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HOMOENOLATE ANIONS AND HOMOENOLATE ANION EQUIVALENTS

MECHANISTIC ASPECTS AND SYNTHETIC APPLICATIONS

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1. INTRODUCTION

Since carbonyl compounds are electrophilic, basic, relatively strong carbon acids, and contain a Π-chromophore, their chemistry is rich and varied. Of the vast number of reactions exhibited by carbonyl compounds, acid-catalyzed and base-catalyzed enolization must be considered as two of the most important transformations in organic chemistry. Provided that stereo-electronic requirements are met, the α-enolizations occur readily at ambient temperature and the mechanistic details of these ubiquitous reactions are well documented in the literature. In principle, deprotonation can occur at a site more remote from the carbonyl group than the α-carbon (Scheme 1) under acid or base catalysis albeit under more vigorous conditions. As far as the author is aware, there have been no reports of acid-catalyzed homoenolization. However, over the past twenty years, beginning with the pioneering work of Nickon[1-3] in the early sixties, there has been a burgeoning interest in the preparation and reactions of homoenolate anions and the area has been the subject of several other reviews.[4-6] Attempts have been made to establish homoenolate anion equivalents as general synthons as well.[7]

Through a documentation of the methods of preparation and reactions of homoenolates and their equivalents, through a discussion of the factors which determine the rates of formation, and rearrangement of homoenolate anions, and through an elaboration of the mechanistic aspects of base-catalyzed homoketonization of homoenols, this relatively new field is to be reviewed.

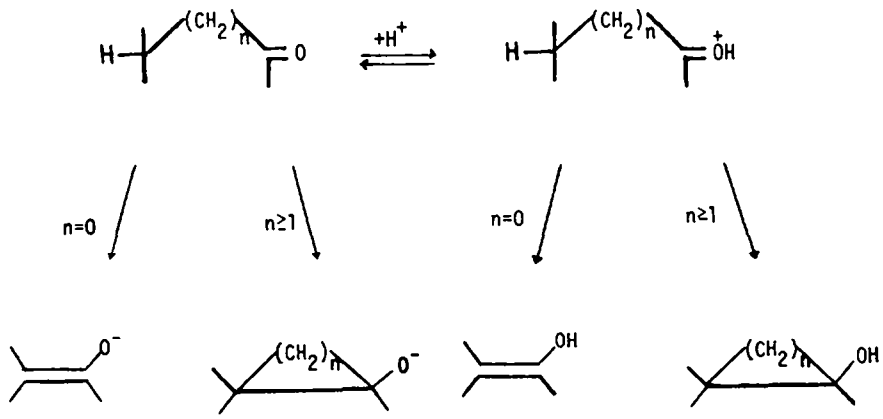
2. PREPARATION

2.1 *Deprotonation of ketones in strongly basic medium*

One route to homoenolates involves heating a ketone with potassium-*tert*-butoxide in *tert*-butyl alcohol in a molar ratio of approximately 1:4:40 at 175–250°. In the publications to date authors have used molar ratios, molarity (M), and molality (m) to indicate the relative concentrations of ketone and base. No attempt has been made in the review to unify the specification of concentrations. Since H–D exchange is used to monitor homoenolate anion formation, *t*-butyl alcohol–O-d is used as a solvent and a source of deuterium. Extreme care must be taken to exclude water for even small amounts reduce the basicity of the medium[8] and solutions are degassed and sealed in pyrex tubes under vacuum. In our laboratory a fresh solution of t-BuOK is prepared for each reaction by dissolving clean potassium in t-BuOH or t-BuOD in a dry-box continuously flushed with nitrogen. All transfers are carried out in the dry-box. While t-BuOK/t-BuOH(D) is the medium of choice for preparing homoenolates from ketones, other base-solvent combinations have been used. Nickon reported that while 3,3-dimethylbicyclo[2.2.1.]heptan-2-one (camphenilone) is destroyed in t-BuOK in DMSO at 20°, homoenolization, as monitored by the degree of racemization, occurs readily at lower temperatures in t-BuOH–DMSO.[2]

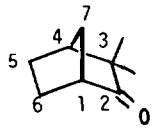
2.1.1 *Polycyclic ketones*

2.1.1.1 *β-Enolization.* The terminology devised by Stothers[17] is used in this review. Deprotonation alpha to the carbonyl may be termed α-enolization, deprotonation beta is termed β-enolization and so on. The first quantitative study of homoenolization (β-enolization) was documented by Nickon and Lambert[1,2] who studied the t-BuOK catalyzed H–D exchange and racemization of optically active 3,3-dimethyl-



Scheme 1.

bicyclo[2.2.1.]heptan-2-one (**1**) as a function of temperature and base concentration. They found that temperature is an important factor. At 150° (0.73 m **1**, 0.46 M t-BuOK) after 166 h no racemization was observed; at 185° (0.30 m **1**, 0.86 m t-BuOK) after 36 h **1** was 69% racemized and at 250° (0.46 m **1**, 0.47 m t-BuOK) racemization was complete. The authors considered several mechanisms for the racemization other than direct abstraction of the exo or endo proton at C-6: thermal cleavage, a mechanism which involves exo addition of $t\text{-BuO}^-$ to the carbonyl group followed by intramolecular abstraction of *endo*-6-H and ring opening–ring closure involving the base adduct. The alternatives were excluded on the basis of control experiments and the nature of the H–D exchange. Under short reaction times of 12–48 h, they found that only three deuterium atoms were incorporated and that the rate of incorporation of the first deuterium and the rate of racemization were identical within experimental error. This provided circumstantial evidence that deuterium was being incorporated at C-1 and C-6, ruled out a major involvement of an isoracemization mechanism, and established that each time a proton is pulled off at C-6 the derived β-enolate anion becomes symmetrical before it is deuteronated by solvent. Thus the homoenolate anion is either the symmetrical species **2** or it is an unsymmetrical species **3** that rearranges faster than it is deuteronated. Because C-1 and C-6 become equivalent in the homoanion, they were unable to assess the importance of bridgehead exchange, although the fact that the rate of racemization was comparable to the rate of incorporation of the first deuteron indicated that bridgehead



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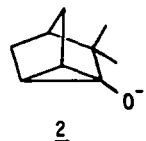

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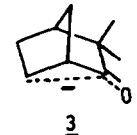

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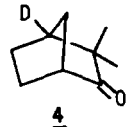

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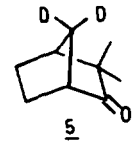

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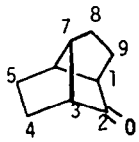

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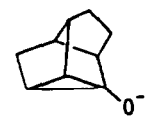

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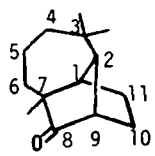

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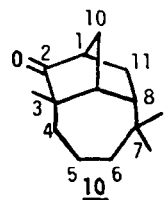

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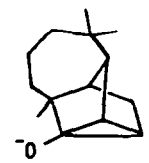

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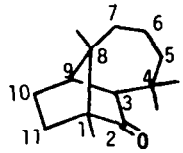

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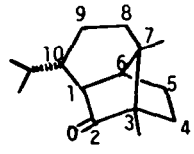

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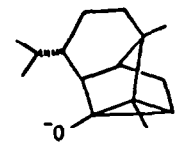

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exchange must be a relatively slow process. In a subsequent report Nickon *et al.*[3] established that up to nine deuterium atoms were incorporated into **1** when deuterated **1** was recycled three times in fresh t-BuOK/t-BuOD. They established by ^{1}H NMR that the methyls at C-3 exchange, and by preparing and twice cycling specifically deuterated ketones **4** and **5** at 185° (**4**, 200 h and 300 h; **5**, 98 h and 200 h) established that there was no detectable exchange at C-4 and C-7. Since C-5 and C-7 become equivalent in **2**, the results establish that γ-enolization at C-5 is not significant either.

In 1965 Nickon *et al.*[9] provided the first example of a non-degenerate anionic rearrangement of a complex polycyclic ketone via β-enolization. They showed that tricyclo[4.3.0.0^{3,7}]nonan-2-one otherwise known as brexan-2-one (**6**) rearranged smoothly in t-BuOK/t-BuOH at 185° to tricyclo[4.2.1.0^{3,7}]nonan-2-one otherwise known as brendan-2-one (**7**). The rearrangement most reasonably proceeds through homoenolate **8** which is generated by abstraction of a proton from C-4 or its equivalent C-9.

Coates and Chen[10] found that 3,3,7-trimethyltricyclo[5.4.0.0^{2,9}]undecan-8-one (longicamphenilone) (**9**) was converted into 3,7,7-trimethyltricyclo[6.2.1.0^{3,9}]undecan-2-one (**10**) under rather vigorous homoenolization conditions; another example of a brexyl-brendyl type transformation. The β-enolate **11** is a viable intermediate in the rearrangement.

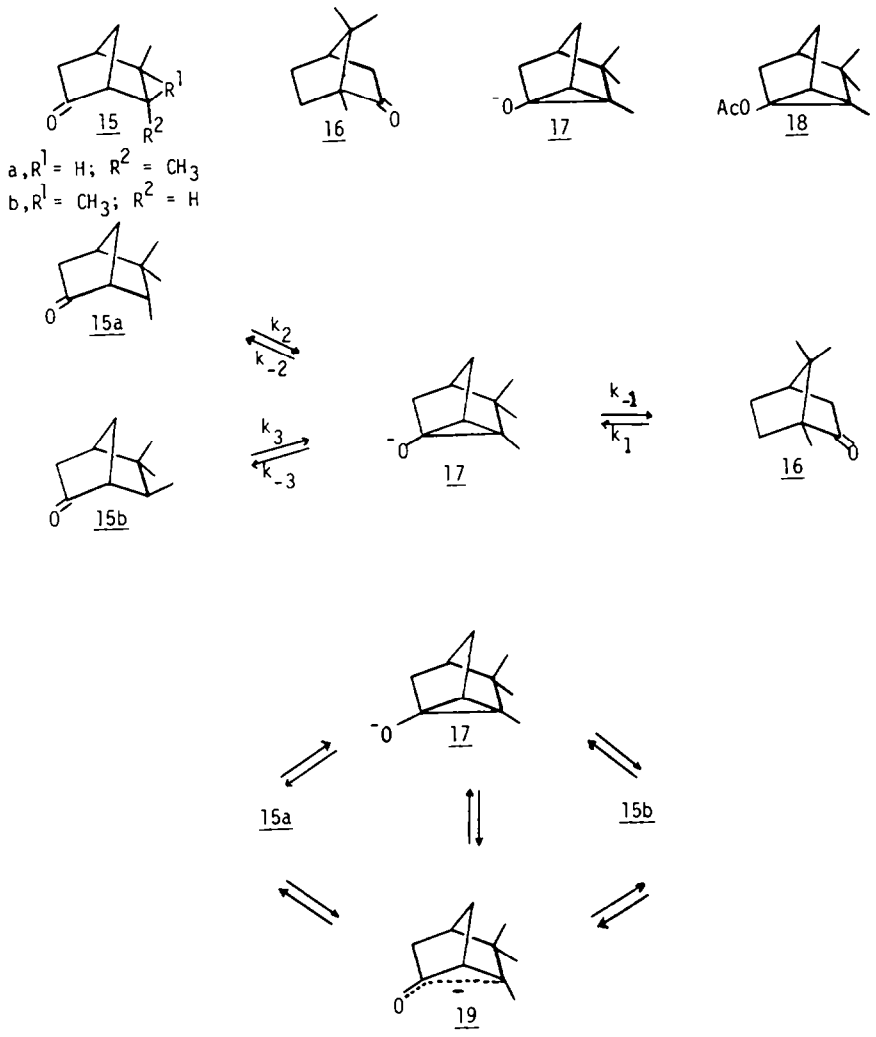
Arigoni *et al.*[11] obtained somewhat surprising results. While 1,4,4,8-tetramethyltricyclo[7.3.0.0^{3,9}]undecan-2-one (longicamphor) (**12**) incorporated up to three deuterium atoms (28.4% d_1, 42.2% d_2 and 21.5% d_3 species) after 48 h in t-BuOK/t-BuOD at 185°, 3,7-dimethyl-exo-10-(2-propyl)tricyclo[4.4.0.0^{3,7}]decan-2-one (copacamphor) (**13**) was deuterated only at C-1 (25% d_0, 75% d_1 species). The authors suggested that **13** does not undergo β-enolization at a significant rate because the 3-membered ring of **14** imposes additional strain on the system. In view of the fact that brexan-2-one (**6**) rearranges smoothly to **7** via **8**, which would appear to be more strained than **14** because it bears a two-carbon bridge, perhaps suggests that strain is not the determining factor. It is interesting to note that **13** bears a structural resemblance to 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (camphor) which also exhibits a reduced rate of homoenolization (*vide infra*). In view of the fact that homoenolization rates are drastically lowered by traces of water, perhaps the study of the homoenolization of **13** should be repeated.

In 1972, in a collaborative communication, Stothers, Nickon *et al.*[12] reported the first example of epimerization at a center remote from a carbonyl group via a β-enolate anion. They studied the homoenolization of 5,5-*endo*-6-trimethylbicyclo[2.2.1]heptan-2-one (*endo*-isocamphanone) (**15a**), 5,5-*exo*-6-trimethylbicyclo[2.2.1]heptan-2-one (*exo*-isocamphanone) (**15b**) and 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (camphor) (**16**) which are in principle interconvertible via homoenolate **17**.

The study was significant because it established that homoenolization of ketones is possible in conjunction with α-enolization and that ^{13}C NMR can be used to monitor H–D exchange. Since then of course, ^{2}H NMR coupled with shift reagents has proved to be invaluable for monitoring H–D exchange directly at a large number of sites. Nickon *et al.* published a complete account of the homoenolization of **15a**, **15b** and **16** in 1976.[13] From the isomerization data on **15a**, **15b** and **16**, assuming that a common homoenolate is involved, they showed that $k_{-2} > k_{-1} > k_{-3}$ and that $k_2 > k_3$; β-abstraction of an exo proton is easier than abstraction of an endo proton. They noted that while homoenolization of **15b** which presumably involves homoion **17** initially yields more **15a** than **16**, homoketonization of 1-acetoxytricyclene (**18**) in t-BuOK/t-BuOH at 20° yields exclusively **16**. To account for their observations Nickon suggested that a more complex situation may prevail where several homoenolates may be involved, **19** being a geometrically distorted form of **17**.

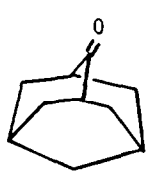
They established that camphor (**16**) homoenolized considerably slower than other polycyclic monoketones. For example, **16** (0.20 m) which was heated for 307 h at 185° in 1.3 m t-BuOK/t-BuOD and recycled in fresh base (490 h) incorporated 3.18 atoms of deuterium (1% d_0, 5% d_1, 15% d_2, 41% d_3, 31% d_4, 6% d_5 and 1% d_6 species). By subtracting the deuterium located at C-3 and the C-8 and C-10 methyls, they established that **16** incorporated 0.53D at C-6 after 797 h. By comparison, 1.22 atoms of deuterium were incorporated into camphenilone[2] predominately at C-6 when it was heated at 185° in 0.86 m t-BuOK/t-BuOD for 48 h. Nickon suggested that steric hindrance by the methyls and competitive α-enolization (perhaps a substantial portion of **16** exists as the enolate) contribute to the reduced reactivity. It is interesting to note that Arigoni has reported[11] that **13** which bears a close structural resemblance to **16** did not homoenolize at a detectable rate at 185°.

In a significant communication published in 1974 Stothers and Tan[14] reported, contrary to earlier reports by Nordlander *et al.*[15] that adamantanone (**20**) underwent β-enolization. Exo exchange was 17 times faster than endo exchange and homo-ion **21** was implicated as an intermediate. They also noted



that exo exchange was only 2 times faster than exchange at the bridgehead. For example, when heated in 0.7 M t-BuOK/t-BuOD at 185° for 213 h **20** incorporated 0.63 atoms of deuterium and was a composite of 51.0% d_0, 37.2% d_1, 10.4% d_2 and 1.3% d_3 species. Deuterium assay by ^2H NMR showed that 12.4% of the exo protons, 0.7% of the endo protons and 5.2% of the bridgehead protons were exchanged. The first-order rate constants for exchange of the β-exo, β-endo and the bridgehead protons were 1.7×10^{-7}, 9.0×10^{-9} and 7.0×10^{-8} s^{-1}, respectively. The publication was significant in that it was the first report of the use of shift reagents ($Pr(fod)_3$) in conjunction with ^2H NMR in monitoring deuterium incorporation via homoenolization of complex polycyclic ketones.

In 1975 Stothers *et al.*[16] published a full account of the work on the homoenolization of 1,3,3-trimethylbicyclo[2.2.1]heptan-2-one (fenchone; **22**) mentioned in a previous communication.[12] Mass spectrometry, ^{13}C NMR and ^2H NMR were used to monitor H–D exchange. By computer-fitting $Pr(fod)_3$ shifted ^2H NMR spectra they established that exchange occurred at C-6 and the C-1 and C-3 methyls and implicated the homo-ions **23**, **24**, **25** and **26** as intermediates. When heated in 0.7 M t-BuOK/t-BuOD for 300 h, **22** incorporated 1.94 atoms of deuterium and was a composite of 7.6% d_0, 28.6 d_1, 31.0% d_2, 19.0% d_3, 5.9% d_4, 1.4% d_5 and 0.5% d_6 species. Deuterium assay by ^2H NMR showed that exchange of *exo*-6-H (65% complete), *endo*-6-H (64%), *exo*-3-CH_3 (14%), *endo*-3-CH_3 (5.3%) and the bridgehead methyl (2%) had occurred. As in the case of camphenilone[3] there was no indication of exchange at C-7. From the H–D exchange results the first-order rate constants for deuteration at *exo*-6, *endo*-6, *exo*-3-methyl, *endo*-3-methyl and the bridgehead methyl were evaluated as 7.0×10^{-6}, 2.0×10^{-6}, 2.0×10^{-7}, 4.8×10^{-8} and 1.9×10^{-8} s^{-1}, respectively. A small amount of reduction to fenchol (~ 1%) was observed and the other possible ketones 3,3-*endo*-6-trimethylbicyclo[2.2.1]heptan-2-one (**27a**) and 3,3-*exo*-6-trimethylbicyclo[2.2.1]heptan-2-one (**27b**) derivable form the homo-ion **23** were detected (5%) in a ratio of 3:1.



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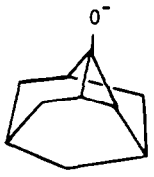

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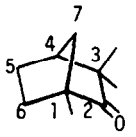

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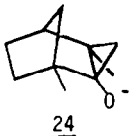

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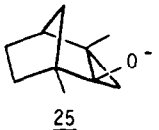

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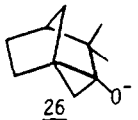

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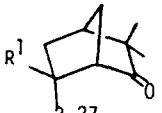

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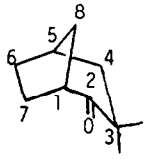
a, R^1 = H; R^2 = CH_3

b, R^1 = CH_3; R^2 = H



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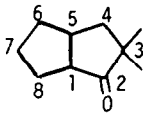

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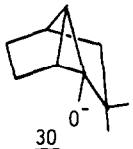

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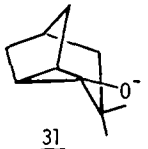

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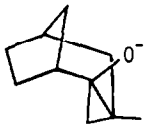

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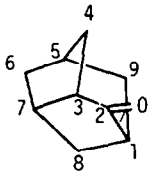

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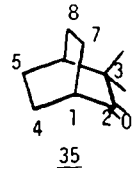
When a 3:1 mixture of **27a** and **27b** was heated in t-BuOK/t-BuOH at 185° for 200 h **22**, **27a** and **27b** were obtained in a ratio of 20:5:75 indicating that **27a** homoenolizes faster than **27b**. This was in keeping with the results obtained for fenchone, the iso-camphenones and adamantanone; *exo*-6-H abstraction was faster than *endo*-6-H abstraction.

In 1974 Stothers *et al.*[17] reported their results on the homoenolization of 3,3-dimethylbicyclo[3.2.1]octan-2-one (**28**) and 3,3,dimethyl[3.3.0]octan-2-one (**29**). The study was significant in that it further illustrated the utility of the combination of ^2H NMR and shift reagents in unraveling complexities of H–D exchange of polycyclic systems and was the second report of a γ-enolization. Ketone **28** rearranges to **29** via β-enolate **30** which homoketonizes to **29** exclusively because no deuterium was detected at C-8 of unrearranged **28**. Deuterium is incorporated at *exo*-7 and *endo*-7 positions via **29** and in the methyl groups by β-enolization suggesting the existence of homoenolates **31**, **32** and **33**. Exchange at C-1 of **28** was rapid with >90% exchange after 1 h at 185°; exo-7-H exchanged faster than endo-7-H and exo-CH_3 exchanged faster than endo-CH_3. The first-order rate constants for exchange of H-1, *exo*-7-H, *endo*-7-H, *exo*-3-methyl and *endo*-3-methyl were $>6\times10^{-4}$, 8.0×10^{-6}, 4.6×10^{-6}, 1.2×10^{-7} and 8.4×10^{-8} s^{-1}, respectively. The first-order rate constant for rearrangement ($\sim3\times10^{-6}$ s^{-1}) may be taken as a rough measure of this rate of deprotonation at C-8. When **29** was exchanged separately, the deuterium distribution was significantly different than the distribution in **29-d$_x$** obtained from **28**. Using $Pr(fod)_3$, eight signals were resolved revealing exchange at C-1, C-6, C-7, C-8 and the methyls. Bridgehead exchange at C-1 of **29** was not as fast an exchange at C-1 of **28**. The exchange at C-6 and C-7 implicates γ-enolates as intermediates and from the extent of exchange at C-6 and C-7 establishes that β- and γ-enolizations are competitive.

In a communication dealing with a study of bridgehead exchange in brendan-2-one (**7**) and bicy-

clo[3.3.1.0^{3,7}]nonan-2-one (**34**) published in 1975, Nickon *et al.*[18] reported in addition to the fact that **34** exchanged H-3 rapidly at 80° and H-1 rapidly at 120°, that additional deuterium is incorporated into **34** at higher temperatures. For example when **34** (0.23 M) was heated at 195° for 50 h in 0.64 M t-BuOK/t-BuOD it incorporated up to five deuterium atoms and was a composite of 5% d_0, 39% d_2, 24% d_3, 2% d_4 and 1% d_5 species (1.82 excess deuterium atoms per molecule). While there are four β-sites (C-4, C-7, C-8 and C-9) and two γ-sites the position of the deuterium was not determined.

In a sequel to a communication[19] that documented the use of ^{13}C NMR for monitoring H–D exchange in bicyclooctanones, Stothers *et al.*[20] published an account of a study of the homoenolization of 3,3-dimethylbicyclo[2.2.2]octan-2-one (**35**) and 7,7-dimethylbicyclo[3.2.1]octan-6-one (**36**) in which computer-fitting of $Pr(fod)_3$ shifted ^2H NMR spectra was used to determine the sites of exchange. That the rearrangement of **35** to **36** via the β-enolate **37** is very slow was established by the fact that deuterated **35** was recycled up to nine times with fresh base in an attempt to reach equilibrium. In **35**, major exchange of *exo*-6-H(*exo*-7-H), *endo*-6-H-(*endo*-7-H) and the methyl occurred, implicating homo-ions **37**, **38** and **39** intermediates. For example, after 240 h at 185° **35** incorporated 2.25 deuterium atoms and was a composite of 47.9% d_0, 21.2% d_1, 20.0% d_2, 8.6% d_3, 2.3% d_4 and 0.4% d_5 species. A small amount of bridgehead exchange, as indicated by a barely discernable signal was observed after reaction periods up to 400 h. From the H–D exchange data the approximate first-order rate constants were 1.5×10^{-6}, 1.5×10^{-7} and 3.9×10^{-8} s^{-1} for exchange at *exo*-6(7)-H endo-6(7)-H and the methyls. In the case of **36**, exchange occurred at C-4, at the bridgehead alpha to the carbonyl group, and at the methyls indicating that homo-ions **40** and **41** are possible intermediates. There was no detectable exchange at C-8, a β-site, or C-3, a γ-site, even after 400 h. For example, after 120 h, **36** incorporated 2.78 deuterium atoms and was a composite of 0.8% d_0, 8.6% d_1, 28.8% d_2, 38.8% d_3, 19.9% d_4, 2.4% d_5 and 0.7% d_6 species. Deuterium assay by ^2H NMR established that there was 0.10 D *exo* at C-4, 0.73 D at C-5, 1.92 D in the *exo* methyl



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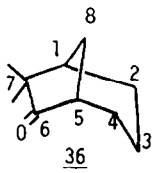

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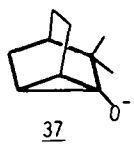

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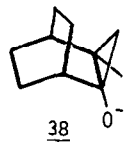

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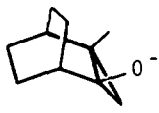

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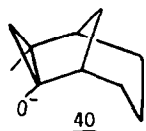

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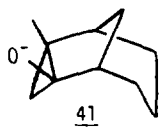

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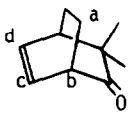

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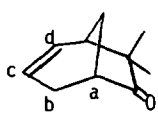

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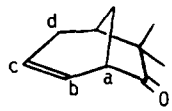

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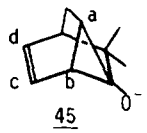

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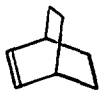
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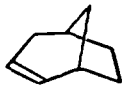
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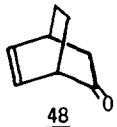


48

and 0.03 D in the *endo* methyl. The approximate first-order rate constants were 1.2×10^{-5}, 2.3×10^{-7}, 3.0×10^{-6} and 2.3×10^{-8} s^{-1} for exchange of H-1, *exo*-H-7 and the *exo*-3 and *endo*-3-methyls, respectively.

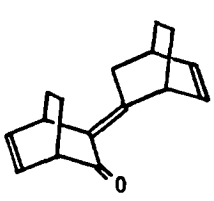
A complete account of the homoenolization and rearrangement of 5,5-dimethylbicyclo[2.2.2]oct-2-en-6-one (**42**), 7,7-dimethylbicyclo[3.2.1]oct-2-en-6-one (**43**) and 6,6-dimethylbicyclo[3.2.1]oct-2-en-7-one (**44**) was published in 1978 by Cheng and Stothers.[21] ^2H NMR coupled with $Pr(fod)_3$ was used to unravel the complexities of the t-BuOK catalyzed exchange and rearrangement of **42**, **43** and **44** studied initially by ^{13}C NMR.[19] **42** rearranged to **43** and **44** undoubtedly via homo-ion **45** approximately 18 times faster than the saturated analog, and, at equilibrium which is achieved after 24 h at 185° in 0.7 M t-BuOK, **44** predominates (**42**:**43**:**44** = 8:44:48). Furthermore, at 155° **42** exchanges more rapidly at C-2 and C-3 than the parent alkene **46** by factors of ~1700 and 30 respectively. At 185° deuterium is incorporated into **42** at C-1(b) and C-7(a). However, as the authors reasonably suggest, most of the exchange likely occurs via **43** and **44** because exchange at C-5(a) and C-4(b) of **43** and C-1(a) and C-2(b) of **44** that correspond to C-7(a) and C-1(b) of **42** is fast, and, **43** and **44** are in equilibrium with **42**. From the studies at 155° the rate constant for deprotonation at C-4(d) of **44** was established as $\sim8\times10^{-5}$ s^{-1}. Since the sum of the rate constants for exo and endo allylic deprotonation of **47** is *ca.* 1×10^{-6} s^{-1} at 185° and assuming that the rate doubles for a 10° increase in temperature the rate enhancement is ~600. This suggests that homoallylic stabilization of the developing anion by the carbonyl group is important. By correcting the apparent rate constant for exo deprotonation at C-4(b) (2×10^{-4} s^{-1}) of **43** for a 30° temperature difference and comparing the estimated value to the rate for exo allylic deprotonation of **47** (*ca.* 7×10^{-7} s^{-1}) it is established that the C-6 carbonyl group of **43** enhances the rate of deprotonation by a factor of ~2300. It is interesting to note that a comparable rate enhancement by a β-carbonyl group has been observed in the deuteroxide-catalyzed α-enolization of bicyclo[2.2.1]heptan-2,5-dione at 25°.[23] Vinylic exchange which occurred at a significant rate at 185° was faster by a factor of >20 than vinylic exchange of **47**. This must be simply an inductive effect of the carbonyl group because it is difficult to visualize a direct interaction between the vinyl anion at C-3 of **43** and **44** with the carbonyl group.

When the parent [2.2.2]-enone **48** was heated at 185° in t-BuOK/t-BuOD it was consumed.[24] Evidence was obtained that the isomer **50** of the aldol condensation product **49** underwent retro-Diels–Alder loss of ethene to form the phenyl derivative **51** which lost a second molecule of ethene to form 2-phenylphenol (**52**). **51** also underwent Haller–Bauer cleavage to a mixture of 4-benzylcyclohexenecarboxylic acids.

In 1976 Nickon *et al.*[13] reported briefly on the exchange of bicyclo[2.2.1]heptan-7-one (**53**). They found, as did Gassman and Zalar,[25] that **53** exchanged only slowly and underwent Haller–Bauer ring opening, a reaction characteristic of highly strained ketones in strongly basic medium. For example, after 97 h at 185° only 0.20 atoms of deuterium were incorporated into **53** which was composed of 84% d_0, 12% d_1 and 4% d_2 species. Although there are four equivalent exo hydrogens and four equivalent endo hydrogens beta to the carbonyl group, formation of β-enolate **54** is difficult in this case, a consequence of the strain and the fact that optimum stereoelectronic requirements are not met.

In an attempt to estimate the rate of exchange at C-1 of camphenilone and to provide rate data to which we could compare the rates of t-BuOK-catalyzed H–D exchange of 3,3,6,6-tetramethylbicyclo[2.2.1]heptane-2,5-dione, we prepared 3,3,6,6-tetramethylbicyclo[2.2.1]heptan-2-one (**55**) by desulfurizing 3,3,6,6-tetramethyl-5-oxo-bicyclo[2.2.1]heptan-2-thione and treated it under homoenolization conditions at 175°.[26] 90 MHz ^1H, 13.4 MHz ^2H, 400 MHz ^1H and 60.1 MHz ^2H NMR and the use of $Eu(fod)_3$ were used to establish that deuterium was incorporated at C-1 ($k_{185°}3.2\times10^{-7}$ s^{-1}) syn at C-7 ($k_{185°}\sim1.4\times10^{-8}$ s^{-1}), in the C-8 and C-9 methyls ($k_{185°}$ total $\sim1.0\times10^{-7}$ s^{-1}) and in the C-11 methyl ($k_{185°}\sim6.0\times10^{-9}$ s^{-1}). Homo-ions **56**, **57** and **58** are possible intermediates. If the rate constants (7.0×10^{-6} and 2.0×10^{-6} s^{-1}) for *exo*-6-H and *endo*-6-H exchange of fenchone (**22**) are good measures of the exo and endo exchange rates of camphenilone (**1**), and the rate constant for bridgehead exchange of **55** is a reasonable measure of the bridgehead exchange rate at C-1 of camphenilone, then exchange at C-6 of **1** is approximately 25 times as fast as bridgehead exchange. This is in accord with Nickon's observation that the rate of racemization of **1** is approximately equal to the rate of incorporation of deuterium into **1**. Our work provides the first evidence of β-enolization at C-7 of a bicyclo[2.2.1]heptan-2-one. It is interesting to note that syn-7-exchange appears to be faster than anti-7-exchange.

2.1.1.1 *γ-Enolization.* The first reports of γ-enolization were published in consecutive communications in 1965 by Winstein *et al.*[27,28] and Fukunaga.[29] Winstein and Fukunaga found that the hexachloro half-cage ketone **59a** was converted, in good yield, to the corresponding hexachlorohomoenol **60a** in



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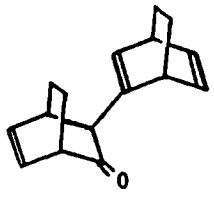

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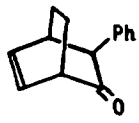

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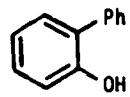

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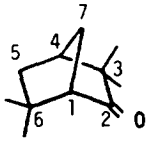

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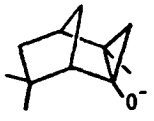

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58

refluxing pyridine at 100° ($k = 2.9 \times 10^{-5}\ s^{-1}$). Surprisingly, **60a** was converted into **60b** by Li and t-BuOH in THF without significant homoketonization. Winstein also studied the γ-enolization of the parent ketone **59b** at a range of temperatures and found, for example, that **59b** rearranged to **61** in 0.9 M t-BuOK/t-BuOH with a rate constant of $7.58 \times 10^{-5}\ s^{-1}$ at 195.5° ($k_{185°} \sim 3.8 \times 10^{-5}\ s^{-1}$). Fukunaga studied the rearrangement of **59b** in t-BuOK/t-BuOH at 250° and established an equilibrium ratio of 4:96 for **59b** and **61**.

In 1974 Stothers *et al.*[17] reported on the H–D exchange of 3,3-dimethylbicyclo[3.3.0]octan-2-one (**29**) providing the second example of a γ-enolization. Using $Pr(fod)_3$ to increase the dispersion of ^2H resonances, eight signals were resolved revealing exchange at C-1, C-6, C-7, C-8 and the methyls and implicating the homo-ions **62**, **63**, **64** and **65** as intermediates. For example, **29** incorporates 2.89 atoms of deuterium after 125 h at 185° and exchange occurs at C-1 (56%), *endo*-6-H (6%), *endo*-7-h (3%), *exo*-7-H (3%), *exo*-8-H (15%), *endo*-8-H (15%), *exo*-3-CH_3 (56%), *endo*-3-CH_3 (4%) and *exo*-6-H and *exo*-7-H (total of 15%). The rate constants for γ-enolization endo at C-6 and C-7 are 1.0×10^{-7} and $5.5 \times 10^{-8}\ s^{-1}$, respectively. On the assumption that the rate constants for exo-γ-enolization at C-6 and C-7 are similar, the exchange data establishes that $k_{exo\text{-}6} = k_{exo\text{-}7} = \sim 2.5 \times 10^{-7}\ s^{-1}$. The rate constants for exchange exo and endo at C-8 are $\sim 3.0 \times 10^{-7}$ and $2.0 \times 10^{-7}\ s^{-1}$ for the exo and endo methyl groups $\sim 1.8 \times 10^{-6}$ and $9.0 \times 10^{-8}\ s^{-1}$, respectively.

In 1976 Nickon *et al.*[13] described the homoenolization of camphor (**16**) in conjunction with a report of the homoenolization of the isocamphanones **15a** and **15b**. Camphor homoenolizes more slowly than other bicyclo[2.2.1]heptan-2-ones and elevated temperatures and long reaction times are required to incorporate significant amounts of deuterium. For example, in the case of **16** (0.2 m), after 168 h at 250° in 1.3 m t-BuOK/t-BuOD the C-8 and C-10 methyls undergo 10.5% and 8.5% exchange, respectively, and the rate constants are $\sim 2.0 \times 10^{-7}$ ($k_{185°} = \sim 2.0 \times 10^{-9}$) and 1.5×10^{-7} ($k_{185°} = \sim 1.5 \times 10^{-9}$) s^{-1}, respectively. Thus γ-enolate **66** is a viable intermediate in the exchange, and, in fact, Money *et al.* have prepared the corresponding homoenol by reducing 8-bromocamphor with Li in t-BuOH and Mg in ether (*vide infra*).

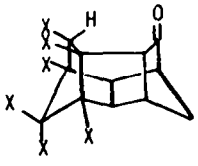
As mentioned previously, we obtained evidence for γ-enolization of the *endo*-6-CH_3 of tetramethyl ketone **55** when it was heated for 500 h at 175° in 1.24 M t-BuOK/t-BuOD. From the small amount of exchange (*ca.* 0.6%) we estimate the first-order rate constant to be in the region of $6.0 \times 10^{-9}\ s^{-1}$ at 185°.

Stothers *et al.*[30] studied the homoenolization of 7,7-dimethyltricyclo[3.2.1.$0^{2,4}$]octan-6-one (**67**) in t-BuOK/t-BuOH(D) at 185° and established that **67** rearranged to 2,2-dimethyltricyclo[3.3.0.$0^{4,6}$]octan-3-

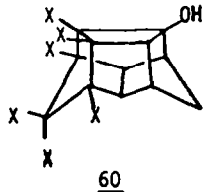
one (**68**). **68** underwent Haller–Bauer ring cleavage and also suffered reduction of the 3-membered ring by electron transfer from t-BuO$^-$ yielding **69** and **70** as products. For example after 47 h the neutral fraction consisted of 8% **67**, 58% **68**, 24% **69** and 9% **70**. The γ-enolate **71** was postulated as the intermediate in the rearrangement. Evidence that **71** is formed reversibly was obtained by carrying out the exchange of **67** in t-BuOD. Samples of **67-d** and **68-d$_x$** were isolated and the deuterium distribution was determined by ^{2}H NMR. In **67**, exchange is most rapid at the bridgehead (C-5), and in order of decreasing rate, exchange also occurs at C-4, C-3 and the *exo*-methyl. Deuterium is found at C-3 only in the exo position and this indicates that homoketonization of γ-enolate **71** occurs stereoselectively with inversion of configuration. This is somewhat surprising since the preferred pathway of ketonization of a γ-enolate is by retention (Table 1). **68** incorporated deuterium at C-4, C-5, C-6 and the *exo*-methyl. No deuterium was detected at C-7, C-8 or the *endo*-methyl establishing that γ-enolization does not occur in **68**.

2.1.2 *Polycyclic diketones*

In the early seventies we undertook a research program designed to establish the extent to which a carbonyl group situated β, γ or δ to an enolizable site enhances the rate of enolization of a ketone. That 1,3-diketones (pK_a *ca.* 10) are substantially more acidic than monoketones (pK_a *ca.* 20) dramatically illustrates the effect of a carbonyl group situated alpha to an α-enolizable system. We planned to study the enolization of monoketones, introduce at least one carbonyl group β, γ or δ to the enolizable site, and determine the magnitude of the rate enhancement. Initially we studied the α-enolization of bicyclo[2.2.1]heptan-2,5-dione (**72**)—a possible source of the α,β-enolate **73**—in NaOH–D_2O-dioxane at 25°



59
a, X=Cl
b, X=H



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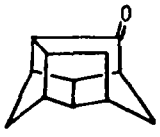

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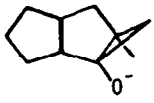

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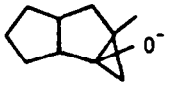

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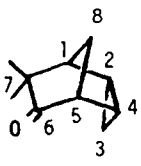

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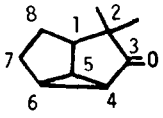

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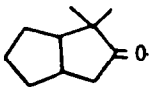

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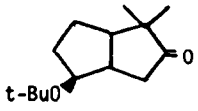

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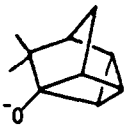
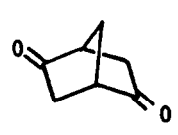


71

and compared the rate constants for exo and endo exchange to the rate constants for exchange of bicyclo[2.2.1]heptan-2-one (**74**).[23] We found a rate enhancement in the order of 10^3, and attempted to divide the enhancement into homoconjuative and inductive components. To expand our studies to β,β-enolates and to establish the effect of a β-carbonyl group on the rate of bridgehead exchange in a bicyclo[2.2.1]heptan-2-one, we prepared 3,3,6,6-tetramethylbicyclo[2.2.1]heptan-2,5-dione (**75**) and studied its exchange and rearrangement in t-BuOK/t-BuOH(D) at 175°. Deprotonation of **75** at C-7 formally generates β,β-enolate **76**. We published preliminary accounts of our studies in 1975 and 1980.[31,32] **75** undergoes H–D exchange at C-1(4), C-7 and the methyl, and undergoes a novel rearrangement to 1,3,3-trimethylbicyclo[2.2.2]octane-2,5-dione (**77**) via a β-homoenolate switch. When heated in 0.9 M t-BuOK/t-BuOD for 45 h, **75** (0.38 M) incorporates 2.60 deuterium atoms and is a composite of 2.1% d_0, 11.1% d_1, 33.0% d_2, 35.5% d_3, 15.2% d_4, 2.7% d_5 and 0.4% d_6 species. The deuterium distribution—1.35 D at C-1(4), 1.06 D at C-7, 0.11 D at C-8 and C-10, 0.08 D at C-9 and C-11—was determined by computer curve fitting the ^2H NMR spectrum of **75**-$d_{2.60}$ and established that exchange was 67.5%, 52.8%, 1.8% and 1.4% complete at C-1(4), C-7, the exo methyls and endo methyls, respectively. GC analysis showed that **77** comprised 27% of the mixture. From these data the rate constants for H–D exchange at C-1(4), C-7, exo-CH_3 and endo-CH_3 and rearrangement at 175° are $\sim 6.9\times10^{-6}\ s^{-1}$, $\sim 4.7\times10^{-6}$, $\sim 1.0\times10^{-7}$, $\sim 7.8\times10^{-8}$ and $\sim 1.9\times10^{-6}\ s^{-1}$, respectively. At 185° the first-order rate constants are $k_{C\text{-}1(4)} \sim 1.4\times10^{-5}$, $k_{C\text{-}7} \sim 9.4\times10^{-6}$, $k_{exo\text{-}CH_3} \sim 2.0\times10^{-7}$, $k_{endo\text{-}CH_3} \sim 1.6\times10^{-7}$ and $k_{rearr} \sim 3.8\times10^{-6}\ s^{-1}$. The conversion of **75** into **77** via **78** and **79** is the first example of a β-homoenolate switch where the homoenolate is generated directly from a ketone by proton abstraction. That the apparent rate constant for exo exchange of **75** is similar to the rate constant for endo-methyl exchange indicates that rearrangement occurs faster than **78** returns to **75**-d_x.



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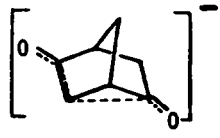

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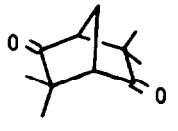
74



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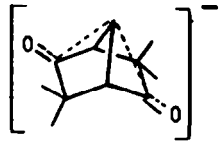

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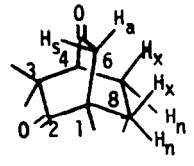

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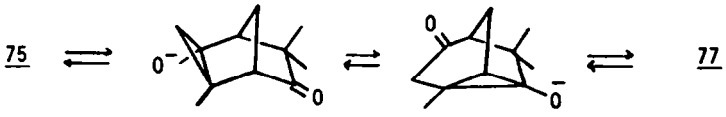
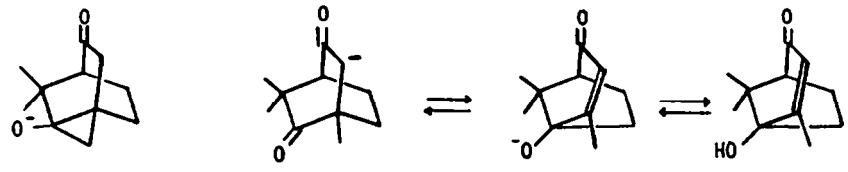


78 79



80 81 82 83

Interestingly, we observed that **77**-d_x obtained from rearrangement of **75** in t-BuOK/t-BuOD at 175° incorporated considerably more deuterium than **75**-d_x and that the bridgehead methyl equilibrated with the deuterium pool. **77** was prepared by rearranging **75** in t-BuOK/t-BuOH and its exchange was studied at a range of temperatures. After 55 h at 175° in 1.14 M t-BuOK/t-BuOD, **77** (0.15 M) incorporated 5.86 atoms of deuterium and was a composite of 0.4% d_0, 0.5% d_1, 1.0% d_2, 3.5% d_3, 10.9% d_4, 22.1% d_5, 28.6% d_6, 20.5% d_7, 8.7% d_8, 2.5% d_9, 0.8% d_{10} and 0.7% d_{11} species. That the deuterium was located at the bridgehead methyl (2.64 D), at C-6 and C-4 (1.63 D) and C-7 and C-8 (1.58 D) was established by curve fitting the Eu(fod)$_3$-shifted ^{2}H NMR spectrum obtained at a **77**:Eu(fod)$_3$ weight ratio of 1.6. In order to determine the amount of exchange at C-4—the signals due to *syn*-6-D, *anti*-6-D and D-4-overlap—**77**-$d_{5.86}$ was treated with NaOH–H_2O-dioxane at room temperature to wash out the deuterium at C-6. The ^{2}H NMR spectrum of **77**-$d_{4.46}$ (**77**-$d_{4.46}$:Eu(fod)$_3$ = 1.6) showed only a small peak at δ 4.6 ($\sim$0.06 D) which corresponded to D-4 and the first-order rate constant was $\sim 3.0 \times 10^{-7}$ s^{-1} at 175° ($k_{185°}$ 6.0×10^{-7}). The ^{2}H NMR spectrum of **77**-$d_{5.86}$ (**77**-$d_{5.86}$:Eu(fod)$_3$ weight ratio = 1.6) showed four major signals at δ 4.3, 2.9, 2.5 and 1.6 and a small shoulder at $\sim \delta$ 1.9 on the peak at δ 1.6. While the signal at δ 4.2 is due to deuterons at C-6 and C-4 and the signals at δ 2.9 and 2.5 are due to the deuterons at C-7 and C-8, the peak at 1.6 corresponds to the deuterated bridgehead methyl. The shoulder at δ 1.9 is due to deuterium in one of the other methyls, most likely the *exo*-3-CH_3. Assuming that $k_{8n} \sim k_{7x}$ and that the peak at δ 2.9 is due to D-8n and D-7x, the apparent rate constant for deprotonation exo to the carbonyl group is $\sim 5.0 \times 10^{-6}$ s^{-1} at 175° ($k_{185°} = \sim 1.0 \times 10^{-5}$ s^{-1}). On the assumption that the signal at δ 2.5 is due to D-7 and D-8 and $k_{8x} \sim k_{7n}$, the apparent rate constant for abstraction endo to the carbonyl group of **77** is $\sim 1.0 \times 10^{-6}$ s^{-1} at 175° ($k_{185°} \sim 2.0 \times 10^{-6}$ s^{-1}). A separate analysis of **77**-$d_{5,16}$ obtained from treatment of **77** (0.17 M) for 50 h in 1.0 M t-BuOD was carried out using high field ^{1}H (400 MHz) and ^{2}H (61.4 MHz) NMR in the absence of Eu(fod)$_3$. The high field ^{2}H NMR of **77**-$d_{5,16}$ showed a doublet centred at δ 2.2 due to *syn*-6-D and *anti*-6-D that overlapped a broad signal at δ 2.15 (tentatively assigned to *endo*-8-D), broad peaks at 1.85 (*exo*-8-D) 1.75 (*endo*-7-D and *exo*-7-D) and a singlet at 0.95 (bridgehead methyl) with a discernible shoulder on the low-field side. A very weak signal was also discernible at $\sim$1.15. From the peak areas it was established that the first-order rate constants at 175° are 3×10^{-6} s^{-1} (6×10^{-6} at 185°), 1.5×10^{-6} (3×10^{-6}), 8.5×10^{-7}(1.5×10^{-6}), 8.5×10^{-7}(1.5×10^{-6}) and 3×10^{-7} s^{-1} (6×10^{-7}) for exchange of *endo*-8-H, *exo*-8-H, *endo*-7-H, *exo*-7-H and the *exo*-3-methyl, respectively, assuming that $k_{endo\text{-}7\text{-}h} \sim k_{exo\text{-}7\text{-}H}$ and the *exo*-3-methyl exchanges faster than the *endo*-methyl.

In order to establish the rate constant for bridgehead methyl exchange, reactions were carried out at 100°.[33] For example, after 25 h in 1.03 M t-BuOK/t-BuOD **77** (0.11 M) incorporates 2.01 deuterium atoms. Deuterium assay by ^{2}H NMR established that deuterium was located at C-6 (1.50 D) and at the bridgehead methyl (0.51 D). The first-order rate constant is *ca.* 2×10^{-6} s^{-1} at 100° and at 185° k *ca.* 8×10^{-4} and establishes that exchange of the bridgehead methyl is *ca.* 42,000 times faster than exchange of the bridgehead methyl of fenchone at 185° (k = *ca.* 1.9×10^{-8} s^{-1}). This fact suggests, even though the rate of exchange of a bridgehead methyl of a bicyclo[2.2.2]octan-2-one has not yet been established, that the C-11 methyl of **77** does not exchange via formation of the β-enolate **80**, but proceeds via a different route. That this is in fact the case is supported by the observation that deuterium is incorporated into **77** in an unusual sequence. If exchange of **77** occurs via β-enolate **80**, then the methyl hydrogens will be replaced sequentially with $d_0 \xrightarrow{k_1} d_1 \xrightarrow{k_2} d_2 \xrightarrow{k_3} d_3 \xrightarrow{k_4} d_4 \xrightarrow{k_5} d_5$ and $k_1 \sim k_2 \gg k_3 \sim k_4 \sim k_5$. Such a scheme would lead to a build-up and then a gradual decrease of d_3 and d_4 species as conversion to **77**-d_5 takes place. However, ms analysis of **77**-$d_{1.68}$ (100°, 5 h) showed that the deuterated dione was a composite of 1.4% d_0, 14.7% d_1, 43.7% d_2, 4.1% d_3, 12.5% d_4, 22.5% d_5 and $< 1\%$ d_6 species and established conclusively that exchange via the β-enolate is not the major exchange pathway. Thus exchange of **77** must occur via an isomer which is in equilibrium with **77** and the rate determining step is conversion of **77** to its isomer rather than exchange. In our view α-enolate **81** rearranges to enone **82** via an alkyl shift. Of course the methyl group of enone **83** undergoes rapid H–D exchange in 1 M t-BuOK/t-BuOD.

2.1.3 *Monocyclic ketones*

There are only two reports of homoenolization of monocyclic ketones. In 1976 Nickon *et al.*[13] studied the homoenolization of 2,2,4,4-tetramethylcyclobutanone (**84**), cyclodecanone-2,2,10,10-d_4 (**85a**), 2,2,10,10-tetramethylcyclodecanone (**85b**), cyclododecanone-2,2,12,12-d_4 (**86a**) and 2,2,12-trimethylcyclododecanone (**86b**). In 0.95 M t-BuOK/t-BuOD after 210 h at 185°, **84** incorporated 0.07 deuterium

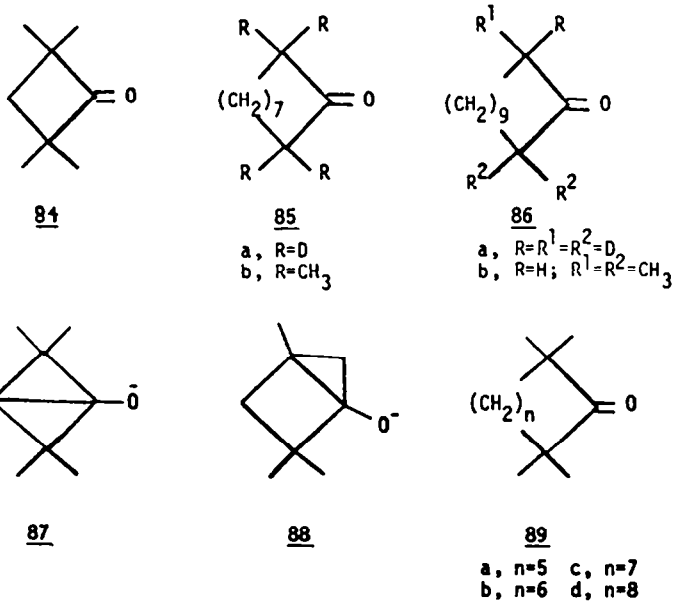
atoms (5% d_1, 1% d_2 species) and underwent substantial Haller–Bauer cleavage. From the MS fragment ion patterns of **84** and **84**-$d_{0.07}$, it was established that the deuterium was approximately equally distributed between the methyl and the methylene positions. On this basis the first-order rate constants are 4×10^{-9} and $\sim 2 \times 10^{-8}\ s^{-1}$ for exchange of the methyls and methylene, respectively, and the homo-ions **87** and **88** are implicated as intermediates.

While the tetradeuterocycloalkanones **85a** and **86a** did not incorporate additional deuterium after 100 h at 185°, deuterium was incorporated into the α-methyl groups of **85b** and **86b**. **85b** incorporated 0.37 deuterium atoms (71% d_0, 22% d_1, 6% d_2, 1% d_3 species) after 97 h in 0.46 M t-BuOK/t-BuOD. On the assumption that exchange occurs predominately at the methyls, the first-order rate constant for methyl exchange is $\sim 1 \times 10^{-7}\ s^{-1}$ at 185°. Exchange of the methyls of **86b** is somewhat slower and after 103 h at 250° in 0.45 M t-BuOK/t-BuOD **86b** incorporated 1.06 deuterium atoms and was a composite of 29% d_0, 48% d_1, 17% d_2, 3% d_3, 1% d_4, 1% d_5 and 1% d_6 species. On the assumption that the multiple labelled species are a measure of the β-enolization (α-enolization is extremely slow) $k \sim 2 \times 10^{-9}\ s^{-1}$ at 185°. No rearrangement products were detected and 9-decalol, the homoenol of **85** did not homoketonize even at 250°.

In 1977 Stothers *et al.*[20] reported on their studies of the homoenolization of $\alpha,\alpha,\alpha',\alpha'$-tetramethyl C_5, C_6, C_7 and C_8 cycloalkanones. In 1 M t-BuOK/t-BuOD at 185° the 6-, 7- and 8-membered ring ketones rearranged very slowly (< 1% in 375 h) to compounds which were not identified. ^2H NMR analysis showed that exchange occurred almost entirely at the methyls and only in the 6- and 7-membered rings was deuterium detected at the methylene sites (< 0.02 deuterium atoms after 200 h at 185°). In the case of **89d** no exchange was observed at C-5 that is transannularly proximate to the carbonyl group even after 375 h at 185°. Based on the assumption that the deuterium incorporated is located only at the methyls the first-order rate constants are $\sim 5 \times 10^{-8}\ s^{-1}$, 3×10^{-8} and $6 \times 10^{-8}\ s^{-1}$ for **89b**, **89c** and **89d**, respectively. The rate constant for methyl exchange of **89a** is $\sim 4 \times 10^{-7}\ s^{-1}$.

2.1.4 *Acyclic ketones*

As is the case for monocyclic ketones, there are only several reports of the homoenolization of acyclic ketones. Cram reported in 1965 that di-t-butyl ketone (**90a**) undergoes H–D exchange in t-BuOK/t-BuOD at 230°, but made no mention that **90a** rearranged.[34] Subsequently Rampersad and Stothers[35] published their work on the homoenolization of **90a**, 5,5,7,7-tetramethylundecan-6-one (**90b**), 5,5,7-trimethylundecan-6-one (**90c**) and 2,2,5-trimethylhexan-3-one (**91a**). After 150 h in 0.7 M t-BuOK/t-BuOH at 185° **90a** (0.20 M) underwent 20% rearrangement to **91a** with $k = 2.5 \times 10^{-8}\ s^{-1}$ for each hydrogen exchanged. In t-BuOK/t-BuOD H–D exchange occurs three times as fast as rearrangement. Homoenolate **92a** is a mandatory intermediate. After very long reaction times, less than 1% of 2,6-dimethylheptan-4-one, the product of β-enolization on both sides of the carbonyl group. was formed. Separate H–D exchange experiments on **91a** established that α- and β-enolizations occur at comparable rates. In 0.7 M



84

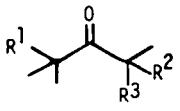
85
a, R=D
b, R=CH_3

86
a, R=R^1=R^2=D
b, R=H; R^1=R^2=CH_3

87

88

89
a, n=5 c, n=7
b, n=6 d, n=8

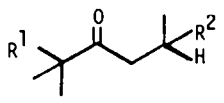


90

a, $R^1=R^2=R^3=CH_3$

b, $R^1=R^2$=n-butyl; $R^3=CH_3$

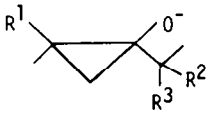
c, $R^1=R^2$=n-butyl; R^3=H



91

a, $R^1=R^2=CH_3$

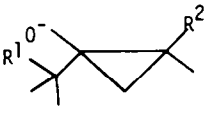
b, $R^1=R^2$=n-butyl



92

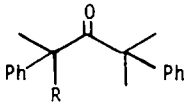
a, $R^1=R^2=R^3=CH_3$

b, $R^1=R^2$=n-butyl; $R^3=CH_3$



93

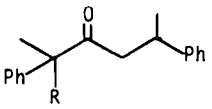
a, $R^1=R^2$=n-butyl



94

a, R=CH_3

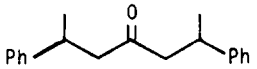
b, R=H



95

a, R=CH_3

b, R=H



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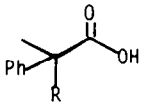
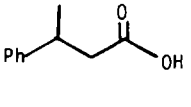


97

a, R=CH_3

b, R=H



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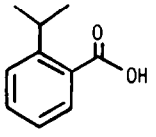

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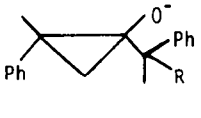
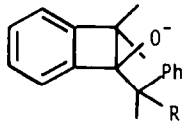


100

a, R=CH_3

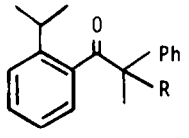
b, R=H



101

a, R=CH_3

b, R=H



102

a, R=CH_3

b, R=H

t-BuOK/t-BuOH after 70 h at 185°, undecanone **90b** was converted (10%) into **91b** and $k \sim 3.5 \times 10^{-8}$ s^{-1} on a per hydrogen basis. In deuterated medium **90b** exchanged only at the methyls and $k = ca.\ 1 \times 10^{-7}$ s^{-1}. Once again exchange is three times as fast as rearrangement and the homoion **92b** is a viable intermediate. In 0.7 M t-BuOK/t-BuOD **90c** underwent α- and β-enolization at comparable rates and no isomerization was observed. The β-enolates **92b** and **93** were implicated as intermediates.

Recently, Dyllick-Brenzinger and Stothers[36] described a study of the homoenolization of 2,4-dimethyl-2,4-diphenylpentan-3-one (**94a**) and 2-methyl-2,4-diphenylpentan-3-one (**94b**). Both ketones underwent H-D exchange, rearranged and cleaved to carboxylic acids. The pentane extract obtained from the reaction of **94a** (0.35 M) was comprised of **94a** (33%), **95a** (30%), **96** (30%) and 7% of an unidentified component which is isomeric with **94a**. The acidic fraction (28% yield) was composed of **97a** (25%), **98** (40%) and **99** (35%). Similar treatment of **94b** 223 h led to a neutral fraction (55% recovery) containing **94b** (21), **95b** (57%), **92a** (17%) and small amounts (*ca.* 5%) of unidentified material. The acidic fraction was composed of **97a** (15%), **97b** (24%), **98** (53%) and **99** (8%). In t-BuOD unrearranged **94a** incorporated 3.5 and 5.3 atoms of deuterium per molecule after 16 h and 83 h, respectively. Deuterium assay by ^2H NMR established that deuterium was located only on the aromatic ring, with no detectable signals from methyl deuterons. Thus homo-ions **100a** and **100b** ring open to yield the tertiary benzylic anions rather than the primary anions and this accounts for the fact that no deuterium was detected in

the methyls of **97a**. The isolation of acid **99** implicates the intermediacy of γ-enolates **101a** and **101b** and ketones **102a** and **102b**.

2.1.5 *Acyclic diketones*

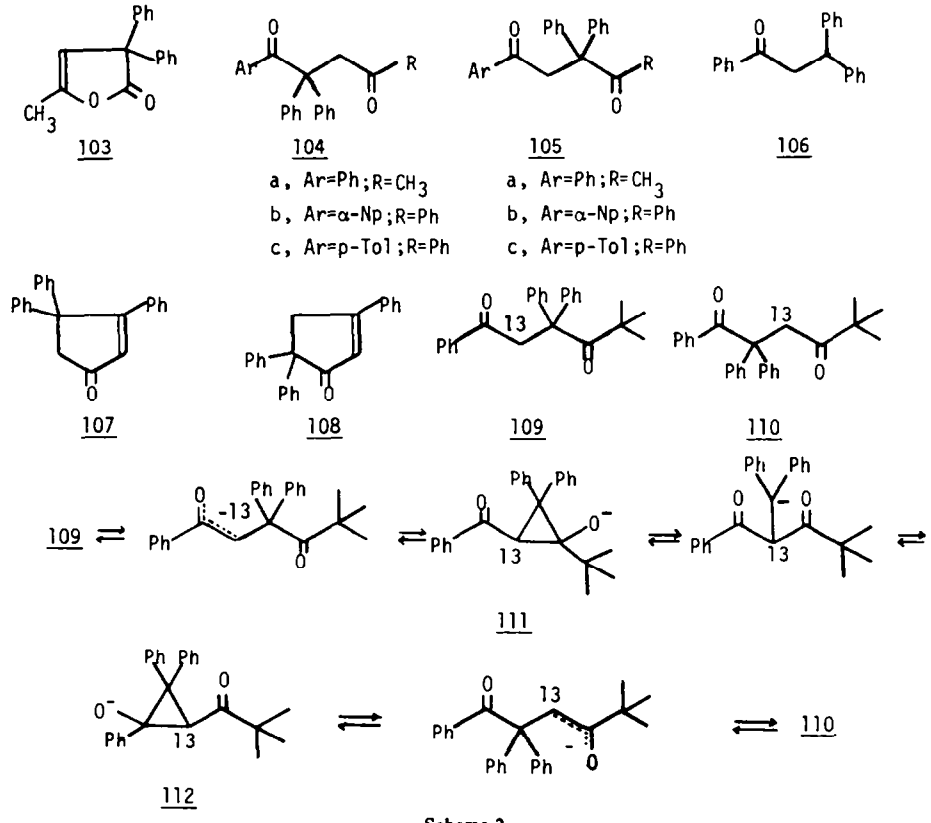
As a consequence of the finding that 4-hydroxy-4-methyl-2,2-diphenyl-3-butenoic acid lactone (**103**) yields 1,3,3-triphenylpentane-1,4-dione (**104a**) in addition to **105** and **106** when treated with PhLi followed by aqueous work-up and **104** yields enones **107** and **108** when treated with CH_3ONa, Yates and Betts[37,38] studied the rearrangement of 5,5-dimethyl-1,3,3-triphenyl-1,4-hexanedione-2-^{13}C (**109**) in CH_3ONa/ether. That **109** yields only **110** establishes that rearrangement proceeds via homoenolates **111** and **112** (Scheme 2) rather than by sequential 1,2-phenyl shifts. Further support for the mechanism was obtained from equilibration studies. **104b** and **105b** when reacted separately in CH_3ONa/ether at ambient temperature yield an equilibrium mixture of *ca.* 20% **104b** and 30% **105b**; **104c** and **105c** yield an equilibrium mixture of *ca.* 38% **104c** and 62% **105c**.

2.2 *Base induced cleavage of esters and trimethylsilyl ethers*

2.2.1 *β-Enolates.*

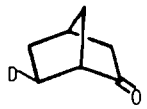
A second useful route to homoenolate anions involves base induced cleavage of homoenol acetates prepared by Bayer–Villiger oxidation of ketones. The first study where a homoenol acetate was used to generate a homoenolate anion was reported by Nickon *et al.* in a preliminary communication[39] in 1963 and followed by a full paper in 1966.[40] Base cleavage of tricyclo[2.2.1.$0^{2,6}$]heptan-1-ol acetate (**113**) in t-BuOK/t-BuOD, CH_3OK/CH_3OD, CH_3OK/CH_3OD/DMSO (1:1) or $(CH_3)_4N^+OD/CH_3OD$ yields exclusively bicyclo[2.2.1]heptan-2-one-6-d (**114**) in which the deuterium is >94.5% stereochemically pure exo. Certainly, homo-ion **115** is an intermediate.

In 1972 Joshi and Warnhoff[41] in studying the specific deuteration of camphor, homoketonized 2,3,3-trimethyltricyclo[2.2.1.$0^{2,6}$]heptan-1-ol acetate (**116**) (acetoxyapocyclene) in KOD/CH_3OD and obtained camphor-6-d (**117**), the product of the ring opening β-enolate **118**. Although the stereochemistry of the deuterium was not determined quantitatively, the authors estimated from the loss of coupling that the deuterium was >90% exo.



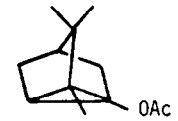
Scheme 2.

113



114

115



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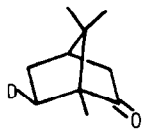
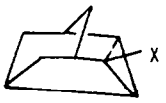


117

118



119

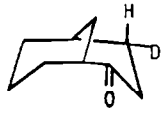
a, X=OAc

b, X=O⁻

120

a, X=OAc

b, X=O⁻



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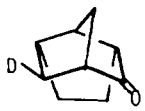


122

In 1975 Nickon *et al.*[42] in continuing their studies on base induced homoketonization of homoenols, reported on a study of the homoketonization of 2-acetoxytriaxane (**119**) and 2-acetoxydeltacyclene (**120**) in CH_3ONa/CH_3OD and t-BuOK/t-BuOD at 25°. Substrate **119** yielded exclusively noradamantan-2-one-4-d (**121**) with 82–85% and 72–79% inversion, respectively, at the electrofugal center. Compound **120a** when ketonized in CH_3ONa/CH_3OD at 25°, yielded brendan-2-one (**122**) rather than brexan-2-one with the deuterium being 95–100% stereochemically pure exo at C-6. Beta-enolates **119b** and **120b** must be considered as intermediates in the reactions.

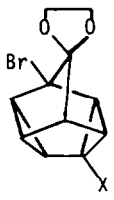
As a continuation of their work on the homoketonization of pentacyclic alcohols and acetates,[43] Klunder and Zwanenburg[44] studied the base induced homoketonization of homocuneane acetates **123a**, **124a** and **125a** to probe the effect of structure on the steroechemistry of the S_E reaction. Substrate **123a** reacts instantaneously in CH_3ONa/CH_3OD at 25° to yield ketones **126** and **127** in which the deuterium, as shown by ^1H NMR—$Pr(fod)_3$ studies, was >96% endo. Similarly **124a** yields ketone **128** and again the S_E reaction proceeds with retention of configuration since the deuterium is >95% endo at the electrofugal carbon. Compound **125a**, as did **123a**, yields two monodeuteroketones, **129** and **130**, in which the deuterium is >95% stereochemically pure endo. The β-enolates **123b**, **124b** and **125b** are implicated as intermediates in the homoketonizations.

2.2.2 *γ-Enolates*

In 1960 Hurst and Whitham[45] reported that hydrolysis of the 3,5-dinitrobenzoate **131a** of *exo*-6-hydroxy-2,7,7-trimethylbicyclo[3.1.1]heptan-2-ol (**131b**) (chrysanthenol) in refluxing 5% methanolic KOH yielded 4-formyl-1,3,3,trimethylcyclohexene (**132**). The reaction must proceed via ketonization of γ-enolate **131c**.

In publications in 1971 and 1973 Klunder and Zwanenburg[46,47] reported their interesting work on the base induced homoketonization of cubyl, homocubyl and 1,3-bishomocubyl acetates. In CH_3ONa/CH_3OD at 25°, homocubyl acetates **133a** and **134a** yielded half-cage ketones **135** and **136**, respectively, via homo-ions **133b** and **134b**. The deuterium at the electrofugal carbon was >96% stereochemically pure endo. While homoketonization of **133a** and **134a** proceeded cleanly to yield a single product in each case, cubyl acetate **137a** in CH_3ONa/CH_3OH or KOH/CH_3OH yielded a mixture of unidentified products.

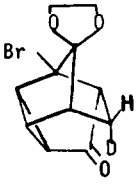
Miller and Dolce[48] have shown that treatment of homocubyl di-trimethylsilyl ether **138** with CH_3Li at −15° followed by quenching with a cold saturated NH_4Cl solution yielded an unstable product **139**. γ-enolate **140a** formed by elimination or substitution at silicon is a logical intermediate in the transformation, and, in fact, is trapped by ethylation with triethyloxonium tetrafluoroborate as the mixed ether **140b**.



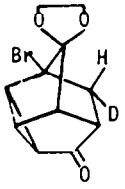
123
a, X=OAc
b, X=O⁻

124
a, X=OAc
b, X=O⁻

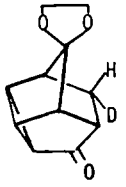
125
a, X=OAc
b, X=O⁻



126



127



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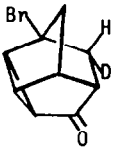
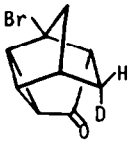
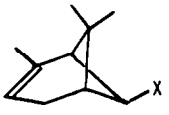


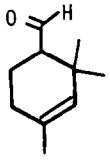
129



130



131
a, X=3,5-DNB
b, X=OH
c, X=O⁻



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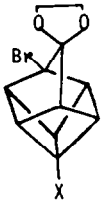
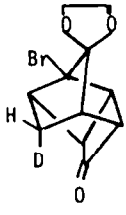
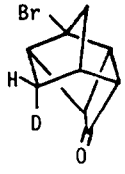


133
a, X=OAc
b, X=O⁻
c, X=OH

134
a, X=OAc
b, X=O⁻

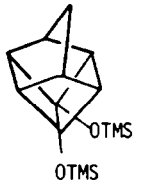


135

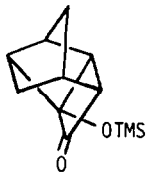


136

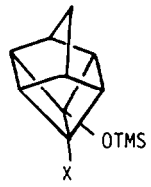
137
a, X=OAc
b, X=OH



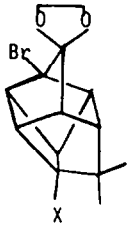
138



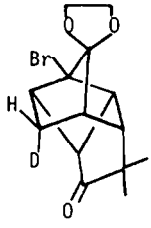
139



140
a, X=O⁻
b, X=OC$_2$H$_5$



141
a, X=formate
b, X=O⁻
c, X=OH



142

2.2.3 *δ-Enolates*

Formate **141a** of 1,3-bishomocubyl alcohol **141c** is less reactive than the homocubyl systems and refluxing CH_3ONa/CH_3CH_2OD was required for homoketonization to occur at a significant rate.[42] Half-cage ketone **142** formed via homo-ion **141b** is the sole product, and the deuterium is >96% stereochemically pure endo at the electrofugal carbon.

2.3 *Base induced cleavage of cycloalkanols*

2.3.1 *Cyclopropanols*

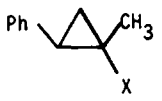
Cycloalkanols are useful precursors of homoenolate ions only if the alcohols are sufficiently stable to be easily prepared and handled. Simple substituted cyclopropanols not incorporated into strained ring systems are readily available[49] and are useful sources of β-enolates. In fact, the first homoketonization of a β-enol was discovered by Stahl and Cottle[50] who observed that cyclopropanol when dried over K_2CO_3 yields 2-methyl-2-pentenal, the aldol product of propanal. Up to the present there have been a considerable number of reports documenting the chemistry of homoenolates generated from the corresponding cycloalkanol by proton abstraction from oxygen.

In 1966 DePuy *et al.*[51] reported that *cis*-1-methyl-2-phenylcyclopropanol (**143**) yielded exclusively deuterated 4-phenyl-2-butanone (**144**) in 0.1 M NaOD/D_2O/dioxane (50:50). By using optically active **143a** they showed that homoketonization occurs with inversion of configuration at C-4.

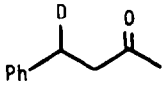
In 1966 Wharton and Bair[52] published their work on the base induced homoketonization of *exo*-(**145a**) and *endo*-7-hydroxy-1,6-dimethylbicyclo[4.1.0]heptane (**145b**). In 1 M t-BuOK/t-BuOH and 1 M $HOCH_2CH_2ONa/HOCH_2CH_2OH$ at 57° **145a** and **145b** yielded the *cis* and *trans*-1,2-dimethyl-cyclohexylcarboxyaldehydes **146** and **147** as products. Wharton and Bair also established that while **145a** and **145b** homoketonized in t-BuOK/t-BuOH with >90% retention of configuration, in $HOCH_2CH_2ONa/HOCH_2CH_2OH$ **145a** opened with 70% inversion and **145b** with 40% inversion.

In 1972 Denis and Conia[53] prepared bis-trimethylsilyl ether **148a** via cyclopropanation of the corresponding bis-trimethylsilyvinyl ether and hydrolyzed it to the corresponding diol **148b** in refluxing CH_3OH or refluxing aqueous acetone. In 0.1 M NaOH at 100° **148b** slowly isomerized to 1-ethyl-2-oxo-cyclobutanol (**149**). Presumably the reaction proceeds via a sequence which includes as intermediates, β-enolate **148c**, ketone **150a** and β-enolate **150b** that rearranges to **149** faster than it ring opens to hexane-3,4-dione.

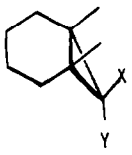
In a subsequent publication Conia and Girard[54] prepared a series of siloxycyclopropanes **152a–152c** and **155a–155d** from aldehydes **151a–151c** and ketones **154a–154d**, respectively, and hydrolyzed the ethers in refluxing aqueous-alcoholic NaOH. The intermediate cycloalkanols which homoketonize via



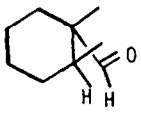
143
a, X=OH
b, X=O⁻



144



145
a, X=OH; Y=H
b, X=H; Y=OH



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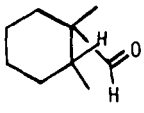
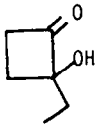
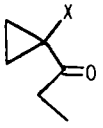


147

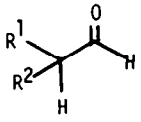
148
a, X=Y=OTMS
b, X=Y=OH
c, X=OH; Y=O⁻



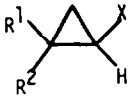
149



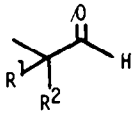
150
a, X=OH
b, X=O⁻



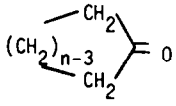
151
a, R^1=CH_3; R^2=H
b, R^1=R^2=CH_3
c, R^1=n-pentyl; R^2=H



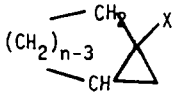
152
a, R^1=CH_3;R^2=H;X=OTMS
b, R^1=R^2=CH_3;X=OTMS
c, R^1=n-pentyl;R^2=H;X=OTMS
d, R^1=CH_3; R^2=H, X=O⁻
e, R^1=R^2=CH_3; X=O⁻
f, R^1=n-pentyl; R^2=H; X=O⁻



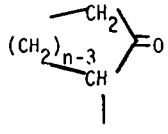
153
a, R^1=CH_3;R^2=H
b, R^1=R^2=CH_3
c, R^1=n-pentyl;R^2=H



154
a, n=5
b, n=6
c, n=7
d, n=8



155
a, n=5; X=OTMS
b, n=6; X=OTMS
c, n=7; X=OTMS
d, n=8; X=OTMS
e, n=5; X=O⁻
f, n=6; X=O⁻
g, n=7; X=O⁻
h, n=8; X=O⁻



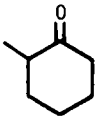
156
a, n=5
b, n=6
c, n=7
d, n=8

homoenolates **152d–153f** and **155e–155h** yielded methylated aldehydes **153a–153c** (> 90%), and, except in the case of ether **155a** where cyclohexanone (*ca.* 10%) accompanied the formation of 2-methylcyclopentanone, α-methylcycloalkanones **156a–156d** (> 90%). Homoketonization of trimethylsiloxycyclopropanes **158** and **159a**, obtained by cyclopropanation of trimethylsilyl enol ethers derived selectively from 1-methylcyclohexanone (**157**) gave 2,2-dimethylcyclohexanone (**160a**) and 2,6-dimethylcyclohexanone (**160b**), respectively, in 95% yields.

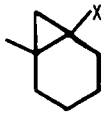
In an interesting extension Conia and Girard homoketonized trimethylsiloxycyclopropane **161a** derived from the TMS enol ether of testosterone and obtained 4-methyltestosterone (**162**). It is interesting to note that β-enolate **161b** yields **162** rather than ring expands to form an allylic anion intermediate.

Wharton and Fritzberg[55] have found that trans-2,3-di-n-butyl-2,3-dimethylcyclopropanol (**163**) and tricyclo[4.4.1.$0^{1,6}$]undecan-11-ol (**164**) homoketonize with almost complete retention of configuration in t-BuOK/t-BuOH, yielding **165** and **166**, respectively. Considerable inversion was observed in $HOCH_2CH_2ONa/HOCH_2CH_2OH$. These results were in accord with the previously recognized influence of solvent; low dielectric, non-dissociating solvents favour retention and high dielectric dissociating solvents afford substantial inversion.

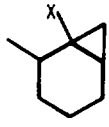
Miller and Dolce, in a series of communications in 1973[48] and 1977[56] reported interesting studies on the homoketonization of pentacyclo[4.3.$0^{2,5}0^{3,8}0^{4,7}$]nonane-4,5-diol **167a** and its bis-trimethylsilyl ether **167b**. Hydrolysis of bis-trimethylsilyl ether **167b** in CH_3OH at ambient temperature which, in fact, is a general route to the corresponding cycloalkanols, gave diol **167a**. Then **167a** homoketonized to dione **168a** in 50–60% yield in 0.5 M CH_3ONa/CH_3OH at 25°C. When the homoketonization was carried out in CH_3ONa/CH_3OD the dideuterio ketone **168b** was obtained. It was proposed that γ-enolate **167c** ketonizes with retention of configuration and the resultant ketol **169a** rearranges via γ-enolate **169b** to α-ketohomoenolate **170a**, which ketonizes with inversion configuration at the electrofugal center. To provide support for this proposal, Miller and Dolce treated **167b** with CH_3Li at −15°, quenched the



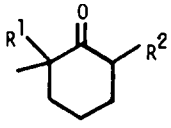
157



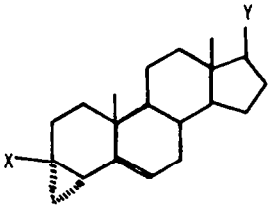
158
a, X=OTMS
b, X=O⁻



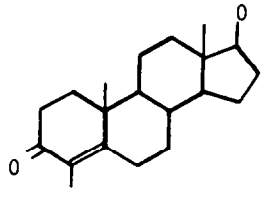
159
a, X=OTMS
b, X=O⁻



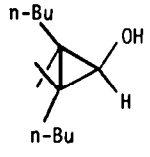
160
a, R^1=CH_3; R^2=H
b, R^1=H; R^2=CH_3



161
a, X=Y=OTMS
b, X=O⁻; Y=OH

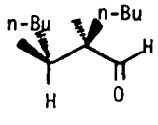


162



163

164



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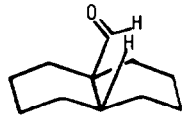


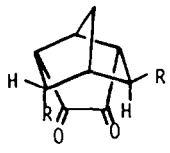
166

167

a, X=Y=OH

b, X=Y=OTMS

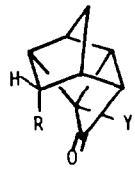
c, $X=O^-$; Y=OH



168

a, R=H

b, R=D

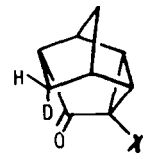


169

a, R=D; Y=OH

b, R=D; $Y=O^-$

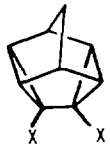
c, R=D; Y=OTMS



170

a, $X=O^-$

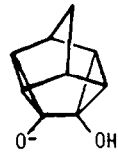
b, X=OTMS



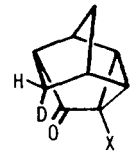
171

a, X=OTMS

b, X=OH



172



173

a, X=OH(D)

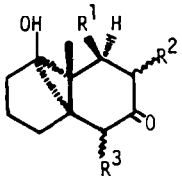
b, $X=O^-$

solution with ND_4Cl/D_2O, rearranged thermally unstable **169c** to the ketotrimethylsilylether **170b**. Homoketonization of **170b** in CH_3ONa/CH_3OD gave dideuterioketone **168** isolated from treatment of **167a** in deuterated medium and therby provided support for their proposal.

In an interesting extension of their work the authors obtained pentacyclic diol **171b** by hydrolysis of bistrimethylsilyl ether **171a** in methanol at 25°. Homoketonization **171a** or **171b** in CH_3ONa/CH_3OH and CH_3ONa/CH_3OD yielded **168a** and **168b**, respectively, the same diones obtained from diol **167a**. In this case homoketonization of two β-enolates proceeds with opposite stereochemistry. Presumably **172** opens with retention and **173** opens with inversion at the electrofugal center. That the first homoketonization proceeds with retention of configuration is consistent with Zwanenberg's observation that homocuneanes **123a**, **124a** and **125a** homoketonize with retention.

In 1977 Reusch *et al.*[57] described their work on the base induced homoketonization of 6-methyl-7-hydroxytricyclo[4.4.0.$0^{1,7}$]decan-3-one (**174**) and several of its methyl derivatives **174b**, **174c** and **174d**. Substrate **174** was transformed under a variety of basic conditions to bicyclic isomers having spiro[5.4]decane, decalin or perhydroindane skeletons. In $KOH/CH_3OH/H_2O$ at 25° **174a** yields **175** (1%), **176** (20%) and **178** (79%). In t-$BuOK/(CH_3)_2SO$ only **178** was detected although the yield was low. Interestingly, in THF/HMPA at 25° with 20 equivalents of guanidine **174a** homoketonized to **176** (20%), **178** (79%) and a trace of **177**. In the presence of 0.01 equivalents of guanidine the product distribution was entirely different; **175** (76%), **176** (8%) and **177** (15%). The spiro[5.4]-skeleton also predominated (80%) when the salt of the α-enolate generated in NaH/benzene was quenched in CH_3OH. The results can be rationalized on the basis that β-enolates **179** and **180** are in equilibrium.

Homoenolate **179** generated by NaH in benzene/DMF can be trapped by alkylation with CH_3I to yield methyl ether **181a**. The β-enolates can also be trapped by acetylation. When **174a** was treated with lithium diisopropylamide at 5° and quenched with acetic anhydride, acetate **181b** was the major product (97%). When the experiment was repeated at ambient temperature in the solvent mixture glyme/HMPTA/TMEDA the product distribution depended on the quench time. After 45 min, acetates **181b** (72%) and **182** (18%) were the major products. When the reaction was quenched after 90 min the products were **181b** (40%), **181** (30%), **178** and an enol acetate (11%). That there is only a moderate increase in the amount of acetate **182** with time indicates that the conversion of β-enolate **179** into **180** is a relatively slow process. To determine whether β-enolate **180** isomerizes readily to **179**, acetate **182** was homoketonized in KOH/CH_3OH. That **178** was the major product (99%) and $< 1\%$ **176** was formed establishes that ring-opening protonation is faster than rearrangement.



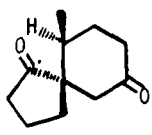
174

a, $R^1=R^2=R^2=H$

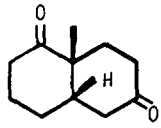
b, $R^1=CH_3$; $R^2=R^3=H$

c, $R^1=H$; $R^2=CH_3$ $R^3=H$

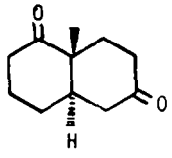
d, $R^1=R^2=H$; $R^3=CH_3$



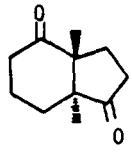
175



176



177



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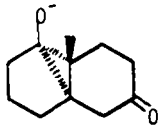
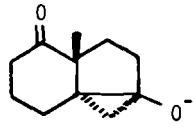
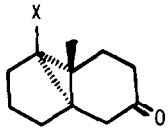


179



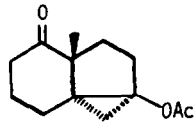
180



181

a, $X=OCH_3$

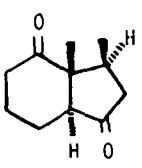
b, X=OAc



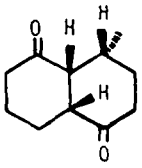
182

In a subsequent paper Yordy and Reusch[58] reported on the effect of a methyl substituent on the homoketonization of **174a**. Homoketonization of the 5-β-methyl analog **174b** in KOH/CH_3OH yielded predominantly dione **183** (89%). Its 5-α-methyl epimer yielded the decalin derivative **184** (29%) and the twistyl ketol **185** (71%). Base induced homoketonization of a mixture of 4-α- and 4-β-methyl epimers **174c** yielded a mixture of epimers of the decalin (35%) and perhydroindene (40%) skeletons **186** and **187** as the major products. A mixture of 2-α- and 2-β-methyl epimers **174d** was homoketonized in base to a mixture consisting mainly of **188** (6%), **189** (48%) and **190** (24%). The authors rationalized the effect of the methyl substituent (*vide infra*) on the product distribution on the basis of the equilibrium involving conformers **C1** and **C2** in which a methyl group can be located at C-2, C-4 and C-5.

Recently, Patel and Stothers[59] prepared a series of trimethylsiloxycyclopropanes **191a–191d** by cyclopropanation of TMS enol ethers derived from a number of 3-methyl bicyclic ketones and hydrolyzed the TMS ethers in dilute acid to the corresponding cyclopropanols **192a–192d**. Ketones **194a–194d** and **195a–195d** were obtained by ketonization of the cyclopropanols in t-BuOK/t-BuOH. In a related study Stothers *et al.* prepared cyclopropanols **197a–197e** by hydrolysis of the corresponding trimethylsilyl ethers **196a–196e** and homoketonized the cyclopropanols in t-BuOK/t-BuOH at 25° and at reflux (82°, 10 min). They observed both ring expansion to **199a** and **199e** and opening to the α-methyl ketones **200a–200e**. They also showed that **201a** homoketonizes to ketones **202** and **203** via β-enolate **201b**. The stability of the putative carbanion, ease of protonation and strain effects were considered to be the factors which controlled the course of the homoketonizations.



183



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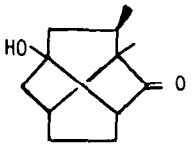

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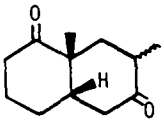
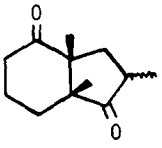


186



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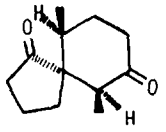

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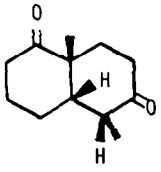

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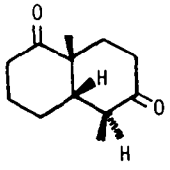

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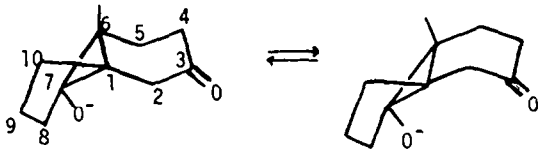


C1 C2

2.3.2 *Cyclopropenols*

Several examples of homoketonization of cyclopropenoxides have been reported. The highly strained methylenecyclopropene **204** cleaves to propargyl ketone **206** under mild conditions presumably via cyclopropenoxide **205**.[61] Ring opening can be concerted or stepwise as depicted by **207** and **208**, respectively.

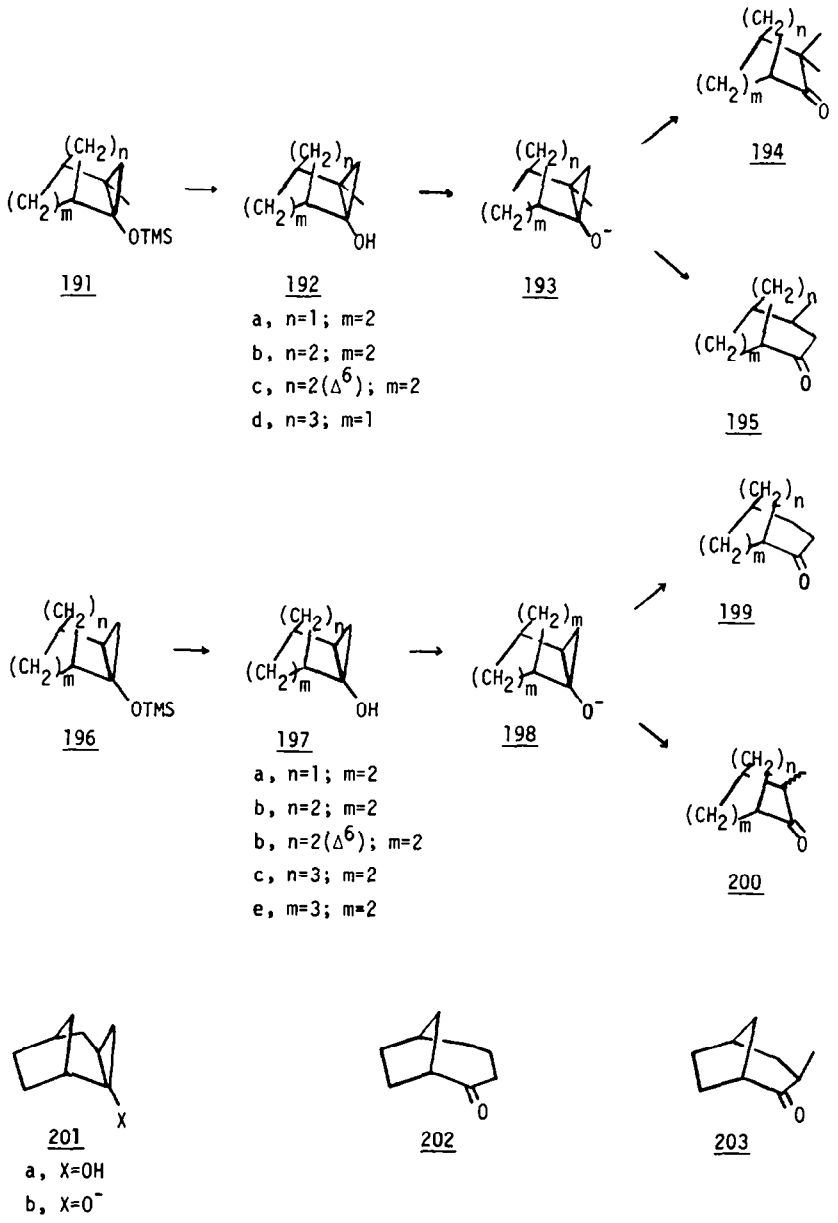
Cyclopropenol **209** was converted to **210** readily in CH_3ONa/CH_3OH under mild conditions.[62] The unsaturated β-enolate **211** can ring/open to **212** which cyclizes, or it may rearrange directly to **210** via a semibenzylic acid-like rearrangement. It is interesting to note that homoenolate equivalents of the type **213** have been prepared and used as synthons.

2.3.3 *Cyclobutanols*

In 1972 Padwa and Eisenberg[63] reported on the base induced homoketonization of 7-phenyltricyclo[3.2.0.$0^{2,6}$]heptan-7-ol (**214**) in $CH_3OK/CH_3OH(D)$ at 25°. Alcohol **214** was extremely labile in CH_3OK/alcohol solutions (0.5 h) and the sole product in deuterated medium was *exo*-5-benzoylbicyclo[2.1.1]hexane-*syn*-6-d (**215**), the product of cleavage of the γ-enolate with >98% retention of configuration at C-6.

Klunder and Zwanenburg, in two papers[46,47] described the homoketonization of polycyclic bridgehead alcohols **133c** and **137b** in conjunction with the homoketonization of the corresponding acetates. In both cases the results obtained were identical to base induced homoketonization of the acetates.

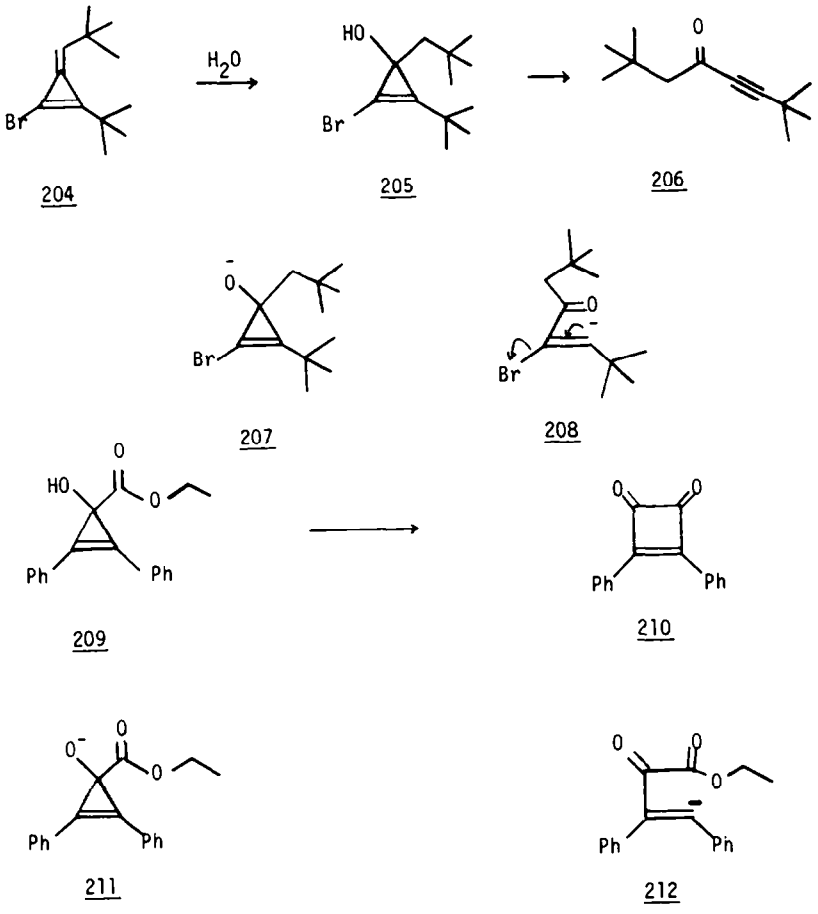
Caubere *et al.* have reported on the $NaNH_2$ induced homoketonization of a series of alkylated 7,8-benzobicyclo[4.2.0]oct-7-en-1-ols (**216a**) and benzobicyclo[5.2.0]non-8-en-1-ols (**217a**) in aprotic solvents (DME, HMPA, THF) at temperatures of 20–60°.[64] If a methyl group was located at C-6 of the



[4.2.0]-system or C-7 of the [5.2.0]-system γ-enolate ketonization was specific yielding the corresponding α-phenylcycloalkanones **218a** and **218b** regardless of whether DME or HMPA was used. When C-6 of **216a** or C-7 of **217a** bears a hydrogen, products of cleavage of both strained cyclobutene bonds—**218a** and **219a** from the [4.2.0]-system and **218b** and **219b** from the [5.2.0]-system—were observed except in HMPA where in most cases ring-opening occurred specifically in the direction of the 2,3-benzocyclenones **219a** and **219b**.

In a subsequent publication Caubere *et al.*[65] described a general synthesis of benzocyclenones as a continuation of their studies of the condensation of benzyne with α-enolates.[66] Addition of α-enolates of alicyclic ketones followed by ketonization of the γ-enolates gave benzocyclanones as well as α-phenylcycloalkanones (Scheme 3), but the benzocyclanones predominated (70–80%). Thies and Shih[67] have prepared 2,3-benzocyclooct-2-en-1-one by a modification of Caubere's reaction.

In 1976 Crow and Borden[68] determined the stereochemistry of the homoketonization of birdcage alcohol **220a** in 1 M t-BuOK/t-BuOD at 100° and 1 M $DOCH_2CH_2OK/DOCH_2OD$ at 200°. From analysis of Eu(fod)$_3$ shifted ^1H NMR spectra of the endo alcohols derived from the half-cage ketone **221**, they established that homoketonization of **220** in t-BuOD and $DOCH_2CH_2OD$ proceeds with 95 ± 3% and 90 ± 3% retention of configuration, respectively. It is interesting to note that Winstein and Howe[28]



Scheme 3.

speculated earlier that homoketonization of **220** should proceed with inversion based on a limited number of examples of homoketonization of cyclopropanols.

Fukunaga and Clement[69] have reported that **220a** homoketonizes in 0.54 M t-BuOK/t-BuOH at 250° (4 h) to a 96:4 mixture of **61** and **59b**.

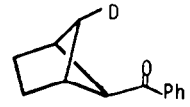
Dadson and Money[70] recently reported the preparation and homoketonization of **222**, the γ-homoenol of camphor. Treatment of **222a** with t-BuOK/t-BuOD at 80° for 16 h provides 8-deuteriocamphor **223**). Apparently **222a** also homoketonized in NaH–HMPA at 80° and gave camphor in 98% yield after aqueous work up. The homoketonization of γ-enolate does not occur at a significant rate below 40° and, in fact, **222b** when generated by NaH in HMPA in the presence of methyl iodide or benzyl chloride yielded the corresponding ethers.

2.3.4 *Cyclopentanols*

In 1965 Corey and Lowry[71] reported on the stereochemistry of the cleavage of cyclic sulfone **224** of unidentified configuration at the carbon bearing hydroxyl in aqueous ethanolic NaOH. Sulfone aldehyde **225** which is the initial product undergoes further cleavage. The high degree of inversion observed for the cleavage of **224** contrasts the high degree of retention found for cleavage of open-chain sulfones.

In 1968 Hoffman and Cram[72] described the base-catalyzed epimerization, racemization, and cleavage of optically active diastereomeric 1,2-dimethyl-2-phenylcyclopentanols **226a** and **227a**. In 0.209–0.247 M t-BuOK/t-BuOH solution at 135° optically pure **226a** yielded 35% of **226a** (99.4% optical purity), 2.4% of

214
a, X=OH
b, X=O⁻



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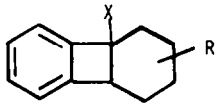
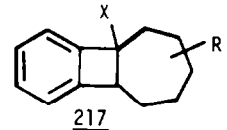
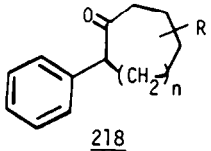


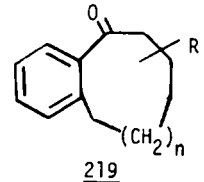
216
a, X=OH
b, X=O⁻



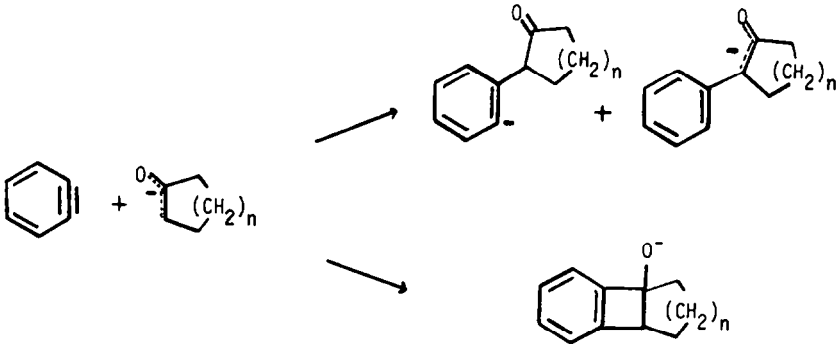
217
a, X=OH
b, X=O⁻

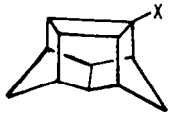


218
a, n=0
b, n=1

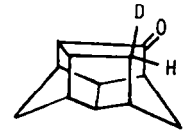


219
a, n=0
b, n=1





220
a, X=OH
b, X=O⁻



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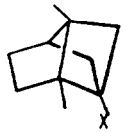
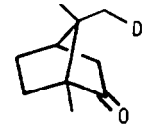


222
a, X=OH
b, X=O⁻



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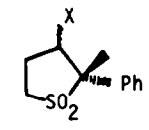
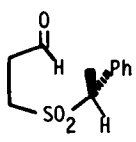


224

a, X=OH
b, X=O⁻



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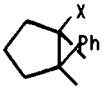
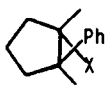


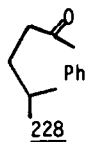
226

a, X=OH
b, X=O⁻



227

a, X=OH
b, X=O⁻



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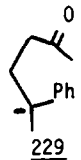

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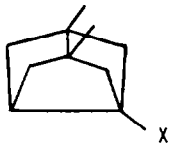
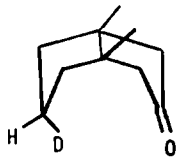


230

a, X=OH
b, X=O⁻



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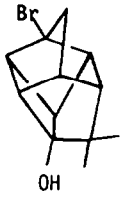

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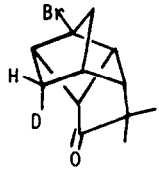


233

227a (90% optical purity) and 20% (+)-(S)-6-phenyl-2-heptanone **228** (61% optical purity). The cleavage reaction via δ-enolate **228b** proceeded with 61% retention of configuration at the benzyl carbon. Optically pure **227a** yielded 36.4% of **227a** (99.9% optically pure), 2.5% **226a** (96% optically pure) and 8% of (−)-(R)-6-phenyl-2-heptanone (**228**) (56% optically pure) indicating that cleavage of **227b** proceeded with 56% retention of configuration. They interpreted the results on the basis of trimethylene-ketocarbanion intermediates of the type **229** whose fates are determined by the relative rates and directions of rotation of the phenyl- and oxygen-carrying carbons, the rate of protonation of the benzyl carbon, and the rate of addition of the carbanion to the carbonyl group.

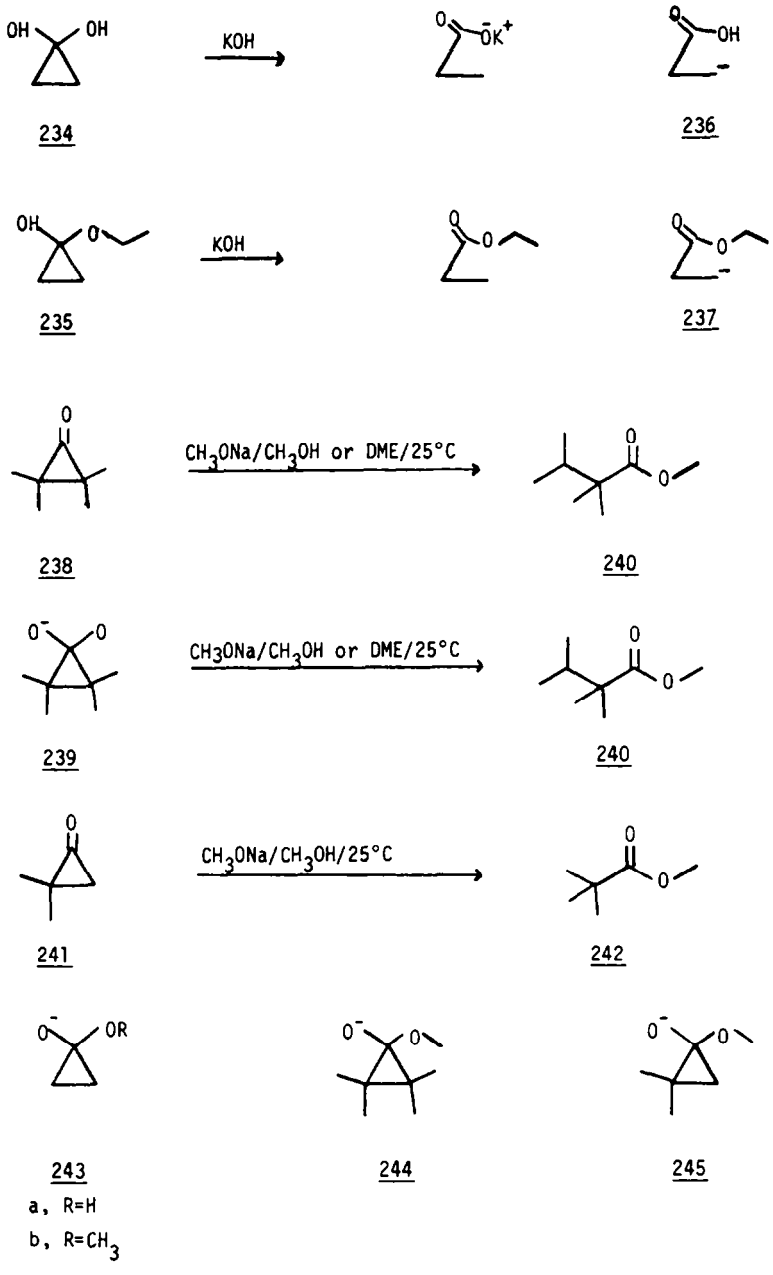
Borden *et al.*[73] reported that 3,7-dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol (**230**) homoketonizes in t-BuOK/t-BuOD (70°) and $DOCH_2CH_2OK/DOCH_2CH_2OD$ (175°) to yield exclusively 1,5-dimethyl-bicyclo[3.3.0]octan-3-one-7-endo-d (**231**) the product of cleavage with retention of configuration at C-7.

Klunder and Zwanenburg[47] reported the homoketonization of the bishomocubyl alcohols **141c** and **232** which are much less reactive than the homocubyl bridgehead alcohol **133c**. In fact, the reactions must be carried out in refluxing $CH_3CH_3OH(D)$ rather than in $CH_3OH(D)$ at ambient temperature for the homoketonization to proceed at a significant rate. In deuterated medium **141c** yielded **142** and **232** yielded ketone **233** as the sole product.

2.4 *Addition of nucleophiles to cycloalkanones*

2.4.1 *Cyclopropanones*

Cyclopropanone hydrate (**234**) and cyclopropanone ethyl hemiketal **235** were the first cycloalkanols to be homoketonized.[74] In potassium hydroxide solutions **234** yielded potassium propionate and **235**



yielded ethyl propionate. It is interesting to note that the homoenolate equivalents **236** and **237** have been developed and used as synthons (see Section 6).

Turro and Hammond[75] have shown that tetramethylcyclopropanone **238** or its methyl hemiketal **239** yielded predominately methyl ester **240** in base. 1,1-Dimethylcyclopropanone (**241**) was cleaved by methoxide exclusively to methyl trimethylacetate (**242**).[76] The cyclopropoxides (β-enolates) **243a**, **234b**, **244** and **245** are mandatory intermediates in the ring-openings and the regiochemistry of cleavage of **245** is in accord with the relative stabilities of the putative carbanions which can be generated by cleavage of the C–C bonds. Crandall and Machleder[77] prepared 2,2-di-t-butylcyclopropanone (**246**) by the epoxidation of 1,1-di-t-butylallene and studied its cleavage in 0.7 M methanolic sodium methoxide. A two day reflux was required to convert **246** into methyl esters **247** and **248**.

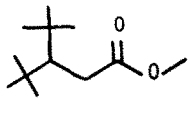
Surprisingly, unlike the ring-opening of **245**, products of cleavage of both bonds were observed. The authors suggested that relief of steric strain favours cleavage of the more congested bond of the β-enolate **249**.

One of the mechanisms required to explain the results of the Favorskii rearrangement of α-haloketones to carboxylic acids and their derivatives involves the cleavage of intermediate cyclopropanones via the addition of a base to the carbonyl group and ring-opening of the cyclopropoxide.[78]

Rappe *et al.*[79] studied the Favorskii rearrangement of a series of 2-halo- and 4-halo-2-methyl-3-pentanones in a variety of bases and compared the products with the products (regiochemistry) of the cleavage of 2,2,3-trimethylcyclopropanone (**250**) and its alkyl hemiketals **251a** and **251b** in CH_3ONa and t-BuOK. That the product compositions were similar was taken as evidence for the intermediacy of cyclopropanones in the Favorskii rearrangements. In the case of the Favorskii reactions the authors noted that a larger group than a methyl in the cyclopropanone increases the amount of ester derived from the incipient less-stable carbanion, while t-butoxide almost exclusively yields the ester derived from the incipient most-stable carbanion. The authors corroborated Crandall's and Machleder's findings that 1,1-di-t-butylcyclopropanone (**246**) ring opens in CH_3ONa/CH_3OH to a mixture of 75% **247** and 25% **248**. They pointed out also that **252** generated from 2-chloro-3-heptanone and 4-chloro-3-heptanone ring opens to yield more **253** (80%) than **254** (20%) and were puzzled, on the assumption that free carbanions were involved as intermediates, why the propyl substituted carbanion should be less stable than a methyl substituted species.

Wharton and Friztberg[55] determined the stereochemistry of ring-opening of the oxyanions of trans-2-3-di-t-butylcyclopropanone hemiketals (alkoxyl-β-enolates) **256a** and **256b** by reacting cyclopropanone **255** with CH_3ONa/CH_3OD and $DOCH_2CH_2ONa/(DOCH_2)_2$. Ketone **255** yielded C-3 deu-

246



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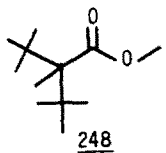

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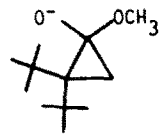

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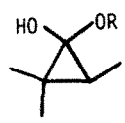
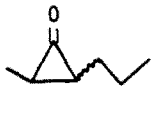


251
a, R=CH_3
b, R=t-Bu



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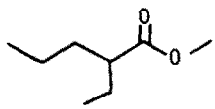

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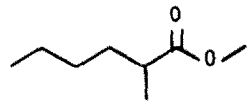
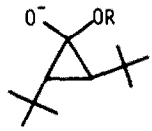
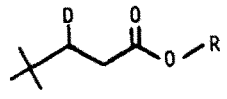


254

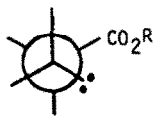
255



256
a, R=CH_3
b, R=CH_2CH_2OH



257
a, R=CH_3
b, R=CH_2CH_2OH



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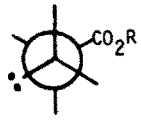


259

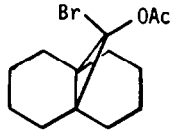
terated 2-t-butyl-4,4-dimethyl pentanoate esters **257a** and **257b**, which result from ring cleavage with 97% and 93% retention of configuration. As has been the case in all cyclopropanone cleavages, the authors assumed an S_E1 mechanism and accounted for the stereochemistry on the basis that **258** is better "solvated" by the alkoxycarbonyl group than **259**. Considering that Jencks' has provided evidence that cleavage of simple cyclopropoxides proceeds via a preassociation or S_E2 mechanism this explanation requires reassessment.

Base hydrolysis of bromo-ester **260** followed by acid work-up yields acid **261**.[80] The β-enolate **263** can either eliminate bromide ion to give cyclopropanone **265** which is cleaved in the usual manner or ring-opening occurs to the corresponding acid bromide.

In all other cases where the stereochemistry of cleavage of cyclopropanones initiated by addition of a base to the carbonyl group has been established, ring opening occurs with retention; **263**,[81] **264**,[82] **265**,[82] **266**,[83] **267**[84] and **268**[85] ring open with retention of configuration. Substrates **263** and **268** yield **269** and the *cis*-carboxylic acids and **270** and **271**, respectively. Warnhoff[6] has suggested that ring opening which occurs via a S_E2 mechanism is subject to steric effects; the backsides of incipient hindered secondary and tertiary anions are shielded from effective solvation. Consequently, protonation takes place with retention from the solvent shell around the oxygens adjacent to the site of cleavage.

2.4.2 *Cyclopropenones*

As documented in a review by Potts and Baum[86] the reactions of cyclopropenones with nucleophiles have received considerable attention. In sodium or potassium hydroxide solution α,β-unsaturated carboxylic acids are formed presumably via homoketonization of the corresponding hydroxycyclo-



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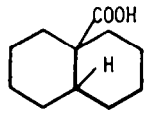

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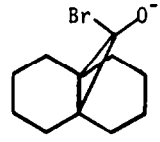

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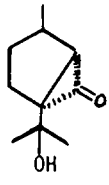

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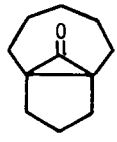

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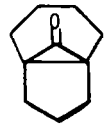

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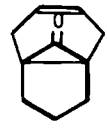

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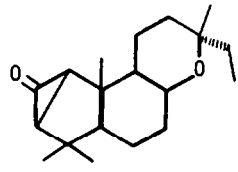

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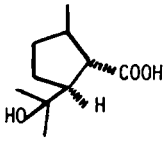

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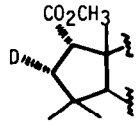

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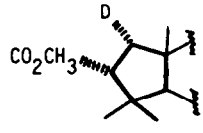

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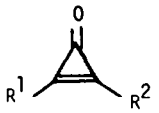

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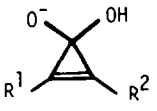

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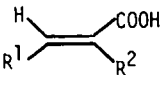

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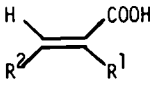
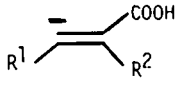


275

a, R^1=H; R^2=CH_3
b, R^1=R^2=n-C_3H_7
c, R^1=R^2=Ph
d, R^1=Ph; R^2=Ph-X
e, R^1=R^2=OC_2H_5



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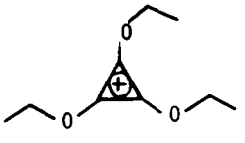


277

propenoxides **273**. **272a** yielded **274a** and **275a** in 0.05 N NaOH/H_2O in a ratio of 3:1 reflecting the expected stability of the putative vinyl carbanions.[87] Furthermore, **272b** was much less reactive than **272c** and was recovered unchanged after 1 h at 31° in 0.1 M NaOH/CH_3CH_2OH while **272c** was 90% reacted after 3 min.[88] This too is in keeping with the expected stability of the incipient carbanions although $^-$OH attack on the carbonyl group in fact may be rate controlling or partially rate controlling. That the (E)-α,β-unsaturated acids are formed indicates that the cleavage occurs with retention of configuration. It is interesting to note in this connection that in all cases vinyl anions **276** were considered as intermediates for cyclopropenone cleavages, implying involvement of S_E1 reactions.

That a satisfactory correlation ($\rho = 0.75$; $r = 0.98$) of the regiochemistry of cleavage (the **274d**:**275d** ratio) with σ was observed for cleavages of a series of substituted cyclopropenones in KOH/CH_3CH_2OH was taken as evidence by Bird and Harmer[89] that vinyl anions are intermediates in the ring openings. However, in light of Jencks' study on the homoketonization of **344** which provides evidence for a preassociation or S_E2 mechanism, further studies are required to concretely establish the mechanisms of ring opening of cyclopropenones.

Interestingly, Dehmlow[90] has shown that while **272e** reacts slowly with H_2O or EtOH to yield the corresponding α,β-unsaturated acids and esters, trioxylcyclopropenium ion **277** reacted immediately in EtOH and yielded the corresponding ester.

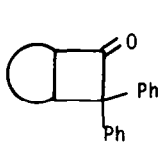
2.4.3 *Cyclobutanones*

Cleavage of non-enolizable ketones by base is a well established phenomenon[25,91] and the only investigated general method is the classical Haller–Bauer reaction. Sodium amide is employed as the base in a hydrocarbon solvent and the products are amides and hydrocarbons.

Substituted cyclobutanones however undergo ring cleavage under mild conditions in alcoholic alkoxide or hydroxide solutions presumably via the corresponding alkoxy or hydroxy β-enolates. The hydroxide and methoxide cleavage of α,α-diphenylcyclobutanones **278**, the products of addition of diphenyl ketone to cycloalkenes and cyclodienes, have been studied.[92–94] As expected homoketonization of γ-enolates **279a** and **279b** was regiospecific yielding acids and esters **280a** and **280b** derived from the putative diphenyl carbanion. Although an S_E1 mechanism is likely in this case, whether the reactions occur via S_E1 or S_E2 mechanisms is unknown.

While saturated 4-membered ring ketones containing a bicyclic ring structure of the type **281** are stable to refluxing methanolic potassium hydroxide, the corresponding β–γ-unsaturated ketones **282** react quite readily and yield the anions of the isomeric carboxylic acids **282** and **284**. Treatment of bicyclo[5.1.1]non-2-en-8-one (**285**) with 20% CH_3OH/KOH yielded after acidification approximately equimolar quantities of **286** and **287**.[95]

Erman, Wenkert and Jeffs[95] also studied the reasonably efficient ring opening of chrysanthenone (**288**) and the isomeric ketone 2,4,4-trimethylbicyclo[3.1.1]heptan-2-en-6-one (**289**) with hydroxide and



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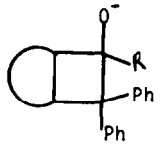
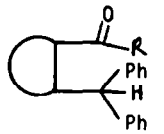


279

a, R=H

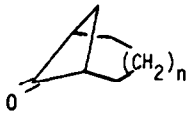
b, R=OH



280

a, R=H

b, R=OH



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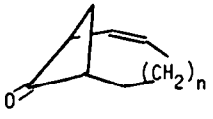

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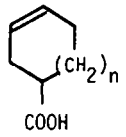

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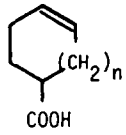

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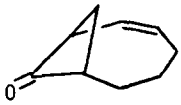

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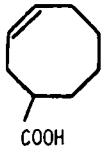

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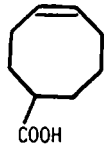


287

methoxide ions under a variety of conditions and determined the product ratio **290**:**291** as a function of reaction conditions. Both **288** and **289** can yield the same allylic anion **294** upon cleavage of γ-enolates **292** and **293**. **294** can be protonated at C-3 or C-5 to yield **290** and **291**, respectively. The variation of the product distribution with reaction conditions was interpreted by the authors as indicating that both intramolecular (in the case of $^-$OH addition) and intermolecular protonations were concerted with ring opening. This is in keeping of course with Jencks' observations in the case of homoketonization of β-enolate **354**. The authors also studied the cleavage of **295** which is rather sluggish and established that the isomeric acids **296** and **297** are produced in a ratio of approximately 65:35.

Particularly interesting is the ring opening of 7,7-dichloro[3.2.0]hept-2-en-6-one (**298**). Addition of methoxide and hydroxide ions, ammonia and hydrazine to **298** leads to the *cis*-dichloromethyl cyclopentenecarboxylic acid derivatives **299a**–**299d**.[96,97] Presumably the ring-opening occurs via γ-enolate **300** and the authors proposed the intermediacy of anions **301**. The corresponding γ-enolate **302a**, however, undergoes exclusive ring contraction to α-chlorocyclopropane carboxyaldehyde **303a**. Steric effects which would weaken the 6,7-bond appear not to be the source of the difference because **302b** also undergoes ring contraction to **303b**. The authors suggested that it is the electron withdrawing groups which control the course of the reaction and pointed out that the mono-chloro analogs **304** undergo ring contraction.

Wenkert *et al.*[98] have obtained comparable results for the cleavage of **305**, **306**, **307** and **308** in KOH/H_2O/dioxane at 85°. Only cyclopropane carboxylic acids were isolated in each case.

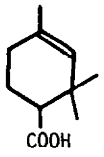
By analogy to the Favorskii rearrangement of β-haloketones the homo-Favorskii reaction of structurally suitable β-haloketones can be envisaged as shown in Scheme 4.

In an attempt to gain information on the mechanistic details of the homo-Favorskii rearrangement of 6-dichloromethyl-6-methyl-2-cyclohexenone (**309**) Wenkert *et al.*[98] prepared [3.1.1]-enone **310** and subjected it to the conditions of the homo-Favorskii rearrangement (KOH/H_2O/dioxane/85°). That only **311** and **312** are formed via ketonization of γ-enolate **313** established that these acids, of the five obtained from **309**, are homo-Favorskii products. The regiochemistry of the cleavage is what would be expected on the basis of the stability of the incipient carbanion although formation of a free carbanion is not mandatory.

Trost and Preckel[99] generated spirocyclobutanones (**314**) from tetralone, 4-cyclohexenecarboxyaldehyde and *cis*-2,6-dimethylcyclohexanone and converted the cyclobutanones into the trimethylenedithio

288

289



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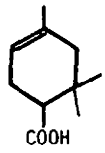

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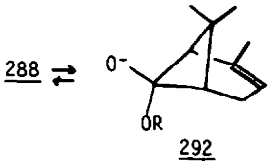

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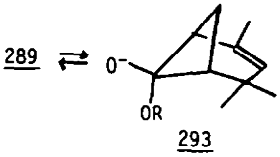

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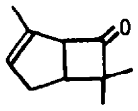

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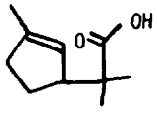

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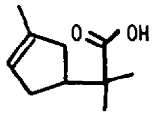

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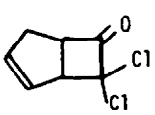

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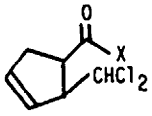
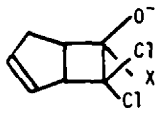


299

a, X=OCH_3
b, X=OH
c, X=NH_2
d, X=$NHNH_2$



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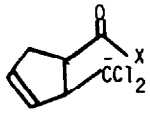

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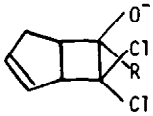
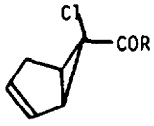
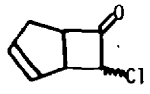


302
a, R=H
b, $R=CH_3$



303
a, R=H
b, $R=CH_3$



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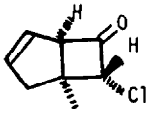

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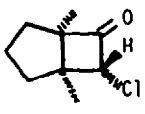

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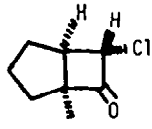

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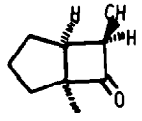

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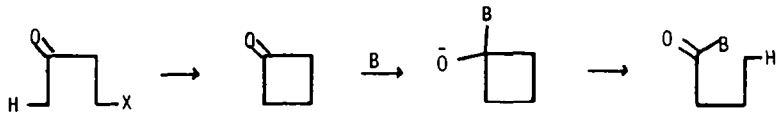
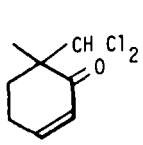


Scheme 4



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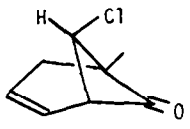

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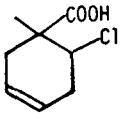

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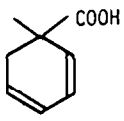

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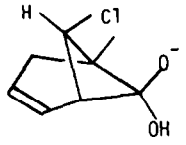


313

analogs **315**. Cleavage of the adducts **317a** and **317b** by CH_3ONa/CH_3OH or $NaOH/H_2O$ yielded the corresponding acids or methyl esters **317a** and **317b** via regiospecific opening of the γ-enolates. The sequence provides a useful method for stereoselective geminal alkylation of ketones because the spiroannelation is stereoselective. The method was used to synthesize methyl desoxypodocarpate (**319**) from tricyclic ketone **318**. Interestingly, cyclobutanol **320a** derived from the corresponding spirocyclobutanone when treated with CH_3ONa/CH_3OH gave via **320b** ketone **321** which was elaborated into spirocyclopentenone **322**.

2.4.4 *Other cycloalkanones*

As continuation of their studies Marshall and Setiz[100] prepared a series of cyclic (C_6–C_8) α-diketone monothioketals **323** and studied their cleavage in KOH/t-BuOH. Excellent yields of the ω-1,3-dithianylcarboxylic acids **324** (88–95%) were obtained after acidification. Methanolic sodium methoxide or methanolic potassium hydroxide were ineffective in the cleavage reaction. Cleavage of **325** did not occur and thienone **326** yielded β,γ-isomer **327** and unreacted starting material.

2.5 *Metal reduction of halo-carbonyl carbons*

2.5.1 *β-enolates*

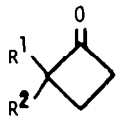
In 1968 Hamon and Sinclair[101] reported that β-enolates **329a** and **329b** were generated by lithium in ether reduction of 3-bromo-2,2-dimethyl propanol (**328a**) and 3-bromo-2,2-dimethylpropiophenone (**328b**), respectively. The β-enolates were converted to the corresponding acetates **329c** and **329d** by quenching the reaction mixture in acetic anhydride.

2.5.2 *γ-Enolates*

Recently Dadson and Money[70] established that γ-enolate **222b** was obtained by calcium in liquid ammonia (−33°) or magnesium in refluxing tetrahydrofuran reduction of 8-bromocamphor (**320**). The corresponding γ-homoenol **222a** which was obtained readily by quenching the calcium and magnesium salts in methanol and dilute aqueous HCl, respectively, was homoketonized in basic medium to camphor (*vide supra*).

2.6 *Decomposition of azo compounds*

During the investigation of the base hydrolysis of a series of 3-acetoxy-Δ^1-pyrazolines **331a–331c** Freeman and Plonka[102] observed skeletal rearrangement that appeared to involve β-enolate inter-



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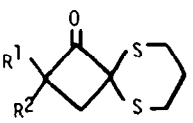

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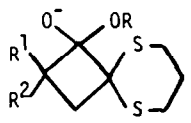
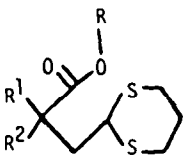


316

a, R=H

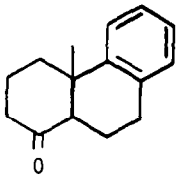
b, R=CH_3



317

a, R=H

b, R=CH_3



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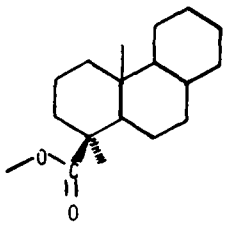

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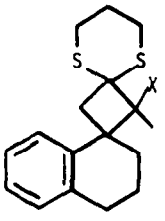
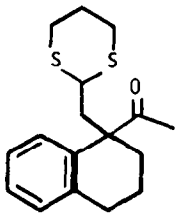


320

a, X=OH

b, $X=O^-$



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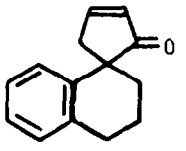

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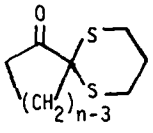
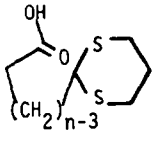


323

n=6,7,8



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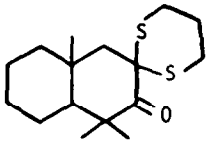

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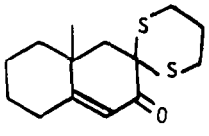

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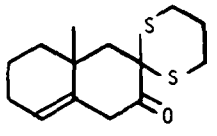
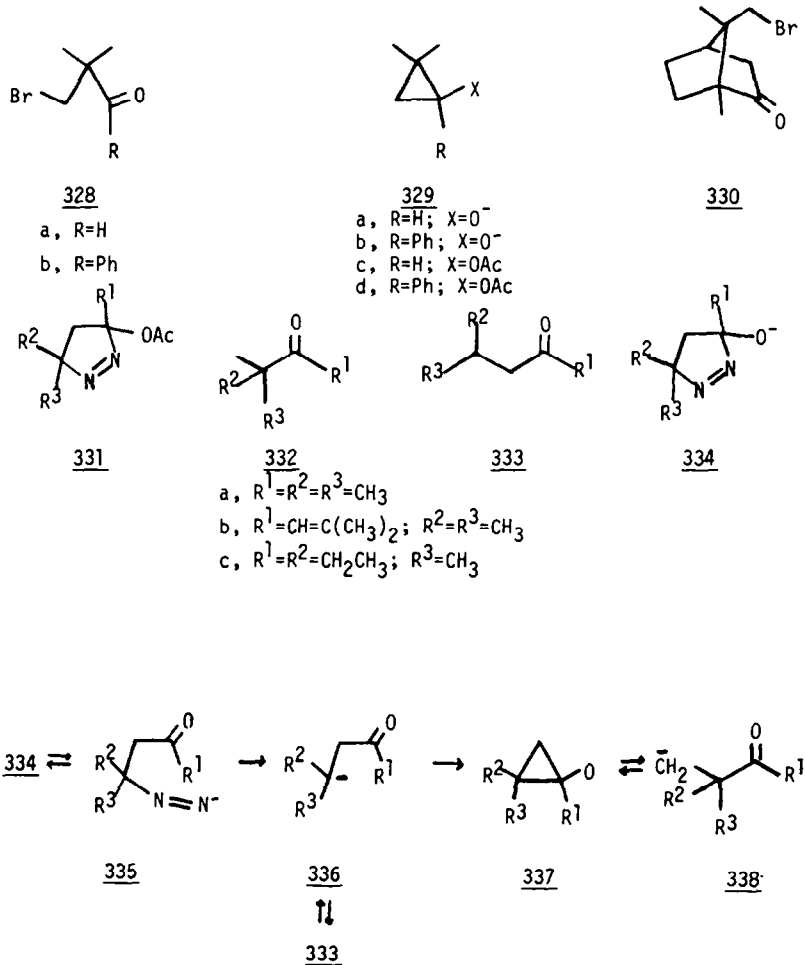


327

mediates. The major product of hydrolysis of **331a** was pinacoline (**332a**) along with a lesser amount of the expected ketone **333a**. Substrate **331b** yielded only **332b**, the product of rearrangement, and no **333b** was formed. Analog **331c** yielded predominately ethyl t-amyl ketone **332c** and a lesser amount of **333c**. The authors proposed Scheme 5 for the reaction. Oxyanion **334** ring opens to imide ion **335**. **335** loses nitrogen forming β-enolates **336** and **337** which yield rearranged ketone via **338**.



Scheme 5.

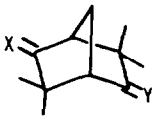
3. HOMOTHIOENOLATES

Unlike the case for ketones, homoenolization of thiones and homoketonization of homothioenolates have been studied little, primarily due to the fact that thiones are considerably more reactive than ketones.

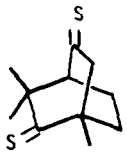
In connection with our studies on the homoenolization of [2.2.1]-dione **75** we prepared ketothione **339a** and dithione **339b** and carried out exploratory homothioenolization studies in 0.8–1.0 M t-BuOK/t-BuOD at 175° for short reaction periods (6–10 h).[103] Although some products of S–O exchange were observed after aqueous work-up preliminary analyses indicated that rearrangement of **339b** to **340** via **341** proceeded more rapidly than the rearrangement of the [2.2.1]-dione to the corresponding [2.2.2]-dione under identical conditions. That the β-thioenolization appears to be faster than β-enolization of ketones is in keeping with our findings that thiocamphor α-thioenolizes faster than camphor.[104]

In an interesting study, Gassman and Mullins[105,106] reacted cyclobutane-1,3-dithione **342a** and ketothione **342b** with organolithium reagents and gained evidence for formation of bis-homothioenolate anions. Addition of CH_3Li to **342a** followed by CH_3I yielded *bis*-thiomethyl ether **343a** indicating that addition of CH_3Li initially occurred at sulfur. The β-thioenolate **343b** appears to be a mandatory intermediate in the formation of **343a**. Treatment of ketothione **342b** with CH_3Li followed by aqueous work-up yielded **344a**. When CH_3Li was added followed by CH_3I, **344b** (69%) was obtained. However when $(CH_3)_3SiCl$ was used instead of CH_3I, **343c** was obtained in 76% yield indicating the intermediacy of **343b**.

Dodson and Fan[107] studied the rearrangement of 1,3-diphenylthietane in base and obtained a complex mixture of products. The authors suggested that the products resulted from thione **345** formed by homothioketonization of thiolate anion **346**, the product of rearrangement of anion **347** derived from diphenylthietane.



339
a, X=O; Y=S
b, X=Y=S



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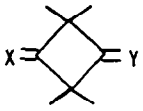
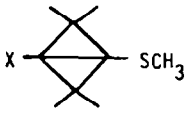
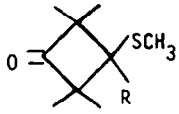
341



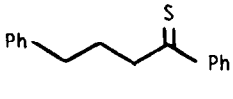
342
a, X=Y=S
b, X=O; Y=S



343
a, X=SCH_3
b, X=SLi
c, X=$OSi(CH_3)_3$
d, X=OLi



344
a, R=H
b, R=CH_3



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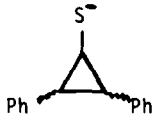
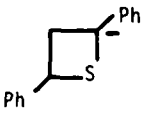


346



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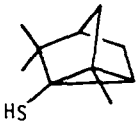
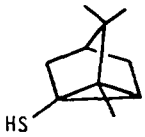


348



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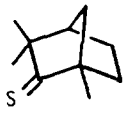
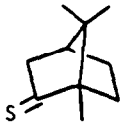


350

351



352

Blackwell and de Mayo[108] obtained homothioenols by photolysis of the corresponding thiones and studied their thionization. While **348** when heated in a sealed tube at 135° yielded **350** and **351** in a ratio of 3:2, **349** yielded only **352**. While thionization can be considered to occur via the corresponding homothioenolate anions the exact mechanisms are unknown.

4. MECHANISTIC ASPECTS

4.1 *Homoketonization*

Since there have been a greater number of homoketonization studies documented in the literature[4–6,109] the mechanistic details of base-induced homoketonization will be summarized and

discussed initially. By integrating this discussion with information obtained from homoenolization studies an attempt will be made to gain some insight into mechanisms of homoenolization and homoketonization. Most of the studies on homoketonization have been conducted to determine the stereochemistry of the S_E ring opening and the effect of structure on the regiochemistry of homoketonization. Table 1 summarizes the results of stereochemical studies involving β-, γ- and δ-enolates.

It is seen that, in general, the S_E cleavages are highly stereoselective. While in the case of β-enolates

Table 1. Stereochemistry of homoketonization of homoenolates

Substrate	Conditions[a]	Type	Product(s)	Stereochemistry
113	tB(D) or M(D)	β	114	> 94.5% inv.
116	KOD/CH_3OD	β	117	> 90% inv.
119a	tB(D) or M(D)	β	121	82-85% inv.
120a	tB(D) or M(D)	β	122	72-79% inv.
123a	M(D)	β	126 & 127	> 96% ret.
124a	M(D)	β	123	> 95% ret.
125a	M(D)	β	129 & 130	> 95% ret.
143a	NaOD/D_2O/dioxane	β	144	~ 100% inv.
145a	tB(H)	β	146 & 147	> 90% ret.
145b	tB(H)	β	146 & 147	> 90% ret.
145a	EG(H)	β	146 & 147	70% inv.
145b	EG(H)	β	146 & 147	40% inv.
163	tB(H)	β	165	high degree ret.
164	tB(H)	β	166	high degree ret.
170a	M(D)	β	168b	> 95% inv.
171b	M(D)	β	173a	> 95% ret.
173a	M(D)	β	168b	> 95% inv.
255	M(D)	β	257a	97% ret.
255	EG(D)	β	257b	93% ret.
262	KOH/H_2O	β	261	high degree ret.
263	CH_3ONa/DME	β	269	high degree ret.
264	NaOD/EtOD/D_2O	β	cis-acid	high degree ret.
265	tB(D)	β	cis-acid	high degree ret.
266	KOH/dioxane/H_2O	β	cis-acid	high degree ret.
267	NaOH(KOH)/H_2O	β	cis-acid	high degree ret.
268	M(D)/DME	β	270 & 271	high degree ret.
272	NaOH/H_2O	β	274 & 275	high degree ret.
133a	M(D)	γ	135	> 96% ret.
133c	M(D)	γ	136	> 96% ret.
167a	M(D)	γ	169a	> 95% ret.
214a	M(D)	γ	215	> 95% ret.
220a	tB(D); 100°C	γ	221	95 ± 3% ret.
220a	EG(D); 200°C	γ	221	90 ± 3% ret.
141a	M(D); reflux	δ	142	> 96% ret.
224a	NaOH/H_2O	δ	225	high degree ret.
226a	tB(H); 135°C	δ	228	61% ret.
227a	tB(H); 135°C	δ	228	56% ret.
230a	tB(D); 70°C	δ	231	> 98% ret.
230a	EG(D); 70°C	δ	231	> 98% ret.
232	CH_3ONa/CH_3CH_2OD reflux	δ	233	> 98% ret.

[a] tB(D) = t-BuOK/t-BuOD; tB(H) = t-BuOK/t-BuOH;
M(D) = CH_3ONa/CH_3OD; EG(D) = $DOCH_2CH_2ONa/DOCH_2CH_2OD$;
EG(H) = $HOCH_2CH_2ONa/HOCH_2CH_2OH$
The reactions were carried out at 20-25°C unless otherwise stated.

high degrees of retention and inversion are observed, ketonization of γ- and δ-enolates in rigid polycyclic systems appears to proceed with a high degree of retention. The effect of solvent on stereochemistry cannot accurately be assessed at this time due to the lack of sufficient data.

In Table 2 are summarized selected data which are useful in assessing the factors which control the regiochemistry of base-induced homoketonization. Relief of strain, product stability and the stability of the incipient carbanion are the major factors determining the regiochemistry of S_E cleavage.

The basic features of the S_E1 and S_E2 mechanisms which must be considered for base-induced cleavage of a cycloalkanol (homoenol) are illustrated in Fig. 1 which includes the reverse processes corresponding to the possible modes of base induced homoenolization. Presently there is some divergence of opinion as regards the mechanism of homoketonization. Recent publications by Thibblin and Jencks[110] and Arts, Klunder and Zwanenburg[46] serve to illustrate this point. Thibblin and Jencks studied the homoketonization of 1-phenylcyclopropanols **353a** and **353b** to the corresponding propiophenones **355** and established that cleavage of **354a** in aqueous solution is subject to general acid catalysis ($\alpha = 0.25$) by protonated amines, that there is a primary deuterium (discrimination) isotope effect of 1.9 ± 0.2 for quinuclidine-H^+ and H_2O as proton donors to carbon, and that k_{OH}/k_{OD} is 1.22 ± 0.05. They found that cleavages of the more reactive 1-phenyl-2-arylcyclopropanols **353b** are still subject to acid catalysis ($\alpha \leq 0.1$) and that k_{OH}/k_{OD} is inverse (0.7 ± 0.1) indicating that there is less proton transfer in the cleavage step. The Hammett ρ values for a small series of *cis*- and *trans*-1-phenyl-2-arylcyclopropanols are 5.0 and 4.0, respectively, consistent with development of considerable negative charge at C2 in the transition state. This is consistent with the observation (Table 2) that the stability of the incipient anion ($1° > 2° > 3°$) is important in determining the regiochemistry of homoketonization.

Table 2. Regioselectivity of homoketonization of homoenolates

Homoenolate	Major Product	Factor(s)
118	117	2° vs 3°
119b	121	relief of strain; product stabilty
120b	122	product stability
123b	126 & 127	relief of strain; product stability
131c	132	2° allylic vs 2°
133b	135	relief of strain; product stability?
141b	142	relief of strain; product stability? 2° vs 3°
143	144	2° benzylic vs 1°
152d-f	153a-c	1° vs 3°, 1° vs 2°
155e-h	156a-d	1° vs 2°
161b	162	1° vs 2° allylic
170a	168	relief of strain; product stability
179	175(1%) + 176(20%) + 178(79%)	anion stability
193a-d	194	1° vs 2°
198a-c	199	1° vs 2°; relief of strain
198d	200	1° vs 2°; strain
198e	200	1° vs 2°; strain
220b	221	product stability
222b	223	1° vs 3°; product stability
224b	225	3° benzyl vs 1°; inductive stabilization
226b	228	3° benzyl vs 1°
230b	231	relief of strain; product stability
245a	242	1° vs 3°
249	247	relief of strain
263	269	relief of strain
272a	274	anion stability
279	280	anion stability
300	299	anion stability
313	311 + 312	2° allylic vs 3°
316	317	anion stability

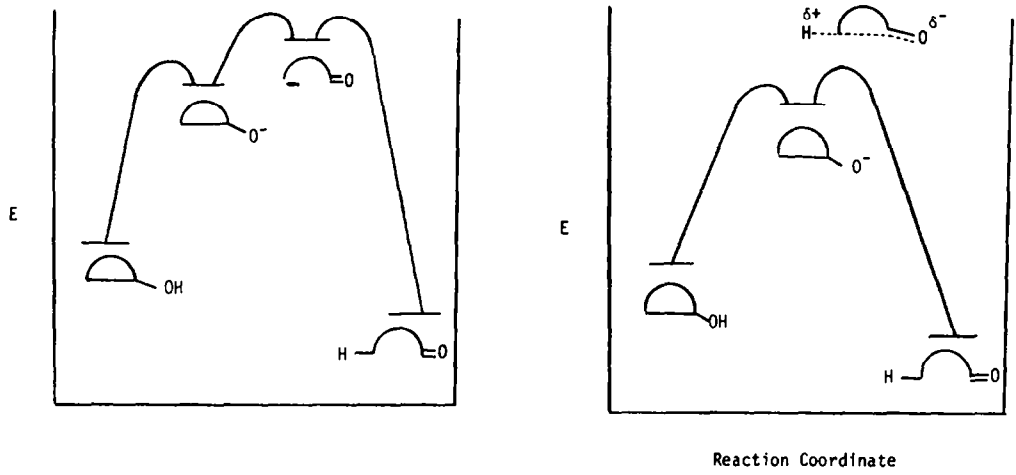


Fig. 1. Possible energy profiles for homoenolization of ketones and homoketonization of the corresponding homoenols.

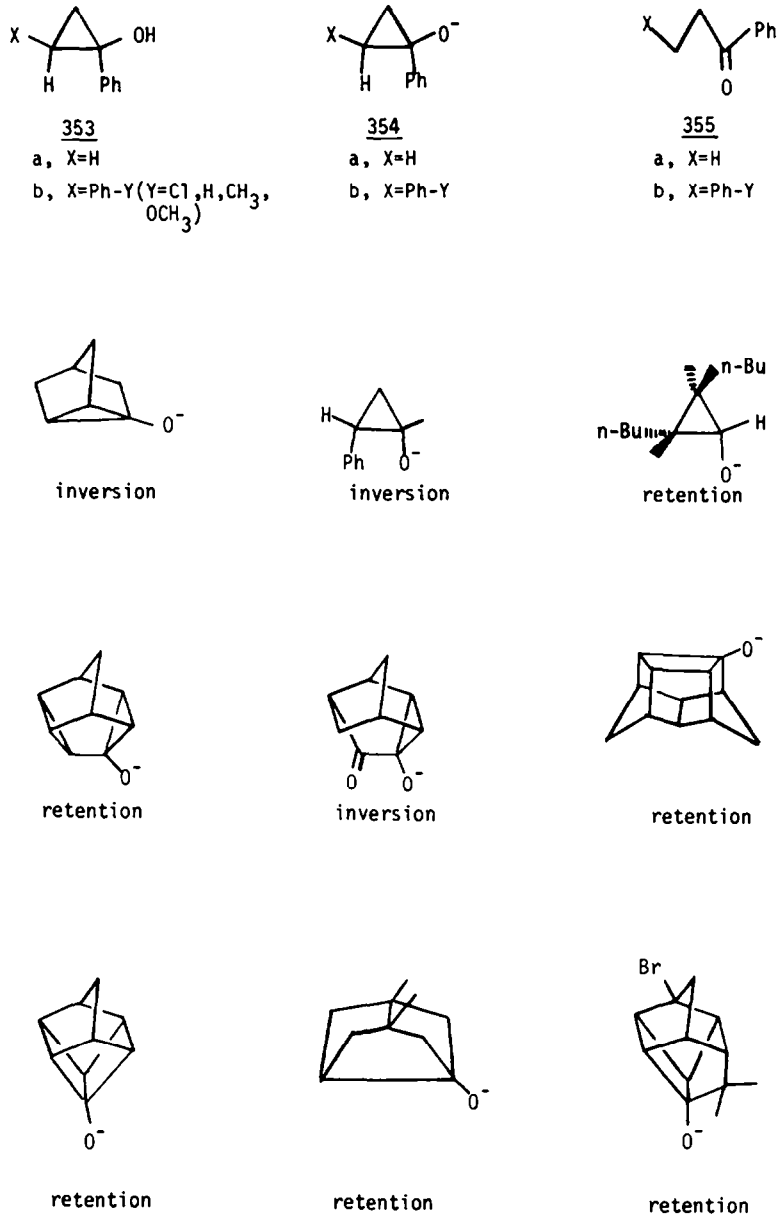
They concluded that ketonization of homoenolates **354a** and **354b** proceeds via a mechanism which involves movement of a proton donor into position (pre-association?) followed by proton transfer to the backside of an orbital which is involved in the C–C bond undergoing cleavage. According to Jencks the stereochemistry of the ketonization of β-enolates **115** and **143b** is consistent with such pre-association—S_E2 mechanism which is enforced by the expected extremely short life-time of the putative carbanion intermediate. That there is a small amount of proton transfer during homoketonization indicates that in homoenolization (the reverse of homoketonization) there is considerable charge development at the carbon undergoing deprotonation.

It is difficult however to account for the remarkable divergency in the stereochemistry of cleavage of β-, γ- and δ-enolates on the basis of a pre-association—S_E2 mechanism. In particular it is not immediately obvious why in most cases β-ketonization proceeds with preferred backside pre-association while frontside pre-association is preferred in γ- and δ-ketonization as illustrated by the examples in Scheme 6.

Zwanenburg[46] proposes that the first step in the homoketonization process involves formation of a carbanion (S_E1) and in highly strained polycyclic structures the anionic center will move rapidly away from the developing C=O group as strain energy is released. As a consequence the anionic center will not be shielded by the C=O group and the anion will be protonated rapidly by solvent molecules with retention. In less strained systems he suggests that strain is not large enough to force the anionic center to separate completely from the C=O group and this results in substantial homoconjugative stabilization of the anionic species. Protonation of the delocalized carbanion would occur from the backside away from the side homoconjugatively shielded by the C=O group. Borden, however, takes the opposite view and suggests that a homoconjugatively stabilized anion should be protonated with retention.[111]

Certainly if the putative primary anion derived from the homoketonization of **354a** cannot exist as an intermediate with a significant lifetime which according to Jencks is the prerequisite for a pre-association or connected mechanism, then the secondary anions derived from the ketonization of polycyclic homoenolates also are not expected to exist as intermediates with a significant lifetime. Consequently, homoketonization via a S_E2 mechanism should be general in all the systems studied thus far.

That a S_E2 mechanism operates seems to be supported by Borden's finding that the putative carbanion, derivable from δ-enolate **230b** by an S_E1 process, when generated by oxidation of the hydrazoketones is protonated stereorandomly. Possibly the polarizability (basicity) of highly strained bonds and/or the nature of the HOMO play an important role in determining the stereochemistry of the ring openings. Perhaps the strength of the edgewise pre-association (H-bonding?) increases as the strain in a bond increases and thereby plays a role in the stereochemical outcome of the cleavage reaction. Steric effects on pre-association or protonation may also be important and may account for the fact that **145** and **163** homoketonize with retention because backside pre-association or protonation is hindered. Stothers[59,60] has suggested that steric effects are important in determining the regiochemistry of cleavage



Scheme 6.

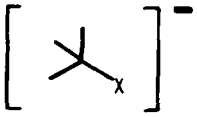
of homoenolates **193** and **198**. It seems unlikely, however, that steric inhibition to backside pre-association or protonation is the major reason for ring opening by retention of **123b**, **124b**, **125b**, **133b**, **134b**, **141b**, **167c**, **214b**, **220b** and **230b**.

Warnhoff[6] has suggested that steric effects on S_E2 cleavage of cyclopropoxides generated by the addition of RO^- (R=H or alkyl) to cyclopropanones **263**, **264**, **265**, **266**, **267** and **268** results in ring opening with retention.

Erman and Wenkert[95] interpreted the results of a study of the ring opening of **288** and **289** via γ-enolates **292** and **293** on the basis of an S_E2 mechanism.

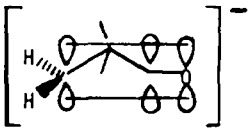
It is interesting to note that Noest and Nibbering[112] using ICR have found that 2-methyl-2-nitrosopropane (**356a**) and 2,2-dimethylpropanal (**356b**) undergo facile β-exchange in the gas phase in the presence of $\bar{O}D$–D_2O; the $(M-H(D))^-$ ions contain up to 8 deuterium atoms. They established that the gas phase acidities of **356a** and **356b** lie between H_2O (1638.6 kJ mol^{-1}) and CH_3OH (1584.2 kJ mol^{-1}) and based on the gas phase acidity of CH_4 (1738.9 kJ mol^{-1}), anions **357a** and **357b** are stabilized by

356
a, X=NO
b, X=CHO



357
a, X=NO
b, X=CHO

358



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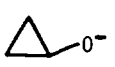

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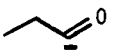

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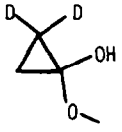

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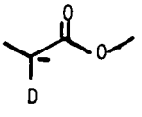

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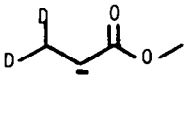

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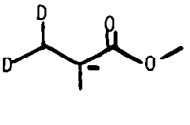

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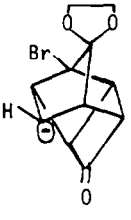


366

104–155 kJ mol^{-1}. Using simple electrostatic theory and the conformation **358** they calculated that dipolar stabilization of the anion by the carbonyl group is in the order of 84 kJ mol^{-1} which could account for a major portion of the stabilization of the anions. They suggested that polarizability effects and hyperconjugation might also be important, but it would be difficult to establish their importance. In the authors view homoconjugation maximized by a p–π interaction, as illustrated in **359**, would lead to closure to the cyclopropoxide ion. In their opinion the facile exchange with incorporation of up to 8 deuterium atoms into **357b** indicates that isomerization to the cyclopropoxide ion in the gas phase is slow. However, Schleyer *et al.*[113] have calculated in conjunction with a theoretical study of the stability of carbonyl anions that simple cyclopropoxides are expected to be more stable than the open ion or the carbonyl anion. For example **360** is calculated to be *ca.* 20 kJ mol^{-1} stabler than **361**. This finding is in accord with the results obtained by Noest and Nibbering; **356b** exchanges β-hydrogens rather than the aldehydic hydrogen. On the basis of Schleyer's calculations, their suggestion that the open ion is stabler than the cyclopropoxide perhaps should be reconsidered. Noest and Nibbering found that homoketonization of 2,2-dideutero-1-methoxycyclopropanol (**362**) by $\bar{O}D/D_2O$ in the gas phase yields anions of *m/z* 88, 89 and 90 to which structures **363**, **364** and **365** were assigned. That **363**, **364** and **365** were obtained in 13%, 63% and 21%, respectively establishes that S_E2 cleavage followed by deprotonation alpha to the carbonyl group cannot be the major pathway of formation of the α-anions. The authors suggested that open β-anions must be involved as intermediates.

If Noest's and Nibbering's estimate is accurate, it is conceivable that dipolar stabilization may be significant if a carbanion located in a non-polar cavity is sufficiently far from a C=O group so that homoconjugation is minimal. The electrostatically stabilized inside-anion, as for example **366** derivable

from highly strained **133b**, could be the stable species and is expected to be deuteronated with retention. Perhaps this is the reason that ketonization of highly strained polycyclic systems **123**, **124b**, **125b**, **134b**, **167c** and **172** proceeds with retention.

There is no doubt, however, that additional mechanistic studies are required to detail the intracies of base-induced homoketonization.

4.2 *Homoenolization*

Figure 2 summarizes the approximate first-order rate constants for methylene (■), methyl (●) and bridgehead (▼) exchange of polycyclic systems expressed relative to syn-7-H of **55**, the bridgehead methyl of **16** and the bridgehead proton of **20**, respectively. Pseudo-first-order rate constants were evaluated from published H–D exchange data using a one-point kinetic analysis and where data were available rate constants were obtained from three or four separate exchanges and averaged. As a consequence of the one-point kinetic analysis and averaging, the first-order rate constants derivable from the data in Fig. 2 differ slightly from published values. Nevertheless, agreement, in general, is good.

Relative reactivities within a group and rate constants are readily derivable from the data in Fig. 2.

It is evident from the rate data that exo abstraction of a β-proton is preferred over endo abstraction in [2.2.1]-, [2.2.2]- and [3.2.1]-systems by a factor ranging between 2 and 10 and this is in accord with the

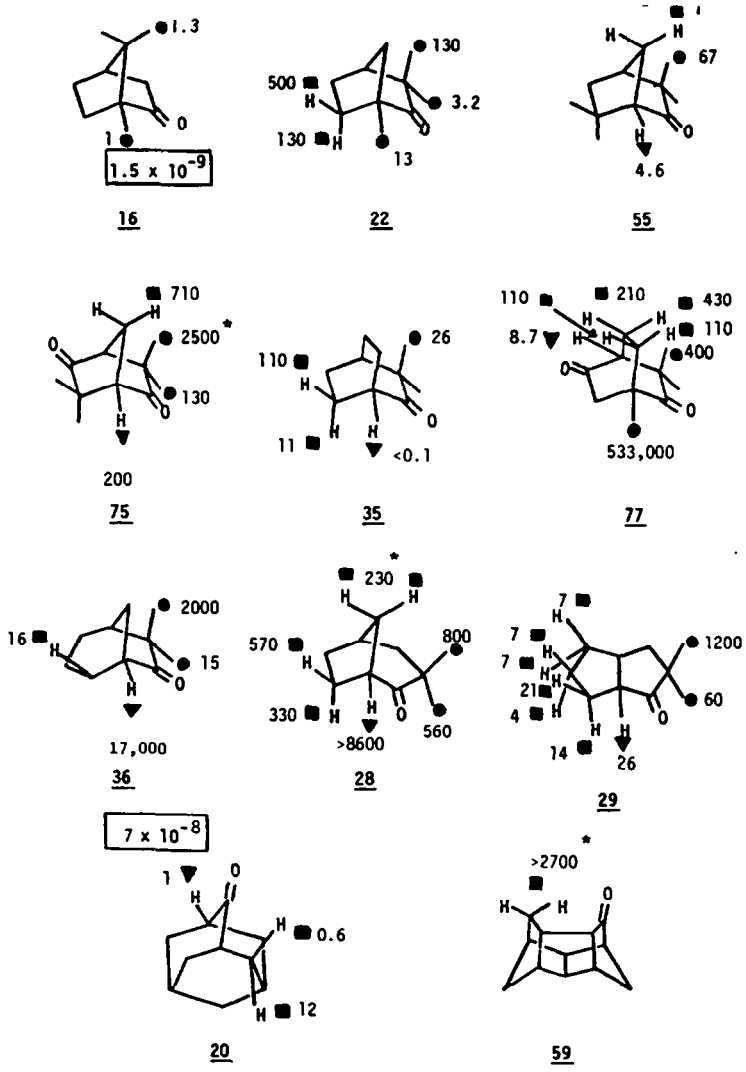
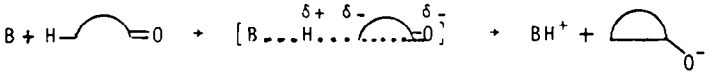


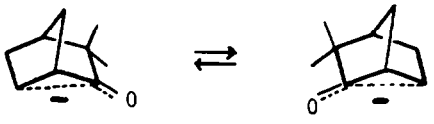
Fig. 2. Rate factors for β- and γ-enolization of methylenes (■) relative to syn-7-H of **55**, β- and γ-enolization of methyls (●) relative to the bridgehead methyl of **16** and bridgehead exchange (▼) relative to the bridgehead hydrogen of **20**. The rate factors marked with an asterisk were obtained from the rate of rearrangement. Factors ≤ 99 rounded to the nearest unit, ≤ 999 rounded to the nearest 10 and those ≥ 1000 rounded to the nearest hundred.

observations that homoketonization of β-enolates generally proceeds with a high degree of inversion. In the case of adamantanone the exo:endo ratio is 17 and in the [3.3.0]-system **29** there appears to be no stereoselectivity. The correlation between H–D exchange rates and intrinsic reactivities is predicated, of course, on the assumption that internal return[115] in t-BuOK/t-BuOD is comparable for exchange at the various sites in polycyclic and acyclic substrates. Second-order rate constants cannot be evaluated because t-BuOK aggregates and an increase in t-BuOK concentration does not necessarily result in an equivalent increase in rate;[114] the reactions are not first-order in t-BuOK.

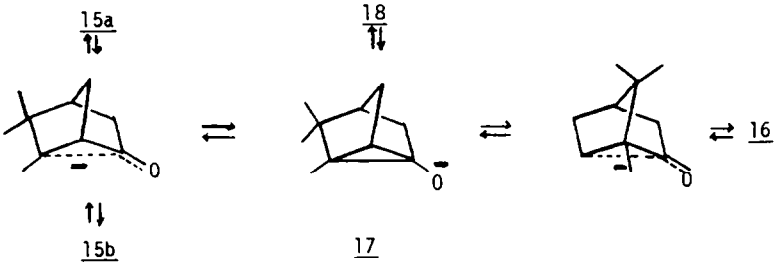
It has been estimated[4] that the pK_a of homoenolizable methylene hydrogens is in the region of 35–36 midway between normal methylenes such as cyclohexane (45 on the MSDA scale) and ketones ($pK_a \sim 20$). This coupled with the fact that there is significant stereoselectivity for anion formation in **20**, **22**, **23** and **35** suggests that there is delocalization of the negative charge onto the carbonyl group during deprotonation which leads to cycloalkoxide. This is essentially the reverse of the S_E2 process for which



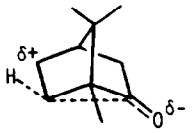
Jenck's has experimental evidence (*vide supra*). However as pointed out previously, it has been suggested that in the gas phase β-anions are open species, stabilized predominately by electrostatic interaction with the dipolar carbonyl group. Nickon's finding that the rate of racemization of optically active camphenilone (**1**) equals the rate of H–D exchange supports the concerted mechanism although it is possible that rearrangement of an unsymmetrical intermediate competes effectively with deuteronation at elevated temperatures (Scheme 7). However, there is difficulty in rationalizing the homoenolization of isocamphanones **15a** and **15b** and the homoketonization of **18** on the basis that a single homoenolate **17** is the sole intermediate (Scheme 8). While homoenolization of **15b** at 185°, presumably proceeding through homo-ion **17**, yields more **15a** than **16**, homoketonization of **18** at 20° yields only **16**. Perhaps these data indicate that homoenolization, as Nickon suggests,[3] is a rather complex process. Possibly a complex equilibrium exists between a variety of anionic species as shown in Scheme 8. While the effect of increasing temperature on the rate of protonation should be minimal, the equilibrium distribution of the various species and the rate at which equilibrium is achieved should be temperature dependent. If **17** was the sole intermediate connecting **15a**, **15b** and **16** then camphor should be formed preferentially because of the stability of the incipient anion (2° vs 3°) and the steric effect on protonation; backside protonation at C6 as illustrated in **367** should be easier than protonation at C-1 as shown in **368** and **369**. Warnhoff's findings that **18** homoketonizes at 20° to camphor with immersion of configuration supports this prediction. Possibly at higher temperature ketonization of **17** via **368** and **369** compete with homoketonization via **367**. Had homoenolization of **15a** been carried out in deuterated medium, the extent to which exchange (homoketonization via **368**) competes with rearrangement (homoketonization via **367**) at 185° would have been established and would have shed light on this point. If ketonization via



Scheme 7



Scheme 8.



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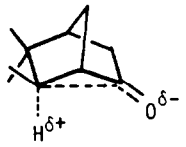


369

368 competes with **367** at higher temperatures then by the same token the stereoselectivity of homoenolization should decrease as the temperature is increased. That there appears to be greater stereoselectivity in homoketonization of [2.2.1]-systems at 20° than there is in homoenolization at 185° suggests that, in fact, this may be the case.

Stereoelectronic effects on deprotonation and strain in the incipient cycloalkoxide appear to play an important role in determining the ease of deprotonation remote from the carbonyl group. For example β-exchange at C6 of **22** is *ca.* 300 faster than exchange at C7 of **55** and bridgehead methyls (**16** and **22**) are less reactive than other β-methyls except in the case of **77** where exchange occurs by a different route. Furthermore, β-methyls of [3.3.0]- and [3.2.1]-systems appear to be more reactive than methyls on the 2-carbon bridge of a [2.2.1]-system. It is also interesting to note that γ-enolization of half-cage ketone **59b** occurs more readily than β-enolization of [2.2.1]-, [3.2.1]- and [3.3.0]-systems.

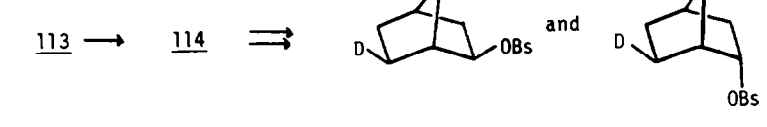
That introduction of a β-carbonyl group in an orientation such that only an inductive effect operates enhances exchange by a factor of *ca.* 50 is seen from the rate data for bridgehead exchange of **55** and **75**. This observation is in accord with our previous studies on the exchange of dione **72** in $NaOD/D_2O$/dioxane where we estimated that the β-carbonyl inductively enhances the rate of α-enolization by a factor of *ca.* 75.[23] Bridgehead exchange of **35** is extremely slow and only a rough estimate of the rate constant ($\sim 1 \times 10^{-8}\ s^{-1}$) can be made. The estimate seems reasonable based on the fact that C-4-H of 2,5-dione **77** exchanges *ca.* 100 times faster than C-1-H of **35**. Consequently, the majority of the increase in rate of β-exchange at C-7 of the dione **75** (*ca.* 500) over exchange at C-7 of monoketone **55** undoubtedly results from an inductive effect. However, that the rate increase is somewhat larger perhaps indicates that anion is homoconjugatively stabilized to some extent by the C-5 carbonyl group. From these data it is clear that strategic introduction of at least one carbonyl group into a polycyclic ketone indirectly can provide information on exchange at relatively non-reactive positions of the parent monoketones.

That half-cage ketone **59b** homoenolizes at a significant rate only in t-BuOK/t-BuOH at 195° and the hexachloro analog **59a** homoenolizes readily in refluxing pyridine provides further evidence for the importance of electronic effects.

5. SYNTHETIC APPLICATIONS

5.1 *Hydrogen isotope labelling*

One obvious application of homoenolization of ketones and especially homoketonization of homoenols is hydrogen isotope (^2H or ^3H) labelling. While homoenolization usually results in poly-labelling, ketonization of β-, γ- or δ-enolates usually results in the stereoselective incorporation of deuterium which may be useful in unrevelling the complexities of ^1H and ^{13}C NMR spectra of polycyclic systems. Stereoselective incorporation of deuterium via homoketonization has been used to prepare selectively deuterated norbornyl brosylates **370** and **371** required for solvolytic γ-deuterium kinetic isotope effect studies[116] designed to probe the nature of the bonding in the 2-norbornyl cation. Stereospecifically *exo*-C-6 deuterated *exo*- and *endo*-2-norboryl brosylates were also used in a study of 1,3 elimination in the [2.2.1]-system.[117,118] Ketonization of β, γ- and δ-enolates must be considered as a viable general route to ^2H and ^3H labelled polycyclic aldehydes, ketones, esters and carboxylic acids selectively labelled at β-, γ- and δ-sites.



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5.2 *Preparation of ketones*

5.2.1 *Rearrangement of polycyclic monoketones*

While there are documented a considerable number of rearrangements of polycyclic monoketones and the mechanistic aspects of homoenolization and homoketonization are reasonably well understood, there has been no systematic attempt to use anionic rearrangements via homoenolization to prepare specific targets which are not readily accessible by other routes.

5.2.2 *Rearrangement of polycyclic polyketones*

Base induced rearrangement of polycyclic polyketones via β- or γ-enolate switches may be synthetically useful. While there is only a single report of such a rearrangement[32] whereby [2.2.1]-dione **75** is converted into [2.2.2]-dione **77** such transformations may prove to be synthetically useful in that ring expansion is achieved by conversion of a methyl group into a methylene.

5.2.3 *Rearrangement of acyclic polyketones*

By studying the rearrangement of **104a–104c** to **105a–105c** and **109** to **110** Yates *et al.* have established that acyclic 1,4-diketones which have an α-enolizable hydrogen and anion stabilizers on the adjacent carbon undergo facile rearrangement in CH_3ONa/ether. Perhaps this rearrangement will find synthetic applications.

5.2.4 *Homoketonization of cycloalkanols*

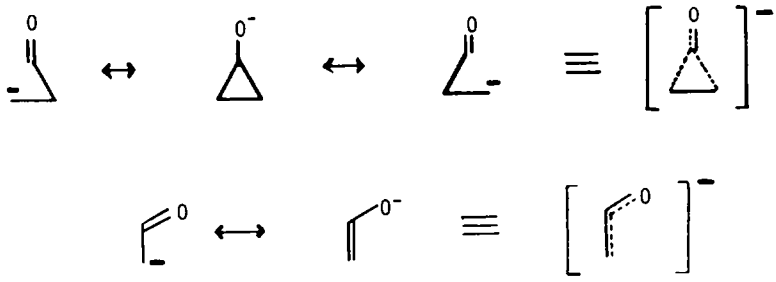
Homoketonization of polycyclic alcohols provides a useful route to ketones which would be difficult to obtain via other routes. While most homoketonizations have been carried out to gain mechanistic information only a limited number of attempts have been made to establish the scope and limitations of the reaction.

Especially promising is the sequence of reactions involving the ketonization of homoenolates generated by hydrolysis of cyclopropyl trimethylsilylethers prepared by cyclopropanation of enol trimethylsilyl ethers, first studied by Conia and recently by Stothers (Section 2.3.1). Conia showed that a series of aldehydes (presumably simple acyclic ketones will exhibit similar reactions) can be monoalkylated using this sequence. While Conia[59] established that C_5, C_6, C_7 and C_8 cycloalkanones can be monoalkylated, Stothers showed by studying a series of homoenolates generated from bicyclic ketones that ring expansion can accompany formation of α-methyl ketone in polycyclic systems.[59,60] Reusch *et al.*[56,57] have studied the effect of alkyl substitution on the homoketonization of tricyclic alcohol **174** to bicyclic isomers having spiro[5.4]decane, decalin and perhydroindane skeletons, the latter being formed via a sequence involving a β-enolate switch. Caubere *et al.* have developed a synthesis of 2,3-benzocycloalkenones utilizing the homoketonization of γ-enolates generated by the reaction of α-enolates with benzyne. They studied the homoketonization of **216b** and **217b** and several of their alkylated derivatives in aprotic medium and established the effect of alkyl substitution at various sites (Section 2.3.2) on the regiochemistry of the homoketonization.

6. HOMOENOLATE ANION EQUIVALENTS: PREPARATION AND SYNTHETIC APPLICATIONS

Carbonyl compounds are the most important classes of compounds used for generating C–C bonds because the carbonyl or acyl carbon is electrophilic and the functional group promotes facile conversion of carbonyl compounds into nucleophiles. Furthermore, by utilizing the concept of "Umpolung" or charge affinity inversion,[111] the normally electrophilic carbonyl or acyl carbons are rendered nucleophilic thereby further expanding the synthetic utility of carbonyl compounds. A variety of useful reagents for one- and two-carbon elongations have been developed. Homoenolates, as for example those of the β-type, can be considered as charge-affinity-inverted species and are analogous to ambident α-enolates (Scheme 9).

Unlike α-enolization which is readily carried out under mild conditions to yield high equilibrium concentrations of α-enolates, vigorous conditions are required to generate even low concentrations of homoenolates. This problem has been overcome through development of a variety of equivalents based on the open form of homoenolates. Although a variety of approaches have been used they are in general of two types: the first includes systems which possess a single nucleophilic site beta to a masked carbonyl group and in some cases the anion is stabilized by a substituent at the β-site; in the second approach attempts have been made to control the ambident nucleophilicity of heteroatomically substituted allylic anions.



Scheme 9.

6.1 *Masked β-carbonyl anions*

6.1.1 *Acetals and ketals*

Kondo and Tunemoto[120] prepared phenylsulfone acetals **372a–372b** and ketal **372d** and studied the alkylation of the β-anions with a series of alkyl halides. Acid hydrolysis followed by elimination of benzenesulfonic acid yielded the corresponding alkylated α, β-unsaturated carbonyl compounds **373**. Dolby *et al.*[121] β-benzylated methylvinyl ketone and β-methylated cyclohex-2-enone via a similar route which involved alkylation of the anions of the corresponding toluenesulfonyl ethylene ketals.

The Grignard reagents derived from β-haloacetals and β-haloketals have been used as β-enolate equivalents. Ponaras[122] prepared 3,3-ethylenedioxybutylmagnesium bromide (**374**) and established its utility as a four-carbon annelation synthon which provides a good route to 1,4-diketones from acyl halides. The 1,4-diketones are useful intermediates in the synthesis of cyclopentenones, furans and other heterocycles. Grignard reagent **374** is unstable at elevated temperatures and yields the cyclopropyl ether **375**.

Eaton *et al.*[123] used β-enolate equivalent **376** as a source of two- and three-carbon units in the synthesis of the peristylane ring system, but due to experimental difficulties found that organolithium **377** a much better three-carbon source.

Marfat and Halquist[124] found that conjugate addition of **376** to cyclic C_5-, C_6- and C_7-α, β-unsaturated ketones following by acid work-up yielded the corresponding bicyclic enones and thereby developed a convenient cyclopentene annelation.

Corey *et al.*[125] used the conjugate addition of the anion of 3-nitropropanal dimethyl acetal (**378**) to 9-cyano-2-nonenal (**379**) in the initial step of the synthesis of prostaglandins of the E_1 and F_1 series including 11-epiprostaglandins.

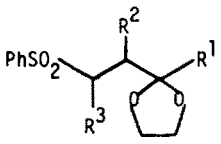
A series of β-diphenylphosphonyl ketals **380** which readily formed the masked β-enolate anions with n-BuLi/THF were prepared and studied by Warren *et al.*[126] Addition of the anions generated from **380a** and **380b** to acetone and benzaldehyde yielded the corresponding β,γ-unsaturated ketones after treatment with NaF/THF and deketalization.

While the direct homoenolization of carboxylic acids and their functional derivatives would appear to be experimentally impossible the homoketonization of cyclopropanone and cyclobutanone hydrates and hemiacetals have been studied (see Section 2.4). Beta-enolate equivalents of carboxylic acids and esters have been prepared and extensively studied. Nakamura and Kurrajuna[127] prepared 1-ethoxy-1-trimethylsiloxycyclopropane (**381**) and established that it adds to aliphatic aldehydes in the presence of $TiCl_4$ to yield, in most cases, γ-lactones in good yield. The authors suggested that the reaction most likely involves the intermediate titanium ester **382**.

Corey and Ulrich[128] utilized readily available *cis*-(**383**) and *trans*-2-methoxycyclopropyl lithium (**384**), formally the homoenolate equivalents of the β-anion of propanal **385**, in the synthesis of β, γ-unsaturated aldehydes **386a–386d**.

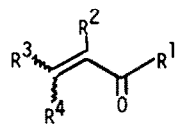
6.2 *β-Substituted carbonyl compounds*

Debal *et al.*[129] established that β-cyanoketones **387**, **388**, **389** and **390** when treated with two equivalents of LDA in ether yielded the corresponding dianions which were selectively alkylated by alkyl halides beta to the carbonyl group. Elimination of HCN yielded the corresponding alkylated α, β- and β, γ-enones. This approach of protecting the carbonyl group by α-enolate formation has been utilized to prepare 3-substituted indanones.[130] For example 6-methoxy-1-indanone when treated with 2 equivalents of LDA followed by 1 equivalent of ethyl iodide yielded 89% of 3-ethyl-6-methoxy-1-indanone, the product of alkylation of the β-enolate.



372

a, $R^1=R^2=R^3=H$
b, $R^1=R^2=H$; $R^3=CH^3$
c, $R^1=R^3=H$; $R^2=CH^3$
d, $R^1=CH_3$; $R^2=R^3=H$



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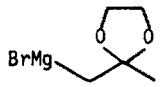

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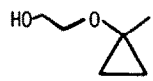

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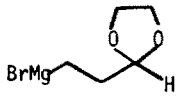

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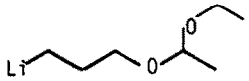

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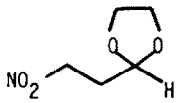

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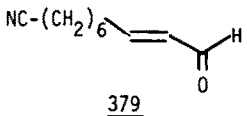

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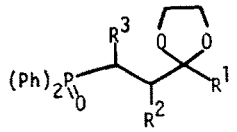


380

a, $R^1=Ph$; $R^2=R^3=H$
b, $R^1=R^3=H$; $R^2=H$

Ylide **391** generated from the corresponding triphenylphosphonium chloride by NaH/THF/DMSO at 0° has been shown to add to m-methoxyacetophenone and cyclohexanone yielding the corresponding β,γ-unsaturated acids **392** and **393** in 60% yield.[131]

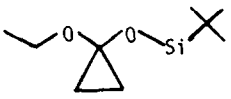
Oda *et al.*[132] established that α,β-unsaturated nitriles and esters react with triphenylphosphine in ethanol or n-hexane yielding ylides of the type **394**. In the presence of an aldehyde addition occurs followed by elimination of Ph_3PO to yield β,γ-unsaturated substrates **395**. Stork *et al.*[133] used this methodology to prepare 4-(m-methoxyphenyl)-3-butenoate, an intermediate used in the synthesis of d,l-lycopodine. The method provides a source of homoenolate equivalents of the type **396**.

Seebach *et al.*[134] reported that lithium enolates **397** add to β-nitropropionylchloride at -80 to $-100°$ in THF to yield nitro-β-dicarbonyl compounds which are cyclized into **398** and elaborated to the β-hydroxy enones **400** via **399**. The acid chloride formally is a source of the β-enolates **401** and **402**.

Bakusis *et al.*[135] have established that ethyl-β-nitropropionate (**403**) adds to aldehydes and reactive enones in the presence of diisopropylamine/THF or t-BuOK/THF and the corresponding α,β-unsaturated esters are generated by elimination of HNO_2. Thus **403** serves as a source of β-enolates **404** and **405**. The methodology was employed in the synthesis of the macrolide antibiotic pyrenophorin.

6.3 *Other methodology*

As an extension of the secoannelation methodology where the $^-CH_2CH_2CONuc$ unit was introduced into α,β-epoxyketones,[136] Trost and Bogdanowicz[137] showed that spiroannelation of carbonyl com-



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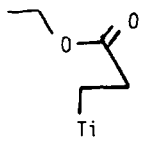
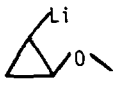


382



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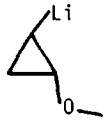

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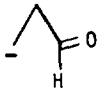
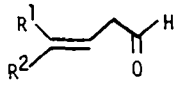
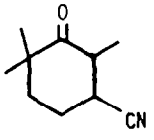


385



386

a, $R^1=(CH_2)_5CH_3$; $R^2=H$
b, $R^1=(CH_2)_6CN$; $R^2=H$
c, $R^1=C\text{-}C_6H_{11}$; $R^2=H$
d, $R^1=2\text{-}(Z\text{-}2\text{-butenyl})$; $R^2=H$
e, $R^1\text{-}R^2=-(CH_2)_5-$



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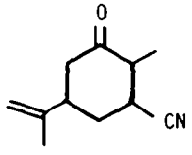

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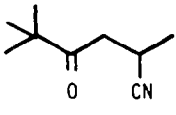
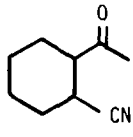


389



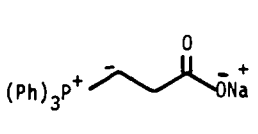
390

pounds utilizing diphenylsulfonium cyclopropyl anion results in the facile conversion of aldehydes and ketones into γ-butyrolactones **407a–407d** via the spiroepoxides and spirocyclobutanones. Thus the diphenylsulfonium cyclopropyl anion is an equivalent of **408**.

Homoenolate dianion **409** has been prepared from 3-bromopropionic acid and added to a variety of aldehydes and ketones.[138] Lactonization of the γ-hydroxyacids yields γ-lactones in reasonable yields. The vinyl analogs **410a**, **410b** and **410c** have been prepared and added to a series of aldehydes and ketones and the adducts were lactonized to the corresponding γ-butenolactones in average yield.[139]

In an interesting variant, Sturtz *et al.*[140] prepared dianions **411a–411c** and two analogs, one bearing a methyl group at C-2 (X=–$N(CH_3)_2$) and the other bearing a methyl at C-3 (X=$N(CH_3)_2$). Addition of the dianions to a series of aldehydes and ketones led to γ-lactone formation in average yields. Addition to epoxides gave δ-lactones and alkylation with saturated and unsaturated alkyl halides yielded the corresponding carboxylic acids. A key step in the transformations is the hydrolysis of acyl phosphonates or phosphonamides to β- or γ-substituted carboxylic acids.

Gange and Magnus[141] have used α-lithiomethoxyallene (**412**), prepared by deprotonation of methoxyallene by nBuLi in THF at −78°, as a homoenolate equivalent of **396**. Addition of **400** to cyclohexenone, cyclopentanone, cyclohexanone and 3-methoxyandrost-3,5-dien-17-one and estrone followed by treatment with t-BuOK and acid work-up gave the corresponding furanones in good yields.



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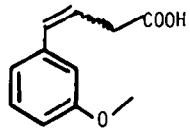
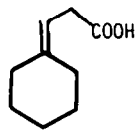
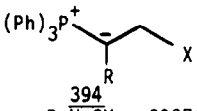


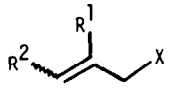
392



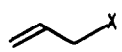
393



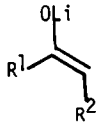
394
R=H, CH_3, COOEt
X=CN, CO_2Et, $CONH_2$



395



396
X=CN, CO_2Et, $CONH_2$



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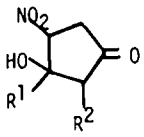

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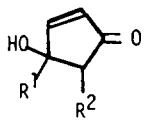

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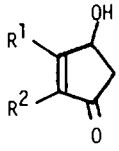
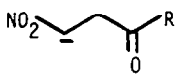


400

a, $R^1=CH_2CH_3$; $R^2=CH_3$
b, $R^1-R^2= -(CH_2)_4-$
c, $R^1-R^2= -(CH_2)_5-$
d, $R^1-R^2= -(CH_2)_6-$
e, $R^1-R^2= -(CH_2)_{10}-$



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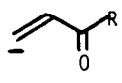
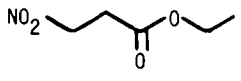


402



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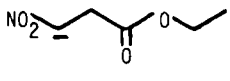

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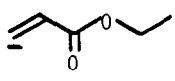


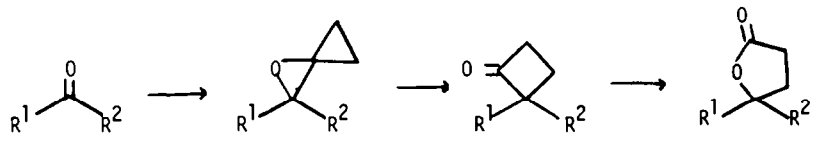
405

6.4 *Heteroatom substituted allylic anions*

It was recognized early both that heteroatom substituted allylic anions **413** could serve as homoenolate anion equivalents and that there would be a problem with the regioselectivity of reaction with electrophiles. Consequently a great deal of effort has been expended in attempts to direct the attack to the γ-position and a number of factors which determine selectivity have been recognized.[7] The nature and size of the groups attached to the heteroatom, the counter cation, the solvent including additives, reaction temperature and reaction time are important. In this connection Gompper and Wagner suggested that the concept of allopolarization permits a description of substituent effects in kinetically controlled reactions. That is, a change in selectivity is related to a change in polarity of ambifunctional anions.[142] Factors affecting the reactivity and regioselectivity of allyl-alkali metal reagents have also been reviewed by Schlosser.[143]

6.4.1 *Nitrogen*

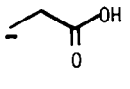
Julia *et al.*[144] metallated a series of N-allycarbazoles **414a–414e** with n-BuLi/TMEDA/Et_2O at $-15°$ and reacted the anions with a series of alkyl chlorides and benzophenone. High γ/α ratios were generally observed and hydrolysis of several adducts yielded ketones **415a**, **415b** and **415c**. Hydrolysis of the



406

a, R^1-R^2= -$(CH_2)_5$-
b, R^1-R^2= -$(CH_2)_6$-
c, R^1=CH_3; R^2=n-hexyl
d, R^1=H; R^2=4-cyclohexenyl

407



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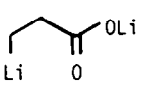
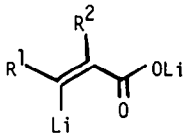
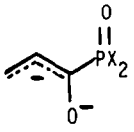


409



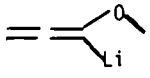
410

a, R^1=R^2=H
b, R^1=H; R^2=CH_3
c, R^1=CH_3; R^2=H



411

a, X=OCH_2CH_3
b, X=$N(CH_3)_2$
c, X=$N(CH_2CH_3)_2$



412

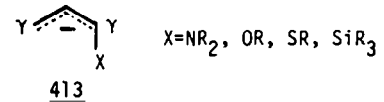
benzophenone adducts derived from **414a**, **414b** and **414c** yielded the γ-lactol from **414a** and the β,γ-unsaturated ketones from **414b** and **414c**.

As an extension of the metallation of enamines and allylamines,[145-147] Ahlbrecht and Vonderheid[148] metallated the substituted enamines **416a–416d** and studied the reaction of the anions with CH_3I, $CH_3CHBrCH_3$, benzaldehyde, acetone and benzophenone. Good yields of the adducts were obtained and with large substituents on nitrogen, Ph or c-C_6H_{11}, the additions occurred regiospecifically at the γ-position. Hydrolysis of the adducts of **416a** and benzaldehyde and acetone yielded the γ-lactones **417a** and **417b**. It was reported that **418** also is metallated and alkylated with CH_3I exclusively at the γ-position.

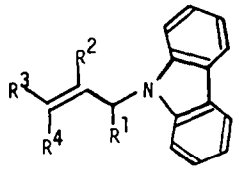
Renger and Seebach[149] studied the lithiation of allyl t-butylnitrosoamine (**419a**) and allyl methylnitrosoamine (**419b**) and reacted the anions with alkylating and hydroalkylating reagents. While both allylic anions showed kinetically favoured α-addition, the addition of the anion of **419a** to benzaldehyde and cyclohexanone is reversible and under thermodynamic control the γ-products are favoured. The γ-product derived from benzaldehyde when denitrosated and hydrogenated gave aminoalcohol **420**. Compound **421**, the *trans*-adduct of benzophenone was shown to rearrange to oxime **422**.

Martin and DuPriest[150] lithiated allylpyrolidine and studied the reaction of the anion **423** with n-butyl bromide, chlorotrimethylsilane and cyclohexylcarboxaldehyde, benzaldehyde, acetone, acetophenone and cyclohexanone. While the alkylation proceeded with a high degree of regioselectivity to yield >95% of the γ-adducts **424a** and **424b**, the additions to the aldehyde and ketones yielded approximately equal amounts of α- and γ-products, and the γ-products were cyclized to the aminoacetals **425a**. Treatment of the mixture of products derived from the aldehydes and ketones with ethanolic HCl yielded the corresponding lactols **425b** and the products of α addition.

In continuing their studies on the anions of α,β-unsaturated nitriles as homoenolate equivalents, Johnson and Clader[151] prepared anions **426a** and **426b** from the corresponding amines with LDA in THF

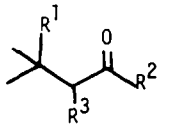


413



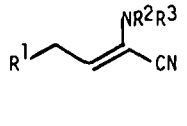
414

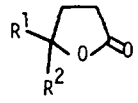
a, $R^1=R^2=R^3=R^4=H$
b, $R^1=CH_3$; $R^2=R^3=R^4=H$
c, $R^2=CH_3$; $R^1=R^3=R^4=H$
d, $R^3=CH_3$; $R^1=R^2=R^4=H$
e, $R^3=R^4=CH_3$; $R^1=R^2=H$

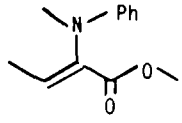


415

a, R^1=n-Bu; $R^2=R^3=H$
b, R^1=n-Bu; $R^2=CH_3$; $R^3=H$
c, R^1=i-Pr; $R^2=H$; $R^3=CH_3$





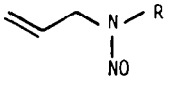


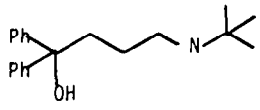
416

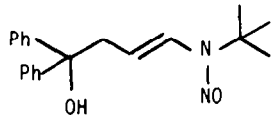
a, $R^1=H$; $R^2=CH_3$; R^3=Ph
b, $R^1=R^3$=Ph; $R^2=CH_3$
c, R^1=Ph; R^2-R^3= $-(CH_2)_5-$
d, R^1=Ph; $R^2=R^3=CH_3$
e, R^1=Ph; R^2=c-C_6H_{11}; $R^3=CH_3$

417

418





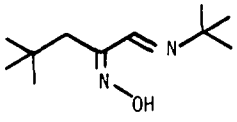


419

a, R=C(CH3)3
b, R=CH3

420

421



422

at −78°. If the solution is warmed to 0° and ketone is added only γ-addition is observed. If the anion is prepared at 0° and anhydrous $ZnCl_2$ is added to the ketone, enolization and hence aldol condensation is reduced. Addition of **426a** or **426b** to cyclohexanone and $ZnCl_2$ gives γ-lactone **427** in 78% yield after aqueous work-up followed by treatment with 0.5 M HCl or oxalic acid in 50% dioxane. Treatment of **427** with 10% P_2O_5 in CH_3SO_3H gave cyclopentenone **428** in 94% yield.

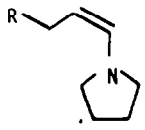
Recently Ahlbrecht *et al.*[152] documented the first preparation of a chiral homoenolate equivalent. Metallated chiral allylamines of the type **429** (M=Li, K) were prepared and alkylated at the γ-position with MeI, EtI, PrI, nBuBr and CH_2=$CHCH_2Br$. Hydrolysis of the resulting enamine yielded β-substituted aldehydes **430** in enantiomeric excesses up to 67%. The authors indicated that preliminary studies with metallated phosphoramidates as chiral homoenolate equivalents were promising.

6.4.2 *Oxygen*

A series of vinyl ethers have been metallated with sec-butyllithium in THF at −65° and the allylic anions **431a–431e** reacted with alkyl halides, 3-methylpropanal and cyclohexanone.[153] In alkylation reactions with n-C_3H_7I the following γ:α ratios were observed:

R=THP,	γ:α = 54:46;	R=Ph,	γ:α = 63:37;
R=C_2H_5,	γ:α = 75:25;	R=t-Bu,	γ:α = 89:11.

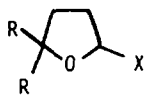
423



424

a, R=n-C_4H_9

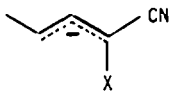
b, R=$Si(CH_3)_3$



425

a, X=pyrrolidino

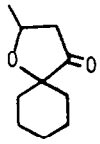
b, X=OCH_2CH_3



426

a, X=$N(CH_3)_2$

b, X=piperidino



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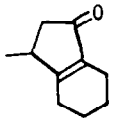
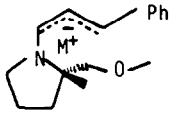
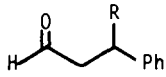


428



429



430

R=CH_3,CH_2CH_3, i-C_3H_{75}

m-C_4H_9, CH_2=CH-CH_2

431

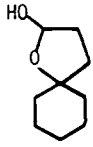
a, R=CH_3

b, R=C_2H_5

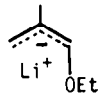
c, R=t-Bu

d, R=THP

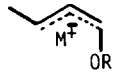
e, R=Ph



432



433



434

Reactions with cyclohexanone gave opposite results:

R=t-Bu,	$\gamma:\alpha = 27:73$;	R=Ph,	$\gamma:\alpha = 24:76$;
R=C_2H_5,	$\gamma:\alpha = 30.70$;	R=CH_3,	$\gamma:\alpha = 72:28$.

The product ratios were cation dependent with the Zn^{2+} reagent showing a high degree of α-addition. Acid hydrolysis of the γ-adduct of Li **431a** gave lactol **432** in 72% yield. Substituted allylic anions **433** and **434** were also prepared and **433** exhibited γ-regioselectivity with alkylating agents but no selectivity with cyclohexanone.

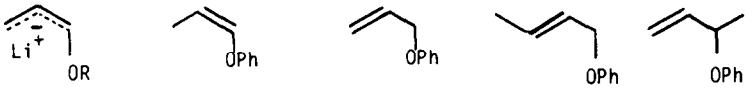
Still and MacDonald[154] prepared a series of allylic anions **435a–435d** and studied the alkylation with MeI, EtI, n-PrI, i-PrI, $C_6H_{13}I$, n-PrBr and CH_2=$CHCH_2Br$. While **435a** reacts with CH_3I to yield 71% of γ-product, anions **435b** and **435c** which gave high yields (>95%) of α- and γ-products showed higher γ-selectivities with primary halides but lower γ-selectivities with $C_6H_{13}I$ (39% γ) and allyl bromide (78% γ). Apparently only the (Z)-enol silyl ethers were formed. In a subsequent publication the authors[155] demonstrated that lithium salt **435a** in THF/HMPA undergoes α-attack with a variety of aldehydes and ketones with a high degree of regioselectivity (71–99%) and stated that the regiochemistry of allyloxy anions is determined by the nature of the electrophilic species; unsymmetrically substituted allyllithium compounds preferentially react with alkyl halides and protons at the site of highest electron density and with carbonyl compounds via a rearrangement process which involves the lithium cation.

Schlosser *et al.*[156] also studied the metallation of ethers **436** and **437** and alkylated the resulting anions with CH_3I. While **436** gave only **438** in 84% yield, **437** yielded **438** (47%) and **439** (16%).

Martin and Garrison[157] prepared phosphonium salt **440** by adding triphenylphosphonium bromide to methoxyallene and converted it into 3-methoxyallylidene triphenylphosphine **441** with n-BuLi in THF at −50°. Wittig reagent **441** was added to a variety of aldehydes and ketones **442a–442h** and the enol ethers **443a–443h** were converted to the corresponding α,β-unsaturated aldehyde **444a–444h** in yields which ranged from 40–73%.

In an interesting approach to the γ-addition of allylic anions **401** (X=OR and SR), Evans *et al.*[158] converted organolithium reagents into organozinc and organocadmium reagents which added with α-regioselectivity to α,β-unsaturated carbonyl compounds **445a–445c** and **446**. The dienols as their potassium salts (e.g. **447**) were thermally rearranged (oxy-Cope) with varying successes (11–93%) to the methyl enol ethers (for example **448**) of the corresponding 1,6-dicarbonyl compounds. Although it was not mentioned in the publication, the enol ethers presumably could be converted into 1,6-diketones or ketoaldehydes. The overall reaction corresponds to the addition of a homoenolate equivalent to an α,β-unsaturated ketone and avoids the persistent problem of the ambident reactivity of enones and allylic anions.

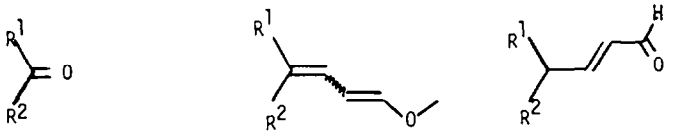
As an extension of the study of chemistry of the adducts of organosilanes R_3SiA (A=C≡N, $P(=O)R_2$, SR) to aldehydes and ketones, Evans *et al.*[159] prepared and metallated allylic α-silyloxyphosphonamides **449a** and **449c** with n-BuLi in THF at −65°. Addition of alkyl halides (CH_3I, $PHCH_2Cl$, $C_6H_{13}Br$) and carbonyl compounds (PhCHO, i-PrCHO, cyclohexanone) at −78° gave high γ-regioselectivities (79%) with bulky alkylating reagents and PhCHO. Hydrolysis of the enol phosphonamides **450** with CH_3ONa/CH_3OH (R_2 = alkyl) yielded the corresponding esters and the aldehyde adducts gave γ-lactols when treated with tetra-n-butylammonium fluoride in THF at 25°. Attempts to prepare the binucleophilic synthon **451** by bismetallating **449** so that bis substitution could be accomplished was thwarted by O-alkylation. For example, the bis-anion prepared from **449a** with 2 equivalents of sec-BuLi in DME at −50° when reacted with excess CH_3I followed by methanolysis gave **452** and **453** in a ratio of 17:83.



435 436 437 438 439

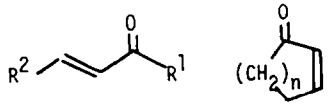
a, R=Ph
b, R=Si(CH$_3$)$_3$
c, R=Si(CH$_3$)$_2$n-C$_4$H$_9$
d, R=Si(CH$_3$)$_3$

440 441



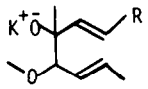
442 443 444

443
a, R^1=H; R^2=n-C$_6$H$_{13}$
b, R^1=H; R^2=c-C$_6$H$_{11}$
c, R^1=H; R^2=H
d, R^1=CH$_3$; R^2=(CH$_2$)$_2$CH(CH$_3$)$_2$
e, R^1-R^2= -(CH$_2$)$_5$-
f, R^1-R^2= 1-methylcyclohexyl
g, R^1-R^2= norbornyl
h, R^1=CH$_3$; R^2=CH=C(CH$_3$)$_2$

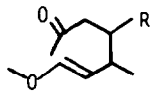


445
a, $R^1=R^2=H$
b, $R^1=CH_3$; $R^2=H$
c, $R^1=R^2=CH_3$

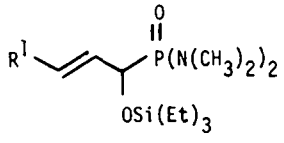
446
n=5,6



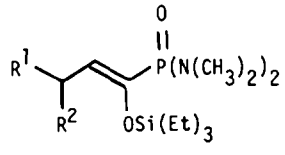
447



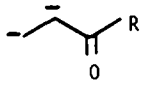
448



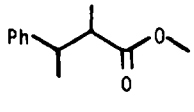
449
a, $R^1=Ph$
b, $R^1=CH_3$
c, $R^1=H$



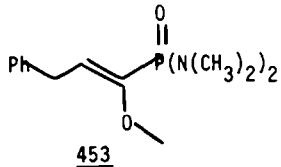
450



451



452



453

Conversion of the lithium enolate to the tetra-n-butylammonium enolate raised the C:O alkylation (**452**:**453**) ratio to 57:43.

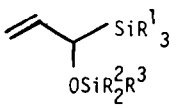
As a continuation of their studies on the chemistry of allylsilanes Sakurai *et al.*[160] prepared a variety of α-siloxyallylsilanes **454a–454e** and reacted them with a series of saturated and unsaturated acid chlorides in CH_2Cl_2 in the presence of $TiCl_4$. The intermediate enol silyl ethers **455** (R^4 = alkyl groups and $(CH_3)_2C{=}CH{-}$), products of γ-addition, were hydrolyzed to the γ-ketoaldehydes in yields which ranged between 20–80%.

In an interesting approach Kuwajima and Kato[161] prepared a series of β-lithiated enol trimethylsilyl ethers **456a–456c** by rearrangement of the lithium salts of the corresponding 1-trimethylsilylallylic alcohols. Alkylation with alkyl halides (CH_3I and n-BuI) gave the corresponding enol ethers **457a–457f** in yields which ranged between 63–74%. High stereoselectivity (Z-isomers) and regioselectivity (γ-addition) were observed.

6.4.3 *Sulfur*

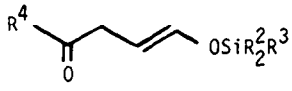
Biellmann and Ducep[162] prepared lithium thioallyl anions **448**, **459** and **460** by reacting the corresponding sulfides with n-BuLi in THF at −30° in the presence of DABCO and alkylated the anions with CH_3I, $CH_2{=}CHCH_2Br$, and $(CH_3)_2C{=}CHCH_2Br$. While **458** yields some γ-addition products (CH_3I, $\alpha:\gamma = 71:22$; $CH_2{=}CHCH_2Br$, $\gamma:\alpha = 62:29$) anions **459** and **460** more highly substituted at the γ-position show a higher α-selectivity (85–100%). In a subsequent publication Biellmann *et al.*[163] described the preparation and addition of **459** to acetone, methyl iodide, allyl bromide and dimethylallyl bromide in the presence of a variety of complexing reagents (DABCO, TMEDA, HMPT and cryptand [2.2.2]. The results were explained on the basis of the involvement of intimate or solvated ion pairs, solvent separated ion pairs and free ions. For example, while in the presence of DABCO **459** reacts with acetone to yield 100% of the γ-adduct, reactions with alkylating agents yield only small amounts of γ-products (1–12%). At −78° substantial amounts of γ-addition was observed (MeI, [2.2.2], $\alpha:\gamma = 60:40$; $CH_2{=}CH_2CH_2Br$, [2.2.2], $\alpha:\gamma = 50:50$; acetone, no complexing agent, $\alpha:\gamma = 25:75$; acetone, TMEDA, $\alpha:\gamma = < 1:90$; acetone, HMPT, $\alpha:\gamma = 40:60$).

Corey *et al.*[164] developed a synthesis of α,β-unsaturated aldehydes utilizing 1,3-bis(methylthio)allyl-



454

a, $R^1=R^2=R^3=CH_3$
b, $R^1=CH_3; R^2=R^3=CH_2CH_3$
c, $R^1=R^2=CH_3$; R^3=t-Bu
d, $R^1=CH_2CH_3$; $R^2=R^3=CH_3$
e, $R^1=R^2=R^3=CH_2CH_3$



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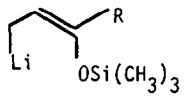
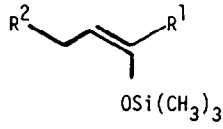


456

a, R=n-Pr
b, $R=CH_2CH_2Ph$
c, $R=C_9H_{19}$



457

a, R^1=n-Pr; $R^2=CH_3$
b, $R^1=CH_2CH_2Ph$; $R^2=CH_3$
c, $R^1=C_9H_{19}$; $R^2=CH_3$
d, R^1=nPr; R^2=n-Bu
e, $R^1=CH_2CH_2Ph$; R^2=n-Bu
f, $R^1=C_9H_{19}$; R^2=n-Bu

lithium **461** in which, unlike other thioallyl anions, both nucleophilic sites are identical. Reaction of **461** with 1-bromopentane yielded 1,3-bis(methylthio)-1-octene (**462**) which when hydrolyzed with 4 equivalents of $HgCl_2$ in aqueous acetonitrile gave *trans*-2-octenal (**463**) in 84% yield. Addition of **461** to aldehydes and ketones gave the corresponding γ-hydroxy-α,β-unsaturated aldehydes in good yield. For example, addition to propanal followed by hydrolysis gave *trans*-4-hydroxy-2-hexenal. Lithium salt **461** reacts with epoxides yielding the corresponding γ-hydroxy-α,β-unsaturated aldehydes, the latter being applied to the synthesis of prostaglandin $F_{2\alpha}$.

Evans *et al.*[165] studied the effect of chelating groups on the regiochemistry of alkylation of thioallyl anion **464** by preparing a series of heteroatom substituted anions and studying their alkylation by n-$C_6H_{13}I$ at low temperature (−30° to −65°). The yields ranged between 78%–95%. The results of the alkylation of **464** and **465** are given in Tables 3 and 4.

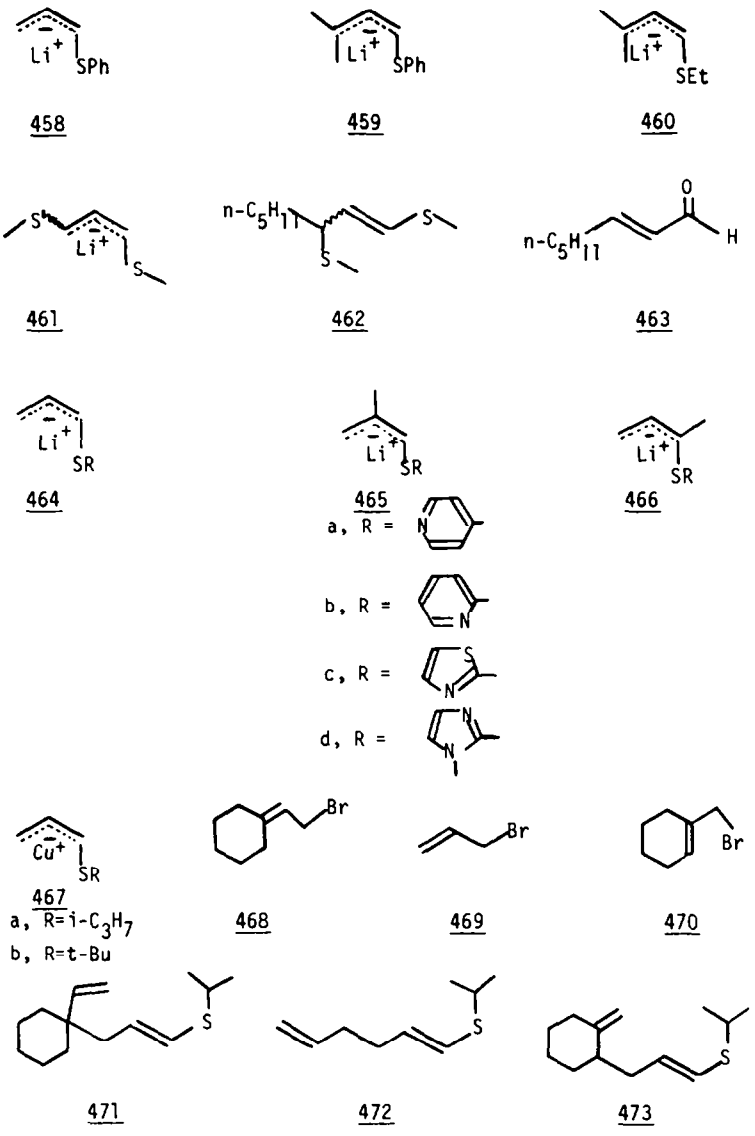
Alkylation of **466b** and **466c** was also studied. Quenching with alkyl bromides or iodides gave the α-

Table 3. Alkylation of **458** and **464**

Substrate	α:γ ratio (THF)	α:γ ratio (THF + 5% HMPA)
458	75:25	68:32
464a	-	88:12
464b	99:1	>99:1
464c	-	>99:1
464d	99:1	>99:1

Table 4. Alkylation of **465**

Substrate	α:γ ratio (THF)	α:γ ratio (THF + 5% HMPA)
465 (R=Ph)	75:25	70:30
465b	90:10	79:21
465c	-	80:20
465d	92:8	84:16



and γ-adducts in excellent yield. In THF **466b** gave α- and γ-adducts in a ratio of 90:10 and in the case of **466c** the α:γ ratio was 80:20. They also observed a dramatic decrease of the α:γ ratio when HMPA was added.

Yamamoto *et al.*[166] studied the regiochemistry of alkylation of the alkylthioallylcopper reagents **467a** and **467b** prepared from the corresponding organolithium at −78° by addition of CuI in ether. Treatment of **467a** with allylic bromides **468**, **469** and **470** yielded **471** (92%), **472** (88%) and **473** (87%), the products of exclusive γ-alkylation to sulfur via an S_N2' process. In contrast, acetone reacts with **467a** with a high degree of α-regioselectivity.

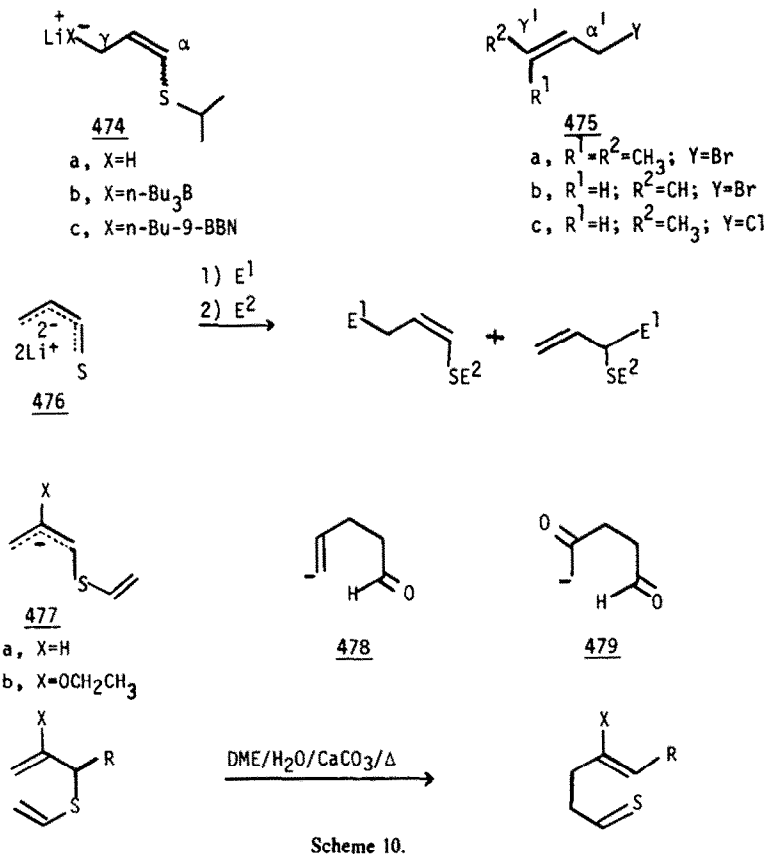
The alkylation of lithium thioallyl borates **474b** and **474c** has also been studied.[167] While **474b** and **474c** react with 3,3-dimethylallyl halides regioselectively α,γ' (92–96%), **474b** and borate **475a** yield substantial amounts of γ,γ' and γ,α' addition: **474a** + **475a** yield 45% γ,α'; **474c** + **475b** yield 18% γ,γ' and 20% γ,α'; **474b** + **475c** yield 15% γ,γ' and 31% γ,α'.

While thioallylic monoanions have been shown to react preferentially at the α-position, Seebach *et al.*[168] established that thioacrolein dianion **476** generated from propenethiol with 2.1 equivalents of n-BuLi in THF at 0° in the presence of 1–2 equivalents of TMEDA reacts preferentially at the γ-position (3:1–4:1) with a variety of electrophiles as shown in Table 5. The yields of addition products ranged from 65–95%.

Yamamoto *et al.*[169,170] in a novel approach elaborated allylvinylsulfide anions **477a** and **477b** into γ-homoenolate equivalents **478** and **479**, respectively. Alkylation of **477a** α to sulfur followed by

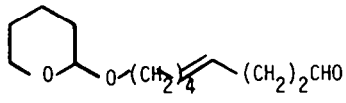
Table 5. Addition of electrophiles to **476**

E^1	E^2	γ:α ratio
C_2H_5Br	C_2H_5Br	77:23
$n\text{-}C_{10}H_{21}Br$	$n\text{-}C_{10}H_{21}Br$	77:23
$C_6H_5CH_2Br$	$C_6H_5CH_2Br$	73:27
$n\text{-}C_5H_{11}Cl$	CH_3I	76:24
$n\text{-}C_6H_{13}Br$	CH_3I	78:22
$n\text{-}C_8H_{17}Cl$	CH_3I	74:26
$i\text{-}C_3H_7Cl$	$C_6H_5CH_2Br$	68:32
$(CH_3)_3SiCl$	$C_6H_5CH_2Br$	76:24
2,2-dimethyloxirane	2,2-dimethyloxirane	78:22
C_2H_5CHO	CH_3I	74:26
C_6H_5CHO	CH_3I	67:33
cyclopentanone	CH_3I	69:31
$C_6H_5COCH_3$	CH_3I	70:30
$(C_6H_5)_2CO$	CH_3I	75:25
CH_3SSCH_3	CH_3I	80:20



Scheme 10.

thio-Claisen rearrangement (Scheme 10) and hydrolysis of the thioaldehyde gave good yields of the corresponding γ,δ-unsaturated aldehydes (R=CH_2Ph, 62%; R=n-C_8H_7, 57%; R = geranyl, 62%). The method was used to construct **480** (55% yield), a key intermediate in the synthesis of the sex attractant of the pink bollworm moth.



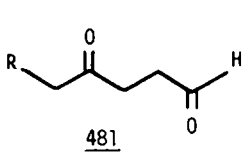
480

Alkylation of anion **477b** with n-amyl bromide, allyl bromide and *cis*-1-bromo-2-pentene, rearrangement of the crude sulfide and hydrolysis gave the γ-ketoaldehydes **481a** (66%), **481b** (70%) and **481c** (56%). The γ-ketoaldehydes served as valuable intermediates in the synthesis of furan, pyrrole and 2-cyclopentenone derivatives. For example, base cyclization (10% $NaOH/CH_3OH/H_2O$) of **481c** yielded **482c** which was converted into *cis*-jasmone by CH_3Li followed by CrO_3 oxidation. Cyclopentenones **483a** and **483b** were also synthesized by a similar sequence.

In a related study the authors[171] elaborated the dianions of thioesters **484a** and **484b** into (*E*)-γ-homoenolate equivalents **486a** and **486b**. Alkylation of dianion **485a** by successive additions of alkyl halide (R^2X; R^2=n-C_8H_{17} and $PhCH_2$) and CH_3I gave the ketene thioacetals **487a** and **487b**. Thio-Claisen rearrangement followed by ethanolysis in the presence of $CuCl_2/CuO$ gave the (*E*)-γ,δ-unsaturated acids **488a** (63%) and **488b** (70%). Anion **485b** was converted via **477c** into disubstituted (*E*)-γ,σ-unsaturated ester **488c** in 70% overall yield. Thio-Claisen rearrangement of the dialkylated product also provides a route to dithioesters.

6.4.4 *Silicon*

While allylisilyl anions were known to react with electrophiles at the α- and γ-sites, it remained for Magnus *et al.*[172,173] to develop the methodology for converting the γ-adducts obtained from addition of



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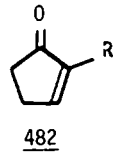
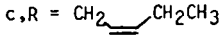
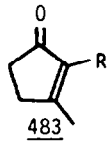


482

a,R = n-C_5H_{11}
b,R = $CH_2CH{=}CH_2$
c,R = 



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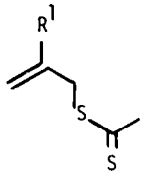

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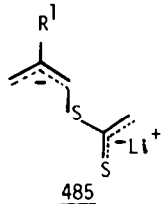
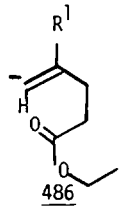


485

a,R^1 = CH_3
b,R^2 = H



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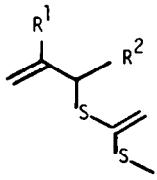
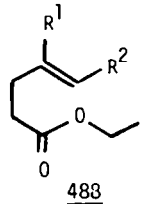


487

a,R^1 = CH_3; R^2 = n-C_8H_{17}
b,R^1 = CH_3; R^2 = CH_2Ph
c,R^1 = H; R^2 = n-C_8H_{17}



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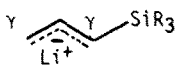

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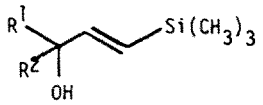

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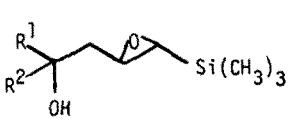

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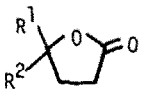

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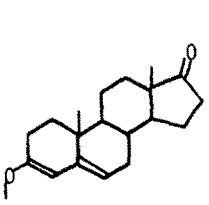
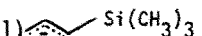
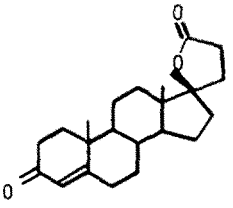


494

1) 
2) H_3O^+
3) $VO(acac)_2$/t-BuOOH
4) $CH_3OH/BF_3(OEt)_2$
5) Jones OX.



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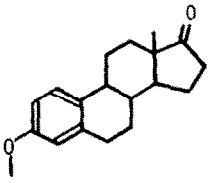

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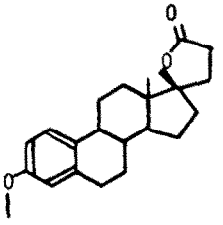

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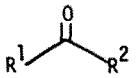

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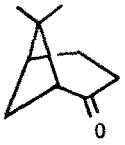

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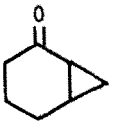

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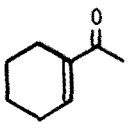

499

a, R^1=H; R^2=c-C_6H_{11}
b, R^1=H; R^2=Ph
c, R^1=H; R^2=$CH(OCH_3)_2$
d, R^1=R^2=Ph

the allyltrimethylsilyl anion (R=CH_3) to aldehyde and ketones into lactols and lactones. Anion **489** (R=CH_3) prepared from commercially available allyltrimethylsilane and sec-butyllithium in THF at −76° containing 1 equivalent of TMEDA was reacted with a variety of aldehydes and monocyclic and bicyclic ketones at a range of temperatures (0° to −78°) and the vinyl silanes **490** were obtained in yields which ranged from 65–97%. The vinyl silanes were converted to α,β-epoxysilanes **491** with m-chloroperbenzoic acid and the epoxysilanes were transformed to the O-methyl lactols **492** by dry CH_3OH in $BF_3{\cdot}O(Et)_2$. The lactols were converted to γ-lactones **493** by Jones' reagent. The results of their study are documented in Table 6.

The steroids 3-methoxyandrosta-3,5-dien-17-one (**494**) and estrone-O-methyl ether (**495**) were converted to the corresponding lactones.

Table 6. Reaction of allyltrimethylsilanion with carbonyl compounds

Carbonyl substrate	Vinylsilane % yield	α,β-epoxide	O-methyl-lactol	lactone
	53	89	51	75
	65	94	78	76
	96(crude)	90	90	80
	86	88	98	77
	66	94	10	-
	71	90	-	-
	89	89	75	75
	97	88	22	-
	65	92	97	80
	80	-	-	-
	65	-	-	-

Table 7. Regioselectivity in the reaction of 1-trimethylsilylallyl carbanion with acetophenone and benzaldehyde

Substrate	Reaction Conditions	Relative Amount γ	α
acetophenone	n-Butyllithium	100%	
	n-BuLi/TMEDA/$ZnCl_2$	100%	
	n-BuLi/TMEDA/CdI_2	100% [a]	
	n-BuLi/TMEDA/$MgBr_2$	8%	92% [b]
	n-BuLi/$MgBr_2$	14%	86% [b]
	n-BuLi/TMEDA/$MgBr_2$ premixed with carbonyl compound	43%	57% [b]
	t-BuLi/HMPA/$MgBr_2$	<5%	>95% [c]
	t-BuLi/HMPA/$MgBr_2$ premixed	~20%	~80% [c]
benzaldehyde	t-BuLi/HMPA	100%	
	t-BuLi/HMPA/$MgBr_2$ premixed	40%	60% [e]
	t-BuLi/HMPA/$MgBr_2$	40%	60% [d]

[a] The yield of the γ-alcohol is poor. There is however no α-product.
[b] 2 diastereomers were formed in a ratio of 2:1 according to nmr.
[c] Obtained as diene. [d] one diastereomer was formed according to nmr.
[e] Some of the α-product was obtained as the diene.

Chan and Law[174] studied the effect of metal halides on the regiochemistry of addition of **489** to carbonyl compounds. While $ZnCl_2$ and CdI_2 promote γ-addition $MgBr_2$ gives predominately α-addition (Table 7). The authors suggested that $MgBr_2$ complexes with the carbonyl group rendering it a more reactive electrophile.

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