Carbonyl Group Transpositions

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1 Introduction

The term carbonyl transposition has been in use for some time and transposition has recently been taken to mean 'the effective movement of functionality within the carbon framework'.[1,2] In most of the work cited in this review carbonyl transposition is the only net chemical change, that is the product and the starting material are isomeric *e.g.* (1)→(2) and (162)→(163). However, two additional cases are considered; first, those in which introduction of an alkyl group accompanies the carbonyl transposition (the so-called alkylative carbonyl transpositions), and secondly, those in which migration of a double bond takes place together with the carbonyl transposition.

In the final section examples of isomerization of ketones are discussed. Although these are not transpositions in a formal sense, they are sufficiently close as to merit inclusion in this review.

The most intensively investigated have been the 1,2 carbonyl transpositions and in this review these have been sub-divided on the basis of the initial functionality introduced (and cross-referenced in those cases in which the same substrate is employed in different reaction pathways). Such sub-division has not proved necessary in the other sections.

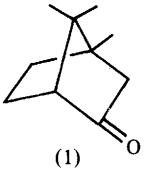
Despite the prevalence of the carbonyl group in organic chemistry, carbonyl transpositions have not been greatly exploited in synthesis. Many of the methods developed have been of the general methods character, or have been specifically designed for the preparation of *say* a steroid with a carbonyl group in a novel position with the objective of examining certain spectral properties.

2 1,2 Carbonyl Transpositions

Much early work on 1,2 carbonyl transposition centred around the synthesis of epicamphor (bornan-3-one) (1) from camphor (bornan-2-one) (2). The first successful synthesis of epicamphor appears to have been that of Lankshear and Perkin[3] in which carboxylic acid group functionality was first introduced in an α-position to the carbonyl group of (2) to give (3). The penultimate intermediate of this multi-stage synthesis was (4), from which epicamphor was obtained by oxidation with potassium permanganate.

[1] P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin Trans 1*, 1977, 1131.
[2] W. Tochtermann and P. Rösner, *Chem. Ber.*, 1980, **113**, 1584.
[3] F. R. Lankshear and W. H. Perkin, *Proc. Chem. Soc.*, 1911, **27**, 167.

Shortly afterwards a joint paper by Bredt and Perkin[4] described a number of vain attempts to synthesize epicamphor and proceeded to describe two further successful syntheses. In the first of these, bornylene-3-carboxylic acid was converted into the azide (5) from which (1) was obtained by refluxing with hydrochloric acid. In order not to involve the potentially hazardous azide (5),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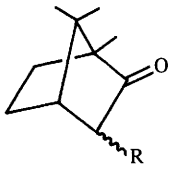
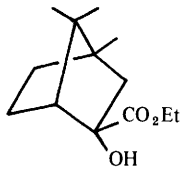

(2) R = H
(3) R = CO_2H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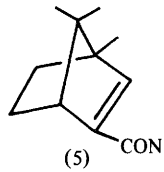
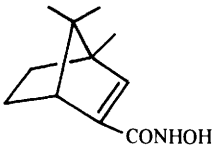

(5)

an alternative synthesis was devised, in which the carboxylic acid (3) gave bornylene-3-hydroxamic acid (6) after reaction with hydroxylamine and sodium ethoxide. Thermolysis of (6) yielded epicamphor directly, *via* successive formation of the isocyanate (and water) and the carbamic acid, from which ammonia and carbon dioxide were lost. More controlled thermolysis, to the same end, was achieved with acetyl and benzoyl hydroxamic acids. By means of a similar series of transformations camphor was regenerated from epicamphor.

Rather later, pinocamphanone (8) was obtained from verbanone (7) in good yield by way of the corresponding azide (9).[5]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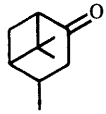
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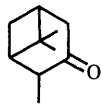
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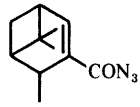
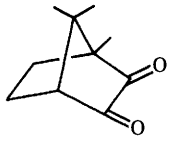

(9)

A further method[6] of effecting the transformation of camphor to epicamphor involved synthesizing camphorquinone (bornan-2,3-dione) (10) and then making use of the differential reactivity of the two carbonyl groups in (10) brought about by the bridgehead methyl group. Thus, from (10) and aluminium amalgam, 2-hydroxyepicamphor (11) was obtained; sodium amalgam then reduced (11) to epicamphor (1), (see also Scheme 9).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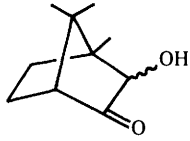
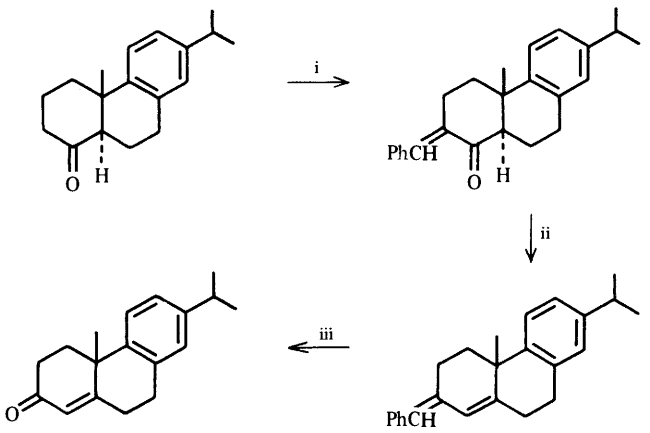

(11)

[4] J. Bredt and W. H. Perkin, *J. Chem. Soc.*, 1913, **103**, 2182.
[5] G. Komppa, A. Klami, and A. M. Kuvaja, *Liebig's Annalen der Chemie* 1941, **547**, 185.
[6] J. Bredt and M. Bredt-Savelsberg, *Chem. Ber.*, 1929, **62**, 2214.

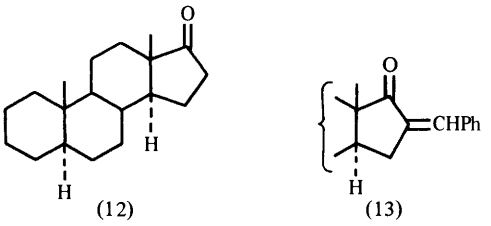
Arylidene Derivatives.—The ready reactivitv. in basic solution, of benzaldehyde with ketones bearing an α-methylene group allowed the development of the 1,2 carbonyl transposition sequence indicated in Scheme 1.[7] This procedure was employed for transposition of the carbonyl group in 5α-androstan-17-one (12).[8]



Reagents: i, PhCHO in aqueous alcoholic NaOH; ii, aluminium isopropoxide, xylene; iii, O_3

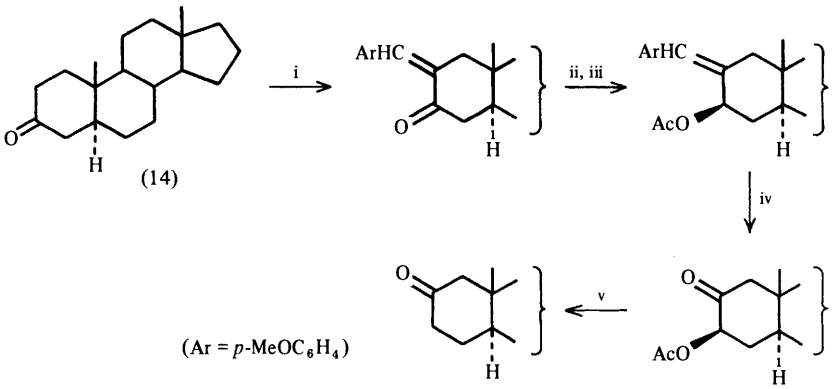
Scheme 1

However, a better method was developed for removal of the 17-oxo group from the 16-benzylidene derivative (13) using a mixture of $LiAlH_4$ and $AlCl_3$ that contained the hydride in appreciable excess over the ratio (1:3) required for formation of the postulated reagent $AlCl_2H$. For the transposition of carbonyl



from C-3 to C-2 in ring A of 5α-androstan-3-one (14),[8] using now the anisylidene derivative (*cf.* ref. 9), a modified route as outlined in Scheme 2 proved necessary. In this way 5α-androstan-3,17-dione was also converted into the 2,16-dione in good yield.

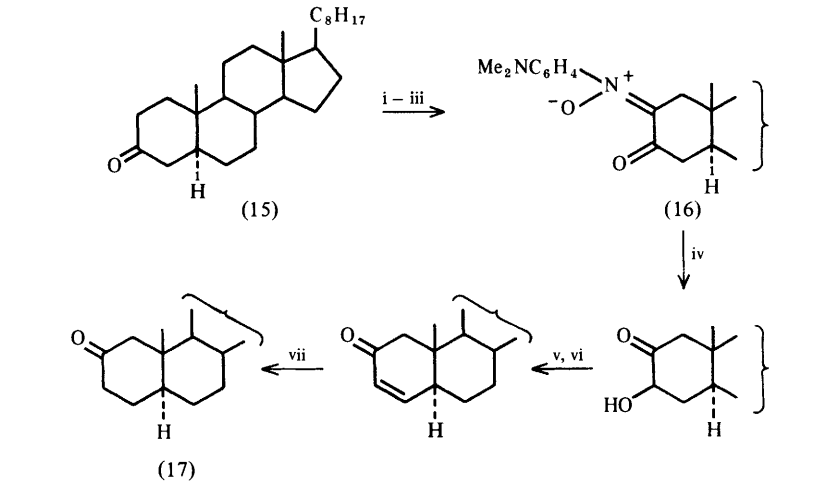
[7] H. H. Zeiss and W. B. Martin, *J. Am. Chem. Soc.*, 1953, **75**, 5935.
[8] J. E. Bridgeman, C. E. Butchers, E. R. H. Jones, A. Kasal, G. D. Meakins, and P. D. Woodgate, *J. Chem. Soc.*, (*C*) 1970, 244; J. E. Bridgeman, E. R. H. Jones, G. D. Meakins, and J. Wicha, *Chem. Commun.*, 1967, 898.
[9] M. Fetizon, J.-C. Gramain, and I. Hanna, *Compt. Rendu.*, 1967, **265C**, 929.



Reagents: i, *p*-$MeOC_6H_4CHO$; ii, $NaBH_4$; iii, Ac_2O–C_5H_5N; iv, O_3; v, Zn–HOAc

Scheme 2

Bromo Derivatives.—A well documented reaction pathway for carbonyl transposition involves initial formation of an α-bromoketone. This pathway is illustrated by the transformation of cholestan-3-one (15) into the corresponding 2-one (17), mediated by the nitrone (16), as shown in Scheme 3[10] (see also Scheme 17). In an analogous manner, 2-bromoandrostan-3,17-dione gives androstan-2,17-dione.[11]

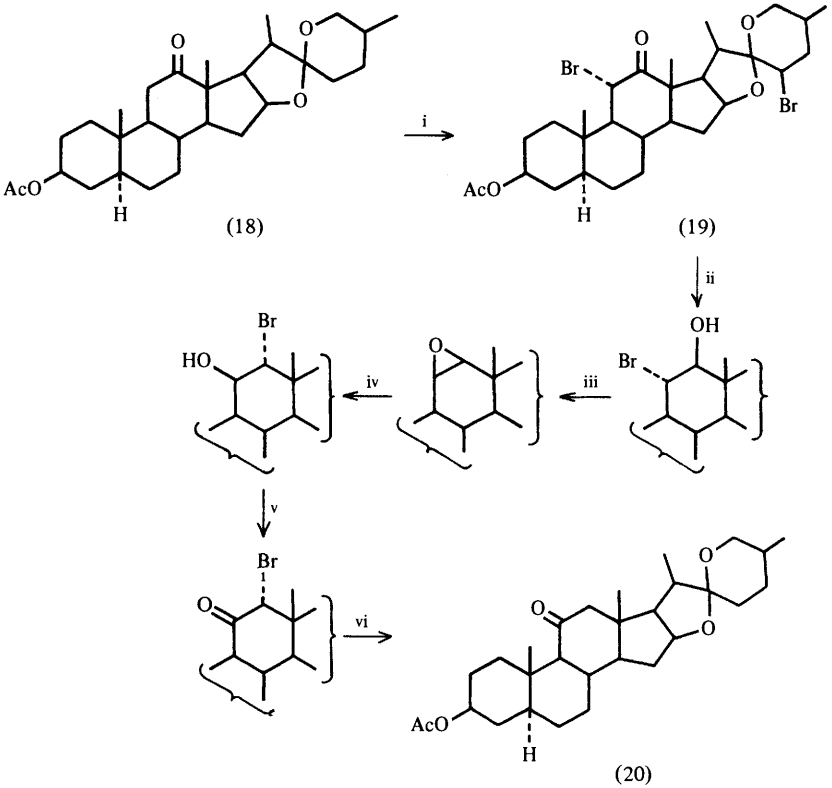


Reagents: i, Br_2; ii, C_5H_5N, Δ; iii, *p*-$Me_2NC_6H_4NO$; iv, HCl; v, TsCl; vi, NaI, Me_2CO, 160 °C, 17 h; vii, H_2, Pt

Scheme 3

[10] L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, 1944, **27**, 524.
[11] C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Am. Chem. Soc.*, 1950, **72**, 5750.

The first step in the transformation of hecogenin acetate (18) into 11-oxotigogenin acetate (20) by Cornforth's group,[12] was reaction with bromine which brought about dibromination, the sites being at C-11 in an α-position to the carbonyl group, and on the pyran ring[13] (Scheme 4). This second bromine was



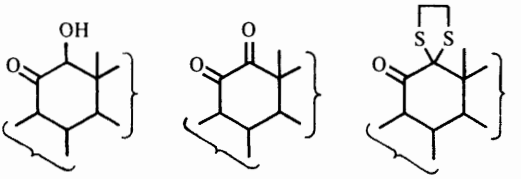
Reagents: i, Br_2; ii, $NaBH_4$; iii, KOH; iv, HBr; v, CrO_3; vi, Zn–HOAc–NaOAc

Scheme 4

carried through until debromination was effected with buffered zinc and acetic acid. A sequence very similar to that in Scheme 4 was employed by Schmidlin and Wettstein.[13] The same initial dibromination of hecogenin acetate to give (19) was used in another synthesis of (20).[14] However (19) was then transformed into (21) by means of a two-phase system consisting of aqueous sodium hydroxide and dioxan; acetylation of (21), debromination (Zn–HOAc) and bis-deacetylation (Ca–NH_3) then yielded 11-oxotigogenin.

[12] J. W. Cornforth, J. M. Osbond, and G. H. Phillipps, *J. Chem. Soc.*, 1954, 907.
[13] J. Schmidlin and H. Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241.
[14] J. Elks, G. H. Phillipps, T. Walker, and L. J. Wyman, *J. Chem Soc.*, 1956, 4330; J. H. Chapman, J. Elks, G. H. Phillipps, and L. J. Wyman, *J. Chem. Soc.*, 1956, 4344.

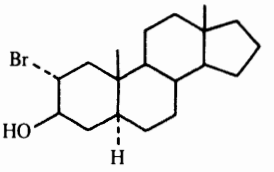
In further investigations on this system[15] the ketol (21) was oxidized to the α-diketone (22). From this, reaction with $HS(CH_2)_2SH$ gave (23) in a reaction at a specific carbonyl of an α-diketone made possible by the disparity of the surrounding molecular structure. Reaction of (23) with Raney nickel yielded 11-oxotigogenin.



(21) (22) (23)

At the same time, Corey converted 2-bromocholestan-3-one into the bromohydrin with $NaBH_4$.[16] Isopropanolic potassium hydroxide then gave 2β,3β-oxidocholestane from the bromohydrin; the epoxide reacted with $LiAlH_4$ to give cholestan-2β-ol, although oxidation to cholestan-2-one, the formal product of transposition, was not attempted.

In a related methodology, 2-bromo-5α-androstan-3-one yielded both the *anti*-bromohydrin (24), and its C-3 epimer (from which it was separated by t.l.c.) from reduction with $LiAl(OBu^t)_3H$.[17] 5α-Androstan-2-one (25) was then obtained by steps very similar to those outlined above.[16]

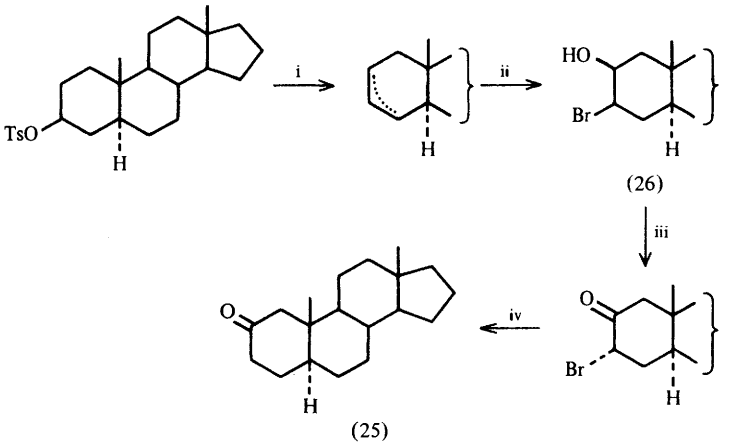


(24)

The same workers[17] prepared a bromohydrin (26), isomeric with (24), by a different route (Scheme 5) and completed the transposition by means of oxidation and debromination.

A fortuitous observation by Clarke led to the formation of a steroidal 2-one. In an attempt to carry out a nucleophilic displacement of bromine from 17β-acetoxy-2α-bromo-5α-androstan-3-one (27) by propanethiol, a solution of the ketone was refluxed with excess propanethiol in chloroform to give a 23% yield of the transposed ketone (28).[18,19] For this transformation the

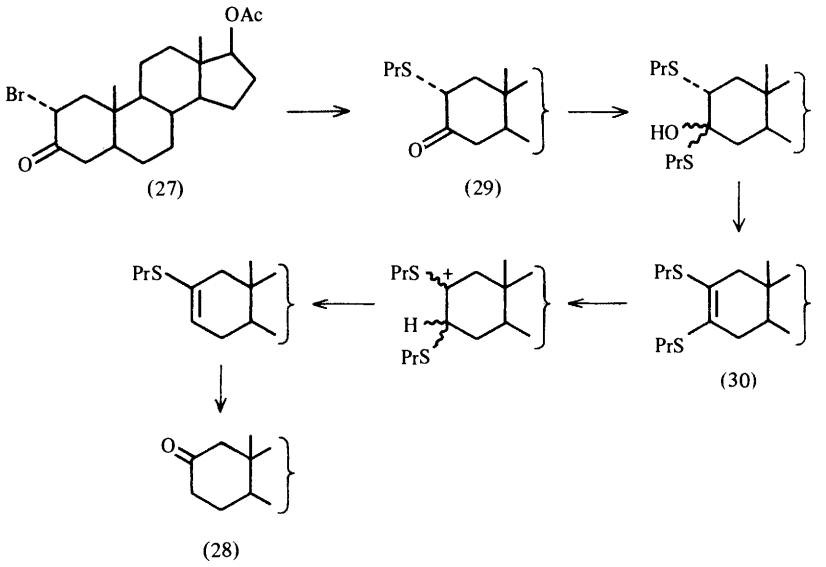
[15] C. Djerassi, H. J. Ringold, and G. Rosenkranz, *J. Am. Chem. Soc.*, 1954, **76**, 5533.
[16] E. J. Corey, *J. Am. Chem. Soc.*, 1953, **75**, 4832.
[17] J. E. Gurst and C. Djerassi, *J. Am. Chem. Soc.*, 1964, **86**, 5542.
[18] R. L. Clarke, *J. Org. Chem.*, 1963, **28**, 2626.
[19] R. L. Clarke and S. J. Daum, *J. Org. Chem.*, 1965, **30**, 3786.



Reagents: i, Δ, collidine or Al_2O_3; ii, HOBr; iii, CrO_3–HOAc; iv, Zn–HOAc

Scheme 5

author proposed the mechanism shown in Scheme 6. In this, direct displacement was indeed the first step, although no configuration was ascribed to the PrS— group in compound (29), which was then converted into (30) by means of a catalysis induced by HBr liberated in the initial step. Both (29) and (30) when exposed to the reaction conditions experienced by (27) gave the

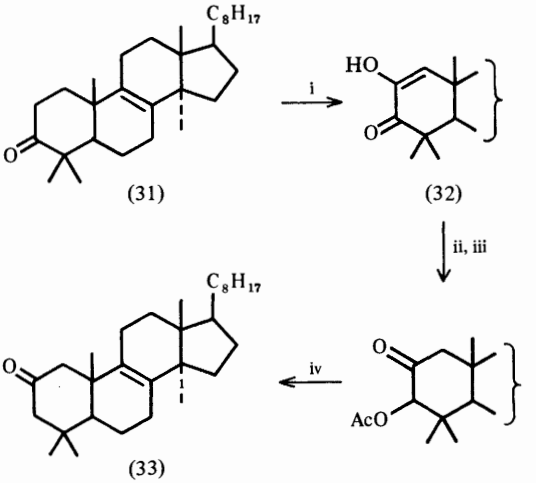


Scheme 6

transposed ketone (28). Under optimized conditions the yields of 2-one and 3-one were both 42%.

The latter ketone formed a bisulphite adduct in high yield, whereas the steric influence of the C-19 axial methyl group precluded formation of an adduct of the 2-one; this differential reactivity provided the basis of a separation.[18]

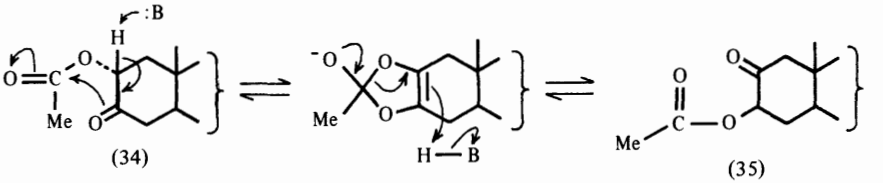
Oxygen Derivatives.—Only a small number of convenient methods are available for introduction of oxygen in a position alpha to a carbonyl carbon in a saturated system; nevertheless some examples which employ this as the initial reaction have been reported. Thus, in the key step lanost-8-en-3-one (31) gave the diosphenol (32) after reaction with t-butoxide ion in t-butanol under an atmosphere of oxygen (Scheme 7). Alternatively, reaction of (31) with



Reagents: i, Bu^tO^-, Bu^tOH, O_2; ii, H_2, Pt; iii, Ac_2O; iv, Ca–NH_3

Scheme 7

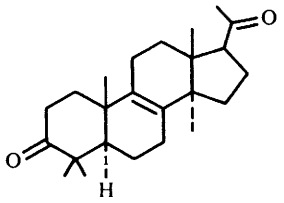
$Pb(OAc)_4$–BF_3 gave the vicinal acetoxyketone (34). Isomerization to (35) occurred in the presence of basic alumina (Scheme 8) with the last step to (33) executed as shown above.[20]



Scheme 8

[20] A. Lablache-Combier, B. Lacoume, and J. Levisalles, *Bull. Soc. Chim. Fr.*, 1966, 897.

The diosphenol, catalytic hydrogenation, acetylation route enabled 4,4,14α-trimethylpregn-8-en-3,20-dione (36), to be converted into a mixture of (37) and the 2-oxo-3-acetoxy isomer, the former of which was obtained pure by recrystallization.[21] Reduction of (37) with calcium in liquid ammonia and re-generation of the carbonyl group at C-20 yielded (38).



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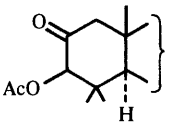

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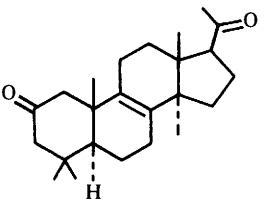
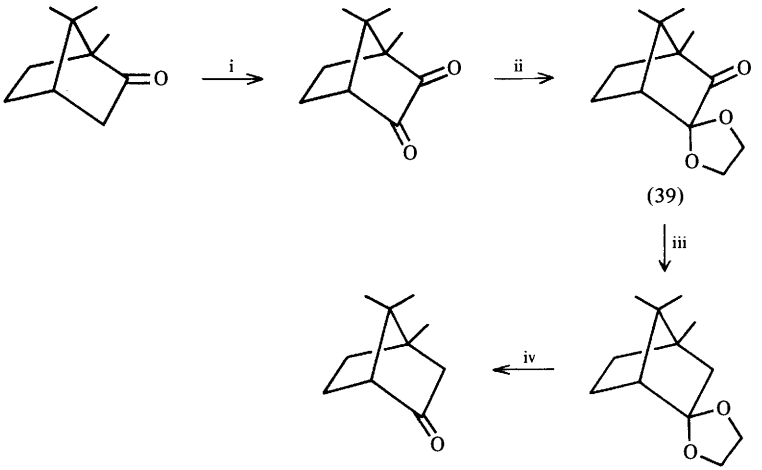


(38)

An improved synthesis of epicamphor (1) in good yield has been published[22] (Scheme 9). The key to this sequence is again the methyl group at C-1 in (10) which enables selective protection of C-3, (39), to be made, after which the carbonyl group at C-2 is removed (see also Introduction).



(39)

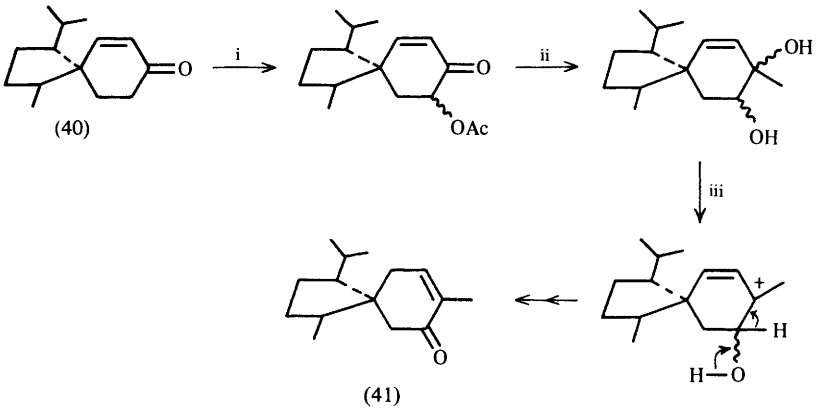
(1)

Reagents: i, SeO_2; ii, $HOCH_2CH_2OH$, TsOH, PhH, Δ; iii, $NH_2{\cdot}NH_2$; iv, 2M-HCl, aq·MeOH, Δ

Scheme 9

[21] D. H. R. Barton, D. Giacopello, P. Manitto, and D. L. Struble, *J. Chem. Soc.*, (*C*), 1969, 1047.
[22] S. Thoren, *Acta Chem. Scand.*, 1970, **24**, 93.

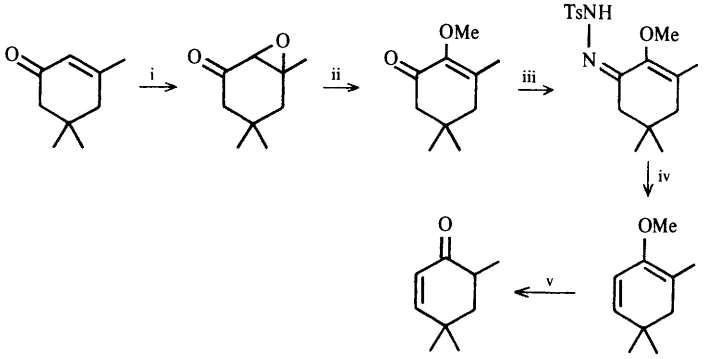
This section is concluded with two examples of enone migration. In the first of these, a synthesis of (±)-acorenone-B from (40) is outlined in Scheme 10;[23] the acetoxy-group is introduced with lead tetra-acetate as the first step of an alkylative transposition.



Reagents: i, $Pb(OAc)_4$; ii, excess MeLi; iii, TsOH, PhH, Δ, 1h

Scheme 10

In the second, a 1,2 carbonyl migration within a cyclohexenone, though with the double bond 'on the other side' of the carbonyl group in the product, has been reported by Reusch's group[24] (Scheme 11).



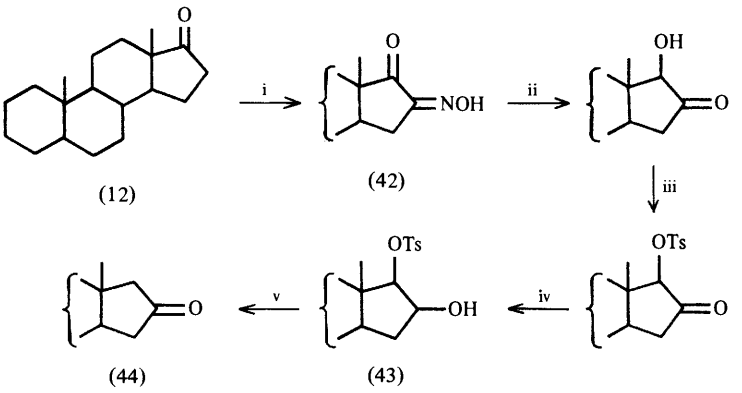
Reagents: i, alkaline methanolic H_2O_2; ii, methanolic KOH; iii, $TsNH{\cdot}NH_2$; iv, 2 mol MeLi; v, aq. HCl–THF

Scheme 11

[23] W. Oppolzer and K. K. Mahalanabis, *Tetrahedron Lett.*, 1975, 3411.
[24] K. M. Patel and W. Reusch, *Synth. Commun.*, 1975, 27.

Oximes, Nitro-compounds, and Hydrazones.—In the presence of base, α-methylene ketones react with alkyl nitrites to give α-oximino-ketones; alkyl nitrates give α-nitro-ketones under the same conditions. These derivatives can then be made the basis of successful 1,2 transpositions of the carbonyl group. Alternatively, the ketone can be converted into an arylsulphonylhydrazone which is subsequently functionalized in the α-position.

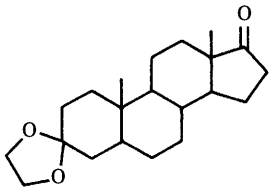
Thus 5α-androstan-17-one, (12), gave (42)[25] (Scheme 12), which was converted into the α-hydroxytosylate (43); this gave the transposed ketone (44)



Reagents: i, KOBu^t–isoamyl nitrite; ii, Zn–HOAc; iii, TsCl–C_5H_5N; iv, $NaBH_4$; v, NaOH–$MeOCH_2CH_2OH$

Scheme 12

by base-induced elimination. The authors remarked[25] that (42) was produced in good yield from (12) irrespective of whether one or two moles of KOBu^t were used, whereas when (45) was the substrate, two moles of this base were necessary to produce the ketoxime. When only one mole of KOBu^t was employed with (45) the reaction took a different course.



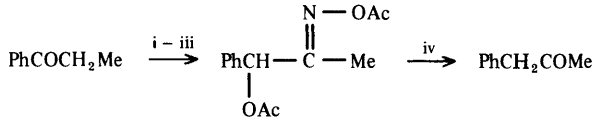
(45)

Alternatively, the α-ketoxime (42), when subjected to mild Huang-Minlon reduction, gave the oxime of (44) from which the ketone was liberated on sequential treatment with bisulphite and acid.[26] This latter method was

[25] D. Varech and J. Jacques, *Bull. Soc. Chim. Fr.*, 1965, 67.
[26] M. N. Huffman, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, 1955, **217**, 107.

employed[27] for the preparation of 3β-hydroxyandrost-5-en-16-one in good yield from the corresponding 17-one.

Corey's group has developed a procedure for 1,2 carbonyl transposition using propiophenone as a substrate, under the particular conditions outlined in Scheme 13.[28] The key to this sequence lies in construction of the penultimate intermediate (46) which undergoes both deoximation and bis-deacetoxylation in one pot.

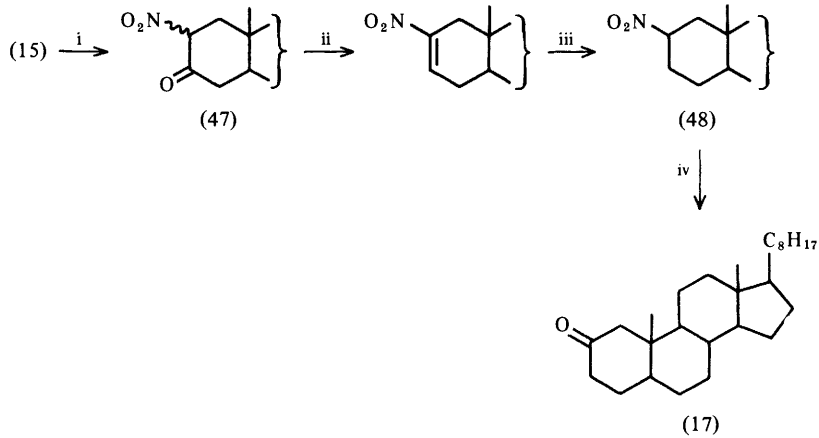


(46)

Reagents: i, RONO; ii, $NaBH_4$; iii, Ac_2O; iv, chromous acetate in THF–H_2O (10 : 1), 65 °C, 34h

Scheme 13

Reaction of cholestan-3-one (15) with n-butyl nitrate in the presence of both $^-OBu^t$ and Bu^tOH led to α-nitro-ketone (47);[29] the nitro-group at C-2 of (48) became the subject of a Nef reaction after removal of the 3-oxo-group (Scheme 14) in the formation of cholestan-2-one (17) in satisfactory overall yield. A similar manipulation was also carried out on a ring D carbonyl group,[29] 3β-hydroxyandrost-5-en-16-one being converted into the 17-oxo-isomer.

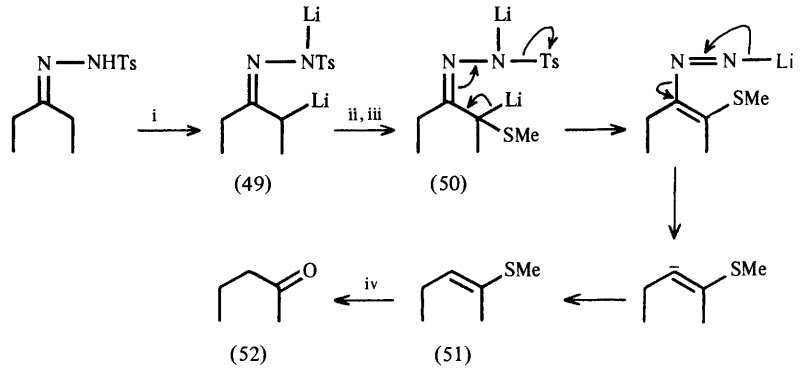


Reagents: i, Bu^tNO_3–Bu^tO^-–Bu^tOH; ii, $NaBH_4$, H^+, column chromatography; iii, $NaBH_4$, H^+; iv, ^-OH

Scheme 14

[27] G. Just and Y. C. Lin, *Chem. Commun.*, 1968, 1350.
[28] E. J. Corey and J. E. Richman, *J. Am. Chem. Soc.*, 1970, **92**, 5276.
[29] A. Hassner, J. M. Larkin, and J. E. Dowd, *J. Org. Chem.*, 1968, **33**, 1733.

In a general procedure developed explicitly for 1,2 carbonyl transposition,[30] a toluene-*p*-sulphonylhydrazone was dilithiated to give (49) and then converted into (50). This complex intermediate broke down to the vinyl thioether (51) which was hydrolysed in the conventional manner with $HgCl_2$ in aqueous acetonitrile to the transposed ketone (52) (Scheme 15). This was the method chosen by Sorensen[31] for the preparation of 5-methylcyclohexanone from the 6-methyl isomer.

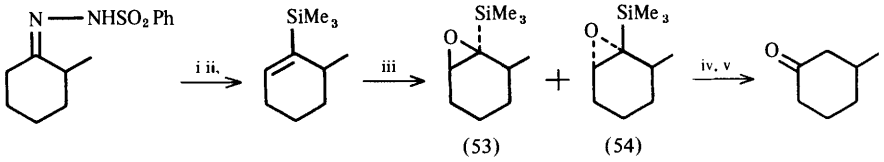


Reagents: i, BuLi (2 mol) in TMEDA–THF (1 : 2) at low temperature; ii, MeSSMe (1 mol); iii, BuLi (1 mol); iv, $HgCl_2$, aq. MeCN

Scheme 15

Although the toluene-*p*-sulphonylhydrazones of 3-methylcyclohexanone were formed in an *E*/*Z* ratio of *ca.* unity (from ^1H n.m.r. spectroscopy), the ratio of 4- and 2-methylcyclohexanones produced was 9:1.[30] The reasons for this pronounced preference in favour of the 4-methyl isomer are uncertain although the nature of the solvent may be relevant.

Benzene sulphonylhydrazones were used in another generally applicable method,[32] illustrated in Scheme 16. As a result of step (iii) two oxiranes (53)



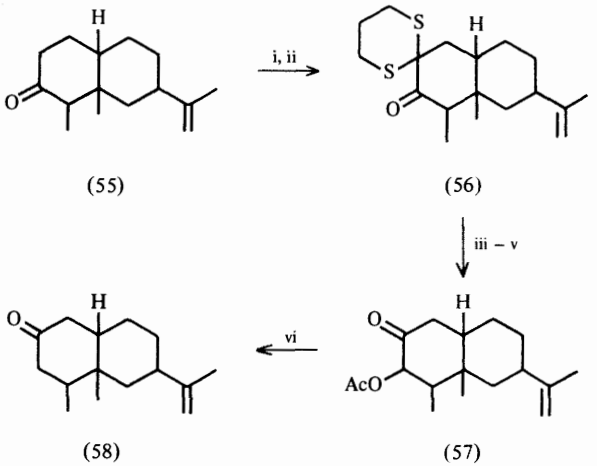
Reagents: i, RLi; ii, Me_3SiCl; iii, *m*-CPBA; iv, $LiAlH_4$; v, H_2CrO_4 in two-phase system (ether–water)

Scheme 16

[30] T. Nakai and T. Mimura, *Tetrahedron Lett.*, 1979, 531 (a review of carbonyl transpositions in Japanese is given by these authors in *J. Synth. Org. Chem. Jpn.*, 1977, **35**, 964).
[31] R. P. Kirchen, N. Okazawa, K. Ranganayakulu, A. Rank, and T. S. Sorensen, *J. Am. Chem. Soc.*, 1981,**103**, 597.
[32] W. E. Fristad, T. R. Bailey, and L. A. Paquette, J. *Org. Chem.*, 1978, **43**, 1620.

and (54) were formed in a ratio 38:62; these isomers were separable and both 'gave only β-trimethylsilylated alcohol'.

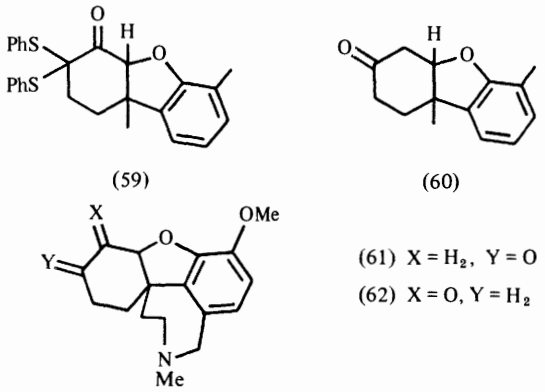
Sulphur Derivatives.—These were introduced by Marshall,[33] who made use of the thioacetal ketone (56), generated from the hydroxymethylene derivative of (55) and $TsS(CH_2)_3STs$ (Scheme 17). The carbonyl transposition to give (58) proceeded by way of the acetoxy-ketone (57).



Reagents: i, HCO_2Et, NaH; ii, $Ts(CH_2)_3Ts$, KOAc; iii, $LiAlH_4$; iv, Ac_2O; v, aq. $HgCl_2$; vi, Ca-NH_3

Scheme 17

In a similar synthesis, a related functionality was introduced in an α-position to the carbonyl group to give (59) with the transposition to (60) completed *via* a mesylate ester; demesylation was brought about in the last step with chromous



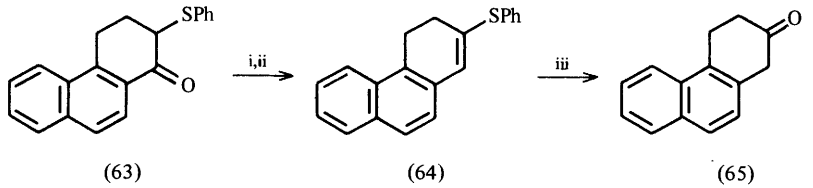
(61) X = H_2, Y = O

(62) X = O, Y = H_2

[33] J. A. Marshall and H. Roebke, *J. Org. Chem.*, 1969, **34**, 4188.

chloride in acetone.[34a] By means of this approach lycoraminone (61) was synthesized from (62).[34b]

Subsequently, a protocol was developed based on the initial introduction of a single sulphur functionality α to a carbonyl group.[35] This involved reaction of a suitable enolate with PhSSPh at low temperature (Scheme 18) to give the vinyl thioether (64) [*cf.* (51) and ref. 30]. Hydrolysis of (64) was brought about by the less common reagent, $TiCl_4$, in refluxing aqueous acetic acid.

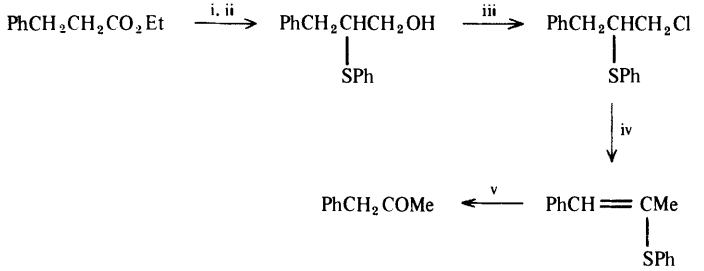


(63) (64) (65)

Reagents: i, $NaBH_4$; ii, TsOH, C_6H_6, Δ; iii, $TiCl_4$ in aq. HOAc, Δ

Scheme 18

The same authors[35] reported the first transposition of the carbonyl group of an ester, with simultaneous conversion into a ketone, by a slightly modified procedure (Scheme 19).



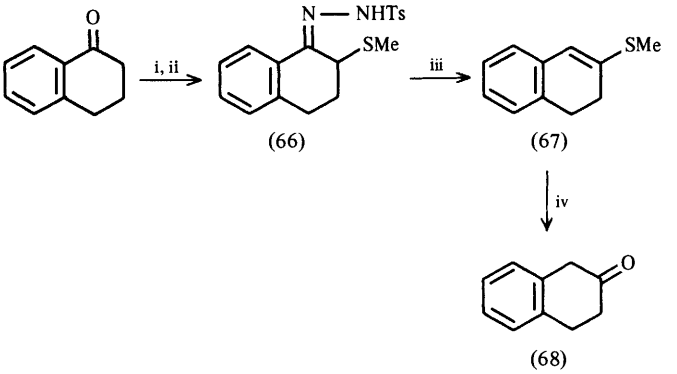
Reagents: i, $LiNR_2$, PhSSPh; ii, $LiAlH_4$, THF; iii, $SOCl_2$; iv, $^-OBu^t$; v, $HgCl_2$, MeCN-H_2O (3 : 1), Δ

Scheme 19

Vinyl thioethers, *e.g.* (67), have also served as the penultimate intermediates in a related procedure for α carbonyl transposition.[36] Thus, tetralone yielded the transposed ketone (68) *via* the initial derivative (66) (Scheme 20) in a pathway reminiscent of that shown in Scheme 15.

An extension to alkylative transposition has also been reported.[36] Thus, from cyclopentanone, the α-phenylthioether (69) gave the olefin (70) after Wittig

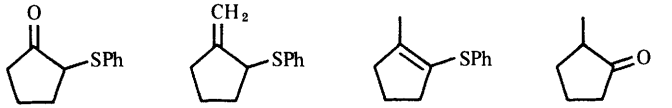
[34a] Y. K. Yee and A. K. Schultz, *J. Org. Chem.*, 1979, **44**, 719.
[34b] A. G. Schultz, Y. K. Yee, and M. H. Bergen, *J. Am. Chem. Soc.*, 1977, **99**, 8065.
[35] B. M. Trost, K. Hiroi, and S. Kurozumi, *J. Am. Chem. Soc.*, 1975, **97**, 438; see also S. R. Wilson, G. M. Georgiadis, H. N. Khatri, and J. E. Bartmess, *J. Am. Chem. Soc.*, 1980, **102**, 3577.
[36] S. Kano, T. Yokomatsu, T. Ono, S. Hibino, and S. Shibuya, *J. Chem. Soc., Chem. Commun.*, 1978, 414.



Reagents: i, MeSSMe; ii, $TsNH.NH_2$; iii, MeLi (excess); iv, aq. $HgCl_2$

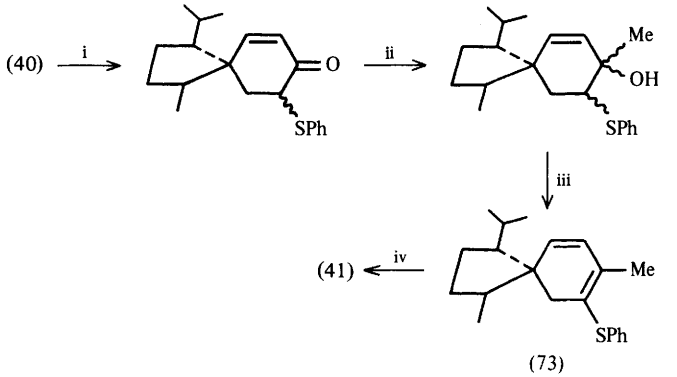
Scheme 20

reaction with $Ph_3P{=}CH_2$. Following isomerization of the double bond with BuLi, leading to (71), the final step to (72) was executed as in Scheme 20.



(69) (70) (71) (72)

α-Sulphenylation also featured as the initial step in a high-yield synthesis of (±) acorenone-B (41) which also involved alkylative transposition[37] (Scheme 21) (*cf.* ref. 23 and 42). The last step, a conventional method, proved



(73)

Reagents: i, $LiNPr^i$(cyclo C_6H_{11}) THF–HMPA, PhSSPh, 25 °C; ii, MeLi(Et_2O), −70 °C; iii, TsOH, C_6H_6, Δ; iv, aq. $HgCl_2$

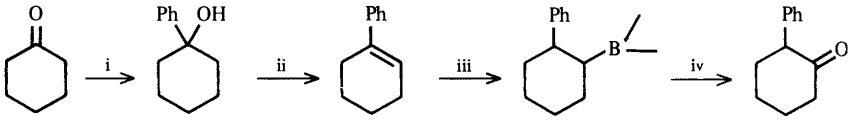
Scheme 21

[37] B. M. Trost, K. Hiroi, and N. Holy, *J. Am. Chem. Soc.*, 1975, **97**, 5873.

troublesome in this instance. After reflux for 48 h with $HgCl_2$ in aqueous dioxan, > 50% of (73) was recovered; the use of an alternative reagent, $TiCl_4$, resulted in extensive decomposition.

Grignard Reagents, Alkyl-lithiums, and Metal Hydrides.—These reagents serve to make alcohols; the next step is olefin-forming elimination with one of the olefinic carbons being the original carbonyl carbon. Re-introduction of oxygen, best performed by means of hydroboration, at a carbon in an α-position to the original carbonyl carbon, provides the means of effecting the transposition.

Thus alkylative transposition of cyclohexanone has been carried out successfully (Scheme 22); 2-methylcyclopentanone was also synthesized by the same method.[38]



Reagents: i, PhMgBr; ii, $-H_2O$; iii, B_2H_6; iv, H_2CrO_4

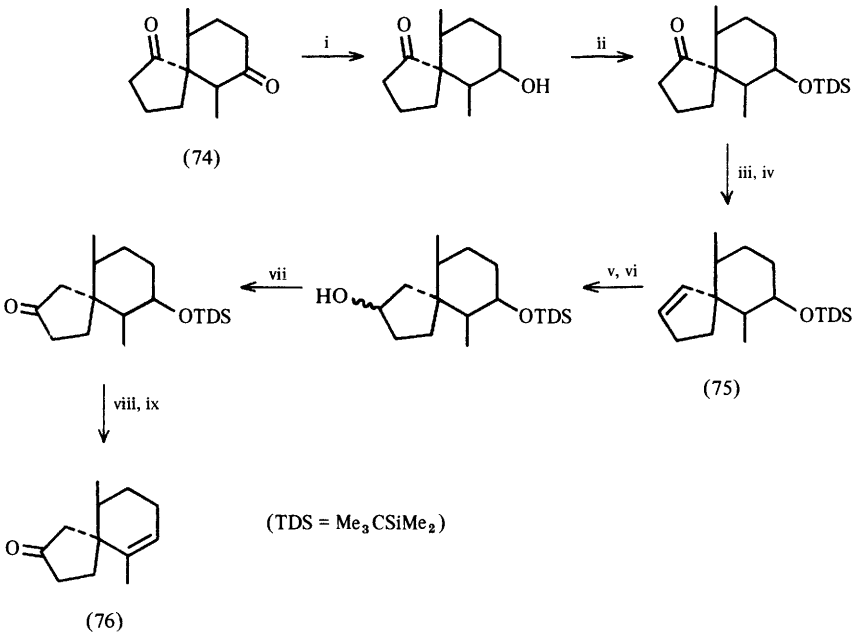
Scheme 22

A novel transposition route has been developed for the synthesis of the spirovetivane intermediate (76),[39] that devised by Trost[35] having proved inadequate. Thus, after selective reduction and protection of the carbonyl group in the six-membered ring of (74) had been achieved, the other carbonyl group became one site of an endocyclic olefin (75) (Scheme 23). Regiospecific re-introduction of oxygen was brought about with thexylborane (and subsequent oxidation), although the authors noted that this bulky reagent may not be necessary since regioselective addition of diborane has been observed in a related system.

In a transposition made possible by an acid-catalysed hydride shift, the diol (78), itself obtained from reaction of (77) with excess MeLi, gave (80), *via* the carbo-cation (79); the product (81) was obtained after movement of the double bond into conjugation with the carbonyl group.[40]

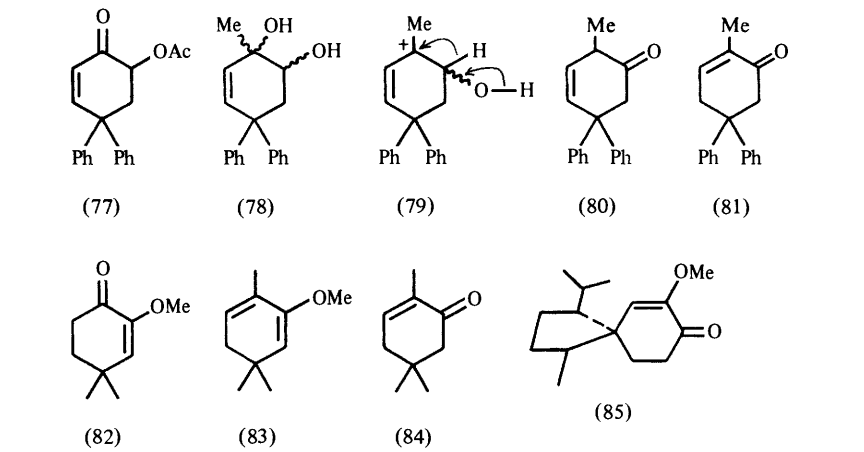
The tertiary alcohol from (82) and MeMgI likewise underwent dehydration to the rearranged desmethoxy-ketone (84) *via* (83) as a purported intermediate.[41] A similar procedure was employed[42] by this research group for the synthesis of (−)-acorenone-B (41) from (85) (see also ref. 23 and 37).

[38] H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, 1961, **83**, 2951.
[39] K. P. Subrahamanian and W. Reusch, *Tetrahedron Lett.*, 1978, 3789.
[40] W. Oppolzer, T. Sarkar, and K. K. Mahalanabis, *Helv. Chim. Acta*, 1976, **59**, 2012.
[41] G. L. Lange, D. J. Wallace, and S. So, *J. Org. Chem.*, 1979, **44**, 3066.
[42] G. L. Lange, E. E. Neidert, W. J. Orrom, and D. J. Wallace, *Can. J. Chem.*, 1978, **56**, 1628.

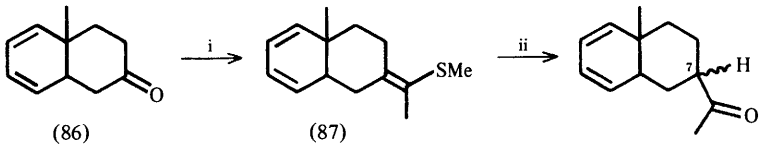


Reagents: i, $NaBH_4$; ii, Me_3CSiMe_2Cl, imidazole; iii, $LiAlH_4$; iv, $MeSO_2Cl$, C_5H_5N, Δ; v, thexylborane; vi, H_2O_2, NaOH; vii, CrO_3, C_5H_5N; viii, H_3O^+; ix, $C_7H_7SO_3H$, C_6H_6, Δ

Scheme 23



Organophosphorus Reagents.—1,2 Carbonyl migration along a side chain which is being simultaneously generated has been reported in a few instances. Such examples represent carbonyl migration associated with homologation and accordingly may be regarded as a special case of alkylative transposition. In particular (86) was converted[43] into (88), as a mixture of epimers, with a ratio 7α:7β acetyl of 2.9:1 (Scheme 24). The key intermediate (87) was produced by a Horner–Emmons reaction using the specifically designed phosphonate $MeSCH_2P(O)(OEt)_2$.

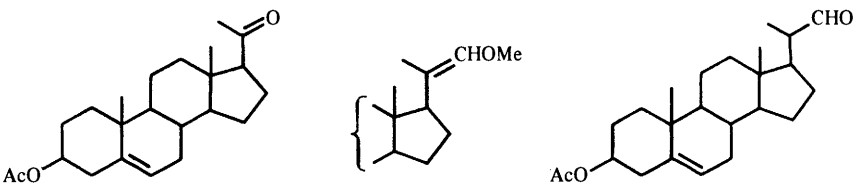


(86) (87) (88)

Reagents: i, $MeSCH_2P(O)(OEt)_2$ (3 mol) HMPA–DME (1 : 4), 62 °C, 12h; ii, $HgCl_2$ (2 mol), aq. MeCN, 25 °C, 3h

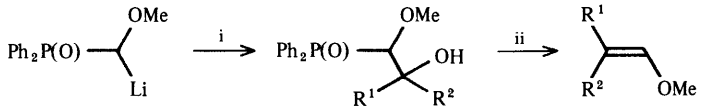
Scheme 24

In a similar vein, a 30% yield of (90) was obtained from reaction of (89) $Ph_3\overset{+}{P}-\overset{-}{C}HOMe$.[44] After conversion of the 3-acetoxy-group into a tetrahydropyranosyloxy derivative, the vinyl ether was readily hydrolysed to the aldehyde (91). However, the reagent $Ph_3\overset{+}{P}-\overset{-}{C}HOMe$ was of only limited utility



(89) (90) (91)

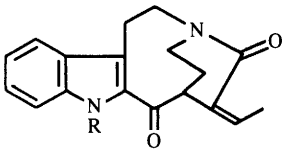
and the sequence in Scheme 25 was preferred [45] for the formation of (93) from the acyl indole (92). Further uses of organophosphorus reagents in alkylative carbonyl transposition are shown for (72).[36]



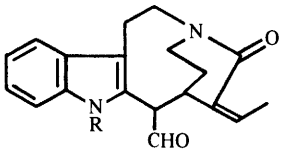
Reagents: i, R^1R^2CO; ii, NaH, THF

Scheme 25

[43] D. S. Watt and E. J. Corey, *Tetrahedron Lett.*, 1972, 4651.
[44] G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *J. Org. Chem.*, 1970, **35**, 1385.
[45] C. Earnshaw, D. J. Wallis, and S. Warren, *J. Chem. Soc., Perkin Trans 1*, 1979, 3099; S. Warren *Top. Curr. Chem.*, 1980, **91**, 1.



(92)

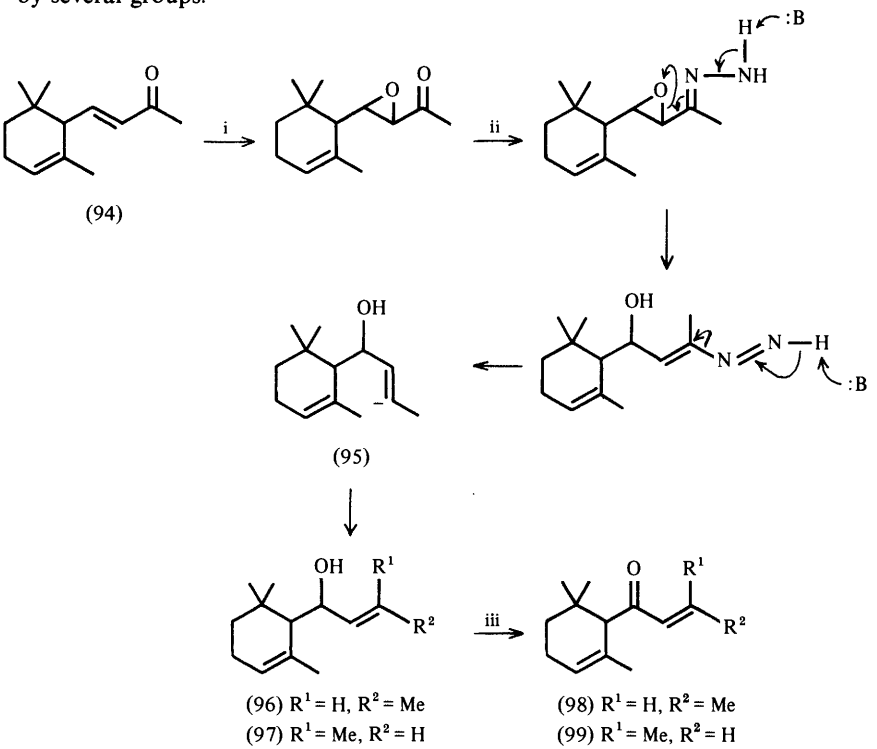


(93)

3 1,3 Carbonyl Transpositions

Study of these transpositions is a relatively recent development. The methods so far employed are based, in the main, on the Wharton reaction, a [2,3] sigmatropic rearrangement or some direct bridging between the initial and final carbonyl sites.

The Wharton reaction involves a rapid reaction at room temperature between hydrazine and an α,β-epoxy-ketone.[46] Although not explicitly used for carbonyl transposition by Wharton, this elegant reaction has been exploited by several groups.



(94)

(95)

(96) R^1 = H, R^2 = Me
(97) R^1 = Me, R^2 = H

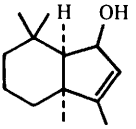
(98) R^1 = H, R^2 = Me
(99) R^1 = Me, R^2 = H

Reagents: i, H_2O_2, ^-OH; ii, $H_2N{\cdot}NH_2$; iii, H_2CrO_4 (or MnO_2)

Scheme 26

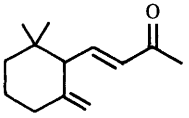
[46] P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615.

The mechanistic interpretation given to the Wharton reaction is indicated in Scheme 26, where (+)-α-ionone (94) was the substrate.[47] The geometric isomers (96) and (97), formed in a ratio *ca.* 1:1 and separated by g.l.c., were oxidized to give *E*-α-damascone (98) and its *Z* counterpart (99). Evidence in favour of the intermediacy of the vinyl anion (95) was provided by the formation of *both* geometric isomers (96) and (97), and also the cyclic allylic alcohol (100).

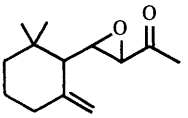


(100)

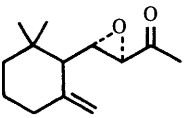
Ohloff's group also converted (±)-γ-ionone (101) into a separable mixture of the epoxy-derivatives (102) and (103). These then gave *inter alia*, the *Z*- and *E*-γ-damascones (104) and (105) respectively.[48]



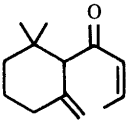
(101)



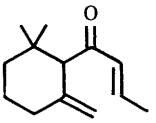
(102)



(103)

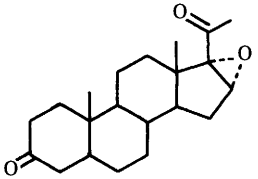


(104)

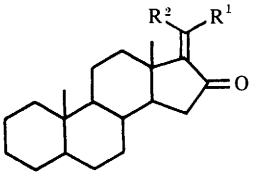


(105)

Similarly, the dione (106) gave two alcohols in combined yield of 30% after chromatographic separation following reaction under Huang-Minlon conditions; the carbonyl at C-3 was simultaneously reduced to a methylene group.[49] The ketones (107) and (108) that formed after oxidation of these alcohols could be equilibrated by either base- or light-catalysed reactions.



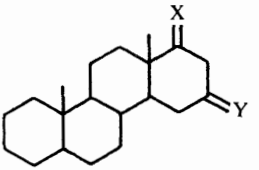
(106)



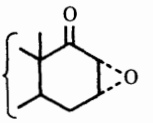
(107) R^1 = Me, R^2 = H
(108) R^1 = H, R^2 = Me

[47] G. Ohloff and G. Uhde, *Helv. Chim. Acta*, 1970, **53**, 531.
[48] K. H. Schulte-Elte, V. Rautenstrauch, and G. Ohloff, *Helv. Chim. Acta*, 1971, **54**, 1805.
[49] C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, 1964, **86**, 269.

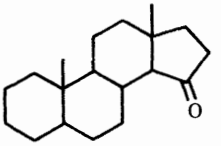
In further syntheses using the Wharton reaction a low yield of D-homo-5α-androstan-16-one (111) was prepared from the 17-one (109) *via* the epoxy-ketone (110);[50] Djerassi's group[51] converted 5α-androstan-17-one (12) into (112), which is capable of base-catalysed epimerization at C-14, and cholestan-1-one (113) was obtained from the 3-one.[52]



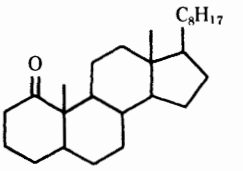
(109) X = O, Y = H_2
(111) X = H_2, Y = O



(110)

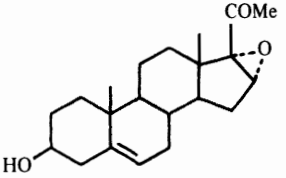


(112)

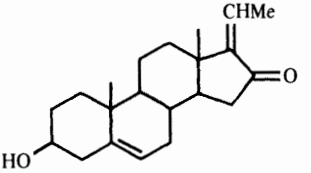


(113)

A similar concept enabled Huang-Minlon[53] to prepare the exocyclic olefin (115) (of unspecified configuration) from (114).



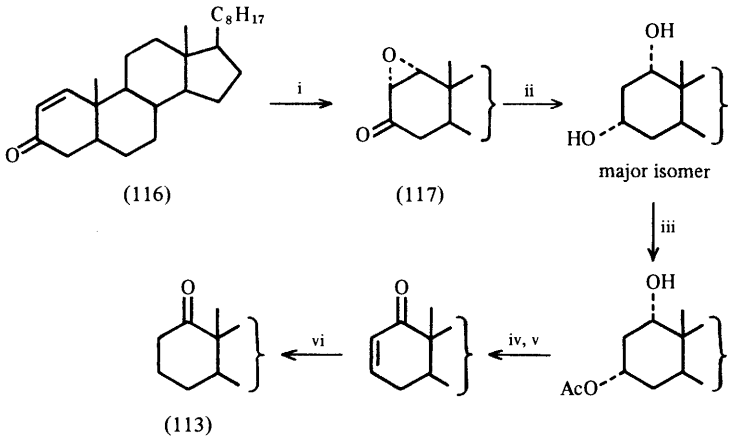
(114)



(115)

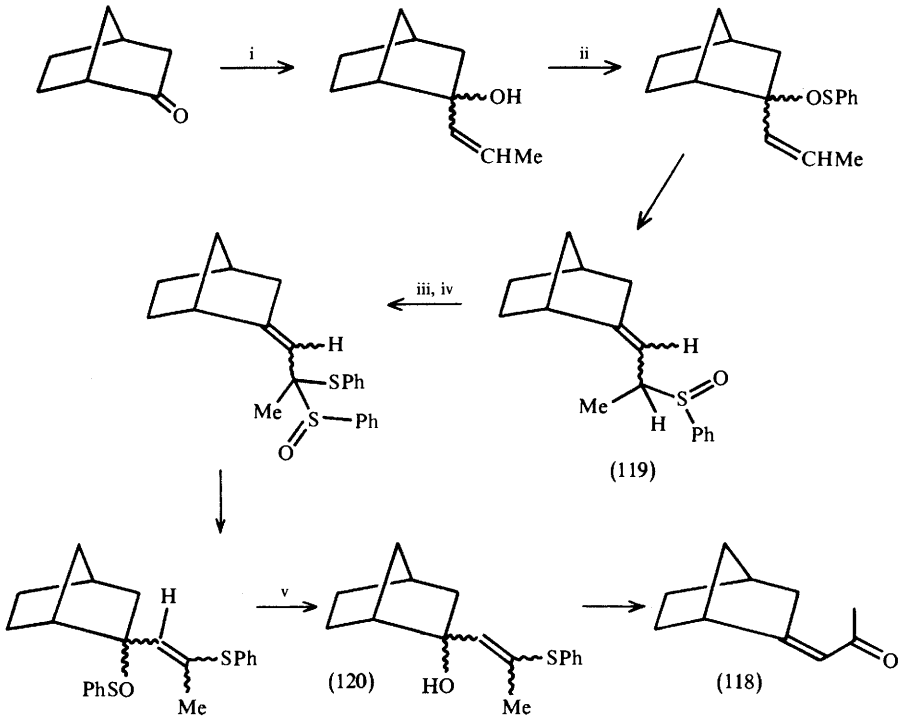
An epoxy-ketone (117), derived from cholest-1-en-3-one, (116) was involved in another route to cholestan-1-one (113).[54] This time, however, the epoxy-ketone was hydrogenated catalytically to a pair of diols that were epimeric at C-3; these diols were then selectively acetylated at C-3 prior to elimination of acetic acid (Scheme 27).

[50] D. N. Kirk, W. Klyne, C. M. Peach, and M. A. Wilson, *J. Chem. Soc.*, (*C*), 1970, 1454.
[51] C. Djerassi, G. von Mutzenbecher, J. Fajkos, D. H. Williams, and H. Budzikiewicz, *J. Am. Chem. Soc.*, 1965, **87**, 817.
[52] C. Djerassi, D. H. Williams, and B. Berkoz, *J. Org. Chem.*, 1962, **27**, 2205.
[53] Huang-Minlon and Chung-Tungshun, *Tetrahedron Lett.*, 1961, 666.
[54] P. Streibel and C. Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.



Reagents: i, H_2O_2, NaOH; ii, H_2, Pt; iii, Ac_2O; iv, CrO_3; v, Al_2O_3; vi, H_2, Pt

Scheme 27

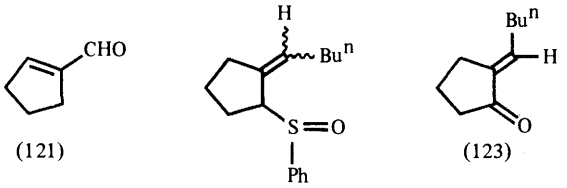


Reagents: i, MeCH=CHMgBr; ii, PhSCl; iii, $LiNEt_2$; iv, PhSSPh; v, $HgCl_2$

Scheme 28

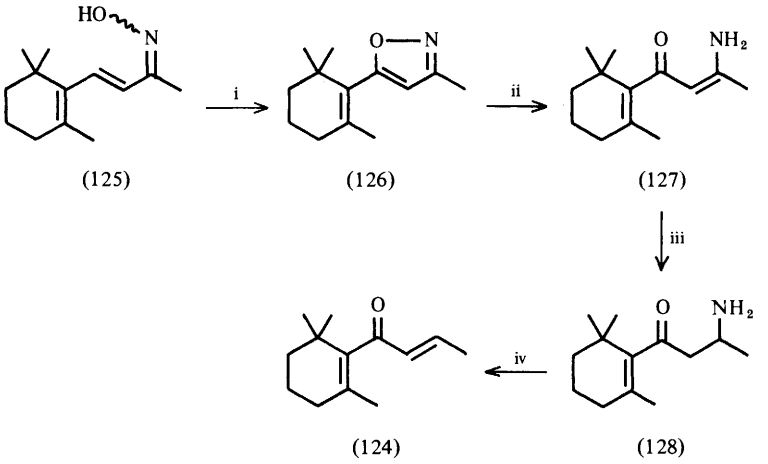
A useful method of 1,3 carbonyl transposition, which gives products in yields of 44—80%, depends on a [2,3] sigmatropic rearrangement as a means of introducing functionality into the position which is to become the carbonyl group.[55] The rather involved reaction sequence is given for the synthesis of the bicyclic ketone (118) in 70% yield (Scheme 28). A noteworthy point is the regeneration of diphenyl disulphide in the penultimate stage, leading to the thio-ether (120), from the addition of this reagent to the sulphoxide (119).

In the case of cyclopentenecarboxaldehyde (121), however, the allylic anion derived analogously from (122), using now BuLi, was sulphenylated both α and γ to the sulphoxide group.[55] The former product of sulphenylation underwent rearrangement and desulphenylation analogous to that shown in Scheme 28, whereas the product of γ-sulphenylation was isolated unchanged.



(121) (122) (123)

Since epoxydihydro-α-ionone and its γ-isomer underwent cyclization with hydrazine, an alternative method to the Wharton reaction was developed for the synthesis of β-damascone (124).[56] In this, the key feature was intramolecular migration of oxygen from the oxime of β-ionone (125) to the remote



(125) (126) (127) (128) (124)

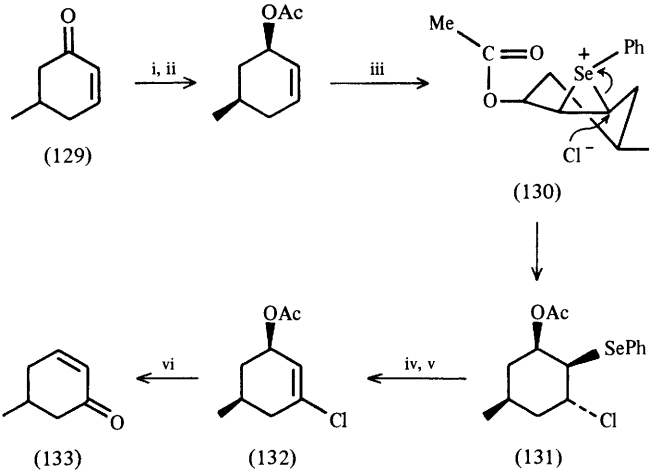
Reagents: i, I_2–KI, aq. THF, $NaHCO_3$; ii, Pt–H_2; iii, Na–NH_3–Bu^{t}OH

Scheme 29

[55] B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, 1975, **97**, 4018.
[56] G. Büchi and J. C. Vederas, *J. Am. Chem. Soc.*, 1972, **94**, 9128.

carbon of a conjugated double bond. This oxidation, which was carried out with I_2 and KI in aqueous THF buffered with $NaHCO_3$, gave rise to an isoxazole (126) in 90% yield; strong base produced complex mixtures (Scheme 29). The vinylogous amide (127) was reduced to the labile β-amino-ketone (128) which was then converted directly into β-damascone (124). The instability of isoxazoles derived from aldehydes limits the starting material to ketones.

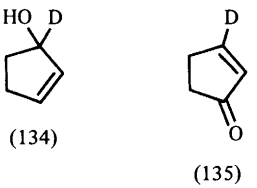
The regio- and stereo-selectivity of PhSeCl addition to allylic acetates has been made the basis of another 1,3 carbonyl transposition, and is exemplified (Scheme 30) by the conversion of (129) into its optical antipode (133).[57a]



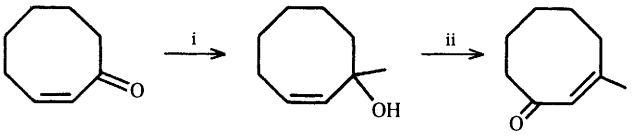
Reagents: i, $LiAlH_4$; ii, MeCOCl, C_5H_5N; iii, PhSeCl, CH_2Cl_2, −78 °C; iv, O_3, CH_2Cl_2; v, Et_2NH, CH_2Cl_2, Δ; vi, 90% HCOOH

Scheme 30

Accordingly, (130) was produced with the selenium moiety being delivered to the double bond after initial co-ordination between selenium and carbonyl oxygen. This selenonium ion then gave (131) as the only observable product; in accord with precedent, elimination from the selenoxide of (131) took place away from oxygen to give (132). The final step is based on work by Lansbury.[57b] The specifically deuterated cyclopentenone (135) was synthesized from cyclopentenone itself *via* (134).



[57a] D. Liotta, G. Zima, and M. Saindane, *J. Org. Chem.*, 1982, **47**, 1258.
[57b] P. T. Lansbury, *Acc. Chem. Res.*, 1972, **5**, 311.

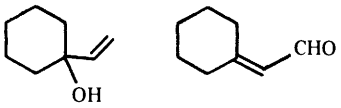


(136)

Reagents: i, MeMgBr; ii, pyridinium chlorochromate

Scheme 31

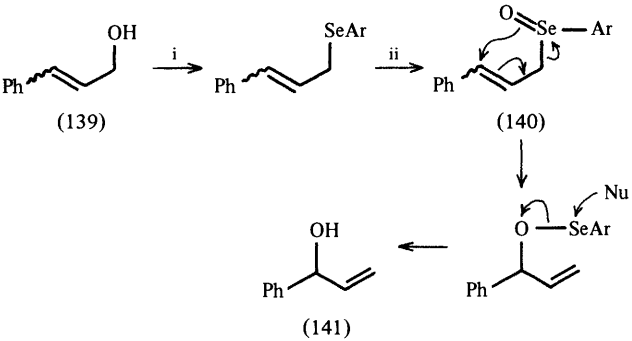
An independent procedure for 1,3 alkylative transposition of a carbonyl group has been devised by Dauben.[58] In this, cyclo-oct-1-en-3-one gave (136) (Scheme 31) and, in a reaction related to the 1,2 carbonyl shifts described in references 43—45, cyclohexanone was converted successively into (137) and (138). Acyclic ketones gave appreciably lower yields.



(137) (138)

A number of methods, collated here on account of their potential utility, are capable of effecting 1,3 transposition although the final step was not executed.

Scheme 32 shows how [2,3] sigmatropic rearrangement of the selenoxide (140) enabled the contrathermodynamic isomerization of (139) to (141) to take place; typically yields of *ca.* 80% were encountered.[59]

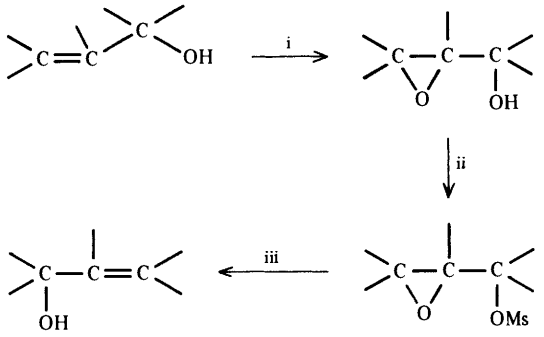


(139) (140) (141)

Reagents: i, *p*-$NO_2C_6H_4SeCN$ in C_5H_5N with Bu^n_3P; ii, 15% v/v H_2O_2 (20 equiv)

Scheme 32

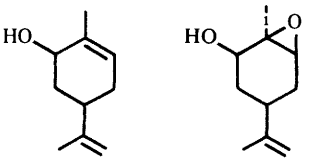
[58] W. G. Dauben and D. M. Michno, *J. Org. Chem.*, 1977, **42**, 652.
[59] D. L. J. Clive, G. Chittatu, N. J. Curtis, and S. M. Menchen, *J. Chem. Soc., Chem. Commun.*, 1978, 770.



Reagents: i, $VO(acac)_2$, Bu^tOOH; ii, Et_3N, $MeSO_2Cl$; iii, $Na-NH_3$

Scheme 33

Oxiranes mediate the transformation of allylic alcohols (Scheme 33) such that (−)-carveol (142) can be converted into the (+)-isomer *via* the *cis*-epoxy-alcohol (143).[60]



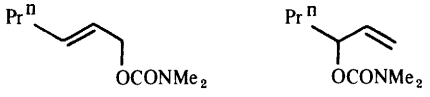
(142) (143)

The allylic acetates (144) and (145) are equilibrated in a ratio 1.9:1 by heating the former at 70 °C for 3h with 3 mol% Pd $(OAc)_2$ and 3 mol PPh_3 in the presence of KOAc and with t-butanol as solvent.[61]

$Me(CH_2)_4CH{=}CHCH_2OAc$ $Me(CH_2)_4CH(OAc)CH{=}CH_2$

(144) (145)

A catalytic quantity of mercuric acetate in THF at 25 °C enabled the allylic carbamates (146) and (147) to be equilibrated in a ratio $52 \pm 4\%$ and $41 \pm 3\%$,[62] together with a small amount of the *cis*-isomer of (146).



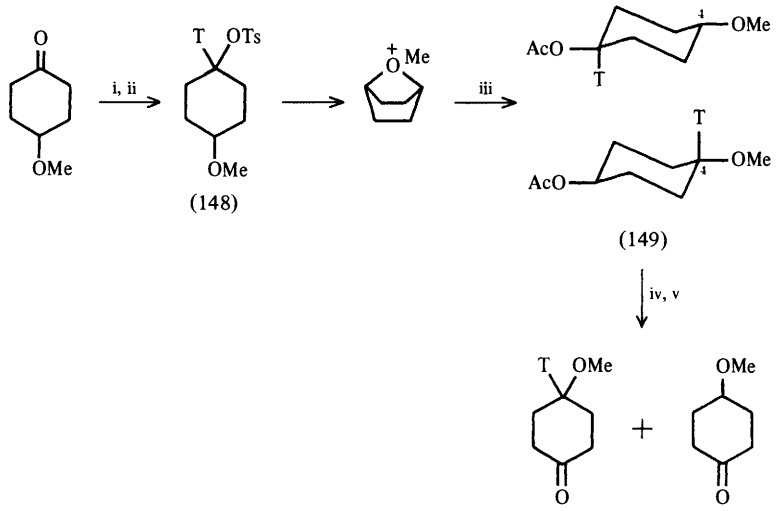
(146) (147)

[60] A. Yasuda, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, 1976, 2621.
[61] J. Tsuji, K. Tsuruoka, and K. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1701.
[62] L. E. Overman and C. B. Campbell, *J. Org. Chem.*, 1976, **41**, 3338.

4 1,4 Carbonyl Transpositions

Only a limited number of methods are known for bringing about 1,4-transfer of a carbonyl group, and two of these involve additional bridging.

After acetolysis of the ester (148), specifically tritiated at C-1, the product was shown to consist *inter alia* of *trans*-4-methoxycyclohexyl acetate (149) (Scheme 34) in which 43% of the label was located at C-4, the remainder[63] being at C-1. The assay for label involved successive saponification and oxidation of (149) to 4-methoxycyclohexanone. 1,4 Carbonyl transposition had occurred in that part of the ketone which contained tritium.



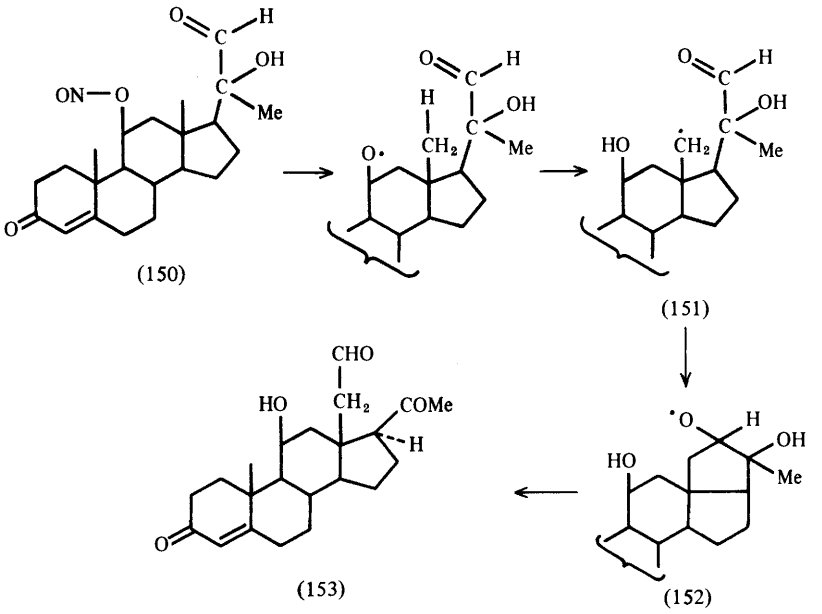
Reagents: i, $NaBT_4$; ii, TsCl, C_5H_5N; iii, HOAc; iv, ^-OH; v, CrO_3

Scheme 34

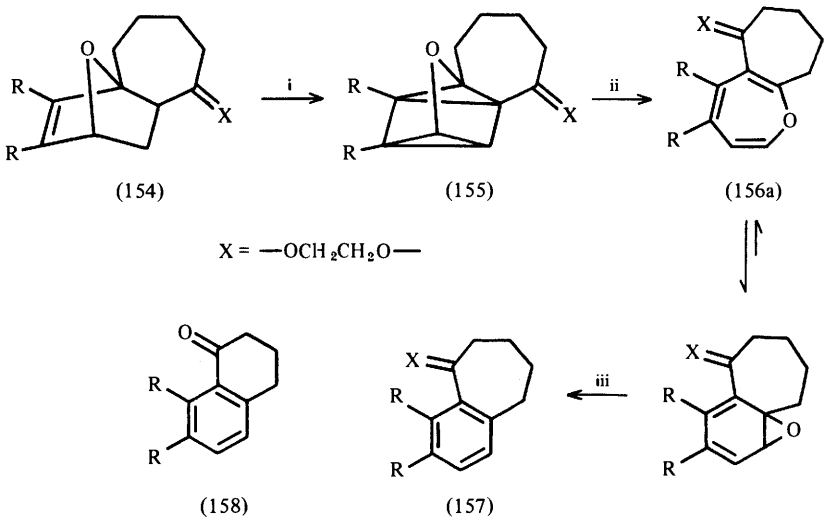
A C-18 radical (151) was generated by photolysis of the 11-β nitrite (150) and subsequent hydrogen abstraction, Scheme 35. In (151) the radical centre is favourably located with the exocyclic carbonyl group to give (152). This electron deficient intermediate can undergo ring opening to give compound (153).[64]

In an elegantly designed series of reactions Tochtermann's group executed a 1,4 carbonyl transposition on the oxanorbornadiene dioxolan (154) (Scheme 36).[2] Irradiation gave the sensitive quadricyclene derivative (155), which was directly converted into (156) (two valence tautomers) in refluxing toluene. Although deoxygenation of (156) proceeded readily, the formal transposition sequence was frustrated by the inability to 'de-protect' the dioxolan (157).

[63] D. S. Noyce and B. N. Bastian, *J. Am. Chem. Soc.*, 1960, **82**, 1246.
[64] J. Kalvoda and J. Grob, *Helv. Chim. Acta*, 1978, **61**, 1966.



Scheme 35

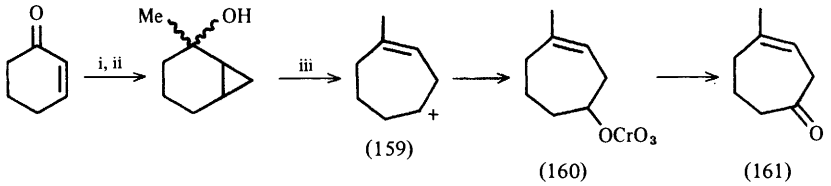


Reagents: i, *hν*; ii, Δ, PhMe; iii, $[Rh(CO)_2Cl]_2$

Scheme 36

Notwithstanding this, however, the lower homologue (158) was subsequently obtained without difficulty by an analogous procedure.[65]

In a method of 1,4 carbonyl transposition associated with ring expansion, cyclohexenone yielded (161) by the mechanism, indicated in Scheme 37, which included both a homoallylic cation (159) and a chromate ester (160); the latter is normally a product-forming intermediate in alcohol oxidation by chromic acid.[66]



(159) (160) (161)

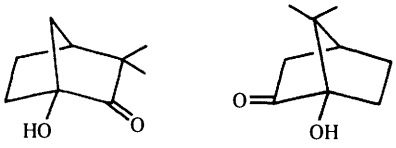
Reagents: i, MeLi; ii, *m*-CPBA; iii, pyridinium chlorochromate

Scheme 37

5 Transposition of Hydroxy-ketones

Transposition of carbonyl and hydroxy-groups can occur in hydroxy-ketones in cases in which the number of carbon–carbon bonds separating the carbons bonded to the oxygen atoms varies between 1 and 6. The reactions are characterized by hydride or, less commonly, carbon–carbon bond migration and although definitive evidence is not available from all investigations, intermolecular migration appears to be uncommon. A review of earlier work is given in references 67 and 68.

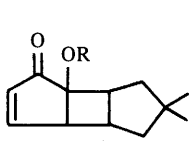
1,2 Transpositions.—With NaOH in aqueous methanol 1-hydroxycamphenilone (162) equilibrated with (163); the greater stability of (163), where the *gem* dimethyl group also forms the methylene bridge, is indicated by its predominance over (162) by 2:1 at 31 °C.[69]



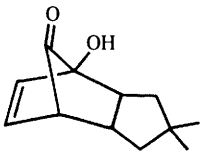
(162) (163)

[65] W. Tochtermann and H. Köhn, *Chem. Ber.*, 1980, **113**, 3249.
[66] E. Wada, M. Okawara, and T. Nakai, *J. Org. Chem.*, 1979, **44**, 2952.
[67] S. Selman and J. F. Eastham, *Quart. Rev. Chem. Soc.*, 1960, **14**, 221.
[68] N. L. Wendler in 'Molecular Rearrangements', ed. P. de Mayo, Interscience, New York, 1963, p. 1114.
[69] A. Nickon, T. Nishida, J. Frank, and R. Muneyuki, *J. Org. Chem.*, 1971, **36**, 1075.

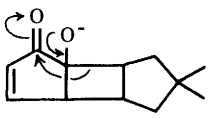
In the course of the synthesis of methyl isomarasmate the transformation of (164) into (166) was effected with 1% methanolic sodium hydroxide.[70] After initial ester hydrolysis to (165) the rearrangement proceeded as shown in (167).



(164) R = Ac
(165) R = H

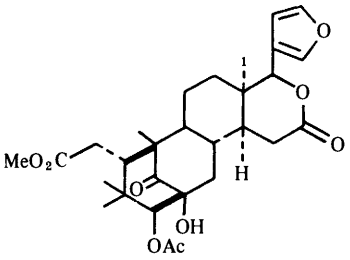


(166)

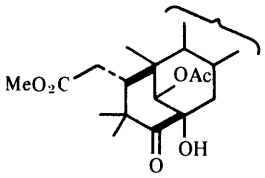


(167)

1,3 Transpositions.—Base-catalysed hydrolysis of (168) gave an alcohol, which after acetylation, yielded an acetate isomeric with (168).[71] The rearranged acetate was shown to be (169) and this was considered to have arisen *via* a 1,3 hydride shift at some stage during the hydrolysis (see however ref. 72).



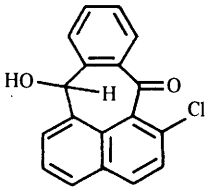
(168)



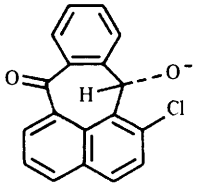
(169)

1,4 Transpositions.—These are more common and occur in ring systems in which hydride can be readily transferred to a transannular carbonyl group.

Such was shown to be the case for (170); in DMSO–Bu^{t}OH (95:5) a value $E_a = 24.5$ kcal mol^{-1} and an associated primary deuterium isotope effect, $k_H/k_D \approx 3$ were found for the conversion of the potassium salt of (170) into



(170)

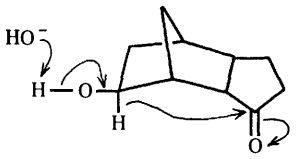


(171)

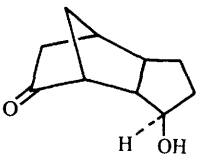
[70] D. Helmlinger, P. de Mayo, M. Nye, C. Westfelt, and R. B. Yeats, *Tetrahedron Lett.*, 1970, 349.
[71] D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1970, 336.
[72] E. W. Warnhoff, *Can. J. Chem.*, 1977, **55**, 1635; E. W. Warnhoff, P. Reynolds-Warnhoff, and M. Y. H. Wong, *J. Am. Chem. Soc.*, 1980, **102**, 5956.

(171).[73] It was subsequently pointed out, however (see ref. 76), that the hydroxy-ketone exists in the form of an internal hemiacetal in which the hydroxy-group is more acidic than in a secondary alcohol; accordingly the above activation energy may represent the value for the interconversion of the isomeric hemiacetal salts.

More recently formal incorporation of 4 deuterons into (172) under basic conditions in the presence of D_2O led to the postulation of a 1,4 hydride shift leading to (173).[74] The authors considered that 3 protons are exchangeable in (172) and 1 in (173); however there was no evidence on the relative amounts of (172) and (173) at equilibrium.

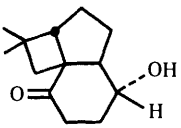


(172)

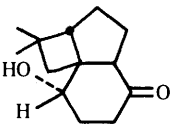


(173)

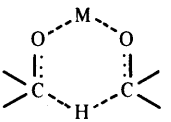
In the Meerwein–Pondorff–Varley–Oppenauer type reaction which transformed (174) into (175) there was both intra- and inter-molecular hydride transfer.[72] Here, in the presence of Pr^iOM, the rate of intermolecular hydride transfer increased with increasing Lewis acidity of the cation (M) ($Al^{3+} > Li^+ > Ba^{2+} > Na^+ > K^+$). For the intermolecular process the authors therefore invoked a cyclic transition state (176).



(174)



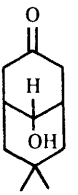
(175)



(176)

The transposed ketones (177) and (178) were interconverted by a 1,4 hydride shift; in base the equilibrium mixture contained 98.96% (177), corresponding

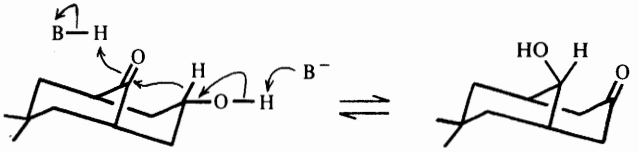
(177)



(178)

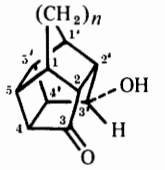
[73] P. T. Lansbury and F. D. Saeva, *J. Am. Chem. Soc.*, 1967, **89**, 1890.
[74] J. M. Shepherd, D. Singh, and P. Wilder, *Tetrahedron Lett.*, 1974, 2743.

to this ketone being more stable by 2.7 kcal mol^{-1}.[75] In order for this hydride shift, presumably intramolecular, to occur a small standing concentration of the boat conformation is needed in that six-membered ring which contains both oxygen bearing carbons (Scheme 38). This hydride transfer is *ca.* $\times 10^2$ slower than the corresponding 3,7 shift in a related system (188) (*vide infra*).



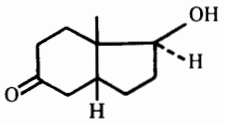
Scheme 38

Anions of a series of ketols (179)—(181), which are held in frameworks of slightly varying rigidity, underwent degenerate rearrangement.[76] Solutions of the sodium salts of these ketols in dimethyl sulphoxide exhibited the following barriers, $\Delta G^{\ddagger}$, to rearrangement, as indicated by dynamic ^{13}C n.m.r. spectroscopy: for (179), >21.7 (100 °C); (180), 19.0 (100 °C); (181), 17.3 (72 °C) kcal mol^{-1}. Extension of the methylene bridge has the effect of bringing C-3 and C-3′ closer together; this intuitive expectation is reinforced by molecular mechanics calculations.

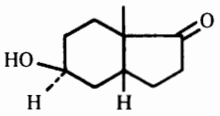


(179) $n = 1$
(180) $n = 2$
(181) $n = 3$

1,5 Transpositions.—The first report of a 1,5 hydroxy-ketone transposition appears to have been that of Acklin and Prelog[77] wherein the *cis* fused (183) was formed from (182) by means of activated alumina. 1,5 Carbonyl transpositions to cyclohexanone have been reported both in cases in which the

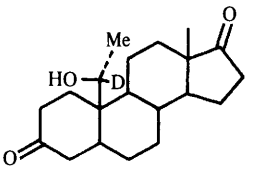


(182)

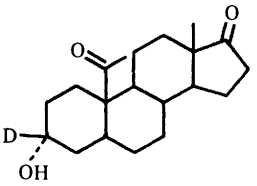


(183)

[75] I. Watt, *Tetrahedron Lett.*, 1978, 4175.
[76] G.-A. Craze and I. Watt, *J. Chem. Soc., Perkin Trans 2*, 1981, 175.
[77] W. Acklin and V. Prelog, *Helv. Chim. Acta*, 1959, **42**, 1239.

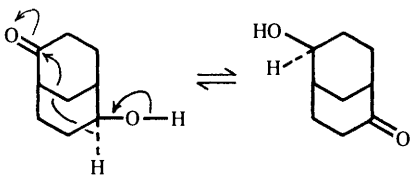


(184)

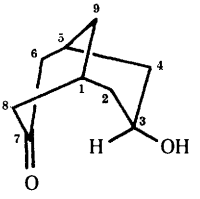


(185)

migrating hydride (deuteride) is exocyclic, (184)—(185),[78] and also when the hydride is located on an adjacent, and fused, ring (186)—(187).[79] In order that intramolecular migration might occur, a boat conformation is required for ring A in the former case, whereas in the latter the preferred twin chair conformation facilitates hydride transfer. A similar conclusion is in order for the isomeric (188);[80] by means of variable temperature ^{1}H n.m.r. spectroscopy, a value $\Delta G^{\ddagger} = 19.4 \pm 0.2$ kcal mol^{-1} at 113 °C was determined for the 3,7 hydride transfer of the sodium salt of (188) in DMSO. It was estimated that the lowest energy position for the migrating hydride places it *ca.* 1.9 Å from the carbonyl and locates it behind the orthogonal to the plane of the carbonyl group running through the carbonyl carbon atom. This implies that the hydride approached the carbonyl carbon along the optimum (least energy) direction. Similar considerations are relevant to other additions to carbonyl groups in this review.



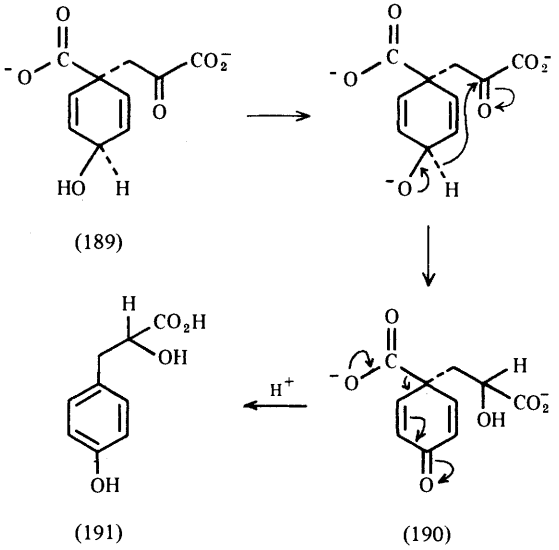
(186) (187)



(188)

1,6 Transpositions.—A mechanism for the 1,6 transfer of hydride within (189) leading to (190) and ultimately to *p*-hydroxyphenyl-lactic acid (191) was proposed by Plieninger.[81] The intramolecular nature of the hydride transfer, established recently by means of labelling experiments,[82] is shown in Scheme 39.

[78] J. Wicha and E. Caspi, *J. Org. Chem.*, 1973, **38**, 1281.
[79] W. Parker and J. R. Stevenson, *Chem. Commun.*, 1969, 1289.
[80] R. S. Henry, F. G. Riddell, W. Parker, and C. I. F. Watt, *J. Chem. Soc., Perkin Trans 2*, 1976, 1549.
[81] H. Plieninger, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 367.
[82] S. Danishefsky and M. Hirama, *J. Am. Chem. Soc.*, 1979, **101**, 7013.



(189)

(191) (190)

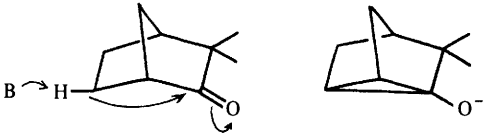
Scheme 39

An acyclic example of a 1,6 carbonyl transposition (192)—(193) has also been demonstrated recently.[72]

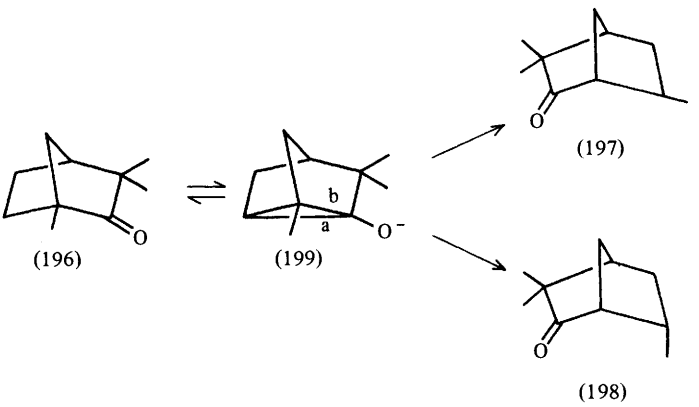
(192) (193)

6 Isomerization of Ketones *via* Homoenolization

In the presence of the strong base, KOBu^t in Bu^{t}OH at high temperatures and for prolonged reaction times, often of the order of a week, many bicyclic ketones undergo isomerization. These reactions involve abstraction of protons β (or occasionally γ) to the carbonyl carbon to form homoenolate anions. In some instances, high yield conversions, which are synthetically useful, are achieved.



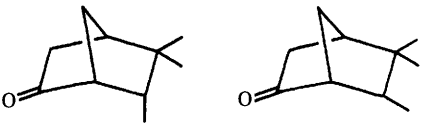
(194) (195)



(196) (199) (197) (198)

Scheme 40

The formation of homoenolates was first noted by Nickon[83] in the racemization of camphenilone (194) by way of (195). Fenchone (196) also underwent a homoenolization reaction, outlined in Scheme 40, wherein two isomeric ketones (197) and (198) were formed after 60—400 h.[84] From the homoenolate (199), cleavage of bond 'a' is favoured over bond 'b' by *ca.* 20:1. The latter cleavage led to the *endo* methyl ketone (198) and the *exo* methyl counterpart in a ratio 3 : 1. Under comparable conditions camphor, (2), was only partially (2.5%) equilibrated to the ketones (200) and (201).[85]

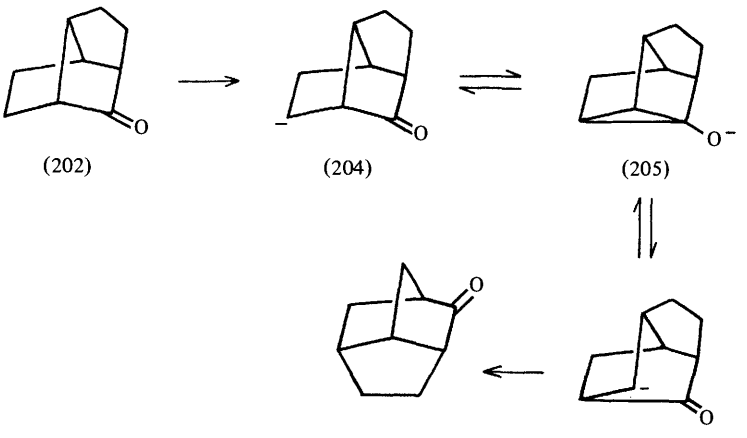


(200) (201)

The bridged norbornanone derivative (202) (brexan-2-one) was completely converted into brendan-2-one (203) (Scheme 41).[86] Molecular mechanics calculations indicated the latter ketone to be more stable by 2.90 kcal mol^{-1}. The three negatively charged species (204)—(206) are considered either to be in equilibrium or to be contributors to a resonance hybrid.

At still higher temperatures, 275 °C, longicamphenilone, (207) was converted into an equilibrium mixture with (208) which contained these compounds in a ratio 7:1.[87]

[83] A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, 1966, **88**, 1905.
[84] A. L. Johnson, J. B. Stothers, and C. T. Tan, *Can. J. Chem.*, 1975, **53**, 212.
[85] A. Nickon, J. L. Lambert, J. E. Oliver, D. F. Govey, and J. Morgan, *J. Am. Chem. Soc.*, 1976, **98**, 2593.
[86] A. Nickon, H. R. Kwasnik, C. T. Mathew, T. D. Swartz, R. O. Williams, and J. B. DiGorgio, *J. Org. Chem.*, 1978, **43**, 3904.
[87] R. M. Coates and J. P. Chen, *Chem. Commun.*, 1970, 1481.

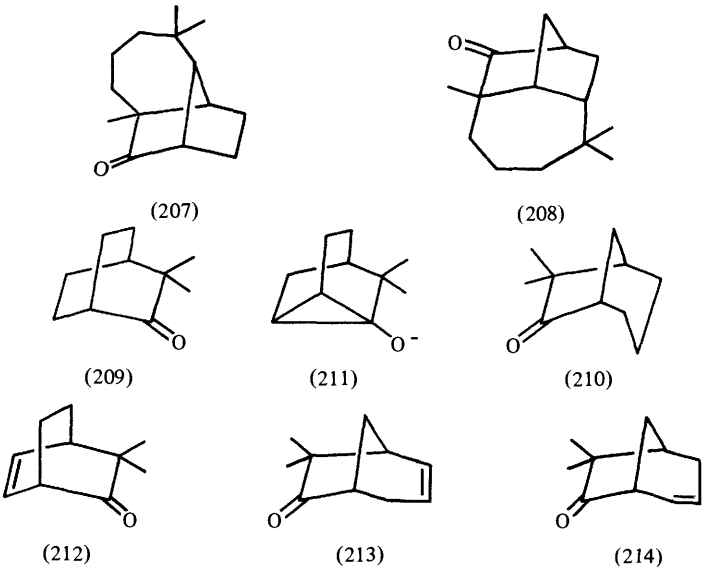


(202) (204) (205)

(203) (206)

Scheme 41

Attempts to generate homoenolates from the bicyclo[2.2.2]octane skeleton have only been partially successful. Thus, 400 h were necessary to achieve a 30% conversion of (209) into (210).[88] However, attempts to generate the common homoenolate ion from (210) were appreciably more difficult, since after the same reaction time, <5% of (211) had been formed. After 168 h, however, the bicyclo[2.2.2]octenone (212) gave rise to two new ketones (213) and (214) in an equilibrium ratio 2:9:9.

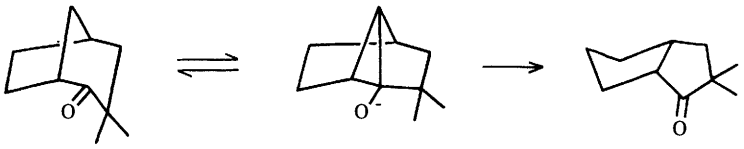


(207) (208)

(209) (211) (210)

(212) (213) (214)

[88] D. M. Hudyma, J. B. Stothers, and C. T. Tan, *Org. Magn. Reson.*, 1974, **6**, 614.

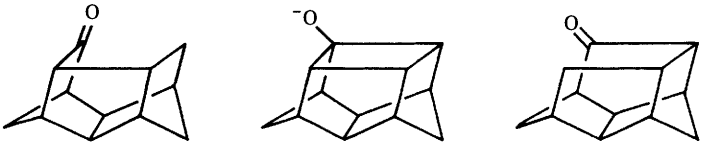


(215) (216)

Scheme 42

In a manifestation of the greater stability of the bicyclo[3.3.0]octane ring system,[89,90] the ketone (215) gave an 80—90% yield of (216)[91] (Scheme 42).

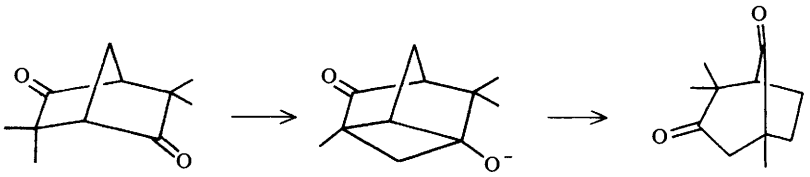
Two groups reported simultaneously that the birdcage ketone (217) was completely isomerized to (219) *via* the homoenolate (218).[92,93]



(217) (218) (219)

Homoketonization of (218) is *ca.* 33000 times more rapid than homoenolization of (217) at 100 °C. In contrast to the previous examples cited in this section, homoenolate (218) is formed by abstraction of a proton from a carbon in a γ-position from the carbonyl group.

Rather later a further example of abstraction of a γ proton was reported.[94] This is indicated in Scheme 43, in which (220) was transformed into (221) by means of proton abstraction from the C-6 *endo* methyl group. Concurrently with this reaction a β proton on C-7 of (220) was also being exchanged. Abstraction of a proton γ to a carbonyl group has also been reported for the C-9 methyl group of camphor[85] and both γ proton sites of *cis*-3,3-dimethyl bicyclo[3.3.0]octan-2-one,[91] although these do not lead to synthetically useful reactions.



(220) (221)

Scheme 43

[89] P. von R. Schleyer, K. R. Blanchard, and C. D. Woody, *J. Am. Chem. Soc.*, 1963, **81**, 1358.
[90] H. M. R. Hoffmann and H. Vatke-Ernst, *Chem. Ber.*, 1981, **114**, 2898.
[91] A. L. Johnson, M. W. Petersen, M. B. Rampersad, and J. B. Stothers, *Can. J. Chem.*, 1974, **52**, 4143.
[92] R. Howe and S. Winstein, *J. Am. Chem. Soc.*, 1965, **87**, 915.
[93] T. Fukunaga, *J. Am. Chem. Soc.*, 1965, **87**, 916; T. Fukunaga and R. A. Clement, *J. Org. Chem.*, 1977, **42**, 270.
[94] N. H. Werstiuk, *Can. J. Chem.*, 1975, **53**, 2211.