Tetrahedron Vol 39, No 3, pp 345 to 394, 1983
Printed in Great Britain

0040-4020/83/030345-50$25.00/0
Pergamon Press Ltd

TETRAHEDRON REPORT NUMBER 142

THE CHEMISTRY OF 1,2-CARBONYL TRANSPOSITION

VINAYAK V. KANE*
Department of Chemistry, University of Arizona, Tucson, AZ 85721, U.S.A.

and

VISHWAKARMA SINGH and ARNOLD MARTIN
Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, AZ 85721, U.S.A.

and

DONALD L. DOYLE
108 Berger Street, Somerset, NJ 08873, U.S.A.

(*Received in USA 22 September* 1981)

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INTRODUCTION

There has been considerable interest over the years in finding suitable methods in organic synthesis for the selective chemical transformation of a functional group. Functional group transposition in most cases means a reaction or sequence of reactions in which a functional group (E), originally attached to carbon atom C-3, is transferred to a carbon atom other than C-3 in the same molecule as illustrated below (Scheme 1).

Scheme 1.

In 1974, Evans and Andrews[1] proposed a new concept by defining the reactions involving functional group transfer as a "1,n-inversion operation" and discussed its relation with the "charge affinity inversion operation". More recently the relocation or transposition of functional groups has been given a new general name, "functional metathesis" (metathesis, from the Greek word *metatithenai* meaning to transpose), by Reusch.[2]

The carbonyl group (C=O), in its various forms (aldehydes, ketones, carboxylic acids and derivatives), is the most important functional unit in organic chemistry. It is generally considered a functional group of choice in organic synthesis. The unparalleled importance of carbonyl compounds has promoted a continuous search for newer methods for their preparation. This activity has not only resulted in novel syntheses of carbonyl compounds and their derivatives but has also resulted in development of a new and fascinating synthetic methodology based on the carbonyl functionality.

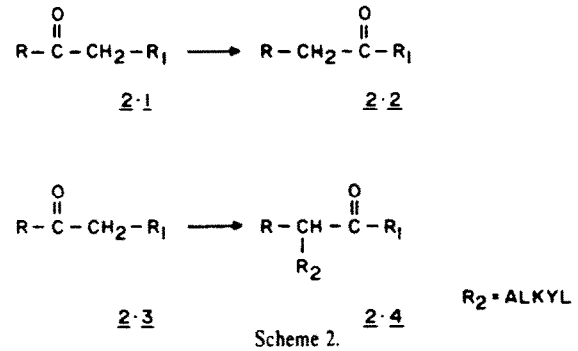
The versatility of the carbonyl function in organic synthesis is based on its capability to undergo a wide variety of bond forming reactions both at the carbonyl carbon atom and sites influenced by its polarity. The carbonyl group participates as a direct electrophilic site for the attack of nucleophiles in

the formation of carbon–carbon or carbon–hetero atom bonds. Another role it plays is in the formation of ketone enolates. These ketone enolates are some of the most useful intermediates in organic synthesis and their nucleophilic properties are extensively used in the formation of carbon–carbon bonds in a number of fundamental reactions such as alkylation,[3] Michael addition[4] and, in recent years, stereospecific aldolization.[5]

Since 1966 another facet of the carbonyl function which has gained considerable attention is reversal of the normal polarity of the group. In the literature, this has been referred to as symmetrization,[6] charge affinity inversion,[1] or dipole inversion. Seebach has suggested the term *Umpolung* as an expression for this general concept.[7] The overall effect is to render the carbonyl carbon nucleophilic, creating the synthetic equivalent of the inherently unstable carbonyl anion. The reaction of the carbonyl anion with electrophiles is known as nucleophilic acylation.

Excellent reviews on various aspects of the chemistry of carbonyl compounds are available.[8] However, despite the importance of carbonyl transposition only one review of limited scope on this significant topic has appeared.[9]

Since the beginning of the twentieth century interest has been very high in finding suitable methods for the transposition of a carbonyl group from its original position to carbon atoms α, β, and γ to it within a molecule (intramolecular). The most common transposition is the exchange of a carbonyl function with an adjacent methylene, referred to as 1,2-carbonyl transposition (Scheme 2). In addition to the straightforward transposition just described, other procedures discussed in this report describe an alkylative 1,2-carbonyl transposition as indicated in **2.3** to **2.4**.

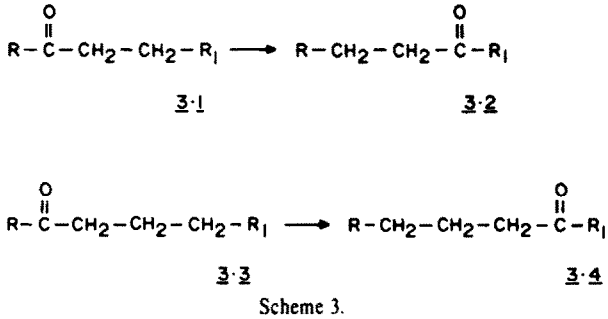


2·1 2·2

2·3 2·4

Scheme 2.

Other forms of transposition of carbonyl groups, important from a synthetic organic chemist's viewpoint, are 1,3-carbonyl transposition[1,9,10,11,12] and 1,4-carbonyl transposition,[13] as shown below (Scheme 3).



3·1 3·2

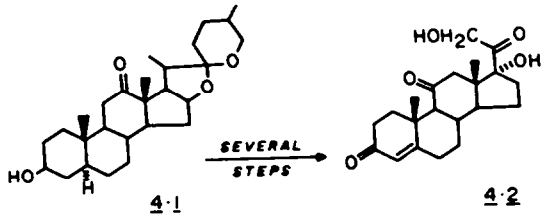
3·3 3·4

Scheme 3.

This review will deal with the subject of 1,2-carbonyl transposition reactions (including those of carboxylic acids, esters and lactones) with *special emphasis* on methods developed since 1966 and up to August 1981. Such related topics as intermolecular 1,2-carbonyl transpositions, homologation reactions, insertions of diazo-alkanes with ketones, and one carbon elongation of ketones and aldehydes,[14] will not be included.

Circumstances requiring 1,2-ketone transposition methodology are of two general types. The most obvious involves the conversion of a readily accessible to an otherwise difficulty obtainable compound.

This is clearly demonstrated in the work of Cornforth[15] and Djerassi[16] in the conversion of hecogenin a 12-keto steroid **4.1** which is obtained as a by-product in the manufacture of sisal fiber to cortisone **4.2**, a therapeutically active 11-keto steroid (Scheme 4).

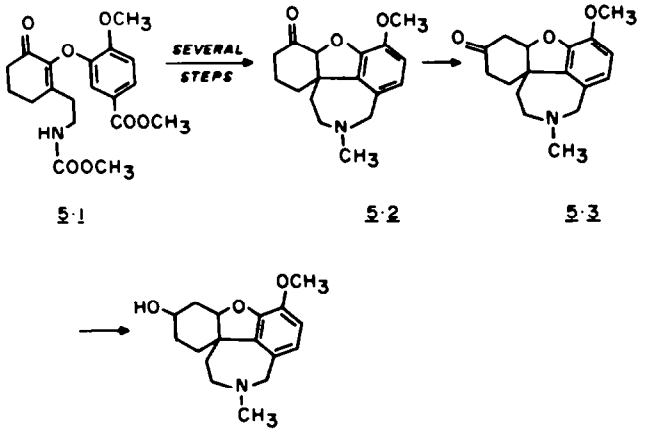


4·1 4·2

Scheme 4.

The transposition of a ketone group from its original position to an adjacent methylene may also ultimately be required as a part of the strategy involved in the synthesis of a complex organic structure. The three examples which follow will serve to illustrate this point.

An interesting example of this type of conversion was provided by Schultz[17] in an elegant synthesis of dl-lycoramine **5.4** (Scheme 5).

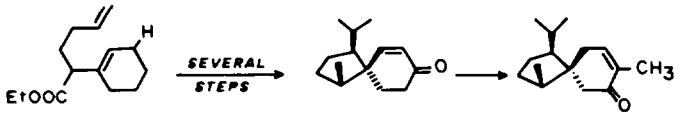


5·1 5·2 5·3

5·4

Scheme 5.

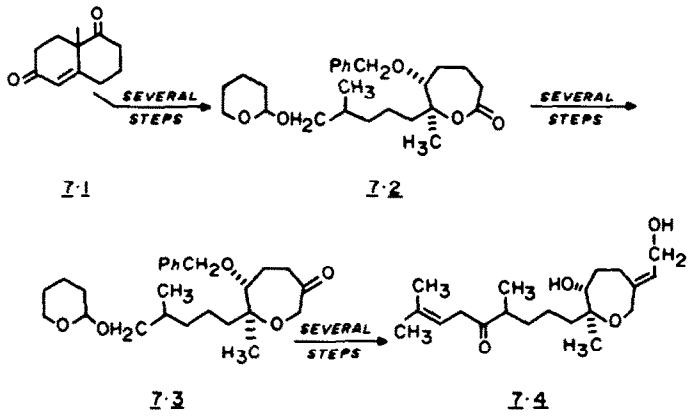
In a very novel approach to (±) acorenone-B **6.3** Oppolzer and Mahalanabis[18] have utilized a 1,2-alkylative ketone transposition (Scheme 6).



6·1 6·2 6·3

Scheme 6.

During the course of our own work on the recently isolated monocyclic diterpenoid zoapatanol **7.4**,[19] we had the opportunity of transposing lactone **7.2** to β-ketoether **7.3**.[20] (Scheme 7).

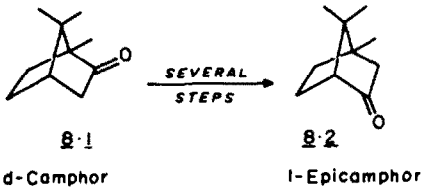


7·1 7·2 7·3 7·4

Scheme 7.

EARLIER TRANSPOSITION WORK ON TERPENES (1912–41)

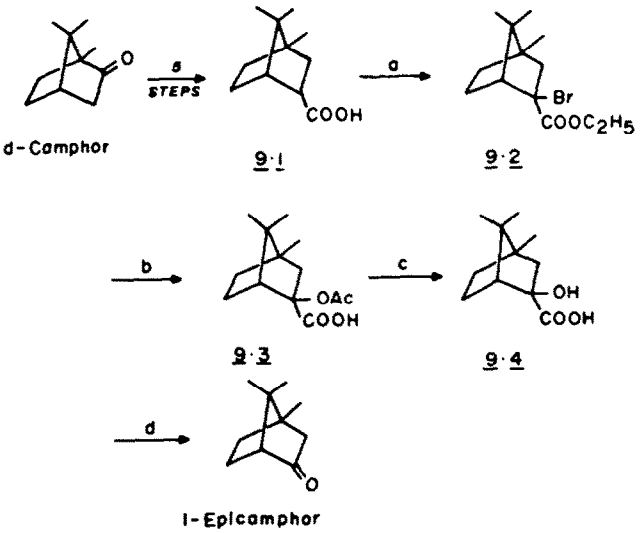
A survey of the literature revealed several unsuccessful attempts at 1,2-carbonyl transposition prior to the successful procedures simultaneously reported by Perkin[21] and Bredt[22] in 1911. The study refers to the transposition of d-camphor **8.1** to l-epicamphor **8.2** (Scheme 8).



8·1 d-Camphor 8·2 l-Epicamphor

Scheme 8.

Lankshear and Perkin[21] prepared l-epicamphor starting from camphane-3-carboxylic acid **9.1** in four steps according to the route outlined below (Scheme 9). The carboxylic acid **9.1** was converted in three steps to the corresponding α-hydroxy camphane-3-carboxylic acid **9.4** which was oxidized to l-epicamphor by permanganate or lead peroxide in acetic acid.

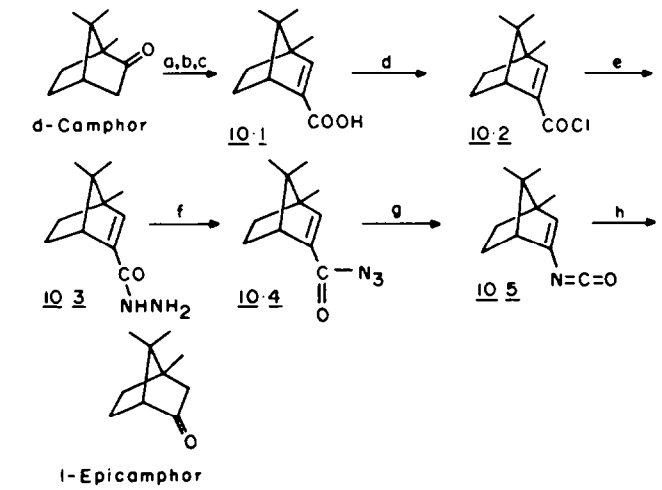


d-Camphor 9·1 9·2 9·3 9·4 l-Epicamphor

a) PCl_5-Br_2; b) KOAc-CH_3COOH;
c) KOH-MeOH-H_2O; d) $KMnO_4$.

Scheme 9.

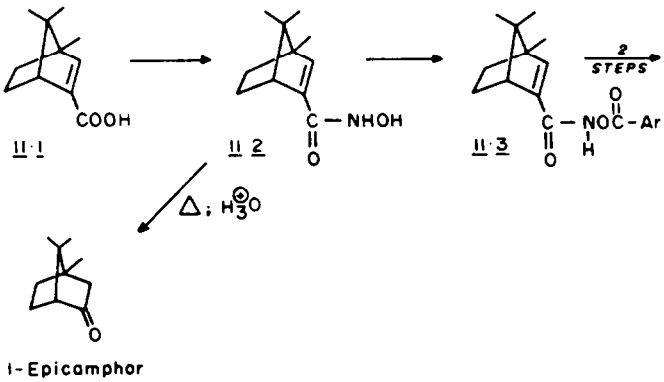
Bredt *et al.*[22] devised another sequence towards l-epicamphor. The requisite starting material, unsaturated carboxylic acid **10.1**, was readily available[23] from d-camphor in four steps. This unsaturated acid **10.1** was converted to **10.4** via the acid chloride **10.2** and hydrazide **10.3**. The azide **10.4** was subjected to Curtius rearrangement, followed by acid hydrolysis to give l-epicamphor (Scheme 10).



a) $NaNH_2$-Et_2O-CO_2; b) Electrolytic Reduction;
c) $(CH_3CO)_2O$-Δ; d) $SOCl_2$; e) NH_2-NH_2;
f) HNO_2; g) Pyrolysis; h) HCl.

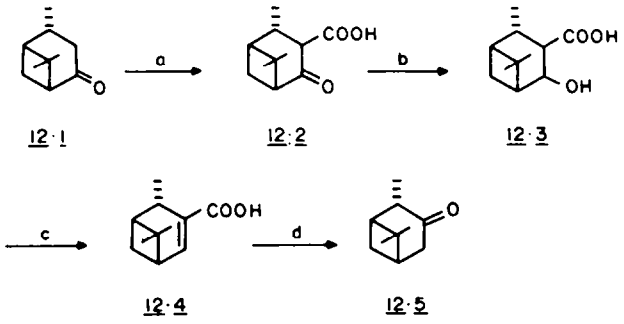
Scheme 10

In a later study Bredt and Perkin,[24] in order to avoid the use of an azide, found that l-epicamphor can be obtained in one step from the hydroxamic acid of bornylene-3-carboxylic acid **11.1**. They report[24] the preparation of the α-hydroxamic acid of bornylene-3-carboxylic acid **11.2** which upon pyrolysis loses water and then undergoes a molecular rearrangement giving l-epicamphor. However, this thermal rearrangement, like that of the azide, was extremely violent. The authors found that this rearrangement can be carried out under very mild conditions by employing an acetyl or a benzoyl derivative of the α-hydroxamic acid **11.3**. By this modification they were able to safely prepare l-epicamphor on a large scale. The authors have also observed that the sodium salt of hydroxamic acid **11.2** undergoes similar transformation to l-epicamphor (Scheme 11).



Scheme 11.

A sequence very similar to that of Bredt[22,23] was utilized by Komppa[25] in the conversion of 2βH-pinan-4-one (verbanone) **12.1** to 2βH-pinan-3-one (pinocamphone) **12.5** as illustrated below (Scheme 12).



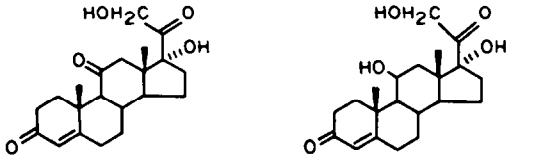
a) $NaNH_2$-Et_2O-CO_2; b) Electrolytic Reduction;
c) $(CH_3CO)_2O$-Δ; d) $SOCl_2$, NaN_3 at 130°, $H_3O^{\oplus}$.

Scheme 12.

Methodology developed in the last decade specifically designed to solve the problem of 1,2-ketone transposition has led to the conversion of *d*-camphor to l-epicamphor in three steps as illustrated in Scheme 56. The simplicity of this conversion does not however detract from the excellent chemistry developed more than half a century earlier by Bredt and Perkin.

1,2-CARBONYL TRANSPOSITION IN STEROIDS

The importance of 1,2-ketone transposition in the steroid field has been well recognized for some time. As early as 1944 Ruzicka and co-workers developed a method for the conversion of cholestan-3-one to cholestan-2-one.[26] Although the chemical characterization of the biologically active steroids (notably cortisone **13.1** and 17α-hydroxycorticosterone **13.2** by Hench, Kendall[27] and Reichstein[28]) occurred much earlier, it was not until the 1950s that a ketone transposition technique was applied to the cortisone problem (Scheme 13). Here also the methodology found its success in transforming readily available 12-ketosteroids occurring in bile acids and sapogenins to the otherwise inaccessible 11-ketosteroids. Since this time, numerous ketone transposition procedures have appeared in the literature as solutions to problems, especially in steroid chemistry, and have employed a wide spectrum of organic reagents in the transposition step. These methods are described below.

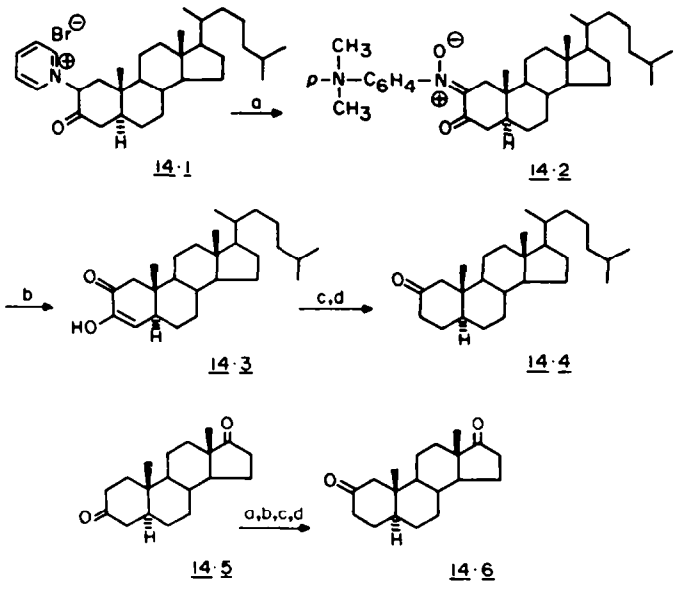


Cortisone — 13·1

17α-Hydroxycorticosterone — 13·2

Scheme 13.

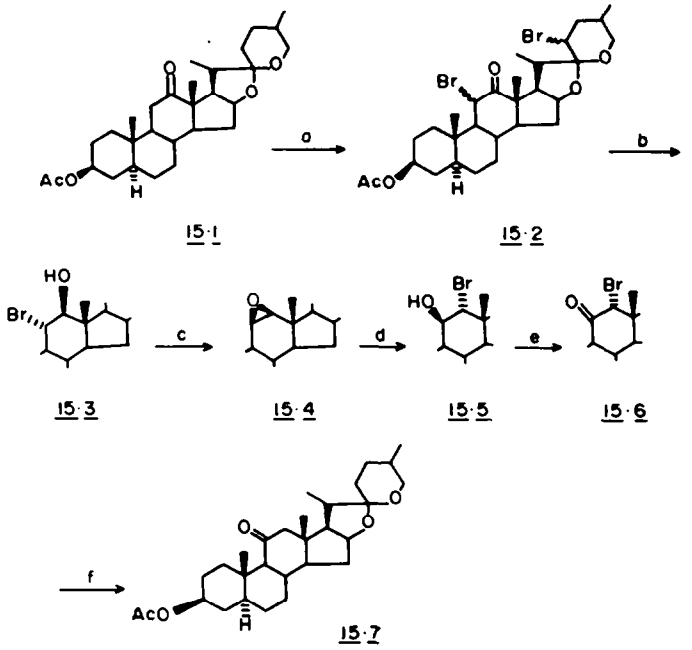
Ruzicka and his associates,[26] as a part of their pioneering studies in steroids, devised a classical synthetic route for 1,2-ketone transposition (Scheme 14). The pyridinium salt of 2α-bromocholestan-3-one **14.1** on treatment with p-nitrosodimethylaniline gave the nitrone **14.2** which on hydrolysis with dilute hydrochloric acid gave Δ^3-cholestene-2-one-3-ol **14.3**. Conversion of **14.3** to its enoltosylate, and subsequent Raney nickel reduction, furnished cholestan-2-one **14.4** (Scheme 14). In 1950 Djerassi and his co-workers[29] applied the sequence described by Ruzicka to synthesize androstan-2,17-dione **14.6** from androstan-3,17-dione **14.5** (Scheme 14).



a) *p*-Nitrosodimethylaniline - $CHCl_3$ - C_2H_5OH, b) $H^{\oplus}$ dilute;
c) TsCl - C_5H_5N; d) W-4 Raney Nickel - C_2H_5OH.

Scheme 14.

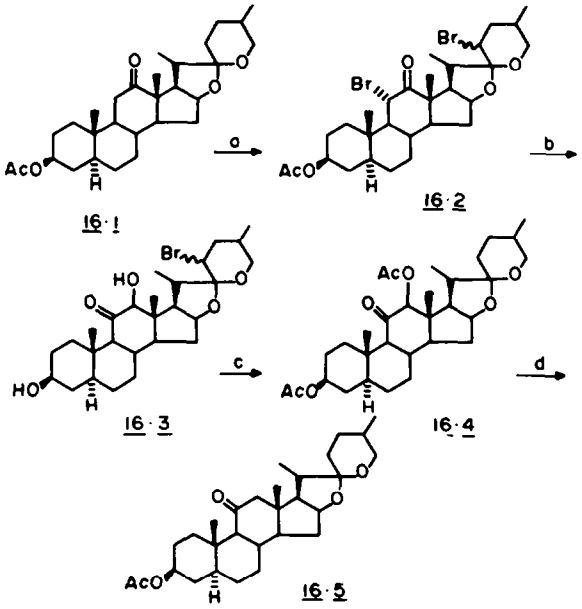
In the early 1950s several groups simultaneously reported[15,16,30] the conversion of hecogenin acetate (12-ketospirostan) to 11-oxotigogenin acetate, the latter being an attractive starting material for the synthesis of cortisone and related steroid hormones. In 1953 Schmidlin and Wettstein[30] published a full account of their work, a six step conversion for this transformation which is outlined below. (Scheme 15). The procedure involved the bromination of the acetoxy ketone (hecogenin acetate) **15.1** to the dibromospirostan **15.2**, which on reduction was transformed to the bromohydrin **15.3**. Treatment of **15.3** with silver oxide gave the β-epoxide **15.4**, which on reaction with hydrobromic acid, gave the bromohydrin **15.5** regioselectively. Subsequent oxidation and reductive dehalogenation gave 11-oxotigogenin acetate **15.7**.



a) Br_2, $CHCl_3$; b) $NaBH_4$; c) $OH^{\ominus}$; d) HBr;
e) CrO_3 - CH_3COOH; f) Zn - CH_3COOH.

Scheme 15.

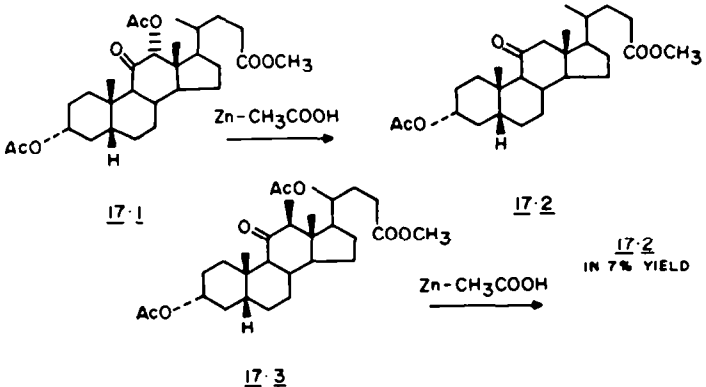
The Glaxo group devised a modified route to carry out the same transposition[31] which is outlined below (Scheme 16). In this sequence the 3-acetoxyketospirostan **16.1** was converted to the dibromo derivative **16.2** which, on alkaline hydrolysis in dioxane or t-butyl alcohol, afforded **16.3**. Acetylation of **16.3** with subsequent debromination with zinc-acetic acid gave the ketol diacetate **16.4**. Further reduction of the acetate **16.4** with calcium and liquid ammonia gave the desired 11-oxotigogenin acetate **16.5**. It is worth mentioning that a considerable amount of experimental work was carried out by the Glaxo group so as to improve the yields in the alkaline hydrolysis step (**16.2** to **16.3**) and also in the removal of 12-hydroxy group (or its derivative). Furthermore, it was shown that the removal of 12-hydroxy group via its mesylate or tosylate was unsuccessful and even the reduction with alkali metals such as sodium, lithium, and potassium in liquid ammonia resulted in a mixture of products. This newly developed reagent, calcium in liquid ammonia, has found considerable use subsequently (Schemes 32, 33, 48).



a) Br_2-C_6H_6 ; b) KOH-MeOH ; c) $(CH_3CO)_2O$, Zn-CH_3COOH ; d) Ca-liq. NH_3.

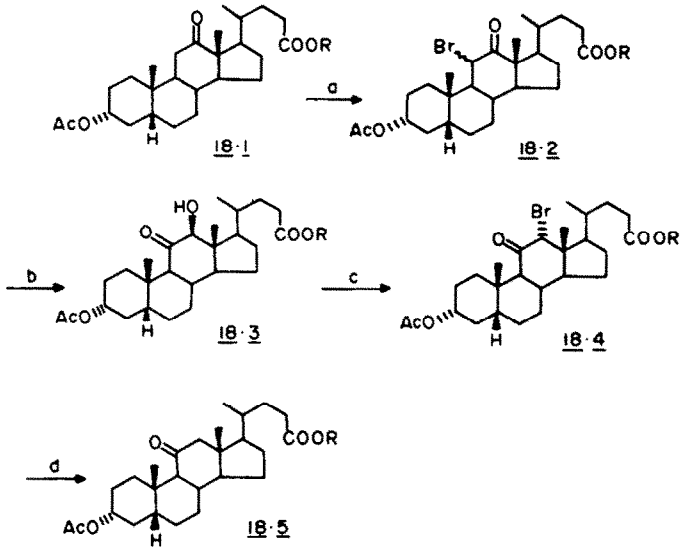
Scheme 16.

Rosenfield and Gallagher[32] studied deacetoxylation of ring C in bile acids and found a remarkable stereoelectronic requirement for deacetoxylation. They found that methyl 3α,12α-diacetoxy-11-ketocholante **17.1** (with the C_{12} acetoxy group axial), upon refluxing with zinc in acetic acid for 24 hours, gave a deacetoxylated product **17.2** in good yield, whereas its epimer, methyl 3α,12β-diacetoxy-11-ketocholante **17.3** (with the C_{12} acetoxy group equatorial), under the same conditions afforded **17.2** in only 7% yield. This stereochemical dependence was in accord with the observation of Barton *et al.*[33] that (a) the four centers involved in 1,2-elimination should lie in one plane and (b) participants should be *trans* and *axial*.



Scheme 17.

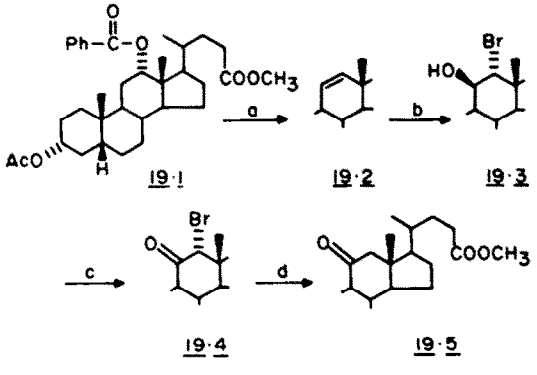
Gallagher[34] found a solution to this problem which they applied in the bile acids as is illustrated below (Scheme 18). The important step of the sequence was the reaction of the ester **18.3** with phosphorus tribromide in chloroform which effected the inversion of the C_{12}-equatorial-hydroxyl to C_{12}-axial-bromide **18.4**, the latter being easily removed by zinc and acetic acid. This was in accordance with the observation regarding the removal of a functional group at the C_{12} position.



a) Br_2-C_6H_6; b) KOH-MeOH; c) PBr_3; d) Zn-CH_3COOH.

Scheme 18.

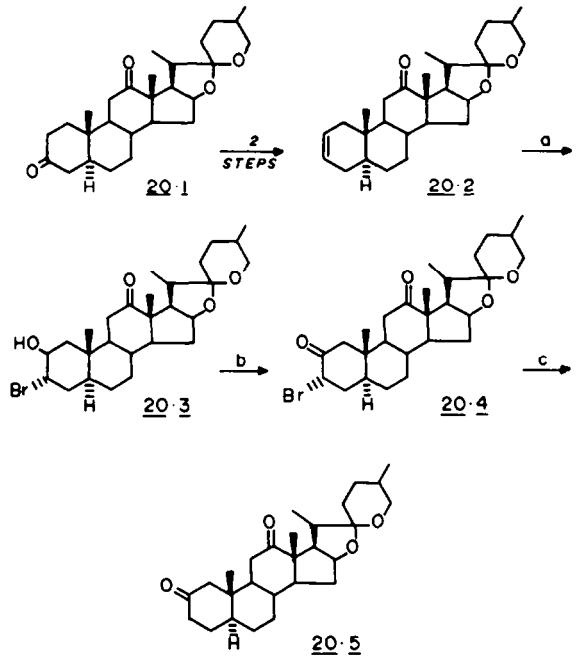
The successful transfer of the C_{12}-oxygen function present in the bile acids to the C_{11}-position was achieved by Reichstein,[35] by a method which utilized an 11-unsaturated steroid. An example of the latter was available by methods involving pyrolysis of 12α-benzoate **19.1**. Methyl 3α-acetoxy-Δ^{11}-cholenate **19.2** was transposed to the C_{11} ketone by the following method. Reaction of **19.2** with hypobromous acid in the form of N-bromoacetamide and water yielded **19.3** as a mixture of bromohydrins). Oxidation of this mixture with chromium trioxide, followed by debromination with zinc and acetic acid, then furnished 3α-acetoxy-11-ketocholanate **19.5** (Scheme 19).



a) Pyrolysis; b) NBA(HOBr)-H_2O; c) CrO_3; d) Zn-CH_3COOH.

Scheme 19.

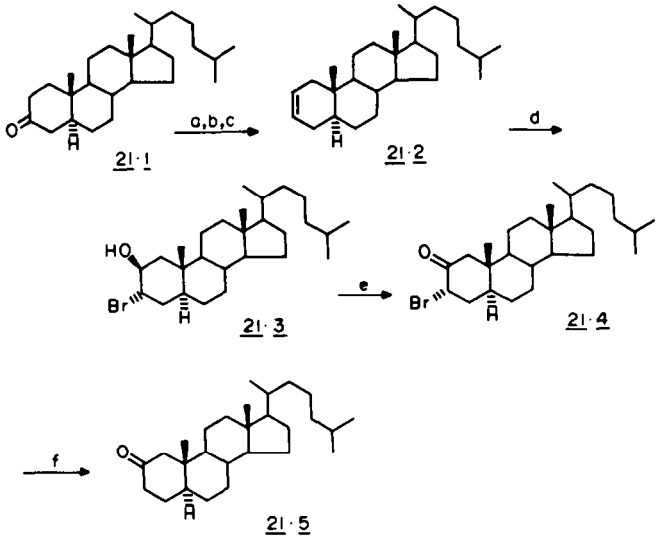
This relatively shorter sequence was very elegantly and independently used by Slates and Wendler[36] for the conversion of 22a, 5α-spirostane-3,12-dione **20.1** to 22a, 5α-spirostane-2,12-dione **20.5** (Scheme 20).



a) HOBr; b) CrO_3-H_2SO_4-$(CH_3)_2CO$; c) Zn-CH_3COO

Scheme 20.

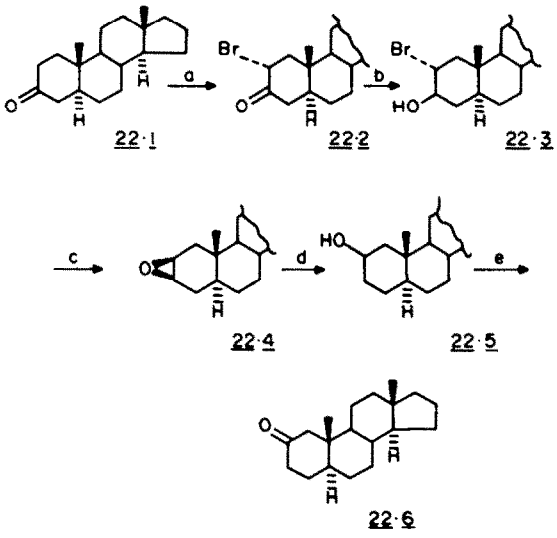
Gurst and Djerassi,[37] as an additional example, in a mass spectrometric study of 2-oxo-5α-steroids and 3-oxo-5α-steroids, converted the 3-oxo-steroids to the 2-oxo-compounds. They investigated two routes which are outlined below. Their route, (Scheme 21) although independently investigated, was similar to routes described above.



a) $NaBH_4$; b) TsCl-C_5H_5N; c) Collidine or Al_2O_3;
d) NBS-$HClO_4$; e) CrO_3-H_2SO_4-$(CH_3)_2CO$; f) Zn-CH_3COOH.

Scheme 21.

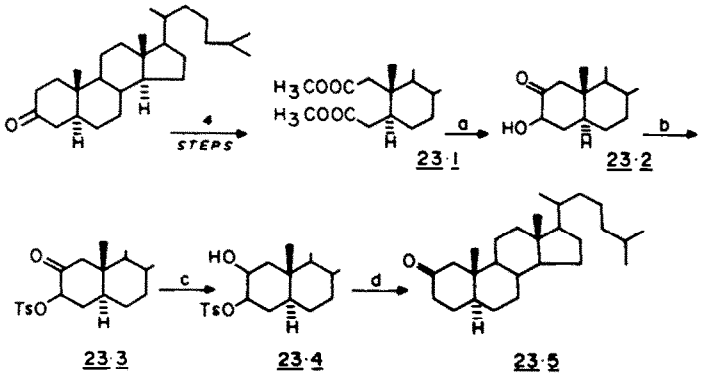
Edwards and his associated at Syntex,[38] Counsell and his group at Searle,[39] as well as Gardi *et al.*[40] have published similar transpositions in the androstane series. The yields were low in these procedures because of mixtures obtained in the tosylate elimination and also in the hypobromous acid addition. A second procedure outlined below eliminates some of these problems.[37] The 3-oxo-steroid **22.1** was brominated, then reduced with lithium tri-t-butoxyaluminum hydride to give a mixture containing the diequatorial bromohydrin **22.3**, which was purified by chromatography. The bromohydrin **22.3** on treatment with potassium hydroxide in methanol gave the epoxide **22.4**. Reduction with lithium aluminum hydride (diaxial opening) gave the alcohol **22.5**, which was subjected to Jones oxidation to afford the desired 2-oxo-5α-steroid **22.6** in approximately 20% overall yield (Scheme 22).



a) Br_2-$CHCl_3$; b) $NaBH_4$-CH_3OH; c) KOH;
d) $LiAlH_4$-Ether; e) CrO_3-H_2SO_4-$(CH_3)_2CO$.

Scheme 22.

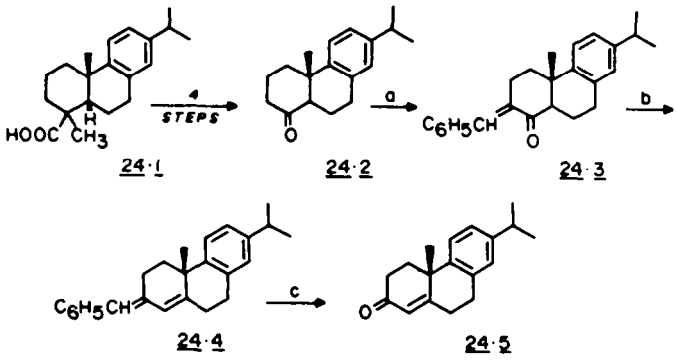
A totally different approach to 1,2-ketone transposition was provided by Sheehan and Erman.[41] Acyloin condensation (Na in liquid ammonia and ether) of 2,3-secocholestane-2,3-dioicacid dimethyl ester **23.1** afforded a mixture from which 3β-hydroxycholestan-2-one **23.2** was isolated by chromatography. Treatment of **23.2** with *p*-toluenesulfonyl chloride in pyridine gave the tosylate **23.3**. Subsequent reduction of **23.3** with sodium borohydride and treatment with collidine gave cholestan-2-one **23.5**. Although the overall yield was about 40%, this method employed rather extreme conditions of oxidative cleavage and reductive recyclization, which would certainly preclude its use in the presence of other functional groups sensitive to oxidation, reduction, or a strong base (Scheme 23).



a) Na-liq. NH_3; b) TsCl-C_5H_5N; c) $NaBH_4$-C_5H_5N-CH_3OH;
d) Collidine.

Scheme 23.

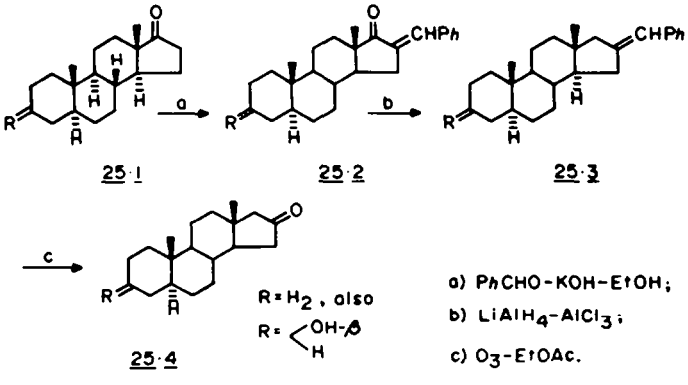
A convenient methodology for 1,2-carbonyl transposition with the incorporation of a double bond was developed as early as 1953 by Zeiss and Martin[42] during their investigation on dehydroabietic acid. They reported the conversion of 1-ketonordehydroabietane **24.2** to 2-keto-$\Delta^{1,11}$-nordehydroabietane **24.5**. The key reactions involved were the introduction of an α-arylidene group by aldol condensation of an aromatic aldehyde with the carbonyl group, and its removal in the last step by ozonolysis to create the newly transposed carbonyl function. The ketone **24.2** (previously obtained from dehydroabietic acid **24.1** in four steps) was condensed with benzaldehyde in aqueous, alcoholic sodium hydroxide and gave the benzylidene derivative **24.3**. Reduction with aluminum isopropoxide in boiling xylene was accompanied by elimination to yield **24.4**. Selective ozonolysis of **24.4** in ethyl acetate at −60° afforded the desired transposed ketone **24.5** in less than 20% overall yield. This sequence is outlined below (Scheme 24). As will be observed later, ozonolysis was the reagent of choice of many investigators in the creation of new ketonic functionality.



a) C_6H_5CHO–Ethanolic KOH; b) $Al(OC_3H_7)_3$ in Xylene;
c) O_3–EtOAc.

Scheme 24.

Jones, Meakins, and their co-workers[43] utilized the above method with a modification to synthesize 16-keto steroids from 17-keto derivatives in three steps as outlined below (Scheme 25). The α-benzylidene derivative **25.2** obtained from 17-keto-steroid **25.1** ($R=H_2$) was reduced with lithium aluminum hydride and aluminum chloride to the 16-benzylidene derivative **25.3**. Ozonolysis of the latter gave the desired 16-ketone **25.4** ($R=H_2$) in 82% overall yield.

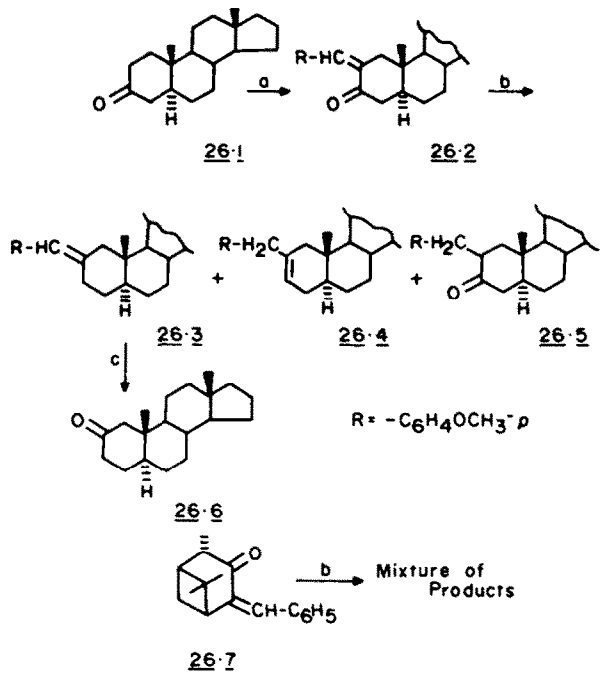


a) PhCHO–KOH–EtOH;
b) $LiAlH_4$–$AlCl_3$;
c) O_3–EtOAc.

Scheme 25.

Reduction with lithium aluminum hydride and aluminum chloride in tetrahydrofuran, although highly successful in the five membered ring benzylidene ketone, was shown by Fetizon and colleagues[44] in their 1,2-ketone transposition in ring A-steroids to give a mixture of products (Scheme 26). Also, Jones and

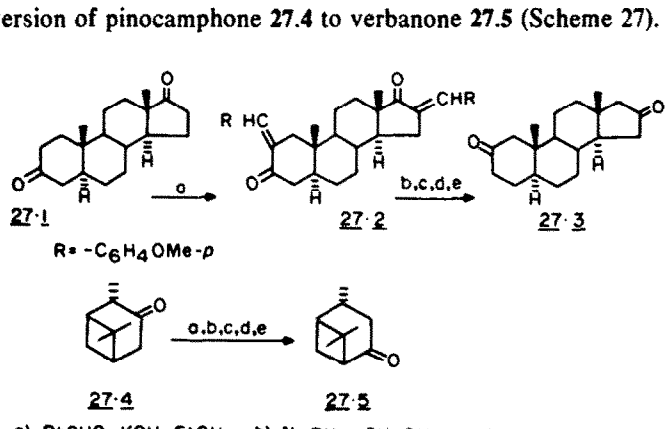
Webb[45] have shown that benzylidene ketone **26.7** on reduction with lithium aluminum hydride and aluminum chloride leads to a mixture of products. Success in the reduction of **25.2** to **25.3** has been attributed to the higher relative stability of the conjugated olefin system exocyclic to ring D when compared to ring A.[44]



a) CHO-C_6H_4-OCH_3-*p*-KOH-EtOH;
b) $LiAlH_4$-$AlCl_3$; c) O_3-EtOAc.

Scheme 26.

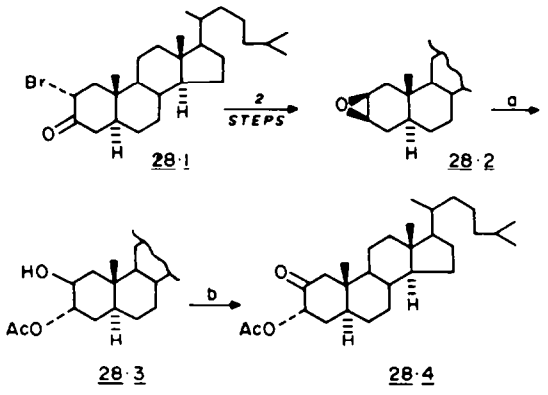
In a later study Jones, Meakins, and their associates[46] reported a general route by which a double transposition of steroidal 3,17-diketone to steroidal 2,16-diketone could be carried out. This pathway is illustrated below (Scheme 27). Reduction of the bisbenzylidine ketone **27.2** with sodium borohydride followed by acetylation and ozonolysis gave 3β,17β,-diacetoxy-5α-androstane-2,16-dione, which on treatment with zinc and acetic acid, gave the desired diketone **27.3** in 46% yield. Although it has been pointed out before that only axial acetoxy groups are easily removed, this result suggests that the flexibility of ring-A allows the departing acetoxy group to adopt a quasi-axial conformation and thus to be removed considerably faster than the more rigidly confined 17β-acetoxy group. This explains the modest yield obtained in the zinc and acetic acid reduction. This method was adopted by Jones and Webb[45] for the conversion of pinocamphone **27.4** to verbanone **27.5** (Scheme 27).



a) PhCHO-KOH-EtOH; b) $NaBH_4$-CH_3OH; c) $(CH_3CO)_2O$-C_5H_5N;
d) O_3-EtOAc; e) Zn-CH_3COOH.

Scheme 27.

In the preceding paragraphs, it has been shown that 1,2-ketone transposition of 3-keto-steroids has proceeded through the intermediacy of 3β-acetoxy-2-keto-steroids. Williamson and Johnson[47] had clearly demonstrated that such intermediates could be synthesized very easily from 3-keto-steroids. Hence, in a formal sense, this sequence constitutes the 1,2-ketone transposition outlined below (Scheme 28). The 2α-bromocholestane-3-one **28.1** was reduced to a mixture of bromohydrins, one of which was converted to 2β,3β-oxidocholestane **28.2**. This epoxide was cleaved with acetic acid to 2β-hydroxy-3α-acetoxycholestane **28.3** which, on oxidation with Jones' reagent, gave 3α-acetoxycholestane-2-one **28.4**.

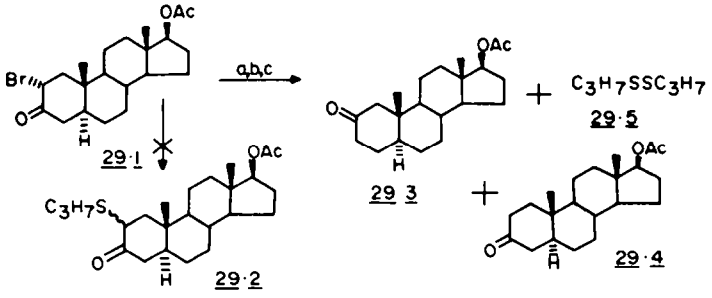


28·1 28·2 28·3 28·4

a) CH_3COOH; b) CrO_3-H_2SO_4-$(CH_3)_2CO$.

Scheme 28.

Clarke,[48] in an attempt to prepare 17β-acetoxy-2ξ-n-propylmercapto-5α-androstan-3-one **29.2** from the corresponding 2α-bromosteroid **29.1**, discovered an unusual reaction (Scheme 29). When a solution of 17β-acetoxy-2α-bromo-5α-androstan-3-one **29.1** and four molar equivalents of n-propyl mercaptan in chloroform was refluxed the expected product **29.2** was not obtained but instead, after hydrolytic work-up, followed by reacylation 17β-acetoxy-5α-androstan-2-one **29.3** was isolated (in 41% yield) along with n-dipropyl disulphide **29.5** and 17β-acetoxy-5α-androstan-3-one **29.4**. It is interesting to note that a separation of **29.3** and **29.4** was simply achieved via formation of the sodium bisulfite adduct; **29.4** forms a bisulfite addition product in high yield whereas the corresponding **29.3** does not form an addition product. This novel transformation constitutes a short method for ketone transposition in moderate yield.



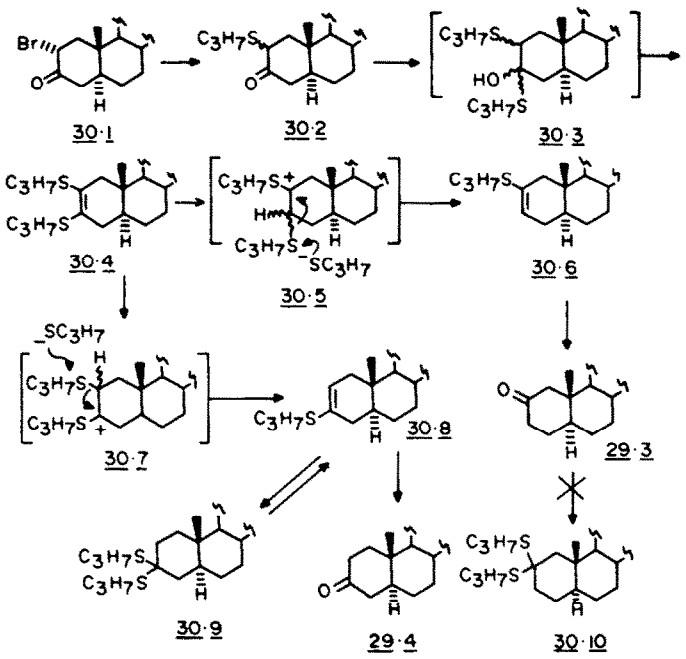
29·1 29·5 29·3 29·4 29·2

a) C_3H_7SH-$CHCl_3$; b) $(CH_3CO)_2O$-C_5H_5N;
c) Silica-Gel Chromatography.

Scheme 29.

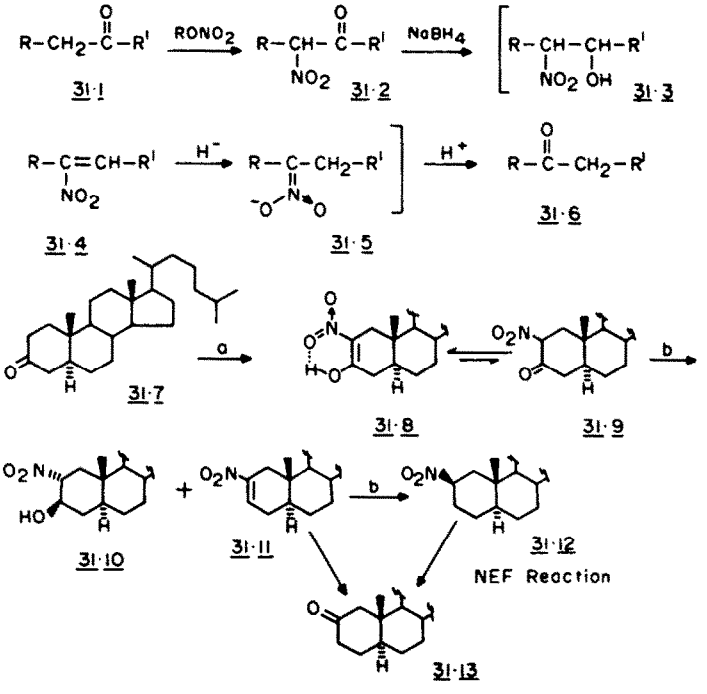
However, the procedure described by Clarke is not of general applicability.[49] The proposed mechanism of this reaction is outlined (Scheme 30). A symmetrical intermediate **30.4** has been proposed. Gas chromatographic analysis of the product mixture obtained on treatment of **30.4** with dry *n*-propyl mecaptan and dry hydrogen bromide in dry chloroform suggested the formation **30.6**, **30.8** and **30.9** but not of **30.10**. However, hydrolysis with aqueous methanolic hydrochloric acid did not yield any ketonic

material. Further work is needed to clarify these points. The nonformation of **30.10** has been attributed to 1,3-diaxial interaction involving the 19-angular methyl group. It would be interesting to investigate the 19-nor series to see if an intermediate similar to **30.10** could be isolated.



Scheme 30.

A novel 1,2-ketone transposition of carbonyl groups via 2-nitroketones was invented by Hassner and his group.[50] The scheme which they envisioned is outlined below (Scheme **31**). It was known that nitration of ketones with alkyl nitrate in the presence of potassium t-butoxide can be carried out successfully in good yield to give α-nitro ketones **31.2**.[51] Sodium borohydride reduction leads to nitro alcohol **31.3**, which *in situ* under the basic reaction conditions can give a nitro vinyl derivative **31.4**. This nitro vinyl compound would be reduced further by hydride in a 1,4-fashion to furnish **31.5**,[52] which on

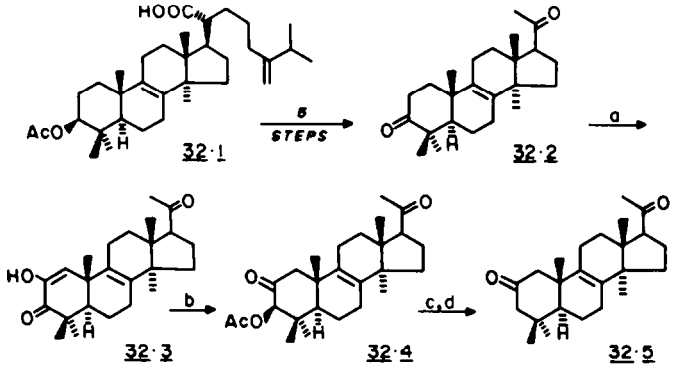


a) $RONO_2$-tBuOK (90%) ; b) $NaBH_4$;
c) NEF Reaction (KOH-EtOH, and then $H^{\oplus}$) or Zn-HOAc.

Scheme 31.

acidification with strong acid should produce the transposed ketone **31.6** (Nef Reaction).[53] This transformation would then occur essentially in two steps. In practice the reaction sequence often gave poor yields. However, modifications were introduced to give a compound containing the transposed carbonyl group in fair yield. A number of ketones, including steroidal A-ring ketones, 2,2-disubstituted cyclopentanones, 2,2-disubstituted cyclohexanones and steroidal D-ring ketones were used as substrates to establish the generality of this route. As an illustration, a sequence of reactions carried out in the conversion of cholestan-3-one **31.7** to cholestan-2-one **31.13** is outlined (Scheme 31).

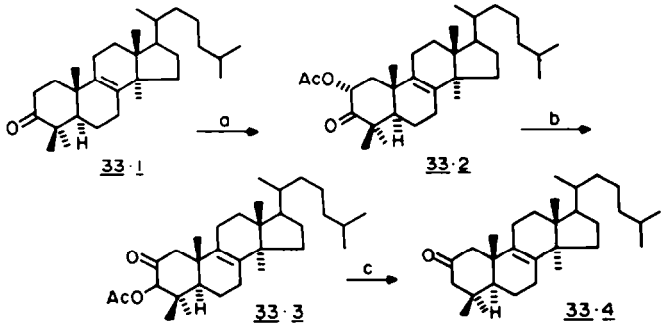
The use of an enolized α-diketone in a 1,2-carbonyl transposition was elegantly described by Barton[54] in the conversion of eburicoic acid **32.1** into 4,4,14α-trimethylpregn-8-ene-2,7,11,20-tetra-one. Barton[55] had earlier developed a new method for the preparation of enolized α-diketones from cyclic ketones. The sequence for carrying out this transformation is outlined below (Scheme 32). Autooxidation[56,57] of **32.2** (previously obtained from eburicoic acid **32.1** in five steps) in t-butyl alcohol-benzene containing potassium t-butoxide gave the diosphenol **32.3**. This, on hydrogenation followed by acetylation, gave a mixture of 2-oxo-3-acetoxy and 3-oxo-2-acetoxy derivatives. Simple crystallization gave the ketol acetate **32.4** which on reduction with calcium in liquid ammonia[31] followed by reoxidation of the 20-hydroxy group with Jones' reagent, gave the desired ketone transposition product **32.5**.



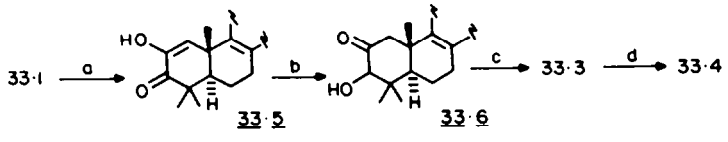
a) O_2-tBuOK; b) Pd/c in EtOAc, Ac_2O-C_5H_5N;
c) Ca-liq. NH_3; d) CrO_3-H_2SO-$(CH_3)_2CO$.

Scheme 32.

Levisalles *et al.*[58] have carried out 1,2-carbonyl transpositions on triterpenoids and steroids such as lanost-8-en-3-one, 4,4-dimethylcholestan-3-one. Specifically we report here their transformation of lanost-8-en-3-one **33.1** to lanost-8-en-2-one **33.4** (Scheme 33). Lead tetraacetate oxidation of **33.1** gave acetoxy ketone **33.2** which was isomerized on basic aluminum oxide to **33.3**. Cleavage of the acetoxy group with calcium in liquid ammonia[31] gave lanost-8-en-2-one **33.4**. Another variant of this transformation independently carried out is outlined (**33.1** → **33.5** → **33.6** → **33.3** → **33.4**).



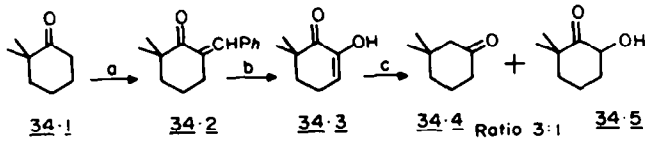
a) $Pb(OAc)_4$-BF_3; b) Al_2O_3-KOH; c) Ca-liq.-NH_3.



a) O_2-tBuOK; b) Pd/C in EtOAc; c) Ac_2O-C_5H_5N; d) Ca-liq.-NH_3.

Scheme 33.

Reusch and LeMahieu[59] have also investigated a 1,2-carbonyl transposition using α-diketones, the derived enol methyl ethers and α-ketols by taking advantage of the ability of hydriodic acid to function as a reducing agent. A substituted cyclohexanone **34.1** having a quaternary α-carbon was oxidized to the corresponding α-diketone **34.3**. The diketone **34.3** when refluxed with hydriodic acid in acetic acid gave a mixture of a transposed ketone **34.4** and α-ketol **34.5** as outlined in Scheme 34. This method is somewhat drastic and also gives a product mixture which can only be separated by chromatography.

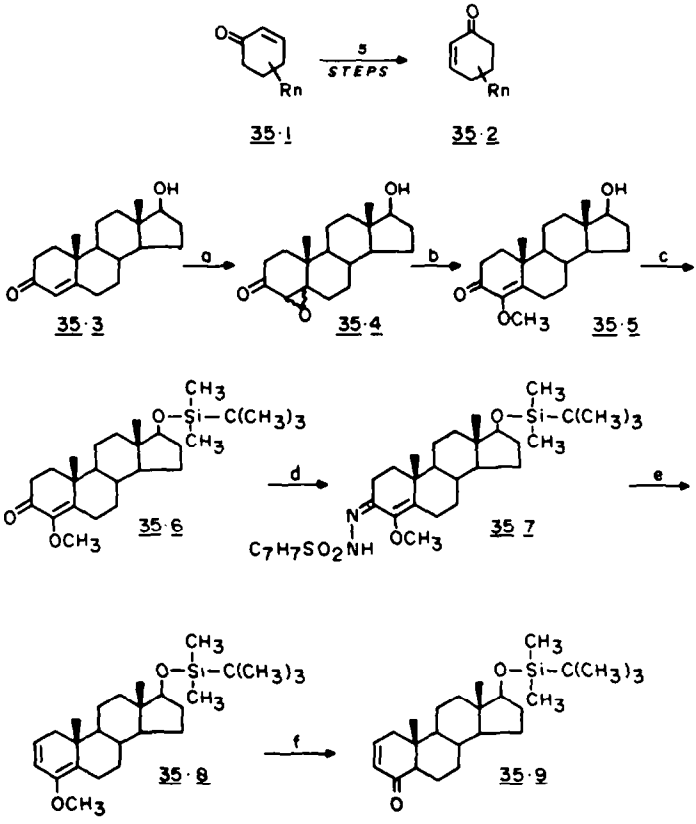


34·1 34·2 34·3 34·4 34·5

a) PhCHO-KOH-EtOH; b) $KMnO_4$-Acetone; c) HI.

Scheme 34.

More recently Reusch and Patel[2] have developed a very mild synthetic route for 1,2-carbonyl transposition which involves an α-ketovinyl ether intermediate. The five steps starting from an α,β-unsaturated ketone (**35.1**) are summarized in Scheme 35. The unsaturated ketone **35.3** was treated with sodium hydroxide-30% hydrogen peroxide in methanol to give a mixture of epoxides **35.4** which was opened to give ketone enol ether **35.5**. Protection of the C-17 hydroxyl function gave **35.6**. Treatment of **35.6** with p-toluenesulfonylhydrazide gave the hydrazone **35.7**, which on treatment with methyllithium in ether gave vinyl ether **35.8**. Subsequent hydrolysis of **35.8** yielded the desired transposed ketone **35.9**.



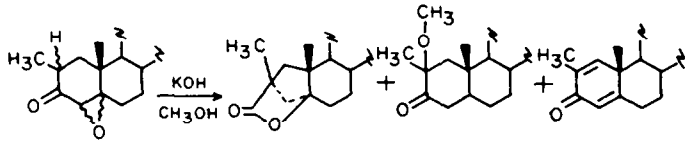
35·1 35·2 35·3 35·4 35·5 35·6 35·7 35·8 35·9

a) 30% H_2O_2-NaOH; b) KOH or NaOH in MeOH; c) t-Bu$(CH_3)_2$SiCl-DMF; d) $C_7H_7SO_2NHNH$ in EtOH; e) MeLi in $(Et)_2O$; f) 5% HCl in THF.

Scheme 35.

Unfortunately this mild method[2] has been shown to have limitations; i.e. when the compound was substituted α′ to the ketone, as in **36.1**, no methoxy enone derivative could be formed.[2] Furthermore,

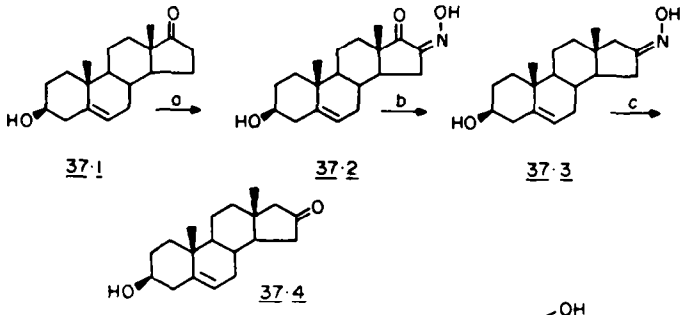
these α,β-epoxy ketones were found to undergo Favorskii-like reactions[60] with methoxide ion to give a mixture of products (Scheme 36).



36·1 36·2 36·3 36·4

Scheme 36.

We have seen that, of the several ways to induce 1,2-carbonyl transposition thus far described, many of the methods use reagents such as bromine, ozone, hypobromous acid, and hydriodic acid, which may not be compatible with sensitive functionalities elsewhere in the system. In order to avoid oxidative conditions Just and Lin[61] devised a three step sequence for 1,2-carbonyl transposition (Scheme 37). Thus, 3β-hydroxyandrostan-5-en-17-one **37.1** was converted into the 16-oximino-17-ketone **37.2**, which was then reduced with hydrazine hydrate and potassium hydroxide in ethylene glycol at 140° to give **37.3**. Further hydrolysis afforded 3β-hydroxyandrost-5-en-16 one **37.4**. The general applicability of this procedure has not been evaluated.

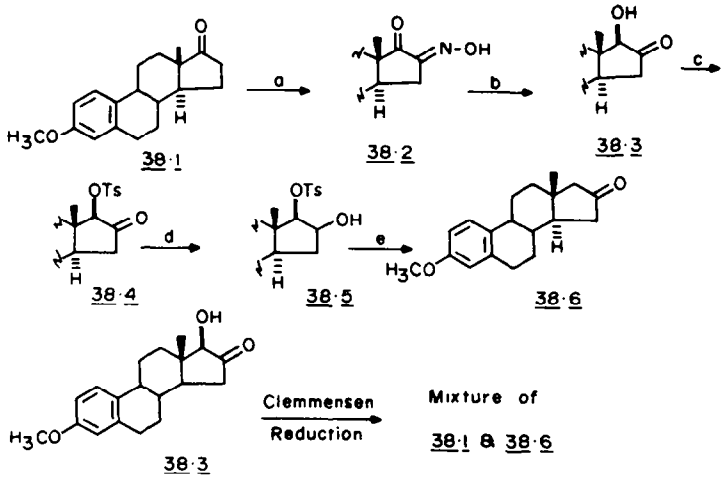


37·1 37·2 37·3 37·4

a) $C_5H_{11}ONO$-KOBu-t; b) $NH_2NH_2-H_2O$ 85%, 1 eq, ethylene glycol, KOH
Δ at 140° for 16 hrs.; c) $NaHSO_3$-EtOH-H_2O, reflux, then $H^{\oplus}$.

Scheme 37.

The use of an α-oximinoketone in 1,2-carbonyl transposition was well documented as early as 1951, due mainly to the efforts of Huffman and his colleagues,[62] and is outlined below (Scheme 38). The key step involved was the reduction of α-oximono ketone **38.2** with zinc and acetic acid to 17β-hydroxy-16-ketone **38.3** and its subsequent conversion to **38.6**. Since the latter conversion has been described in another sequence (Scheme 23), it will not be discussed in further detail here. Direct conversion of **38.3** to **38.6** involving Clemmensen reduction[63] was unsatisfactory, since such a reduction yielded a mixture of 16- and 17-keto steroids.

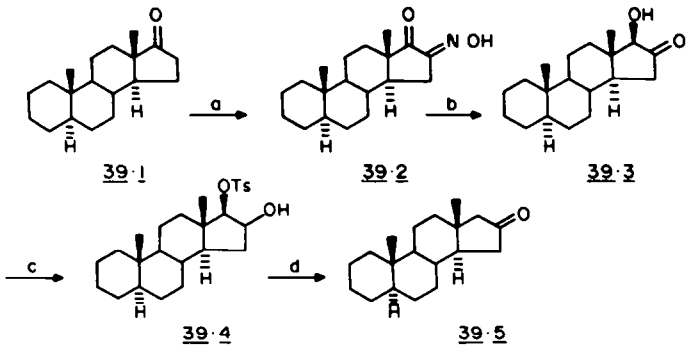


38·1 38·2 38·3 38·4 38·5 38·6

a) $C_5H_{11}ONO$-KOBu^t; b) Zn-CH_3COOH; c) TsCl-C_5H_5N;
d) $LiAlH_4$-Ether; e) KOH-EtOH-H_2O.

Scheme 38.

Although this sequence has been utilized by several groups,[64] only one such procedure, using non-aromatic ring A steroids, developed by Varesch and Jacques[65] is outlined below (Scheme 39).

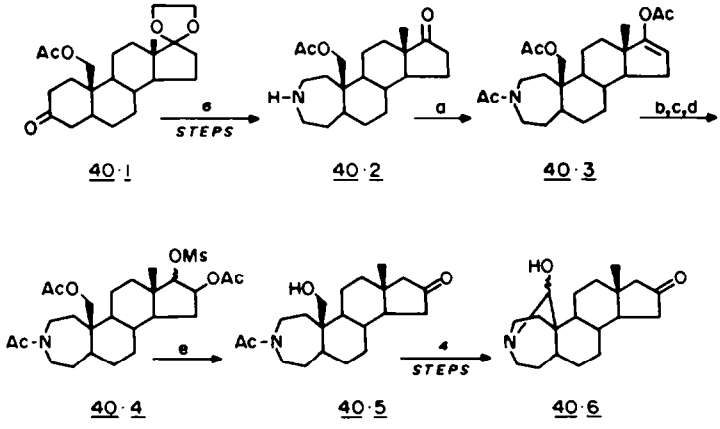


39·1 39·2 39·3 39·4 39·5

a) $C_5H_{11}ONO$-KOBu-t; b) Zn-CH_3COOH; c) TsCl-C_5H_5N, $NaBH_4$; d) NaOH-$MeOCH_2$-CH_2OH.

Scheme 39.

In recent years Oka and Hara[66] have very effectively utilized a 1,2-carbonyl transposition in their synthetic work leading to the synthesis of biologically active salamander alkaloids. The key step in this sequence was the conversion of the α-acetoxy-mesylate **40.4** to **40.5** on treatment with methanolic-potassium hydroxide. The latter was then converted by these authors in four steps to cycloneosamandione **40.6** (Scheme 40).



40·1 40·2 40·3 40·4 40·5 40·6

a) isopropenyl acetate, $H^{\oplus}$; b) $Pb(OAc)_4$-CH_3COOH-trace $(CH_3CO)_2O$; c) $NaBH_4$-CH_3OH; d) MsCl-C_5H_5N; e) KOH-CH_3OH.

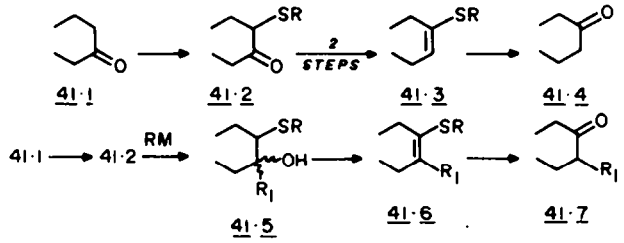
Scheme 40.

It is unfortunate that many of the earlier methods developed in steroid 1,2-carbonyl transpositions have only limited application due to low overall yields and/or the presence of reagent sensitive functional groups. These methods, with the exception of a few, can be categorized as oxidative procedures for 1,2-carbonyl transposition. On the positive side several reagents have emerged: (1) autooxidation of cyclic ketones to α-diketones using oxygen and potassium t-butoxide, (2) hypobromous acid additions to unsaturated steroids, and (3) calcium in liquid ammonia reduction of α-acetoxy ketones. However, the need for milder, non-oxidative, procedures have inspired organic chemists to develop the new methodologies which will be discussed in subsequent sections of this report.

1,2-CARBONYL TRANSPOSITION BASED ON SULFUR REAGENTS

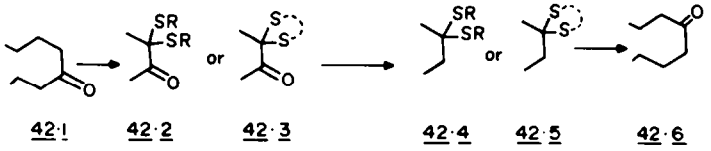
The unique ability of sulfur to stabilize both negative and positive charges on an adjacent carbon atom has been thoroughly exploited in recent years for the development of many new synthetic methodologies.[67] A sulfur substituent can be introduced α- to a carbonyl group relatively easily by a process known as sulfenylation and the resulting β-keto sulfide[67] can be manipulated in several ways.[67–70]

It has been put to excellent use in carrying out a 1,2-carbonyl transposition (Scheme 41) and an alkylative 1,2-carbonyl transposition (Scheme 41). The key steps in both the processes are the generation of the enol thioether (**41.3** or **41.6**) and its subsequent hydrolysis to form the transposed ketone. The latter, a combined process of 1,2-carbonyl transposition with the introduction of an alkyl or aryl substituent, which has found a considerable synthetic utility in natural product synthesis, is outlined in subsequent paragraphs.



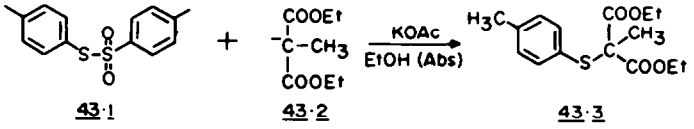
Scheme 41.

It was recognized quite early that introduction of two sulfur substituents α- to a ketone group in a molecular framework constitutes a net oxidation of a methylene group.[71] It is this property which also has been explored for the transposition of carbonyl group (Scheme 42).



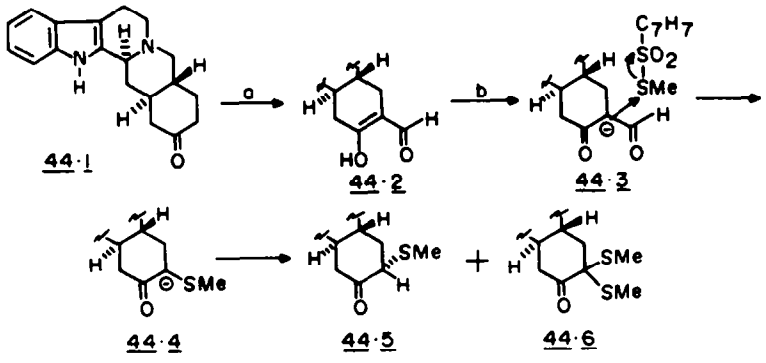
Scheme 42.

Methods used for the preparation of β-keto sulfides have been reviewed;[67] only the methods which ultimately lead to the ketone transposition and are pertinent to this review have been considered here. Smiles, as early as 1926, had successfully demonstrated the use of arylthiotoluenesulfonates to prepare β-keto sulfides of malonic and substituted malonic acids using a mild base[72] (Scheme 3).



Scheme 43.

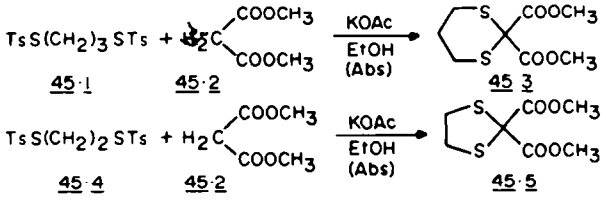
However, the potential use of these reagents in organic synthesis and especially in a complex natural product remained unnoticed until it was pointed out by Autrey and Scullard in their work on corynantheine.[73] As would be expected they have used this reagent with modification since Smiles' studies[72] had indicated this need. The use of methyl thiotosylate in the formation of β-keto sulfides as used by these authors is outlined (Scheme 44). The condensation of yohimbone **44.1** with ethyl formate in the presence of sodium hydride in methanol gave formyl yohimbone **44.2**, which on treatment with methyl thiotosylate in the presence of potassium acetate gave the monosulfenylation product **44.5** and the bissulfenylation product **44.6**. It is worth noting that the methylene group adjacent to the carbonyl was activated by the formation of the formyl derivative **44.2**.



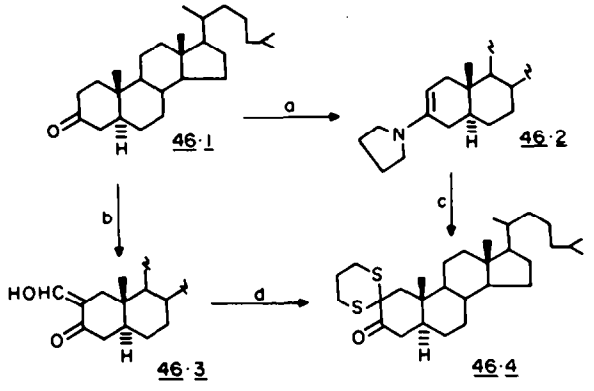
a) HCOOEt-NaH; b) KOAc-$MeSSO_2C_7H_7$-C_2H_5OH(abs).

Scheme 44.

Woodward and his group developed reproducible preparative methods for the synthesis of trimethylene dithiotosylate **45.1** and ethylene dithiotosylate **45.4**.[71] They pointed out that these reagents could serve to introduce a dithiane group to a ketone under mild conditions and in high yields. The use of an enamine (**46.2**)[71,74] and of a formyl group (**46.3**)[71] to activate the C_2-methylene (adjacent to a ketone) were also described by these authors (Scheme 46).



Scheme 45.

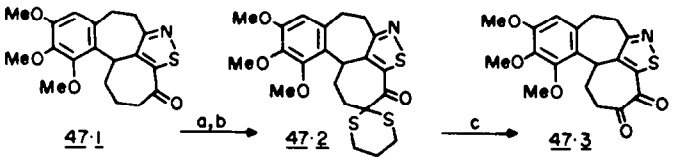


a)  b) HCOOEt-NaH;

c) $TsS(CH_2)_3STs$-KOAc-EtOH(Abs).

Scheme 46.

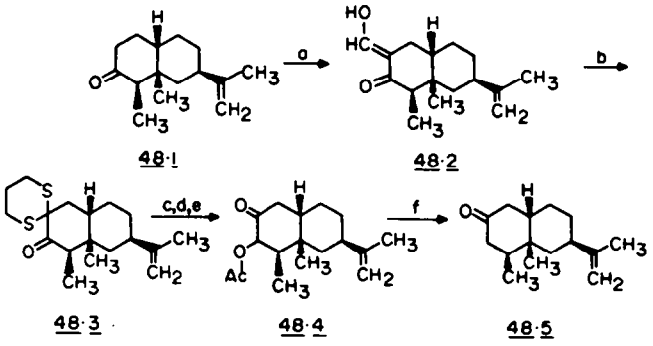
Woodward further utilized this reagent (**45.1**) to generate an intermediate in the synthesis of the complex natural product colchicine[75] (Scheme 47). This was one of the early applications of the use of geminal sulfur substituents as a masked carbonyl function, where mild removal of these sulfur units affords a diketone.



a) NaH, HCOOEt; b)  , KOAc; c) $HgCl_2$, CH_3COOH, H_2O.

Scheme 47.

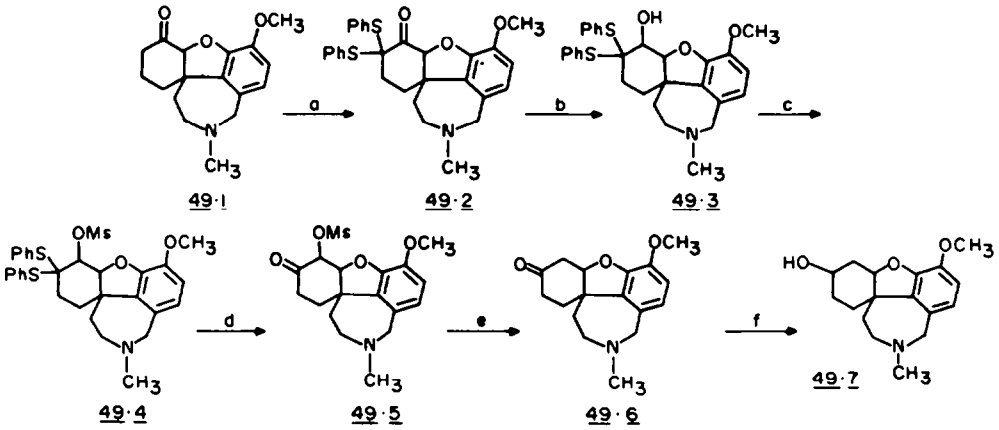
Marshall and Roebke[76] were the first to use this process to effect 1,2-carbonyl transposition (Scheme 48). Ketone **48.1** was converted through an intermediate hydroxymethylene ketone **48.2** to the thioketal ketone **48.3**. Reduction of **48.3** with lithium aluminum hydride gave the alcohol, which on acetylation followed by hydrolysis using mercuric chloride in acetonitrile-water afforded the acetoxy ketone **48.4**. Reduction of **48.4** with calcium and liquid ammonia afforded the desired ketone **48.5**. This conversion proceeded in an overall yield of 50% from ketone **48.1**.



a) HCO_2Et, NaH; b)  , KOAc; c) $LiAlH_4$; d) Ac_2O;
e) $HgCl_2$, H_2O; f) Ca, liq. NH_3.

Scheme 48.

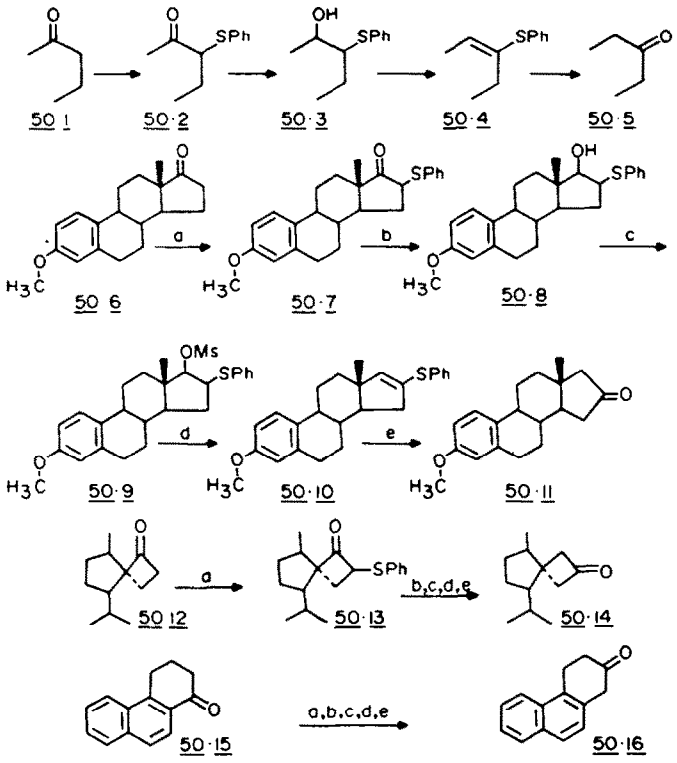
Another excellent, 1,2-carbonyl transposition was provided by Schultz[17] in his work on the total synthesis of the *Amaryllidaceae* alkaloid lycoramine **49.7** via a thioketal ketone intermediate **49.2** which is outlined (Scheme 49). The previously obtained intermediate ketone **49.1** was directly converted to the bisulfenylated ketone **49.2** using lithium tetramethyl piperidide, (a nonnucleophilic base) and phenyl phenylthiosulfonate. Reduction of the ketone gave the alcohol **49.3** which on treatment with mesyl chloride in pyridine gave the mesylate **49.4**; hydrolysis with mercuric chloride gave the mesyloxy ketone **49.5**. Reduction with chromous chloride in aqueous acetone gave the transposed ketone **49.6**. The ketone **49.6** on reduction with lithium aluminum hydride gave (±) lycoramine **49.7**. In a later study Yee and Schultz[77] have pointed out the inherent difficulties in carrying out a 1,2-carbonyl transposition in model systems closely resembling structure **49.1**.



a) Lithium tetramethyl piperidide-THF-HMPA, $PhS-SO_2Ph$;
b) $LiAlH_4$-THF; c) CH_3SO_2Cl-C_5H_5N; d) $HgCl_2$-HgO, CH_3CN-H_2O;
Chromous chloride, Acetone-H_2O; f) $LiAlH_4$-THF.

Scheme 49.

One of the most general procedures for carbonyl transposition has been provided by Trost and his colleagues.[78] The 1,2-carbonyl transposition was accomplished by monosulfenylating the ketone, reducing and resulting β-keto sulfide, formation of mesylate and its elimination with base to give the enol thioether. The last step was the hydrolysis which yields the transposed ketone (Scheme 50).

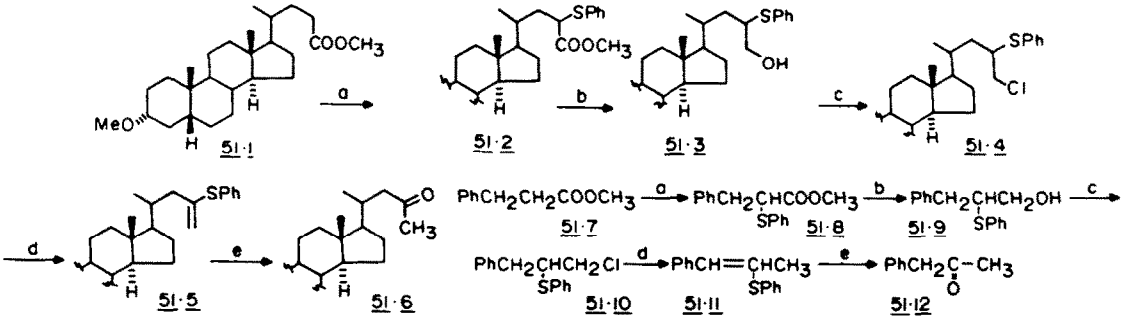


a) $LiN(i\text{-}C_3H_7)(c\text{-}C_6H_{11})$-HMPA-THF-PhSSPh; b) $LiAlH_4$-THF;
c) CH_3SO_2Cl-C_5H_5N; d) KOC_4H_9-t-DMSO; e) $HgCl_2$,CH_3CN-H_2O.

Scheme 50.

More specifically, as outlined in the scheme, ketone **50.6** was treated with lithium N-cyclo-hexyl-N-isopropylamide in tetrahydrofuran at −78°C then with diphenyl disulfide, to give the β-keto sulfide **50.7**. This was reduced with sodium borohydride to the alcohol **50.8** which was treated with mesyl chloride in pyridine. The mesylate **50.9** was eliminated with potassium-t-butoxide in dimethyl sulfoxide. Hydrolysis of the resulting enol thioether **50.10** with mercuric chloride in acetonitrile-water (or with titanium tetrachloride in acetic acid) gave the transposed ketone **50.11**. The general applicability of this approach to four, five and six-membered rings in overall yields of 50–70% is illustrated (Scheme 50).

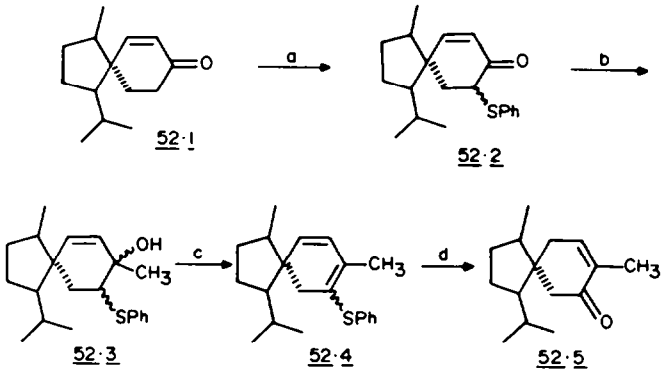
Furthermore this method is so general in nature that it can transpose the carbonyl group of an ester to methyl ketone.[78] In Scheme 51 two additional examples have been provided. We wish to emphasize that this is one of the best known, high yielding methods for carrying out this transposition.



a) $LiN(i\text{-}C_3H_7)(c\text{-}C_6H_{11})$-THF-PhSSPh; b) $LiAlH_4$,THF;
c) $SOCl_2$-C_6H_6; d) KOC_4H_9-t-DMSO; e) $HgCl_2$-CH_3CN-H_2O.

Scheme 51.

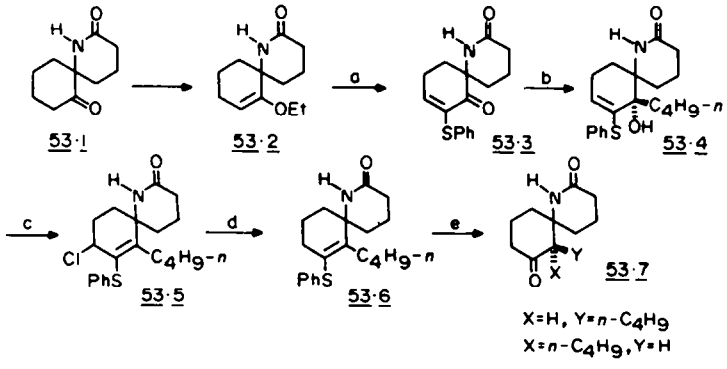
The versatility of the method was further illustrated in a later study involving a regiospecific alkylative 1,2-carbonyl transposition in the stereo-controlled synthesis of the sequiterpene, (±) acorenone-B[79] (Scheme 52). Sulfenylation of the spiroenone **52.1** (prepared from 2-methyl-cyclopentanone) gave the β-keto sulfide **52.2**. Addition of methyllithium followed by dehydration gave the thioether **52.4** which on hydrolysis gave (±) acorenone-B **52.5**.



a) LiN(i-C_3H_7)(C-C_6H_{11})-HMPA-THF-PhSSPh; b) MeLi-Ether;
c) TsOH-C_6H_6, Reflux; d) $HgCl_2$-Dioxane-H_2O.

Scheme 52.

Another example of a 1,2-carbonyl transposition based on this methodology was provided by Kishi[80] in the stereo-controlled synthesis of (±) perhydrohistrionicotoxin in which spiro ketolactam **53.1** was converted to the transposed spiro ketolactam **53.7** as outlined (Scheme 53). The key step was the conversion of the enol ether **53.2** to the thioenol ether **53.6**. Reaction of the enol ether **53.2** with phenylsulfenyl chloride gave thiopheylenone **53.3**, which on treatment with butylmagnesium chloride gave the carbinol **53.4**. Thionyl chloride treatment of **53.4** gave the chloride **53.5** which was reduced with zinc-hydrogen chloride to the thioenol ether **53.6**. Hydrolysis with concentrated hydrobromic acid gave a mixture of two epimeric transposed ketones in overall yield of about 20% (from **53.1**). The selectivity obtained in the sulfenylation of the ketone carbonyl via the enol **53.2** compared to an amide is worthy of note.

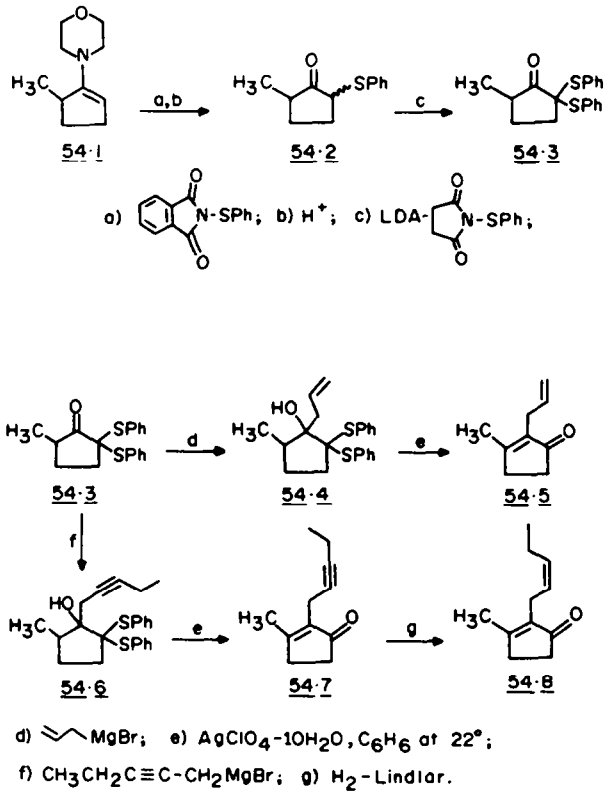


a) PhSCl, CH_2Cl_2; b) n-C_4H_9MgCl-THF; c) $SOCl_2$;
d) Zn-HCl; e) CON. HBr.

Scheme 53.

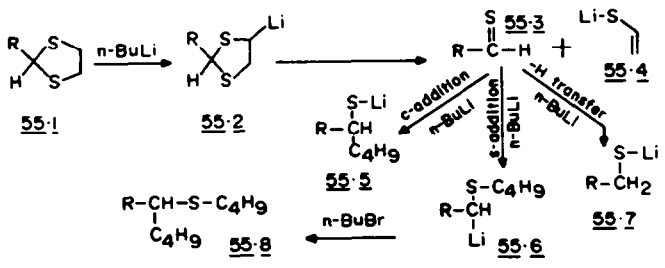
Mukaiyama *et al.* have shown that two alkythio or arylthio groups[81,82] can be introduced adjacent to a carbonyl group by the reaction of active methylene compounds such as ketones with sulfenamides in a step-wise fashion (Scheme 54). Utilizing the bissulfenylated ketone **54.3** thus prepared (from 2-methylcyclopentanone) they carried out alkylative 1,2-carbonyl transpositions in their synthesis of allylrethone **54.5** and cis-jasmone **54.8**.[82] Reaction of the allyl Grignard with the bis-sulfenylated ketone

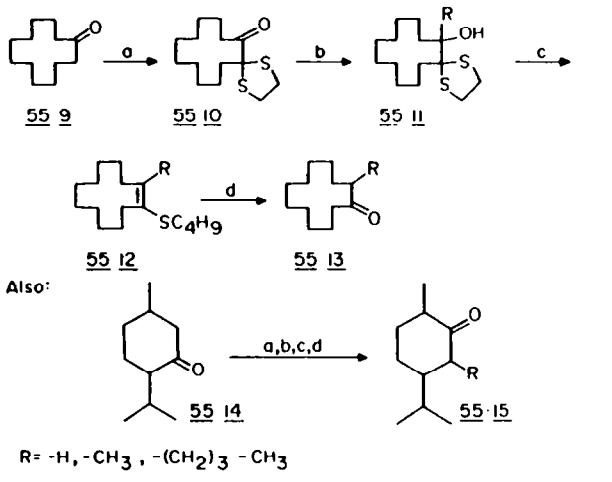
gave the alcohol **54.4** which on hydrolysis with silver perchlorate directly formed the unsaturated transposed ketone **54.5**. In a similar fashion, **54.3** was converted to *cis*-jasmone **54.8**.



Scheme 54.

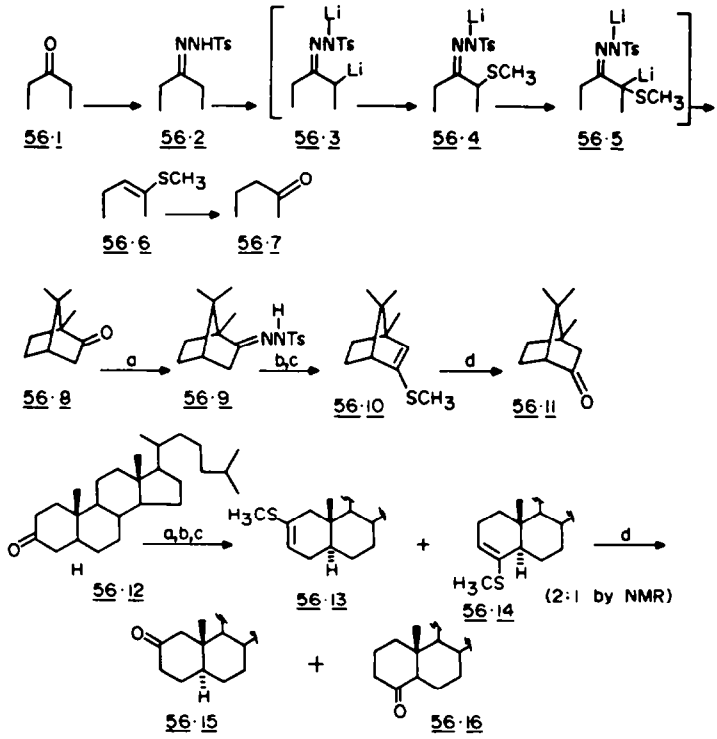
Wilson *et al.*[83] reported the cleavage of dithiolane with n-butyllithium for the preparation of thiocarbonyl compounds (Scheme 55), and illustrated its utility in 1,2-carbonyl transposition and alkylative 1,2-carbonyl transposition reactions. They have illustrated this transposition reaction using C_{12}-ketone **55.9** and menthone **55.14** as model systems as outlined below (Scheme 55). α-Ketodithiolane **55.10** was prepared from ketone **55.9** procedures developed earlier by Woodward.[71] Reaction of the bissulfenylated ketone **55.10** with methyllithium gave the alcohol **55.10** (R=CH_3), and further treatment with excess n-butyllithium gave the enol thioether **55.12** (R=CH_3), which on hydrolysis gave the ketone **55.13** (R=CH_3) in 40% overall yield. Similar reactions using menthone **55.14** as a substrate yielded transposed ketone (carvomenthone) **55.15** and its derivatives.





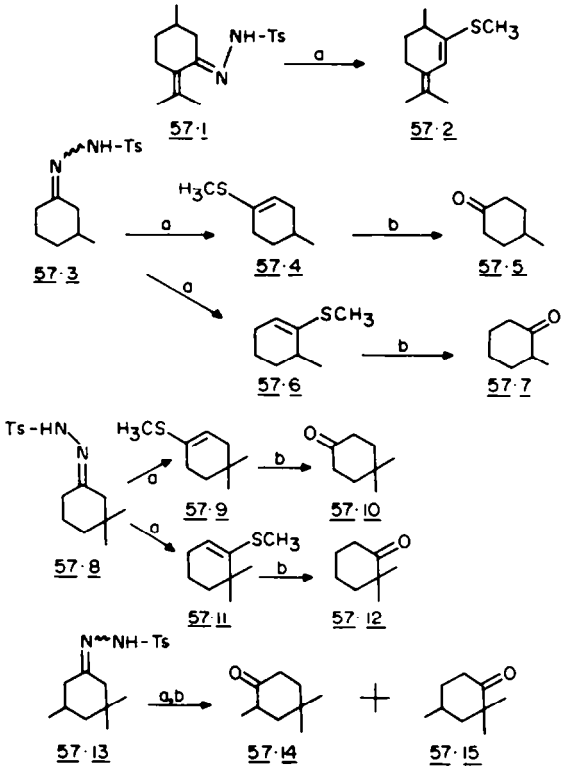
Scheme 55.

A facile, one-pot transformation of a ketone tosylhydrazone to the thioenol ether of the transposed ketone was developed by Nakai and Mimura.[84] This method is based upon the regiospecific sulfenylation of a dianion obtained by the addition of an organolithium reagent to the tosylhydrazone, followed by Shapiro-Shechter reaction[85,86] of the regenerated dianion to furnish a thioenol ether (Scheme 56). The transformation of thioenol ethers to ketones is now well established and thus this method provides an additional example of 1,2-carbonyl transposition. The versatility of this procedure was demonstrated by conversion of menthone to carvomenthone and d-camphor to l-epicamphor (30% yield, Scheme 56). It is interesting to note that conversion of cholestan-3-one **56.12** gave a mixture of cholestan-2-one **56.15** and the 4-keto derivative **56.16** in a ratio of 2:1 (by NMR).



Scheme 56.

These authors have also studied the effect of hydrazone stereochemistry upon the regioselectivity. It is well documented that there is a *syn* preference in the formation of the tosylhydrazone dianion in certain cases[87] and with the use of pure tosylhydrazones, this method affords a highly regioselective 1,2-carbonyl transposition. This was exemplified in E-pulegone tosylhydrazone **57.1** which afforded exclusively the *syn* sulfenylated product **57.2** in 26% yield (Scheme 57) and no γ-sulfenylation product was detected. However when an isomeric mixture of 3-methylcyclohexanone tosylhydrazones (E/Z = 1.0) was subjected to the transposition sequence (Scheme 57), 4- and 2-methylcyclohexanone were isolated in the ratio of 9:1. It was concluded that under these reaction conditions, the course of sulfenylation of the dianions is independent of the stereochemistry of the tosylhydrazone.



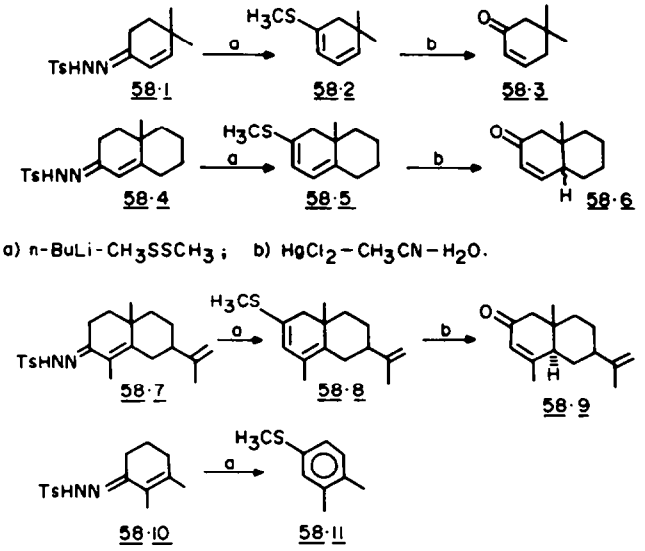
a) BuLi-CH_3SSCH_3; b) $HgCl_2$-CH_3CN-H_2O.

Scheme 57.

Furthermore Nakai and Mimura[84] have studied in detail the effect of the solvent and of the base on the transformations of 3-methylcyclohexanone tosylhydrazone. The optimum selectivity (91:9) was observed with butyllithium as base in tetrahydrofuran–tetramethylethylenediamine-hexane in a ratio of 11:10:5. The selectivity preference appears to decrease with increasing amounts of tetramethylethylenediamine. Thus when the reaction was carried out using only tetramethylethylenediamine with butyllithium as base, the selectivity dropped to 74:26. Another interesting finding was that there was no increased selectivity when the 2,4,6-triisopropylbenzenesulfonylhydrazone instead of the tosylhydrazone of 3-methylcyclohexanone was used as a substrate. It also appears that selectivity also decreased when an increased proportion of tetramethylethylenediamine was used in the conversion of the trisaryl-substitutedhydrazones to the corresponding thioenol ethers. Further studies included the regiochemical outcome on the β,β′ and γ-carbon atoms. β,β′-Dimethylcyclohexanone tosylhydrazone exhibited high regioselectivity. This result was expected in light of the exclusive E geometry of the tosylhydrazone **57.8** which directs the lithiation (and thus the sulfenylation) to the *syn* orientztion presumably because of the chelation effect of the hydrazone monoanion. This observation does not indicate the effect on the regiochemical control of the carbonyl transposition by the stereochemistry of the tosylhydrazone employed. The regioselectivity was reduced when one methyl group was introduced at the β′ carbon as in **57.13**, probably because the tosylhydrazone existed as a 1:1 mixture of E/Z isomers.

To sum up their own results, Mimura and Nakai concluded that (1) when the tosylhydrazone possesses a single geometry it leads to exclusive *syn* lithiation (sulfenylation) and (2) the stereoisomeric mixtures of the tosylhydrazone indicated a profound base-solvent effect in the dianion formation and seem to lead to a greater preference for the lithiation (sulfenylation) at a less hindered position.

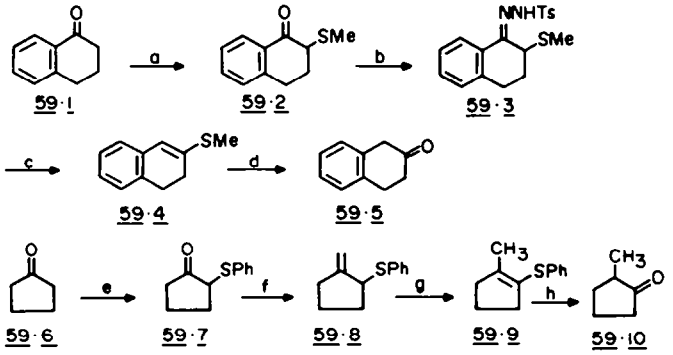
Mimura and Nakai have extended their method to the tosylhydrazones of an α,β-unsaturated ketone.[89] This method, being very similar to Trost's[79] which generates dienol thioethers as intermediates (see Scheme 52), will not be discussed in detail. However, these authors have studied the scope and limitations of this transposition (Scheme 58). They found that hydrolysis of dienol thioether **58.5** gave a mixture of (*cis-trans* = 1:3) **58.6** and in the case of **58.8** gave only the *trans* isomer **58.9**. Hence it appeared that the stereochemical outcome depends upon the structure of the bicyclic dienol thioether and therefore was difficult to predict. Δ^2-Cyclohexenone systems **58.10** in which ring methylenes are not generally substituted gave rise to thioanisole derivatives during work-up.



a) n-BuLi-CH_3SSCH_3; b) $HgCl_2-CH_3CN-H_2O$.

Scheme 58.

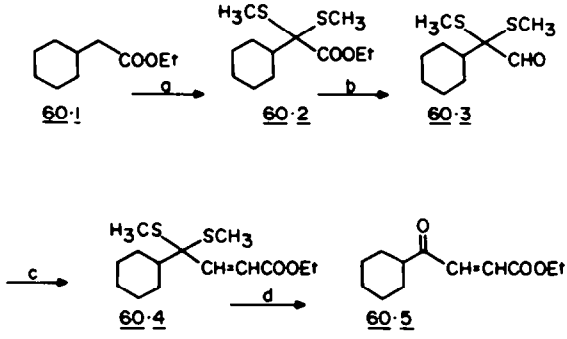
A slightly different sequence was independently employed by Kano and co-workers[90] in carrying out two types of the carbonyl transposition. The β-keto sulfide **59.2** of α-tetralone on treatment with p-toluenesulfonylhydrazide gave p-toluenesulfonylhydrazone **59.3**. Reaction of **59.3** with methyllithium gave thioenol ether **59.4** which on hydrolysis gave β-tetralone **59.5** (Scheme 59). In the case of alkylative 1,2-carbonyl transposition, the β-keto sulfide **59.7** was converted to its olefinic derivative **59.8** via a Wittig reaction; the double bond of **59.8** was isomerized with n-butyllithium to thioenol ether **59.9** which on hydrolysis gave the alkylated transposed ketone **59.10**.



a) LDA-CH_3SSCH_3; b) NH_2NHTs; c) BuLi; d) $HgCl_2-CH_3CN-H_2O$, 85%; e) LDA-$PhSSPh$; f) $(C_6H_5)_3PCH_2Br$-NaH-DMSO; g) BuLi; h) $HgCl_2-CH_3CN\cdot H_2O$.

Scheme 59.

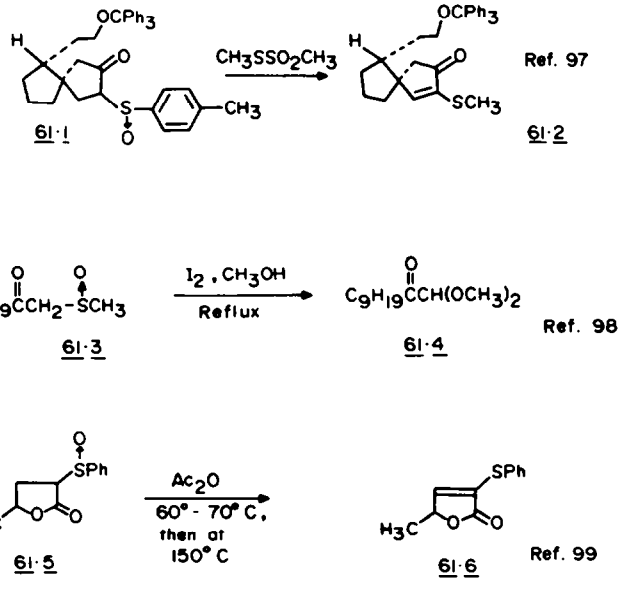
Greene has reported[91] a transformation of a carbalkoxymethyl group to a γ-oxocrotonate derivative in overall yields of 50% in which a carbonyl transposition was utilized and is outlined below (Scheme 60). Specifically ethyl cyclohexylacetate was converted to E-ethyl-4-cyclohexyl-4-oxo-2-butenoate through an intermediary bisthiocyclohexylacetate. The acetate **60.2** (obtained by using lithium diisopropylamide and methyl methanethiosulfonate) was reduced with diisosobutylaluminum hydride to give **60.3** Utilization of the Emmons-Horner reaction followed by hydrolysis gave the desired crotonate ester **60.5**. It was pointed out that this sequence will prove to be useful for the synthesis of other oxygenated crotonate derivatives. Bissulfenylated derivatives have also been prepared from esters[92] (see also Scheme 60), lactones,[93] lactams,[94] imino ethers,[95] and nitriles.[96]



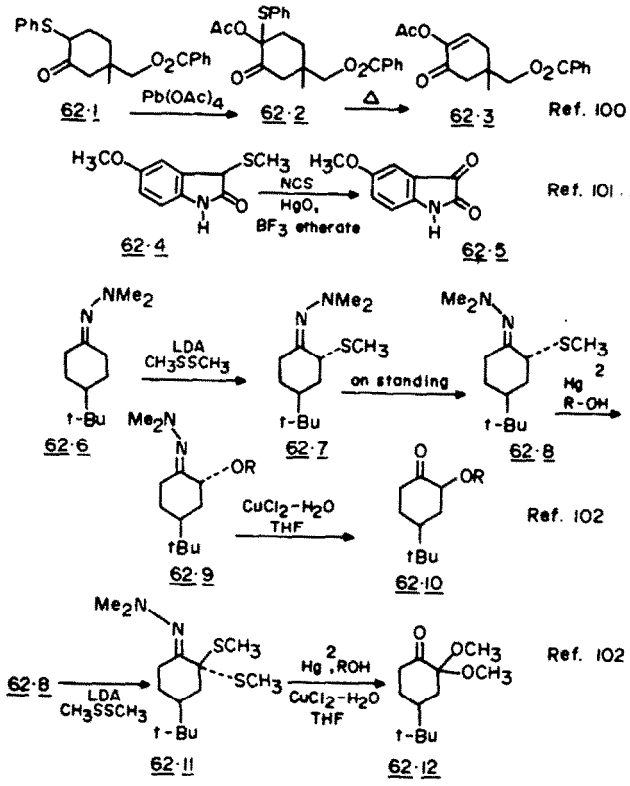
a) LDA-$MeSO_2SMe$; b) Dibal-H; c) Me_3SiCH_2COOEt-NaH-DME; d) NCS-$AgNO_3$-CH_3CN-H_2O.

Scheme 60.

As pointed out in the previous section on steroids, the regiospecific synthesis of α-diketones or diosphenols leads to a 1,2-carbonyl transposition. Following are a few additional examples which have made use of these sulfur reagents for the generation of α-keto carbonyl compounds and their equivalents (Schemes 61 and 62).[97-102]

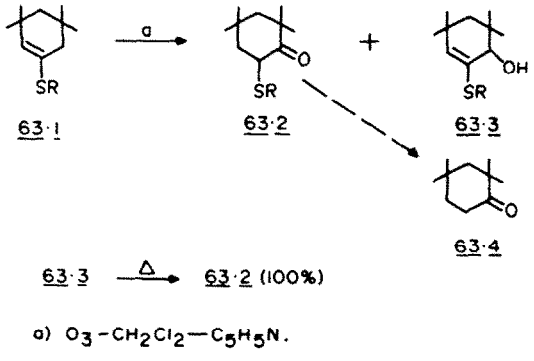


Scheme 61.



Scheme 62.

A recently described procedure by Paquer *et al.*,[103] which we believe could be utilized for 1,2-carbonyl transposition but may have limited application, is described below (Scheme 63). The thioenol ether **63.1** reacted with ozone to give the transposed β-keto sulfide **63.2** and alcohol **63.3** in the ratio of 1:12; however, thermolysis of **63.3** gave exclusively the β-keto sulfide **63.2** which can be converted to the transposed ketone with Raney nickel to give **63.4**. This method would then be the reverse of all of the previous schemes described so far.

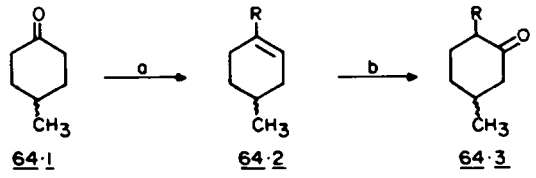


Scheme 63.

To conclude this section, the utility of these sulfur reagents has been clearly demonstrated to have a great versatility in 1,2-carbonyl and alkylative 1,2-carbonyl transpositions. Further, it has been demonstrated that the chemistry of these organosulfur compounds has been exploited to carry out complex natural product syntheses under very mild reaction conditions and also in few steps. A number of reagents have been evaluated to resolve the crucial problem of thioenol ether hydrolysis and this seems to have been addressed adequately[70,91,104] to give transposed ketones in yields ranging from 60 to 80%.

HYDROBORATION IN 1,2-CARBONYL TRANSPOSITION

Since its discovery, hydroboration[105,106] has proved to be an important tool in organic synthesis and has extended the realm of synthetic organic chemistry. It is not surprizing, therefore, to find its application in 1,2-carbonyl and alkylative 1,2-carbonyl transpositions. In 1961, Brown and Garg[107] reported the first alkylative 1,2-carbonyl transposition utilizing hydroboration. The method was based on an observation that the oxidation of organoboranes led to ketones. 4-Methylcyclohexanone **64.1** was treated with a Grignard reagent to give an alcohol. Elimination of water furnished the olefin **64,2** and hydroboration oxidation gave the transposed ketone **64.3** (Scheme 64).

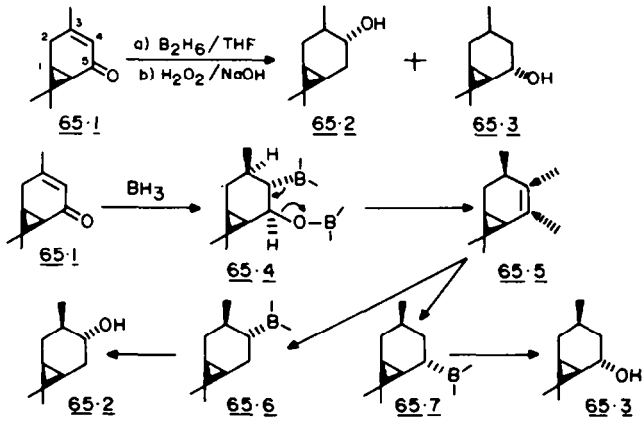


64·1 64·2 64·3

a) $RMgX\text{-}Et_2O$ or THF; b) B_2H_6 in THF, CrO_3.

Scheme 64.

Cocker, *et al.*[108] have reported 1,2-carbonyl transposition in their studies on the oxidation of the monoterpenoid (±)-car-2-ene. They reported the reaction of (−)-car-3-en-5-one **65.1**, an α,β-unsaturated ketone, with diborane followed by alkaline peroxide oxidation which afforded a mixture of the (−) alcohol **65.2** and the alcohol **65.3**. Oxidation with chromic acid gave a (1:11) mixture of transposed ketone *cis*-caran-4- and *cis*-caran-5-one. On the basis of this they have suggested (−) *cis*-car-4-ene **65.5** as an intermediate and its further hydroboration to a mixture of **65.2** and **65.3**. The stereochemistry and product distribution of hydroboration of conjugated ketones was reported by Klein and Dunkelblum[109] and from their results it appears that the hydroboration of (−) car-3-en-5-one **65.1** must be a special case in which a mixture of isomeric monoalcohols has been exclusively obtained (Scheme 65).

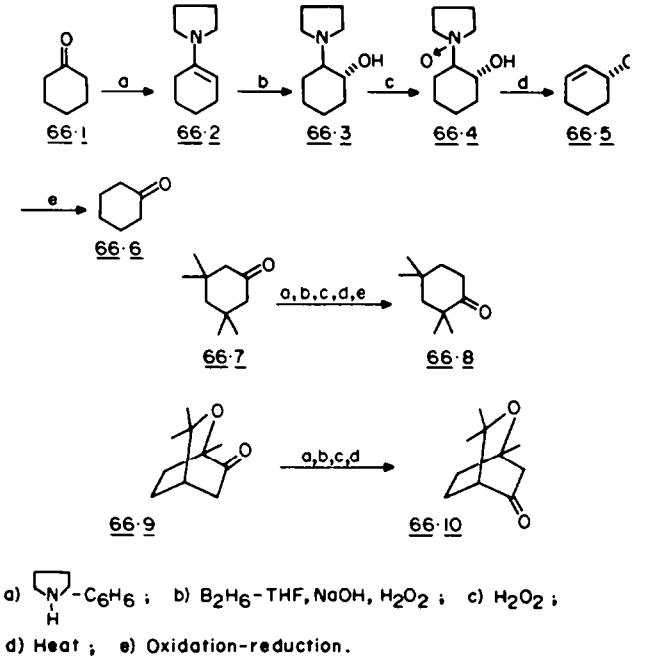


65·1 65·2 65·3 65·4 65·5 65·2 65·6 65·7 65·3

Scheme 65.

Borowitz and Williams[110] reported that the hydroboration of enamines derived from cyclohexanone and 2-methylcyclohexanone, followed by the oxidation of the β-amino aklylborane, gave *trans*-β-aminocyclohexanols. This result was successfully utilized by Gore *et al.*[111] to carry out a 1,2-carbonyl transposition. They envisioned that the critical steps involved in their transformation, the oxidation of an intermediate amino alcohol to the N-oxide followed by Cope elimination of the N-oxide,[112] would result in an allylic alcohol, which on oxidation and reduction, would lead to the transposed ketone. They were successful in performing this transposition using a number of simple monosubstituted ketones in an overall yield of 40% (Scheme 66).

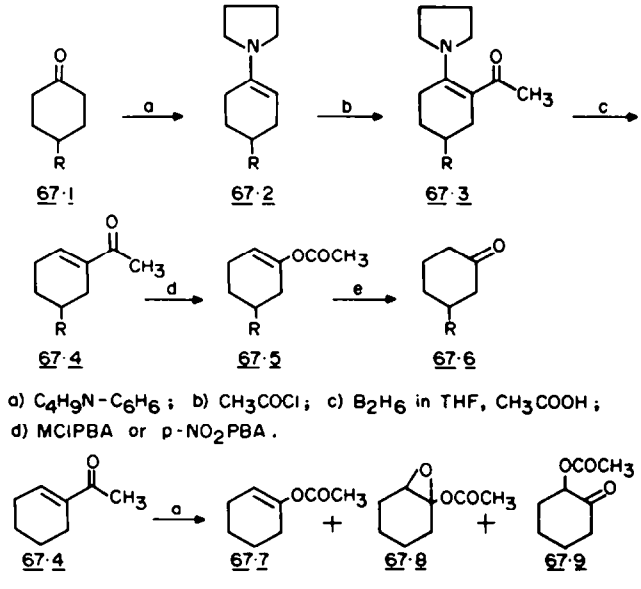
Utilizing this method Schenone and his colleagues[113] have recently reported conversion of a monoterpenoid, 1,3,3-trimethyl-2-oxabicyclo(2.2.2)octan-6-one **66.9**, to 1,3,3-trimethyl-2-oxabicyclo(2,2,2)octan-5-one **66.10** in overall yield of 58% (Scheme 66). In this example[113] the Cope elimination proceeded in high yield (82%), but this was not the case in an another substrate which was examined by Yee and Schultz.[77]



a) C_6H_6 ; b) B_2H_6-THF, NaOH, H_2O_2 ; c) H_2O_2 ;
d) Heat ; e) Oxidation-reduction.

Scheme 66.

Another route attributed to Gore[114] resulted from two observations: (1) that a β-enamino ketone on treatment with diborane gave an α,β-unsaturated ketone and (2) that the Baeyer–Villiger oxidation of the latter resulted in the formation of an enol ether, which on hydrolysis, led to a transposed carbonyl (Froberg *et al.*[115] had previously observed that the hydroboration of a β-enamine methyl ester gave an α,β-unsaturated ester.) Specifically, Gore reported that 4-substituted cyclohexanones were converted to 3-substituted cyclohexanones (Scheme 67), and that in the steroid series 2-keto steroids were obtained from 3-keto steroids with an overall yield of 25%. A drawback to this method is that the oxidation of an α,β-unsaturated ketone gives a mixture of three products (Scheme 67).

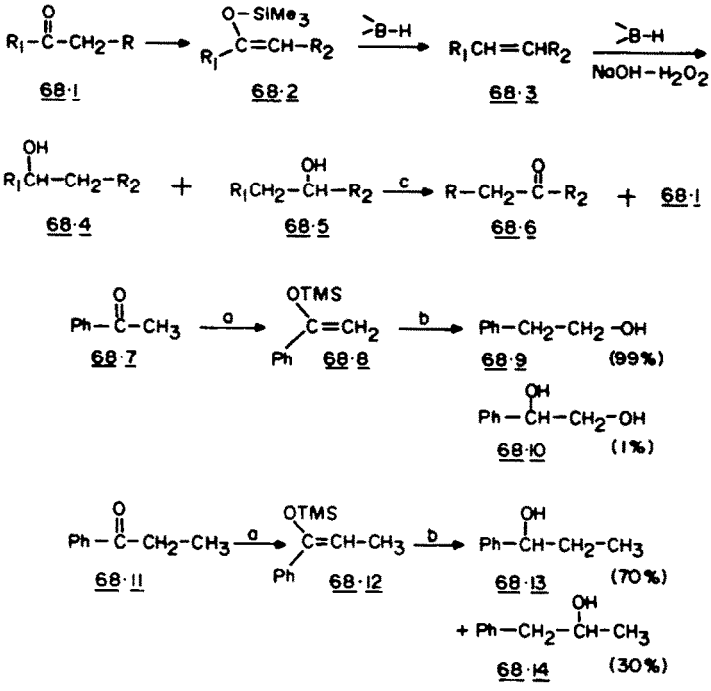


a) C_4H_9N-C_6H_6 ; b) CH_3COCl; c) B_2H_6 in THF, CH_3COOH ;
d) MCIPBA or p-NO_2PBA .

a) p-NO_2PBA .

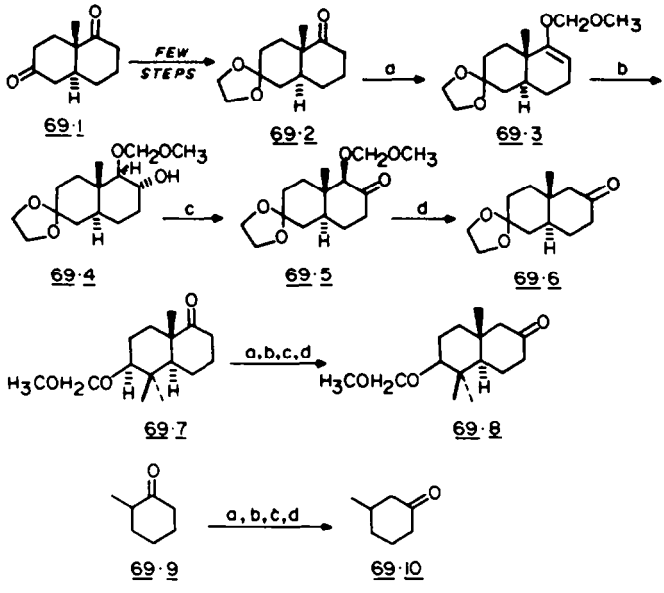
Scheme 67.

Another sequence for 1,2-carbonyl transposition of acyclic ketones reported by Larson *et al.*[116] is based on their previous observation that the hydroboration of the trimethylsilyl enol ether of an acyclic ketone resulted in the elimination of an intermediate trimethylsiloxyborane to form an olefin.[117] The olefin thus formed would undergo further hydroboration after basic oxidation to the transposed alcohol, which could be readily converted to a transposed ketone (Scheme 68). As might be expected, the success of this method depended upon the regioselectivity in the second hydroboration step. To achieve considerable regioselection R_2 had to be smaller than R_1. High selectivity was accomplished by using 9-borabicyclo(3.3.1) nonane as the hydroborating reagent.[118] They obtained the best results when R_2 was hydrogen and R_1 was aryl as in the case of acetophenone (Scheme 68). It is also known from the work of Klein[119] and Stotter[120] that enol trimethylsilyl ethers of monosubstituted cyclohexanones have a mixture of *trans*-1,2-cyclohexanediols in 65% yield. Hence, this reductive transposition is limited to acyclic ketones which fulfil the above requirement.



Scheme 68.

Stotter and Edwards[121] in their synthetic approaches to steroids and fused polycyclic terpenoids developed a four step high yield sequence for ketone transpositions (Scheme 69). The crucial step in their procedure was the treatment of a methoxymethyl enol ether with diborane followed by basic hydrogen peroxide oxidation to yield a β-hydroxymethoxymethyl ether. Specifically, treatment of the kinetically generated lithium enolate of **69.2** with chloromethyl ether in hexamethylphosphoramide gave the methoxymethyl ether **69.3** in an isolated yield of 96% (of O-alkylated product). Hydroboration-oxidation of the enol ether gave exclusively **69.4**, the result of *cis*-hydroboration from the α-face, and further oxidation of **69.4** gave a ketone **69.5**. Reductive cleavage of **69.5** with lithium and ammonia[122] gave the transposed ketone **69.6** in an overall yield of 75% form **69.2**. These authors have also reported carbonyl transpositions in two other model systems (Scheme 69) in overall yields of 65% from the starting ketones.

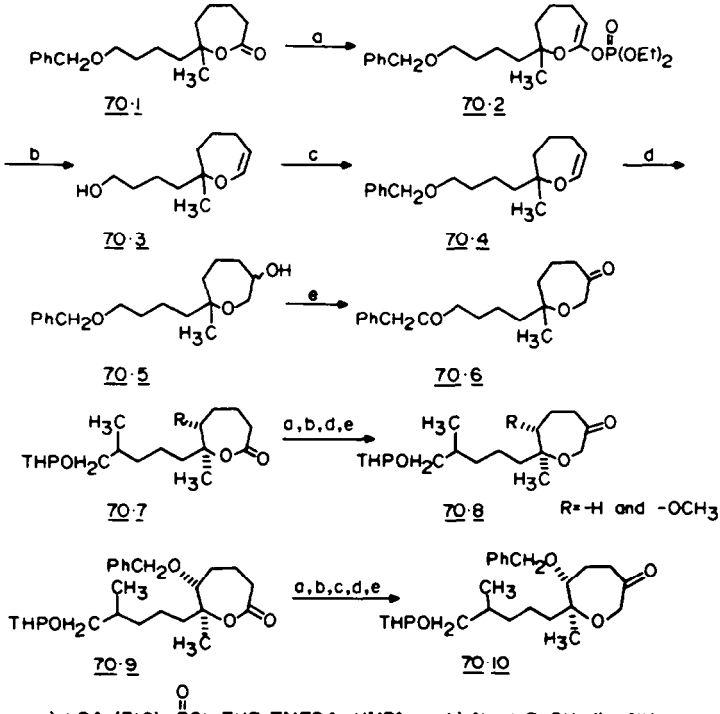


69·1 69·2 69·3 69·4 69·5 69·6 69·7 69·8 69·9 69·10

a) LDA-THF-$ClCH_2OCH_3$; b) B_2H_6-THF, NaOH, H_2O_2;
c) CrO_3-C_5H_5N-CH_2Cl_2; d) 4.4 g Li in dry liq. NH_3.

Scheme 69.

Thus far several new methods have been described using hydroboration as a key step for transposing a ketone carbonyl by one carbon atom. However, until recently, no such transformation had been reported for a lactone to a β-keto ether. During the studies related to the synthesis of biologically active zoapatanol,[19,20] an efficient, general, and selective method for the synthesis of β-keto ethers from lactones (1,2-carbonyl transposition) was needed. We have developed a general scheme for this transformation which is outlined in Scheme 70. Prior to this successful transposition we were not able to carry out the lactone to β-keto ether

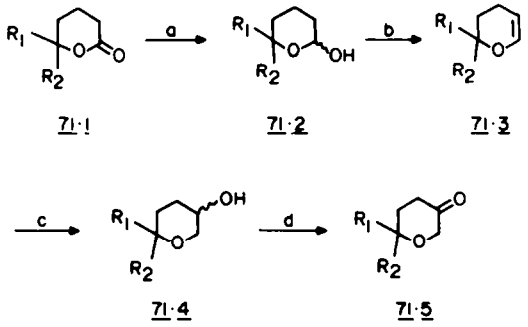


70·1 70·2 70·3 70·4 70·5 70·6 70·7 70·8 70·9 70·10

a) LDA, $(EtO)_2\overset{O}{\overset{\|}{P}}Cl$, THF, TMEDA, HMPA; b) Na, t-BuOH, liq. NH_3;
c) NaH, $PhCH_2Br$, C_6H_6; d) B_2H_6, THF, NaOH, H_2O_2;
e) CrO_3, C_5H_5N, CH_2Cl_2.

Scheme 70.

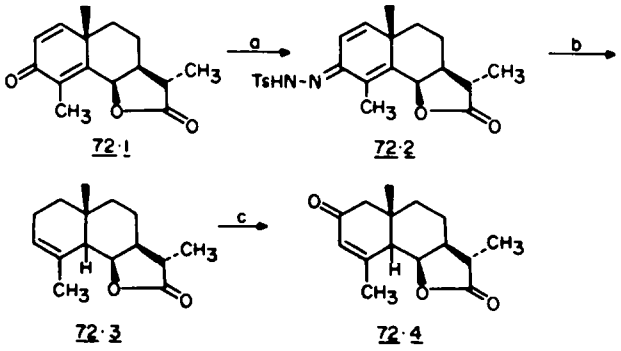
conversion in the seven membered ring by the previously described methods based on sulfur reagents. Two critical steps involved in this transposition were (1) the generation of the enol ether which was based on the observations of Ireland[124] and Fetizon[125] on the deoxygenation of a diethyl enolphosphate by lithium-liquid ammonia to yield an olefin and (2) the previous findings that an enol ether undergoes hydroboration predominantly at the β-position.[126] Reaction of **70.1** with diethyl phosphorochloridate in the presence of lithium diisopropyl amide gave the enol phosphate **70.2**. Reductive cleavage using lithium-liquid ammonia gave the enol ether in 60% yield. Protection of the alcohol gave the benzyl ether **70.4** which on treatment with diborane followed by alkaline hydrolysis gave the epimeric alcohols **70.5** which were oxidized without separation with Collins reagent to give the desired transposed ketone **70.6** in overall yield of about 25%. The application of this method to two other model systems as well as to the crucial intermediate in the zoapatanol synthesis[20] in an overall yield of 25% is outlined (Scheme 70). Utilizing a variant of this method a six-membered lactone was converted to the corresponding β-keto ether (Scheme 71).[127] To make this procedure more efficient the yield in the deoxygenation step needs to be improved above the presently attenable 60%.



a) Dibal-H ; b) PTS-C_6H_6 ; c) B_2H_6-NaOH-H_2O_2 ;
d) CrO_3-C_5H_5N-CH_2Cl_2.

Scheme 71.

In connection with hydroboration and related reactions, we would like to point out a carbonyl transposition which took place during a total synthesis of the diterpenoid antibiotic, (−)-dictyolene,[128] and which could possibly be utilized in other natural product syntheses. This transposition (Scheme 72) makes use of two noteworthy reactions. One is the unusual reduction of a cross conjugated dienone tosylhydrazone with catecholborane in the produce an elofin stereoselectively.[129] Second, the allylic oxidation of this olefin with chromium trioxide pyridine complex in methylene chloride, a procedure developed by Dauben and others,[130] gave the transposed ketone. This reaction was successfully applied to 6-epi-α-santonin **72.1** which gave the transposed enone **72.4** in about 35% yield.[128]



a) $NH_2NHSO_2C_6H_4CH_3$-EtOH ; b) Catecholborane-
NaOAc-H_2O ; c) CrO_3-C_5H_5N-CH_2Cl_2.

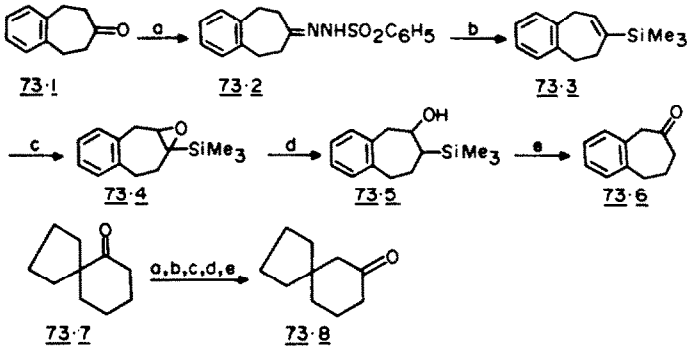
Scheme 72.

The versatility of hydroboration as a key step in a variety of 1,2-keto transpositions is apparent from the preceding discussion. However, the full potential of diborane and diborane derived reagents in transposition methodology has not yet been fully realized.

ORGANOSILICON REAGENTS IN 1,2-CARBONYL TRANSPOSITION

Since 1968 the chemistry of organosilicon reagents has undergone dramatic development and numerous publications describing the use of these reagents in organic synthesis, especially in carbon–carbon bond forming reactions, have appeared.[131] Functional units containing silicon can be easily introduced into an organic molecule by a variety of methods. These units can be manipulated under controlled and very mild conditions to carry out desired transformations very selectively. Because silicon can only be displaced as an electrofugal leaving group, there exists only a limited range of possibilities for its removal. The most effective conditions for the removal of silicon currently available involve treating the silicon containing compound with tetra-n-butylammonium fluoride in dry tetrahydrofuran.[132] At the present time, there are only a few examples of 1,2-carbonyl transposition utilizing organosilicon reagents and this area remains to be further explored.

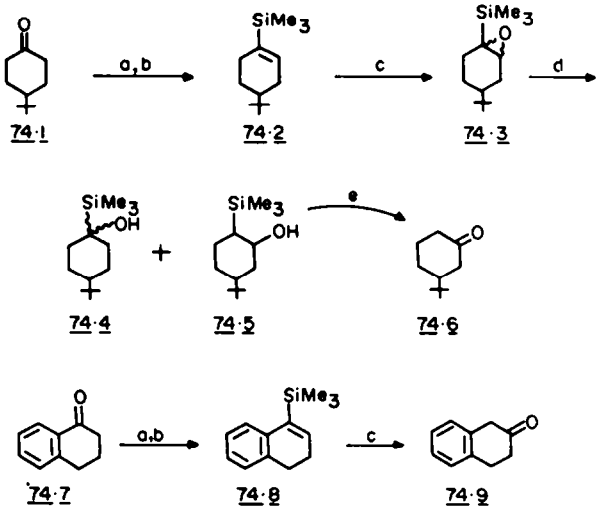
The first report of 1,2-ketone transposition utilizing vinylsilanes[87b,133,134] was provided by Paquette and his co-workers[135] (Scheme 73). The crucial step on which the 1,2-carbonyl transposition depended was the regioselective hydride ring opening of an epoxysilane to give a β-silyl alcohol (cleavage of the α-carbon-oxygen bond). Ample precedent for this ring opening was made available from the work of Eisch[136] and Whitham.[137] The reaction of chlorotrimethylsilane with the vinyl carbanion generated by the treatment of the tosylhydrazone of a ketone **73.2** with alkyllithium furnished the vinylsilane **73.3**. Oxidation of the vinylsilane with m-chloroperbenzoic acid at 0° in buffered sodium bicarbonate gave the epoxysilane **73.4**. Reduction with lithium aluminum hydride generally gave the β-silyl alcohol **73.5** via regiospecific attack of the hydride ion on the carbon atom bearing the silyl group.[136,137]



a) $NH_2NHSO_2C_6H_5$; b) TMEDA-n-BuLi-Me_3SiCl ; c) m-CIPBA ;
d) $LiAlH_4$-THF ; e) CrO_3-Et_2O-H_2O-H_2SO_4.

Scheme 73.

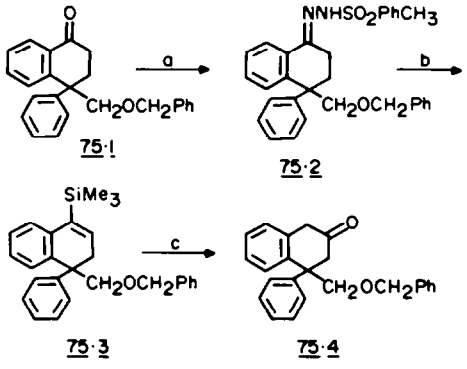
The 4-t-butycyclohexyl system (Scheme 74) gave a mixture of products of which only 24% were β-silyl alcohol **74.5** and the cholestanyl derivative exclusively underwent the usual *trans* di-axial opening under these conditions. A remarkably enhanced specificity for α-attack was obtained in both of these cases when a mixed reducing agent prepared from two equivalents of lithium aluminum hydride and one equivalent of aluminium chloride in anhydrous ether at 0° was used. Oxidation of the β-silyl alcohols using a modification of Brown's procedure[138] gave the desired transposed ketones. It should be noted that the epoxidation of the vinylsilanes derived from α-tetralone **74.7** and its 6-methoxy derivative under epoxidation conditions directly gave the corresponding β-tetralones **74.9** (Scheme 74). The precise mechanistic implications of the latter reaction have not been elucidated.[135] In this manner, several ketones were transposed in an overall yield averaging between 30 and 40% and therefore it appears to be a general and exceptionally efficient method for effecting a 1,2-carbonyl transposition.



a) $NH_2NHSO_2C_6H_5$; b) TMEDA-n-BuLi-Me_3SiCl ;
c) m-ClPBA ; d) $LiAlH_4$ - THF; e) CrO_3-Et_2O-H_2O-H_2SO_4.

Scheme 74.

The transformation has been found to be very useful in our own work[139] on conformationally restricted methadone and methadol analogs as illustrated (Scheme 75) in which the α-tetralone derivative **75.1** (prepared from diphenylacetic acid) was transposed to the β-tetralone derivative **75.4** in an overall yield of 30%.

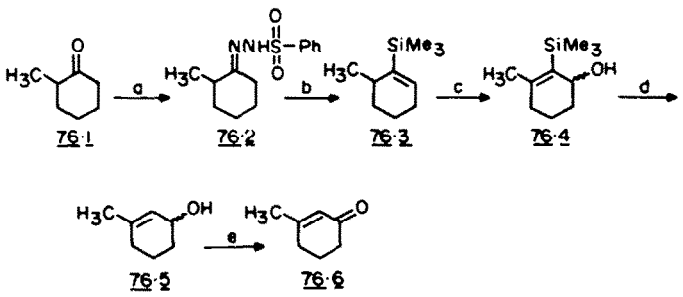


a) $NH_2NHSO_2C_6H_4CH_3$; b) TMEDA-n-BuLi-Me_3SiCl ; c) m-ClPBA .

Scheme 75.

Paquette and his associates[135,140] have also developed a method for 1,2-transposed allylic alcohols (hence transposed allylic ketones) from vinylsilanes prepared from saturated ketones **76.1**. These vinylsilanes **76.3** undergo regiospecific photosensitized oxygenation[141] using the customary dye-sensitization technique to yield allylic hydroperoxides. These intermediate hydroperoxides without isolation were immediately reduced with sodium borohydride in methanol to give only the α-silylated allylic alcohols **76.4** exclusively. This result suggests that the trimethylsilyl group may be directing an ene reaction of singlet oxygen with the vinylsilane in the formation of the hydroperoxide which undergoes a regioselective opening under reducing conditions to given an α-silyl alcohol.[136] In the final step the removal of the silicon moiety from **76.4** was accomplished by using tetra-n-butylammonium fluoride in a dipolar solvent such as acetonitrile[132] to give the desired allylic alcohol **76.5** (Scheme 76). The ease of removal of silicon in these α-silylated allylic alcohols, in contrast to the usual unreactivity of

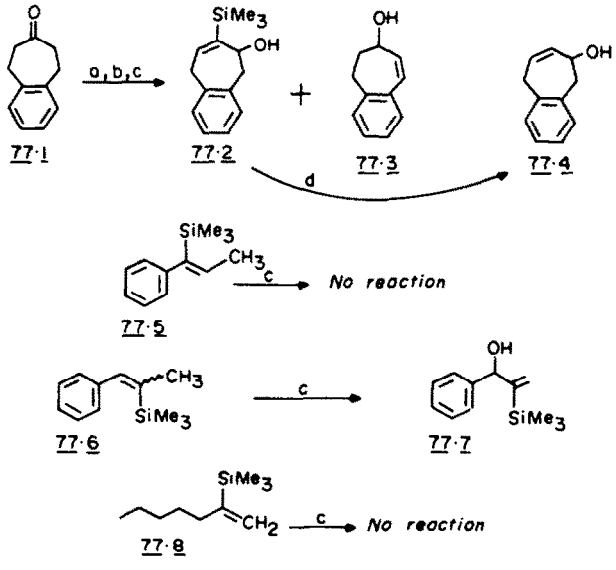
vinylsilanes toward fluoride ion, was attributed to hydrogen bonding of the fluoride ion in a 6-membered ring transition state involving the β-hydroxyl group.[142]



a) NH_2NHSO_2Ph ; b) BuLi-TMEDA, Me_3SiCl ; c) CH_3OH-ROSE BENGAL-hv-O_2, $NaBH_4$; d) $(n\text{-}Bu)_4N^{\oplus}F^{\ominus}$-$CH_3C{\equiv}N$; e) Oxidation.

Scheme 76.

Based upon HOMO and LUMO arguments Paquette[140] has rationalized the regiochemistry of these photooxygenation reactions with vinylsilanes. The examples in Scheme 77 were presented by Paquette as illustrations that such predictions are experimentally realized. When the photooxygenation was performed on the vinylsilane obtained from ketone **77.1** the product derived from the abstraction of the benzylic hydrogen (**77.3**) was obtained as a minor component compared to that derived from removal of an unactivated hydrogen **77.2** (product ratio of 1:3). In the case of **77.5** the starting material was recovered in high yield while **77.6** was transformed to the allylic alcohol **77.7** in 54% yield. The authors also found that photooxygenation did not occur in the case of vinylsilane **77.8** (even when sterically permitted) because this vinylsilane is too electron deficient to react at an appreciable rate with singlet oxygen. The generality of this method was demonstrated with the use of six different substrates with the overall yields ranging from 12 to 45%.



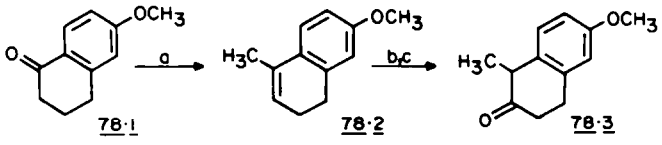
a) NH_2NHSO_2Ph ; b) BuLi-TMEDA-Me_3SiCl ; c) CH_3OH-Rose Bengal-hv-O_2 ; d) $(n\text{-}Bu)_4N^{\oplus}F^{\ominus}$-$CH_3CN$.

Scheme 77.

MISCELLANEOUS METHODS FOR 1,2-CARBONYL TRANSPOSITIONS

In this section all 1,2-carbonyl transposition methods which do not readily fit into one of the above categories are taken into consideration.

During their studies on the synthesis of (+)-α-onocerin, Stork[143] reported an efficient and short method for alkylative 1,2-carbonyl transposition (Scheme 78). Treatment of 6-methoxy-α-tetralone **78.1** with methylmagnesium iodide gave 3,4-dihydro-1-methyl-6-methoxy naphthalene **78.2**. Oxidation of this dihydronaphthalene with perphthalic acid gave an epoxide which was not isolated but which was treated immediately with hydrochloric acid and rearranged *in situ* to the alkylated transposed ketone, 1-methyl-6-methoxy-3,4-dihydro-2-(1H)-naphthalenone **78.3**.

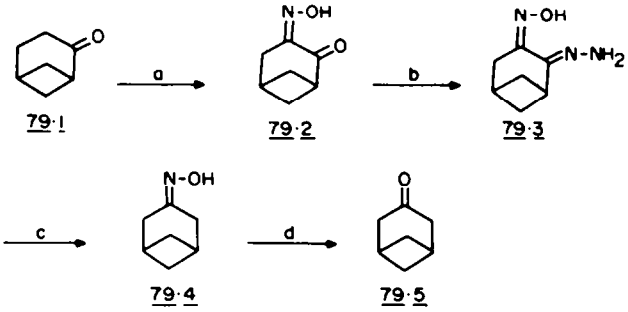


78·1 78·2 78·3

a) CH_3MgI-Et_2O ; b) Perphthalic acid ; c) $H_3^{\oplus}O$.

Scheme 78.

Earlier in this review (Scheme 38), the 1,2-carbonyl transposed utilization of α-oximinoketones as intermediates was described. These intermediates have also beem employed to carry out 1,2-carbonyl transposition in bicyclic and acyclic ketones as described below. In conection with their work on strained hydrocarbons, Musso and his colleagues[144] reported the following ketone transposition (Scheme 79). The bicyclic ketone **79.1** on oximination gave the α-oximino ketone **79.2**, which was converted to the corresponding hydrazone **79.3**. Wolff-Kishner reduction of the hydrazone **79.3** gave the oxime of the transposed ketone **79.4** which was hydrolyzed with pyruvic acid to yield the desired transposed ketone **79.5** in 30% overall yield.

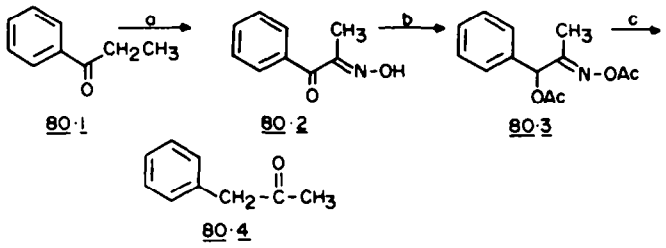


79·1 79·2 79·3 79·4 79·5

a) RONO-$OR^{\ominus}$; b) NH_2NH_2 ; c) KOH-Ethylene Glycol ;
d) NaPyruvate - CH_3COOH - H_2O.

Scheme 79.

Corey and Richman[145] utilized chromium(II) reductive deoximination with α-acetoxy cleavage to transpose a carbonyl function in a 1,2-fashion. Thus, propiophenone **80.1** was oximinated followed by reduction and acetylation to give the α-acetoxy–acetoxime **80.3** which, upon subsequent with chromous acetate in tetrahydrofuran–water (10:1) at 65°C for 34 hours, afforded the phenylacetone **80.4**. Neither yields nor any limitations of this method have been described (Scheme 80).

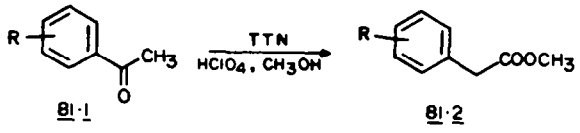


80·1 80·2 80·3 80·4

a) $RONO\text{-}OR^{\ominus}$; b) $NaBH_4$ in CH_3OH, $Ac_2O\text{-}C_5H_5N$;
c) $Cr(OAc)_2$-THF-H_2O.

Scheme 80.

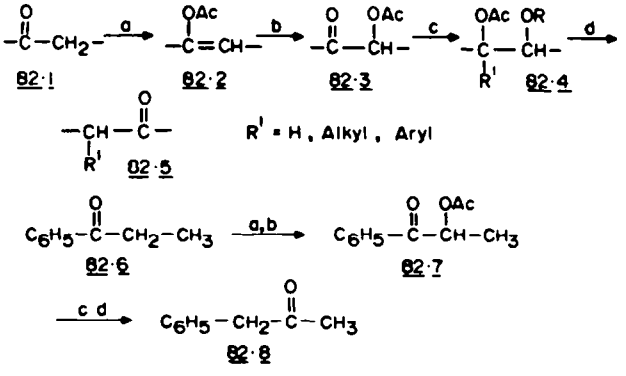
A novel one-step transformation for 1,2-carbonyl transposition was reported by McKillop, Swann, and Taylor.[146] They have found that thallium (III) nitrate in acidic methanol rearranged acetophenones **81.1** to methyl phenylacetates **81.2** in yields ranging from 62 to 94% (Scheme 81). The scope of this method was demonstrated in a wide range of substituted acetophenones in which both electron donating and electron withdrawing groups were present on various positions of the benzene ring. However, our own attempts[147] to carry out the same rearrangement on 3,5-dimethoxyphenylhexyl ketone failed, presumably due to the very electron rich aromatic moiety. Taylor[146] has also pointed out that the reaction was unsuccessful when applied to compounds containing amino substituents due to preferential complexation of the amino group with the thallium electrophile. The above conversion in general certainly represents an improvement over the Willgerodt-Kindler reaction for the conversion of alkyl aryl ketones to arylacetates. However, the published results indicate that up to the present time the Taylor-McKillop reaction[146] has only been applied to alkyl aryl ketones, while several examples of alkyl methyl ketone transformations to substituted acetic acid have been effected by the Willgerodt-Kindler reaction.[148]



81·1 81·2

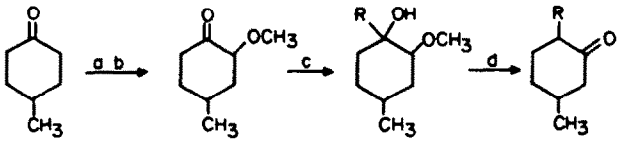
Scheme 81.

Shono and his colleagues devised a sequence for 1,2-carbonyl transposition which involves electrolytic oxidation of an enol acetate as a key step (Scheme 82).[149] Anodic oxidation of the enol acetate **82.2** in acetic acid containing triethylamine as a supporting electrolyte gave the α-acetoxy ketone **82.3**, which was smoothly reduced to the alcohol **82.4** with sodium borohydride. Subsequent dehydration of the vicinal acetoxy alcohol gave the ketone **82.5**. This general sequence was utilized in the conversion of propiophenone **82.6** to phenylacetone **82.8** and α-tetralone to β-tetralone.[150]



82·1 82·2 82·3 82·4 82·5 82·6 82·7 82·8

a) Ac_2O-p-TsOH; b) Anodic oxidation (CH_3COOH);
c) $NaBH_4$-CH_3OH; d) 150-180° with $KHSO_4$.



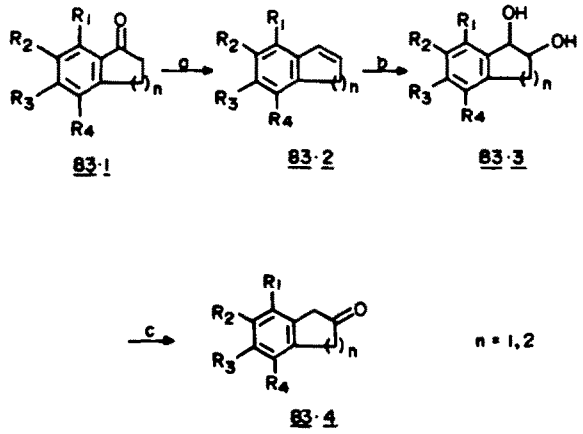
82·9 82·10 82·11 82·12

a) Ac_2O-p-TsOH ; b) Anodic oxidation (CH_3OH) ;
c) RMgBr-Et_2O ; d) 20% H_2SO_4 Reflux.

Scheme 82.

However, when these authors used absolute methanol-tetramethylammonium p-toluenesulfonate as the solvent-supporting electrolyte system in the anodic oxidation of enol acetate, α-methoxy ketones **82.10** were obtained in 50% yield.[150] Treatment of α-methoxy ketones **82.10** with Grignard reagents gave the corresponding alcohols **82.11**. Dehydration with 20% sulfuric acid gave the alkylated transposed ketone **82.12** (Scheme 82). Similarly, the enol acetate of cyclohexanone was converted to 2-phenyl cyclohexanone in an overall yield of 20%.

A sequence utilizing the rearrangement of the diol obtained from a ketone via an olefin was reported by Hauser and Prasanna[151a] (Scheme 83). The indanone derivative was transformed to the olefin **83.2**, followed by oxidation with a catalytic amount of osmium tetroxide in the presence of N-methylmorpholine-N-oxide which gave the diol **83.3** which was rearranged with p-toluenesulfonic acid in benzene to the transposed ketone **83.4** in an overall yield of 75%. The generality of this method was demonstrated by converting 3,4-dihydro-9,10-dimethoxy-1(2H) anthracenone to the corresponding 2-ketone in high yield. The application of this reaction sequence in the total synthesis of (±) daunomycinone has recently been reported.[151b]



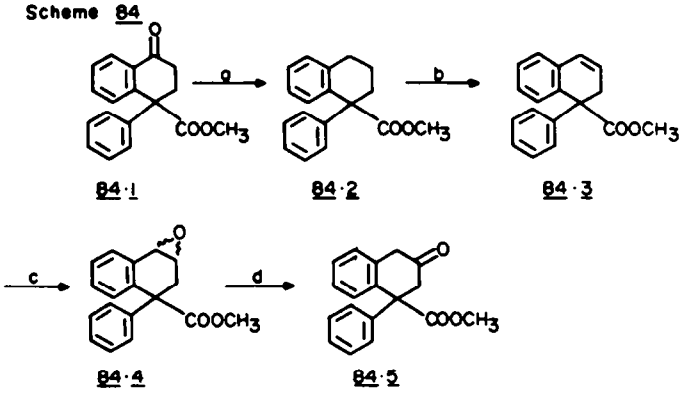
83·1 83·2 83·3 83·4 n = 1,2

a) $NaBH_4$, $H^{\oplus}$-C_6H_6 ; b) OsO_4 (cat)-n-methylmorpholine-N-oxide ;
c) $H^{\oplus}$-C_6H_6.

Scheme 83.

We have employed a sequence utilizing an olefin derived from a ketone as outlined below (Scheme 84).[152] The ketone **84.2** was converted in two steps to the olefin **84.3**. Epoxidation using m-chloroperoxybenzoic acid in ether gave the epoxide **84.4** and subsequent treatment with boron trifluoride etherate gave the β-tetralone derivative **84.5**.

Scheme 84

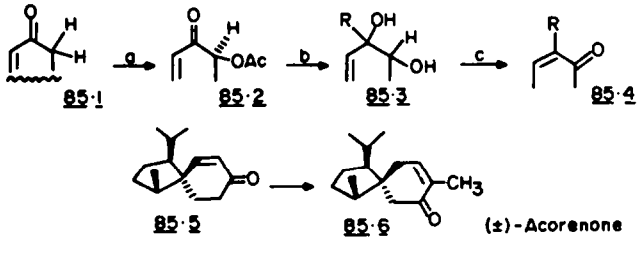


a) Hydrogenation - PtO_2 ; b) NBS - $CaCO_3$ - DMF ;
c) m - ClPBA - CH_2Cl_2 ; d) BF_3 - etherate .

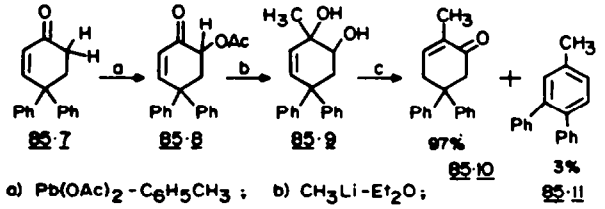
Scheme 84.

In the course of their work on the synthesis of (±) acorenone-B, Oppolzer and Mahalanabis[18] developed alkylative transposition methodology which is outlined below (Scheme 85). The enone **85.1** on treatment with lead tetraacetate afforded on epimeric mixture of the acetates **85.2**, which were converted to the stereoisomeric diols **85.3** with excess methyllithium. Dehydration of the diol mixture **85.3** with p-toluenesulfonic acid in boiling benzene gave the transposed ketone **85.4**. By this general sequence spiroenone **85.5** was converted to (±) acorenone-B **85.6** in an overall yield of 36%. This transformation possibly involves a pinacol-type hydrogen shift followed by migration of the olefinic bond.

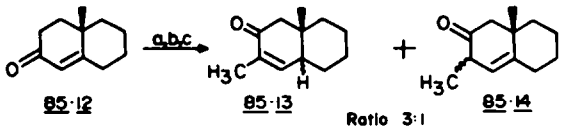
In order to study the scope and limitations of this sequence, Oppolzer and his colleagues[153] investigated three other model systems. They undertook a detailed examination of the dehydration of the diol **85.9** generated by the addition of an organometallic reagent to the acetoxy ketone **85.8**; the best results in the dehydration step were obtained by using p-toluenesulfonic acid in sulfolane at 65°C. These conditions gave a ratio of a transposed ketone **85.10** to a rearranged product **85.11** as 97:3. The reaction of the diol (obtained from the bicyclic enone **85.12**) with p-toluenesulfonic acid in benzene gave a mixture (54% yield) of the alkylated transposed ketone **85.13** and the untransposed enone **85.14** in the ratio of 3:1. However, when methanesulfonic acid in trifluoroethanol was used as a dehydrating agent the ratio of the transposed enone (*cis*; *trans* ratio was 6;1) to the untransposed ketone increased to 9:1 while the yield dropped to 31%. These results illustrate the crucial role played by the acid and the solvent in the dehydration step.



a) $Pb(OAc)_2$ - $C_6H_5CH_3$; b) CH_3Li - Et_2O ; c) p-TsOH - C_6H_6 .



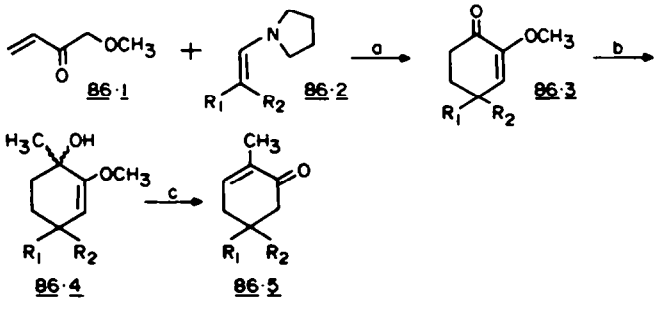
a) $Pb(OAc)_2$ - $C_6H_5CH_3$; b) CH_3Li - Et_2O;
c) p - TsOH - Sulfolene .



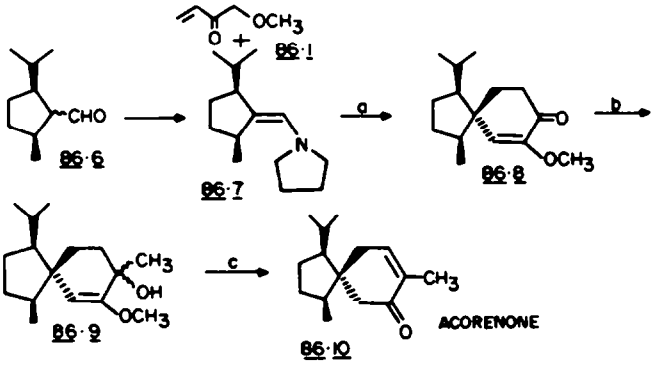
a) $Pb(OAc)_2 - C_6H_5CH_3$; b) $CH_3Li - Et_2O$; c) p-TsOH - C_6H_6 .

Scheme 85.

Lange and his group[154] have reported an alkylative 1,2-carbonyl transposition using 2-methoxy-2-cyclohexenones **86.3** as starting materials (Scheme 86). These enones were synthesized using a variation of the annelation procedure described by Wenkert.[155] Reaction of the enone **86.3** with methyl Grignard accomplished the alkylation step and gave the tertiary alcohol **86.4** which on dehydration with p-toluenesulfonic acid in benzene gave the alkylated transposed ketone **86.5**. These transformations were employed in the synthesis of the monoterpene carvotanacetone **86.5** ($R_1 = (CH_3)_2CH$, $R_2 = H$) and the sequiterpene (−) acorenone-B **86.10**.[156] (See also Schemes 52 and 85 for the synthesis of (±) acorenone-B.)



a) CH_3COOH ; b) CH_3MgI in Et_2O ; c) p-TsOH - C_6H_6 .



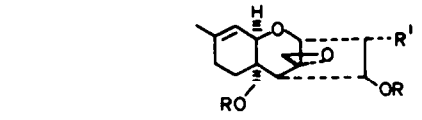
a) CH_3COOH ; b) CH_3MgI in Et_2O ; c) p-TsOH - C_6H_6 .

Scheme 86.

We would like to describe 1,2-carbonyl transposition procedures developed by Kraus[157,158] and White[159] in connection with their synthetic studies towards verrucarol **87.1** and anguidin **87.2**. Verrucarol **87.1** is the sesquiterpene portion of several biologically active macrocyclic dilactones known as verrucarins and roridins.[160] These authors have reported a lactone to β-keto ether transposition. The previously described method for converting a γ-lactone or a δ-lactone[127] to its corresponding β-keto ether is not compatible with verrucarol **87.1** since this substrate has an additional double bond.

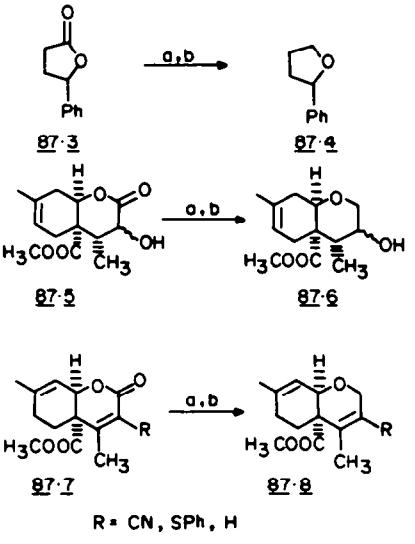
Kraus and his colleagues developed a two-step reductive method for a conversion of a lactone to an ether.[161] The first step was the reduction of a lactone to a lactol with diisobutylalluminum hydride.[162] This was followed by reductive deoxygenation with triethylsilane in the presence of boron trifluoride

etherate.[163] The overall yield for the conversion was 55–88% depending on the nature of the substituents on the lactone ring. It has been demonstrated that unprotected alcohols as well as enol, silyl, benzyl thioethers, and hindered esters were compatible with the mild reducing conditions. It was also shown that unsaturated lactones afforded products in which the position of the double bond remained unchanged. However, this method can only be used in medium ring lactones provided that the lactol remains as a cyclic hemiketal (Scheme 87).



R = R' = H-Verrucarol 87·1

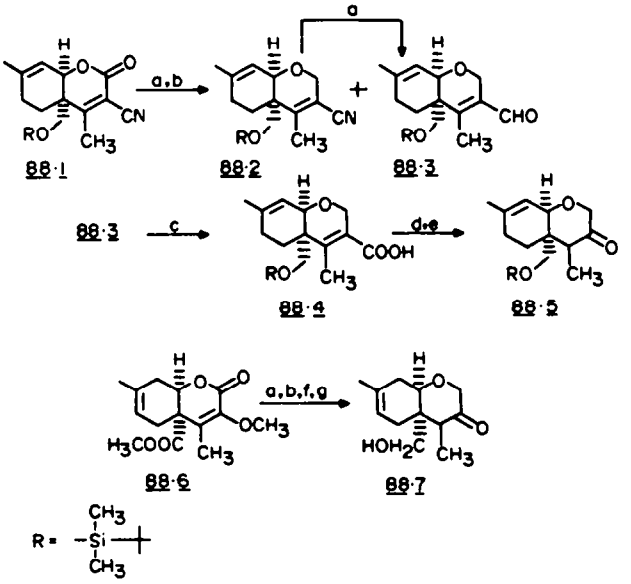
R = $COCH_3$; R' = OH Anguidin 87·2



a) Dibal-H-C_7H_8; b) Et_3SiH-BF_3Et_2O-CH_2Cl_2 at -78° C.

Scheme 87.

Utilization of the above procedure in the conversion of lactones **88.1** and **88.6** to the β-keto ethers is outlined (Scheme 88).



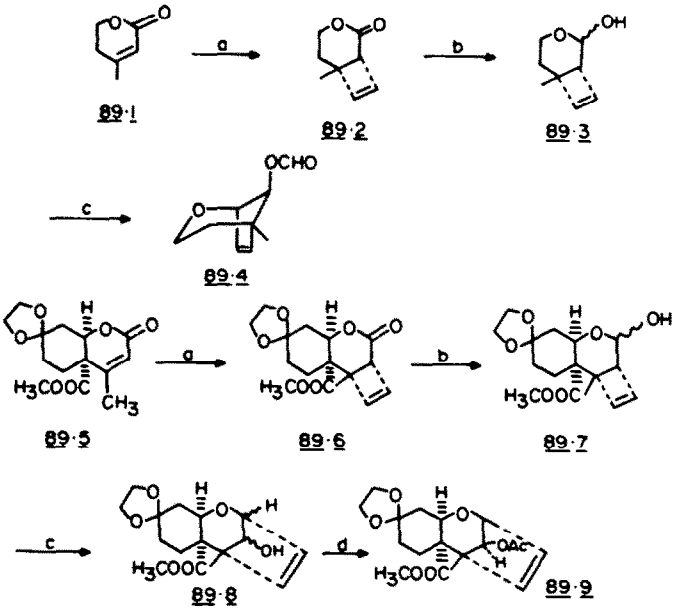
a) Dibal-H-C_7H_8; b) Et_3SiH-BF_3-Et_2O at -78° C;

c) $NaClO_2$ – ⟩=⟨ – t-BuOH-H_2O; d) Et N-ClCOOEt;

e) NaN_3 – Δ – $OH^{\ominus}$; f) $LiAlH_4$; g) $H_3O^{\oplus}$.

Scheme 88.

White *et al.*[159] have carried out a cyclobutylcarbinol to cyclopentenol rearrangement. We would like to point out that this rearrangement is in fact an alkylative 1,2-ketone transposition (alkylative lactone to β-keto ether transposition) when applied in the case of lactol **89.3**. The requisite lactol was synthesized in two steps from anhydromevalonolactone **89.1** (Scheme 89). Solvolytic rearrangement in formic acid gave the transposed ester **89.4** with the formation of a carbon–carbon bond. This then can be converted in two steps to the transposed ketone. Application of this to the tricyclic system present in verrucarol is also outlined (Scheme 89).

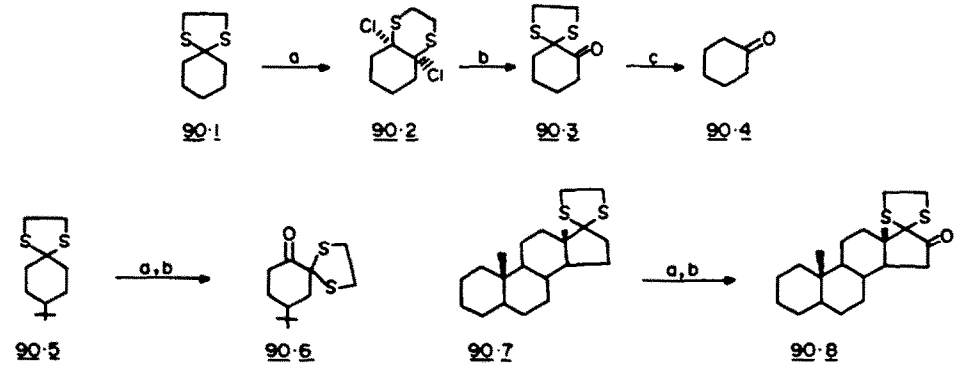


89·1 89·2 89·3 89·4 89·5 89·6 89·7 89·8 89·9

a) hν-CH_3CN-HC≡CH ; b) Dibal-H; c) HCOOH or PTS-wet C_6H_6 ;
d) $(CH_3CO)_2O$-C_5H_5N.

Scheme 89.

Bulman-Page *et al.*[164] have found that sulfuryl chloride reacts with 1,3-oxathiolanes and 1,3-dithiolanes to yield intermediates which can be converted on hydrolytic work-up to α-ketothioacetals. Furthermore, these authors have suggested the synthetic potential of this chemistry for carrying out 1,2-carbonyl transposition by reductive removal of the thioacetal group. Reaction of 1,3-dithiolane **90.1** with sulfuryl chloride gave **90.2**. Work-up with triethylamine and wet silica gel afforded the α-ketodithiolane **90.3** in 86% yield (Scheme 90). However the same reaction sequence with 4-t-butyl-dithiolane **90.5** gave mainly **90.6** and in the case of androstane dithiolane **90.7** very little of the desired product **90.8** was obtained. These latter results suggest that this synthetic sequence is of very limited scope in carbonyl transposition.

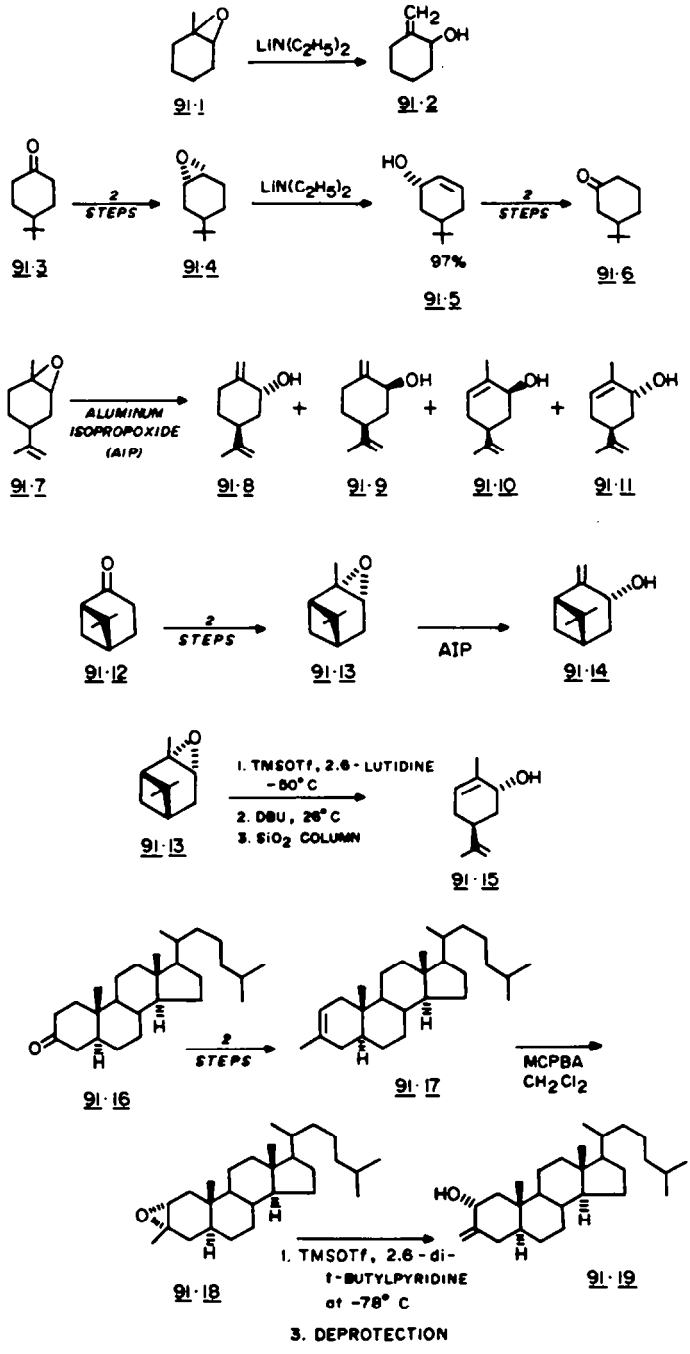


90·1 90·2 90·3 90·4 90·5 90·6 90·7 90·8

a) SO_2Cl_2 ; b) NEt_3, Silica-gel Chromatography ;
c) W-4 Raney nickel - C_2H_5OH.

Scheme 90.

Previously in this report (Scheme 78), the 1,2-alkylative transposed utilization of an epoxide as an intermediate was described. Although known for some time, the rearrangement of epoxides to the corresponding allylic alcohols with a variety of reagents such as lithium diethylamide,[165] aluminum isopropoxide,[166] diisobutylaluminum hydride,[167] and recently with trimethylsilyl triflate,[168] has not been utilized in 1,2-carbonyl transposition. This may be due to the fact that some of these reagents give a mixture of products difficult to separate and therefore may have a limited application. However, we feel that this rearrangement deserves mention. Following are a few examples to illustrate this point (Scheme 91).



Scheme 91.

CONCLUSIONS

Our purpose in writing this report is to provide a comprehensive summary of the methodology currently available for 1,2-carbonyl and alkylative 1,2-carbonyl transpositions, which we hope will be of future use to synthetic organic chemists. It is clear from the number of different methods described in

this report and the corresponding references cited that considerable scientific effort and expertise have been applied to these transformations in a wide variety of systems. Despite these efforts, however, many important problems remain to be explored. For example, the regioselective 1,2-transposition of a carbonyl group flanked on both sides by methylenes has been accomplished only in specialized situations wherein an aromatic group is adjacent to one of the methylenes. Finally, the methodologies have rarely been applied to heterocyclic systems or to alicyclic systems containing heteroatoms. We hope that the high level of current interest in the transposition will lead to new methodology which can successfully be applied to these problems.

Note added in proof—Since submission of this Report we have become aware of a few additional examples in which 1,2-carbonyl transposition methodologies have appeared:

(i) K. Ito, F. Suzuki and M. Haruna, *J. Chem. Soc. Chem. Commun.* 733 (1978).
(ii) R. E. Ireland and D. Habich, *Chem. Ber.* **114**, 1418 (1981).
(iii) C. H. Heathcock, E. G. Delmar and S. L. Graham, *J. Am. Chem. Soc.* **104**, 1907 (1982).
(iv) R. Askani and M. Littmann, *Tetrahedron Letters* 3651 (1982).

Acknowledgements—We have attempted to make this report as comprehensive and relevant as possible. In trying to do this, we might have inadvertently omitted some work that undoubtedly should have been included. For this we would like to extend our apologies. We would like to profoundly thank Ms. Sunanda (Susie) V. Kane for her skill, patience, and care in typing the rough and the final draft of this manuscript. We are grateful to some of our colleagues for allowing us to incorporate their unpublished work. V. V. Kane would like to thank the Department of Chemistry for financial support in the preparation of this manuscript.

REFERENCES

[1]D. A. Evans and G. C. Andrews, *Accounts Chem. Res.* **7**, 147 (1974).
[2]K. M. Patel and W. Reusch, *Synth. Commun.* **5**, 27 (1975).
[3]B. M. Trost, *Accounts Chem. Res.* **7**, 85 (1974).
[4]E. D. Bergmann, D. Ginsburg and R. Pappo, *Org. Reactions* **10**, 179 (1959).
[5]C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.* **45**, 1066 (1980) and references therein.
[6a]E. J. Corey, *Pure Appl. Chem.* **14**, 19 (1967); [b]J. E. McMurry and J. Melton, *J. Am. Chem. Soc.* **93**, 5309 (1971).
[7a]D. Seebach and M. Kolb, *Chem. Ind. (London)* 687 (1974); [b]O. W. Lever, Jr., *Tetrahedron* **32**, 1943 (1976).
[8a]*The Chemistry of the Carbonyl Group* (Edited by S. Patai), Interscience, New York (1966); [b]*The Chemistry of the Carbonyl Group* (Edited by J. Zabicky), Vol. 2. Interscience, New York (1968); [c]C. D. Gutsche, *The Chemistry of Carbonyl Compounds, in the Foundation of Modern Organic Chemistry Series.* Prentice-Hall, Englewood Cliffs, New Jersey (1967); [d]S. Warren, *Chemistry of the Carbonyl Group, A Programmed Approach to Organic Reaction Mechanisms.* Wiley, New York, 1974.
[9]T. Nakai and T. Mimura, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem., Jpn.)* **35**, 964 (1977).
[10]P. S. Wharton and D. H. Bohler, *J. Org. Chem.* **26**, 3615 (1961).
[11a]G. Buchi and J. C. Vederas, *J. Am. Chem. Soc.* **94**, 9128 (1972); [b]G. Buchi and D. Egger, *J. Org. Chem.* **36**, 2021 (1971); [c]P. Grieco, *Ibid.* **37**, 2363 (1972); [d]Y. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.* **95**, 4446 (1973); [e]W. G. Dauben and D. M. Michno, *J. Org. Chem.* **42**, 682 (1977); [f]T. Nakai, T. Mimura, and T. Kurokawa, *Tetrahedron lett.* 2895 (1978).
[12]B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.* **97**, 4018 (1975).
[13]T. Nakai, E. Wada and M. Okawara, *Tetrahedron Lett.*, 1531 (1975).
[14]S. F. Martin, *Synthesis*, 633 (1979).
[15]J. W. Cornforth, J. M. Osbond and G. H. Phillips, *J. Chem. Soc.* 907 (1954),
[16]C. Djerassi, H. J. Ringold and G. Rosenkranz, *J. Am. Chem. Soc.* **73**, 5513 (1951).
[17]A. G. Schultz, Y. K. Lee and M. H. Berger, *Ibid.* **99**, 8065 (1977).
[18]W. Oppolzer and K. K. Mahalanabis, *Tetrahedron Lett.* 3411 (1975).
[19]S. D. Levine, R. Adams, R. Chen, M. L. Cotter, A. Hirsch, V. V. Kane, R. M. Kanojia, C. Shaw, M. Wachter, E. Chin, R. Huttemann, P. Ostrowski, J. L. Mateos, L. Noriega, A. Guzman, A. Mijarez and L. Tovar, *J. Am. Chem. Soc.* **101**, 3404 (1974).
[20]V. V. Kane and D. L. Doyle, *Tetrahedron Lett.* 3027 (1981); 3031 (1981).
[21]F. R. Lankshear and W. H. Perkin, Jr., *J. Chem. Soc.* **27**, 167 (1911).
[22]J. Bredt and von W. Hilbing, *Chem. Zeit* **35**, 765 (1911); see also *Chemisches Zentralblatt*, 2954 (1911).
[23]J. Bredt, *Annalen* **366**, 16 (1909).
[24]J. Bredt and W. H. Perkin, Jr., *J. Chem. Soc.* **29**, 2182 (1913).
[25]G. Komppa, A. Klami and A. M. Kuvaja, *Ann.* **547**, 185 (1941).
[26]L. Ruzicka, P. A. Plattner and M. Furrer, *Helv. Chim. Acta.* **27**, 524 (1944).
[27a]P. S. Hench, E. C. Kendall, C. H. Slocumb and H. F. Polley, *Proc. Staff Meetings Mayo Clinic*, **24**, 181 (1949); [b]H. L. Mason, C. S. Myers and E. C. Kendall, *J. Biol. Chem.*, **114**, 613 (1936); [c]For an excellent review article see Syntheses of Cortisone, by G. Rosenkranz and F. Sondheimer, *Fortschr. Chem. Org. Naturst.* **10**, 275 (1953).
[28]T. Reichstein, *Helv. Chim. Acta.* **19**, 1107 (1936).
[29]C. Djerassi, R. Yashin and G. Rosenkranz, *J. Am. Chem. Soc.* **72**, 5750 (1950).
[30]J. Schmidlin and A. Wettstein, *Helv. Chim. Acta.* **36**, 1241 (1953).
[31]J. Elks, G. H. Phillips, T. Walker, L. J. Wyman, *J. Chem. Soc.* 4330 (1957); [b]J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *Ibid.* 4344 (1957).
[32]R. S. Rosenfield and T. F. Gallagher, *J. Am. Chem. Soc.* **77**, 4367 (1955).
[33a]D. H. R. Barton, *Experentia*, **6**, 316 (1950); [b]D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951); [c]D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.* **72**, 1066 (1950).
[34]E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.* **164**, 791 (1946).
[35]A. Lardon and T. Reichstein, *Helv. Chim. Acta* **25**, 1444 (1942).
[36]H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.* **78**, 3749 (1956).
[37]J. E. Gurst and C. Djerassi, *J. Amer. Chem. Soc.* **86**, 5542 (1964).

[38]J. A. Edwards, P. G. Holton, J. C. Orr, L. C. Ibanez, E. Necoechea, A. De La Roz, E. Segovia, R. Urquiza and A. Bowers, *J. Med. Chem.* **6**, 174 (1963).
[39]P. D. Klimstra, R. Zigman and R. E. Counsell, *Ibid.* **9**, 924 (1966).
[40]R. Gardi, R. Vitali and A. Ercoli, *Gazz. Chim. Ital.* 632 (1962).
[41]J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.* **79**, 6050 (1957). These authors prepared 2,3-secocholestane-2,3-dioic acid dimethyl ester by the oxidation of Δ^2-cholestene with potassium permanganate followed by esterification.
[42]H. H. Zeiss and W. B. Martin, Jr., *J. Am. Chem. Soc.* **75**, 5935 (1953).
[43]J. E. Bridgeman, E. R. H. Jones, G. D. Meakins and J. Wicha, *Chem. Commun.* 898 (1967).
[44]M. Fetizon, J. C. Gramain and I. Hanna, *Compt. rend.* **265**, 929 (1967).
[45]R. A. Jones and T. C. Webb, *J. Chem. Soc.* (*C*), 3926 (1971).
[46]J. E. Bridgeman, C. E. Butchers, E. R. H. Jones, A. Kasal, G. D. Meakins and P. D. Woodgate, *J. Chem. Soc.* (*C*), 242 (1970).
[47]K. L. Williamson and W. S. Johnson, *J. Org. Chem.* **26**, 4563 (1961).
[48]R. L. Clarke, *Ibid.* **28**, 2626 (1963).
[49]R. L. Clarke and S. J. Daum, *Ibid.* **30**, 3786 (1965).
[50a]A. Hassner, J. M. Larkin and J. E. Dowd, *Ibid.* **33**, 1733 (1968); [b]A. Tareda and A. Hassner, *Bull. Chem. Soc.*, (*Jpn.*) **40**, 1937 (1967).
[51a]N. Kornblum, *Org. React.* **12**, 135 (1962); [b]A. Hassner and J. M. Larkin, *J. Am. Chem. Soc.* **85**, 2181 (1963).
[52a]H. Shecter, D. E. Ley and E. B. Robertson, *Ibid.* **78**, 4984 (1956); [b]A. Hassner and C. Heathcock, *J. Org. Chem.* **29**, 1350 (1964).
[53]W. E. Noland and R. Libers, *Tetrahedron, Suppl.* 1, 23 (1963).
[54]D. H. R. Barton, D. Giacopello, P. Manitto and D. L. Strubble, *J. Chem. Soc.*, (*C*) 1047 (1969).
[55a]E. J. Bailey, D. H. R. Barton, J. Elks and J. F. Templeton, *Ibid.* 1578 (1962); These results were reported in the form of a communication in [b]E. J. Bailey, J. Elks and D. H. R. Barton, *Proc. Chem. Soc.* 214 (1960); [c]H. Mori, V. Gandhi and E. Schwenk, *Chem. Pharm. Bull.*, (*Jpn.*) **10**, 842 (1962).
[56]Autooxidation in triterpenes see R. Hanna and G. Ourission, *Bull. Soc. Chim.*, (*Fr.*) 1945 (1961).
[57]Autooxidation in the euphol series, see D. Lavie, E. Glotter and Y. Shvo, *Tetrahedron* **19**, 1377 (1963).
[58]A. Lablache-Combier, B. Lacoumbe and J. Levisalles, *Bull. Soc. Chim.*, (*Fr.*) 897 (1966).
[59]W. Reusch and R. LeMahieu, *J. Amer. Chem. Soc.* **85**, 1669 (1963) and **86**, 3068 (1964).
[60]R. W. Mouk, K. M. Patel and W. Reusch, *Tetrahedron* **31**, 13 (1975).
[61]G. Just and Y. C. Lin, *Chem. Commun.* 1350 (1968).
[62]M. N. Huffman, M. H. Lott and A. Tilletson, *J. Biol. Chem.* **217**, 107 (1955).
[63]M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.* **73**, 878 (1951) and **75**, 4327 (1953).
[64a]J. Fajkos and J. Joska, *Coll. Czech. Chem. Commun.* **25**, 2863 (1960) and **26**, 1118 (1961); [b]J. Fajkos and F. Sorm, *Ibid.* **19**, 349 (1954) and **20**, 1464 (1955); [c]G. Habermehl and A. Haff, *Ber.* **102**, 186 (1969); [d]D. E. Green, A. R. Martin and A. I. White, *J. Pharm. Sci.* **59**, 526 (1970).
[65]D. Varesch and J. Jacques, *Bull. Soc. Chim.*, (*Fr.*) 67 (1965).
[66]K. Oka and S. Hara, *J. Am. Chem. Soc.* **99**, 3859 (1977).
[67a]B. M. Trost, *Chem. Rev.* **78**, 363 (1978), and refs. cited therein; [b]B. M. Trost, T. N. Salzmann and K. Hiroi, *J. Am. Chem. Soc.* **98**, 4887 (1976).
[68]B. M. Trost, *Acc. Chem. Res.* **11**, 453 (1978).
[69]B. M. Trost, in *Organic Sulfur Chemistry* (Edited by C. J. M. Sterling), p. 237. Butterworths, London (1975).
[70]T. Mukaiyama, *Ibid.* p. 265.
[71a]R. B. Woodward, I. J. Pachter and M. L. Scheinbaum, *J. Org. Chem.* **36**, 1137 (1971); [b]D. J. Cram and M. Cordon, *J. Am. Chem. Soc.* **77**, 1810 (1955).
[72a]J. C. A. Chivers and S. Smiles, *J. Chem. Soc.* 697 (1928); [b]G. S. Brookes and S. Smiles, *Ibid.* 1723 (1926); [c]D. T. Gibson, *Ibid.* 2637 (1931).
[73]R. L. Autrey and P. W. Scullard, *J. Am. Chem. Soc.* **90**, 4917 (1968) and **90**, 4924 (1968).
[74]M. E. Kuehne, *J. Org. Chem.* **28**, 2124 (1963).
[75]R. B. Woodward, *Harvey Lect.* **59**, 31 (1965).
[76]J. A. Marshall and H. Roebke, *J. Org. Chem.* **34**, 4188 (1969).
[77]Y. K. Yee and A. G. Schultz, *Ibid.* **44**, 719 (1979).
[78]B. M. Trost, K. Hiroi and S. Kurozumi, *J. Am. Chem. Soc.* **97**, 438 (1975).
[79]B. M. Trost, K. Hiroi and N. Holy, *Ibid.* **97**, 5873 (1975).
[80]M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura and S. Inoue, *J. Org. Chem.* **40**, 2009 (1975).
[81]T. Mukaiyama, S. Kobayashi, K. Kamio and H. Takai, *Chem. Lett.* 237 (1972).
[82]T. Kumamoto, S. Kobayashi and T. Mukaiyama, *Bull. Chem. Soc.* (*Jpn.*) **45**, 866 (1970).
[83]S. R. Wilson, G. M. Georgiadis, H. N. Khatri and J. E. Bartmess, *J. Amer. Chem. Soc.* **102**, 3577 (1980).
[84]T. Nakai and T. Mimura, *Tetrahedron Lett.* 531 (1979).
[85]R. H. Shapiro, *Org. React.* **23**, 405 (1976).
[86a]R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.* **89**, 5734 (1967); [b]G. Kaufmann, F. Cook, H. Shechter, J. Bayless and L. Friedman, *Ibid.* **89**, 5736 (1967).
[87a]W. G. Dauben, G. T. Rivers and W. T. Zimmerman, *Ibid.* **99**, 3414 (1977); [b]A. R. Chamberlin, J. E. Stemke and F. T. Bond, *J. Org. Chem.* **43**, 147 (1978).
[88]T. Mimura and T. Nakai, *Chem. Lett.* 931 (1980).
[89]T. Mimura and T. Nakai, *Ibid.* 1099 (1980).
[90]S. Kano, T. Yokomatsu, T. Ono, S. Hibino and S. Shibuya, *J. Chem. Soc., Chem. Commun.* 414 (1978).
[91]A. E. Greene, C. LeDrian and P. Crabbe, *J. Org. Chem.* **45**, 2713 (1980).
[92]B. M. Trost and T. N. Salzman, *Ibid.* **40**, 148 (1975).
[93a]M. Watanabe, K. Shiai and T. Kumamoto, *Chem. Lett.* 855 (1975); [b]J. Rigby, PhD. thesis, University of Wisconsin, 1977; [c]V. V. Kane and P. C. Ostrowski, unpublished work.
[94a]A. Guzman, J. Muchowski and J. Saldana, *Chem. Ind.* 357 (1977); [b]P. G. Gassman and R. J. Balchunis, *J. Org. Chem.* **42**, 3236 (1977); [c]P. A. Zoretic and P. Soja, *Ibid.* **41**, 3587 (1976).
[95]B. M. Trost and R. A. Kunz, *Ibid.* **39**, 2475 (1974).
[96]D. N. Brattesani and C. H. Heathcock, *Tetrahedron Lett.* 2279 (1974).
[97]B. M. Trost and L. H. Latimer, *J. Org. Chem.* **43**, 1041 (1978).
[98]J. E. Thompson, *Ibid.* **32**, 3947 (1967).

[99a]K. Iwai, H. Kosugi and H. Uda, *Chem. Lett.* 1237 (1974); [b]H. J. Monterro and A. L. Gernal, *Synthesis* 437 (1975).
[100]B. M. Trost and G. S. Massiot, *J. Am. Chem. Soc.* **99**, 4405 (1977).
[101]P. G. Gassman, B. W. Cue, Jr. and T. Y. Luh, *J. Org. Chem* **42**, 1344 (1977).
[102]E. J. Corey and S. Knapp, *Tetrahedron Lett.* 4687 (1976).
[103]L. Morin, D. Barillier, M. P. Strobel and D. Paquer, *Ibid.* 2267 (1981); for the synthesis of substituted cyclohex-1-enylalkylsulphides see F. Akiyama, *J. Chem. Soc., Chem. Commun.* 208 (1976).
[104a]T. Mukaiyama, K. Kamio, S. Kobayashi and H. Takei, *Bull. Chem. Soc., (Jpn.)* **45**, 3723 (1972); [b]Y. Nagao, M. Ochiai, K. Kaneko, A. Maeda, K. Watanabe and E. Fujita, *Tetrahedron Lett.* 1345 (1977; [c]Y. Nagao, K. Kaneko and E. Fujita, *Ibid.* 4115 (1978); [d]R. A. J. Smith and D. J. Hannah, *Synth. Commun.* **9**, 301 (1979); [e]For $AgNO_3$ facilitated hydrolysis of dithioketals, see P. Gosselin, S. Masson and A. Thuillier, *Compt. rend.* **291**, 183 (1980).
[105a]H. C. Brown, *Hydroboration.* W. A. Benjamin, New York (1962); [b]H. C. Brown, *Boranes in Organic Chemistry.* Cornell University Press, Ithaca, New York (1972); [c]G. M. L. Cragg, *Organoboranes in Organic Synthesis.* Marcel Dekker, New York (1973); [d]T. Onak, *Organoborane Chemistry.* Academic Press, New York (1975); [e]H. C. Brown, G. W. Kramer, A. B. Levy and M. M. Midland, *Organic Synthesis via Boranes.* Wiley Interscience, New York (1975).
[106]For reviews see [a]E. R. H. Walker, *Chem. Soc. Rev.* **5**, 23 (1976); [b]C. F. Lane, *Chem. Rev.* **76**, 773 (1976); [c]G. W. Kabalka, *Aldrichimica Acta* **8**, 14 (1975); [d]C. F. Lane, *Ibid.* **8**, 20 (1975); [e]C. F. Lane, *Ibid.* **10**, 41 (1977); [f]H. C. Brown and S. Krishnamurthy, *Ibid.* **12**, 3 (1979); [g]J. A. Gladysz, *Ibid.* **12**, 13 (1979); [h]H. C. Brown and J. B. Campbell, *Ibid.* **14**, 3 (1981).
[107]H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.* **83**, 2952 (1961).
[108a]W. D. P. Burns, M. S. Carson, W. Cocker and P. V. R. Shannon, *J. Chem. Soc., (C)*, 3073 (1968); for reduction of α',β-unsaturated compounds see [b]L. S. Tai and C. T. Chien, *Hua Hsueh Hsueh Pao*, **31**, 370 (1965); [c]C. T. Chien, E. C. Hsieh and L. S. Tai, *Ibid.* **31**, 376 (1965); (*Chem. Abs.*) **64**, 8022 (1966).
[109]J. Klein and E. Dunkelblum, *Tetrahedron* 24, 5701 (1968).
[110]J. J. Borowitz and G. J. Williams, *J. Org. Chem.* **32**, 4157 (1967).
[111a]J. Gore, J. P. Drouet and J. J. Barieux, *Tetrahedron Lett.* 9 (1969); [b]J. J. Barieux and J. Gore, *Bull. Soc. Chim., Fr.* 1649 (1971) and 3978 (1978).
[112]A. C. Cope and N. A. Lebel, *J. Am. Chem. Soc.* **82**, 4656 (1960).
[113]F. Bondavalli, P. Schenone, A. Ranise and S. Lanteri, *J. Chem. Soc. Perkin I*, 2626 (1980).
[114]M. Montury and J. Gore, *Tetrahedron* **33**, 2819 (1977).
[115]J. Froburg, G. Magnusson and S. Thoren, *Tetrahedron Lett.* 1621 (1975). The work is based on the report of Lewis and Pearce that a borane-enamine adduct (obtained from the hydroboration of an enamine) gave olefin in good yields on refluxing in propionic acid. J. W. Lewis and A. A. Pearce, *J. Chem. Soc.* (*B*), 863 (1969).
[116]G. L. Larson and L. M. Fuentes, *Synth. Commun.* **9**, 841 (1979).
[117a]G. L. Larson, D. Hernadez and A. Hernadez, *J. Organometal. Chem.* **76**, 9 (1974); [b]G. L. Larson and A. Hernadez, *Ibid.* **102**, 123 (1975). Cyclic enol trimethylsilyl ethers have been converted to olefins by hydroboration followed by treatment of the intermediate organoborane with an acid catalyst; see [c]G. L. Larson, E. Hernadez, C. Alonso and I. Nieves, *Tetrahedron Lett.* 4005 (1975).
[118]H. C. Brown, E. F. Knights and C. G. Scouten, *J. Am. Chem. Soc.* **96**, 7765 (1974).
[119]J. Klein, R. Levene and E. Kunkelblum, *Tetrahedron Lett.* 2845 (1972).
[120]P. L. Stotter, private communication.
[121]C. L. Edwards, Ph.D. Thesis, Universety of Texas at Austin, 1974. We would like to thank Professor P. L. Stotter for informing us of their results prior to publication and allowing us to incorporate these results in this report.
[122]R. M. Coates and J. E. Shaw, *J. Org. Chem.* **35**, 2597 (1970) and **35**, 2601 (1970). These authors have reported reduction of β-keto ester methoxymethyl enol ethers to saturated esters with lithium in liquid ammonia.
[123]V. V. Kane, D. L. Doyle and P. C. Ostrowski, *Tetrahedron Lett.* 2643 (1980).
[124]R. E. Ireland and G. Pfister, *Ibid.* 2145 (1969).
[125]M. Fetizon, M. Jurion and N. T. Anh, *J. Chem. Soc. Part D* 112 (1969).
[126a]G. Zweifel and J. Plamondon, *J. Org. Chem.* **35**, 989 (1970); [b]D. J. Pasto and C. C. Cumbo, *J. Am. Chem. Soc.* **86**, 4343 (1964).
[127]V. V. Kane, D. Doyle and Y. Williams, unpublished work.
[128]A. E. Greene, *Tetrahedron Lett.* 63 (1979).
[129]In recent years considerable time has been devoted to devising efficient methods for the regiospecific formation of olefins. See Ref. 124 and 125, and [a]R. E. Ireland, D. C. Muchmore and U. Hengartner, *J. Am. Chem. Soc.* **94**, 5098 (1972). For the certainty concerning the ultimate position of the double bond, with borane derived reagents see [b]G. W. Kabalka, D. T. C. Yang and J. D. Baker, Jr., *J. Org. Chem.* **41**, 574 (1976); [c]G. W. Kalbalka, J. D. Baker, Jr. and G. W. Neal, *Ibid.* **42**, 512 (1977); [d]L. Cagliotti, G. Cainelli, G. Maina and A. Selva, *Gazz. Chim. Ital.* **92**, 309 (1962); [e]R. O. Hutchins, M. Kacher and L. Rua, *J. Org. Chem.* **40**, 923 (1975); [f]E. J. Taylor and C. Djerassi, *J. Am. Chem. Soc.*, **98**, 2275 (1976); [g]R. O. Hutchins and N. R. Natale, *J. Org. Chem.* **43**, 2299 (1978); [h]A. E. Greene, *Tetrahedron Lett.* 851 (1978).
[130a]W. G. Dauben, M. Lorber and D. S. Fullerton, *J. Org. Chem.* **34**, 3587 (1969); [b]D. S. Fullerton and C. M. Chen, *Synth. Commun.* **6**, 217 (1976).
[131]For reviews of organosilicon chemistry, see [a]C. Eaborn and R. W. Bott, *Organometallic Compounds of the Group IV Elements*, (Edited by A. G. MacDiarmid), Vol. Part 1, Marcel Dekker, New York (1968); [b]A. E. Pierce, *Silylation of Organic Compounds.* Pierce Chemical Co., Rockford, Ill. (1968); [c]L. Birkofer and R. A. Ritter, In *New Methods in Preparative Organic Chemistry*, (Edited by W. Forest). Academic Press, New York (1968); [d]J. F. Klebe, *Acc. Chem. Res.* 299 (1970); [e]S. S. Washburne, *J. Organometal. Chem.* **83**, 155 (1977) and **123**, 1 (1976); [f]I. Fleming, *Chem. and Ind.* 449 (1975); [g]P. F. Hudrlik, In *Organomettalic Reagents in Organic Synthesis* (Edited by D. Seyferth), Elsevier, Amsterdam (1976); [h]T. H. Chan, *Acc. Chem. Res.* **10**, 442 (1977); [i]J. K. Rasmussen, *Synthesis* 91 (1977); [j]E. W. Colvin, *Chem. Soc. Rev.* **7**, 15 (1978); [k]I. Fleming, In *Comprehensive Organic Chemistry*, (Edited by D. H. R. Barton and W. D. Ollis), Vol. 3. Pergamon Press, Oxford (1979); [l]K. Utimoto, T. Mukaiyama and K. Saigo, *Kagaku No Ryoiki, Zokan* **117**, 114 (1979); [m]D. Habich and F. Effenberger, *Synthesis* 841 (1979); [n]T. H. Chan and I. Fleming, *Ibid.* 784 (1979); [o]P. Magnus, *Aldrichimica Acta* **13**, 43 (1980); [p]A. H. Schmidt, *Ibid.* **14**, 31 (1981); [q]I. Fleming, *Chem. Soc. Rev.* **10**, 83 (1981).
[132a]E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.* **94**, 2549 (1972); [b]E. J. Corey and A. Venkateswarlu, *Ibid.* **94**, 6190 (1972).
[133]T. H. Chan, A. Baldassarre and D. Massuda, *Synthesis* 801 (1976).
[134a]R. T. Taylor, C. R. Degenhardt, W. P. Melega and L. A. Paquette, *Tetrahedron Lett.* 159 (1977); [b]L. A. Paquette, W. E. Fristad, D. S. Dime and T. R. Bailey, *J. Org. Chem.* **45**, 3017 (1980).
[135]E. W. Fristad, T. R. Bailey and L. A. Paquette, *Ibid.* **43**, 1620 (1978) and **45**, 3028 (1980).
[136a]J. J. Eisch and J. T. Trainor, *Ibid.* **28**, 2870 (1963); [b]J. J. Eisch and J. E. Galle, *Ibid.* **31**, 2615 (1976).

[137a]C. M. Robbins and G. H. Whitham, *J. Chem. Soc., Chem. Commun.* 697 (1976); [b]A. P. Davis, G. J. Hughes, P. R. Lowndes, C. M. Robbins, E. J. Thomas and G. H. Whitham, *J. Chem. Soc., Perkin I* 1934 (1981).
[138]H. C. Brown, C. P. Garg and K. T. Liu *J. Org. Chem.* **36**, 387 (1971).
[139]E. Kandeel, V. V. Kane and A. R. Martin, unpublished results.
[140]W. E. Fristad, T. R. Bailey, L. A. Paquette, R. Gleiter and M. C. Bohm, *J. Am. Chem. Soc.* **101**, 4420 (1979).
[141]For reviews see [a]K. Gollinck, *Adv. Photochem.* **6**, 1 (1968); [b]C. S. Foote, *Acc. Chem. Res.* **1**, 104 (1968); [c]D. R. Kearns, *Chem. Rev.* **71**, 395 (1971); [d]R. W. Denney and A. Nickon, *Org. React.* **20**, 133 (1973); [e]A. A. Frimer, *Chem. Rev.* **79**, 359 (1979); [f]A. A. Gorman and M. A. J. Rodgers, *Chem. Soc. Rev.* **10**, 205 (1981).
[142]T. H. Chan and W. Mychajlowskij, *Tetrahedron Lett.* 3479 (1974).
[143]G. Stork, A. Meisels and J. E. Davies, *J. Am. Chem. Soc.* **85**, 3419 (1963).
[144]K. Grychtol, H. Musso and J. F. M. Oth, *Chem. Ber.* **105**, 1798 (1972).
[145]E. J. Corey and J. E. Richman, *J. Am. Chem. Soc.* **92**, 5276 (1970).
[146]A. McKillop, B. P. Swann and E. C. Taylor, *Ibid.* **93**, 4919 (1971).
[147]V. Singh, V. V. Kane and A. R. Martin, *Synth. Commun.* **11**, 429 (1981).
[148a]M. Carmack and M. A. Spielman, *Org. React.* **3**, 83 (1947); [b]F. Asinger, W. Schafer and K. Halcour, *Angew. Chem. Int. Ed. Engl.* **3**, 19 (1964); [c]R. Wegler, E. Kuhle and W. Schafer, *Newer Meth. Prep. Organ. Chem.* **3**, 1 (1964).
[149a]T. Shono, Y. Matsumura and Y. Nakagawa, *J. Am. Chem. Soc.* **96**, 3532 (1974); [b]T. Shono, M. Okawa and I. Nishiguchi, *Ibid.* **97**, 6144 (1975).
[150]T. Shono, I. Nishiguchi and M. Nitta, *Chem. Lett.* 1319 (1976).
[151a]F. M. Hauser and S. Prasanna, *Synthesis* 621 (1980); [b]F. M. Hauser and S. Prasanna, *J. Am. Chem. Soc.* **103**, 6378 (1981).
[152]J. Borovsky, D. F. Gurka, J. Hoffman, E. Kandeel and A. R. Martin, unpublished results.
[153]W. Oppolzer, T. Sarker and K. K. Mahalanabis, *Helv. Chim. Acta.* **59**, 2012 (1976).
[154]G. Lange, D. J. Wallace and S. So, *J. Org. Chem.* **44**, 3066 (1979).
[155]E. Wenkert, N. F. Golob, S. S. Sathe and R. A. J. Smith, *Synth. Commun.* **3**, 205 (1973).
[156a]G. L. Lange, W. J. Orrom and D. J. Wallace, *Tetrahedron Lett.* 4479; [b]G. L. Lange, E. E. Neidert, W. J. Orrom and D. J. Wallace, *Can. J. Chem.* **56**, 1628 (1978).
[157]G. A. Kraus and K. Frazier, *J. Org. Chem.* **45**, 4820 (1980).
[158]G. A. Kraus and B. Roth, *Ibid.* **45**, 4825 (1980).
[159]J. D. White, T. Matsui and J. A. Thomas, *Ibid.* **46**, 3376 (1981).
[160]Ch. Tamm, *Fortschr. Chem. Org. Naturst.* **31**, 63 (1974).
[161]G. A. Kraus, K. A. Frazier, B. D. Roth, M. J. Taschner and K. Neuenschwander, *J. Org. Chem.* **46**, 2417 (1981).
[162]E. Winterfeldt, *Synthesis*, 617 (1975).
[163a]C. T. West, S. J. Donnelly, D. A. Kooistra and M. P. Doyle, *J. Org. Chem.* **38**, 2675 (1973); [b]J. L. Fry, M. Orfanapoulos, M. G. Adlington, W. R. Dittman and S. B. Silverman, *Ibid.* **43**, 374 (1978); [c]F. A. Carey and H. S. Tremper, *Ibid.* **36**, 758 (1971); [d]J. W. Larsen and L. W. Chang, *Ibid.* **44**, 1168 (1979); [e]For an excellent review, see D. M. Kursanov, Z. N. Parnes and N. M. Loim, *Synthesis* 633 (1974).
[164]P. C. Bulman-Page, S. V. Ley, J. A. Morton and D. J. Williams, *J. Chem. Soc., Perkin I* 457 (1981).
[165a]A. C. Cope, M. M. Martin and M. A. McKervey, *Chem. Soc. Rev.* **20**, 119 (1966); [b]J. K. Crandall, *J. Org. Chem.* **29**, 2830 (1964); [c]J. K. Crandall and L. Chang, *Ibid.* **32**, 435, 533 (1967); [d]J. K. Crandall and L. C. Lin, *J. Amer. Chem. Soc.* **89**, 4526, 4527 (1967); [e]B. Rickborn and R. P. Thummel, *J. Org. Chem.* **34**, 3583 (1969).
[166]E. H. Eschinasi, *Israel J. Chem.* **6**, 713 (1968).
[167]W. Kirchhof, *Ber.* **93**, 2712 (1960).
[168]R. Noyori, S. Murata and M. Suzuki, *Tetrahedron* **37**, 3899 (1981); and refs therein.