefficients for the highest occupied molecular oribital (*HOMO*) of one component and the lowest unoccupied molecular orbital (*LUMO*) of the other component for the diene/dieneophile pair,

the regioselectivity for many of these reactions becomes evident (22). Indeed, it has been suggested that one has only to look at the orbitals of the two carbon atoms which will ultimately join to form the ring (23). Some data from CNDO/2 calculations will help clarify this concept (figure 8) (24).

The utility of using the frontier molecular orbitals (FMO), that is, the *HOMO* and *LUMO*, for estimating reaction rates by the equation

$$\ell n\ k_r = K \frac{2}{E_{HOMO} - E_{LUMO}}$$

has recently been examined for some Diels-Alder reactions (25). We have found a general correspondence between product ratios and the energy differences between *HOMO* and *LUMO* in the reaction of methyl vinyl ketone and acrolein (figure 9) (26).



	HOMO	*LUMO*
ε =	-.5275	.0896
C_1	-.5841	.6053
C_2	-.4969	-.3967
C_3	.2832	-.4715
O	.5760	.5035

Figure 8. Frontier Molecular Orbital Approach to Cycloaddition of Acrolein

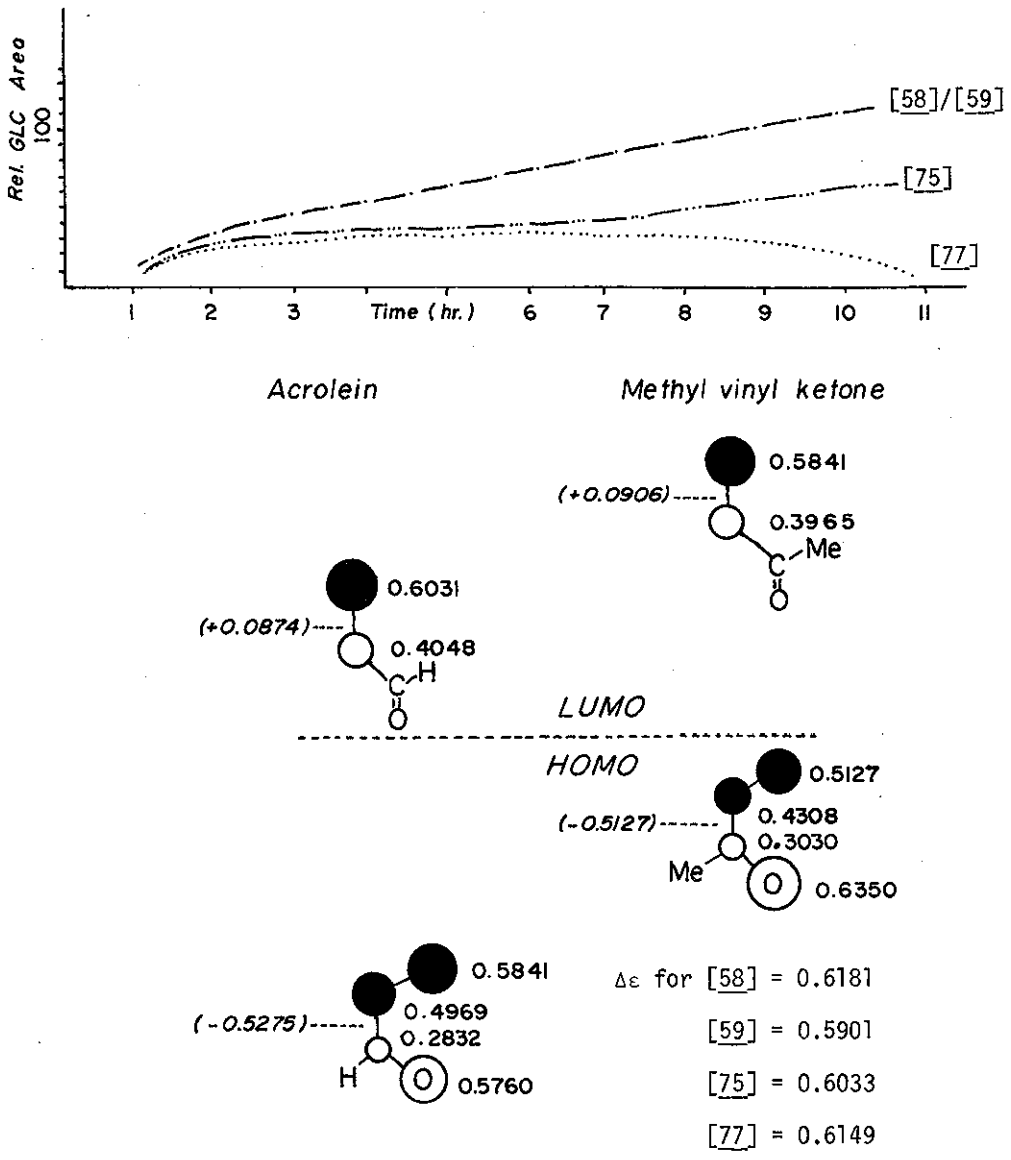
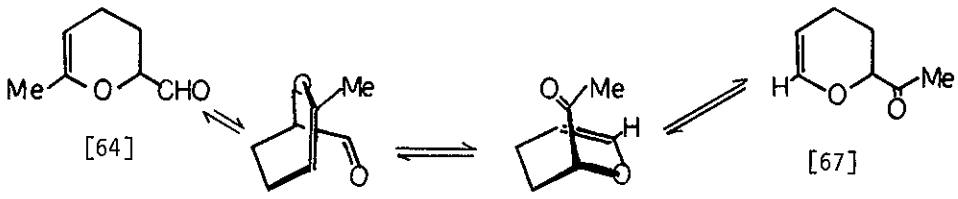


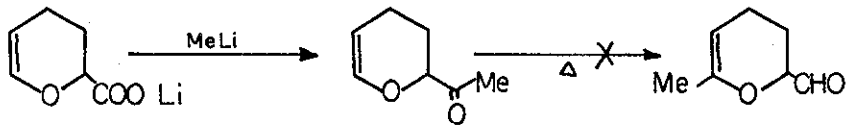
Figure 9. Cycloaddition Reactions of Methyl Vinyl Ketone and Acrolein

From these calculations it would seem that our low-yield brevicomin synthesis should have been a high-yield synthesis. What factors may contribute to this not being the case? The possibility of Cope rearrangement altering or disguising product composition must be considered (*equation 9*).



[64] [65] [66] [67] (9)

This process has literature precedence (27), and has been utilized to good advantage by Buchi (28) in a novel entry into the cyclohexene series. As a test of whether a Cope rearrangement or major Diels-Alder addition in a non-productive manner was the source of our poor yield of brevicomin, we examined the reverse rearrangement (*equation 10*). Both by distilling the product at the same temperature at which the cycloaddition reaction was carried out, and by heating a sample in a sealed ampule at 200°, we obtained no evidence for rearrangement.

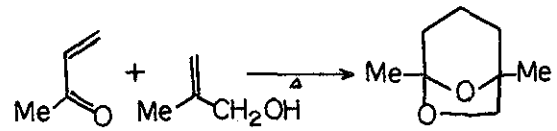


[68] [58] [59] (10)

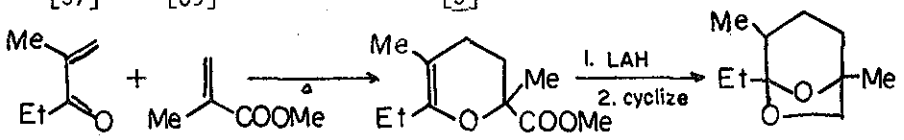
From these results it is tempting to suggest that the Diels-Alder reaction initially formed the desired adduct, as predicted; but that this in turn suffered rearrangement to a more stable, and undesired product.

A cautionary note is now appropriate. We have suggested that the FMO theories may be useful in predicting dimerization products, but that secondary skeletal reorganization may result in unpredicted products. However, the "state of the art" cannot definitively separate a "wrong product" from a "wrong calculation." We anticipate that there will be additional studies in the near future to define the limitations and scope of these methods as predictive tools.

Other syntheses employing the Diels-Alder reaction as the first step are delineated in (*11*) (29) and (*12*) (30).

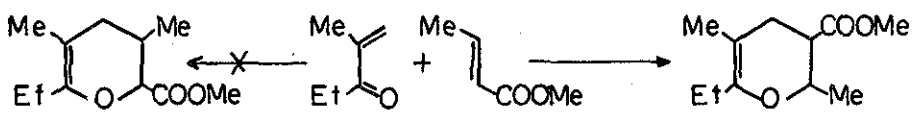


[57] [69] [5] *(11)*



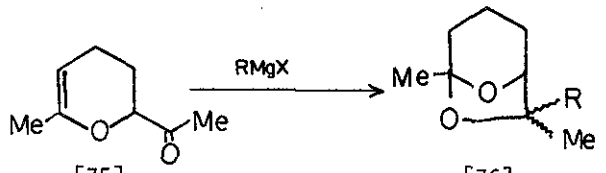
[69] [61] [70] [71] *(12)*

It is of interest to note, particularly with respect to the cautionary suggestion previously given, that the synthesis of multistriatin could not be achieved by a similar reaction sequence (*equation 13*) (31).



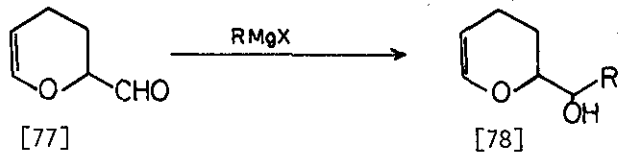
[72] [69] [78] [74] *(13)*

As part of our investigations into cyclizations leading to the ketals, we have added various Grignard and organolithium reagents to the dimer of methylvinyl ketone [75]. In every case, we have not been able to isolate the expected alcohol; but rather, we have found only the bicyclic ketal (*equation 14*) (32).

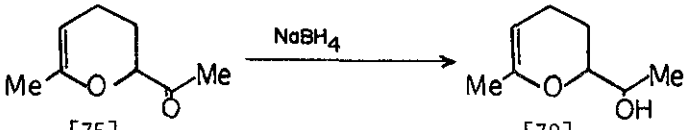


[75] [76] *(14)*

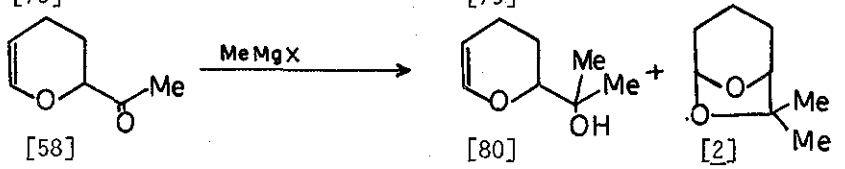
This propensity towards cyclization is not noted for the similar reactions, (*15*) (33), and (*16*) (34). We find in these cases that a secondary alcohol is formed; while in (*14*) a tertiary alcohol would have been formed. This, then is an important, but not determining factor. Substitution about the enol ether moiety appears to have some influence (*17*) (35).



[77] [78] *(15)*



[75] [79] *(16)*

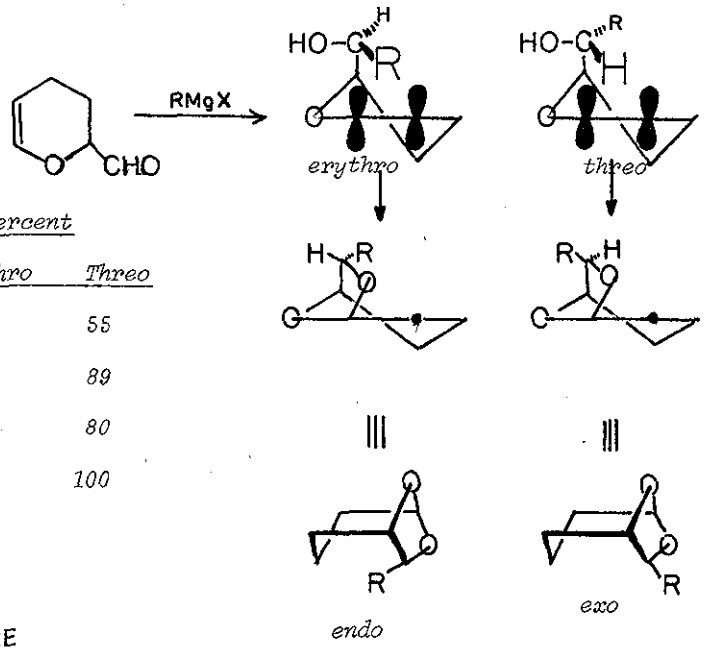


[58] [80] [2] *(17)*

The steric course of addition to the carbonyl, and any predictive arguments that might be made in this regard, would obviously be important. The most thoroughly analyzed data originates from the French research labs (36); however, even this doesn't allow for a definitive analysis (Table 1).

Table 1

Steric Course of Grignard Additions



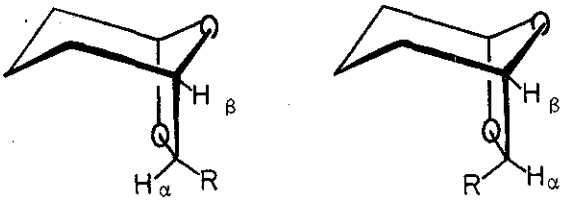
R	*Percent Erythro*	*Threo*
Me	*45*	*55*
i-Pr	*11*	*89*
t-Bu	*20*	*80*
Ph	*0*	*100*

STRUCTURE

Most of the existing structure work for the 6,8-dioxabicyclo[3.2.1] octane series has relied on nmr data--particularly coupling constants. Considering the most simple molecule of this series, we can examine how coupling constants have been utilized (Table 2) (36).

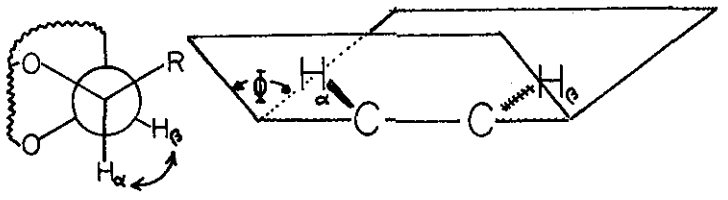
Table 2

NMR Study of Bicyclic Ketals



	$J_{\alpha\beta}$	$J_{\alpha\beta}$
R = Me	*0*	*5.5*
i - Pr	*0*	*4*
t - Bu	*0*	*3.5*
ϕ	*0*	—

From these data it is apparent that for single substituents in the 7-position, coupling constants are quite useful for assigning relative stereochemistry. It is of interest to note that the coupling constant changes with the size of R. This can be attributed to steric effects, and thus dihedral angle (Φ) changes [81].



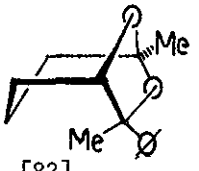
From the Karplus equation

$$J = 8.5 \cos^2 \Phi - 0.28 \quad \text{for } 0° \leq \Phi \leq 90°$$

we can predict that the dihedral angle changes from 34.5° (R=Me) to 44.8° (R=*Pr*) to 48.2° (R=*t*-*Bu*). From this it can be suggested that different groups can effect the structure of these bicyclic ketals; however, little definitive data is available.

Mass spectral fragmentation patterns have been examined by Gore, et. al. (37) and by our own group (38). There seems to be some predictability (Chart 1); however, electron impact data can not be used for differentiating stereoisomers.

We have completed a definitive x-ray analysis of *exo*-7-phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane [82] (39). The coordinates from this structure have been used with the computer program PDIGM (40) to interpret lanthanide shift reagent experiments in this series (41). Gore and Armitage have recently examined frontalin and multistriatin with shift reagents and find best correlation when the lanthanide associates with the 6-oxygen (42). Our work with [82] seems to substantiate this (41); however more work is needed in this series before the use of lanthanide shift reagents can be used as a simple and unambiguous probe for structure.



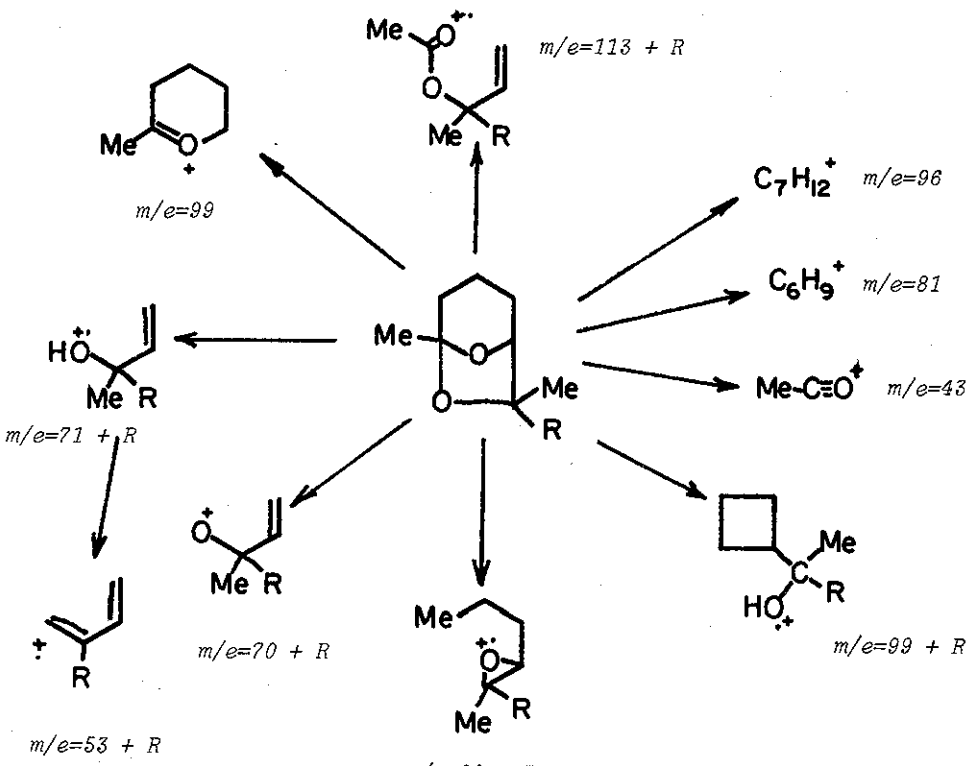
[82]

INTERESTING CHEMISTRY

The bicyclic ketals can be cleaved with lithium aluminum hydride and aluminum chloride (33), such that the resulting alcohols retain the stereochemistry of the starting bicyclic ketal (figure 10).

CHART 1

(Mass Spectral Fragmentation)



Fragmentation	R = H	Me	Ph
a =	✓	✓	✓
b =	100✓	114	175✓
c =	100✓	114	175✓
d =	71✓	85✓	147
e =	72✓	86✓	148
e'=	54✓	55✓	130✓
f =	✓	✓	✓
g =	114✓	128	190
h =		✓	
i =	✓	✓	

✓ means peak present

This is a slightly modified chart of fragmentations, as first presented by Gore, et. al.

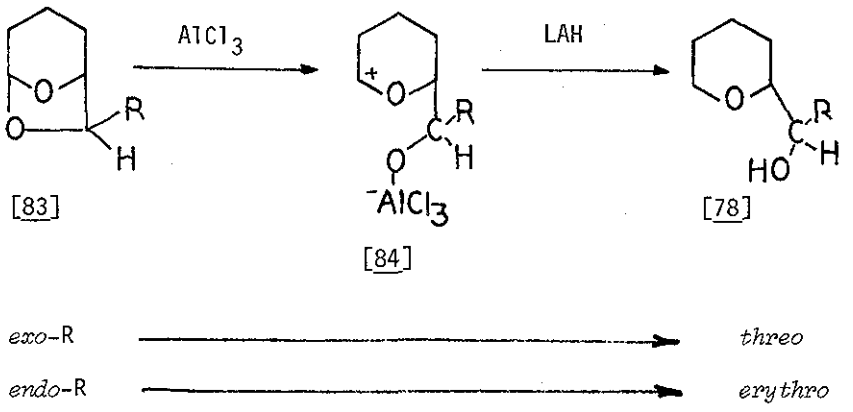
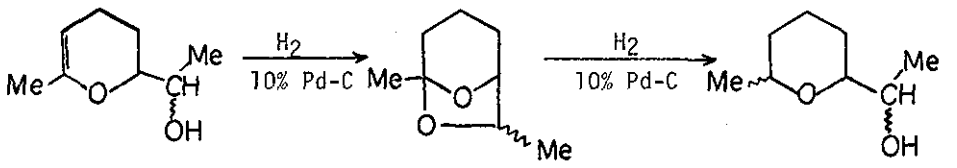


Figure 10. Cleavage of Bicyclic Ketals

We have noted an interesting cleavage of the bicyclic ketals under condition of catalytic hydrogenation (43). An apparent steric effect of an *exo*-methyl group [85] can be noted (figure 11). We have observed that the *exo*-, *endo*-mixture of [85] is formed during hydrogenation of [74], but do not know whether the formation of [85] is required for the reduction of [74] to [86].

We have been able to utilize the steric effect of an *exo*-7-methyl group in a unique isomer enrichment technique (44). By allowing a mixture of *exo*- and *endo*- 5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane to react with a frozen matrix of titanium tetrachloride, preferential complexation of the *endo* isomer occurs. This allows simple separation of the *exo* isomer. Of special significance is the observation that addition of water destroys the complex and the ketal is released, unchanged. We do not know the nature of the complex.



[74] [85] [86]

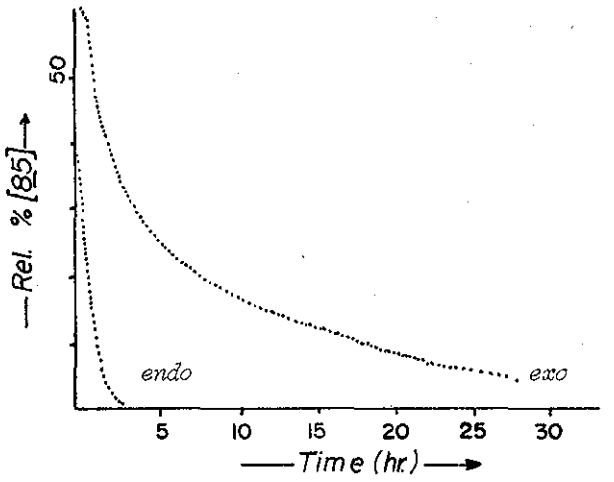


Figure 11. Catalytic Hydrogenation in the Ketal Series

CONCLUSIONS

The 6,8-dioxabicylo[3.2.1]octane series has, over the past few years, been the focus of a considerable activity. We have attempted to examine some of the interesting chemistry already investigated, and to point out areas that need additional work. This review has a bias in our own activities; however, we have attempted to keep our efforts in perspective with those other groups

which are examining this series. We anticipate that new structures in this ketal series will be found as natural products, and that efforts in synthesis and structure will continue. We hope this review will help those researches.

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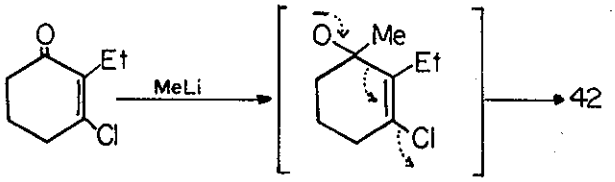

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