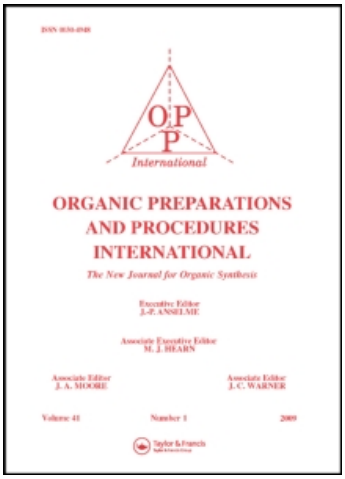

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WHARTON FRAGMENTATIONS OF CYCLIC 1, 3-DIOL DERIVATIVES. A REVIEW

Drury Caine[a]
[a] Department of Chemistry, University of Alabama, Tuscaloosa, AL

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WHARTON FRAGMENTATIONS OF CYCLIC 1,3-DIOL DERIVATIVES. A REVIEW

Drury Caine

Department of Chemistry
University of Alabama
Tuscaloosa, AL 35487

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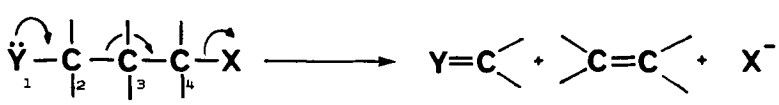
INTRODUCTION

Systems such as 1 containing a nucleophilic atom with a negative charge or an unshared electron pair and a leaving group in a 1,4-relationship are known to undergo heterolytic fragmentation processes as illustrated in Scheme 1. Because of the extensive work of Grob and coworkers, these reactions are widely referred to as Grob fragmentations.[1]



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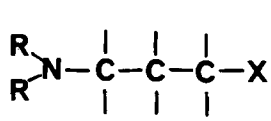
Scheme 1

Carbon chains with a variety of combinations of nucleophilic atoms and leaving groups as well as systems having heteroatoms replacing carbons in the chain may undergo these reactions.[1d] Direct fragmentations of amines (2) have been the subject of extensive mechanistic investigations[1] and there has been considerable interest in similar reactions of organometallic species (3),[2] but base-promoted fragmentations



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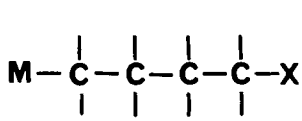

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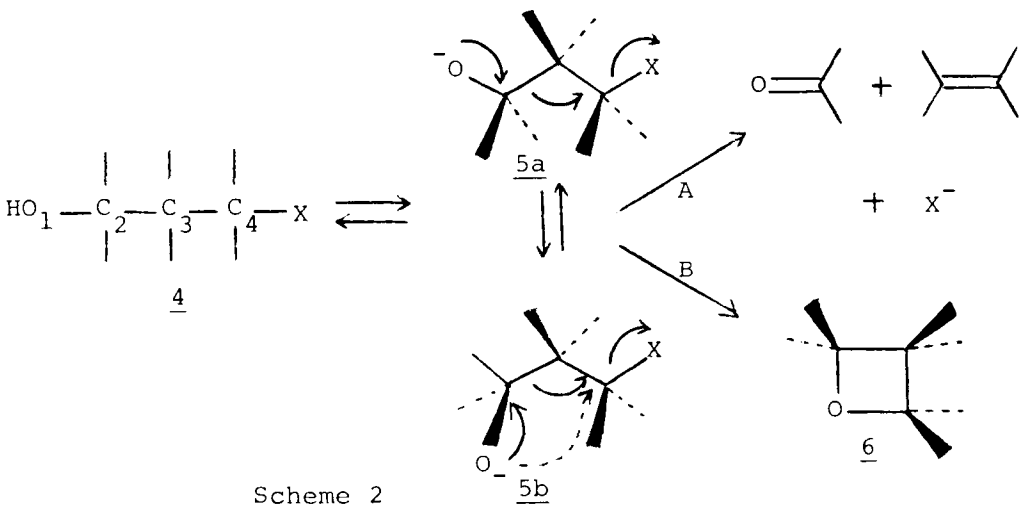
of 1,3-diol derivatives such as 4 (Scheme 2) are probably the processes with the greatest overall synthetic utility.

The alkoxide 5, produced upon deprotonation of a 1,3-diol derivative 4 (or by some other means, such as metal hydride reduction of a β-substituted ketone among others) may undergo concerted fragmentation to give a carbonyl compound, an alkene and an anion (Scheme 2, Path A). In order for a concerted fragmentation to take place an anti relationship must exist



Scheme 2

between the two bonds that undergo cleavage, i.e., the C_2-C_3 and the C_4-X bonds. This condition is satisfied in both conformations 5a and 5b of the anion. In rigid cyclic systems in which the anion is constrained to exist in an extended conformation (cf. 5a), fragmentation is a highly favorable process. If the anion is constrained to or can easily adopt a conformation such as 5b, fragmentation (solid arrows) may also be observed but may be accompanied by intramolecular displacement (broken arrow) leading to an oxetane (Scheme 2, Path B). As a result of conformational mobility of the alkoxide ion, oxetane formation is often the major reaction observed when acyclic

1,3-diol derivatives are treated with bases. Thus, fragmentations of acyclic systems are not generally useful for the synthesis of alkenes and carbonyl compounds. On the other hand, in cyclic systems even though structural features permit the alkoxide ion to adopt a conformation such as 5b, fragmentation is frequently still preferred over intramolecular substitution.

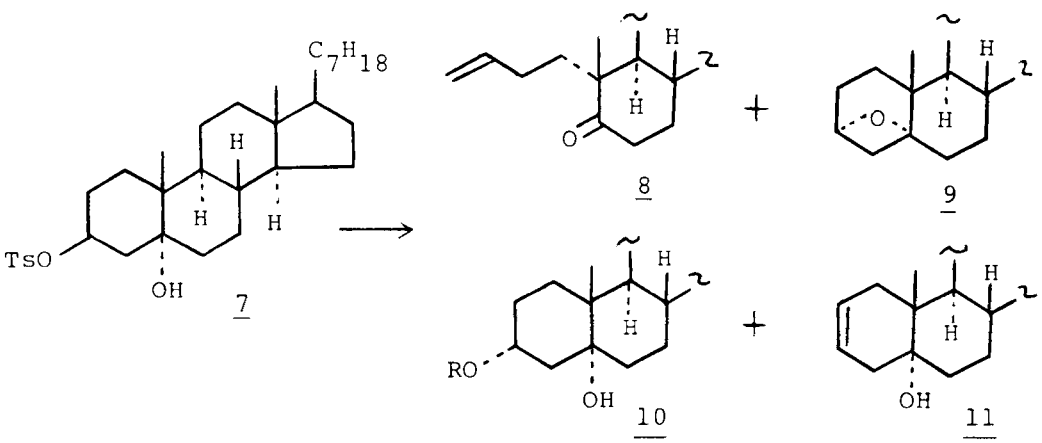
Intermolecular substitution and elimination reactions of the leaving group, which may occur via the alcohol 4 or the alkoxide ion 5, also reduce yields in fragmentation processes. However, it is generally possible to choose conditions to minimize these intermolecular reactions. Alkenes derived from fragmentations of cyclic 1,3-diol derivatives are formed stereospecifically. Therefore, these reactions are extremely useful for the synthesis of unsaturated carbonyl compounds.

This review will emphasize the synthetic applications of fragmentations of cyclic 1,3-diol derivatives. Although several research groups have contributed significantly to the development of this area, in recognition of the early contributions of Wharton and coworkers,[4] who demonstrated the stereoelectronic requirements of the reactions and showed their utility for the stereospecific synthesis of medium-sized ring enones, heterolytic fragmentations of cyclic 1,3-diol derivatives have been referred to as Wharton fragmentations.[5] The literature contains several reviews that provide limited coverage of this area.[6]

I. METHODS OF PERFORMING FRAGMENTATION REACTIONS

a. Bases and Solvents

A wide variety of bases have been used to effect heterolytic fragmentations of 1,3-diol derivatives. Rates of fragmentation (and when structurally possible the competing intramolecular oxetane formation) depend upon the concentration of the anion of the 1,3-diol derivative.[7a] Consequently, stronger and less nucleophilic bases tend to favor fragmentation while weaker and more nucleophilic bases favor intermolecular substitution and elimination reactions involving the leaving group. For example, treatment of the steroidal hydroxy tosylate 7 with the strong base potassium t-butoxide yielded the seco steroid 8 and the oxetane 9 almost exclusively, even at

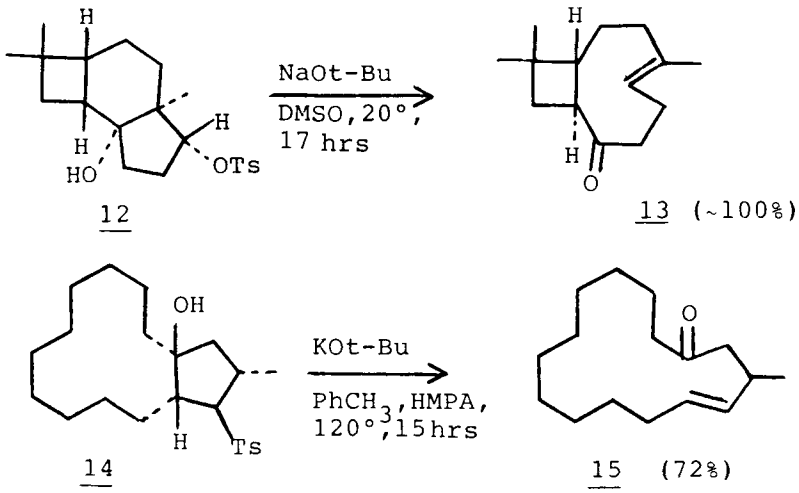


Conditions	8	9	10	11
2 Equiv KOt-Bu, HOt-Bu, 50°, 2 hr	37%	55%	-	-
>2 Equiv KOt-Bu, HOt-Bu, 50°, 2 hr	37%	55%	2%	(R = Ot-Bu)
2 Equiv KOMe HOMe, reflux, 24 hr	12%	22%	29% (R = OMe)	30%
KOAc, MeOH, reflux, 24 hr	-	-	28% (R = OMe)	48%

high base concentration, while the weaker base potassium methoxide in methanol led to low yields of compounds 8 and 9 with the substitution and elimination products 10 and 11, respectively, being favored.[7a] Solvolysis of 7 in methanol with potassium acetate as a buffer, conditions that would be expected to involve little if any alkoxide ion formation, led exclusively to the substitution and elimination products 10 and 11.[7a]

Even with excess potassium t-butoxide, relatively low equilibrium concentrations of alkoxide ions of 1,3-diol derivatives are produced in t-butyl alcohol, particularly when teritary hydroxyl groups are involved.[7] Thus, while potassium t-butoxide in t-butyl alcohol has been the most popular medium for heterolytic fragmentation reactions, other base/solvent combinations have seen considerable use and have been employed advantageously in some cases. The base strength of alkali metal alkoxides is enhanced in aprotic solvents compared with t-butyl alcohol, particularly in dipolar aprotic solvents.[8] The rates of fragmentations are also increased in dipolar aprotic solvents compared with t-butyl alcohol because anionic intermediates produced from 1,3-diol derivatives are poorly solvated and are not stabilized by coordination with the metal ion. Thus, the tricyclic hydroxy tosylate 12 was converted quantitatively with sodium t-butoxide in dimethyl sulfoxide (DMSO) into the bicyclic enone 13 with a trans double bond and a trans ring-fusion (produced by base-catalyzed epimerization after fragmentation).[9] Similarly, the hydroxy sulfinyl derivative 14, which has a relatively poor leaving group, was converted into the macrocyclic enone 15 in good yield using

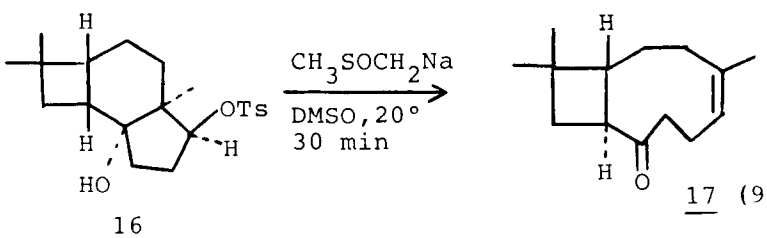
potassium t-butoxide in toluene/hexamethylphosphoramide (HMPA), whereas more conventional base/solvent combinations failed.[10]



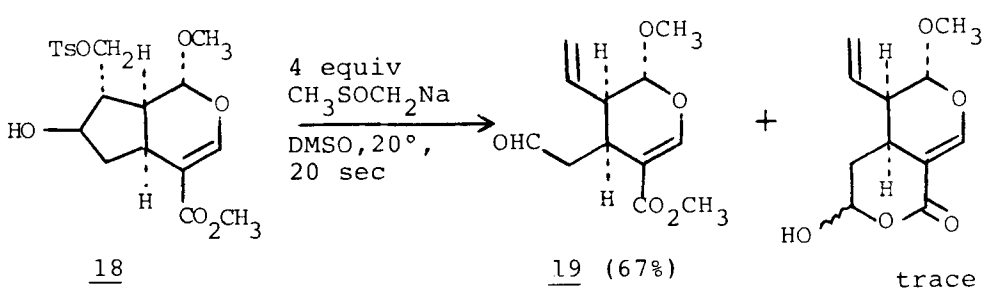
12 → 13 (~100%)

14 → 15 (72%)

The strongly basic dimsylsodium in DMSO[11] is a highly useful base/solvent combination for heterolytic fragmentations. The conversion of hydroxy tosylate 16 into the bicyclic enone 17 with a cis double bond and a trans ring fusion provides the first example of the use of this reagent.[9] It was also employed successfully for the rapid conversion of 18 into 19, a



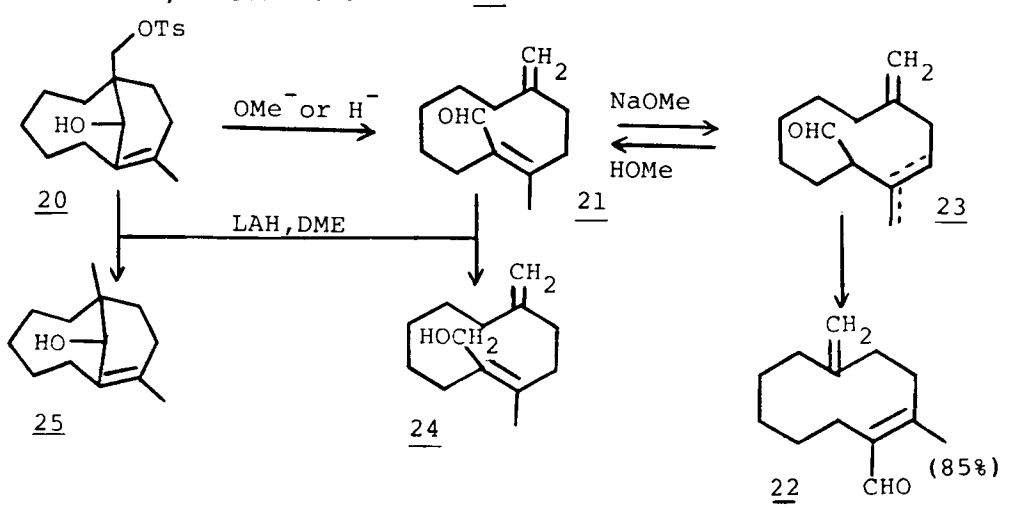
16 → 17 (94%)



18 → 19 (67%) + trace

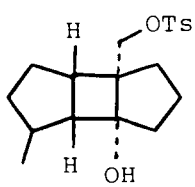
transformation that could not be accomplished with other bases.[12]

The solubility properties and relatively high boiling points of solvents such as t-butyl alcohol, DMSO, and HMPA make them difficult to remove during workup after fragmentation reactions. Fragmentations have been effected using potassium t-butoxide in more easily removable solvents such as THF,[13] but more commonly metal hydrides such as lithium aluminum hydride (LAH)[7,14] and sodium hydride[15] have been employed as basic initiators for the process. Since LAH can serve as both a basic initiator and a reducing agent,[14] it offers the advantage that kinetically formed, unstable fragmentation products can be trapped by reduction of a carbonyl group prior to undergoing various inter- or intramolecular processes. For example, treatment of the bicyclo[5.3.1]undecene derivative 20 with sodium methoxide in methyl alcohol gave the cis-cyclodecenecarboxaldehyde 22.[14c] Apparently, the kinetically formed trans aldehyde 21 underwent isomerization to the more stable cis isomer 22 by base-catalyzed deconjugation to 23 and reconjugation. However, when the 1,3-diol derivative 20 was treated with excess LAH in



1,2-dimethoxyethane (DME) the trans aldehyde intermediate 21 was reduced to the allylic alcohol 24.[14c] In the case of 20 where a relatively easily reducible primary tosylate group is present, LAH reduction to alcohol 25 was a major side-reaction.[14c]

The strength of the base needed to promote fragmentation depends to a large extent on the structure of the substrate. For example, monotosylates, such as 26,[16] or monomesylates, such as 27,[17] of bicyclo[2.3.0]heptane 1,3-diol derivatives, that contain a considerable amount of ring strain, readily undergo fragmentation in the presence of weak bases such as pyridine or triethylamine. Likewise, the bicyclo[4.2.0]octene derivative 28 was readily cleaved under very mildly basic conditions.[18]



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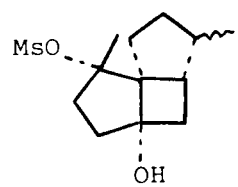

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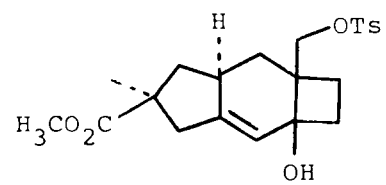

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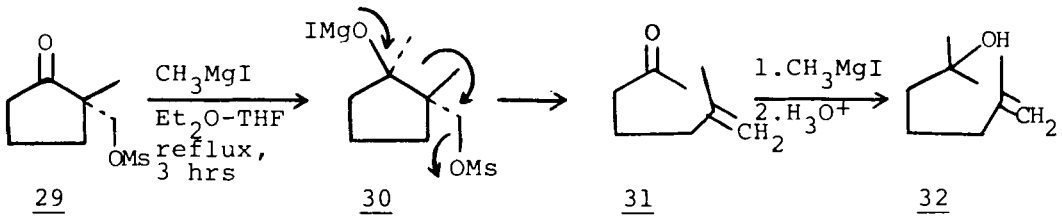
b. Generation of Alkoxides of 1,3-Diol Derivatives by Methods Other than Deprotonation of Hydroxyl Groups

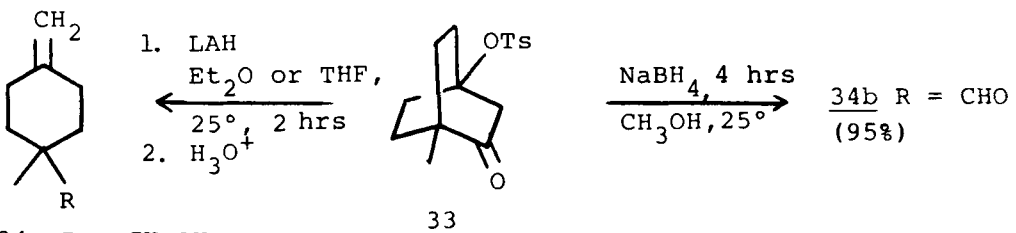
Alkoxides of 1,3-diol derivatives may be generated by a variety of methods that do not involve deprotonation of hydroxyl groups, and reactions leading to alkoxide intermediates are usually accompanied by heterolytic fragmentations provided stereoelectronic requirements are met. Alkoxides of 1,3-diol derivatives are obtained directly by addition of organometallic reagents to carbonyl compounds with leaving groups at the β-position or by metal hydride reduction of such compounds. Apparently, the first example of the frag-

mentation of a 1,3-diol derivative was reported by Eschenmoser and Frey,[19] who showed that treatment of the β-mesyloxy ketone 29 with excess methylmagnesium iodide in ether/THF at reflux gave after protonation the tertiary alcohol 32 in 80% yield. The formation of 32 probably involved addition of the Grignard reagent to 29 to give the iodomagnesium alkoxide 30 which underwent fragmentation to the methyl ketone 31. Addition of a second mole of Grignard reagent to 31 then gave, after work-up, alcohol 32.[19] Several related transformations have been reported.[20]



29 30 31 32

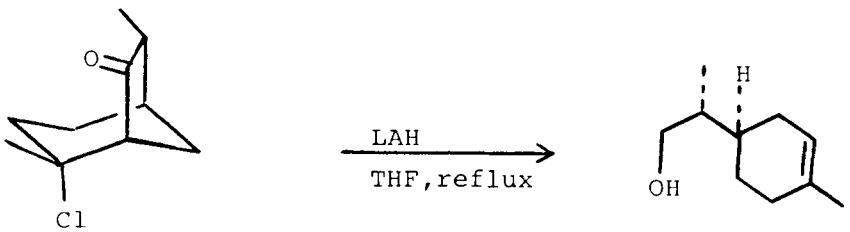
β-Tosyloxy-[21] and β-chloroketones[22] undergo reduction with excess LAH to the corresponding aluminates. These species then undergo heterolytic fragmentation to unsaturated aldehydes which are rapidly reduced to unsaturated primary alcohols. For example, transformations of the bicyclic β-tosyloxy ketone 33[21a] and bicyclic β-chloroketone 35[22a] into the corresponding primary alcohols 34a and 36, respectively, have been reported to occur in high yield. Reduction of 33 with



34a R = CH_2OH
(83%)

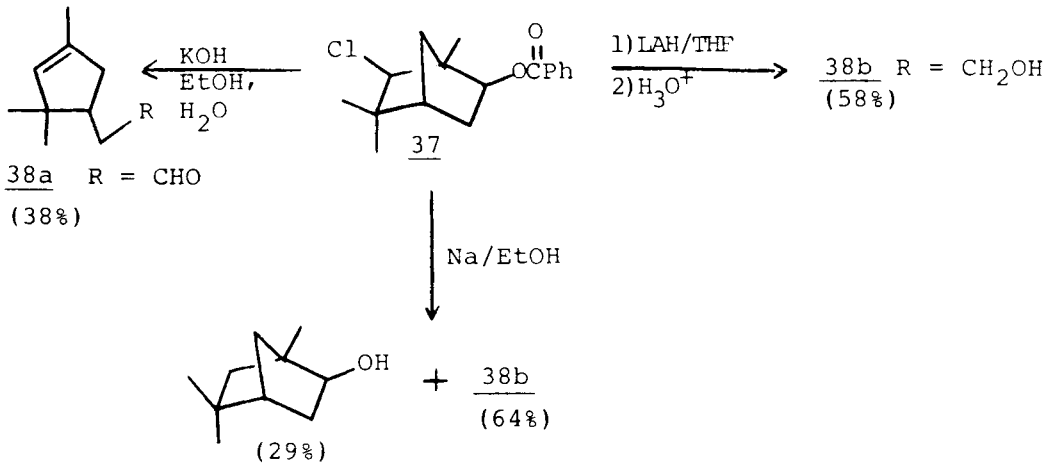
33

sodium borohydride in methanol allowed the isolation of the aldehyde 34b in high yield.[23]



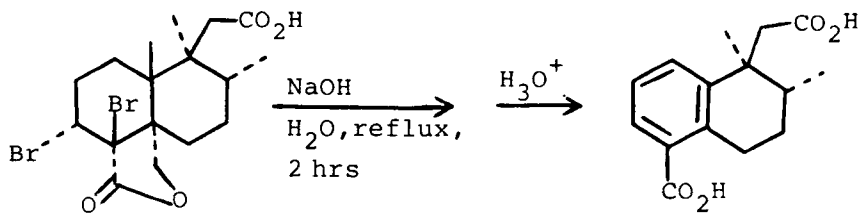
35 36 (90%)

Reactions of carboxylic acid esters have been used to generate alkoxides of 1,3-diol derivatives which undergo fragmentations. For example, hydrolysis of the bicyclic chlorobenzoate 37 with potassium hydroxide in aqueous ethanol gave the monocyclic unsaturated aldehyde 38a.[24] Treatment of compound 37 with LAH was accompanied by reduction of the aldehyde intermediate to give alcohol 38b. There was competition between reductive removal of chlorine and fragmentation when 37 was treated with sodium in ethanol.



Tertiary acetates having mesylate groups at the β-position have been reported to undergo fragmentations upon hydrolysis.[25] A particularly interesting fragmentation involving loss of

formaldehyde followed by elimination of hydrogen bromide occurred during hydrolysis of the dibromo lactone 39.[26] Fluoride-ion induced cleavage of the tricyclic trimethylsilyl ether 40 with a mesylate leaving group was used to produce a perhydroazulenone in good yield; a stereoisomer of 40 behaved similarly.[27]



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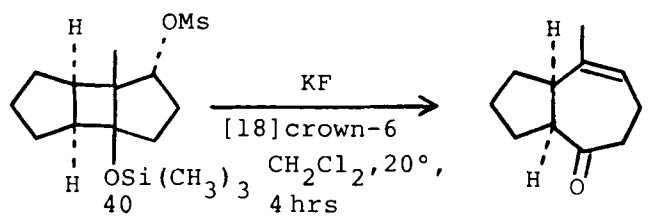

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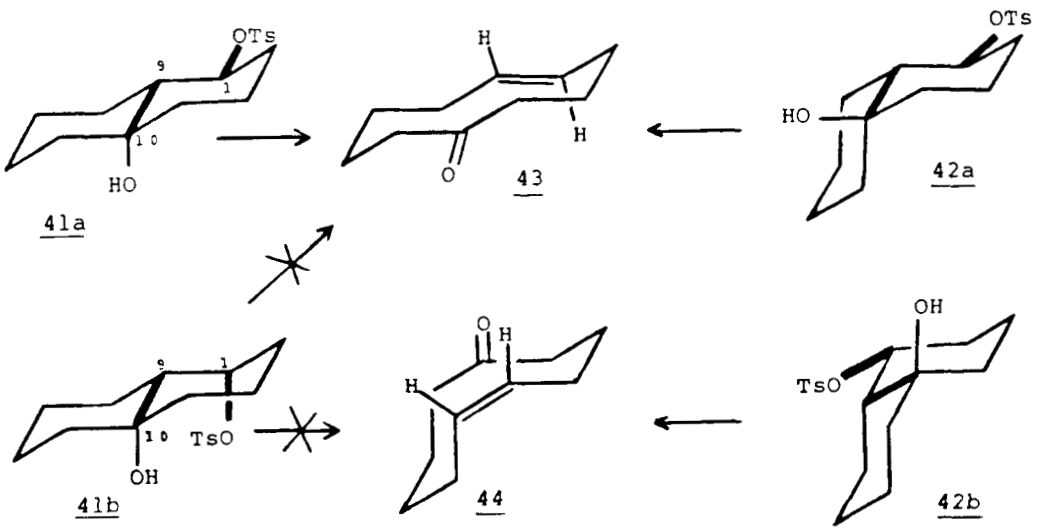
II. INFLUENCE OF STRUCTURE ON FRAGMENTATION

The investigations of Wharton,[4] Henbest,[7a] Corey,[9] and Siddall[15b] and their coworkers have clearly shown that the concerted fragmentation of 1,3-diol derivatives requires that the bonds undergoing cleavage must be anti and that the new carbon-carbon bond, whether it is being generated in a cyclic or acyclic system, is formed stereospecifically. For example, Wharton and Heigel[4c] prepared the epimeric pairs of trans-(41a and 41b) and cis-fused 1,10-decalindiol monotosylates (42a and 42b) and treated them individually with potassium t-butoxide in t-butyl alcohol at 40° for 1 hr. The three compounds in which the bonds undergoing cleavage (heavy bonds) are anti gave fragmentation products in greater than 90% yield.

Isomers 41a and 42a in which the angular hydrogen atom at C-9 and the adjacent hydrogen atom at C-1 are trans to each other gave exclusively trans-5-cyclodecenone 43, while 42b, which has these hydrogen cis gave exclusively cis-5-cyclodecenone 44. The trans isomer 41b which has gauche C_9-C_{10} and C_1-O bonds (heavy lines) was largely unchanged under the same conditions. Under more drastic conditions, i.e., prolonged treatment with potassium t-butoxide or dimsylsodium in DMSO,

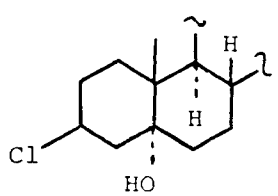


41b gave a complex mixture of products containing none of the cis enone 44 (which should result from a concerted fragmentation) and less than 6% of the trans enone 43 (which could arise from a non-concerted process via a carbonium ion intermediate).

Similarly double bonds may be introduced stereospecifically into nine-membered rings by fragmentations of hydrindandiol derivatives.[9,13a,28,29] As the stereospecific conversions of hydroxytosylates 12 and 16 into the corresponding trans- and

cis-cyclononenone derivatives 13 and 17 indicate, the relative orientation of the angular methyl group and the vicinal leaving group controls the geometry of the incipient double bonds. It is possible that stereoisomers other than the cis-anti-cis structures 13 and 16 shown may have been present.[9] However, the high yields of fragmentation products indicate that regardless of the stereochemistry of the B/C ring fusion, the required anti relationship of the bonds undergoing cleavage was easily achieved.

The stereoelectronic requirement for fragmentation is further illustrated by the behavior of the isomeric 3-chloro-5-hydroxy steroids 45 and 46.[7a] The 3β-chloro compound 45, in which the stereoelectronic requirement is met, reacted with potassium t-butoxide in t-butyl alcohol to give the seco steroid 8 and the oxetane 9 in the same proportions as were obtained from the corresponding tosylate 7. However, the 3α-chloro compound 46 in which the C_3-Cl and C_4-C_5 bonds are gauche gave almost exclusively the elimination product 11.[7a]



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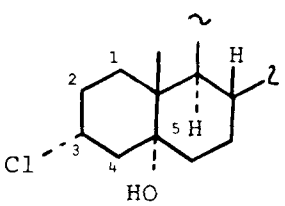

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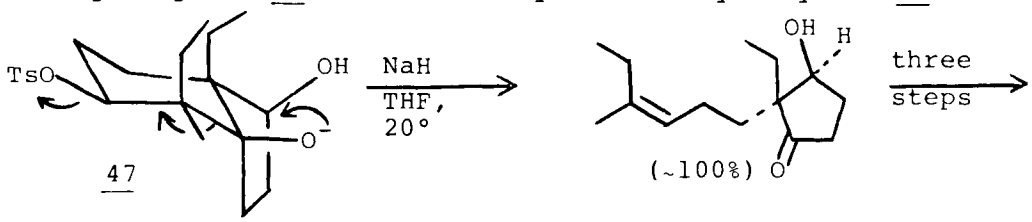
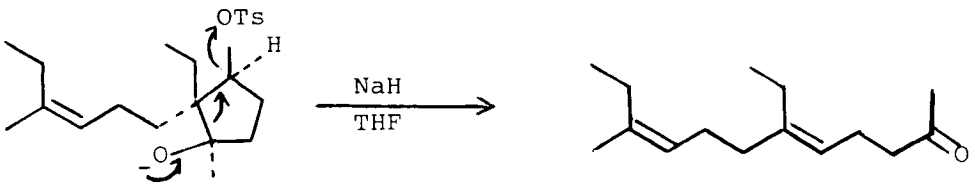
In their construction of the key dienone intermediate 49 for the synthesis of cecropia juvenile hormone, Siddall and coworkers[15b] demonstrated that Wharton fragmentations can be used to stereospecifically generate double bonds in acyclic systems from appropriate cyclic precursors. High yields were obtained in the fragmentations of both the bicyclic

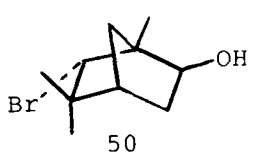
alkoxy tosylate 47 and the monocyclic alkoxy tosylate 48.





48 49 (~100%)

The base-promoted fragmentations of the bicyclic bromohydrin 50 and the related tosyloxy benzoate 51 into cyclopentene derivatives 38 represent exceptions to the requirement that the bonds undergoing cleavage must be anti.[24] In all likelihood, these reactions are non-concerted and involve initial ionization of the leaving group to form a cationic (or zwitterionic) intermediate followed by cleavage of the carbon-carbon bond. In compounds such as 50 and 51, simple intermolecular 1,2-elimination of the leaving group is impossible and intermolecular nucleophilic substitution would be expected to be very slow for steric reasons. Thus, a non-concerted fragmentation that leads to relief of the ring strain in the bicycloheptane system is probably relatively facile.



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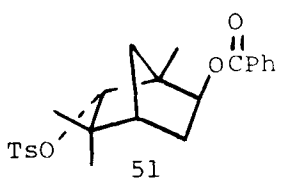

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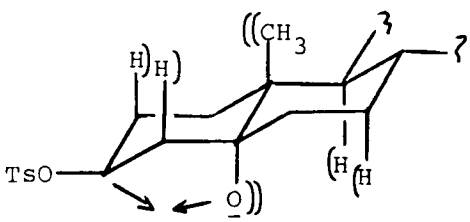
WHARTON FRAGMENTATIONS OF CYCLIC 1,3-DIOL DERIVATIVES

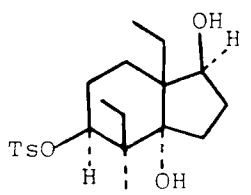
As noted in the Introduction, the optimum geometry for fragmentation of alkoxides of 1,3-diol derivatives is one such as 5a in which the O_1-C_2 and C_3-C_4 bonds are anti. Fragmentations may occur when a gauche relationship exists between these bonds, but intramolecular nucleophilic displacement of the leaving group is also a possibility in these cases. Although oxetane formation is possible in fused-ring systems such as 41a, 42b, and related 6/6 or 6/5-fused ring systems which have tertiary hydroxyl groups and secondary leaving groups, fragmentation actually is the exclusive or major pathway. The steroidal hydroxy tosylate 7 provides a case where oxetane formation is favored over fragmentation.[7a] Here steric interactions between the angular methyl group and the C_2 and C_4 axial hydrogen atoms and the solvated negatively charged C_5 oxygen atom and the C_7 and C_9 axial hydrogen atoms force C_3 and the anion toward each other as depicted in structure 52. This makes intramolecular substitution a very facile process.



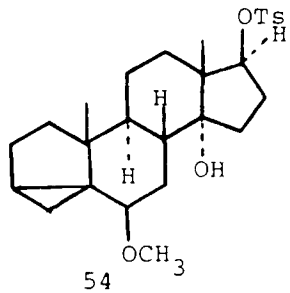
52

Fused-ring hydroxy tosylates 53,[15b] 54,[15a] and 55[30] have a high propensity for oxetane formation upon base treatment. From examination of models, it appears that in these cases steric factors distort the molecule in such a way as to favor intramolecular ring closure. 1,3-Diol derivatives with appropriate stereochemistry and having leaving groups at pri-

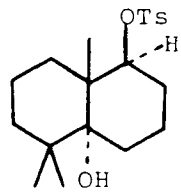
mary or secondary carbon atoms readily yield fused-ring[3b,12,31] or spirocyclic[3b] oxetanes upon base treatment.



53

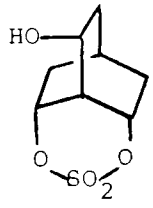


54

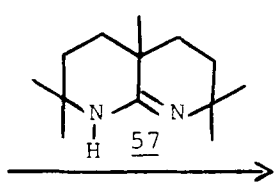


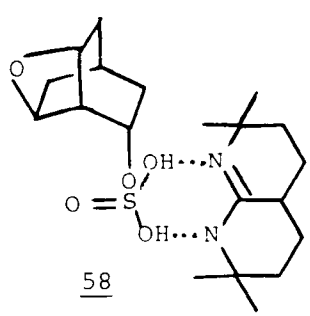
55

In the hydroxy sulfate 56 heterolytic fragmentation may proceed so that the new double bonds are generated in an anti or a syn relationship;[32] thus, its reaction with base provided the opportunity to determine which mode of cleavage is preferred. However, treatment of 56 with bases under standard fragmentation conditions gave no isolable products. Sulfate 56 did undergo reaction with the amidine base 57 in dimethylformamide (DMF), but, unfortunately, the adduct 58 containing an oxetane ring was the only product obtained.[32]



56





58

Hydroxy monotosylates or monomesylates are often prepared selectively by reactions of less hindered hydroxyl groups of unsymmetrical 1,3-diol derivatives with one equivalent of tosyl or mesyl chloride. Thus, tosylate and mesylate groups are by far the most widely used leaving groups in heterolytic

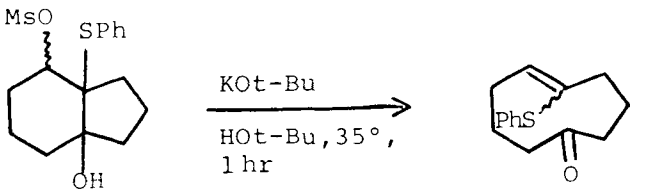
fragmentation processes. Molecules containing these groups seem to have about the same degree of reactivity and usually undergo fragmentations under relatively mild conditions. 1,3-Chlorohydrins, and occasionally 1,3-bromohydrins, have also been utilized in fragmentation reactions.[7a] Apparently, no systematic study has been performed to provide data on how rates of fragmentations vary as a function of the leaving group. The 3β-tosyloxy-5α-hydroxy steriod 7 and the 3β-chloro compound 45 provide the only cases where a direct comparison of the reactivity of tosylates and chlorides has been made.[7a] Chlorides are normally less reactive than tosylates in nucleophilic substitution reactions; and, as expected, 45 underwent fragmentation much more slowly than 7.[7a]

p-Toluenesulfinate,[10] diazo,[33] trimethylamino,[34] and azoxy groups[35] have been employed on rare occasions as leaving groups in fragmentation reactions. Alcohols having a p-toluenesulfinyl group undergo fragmentation slowly and severe reaction conditions are required.[10] Fragmentations involving trimethylammonium hydroxides are best carried out at high temperatures.[34c] These conditions provide a useful means of avoiding base-catalyzed aldol condensations when low molecular weight acyclic aldehydes are formed.

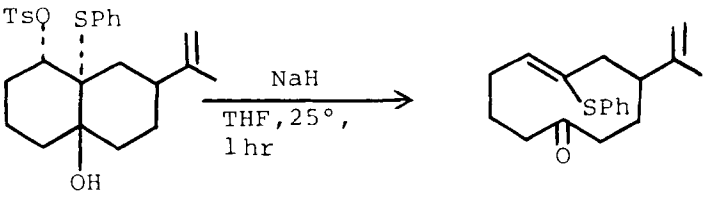
In general, fragmentations that lead to ketones occur more readily than those producing aldehydes. Also carbonyl compounds containing more highly substituted double bonds are formed faster than those containing less highly substituted double bonds. Substrates containing a greater amount of ring strain, such as bicycloheptanes and bicyclooctanes, generally undergo fragmentation faster than less strained systems such

as bicyclononanes and bicyclodecanes.

Until recently fragmentations of cyclic 1,3-diol derivatives have been carried out exclusively on substrates that yield alkyl-substituted carbon-carbon double bonds. However, the conversions of a mixture of hydroxy mesylates 59 into a mixture of nine-membered ring compounds 60[36a] and the hydroxy tosylate 61 into the ten-membered ring compound 62[36b] that contain both ketone and enol phenylthio ether groups demonstrate that substituents other than alkyl groups may be present at C_2 of the 1,3-diol system. In view of the plethora of reactions that enol thio ethers may undergo,[37] compounds such as 60 and 61 are potentially useful intermediates for the synthesis of other bifunctional nine-and ten-membered ring compounds.



59 60 (77%)



61 62 (90%)

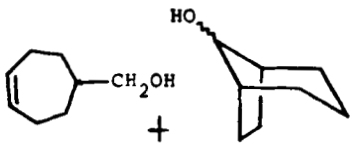
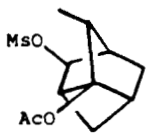
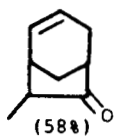
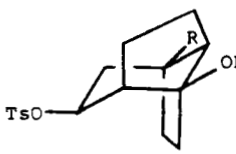
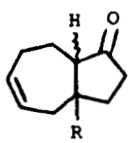
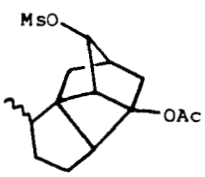
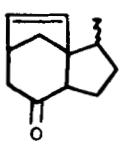
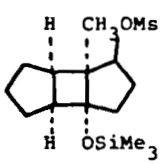
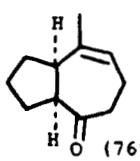
III. FRAGMENTATIONS

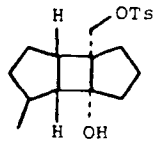
a. Cleavage of Carbon-Carbon Bonds Common to Two Rings

When the carbon-carbon bond that is cleaved in a heterolytic fragmentation is common to two rings, a larger ring compound containing an unsaturated carbonyl system (or the

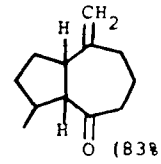
related alcohol if reducing conditions are employed) results. Tables I-V provide a survey of Wharton fragmentations not discussed in the text that produce 7-10-membered and larger rings.

Table I. Wharton Fragmentations Leading to Unsaturated Ketones or Alcohols Containing Seven-membered Rings

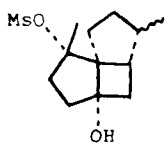
Reactant	Conditions	Product(s) (%)	Ref.
	LAH, Et_2O reflux	 82:18 (90%)	21b
	$NaOH, H_2O$	 (58%)	25a
	KOt-Bu, HOt-Bu, 40°, 1 hr	 R = H, cis/trans = 1/7.5 (64%)	38a
	"	R = CH_3, cis/trans = 3/2 (88%)	
	$NaOH, H_2O$, dioxane, 60°, 1 hr		25b
	KF, 18-crown-6 CH_2Cl_2, 20°, 4 hrs	 (76%)	27



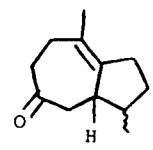
Pyridine,25°, 18hrs



16

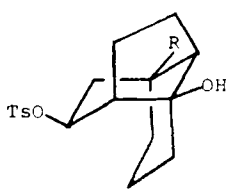


Et_3N, CH_2Cl_2, -25°to25°, 2hrs

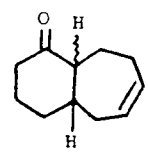


α/β Me = 1/3.3 (67%)

17



KOt-Bu,HOt-Bu, 40°

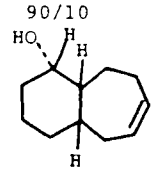


38b

cis/trans 15/85(96%) 90/10

R = H

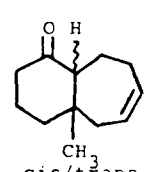
Pyridine,50°, 35 hrs



LAH,THF, 0°

R = CH_3

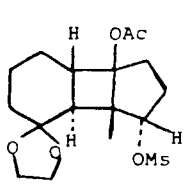
KOt-Bu,HOt-Bu 40°



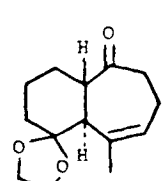
cis/trans 22/78 (88%)

Pyridine,50°,35 hrs

100/0 (98%)



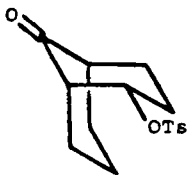
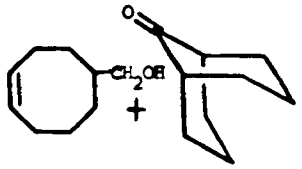
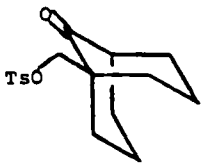
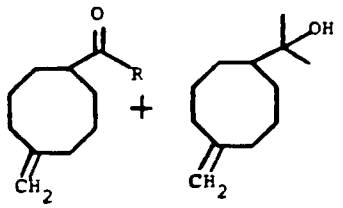
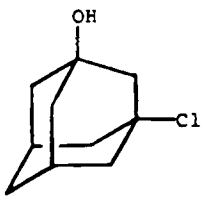
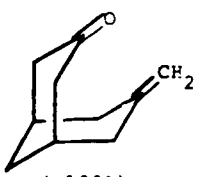
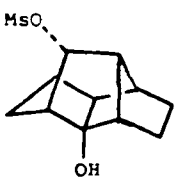
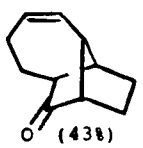
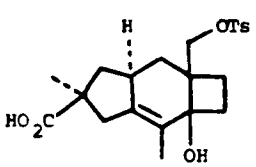
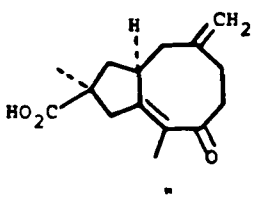
NaOH, H_2O-dioxane 70°, 1 hr

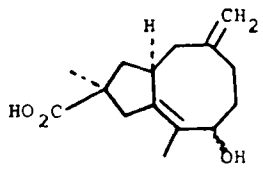


(30%)

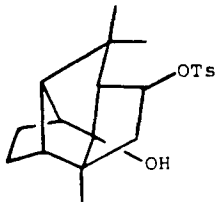
38c

Table II. Wharton Fragmentations Leading to Unsaturated Ketones or Alcohols Containing Eight-membered Rings

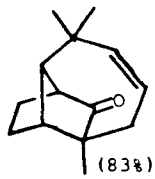
Reactant	Conditions	Product(s)(%)	Ref.
	LAH, Et_2O, reflux	 1:2 (81%)	21b
	Excess CH_3Li, Et_2O, reflux, 3 hrs	 R = CH_3 (11%) (69%)	61a
	2 Equiv. CH_3MgX, Et_2O, reflux, 45 min	(—) + (73%)	
	NaC≡CH, liq. NH_3	R = C≡CH (61%) + (—)	
	NaOH, H_2O	 (~100%)	39
	KOt-Bu, HOt-Bu, 35°, 1 hr	 (43%)	40
	NaI/Zn, HMPA, 105°, 3 hrs Br⁻		18



LAH



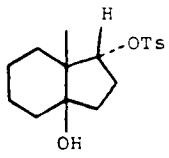
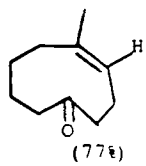
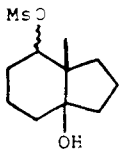
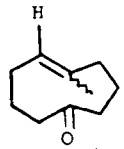
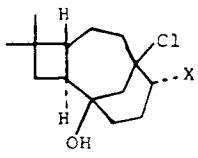
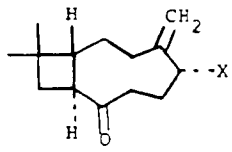
KOt-Bu,HOt-Bu,
35°,1 hr
or
NaH,THF,
25°,1 hr



(83%)

41

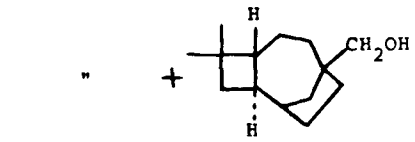
Table III. Wharton Fragmentations Leading to Unsaturated Ketones or Alcohols Containing Nine-membered Rings

Reactant	Conditions	Product(s) (%)	Ref.
	KOt-Bu,THF 25-30°,20 hrs	 (77%)	13a
 α/β OMs = 85/15	KOt-Bu,HOt-Bu 40°,1 hr	 Z/E = 85/15 (85%)	28
 X = OH	KOH,EtOH, H_2O,25°,12 hrs	 X = OH(80%)	42
	Al_2O_3(neutral)	"	
	Zn/HOAc	"	
	H_2/Pd	"	
X = OAc	Al_2O_3(neutral)	X = OAc	

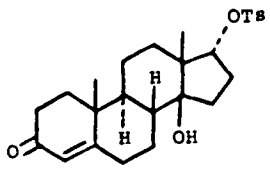
X = OH

LAH, Et_2O, reflux, 5 hrs 25°, 12 hrs

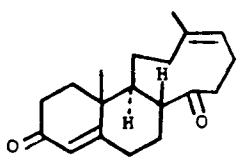
"



~7.3/4.0



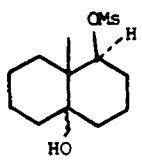
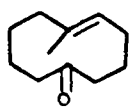
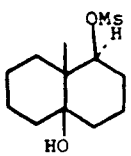
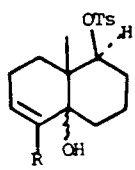
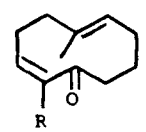
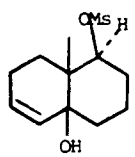
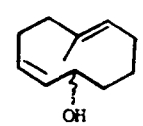
NaH, THF, reflux, 28 hrs

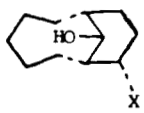


(56%)

29

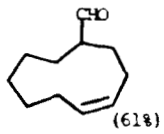
Table IV. Wharton Fragmentations Leading to Unsaturated Ketones or Alcohols Containing Ten-membered Rings

Reactant	Conditions	Product(s) (%)	Ref.
	KOt-Bu, HOt-Bu		4a
 (optically active)	"	" (optically active)	43
 R = H R = CH_3	KOt-Bu, HOt-Bu, 25°, 25 min	 R = H (~100%) R = CH_3 (~100%)	46
	NaOt-Bu, HOt-Bu	R = H	14a
	LAH, Et_2O		



X = OTs

KOt-Bu,HOt-Bu,
25° to reflux, 1 hr



(61%)

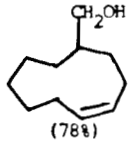
14b

X = OTs

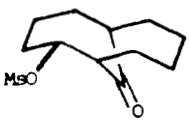
LAH,DME,
25°, 10 hrs

X = OMs

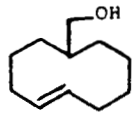
"



(78%)
(70%)

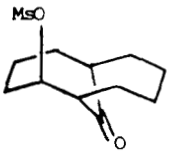


LAH,THF,
reflux, 7 hrs

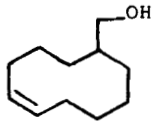


(78%)

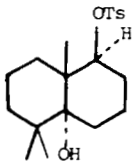
14d



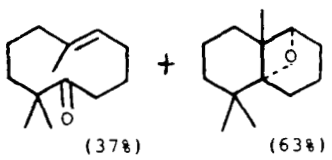
"



(40%)

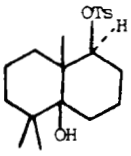


KOt-Bu,HOt-Bu,
60°, 3 hrs

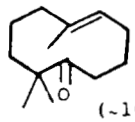


(37%) (63%)

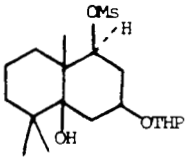
30



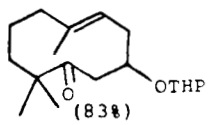
KOt-Bu,HOt-Bu,
60°, 1 hr



(~100%)



NaH,THF,
25°, 15 hrs



(83%)

THP = tetrahydropyranyl
group

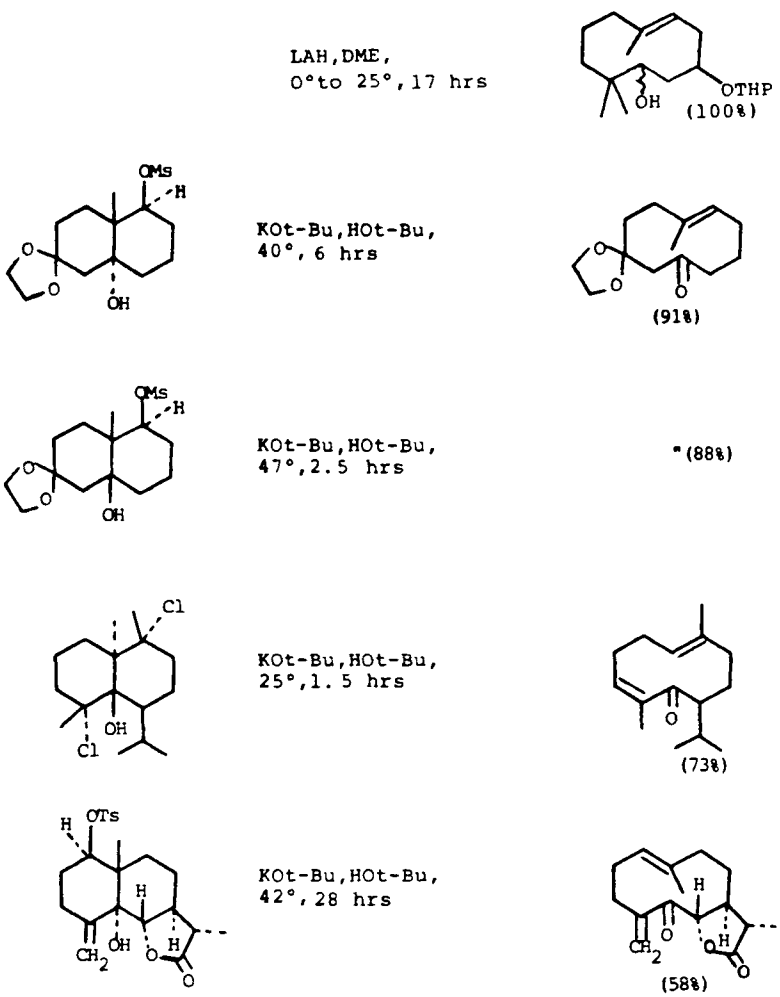
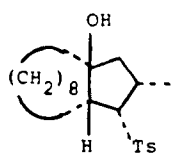
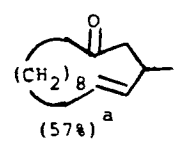
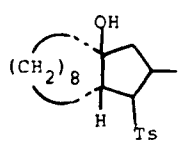
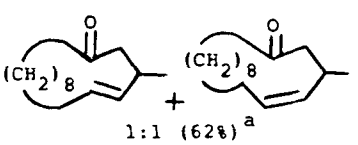
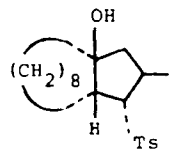
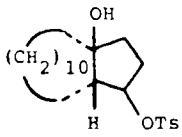


Table V. Wharton Fragmentations Leading to Unsaturated Ketones Containing Large Rings

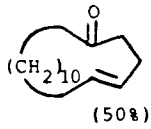
Reactant	Conditions	Product(s) (%)	Ref.
	KOt-Bu,HOt-Bu, $PhCH_3$,HMPA, 120°, 15 hrs	 (57%)[a]	10
	"	 1:1 (62%)[a]	



" " (55%)[a]



KOt-Bu,HOt-Bu



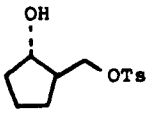
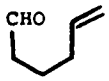
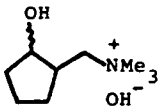
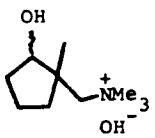
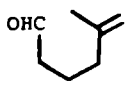
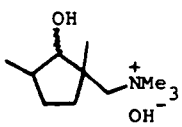
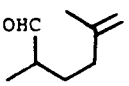
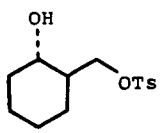
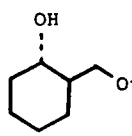
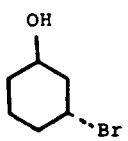
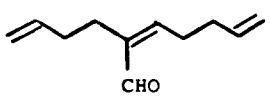
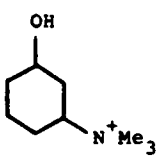
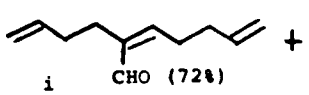
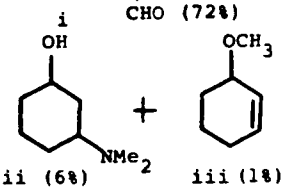
(50%) 47

a. Epimerization of the Ts group occurred prior to fragmentation.

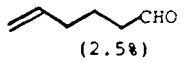
b. Cleavage of a Single Carbocyclic Ring

The literature contains a number of examples of fragmentations of 1,3-diol derivatives that lead to acyclic unsaturated carbonyl systems. Although the concerted fragmentation process is completely stereospecific,[15b] its use for the generation of di- or tri-substituted double bonds with a particular configuration has been limited. If the free hydroxyl group is secondary, the fragmentation leads initially to the formation of an unsaturated aldehyde that is likely to undergo aldol condensation under the basic conditions. For this reason, yields of unsaturated aldehydes are often quite low. Thermolysis of γ-hydroxy quaternary ammonium hydroxides appears to be the method of choice for generating relatively low molecular weight unsaturated aldehydes.[34c] Examples of the use of 1,3-diol fragmentations, including thermolysis of quaternary ammonium hydroxides, to generate acyclic unsaturated aldehydes or ketones not discussed in the text are provided in Table VI. The substrates listed include alcohols with leaving groups at the γ-position or compounds that are converted into alkoxide derivatives of such systems under the reaction conditions.

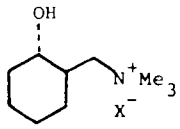
Table VI. Wharton Fragmentations Involving Cleavage of A Single Carbocyclic Ring

Reactant	Conditions	Product(s) (%)	Ref.
	CH_3SOCH_2Na, DMSO, 20°, 2 min	 (8.5%)	12
	350-450°	" (43%)	34c
	"	 (62%)	
	"	 (70%)	
	KOt-Bu, HOt-Bu, 30°, 19 hrs	Aldol polymers +  (14%)	3c
	KOt-Bu, HOt-Bu, 30°, 0.5 hrs		7
 $X^- = Ot\text{-}Bu$	350-450°	 i (72%) +  ii (6%) + iii (1%)	34b

CAINE

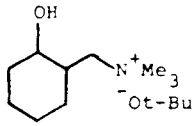
X = OH " i (30%) +  (2.5%)

ii (39%) + iii (9%)

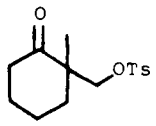


" i (1%) + Substitution and elimination products

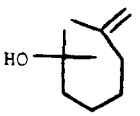
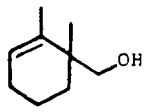
X = OH
X = Ot-Bu " i (4%) + "

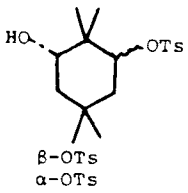


" i (21%) + "

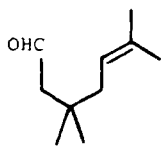


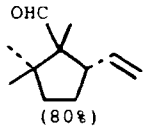
CH_3MgI, Et_2O, reflux, 4 hrs

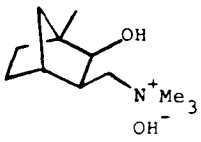
 (30%) +  (15%) 20b



CH_3SOCH_2Na, DMSO, 25°, 0.5 hr

 48

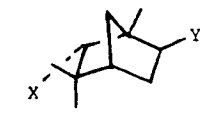
" 



350-450°

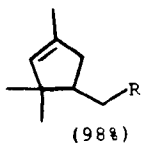
 (80%) 34c

WHARTON FRAGMENTATIONS OF CYCLIC 1,3-DIOL DERIVATIVES



X = Br, Y = OH

LAH,LiH, THF,reflux, 1 hr

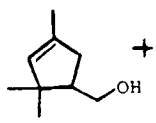


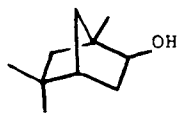
(98%) 24

"

KOH,90°, 15 hrs

Na/EtOH



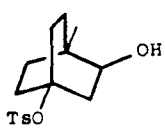


(50%) (42%)

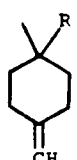
Zn/EtOH, reflux, 8 hrs " (52%) + " (38%)

X = OTs,Y = OH LAH,THF " (58% + " 6%)

X = OTs,Y = O_2CPh " " (57%) + " (0%)



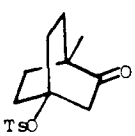
KOt-Bu,HOt-Bu, reflux, 24 hrs



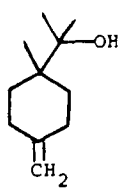
R = CHO (95%) 23

R = CH_2OH (62%)

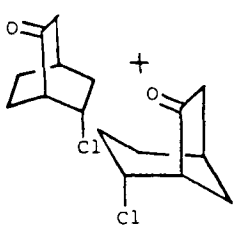
LAH,Et_2O, 25°, 24 hrs



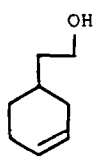
CH_3MgI,Et_2O



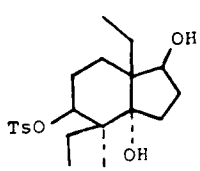
(65%) 20a



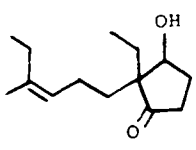
LAH,THF, reflux, 6 hrs



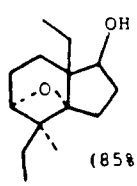
(~75%) 22b



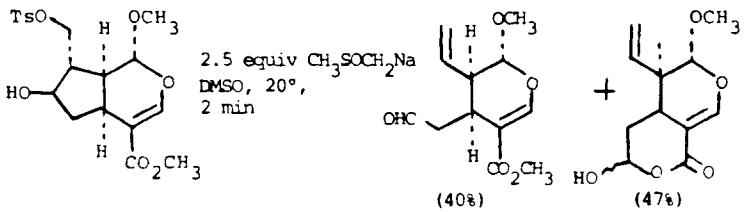
NaH,THF, 25°

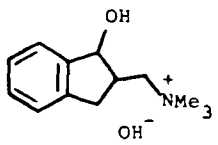


(15%)

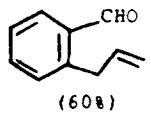


(85%) 12

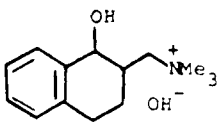




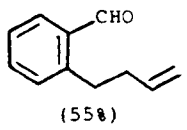
350-450°

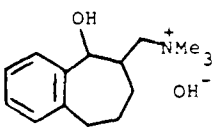


34c

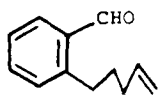


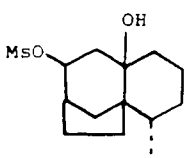
"



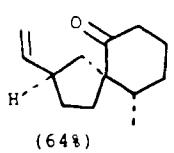


"

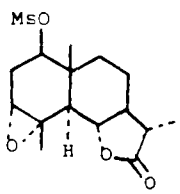




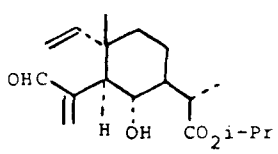
KOt-Bu, HOt-Bu,
reflux, 8 hrs



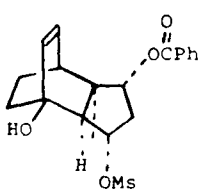
49



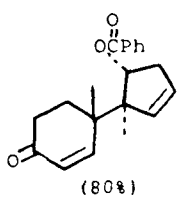
Al(Oi-Pr)3
PhCH3, reflux



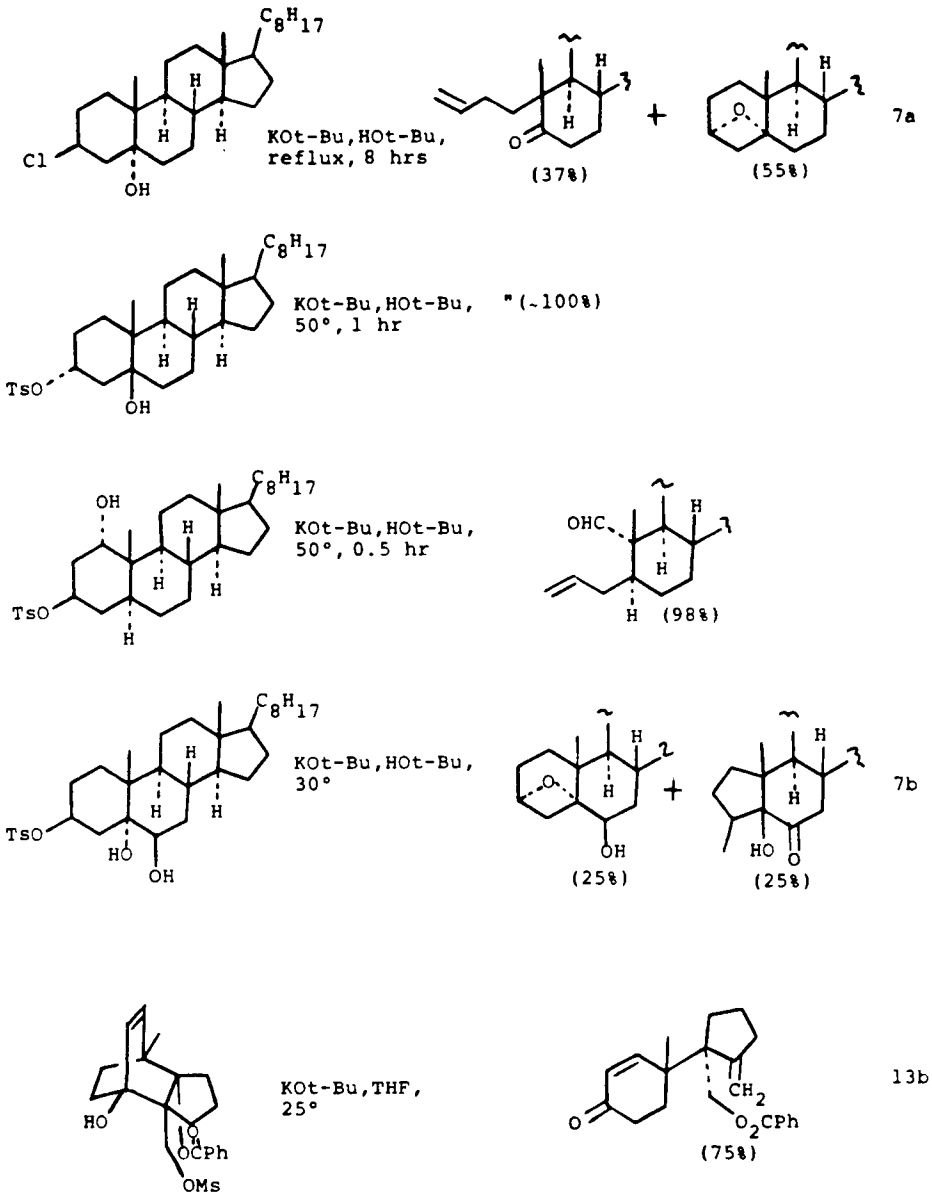
50



NAH, THF,
0°



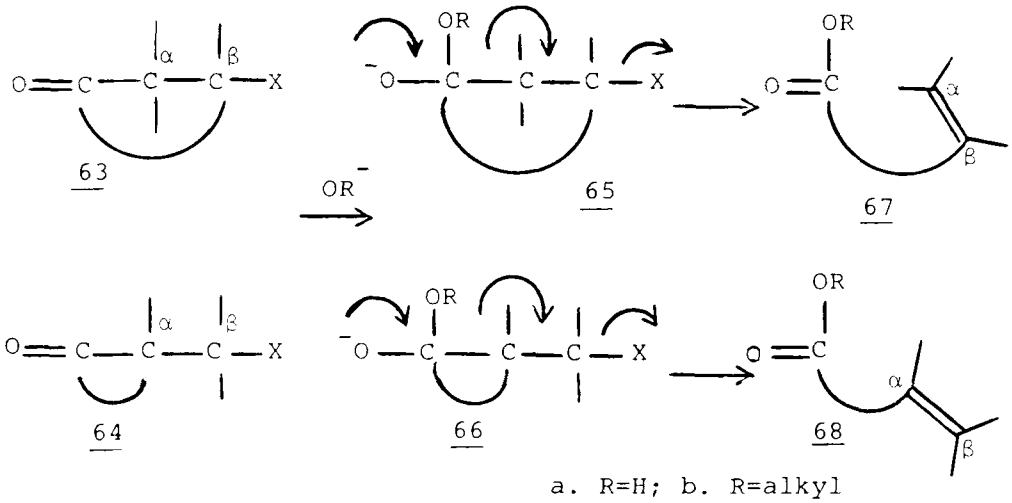
51



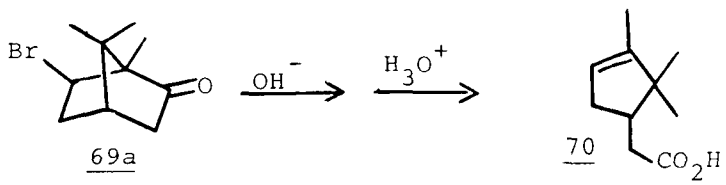
IV. BASE-PROMOTED FRAGMENTATIONS OF CYCLIC KETONES WITH ELECTROPHILIC GROUPS AT THE β-POSITION

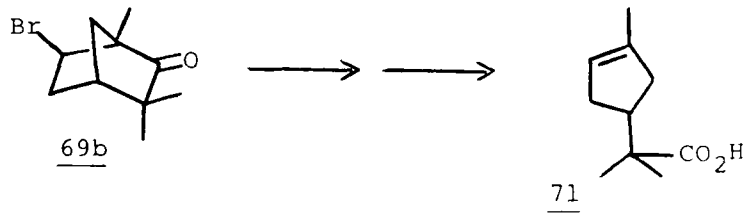
Nucleophilic additions of hydroxide or alkoxides ions to the carbonyl groups of cyclic ketones such as 63 or 64 having leaving groups at the β positions lead to anions of hydrates

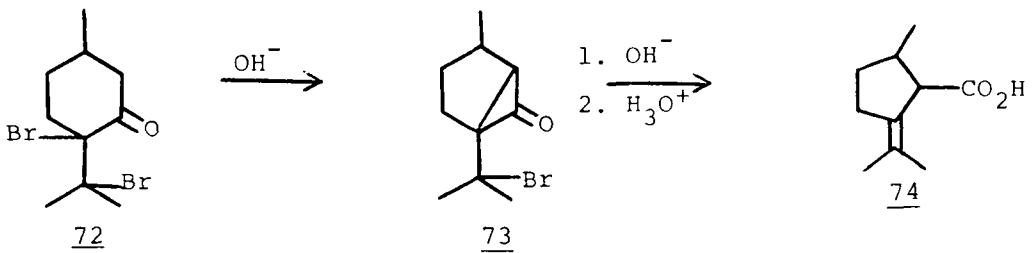
65a or 66a or hemiketals 65b or 66b that undergo fragmentations to unsaturated carboxylic acids 67a or 68a or the corresponding esters 67b or 68b.



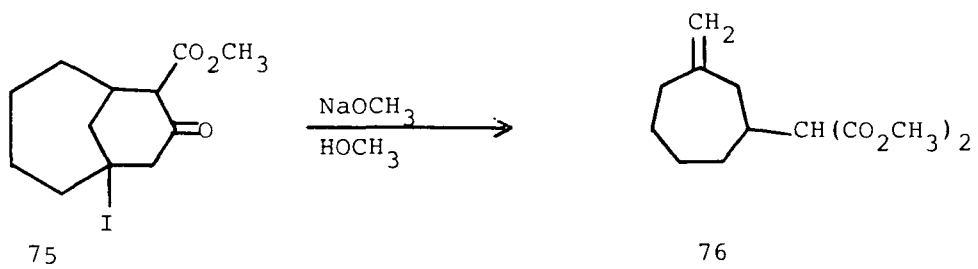
Fragmentations of β-substituted ketones were discovered many years prior to the initial reports of Grob and Wharton-type fragmentations. Reactions of β-bromocamphor 69a[53] and bromofenchone 69b[54] with sodium hydroxide to give the corresponding unsaturated acids 70 and 71, respectively, provide early examples of fragmentations of systems of the type 63. The first example of the fragmentation of a system of the type 64 is provided by the conversion of dibromopulegone (72) into the unsaturated acid 74 via formation and base-promoted cleavage of the cyclopropanone (Favorski) intermediate 73.[55]





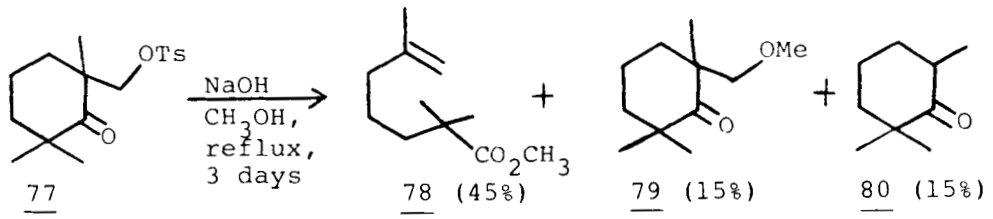


Cyclic ketones containing α-hydrogens and β-leaving groups are usually readily dehydrohalogenated upon base treatment; therefore, fragmentations are not observed in these cases. However, in bicyclic ketone 75 where β-elimination would lead to a violation of Bredt's rule, fragmentation to the diester 76 was observed.[56] In addition to fragmentation direct nucleophilic substitution or simple β-elmination of the leaving group



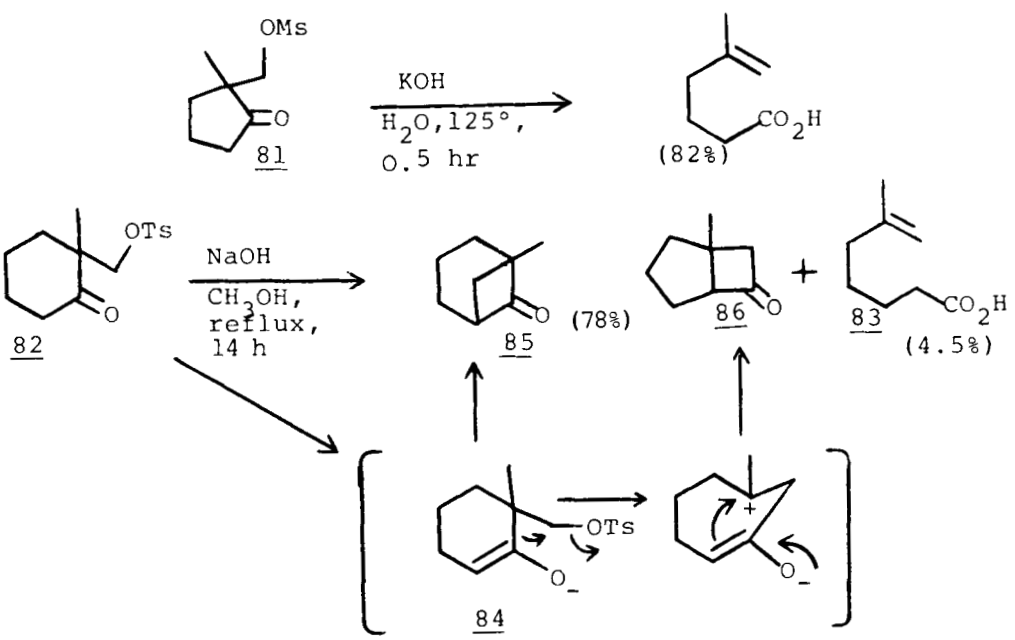
to give a β,γ-unsaturated system may occur. In the reaction of the β-tosyloxycyclohexanone 77 with sodium hydroxide in methanol, substitution to give the cyclohexanone derivative 79, competes effectively with fragmentation to give the unsaturated ester 78. The probable reason for this is that the carbonyl group in 77 is very hindered to attack by the

base. Trimethylcyclohexanone 80 was presumably formed by displacement of the tosyloxy group by hydroxide ion followed by loss of formaldehyde by a retroaldol reaction.[20b]



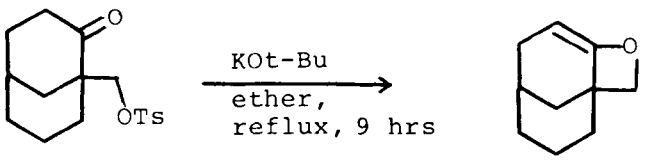
77 78 (45%) 79 (15%) 80 (15%)

2-Methyl-2-mesyloxymethylcyclopentanone (81) underwent base-promoted fragmentation in high yield.[19] Intramolecular alkylation to give a bicyclo[1.1.3]hexanone was not observed. On the other hand, 2-methyl-2-tosyoxymethylcyclohexanone (82) and related ketones having α-hydrogen atoms yielded only a small quantity of the acyclic unsaturated acid 83 upon base treatment.[57] The major reaction products were the intramolecular C-alkylation product 85 and a rearrangement product, the 5/4-fused ketone 86. Both major products are presumably derived from the enolate intermediate 84.[57]



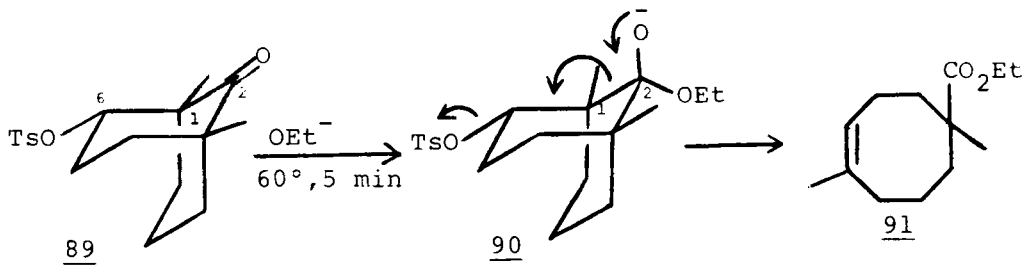
81 82 85 86 83 84

Treatment of the bicyclo[3.3.1]nonanone 87 with potassium t-butoxide in ether gave the tricyclic enol ether 88 in high yield.[20b] Presumably steric hindrance prevents nucleophilic attack on the carbonyl group by the base. Also, the enolate produced upon deprotation of 87 is structurally incapable of undergoing intramolecular C-alkylation. Therefore, intramolecular O-alkylation was observed.

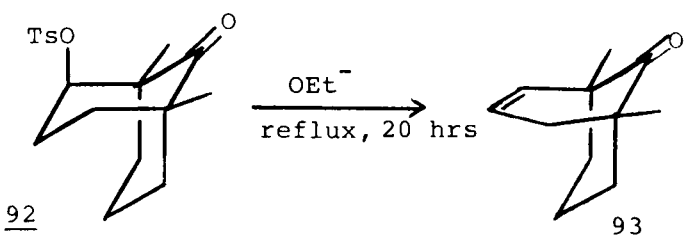


87 88 (88%)

Base-promoted fragmentations of cyclic β-substituted ketones are generally subject to the same stereoelectronic requirements as the Wharton fragmentation itself. For example, the bicyclo[3.3.1]nonanone 89, which has an equatorial tosyloxy group at C-6 and therefore anti arrangement of the leaving group and the C_1-C_2 bond in the hemiketal anion 90, was smoothly converted to the monocyclic ester 91 upon treatment with sodium ethoxide.[58] However, the epimer of 89, i.e., 92 (C-6 tosyloxy group axial), which would have a gauche

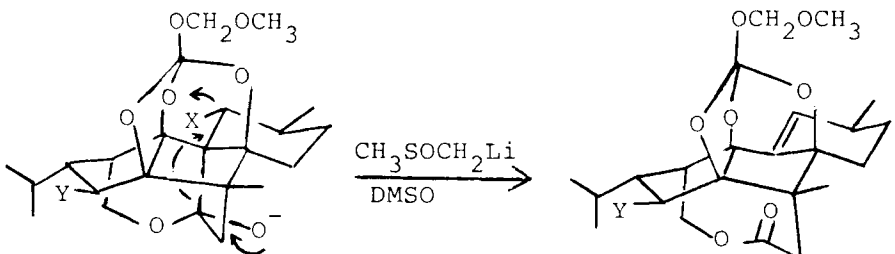


89 90 91



92 93

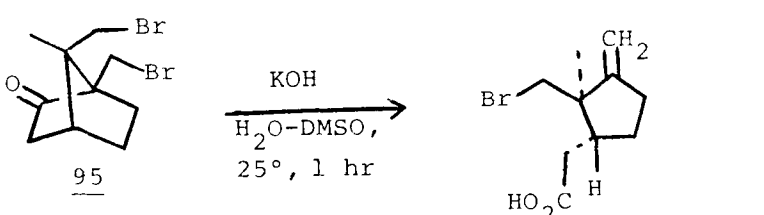
relationship of the leaving group and the C_1-C_2 bond in an anion analogous to 90, underwent simple β-elimination to give the bicyclic alkene 93 under similar conditions.[58] The fragmentation of the complex pentacyclic hemiacetal 94 to the unsaturated lactone 94a with dimsyllithium in DMSO appears to involve a gauche cleavage pathway.[59] However, this reaction may not actually be concerted.



94 (Y = $CH(OCH_3)_2$)
(X = CH_3SO_3)

94a

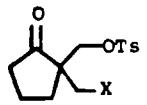
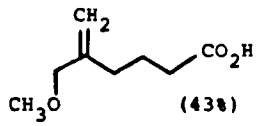
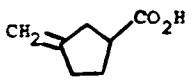
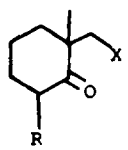
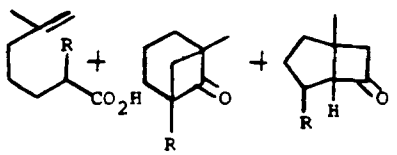
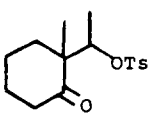
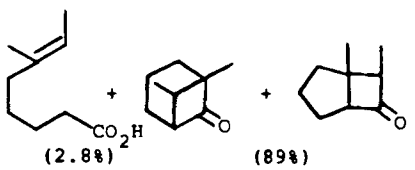
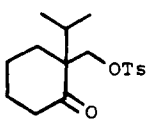
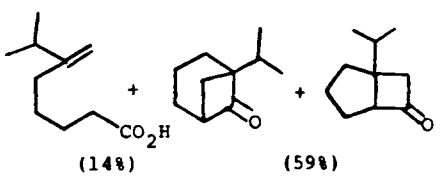
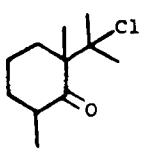
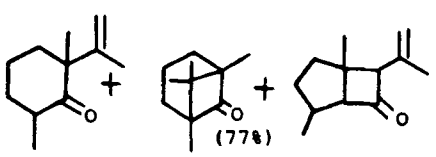
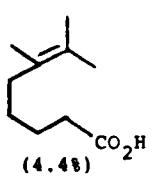
Some of the more synthetically useful examples of fragmentations of β-substituted ketones involve the conversion of various bicyclic ketones into seven,[60] eight[58,60a,61] and nine-membered ring unsaturated acids or esters and the conversion of 9,10-dibromocamphor (95) into the chiral bromoacid 96, a useful intermediate for the synthesis of insect pheromones[62a] and steroids.[62b] Table VII provides examples not specifically discussed in the text of base-promoted fragmentations of cyclic ketones containing leaving groups at the β-position.

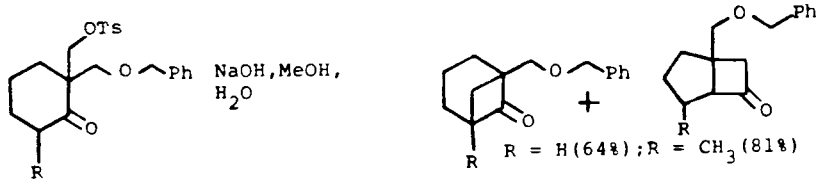


95

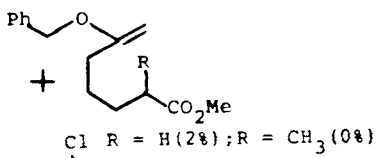
96 (98%)

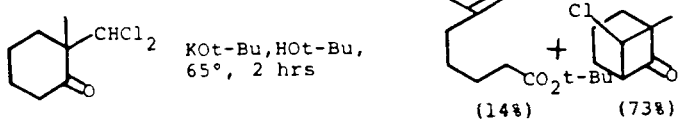
Table VII. Base-promoted Fragmentations of β-Substituted Cyclic Ketones

Reactant	Conditions	Product(s) (%)	Ref.
	NaOH,MeOH	 (43%)	67
X = OCH_3			
X = OTs	"	" +  (41%)	
	NaOH,MeOH, reflux, 14 hrs		57
R = H; X = $\overset{\oplus}{N}Me_3$		(4%) (78%)	
R = CH_3; X = OTs	"	(1%) (90%)	
R = CH_3; X = $\overset{\oplus}{N}Me_3$	"	(26%) (24%)	
		 (2.8%) (89%)	
	"	 (14%) (59%)	
	NaOH,MeOH, reflux, 14 hrs	 (77%)	57
		+  (4.4%)	

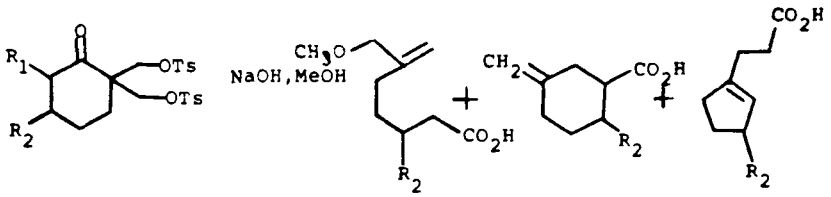


63

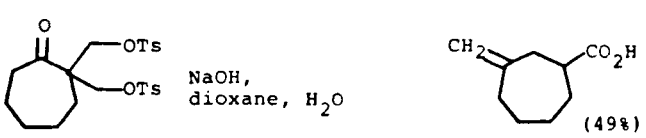


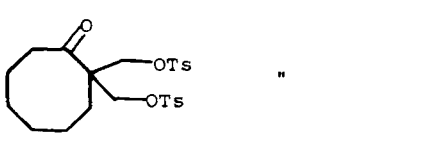


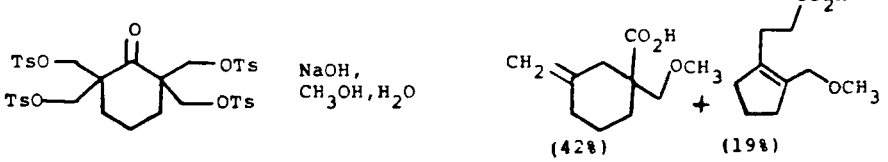
65



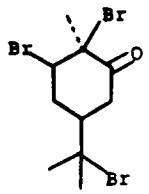
67

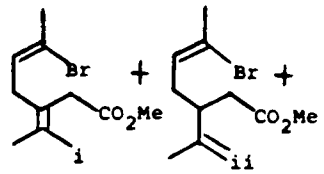




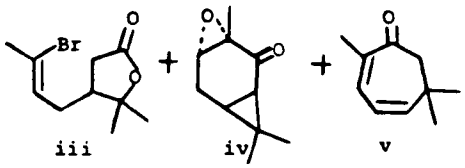


68

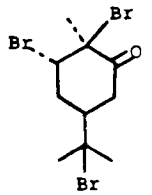




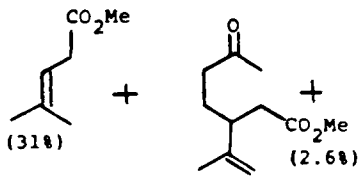
66



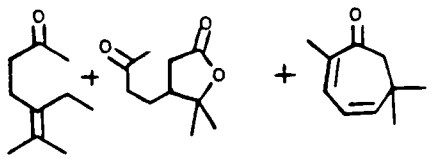
	i	ii	iii	iv	v
1) NaOH,H_2O, 71 hrs 2) CH_2N_2	~7%	~5%	~47%	~26%	0
1) NaOH,H_2O dioxane, 45 hrs 2) CH_2N_2	8%	2%	12%	41%	0
1) NaOH,Et_2O, 64 hrs 2) CH_2N_2	11%	22%	25%	0	13%



1) NaOH,H_2O, 70 hrs
2) CH_2N_2

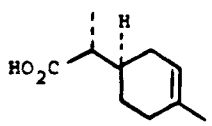


(31%) (2.6%)

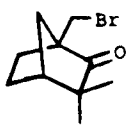


(10%) (36%) (7%)

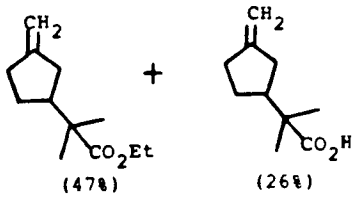
NaOH



22a



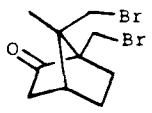
$NaOH,Et_2O$



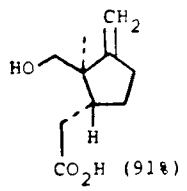
(47%) (26%)

70

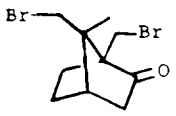
CAINE



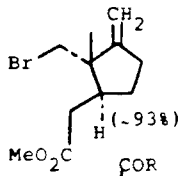
KOH, H_2O, DMSO, 25°, 24 hrs



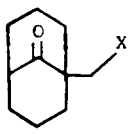
62b



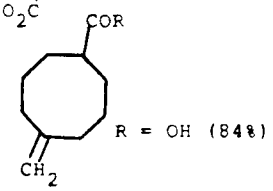
NaOMe, HOMe 25°, 4 hrs



62c



NaOH, MeOH, H_2O 85°, 3 days



61a

X = OTs

KOt-Bu, HOt-Bu, 80°, 6 hrs

R = Ot-Bu (29%)

$NaNH_2$, dioxane, 4 days

$R = NH_2$

X = OTf

NaOH, MeOH, H_2O 85°, 3 hrs

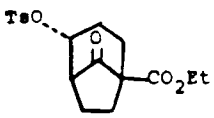
R = OH (88%)

NaOEt, HOEt reflux, 3 hrs

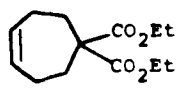
R = OEt

KOt-Bu, HOt-Bu 80°, 1 hr

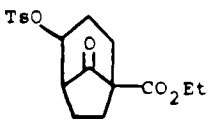
R = Ot-Bu (47%)



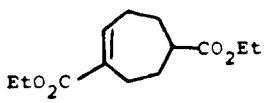
NaOEt, HOEt, 15 min

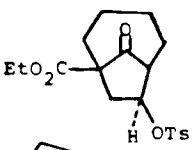


60b

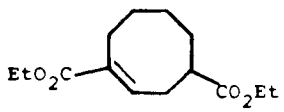


NaOEt, HOEt, 15 min

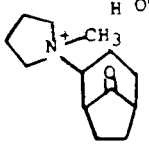




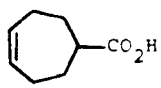
NaOEt, HOEt, reflux, 20 hrs



61b

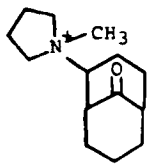


$NaOH, H_2O$

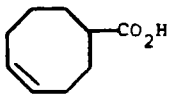


60a

WHARTON FRAGMENTATIONS OF CYCLIC 1,3-DIOL DERIVATIVES



NaOH, H_2O

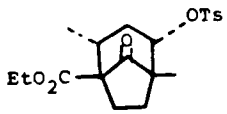


60a

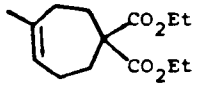
NaOH, H_2O
100°, 50 hrs

" (40%)

61d

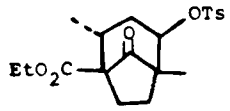


NaOEt, HOEt,
60°, 30 min



(83%)

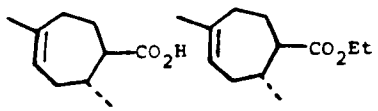
60c

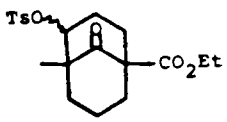


"

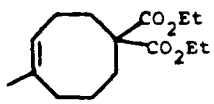
(No reaction)

KOH, EtOH,
reflux, 16 hrs

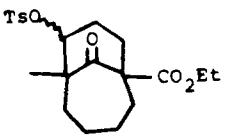




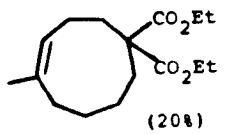
NaOEt, HOEt,
reflux, 2 hrs



61c

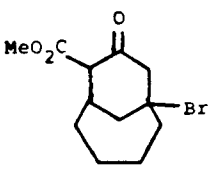


NaOEt, HOEt,
reflux, 2 hrs

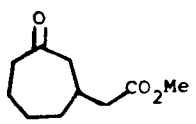


(20%)

61c

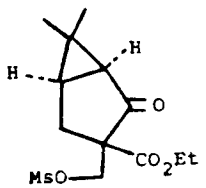


NaCN, HMPA,
70°, 1 hr

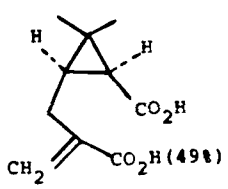


(60%)

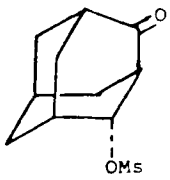
56



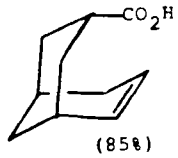
KOH, EtOH,
95°



65



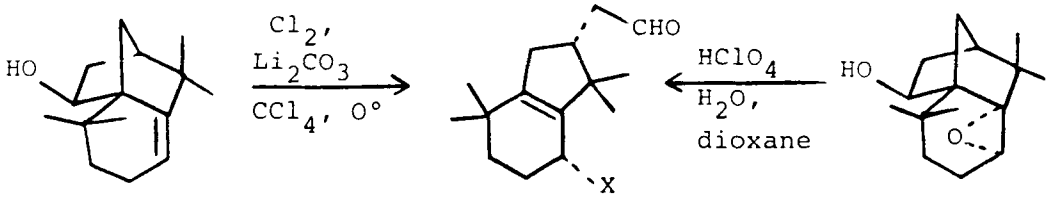
KOH, H_2O



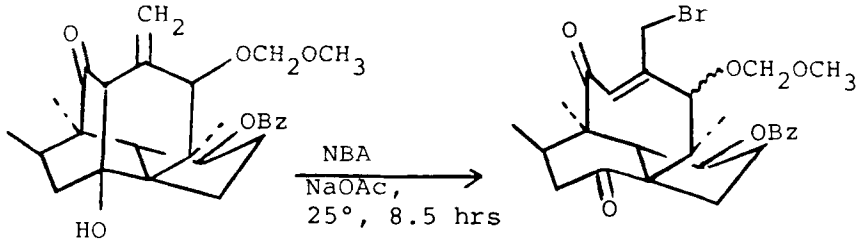
71

V. REACTIONS RELATED TO THE WHARTON FRAGMENTATION

Processes that lead to the generation of an electron-deficient carbon atom γ to a hydroxyl group may result in fragmentations related to the Wharton reaction. For example, treatment of tricyclic γ,δ-unsaturated alcohol 97 with chlorine gave the unsaturated chloroaldehyde 98a quantitatively,[72a] and the reaction of the tetracyclic alcohol 100 with N-bromoacetamide(NBA) gave the tricyclic enedione 101.[72b] Also, treatment of the epoxide 99, derived from the olefin 97, with acid gave the unsaturated hydroxy aldehyde 98b in high yield.[72a]



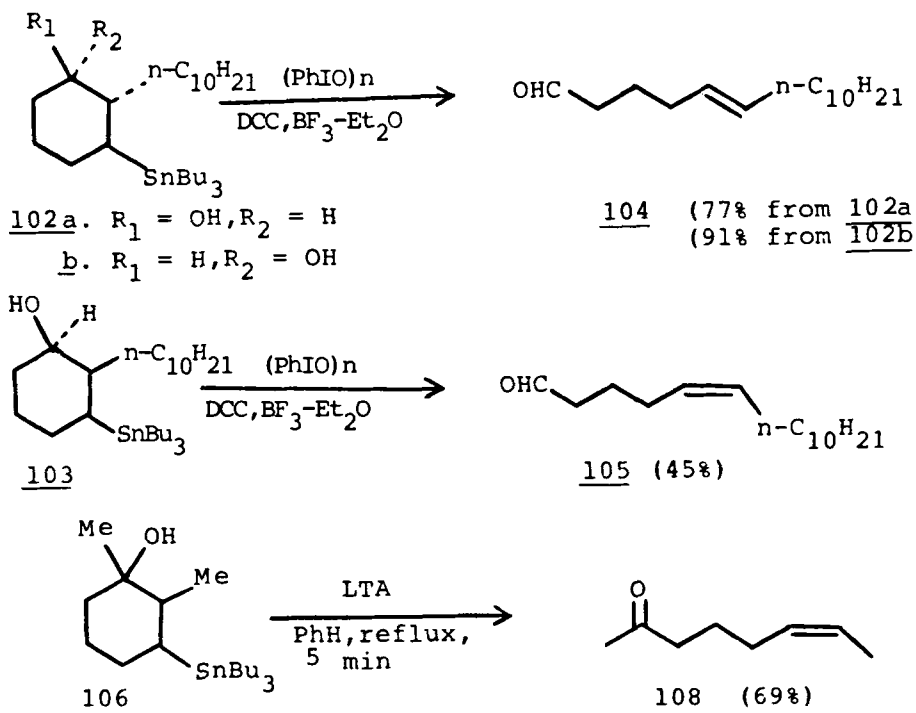
97 98a. X = Cl(100%) 98b. X = OH(100%) 99



100 101

WHARTON FRAGMENTATIONS OF CYCLIC 1,3-DIOL DERIVATIVES

The recently reported oxidative fragmentations of γ-stannyl[73] and γ-silyl alcohols[74] also fall into the category. As illustrated by the conversions of the γ-stannyl secondary alcohols 102 and 103 to the corresponding E and Z unsaturated aldehydes 104 and 105 with iodosylbenzene, dicyclohexylcarbodiimide(DCC) and boron trifluoride etherate in methylene chloride[73a] and the conversions of the γ-stannyl tertiary alcohols 106 and 107 to the corresponding Z and E unsaturated ketones 108 and 109 with lead tetraacetate in benezene, these reactions are completely stereospecific. The conversions of both 102a and 102b into the unsaturated aldehyde 104 demonstrate that, as with the Wharton fragmentation, the stereochemistry of the hydroxyl group is unimportant. On the other hand, Ce(IV) oxidative fragmentations of γ-hydroxy silanes related to 102 and 103 are non-stereospecific.[74b]



102a. R_1 = OH, R_2 = H
b. R_1 = H, R_2 = OH

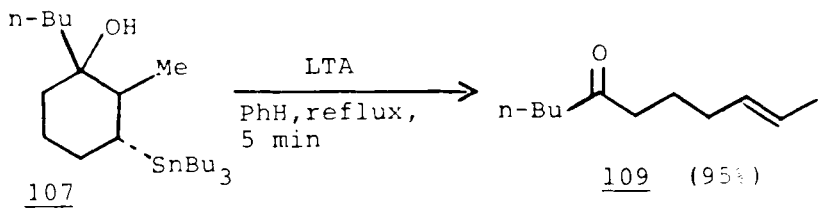
104 (77% from 102a)
(91% from 102b)

103

105 (45%)

106

108 (69%)



107 109 (95%)

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