SYNTHETIC STUDIES IN SESQUITERPENES : Theoretical.

The classical unity of the terpene group of compounds as shown by their simple composition (limited to three organogenic elements, carbon, hydrogen and oxygen) together with their great structural diversity and ubiquity of occurrence has made the terpenes one of the most explored group of compounds. Inspite of the long history of these compounds, the field is far from exhausted and remains a rich source of new findings and fresh inspiration.

Of a large number of terpenoid natural products known today, the sesquiterpenes represent the largest single class consisting of different structural types, the perverse nature of whose ring systems has been taxing the talents and investigative skills of organic chemists since the beginning of modern organic chemistry.

Although the historical background to sesquiterpenoids can be traced back to the early nineteenth century, the real impetus to the study of the varied and fascinating chemistry associated with these compounds stemmed from the pioneering efforts of WALLACH, SEMMLER and RUZICKA. In particular, RUZICKA(238,239) on a limited basis of facts but prophetic insight proposed the "Biogenetic Isoprene Rule" which has proved to be the foundation stone of terpenoid chemistry in general.

BIOGENESIS OF SESQUITERPENES: Research in the field of sesquiterpenoids has increased at an exponential rate closely paralleling modern methods of isolation, purification, structural elucidation and synthesis. The introduction of chromatographic separation techniques and physical methods of structural analysis during the last three decades has made the chemistry of sesquiterpenes to undergo a period of rapid developments.

The large number of sesquiterpene skeletons known today, corresponding to a large number of presently known compounds which is an order of magnitude greater than twenty years ago requires their systematization so that they may be surveyed in a comprehensive manner. According to the well founded concepts developed in recent years for biogenesis of their highly diverse carbon skeletons, the sesquiterpenes have been divided into nine sections dealing respectively with farnesanes, bicyclo farnesols (drimanes, iresanes) bisabolanes, cadinanes, humulanes and caryophyllanes, germacranes, "hydroazulenes", selenanes and eremophilanes, and maalianes and aristolanes. Further groups of sesquiterpenes can be derived from each of these structural types(233). Sesquiterpenes having the same carbon skeleton are classified as a single group. At the first sight, sesquiterpenoid structures present a bewildering collection of acyclic, monocyclic, bicyclic and tetracyclic systems, and it is within the framework of original "Isoprene Rule"(238,239) and later extensions(100,210) that semblance of relationship can be achieved. The focal point in this conceptual scheme is the utilization of 2-*cis*-6-*trans* farnesyl pyrophosphate (III). The corresponding 2-*trans*-6-*cis* farnesyl, or 2-*cis*-6-*cis*-farnesyl or *nerolidyl* pyrophosphate can also serve as a crucial building block of a few sesquiterpenoids for steric reasons. The farnesyl pyrophosphate, the biological precursor of almost all sesquiterpenoids is formed from acetyl co-enzyme-A via mevalonic acid, isopentenyl pyrophosphate (I) and geranyl pyrophosphate (II) (Fig. 1). Removal of the pyrophosphate group from (III) or (IV) yields the nonclassical cations (V) and (VI) or (VII) each of which can cyclise to two cyclic cations [e.g. (IX) and (X) from (VI); (XI) and (XII) from (VII)]. These can afford most of the sesquiterpenes by processes such as 1, 2 or 1, 3 -hydride shifts, electronically and sterically

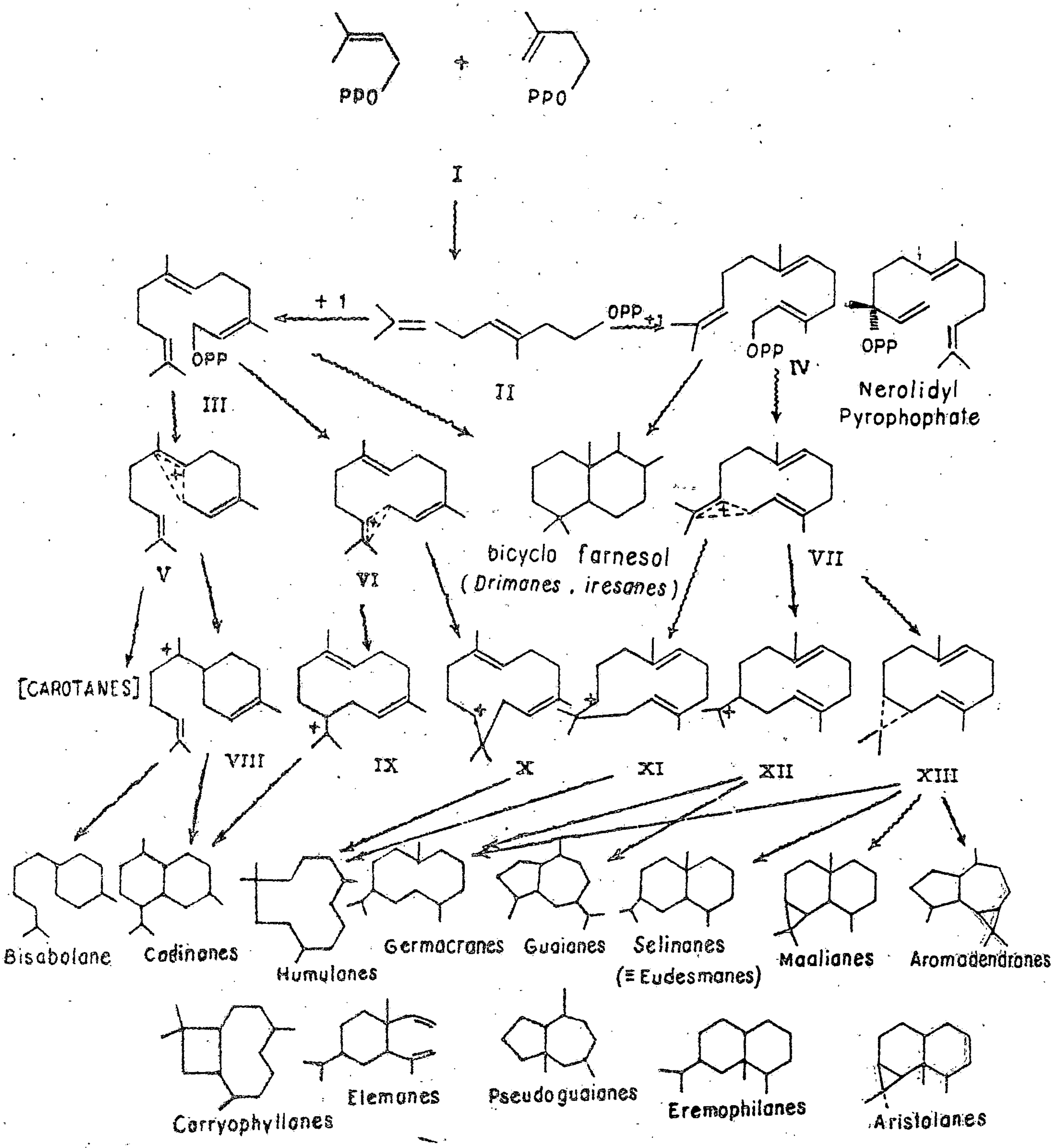


Fig. 1. Biogenesis of the sesquiterpenes. Wavy lines signify biogenatic transitions. The basic skeletons are shown without multiple bonds.

controlled cyclization with two remaining double bonds ("Markownikoff" and "anti-Markownikoff cyclizations), Wagner-Meerwin rearrangements, and 1,2-methyl shifts. It must however be mentioned that many hypotheses based on structure, stereochemistry and reactivity regarding the biosyntheses of sesquiterpenes still require experimental proof in vivo (210,241).

DIFFERENT TYPES OF SESQUITERPENOIDS: The sesquiterpenoids which occur primarily in higher plants, less frequently in lower plants and in the animal kingdom (e.g. insects), comprise not only unsaturated hydrocarbons (including alkynes) but also alcohols, ketones, aldehydes and carbocyclic acids. They may also contain three to seven membered rings, spiro systems and furan rings. Chlorine and bromine substituted sesquiterpenoids as well as nitrogen containing compounds with fifteen carbon atoms (sesquiterpene alkaloids) isolated from *Nymphaeaceae* deserve mention. Compounds with only twelve or fourteen carbon atoms (nor-sesquiterpenes) can also be derived from certain sesquiterpenes.

The sesquiterpene lactones occuring in *Compositae*, and also in other plant families have attracted particular interest. (128) The first compound of this class, *alpha* santonin which was isolated in crystalline form in 1830, is still the object of intensive study (169). A review of sesquiterpenoid lactones in plants of the *Compositae* family has been published by HERZ (101).

Of a large number of sesquiterpene lactones known, worthy of particular mention are the germacranolides (252,253) guaianolides (231,252,253) pseudoguaianolides (102,230,252) selinanolides (Syn:eudesmanolides) (103) and eremophinolides (263). Most of them are saturated or *alpha beta* unsaturated *gamma* - lactones. Apart from a few *delta* - lactones, only two *beta* -lactones (anisatin and neoanisatin) (203) have been found. A trilactone, lilabolide (193), is also known alongside about a good number of dilactones.

CONTRIBUTION OF THE RESEARCH ON TERPENOIDS TO THE WORLD OF CHEMISTRY: In addition to the isolation structural elucidation of numerous new compounds, recent advances in sesquiterpene chemistry have included a better knowledge of the stereochemistry of the molecules, their reactivity and rearrangements and their biogenesis. In this connection the outstanding success achieved in the synthesis of sesquiterpenes should be emphasized. Several earlier structural assignments have been corrected by synthesis and application of modern physical methods (253). Thus the "vetivanes" formerly regarded as hydroazulenes, proved to be spirocyclic agarospiranes or eremophilanes with decalin skeleton (154). The detection of sesquiterpenes with toxic and interesting biological properties e.g., cytotoxic activity (143) also deserves mention (104,143,234).

Undoubtedly the major high light of recent years has been the dramatic eruption of outstanding and elegant syntheses. In the solution of the inherently different problems of skeletal construction and stereochemical control associated with some of these syntheses, new methods have been introduced, which have endowed the synthetic organic chemist with a rich new array of armaments for future use. In particular, the works of Büchi, Corey and Marshall and their respective research teams deserve special mention.

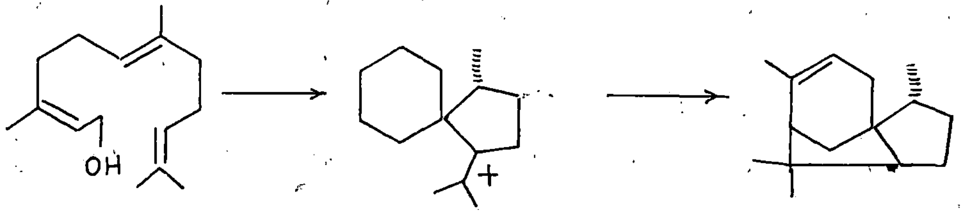
The future of the terpene research will still be concerned primarily with the isolation and structural elucidation of new compounds which could be important as missing biosynthetic links, as biologically active substances or as reactants for the study of chemical problems. The sesquiterpenes throw up problems largely of stereochemical nature. The course of their numerous rearrangements provides information about relationships between stereochemical and electronic factors and the reactivity of the compounds. The chemistry of non-classical carbocations has also profited much from work on sesquiterpenoids. The photochemistry of the sesquiterpenes is still in its infancy. Syntheses of sesquiterpenoids nearly always have to be carried out stereoselectivety and as such they can contribute to the solution of problems in preparative chemistry.

Knowledge of reactivity, photochemistry and syntheses stimulate research into sesquiterpene biogenesis, a field that will become increasingly important in the future. The aim is to elucidate the formation of numerous carbon skeletons and to obtain information about the reasons behind the frequently complex stereospecific biosynthetic pathways that could also be of interest for biogenesis of other natural products. In this connection, importance also attaches the site of formation and of deposition of the sesquiterpenoids in plants and to their distribution throughout the plant and animal kingdom. The biological properties of some sesquiterpenes show that they are not merely metabolic "waste-products". For instance, they are of significance as plant-growth substances, growth regulators and sex attractants of fungi. Others function as the Juvenile hormones essential for normal development of insects or occur as components of insect secretions. These aspects have an area of sesquiterpene research that is of potential interest e.g., for the solution of practical problems of influencing the growth of cultivated plants and in plant protection.

Sesquiterpenes can provide impetus to drug research too. The starting point of such work is the pharmacological effects, determined so far for a relatively small number of compounds. They include cytotoxic, antibiotic, fungistatic, virostatic, anthelmintic, antiphlogistic and sedative properties, thus covering a fairly broad spectrum. Considerable uncertainty still surrounds the extent to which the sesquiterpenes contribute to the manifold and frequently nonspecific action of the essential oils in which they occur. Mention should be made here of the importance of sesquiterpene research for the chemistry of essences and of aromas and flavours.

Studies on sesquiterpenoids, as is evident from the above discussions, have contributed significantly to the advancement of spectroscopic techniques, mechanistic insight, and synthetic methodology, and the trend along these lines shows no sign of letup, as new and increasingly complex structures join the list of known members.

SPIRO (4.5) DECANE SESQUITERPENES: The possibility of farnesol-derived spiro (4.5) decanes was suggested by RUZICKA who postulated the cation (XV) (~~Fig.2~~) as an intermediate in the biosynthesis of cedrene (XVI)(239) . However, the actual occurrence



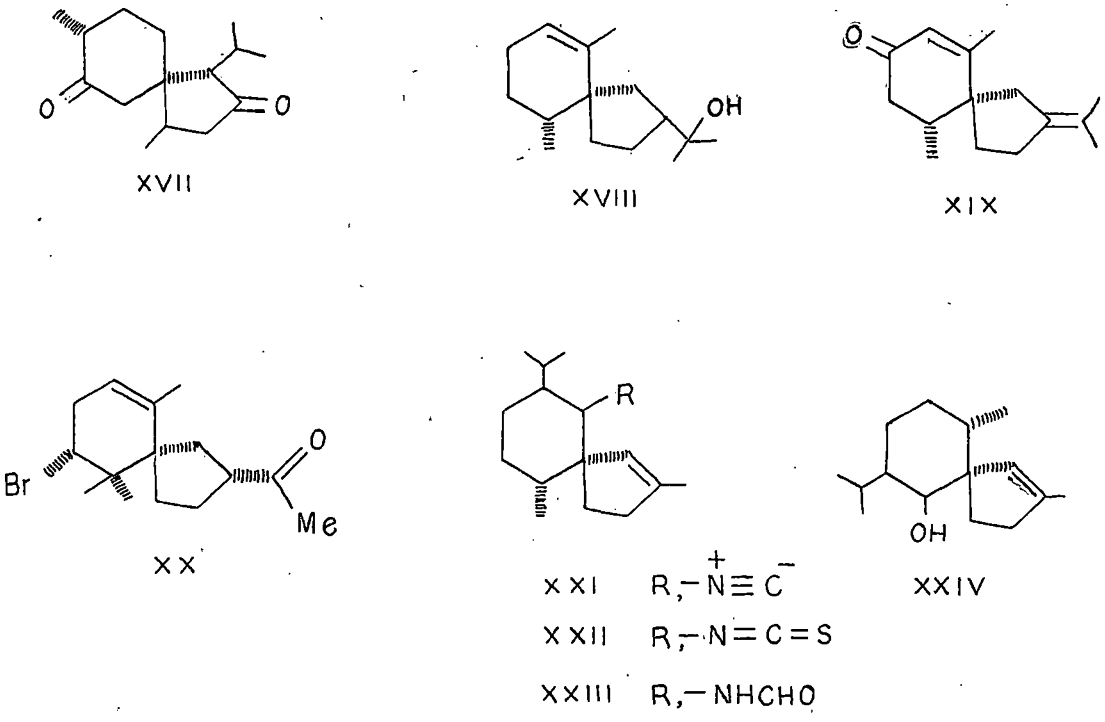
XIV XV XVI

of sesquiterpenes possessing a spiro (4.5) decane carbon frame work was not actually established until 1956 when ŠORM and his co-workers (264) published their interpretation of degradative experiments on acorone (XVII), a constituent of sweet flag oil (264). Further studies led to characterization of a number of related spiro (4.5) decane derivatives from the same oil (279,280). Recent work has uncovered a series of skeletally related enantiomeric compounds, the alaskenes (2,3).

A second type of spiro (4.5) -decane derived sesquiterpene was formulated by BHATTACHARYA, *et al.*, in the course of their studies on constituents of the essential oil derived from fungus infected agarwood (275). The new sesquiterpene, agarospirol (XVIII) differs from the acorane type in the placement of methyl and isopropyl groupings. Recently the number of natural sesquiterpenes possessing this particular skeletal arrangements has increased considerably by the discovery that *beta*-vetivone (XIX) and related vetivane sesquiterpenes, previously thought to be hydroazulenes (216) possess the same carbon skeleton as that proposed for agaroSpirol (154).

The third type of spiro (4.5) decane sesquiterpene may be exemplified by spiro aurenone (Syn:spiro Laurenone ??) (XX) isolated from marine source and which may also be deemed as a representative of a few known natural products containing bromine (262).

Yet another type of (4.5) spiro sesquiterpene is isolated from the marine sponge <u>Axinella Cannabina</u>(72). The new sesquiterpenes, axisonitrile-3 (XXI) axisothiocyanate-3 (XXII) and αxamide-3 (XXIII) are not only the representatives of the new type of sesquiterpenes possessing (4.5) spiro carbon skeleton but also are the first examples of naturally occuring isoprenoids having isonitrile or isothiocyanate functions. Gleenol (~~XXXX~~) (XXIV)(144) is also a member of this group of sesquiterpenoids.



XVII XVIII XIX

XX XXI XXII XXIII XXIV

Fig. 2: REPRESENTATIVE SPIRO [4.5] DECANE SESQUITERPENES.

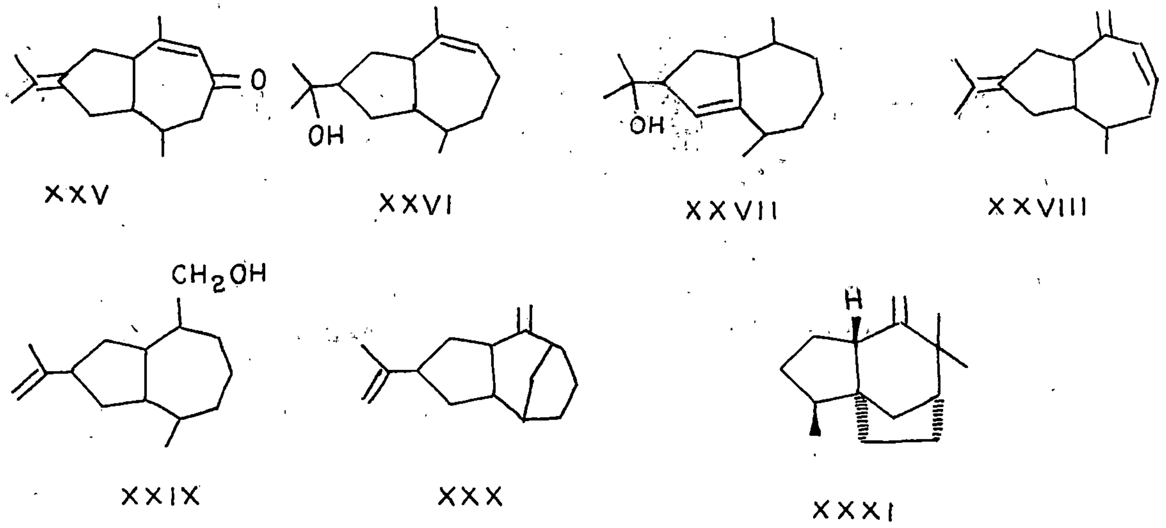
Whereas agarospirol (XVIII) was the first spiro (4.5) decane of its kind to be recognised(275), another sesquiterpene, *beta*-vetivone (XIX), isolated from essential oil of vetiver, was the first naturally occuring member of this class to receive extensive chemical study(196,216,217). However, owing to an undetected skeletal rearrangement which occured in the degradative studies, the structure was incorrectly assigned as a hydroazulene derivative (XXV).(218)

Nonetheless, this assignment, although erroneous for the vetivones, led to the currently accepted formula for azulene thereby solving one of the most puzzling structural problems of the early 1900's.

Further studies on the oil of vetiver and other essential oils, uncovered a number of sesquiterpenes whose structures were deduced through correlation with *beta*-vetivone. For example, structures (XXVI) and (XXVII) (Fig. 3) were proposed for hinesol on the basis of chemical evidences and conversion to vetivazulene(181,301,302). Two other vetiver sesquiterpenes, *alpha* - and *beta*-isovetivenene were thought to be related to structure (XXVIII) by virtue of their spectral properties and their conversion to "isovetivane", the saturated hydrocarbon obtained upon total reduction of *beta*-vetivone(229). Several additional unsaturated hydrocarbons, regarded as double bond isomers of the two isovetivenenes (XXVIII) also came to light in the course of these studies.

One rather interesting aspect of ROMANUK and HEROUT'S work was the finding that alpha and beta-vetivones afforded saturated hydrocarbons, vetivane and isovetivane respectively, whose infrared spectra were "significantly different" from each other(229). This result was some what surprising in view of the epimeric relationship postulated for the vetivones(202,217). More surprising was the fact that the hydrocarbon spectra were fundamentally different from the spectrum of decahydrovetivazulene. These differences were attributed to stereoisomerism. However, it was revealed later that, the three "vetivanes" actually belong to three distinct skeletal classes.

Bicyclo vetivenol, a primary alcohol isolated from oil of vetiver, was accorded structure (XXIX) on the basis of its spectral properties and conversion to "alpha-vetivane" upon acetate pyrolysis followed by hydrogenation(44). A later report described the properties of "tert-bicyclovetivenol" and noted the absence of any primary alcohols in at least one variety of vetiver oil(123,124). "Tricyclovetivene", a hydrocarbon isolated from vetiver oil of Belgian Congo origin, was originally accorded structure (XXX), but this assignment was later revised to (XXXI)(193,240).



XXV XXVI XXVII XXVIII

XXIX XXX XXXI

Fig. 3

The hydroazulene structure was assigned to beta-vetivone by PFAU and PLATTNER on the basis of their degradation studies on beta-vetivone(216), shown in CHART I. beta- vetivone (XXXII) on treatment with sodium in alcohol yielded a mixture (stereo isomers) of dihydrovetivols (XXXIVa) and (XXXIVb). The process involved the reduction of a carbon-carbon double bond along with the reduction of carbonyl grouping. Ozonolysis of this alcohol mixture afforded acetone and the hydroxy ketone (XXXVI). These reactions clearly indicated the presence of an alpha, beta unsaturated ketone and an isopropylidene grouping in beta-vetivone. Further more the compositional analysis required these derivatives to be bicyclic. Partial hydrogenation of beta-vetivone $[\alpha]_D$ (20), - 24° gave a saturated ketone (XXXIII) and the corresponding alcohol (XXXIVb), both of which were devoid of optical activity. This finding constituted a key point in the structure analysis, as it suggested that the hydrogenation products of beta-vetivone contained a symmetry plane.

Hydrogenation of dihydro-beta-vetivol (XXXIV) followed by vigorous oxidation with chromic acid, afforded a dicarboxylic acid (XXXV). This diacid, upon treatment with acetic anhydride at elevated temperature, yielded a cyclic ketone (XXXVII) with loss of carbondioxide. Dehydrogenation of this ketone (XXXVII) then gave 4,7-dimethyl-2-isopropyl-5-indanol (XXXVIII) identified by comparison with an independently synthesized sample. This led PFAU and PLATTNER to conclude that the ketone (XXXVII), the precursor of (XXXVIII) was a cyclopentane fused cyclohexanone. This conclusion defined diacid (XXXV) as a pimelic acid derivative and meant that the alcohol precursor (XXXIV), the related ketone (XXXIII) and beta-vetivone itself (XXXII) must contain a seven membered carbocyclic ring. Dehydrogenation of beta-vetivone with selenium gave results in support of the above conclusion by way of yielding vetivazulene (XXXIX) along with a mixture of C_{14} and C_{15} naphthols, presumably largely (XL).

The confirmation of the structure for vetivazulene (XXXIX) was obtained by the authors through synthesis(217). Thus structure (XXV) was advanced for <u>beta</u>-vetivone.

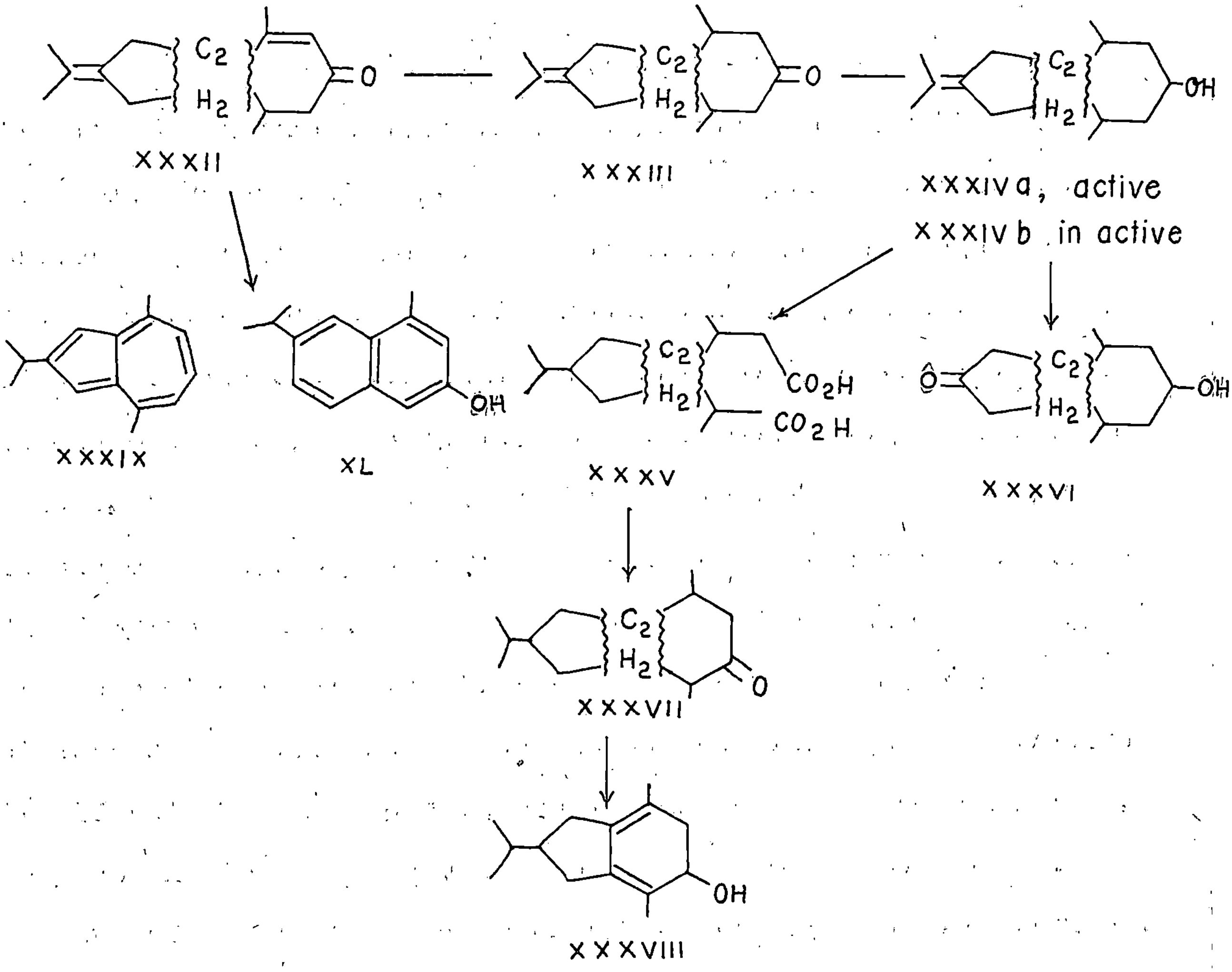


CHART I: DEGRADATION OF BETA-VETIVONE

Interestingly and as can now be appreciated significantly, only traces of vetivazulene were secured upon dehydrogenation of *beta*-vetivone with sulphur or palladium-on-charcoal. In these cases the reactions led almost exclusively to the C_{14} & C_{15} naphthols.

The known chemistry of vetivone related natural products at this point was still consistent with a hydroazulenic skeleton. The degradative studies associated with hinesol deserve some comment as they contain the first definite contradictions (CHART II). The isomeric structures were suggested by Czech (XXVI)(181) and Japanese groups (XXVII)(301). SORM *et al*, converted the crystalline dihydro alcohol (XLI) to ketone (XLII) which was essentially devoid of optical rotation, suggesting the indicated *cis*-methyl arrangement in dihydrohinesol (XLI)(46,181).

Dehydration of dihydro-hinesol (XLI) afforded a mixture containing olefins (XLIII) and (XLIV) (CHART II). Hydrogenation of this mixture afforded a hydrocarbon identical to "isovetivane" according to infrared spectral comparison(229). The "isovetivane" sample was derived from meso dihydro-*beta*-vetivone, suggesting a *cis*-hydroazulene ring fusion and *cis*-relationship between the methyl groups. The correlation was even firmer in an unpublished work of Japanese group(302).

Olefin (XLIV) and ketone (XLII)

were reported to be completely devoid of optical activity. In fact, ketone (XLII) afforded a benzylidene derivative identical to that obtained from "mesodihydro-beta-vetivone. However, dihydrohinesol (XLI) was clearly optically active. Furthermore, hinesol dehydrates partially to olefin (XLV) on chromatography over basic alumina. The olefin (XLV) was proved identical to isovetivene, a congener of hinesol. Hydrogenation of isovetivene afforded optically active isovetivane. The optical activity of these two materials was clearly inconsistent with the hydroazulene formulation which had been accorded to the vetivone sesquiterpene.

ŠORM'S evidence for the position of the double bond came from n.m.r. spectrum and further reactions of the ozonolysis product (XLVI). In their early studies, YOSIOKA, et al obtained an ozonolysis product of hinesol that did not appear to be a methyl ketone(301).

Additional evidence for their assignment came from the formic acid dehydration of hinesol which afforded a conjugated diene (λ_{max} 240 mμ, log ϵ 4.07). Later, YOSIOKA and KIMURA confirmed ŠORM'S assignment by allylic oxidation of hinesol, followed by dehydration, which afforded the enantiomer of beta-vetivone(303).

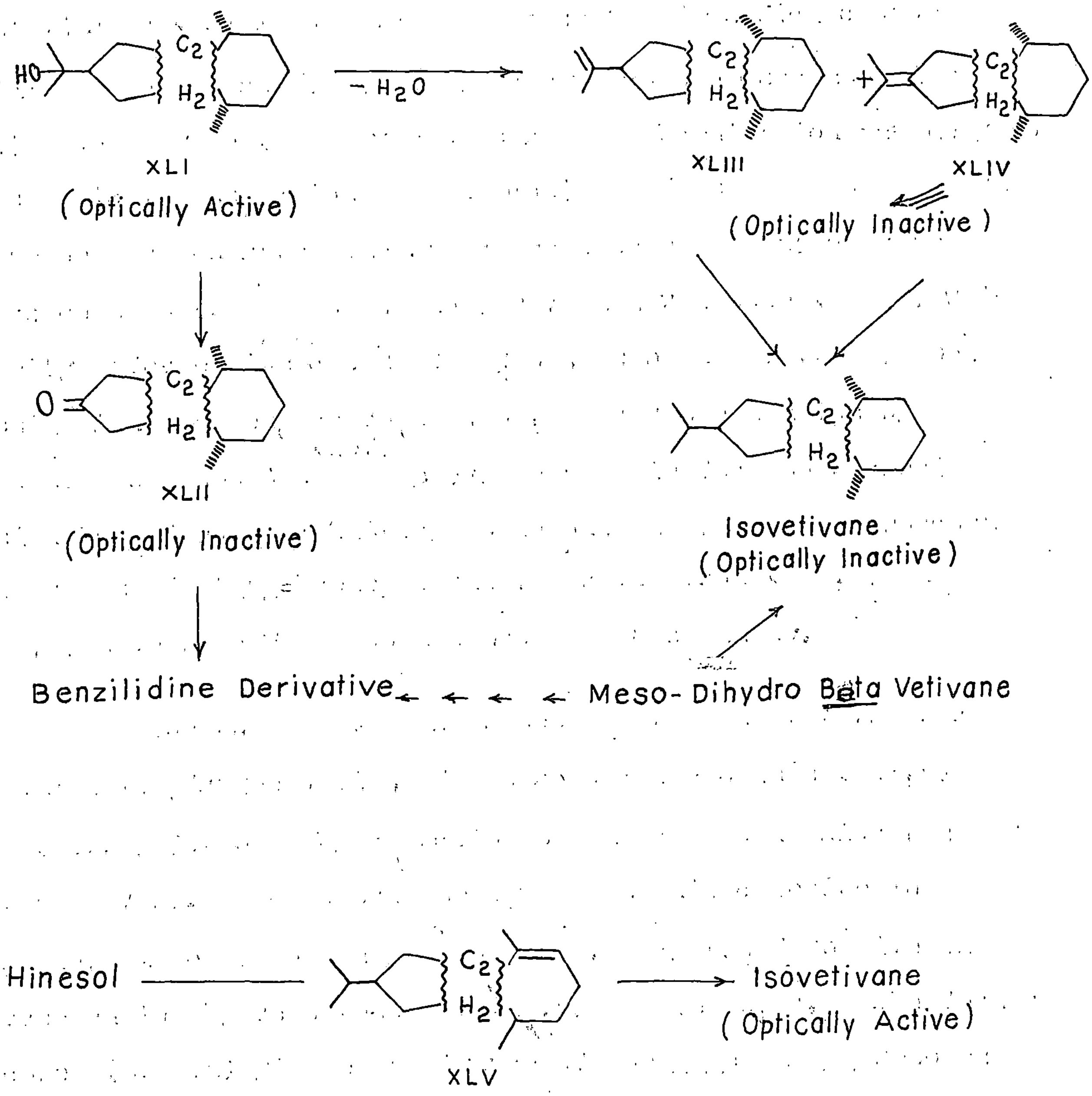
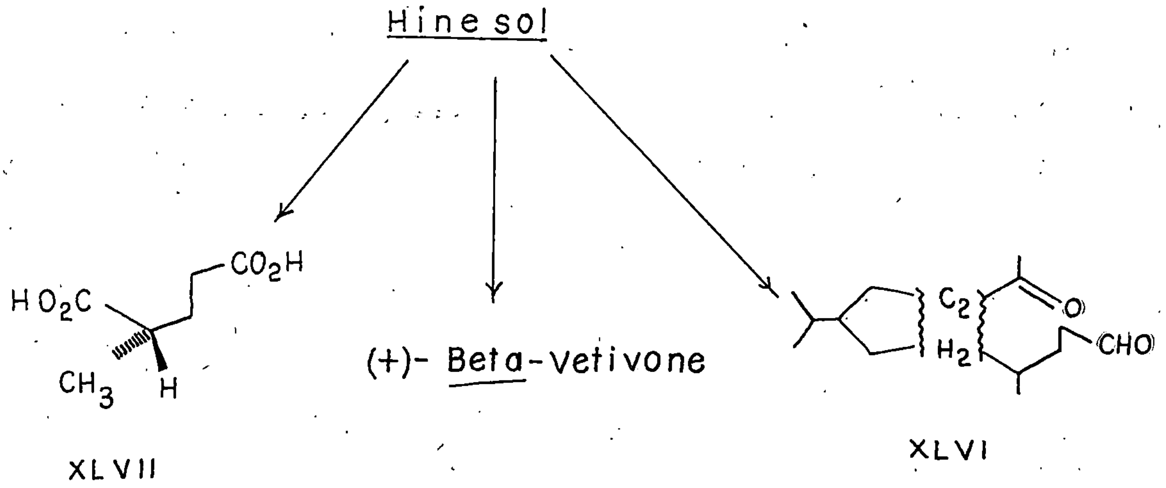


Chart II: Degradation of Hinnesol

This correlation proved to be the keystone of the absolute stereochemistry of this class of sesquiterpenes since vigorous oxidation of hinesol afforded (+) <u>alpha</u>-methyl glutaric acid (XLVII).

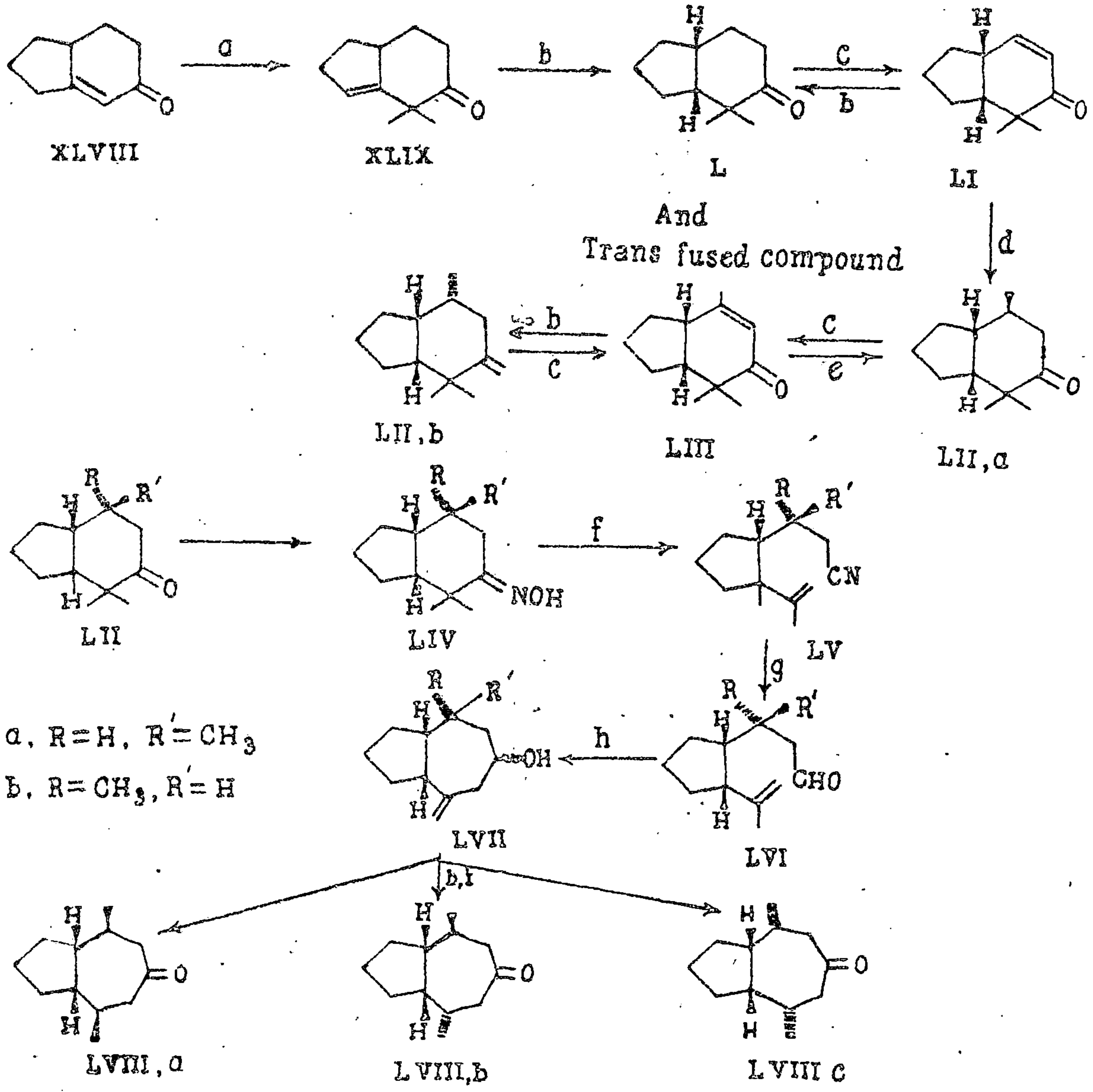


The discovery that many of the vetivone sesquiterpenes actually belong to the spiro (4.5) decane family was brought about by MARSHALL and his group (154,155), as a result of their studies aimed at the synthesis of the postulated hydroazulene structure. In course of their studies they formulated a stereoselective route to substituted hydroazulenes and thereby prepared the three 6,10-dimethyl-<u>cis</u>-decahydroazulene-8-ones (LVIIIa-c) (156), (CHART III), and showed that none of the aforementioned hydroazulenes correspond to either of the epimeric desisopropylidene dihydro-*beta*-vetivones prepared from *beta*-vetivone. This finding indicated not only the structure (XXV) (Fig.3) be accepted any more for *beta*-vetivone, but, by virtue of reported chemical correlations, the proposed carbon frame work of the entire class of bicyclic vetivane sesquiterpene as well (301,303).

This group of chemists secured (-) - *beta*-vetivone from vetivert acetate, Java origin, identified by its melting point (196,216), Optical rotation (196,216), infrared spectrum (199,303), and n.m.r. spectrum (303), and converted it to the epimers of desisopropylidene dihydro-*beta*-vetivone (meso, and dl form) according to the scheme depicted in CHART IV. A sample for comparison was synthesized as follows (CHART III).

Methylation ($K\text{-}OBu^t$, CH_3I) of the known hydrindanone (XLIII) (257) afforded the dimethyl derivative (XLIX) which yielded principally the *cis*-hydrindanone (L) upon hydrogenation over palladium on charcoal in ethanol. The *cis*-hydrindanone (L) was purified via semicarbazone derivative and it was converted to the conjugated ketone (LI) through bromination followed by dehydrobromination. That the isomerization of the ring-fusion did not occur en route to the conjugated ketone (LI) was confirmed by way of regenerating the *cis*-hydrindanone (L) through hydrogeneration (Pd-C). Addition of methyl magnesium iodide to hydrindanone (LI) in the initial presence of cupric acetate afforded the 1,4 adduct (LII,a) from which the corresponding conjugated ketone (LIII) was prepared via bromination and dehydrobromination. Reduction of this conjugated ketone with Lithium in ammonia regenerated the saturated ketone (LII,a) whereas hydrogenation (Pd-C in ethanol) gave a new ketone (LII,b) which readily afforded its conjugated ketone progenitor (LIII) upon bromination and dehydrobromination. Previous studies by MARSHALL and ANDERSEN (157) provided a basis for the α priori assignment of stereochemistry to ketone (LII,a). The spectral properties of *alpha*-bromo ketones, derived from (LII,a) and (LII,b) have been shown to support this assignment.

The unsaturated aldehydes (LVI,a) and (LVI,b) were prepared via fragmentation of the respective oximes (LIV,a) and (LIV,b) followed by reduction of the resulting nitriles (LV,a & LV,b). Upon treatment with stannic chloride in benzene, these aldehydes (LVI,a & LVI,b) cyclized to give the corresponding hydroazulenols (LVII,a) and (LVII,b). The former alcohol (LVII,a) yielded a mixture of the *meso* and *dl* ketones (LVIII,a) and (LVIII,b) (only one enantiomer has been shown in the chart) after hydrogenation and subsequent oxidation. The latter (LVII,b) was likewise converted to the *dl* ketone (LVIII,b) and the *meso*-isomer (LVIII,c).



a = KOBu^t/CH_3I ; b = H_2/Pd-C/EtOH ; c = bromination followed by dehydrobromination
d = $CH_3MgI/Cu(AC)_2$; l = Li/NH_3 f = Tscl/Py ; g = (iso $C_4H_9O)_2$ AlH; h = $Sncl_4$
i = CrO_3

CHART III: SYNTHESIS and COMPARISON of DIMETHYL HYDROAZULENONES

In the next phase of these studies, beta-vetivone was degraded in order to obtain a comparison sample of what should have been either the meso ketone (LVIII,a) or the isomer (LVIII,c) (CHART IV). Since the synthetic route to these ketones unambiguously defined their stereo chemistry, the correspondence of one of them with the vetivone derived ketone would likewise define the relative stereochemistry of beta-vetivone. To this end (-)-beta-vetivone was converted following PFAU-PLATTNER'S hydrogenation-ozonolysis sequences (216) to the meso-dihydro alcohol (a 65:35 mixture of alcohol epimers) and then to the des-isopropylidene compound (XXXVI). The meso hydroxy ketone (XXXVI) was converted to the thioketal derivative and treated with Raney nickel to give the alcohol (LIX). Oxidation then afforded the desired ketone (LX). However, the infrared spectrum of this ketone bore no resemblance to any of the synthesized ketones (LVIII,a-c). In fact the carbonyl stretching band of ketone (LX) (1727 cm^{-1}, 5.81 μ) suggested that the carbonyl grouping was a part of a six-membered ring. The synthetic ketones (LVIII,a &b) gave rise to an infrared band at 1705 cm^{-1} 5.88 μ &(LVIII,c) at 1700 cm^{-1}, 5.90 μ and are consistent with their assigned cycloheptanone structures.

Reduction of (-) -beta-vetivone with Lithium in ammonia-ethanol afforded principally a new dihydro alcohol

(40% yield) alongwith one of the previously obtained *meso*-dihydro alcohols (15% yield) and starting material. Degradation of this new dihydro alcohol along the lines described above afforded a new desisopropylidene dihydro-*beta*-vetivone whose infra red spectra bore no close resemblance to that of its supposed racemic counterpart (LVIIIb) or the synthetic meso compounds (LVIII, a) and (LVIII, c).

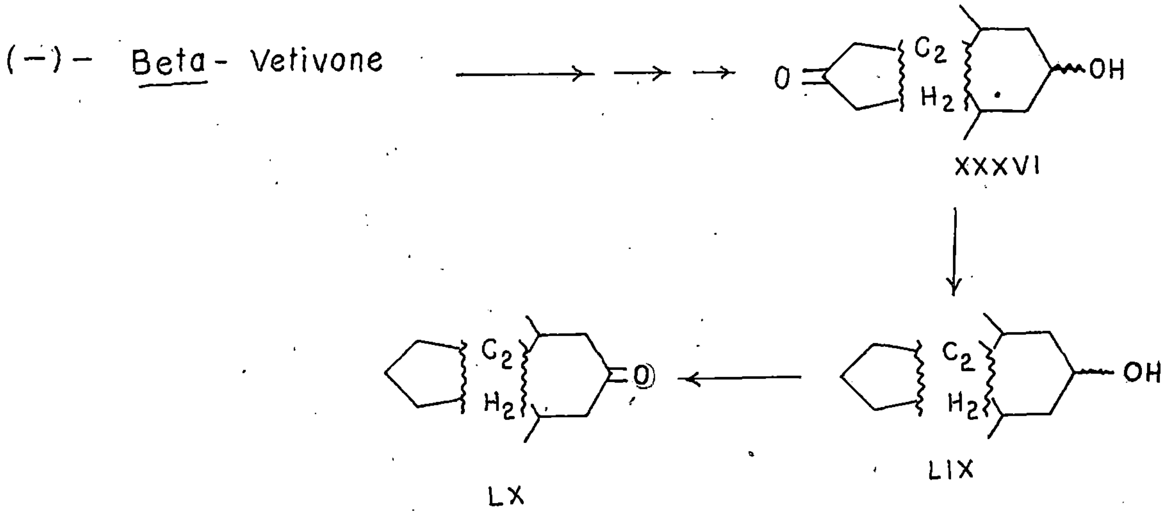
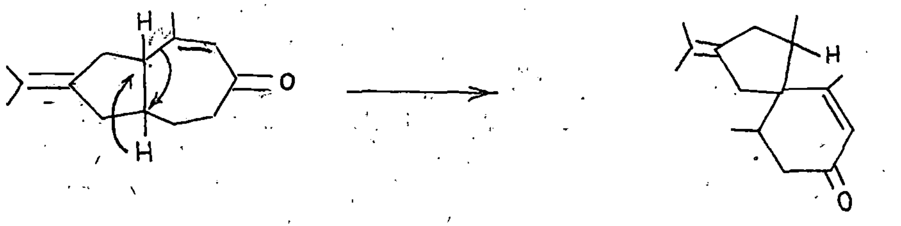


CHART IV: DEGRADATION OF *BETA*-VETIVONE

ROMANUK & HEROUT had previously noted the anomalous carbonyl absorption maximum (1724 cm^{-1}, 5.82 μ) in the infrared spectrum of dihydro-beta-vetivone, but could find no basis in this fact alone for rejecting the proposed structure (229). However, the above studies by MARSHALL et. al., led them to conclude that beta-vetivone cannot be represented by structure (XXV) or a stereoisomer thereof. This conclusion demanded a re-evaluation of the hydroazulenic structure. Since the spectral properties of the both isomers of ketone (LX) were confirmed to those of cyclohexanone derivative and the hydroxy ketone (XXXVI) displayed a cyclopentanone carbonyl band (1739 cm^{-1}, 5.77 μ) in their respective infrared spectrum, either a bicyclo (4.3.0) nonane or a spiro (4.5) decane skeleton could be considered for beta-vetivone. The wealth of chemical and physical data recorded for beta-vetivone (156,260) led MARSHALL et. al., (154) to support the latter possibility. Accordingly they postulated a simple revision in terms of the previously proposed structure by a formalization (XXV) → (XIX), in which a ring fusion hydrogen and a cyclo heptane ring bond merely exchanged places.



XXV XIX

Based on this revised structure of *beta*-vetivone, PFAU and PLATTNER'S degradation scheme could be represented as shown in the CHART V. It should be noted that the geometry of the ketone (LXI) and alcohol (LXII) still permits a symmetry plane and therefore, these compounds can exist as meso form. Thus the postulated structure revision accommodates the crucial feature of the original structure proof. The dicarboxylic acid, initially regarded as pimelic acid derivative (XXXV) (C_2H_2 = CH.CH), would accordingly, be formulated as the adipic acid derivative (LXIV), (XXXV, C_2H_2 = C.CH_2). Cyclization of this diacid would result in the cyclopentanone (LXV), rather than initially postulated cyclohexanone (XXXVII). In the revised scheme, the formation of the indenol (XXXVIII) would require that a skeletal rearrangement take place during dehydrogenation. Similar rearrangements, would be required in the conversion of *beta*-vetivone to vetivazulene (XXXIX) and the naphthol (XL).

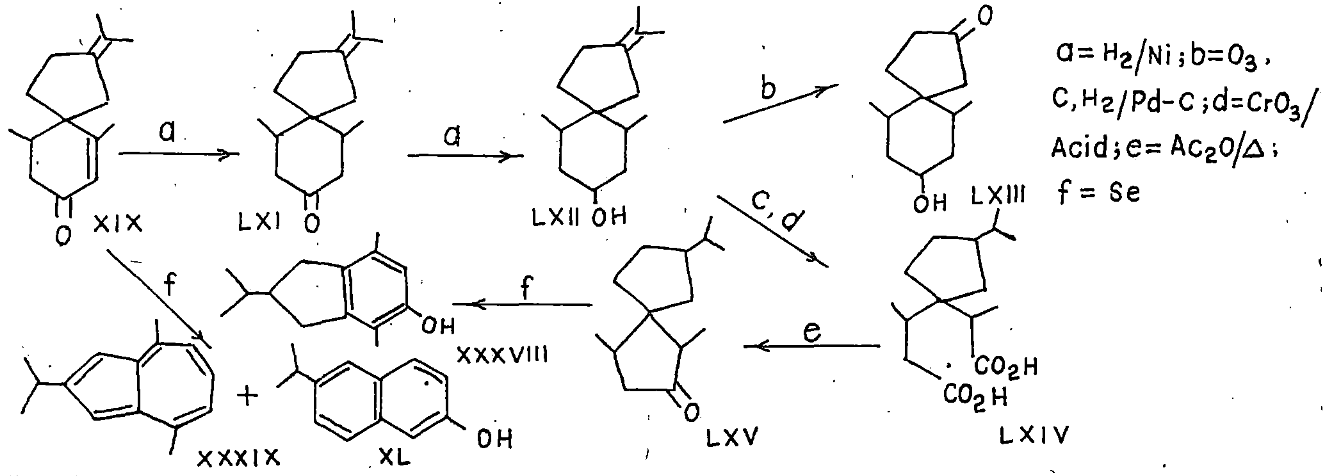
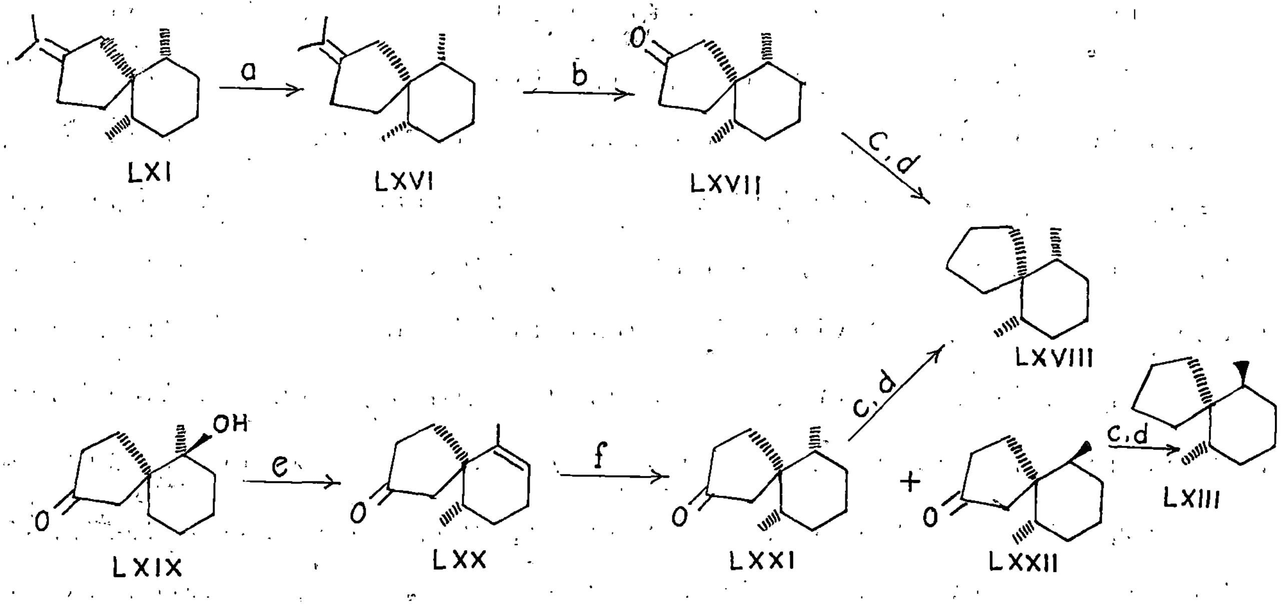


CHART V: REVISED INTERPRETATION OF *BETA*-VETIVONE DEGRADATION

The spiro decane formulation also explains the previously noted optical activity of hinesol degradation products which retain the isopropyl groupings.

Firm support for the postulated spiro (4.5) decane structure of beta-vetivone obtained from synthetic and degradative studies by MARSHALL and JOHNSON(154) which has been outlined in CHART VI. The known meso dihydro beta-vetivone (LXI) yielded the corresponding hydrocarbon (LXVI) on removal of the carbonyl group. Ozonolysis of (LXVI) afforded the cyclopentanone derivative (LXVII) which in turn gave the hydrocarbon (LXVIII) upon desulphurization of its thioketal derivative. An authentic sample of the spiro (4.5) decane (LXVIII) was secured from hydroxy ketone (LXIX) a known photochemical transformation product of trans - 4a -beta, 8-alpha-dimethyl-5,6,7,8-tetra-hydro-2(4a-H)-napththalene(140,141). Dehydration of (LXIX) gave a mixture of olefins mainly (LXX) along with a minor amount of the exocyclic double bond isomer. Hydrogenation afforded a mixture of ketones (LXXI) and (LXXII). The major component was the meso isomer (LXXI). Desulphurization of the thioketal derivative of (LXXI) afforded the same hydrocarbon (LXVIII), previously obtained from beta-vetivone. The ketones (LXVII) and (LXXI) exhibited similar, but clearly distinct spectral and chromatographic properties. The cis-arrangements of the methyl groups in both isomers follow from the meso nature of the ketone (LXI)[and therefore, ketone

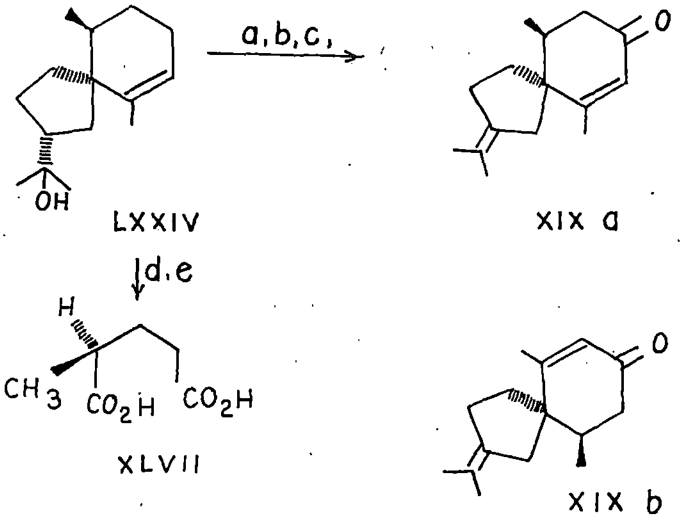
(LXVII)] and their conversion to the same hydrocarbon (LXVIII). Since ketone (LXXI) is stereochemically defined by the synthetic scheme, the relative stereochemistry of the *beta*-vetivone derived isomer must be epimeric at the spiro carbon atom, as shown in the formula (LXVII). The relative stereochemistry of *beta*-vetivone is likewise defined.



a= Wolff kishner reduction of semicarbazone derivative
b= O_3 ; C = $[^{SH}_{SH} / H^{+}$
d, Ni/EtOH
e = $SoCl_2/Py$, (f)= $H_2/Pd-C/EtOH$

CHART VI: STEREOCHEMISTRY OF *BETA*-VETIVONE

The absolute stereochemistry of *beta*-vetivone (XIX) was deduced on the basis of its chemical correlation with hinesol (LXXIV). Hinesol afforded the enantiomer (XIX,a) of natural (-) -*beta*-vetivone upon treatment with chromic anhydride in pyridine followed by dehydration (CHART VII). Hinesol must therefore, not only possess the same spiro (4.5) decane carbon skeleton as beta-vetivone, but the two compounds must also be enantiomeric at the spiro carbon and at the adjacent tertiary center. More extensive oxidation of hinesol (LXXIV) led to (+) -alpha-methyl glutaric acid (XLVII) of known absolute configuration(46). This transformation revealed the absolute stereochemistry of the tertiary methyl center in hinesol and, in view of the aforementioned correlation, in beta-vetivone as well.



$a = CrO_3\ C_5H_5N$

$b = Ac_2O$

$c = BF_3$

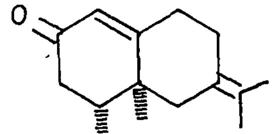
$d = O_3$

$e = HNO_3$

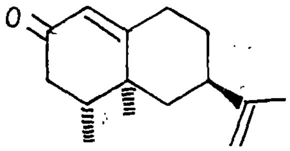
CHART VII: ABSOLUTE STEREOCHEMISTRY OF BETA-VETIVONE

Thus, the absoluteness of the present day knowledge regarding the stereo-chemical structure or the configuration of beta-vetivone is highly dependable on the correctness of the accepted stereochemical structure of hinesol. Although the studies outlined in CHART VII could not assign the orientation of the isopropyl side chain of hinesol, its stereochemistry shown in formula (LXXIV) was determined through an unambiguous total synthesis of recemic hinesol[159]. Further support in favour of this determination was provided by the degradative studies of YOSIOKA and KIMURA[304].

With the structure of beta-vetivone established it became of interest to scrutinize other vetiver-derived sesquiterpenes whose structure assignments are based on correlations with beta-vetivone. Revision of the studies on alpha-vetivone which concluded earlier the epimeric relationship of it with beta-vetivone showed alpha-vetivone (LXXV) to be a hydronaphthalene derivative and a close relative of noot-katone (LXXVI)[149].



LXXV



LXXVI

The striking differences observed for "vetivanes" derived from the isomeric vetivones and vetivazulene can thus be understood on the following basis (Fig. 4). Accordingly, the three "vetivanes" actually represent three different structural types with "vetivane" (LXXVII) corresponding to the hydrocarbon nootkatane(149) and "isovetivane" (LXXVIII) corresponding to agaro spirane(275).

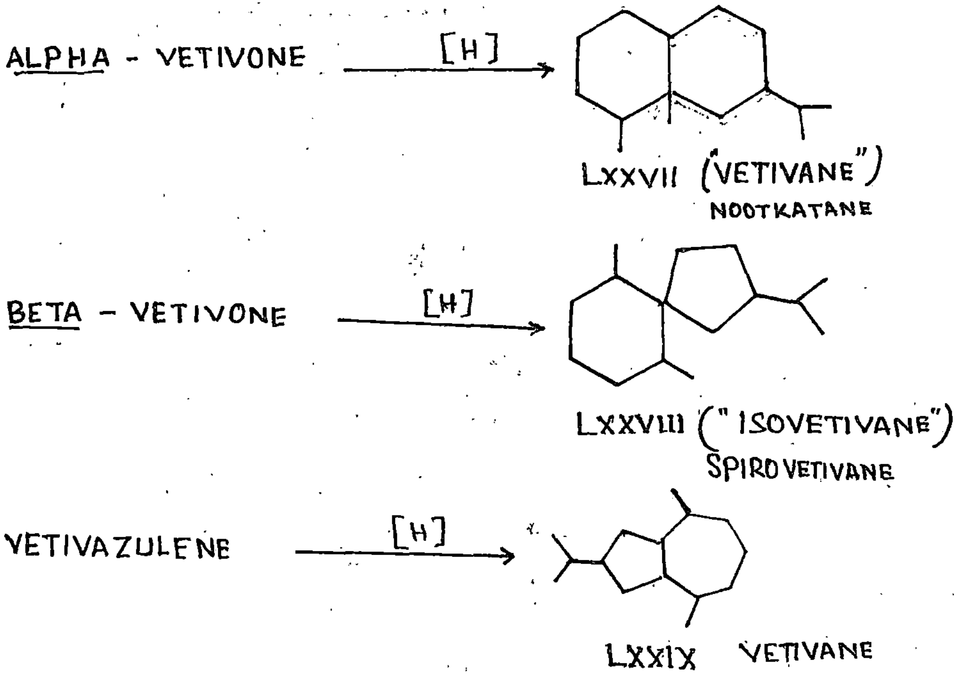
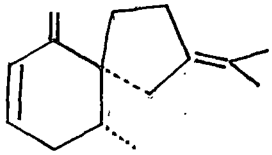


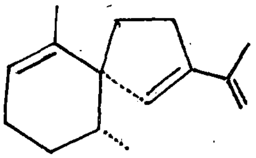
Fig. 4 : The "Vetivanes".

The name "Spiro vetivane" has been suggested for the hydrocarbon (LXXVIII) to point out its relationship to <u>beta</u>-vetivone and vetivazulene, while distinguishing it from the hydrogenation product (LXXIX) of vetivazulene(159). This latter hydrocarbon which should properly bear the name "vetivane" is the skeletal parent of another family of sesquiterpenes.

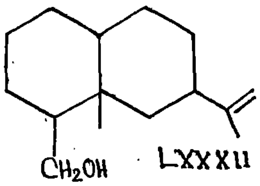
Two hydrocarbons, *beta* and *alpha*-vetispirene have been isolated by ANDERSEN in 1970 from oil of vetiver and assigned structures (LXXX) and (LXXXI) to these compounds on the basis of spectral data and their correlation with spirovetivane (LXXVIII)(5). The oil employed in these studies appears to be devoid of material corresponding to the *alpha*-isovetivenane reported by ROMANUK & HEROUT(229). Finally since bicyclo-vetivenol affords the same hydro carbon (LXXVII) as that derived from *alpha*-vetivone the structure revision from (XXIX) to (LXXXII) would appear reasonable.


LXXX

BETA VETISPIRENE


LXXXI

ALPHA VETISPIRENE


LXXXII

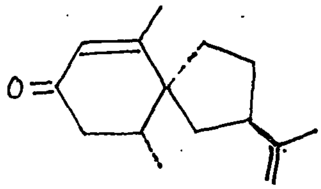
BICYCLOVETIVENOL

The list of naturally occuring spiro compounds and synthetic endeavours to these compounds is continuing to grow. The chemistry of (4.5) decane sesquiterpene (such as *beta*-vetivone, agarospirol *alpha* alaskene and acorane) has been reviewed(160). Studies on phytoalexins resulted in the isolation of some stress metabolites belonging to this group of (4.5) spiro sesquiterpenes e.g., Sola vetivone (LXXXIII)(57,86), dehydro Sola vetivone (LXXXIV)(57), lubimin (LXXXV)(178,255), oxylubimin (LXXXVI)(130)

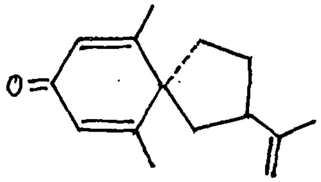
(Syn:epi-oxylubimin ?:)(131), 2-*epi*- and 15-dihydro-2-*epi*-lubimin (LXXXVII and LXXXVIII respectively)(256). Particular mention should be made of cyclo dehydro isolubimin (LXXXIX), isolated from potato tubers, which is essentially a tricyclic spiro compound(58).

Spiro compounds of marine origin are of current interest. Axisonitrile-3 (XXI), axisothiocyanate-3 (XXII), isolated from the marine sponge *Axinella Cannabina*(72), not only comprise a new class of spiro vetivane sesquiterpenes, but also represent the first example of naturally occuring isoprenoids having an isonitrile or isothiocyanate function.

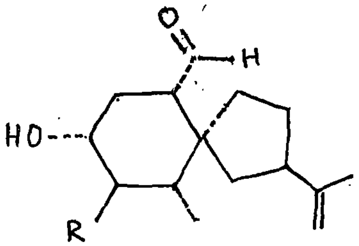
Axamide-3, (XXIII) isolated from the same source i.e., from *Axinella Cannabina*(72), is the third member of this class. The fourth member gleenol (XXIV) has been isolated from *Picea glehnii*(144).



LXXXIII

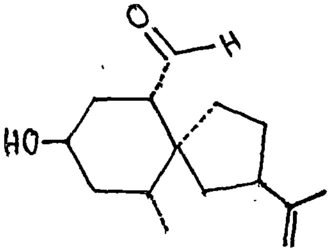


LXXXIV

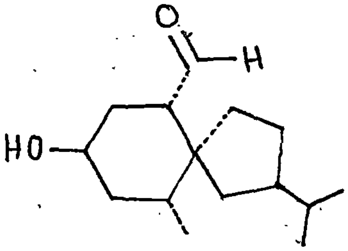


R=H, LXXXV

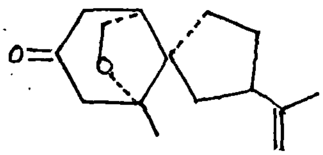
R=OH, LXXXVI



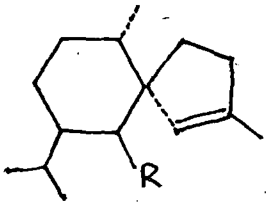
LXXXVII

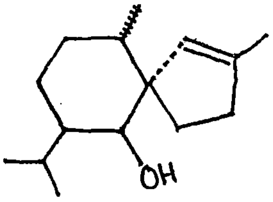


LXXXVIII



LXXXIX





XXI R = NC, AXISONITRILE - 3

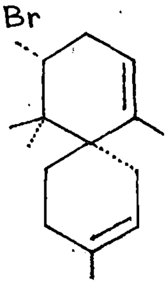
XXII R = NCS, AXISO THIOCYANATE - 3

XXIII R = NHCHO, AXAMIDE - 3

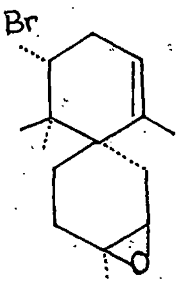
XXIV (GLEENOL)

Fig. 5 : RECENTLY ISOLATED (4:5) SPIRO SESQUITERPENES

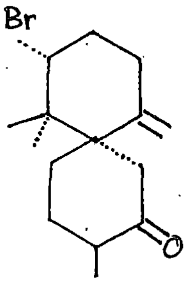
A structurally related group of halogenated spiro (5.5) undecane sesquiterpenes occurs in various species of the algae of genus *Laurencia* e.g., 10-Bromo-*alpha*-Chamigrene (XC)(112). Recently isolated(263) halogenated chamigrene type sesquiterpenoids from the red algae of the genus *Laurencia* are the following: (XC - XCIII).



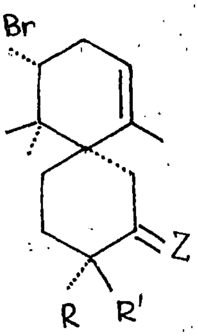
XC



XCI



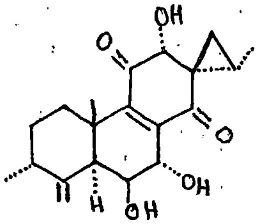
XCII



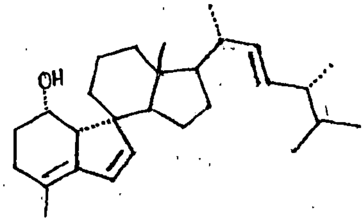
XCIII

R, R', Z = Me, OH, (α-Cl, β-H)
= H, Me, O
= Me, Cl, (α-Br, β-H)

The spiro cyclopropyl cyclo hexene dione diterpene (XCV) has been isolated from the leaves of *coleus somaliensis*(183). Other related systems have also been isolated(11). Several toxisterols$_2$ have been assigned structures similar to toxisterol$_2$-A (XCVI)(13).



XCV



XCVI

SPIRO ANNULATION REACTIONS : The development of Synthetic strategies for the cyclic ring system with good control over the stereo chemistry, continues to be a challenge to organic synthesis. Among the spiro cyclic natural products the spiro (4.5) decane system has been studied more because of the many examples in nature and interesting elements of stereochemistry. The reaction sequences that lead to the spiro cyclic structure may be defined as spiro annulation process. The term annulation,** derived from the Latin word annulatus (ringed) means "the formation of rings". In organic chemistry this term is used to describe the process of building a ring on to a pre-existing system, cyclic or non-cyclic. The added ring may be of any size, although five and six-membered rings are most commonly formed. This broad definition includes, in a general sense, many reactions that are not normally thought of as annulation reactions, such as Diels-Alder reactions, acid catalyzed polycolefinic cyclizations, photo-chemical, radical and thermal cyclizations etc. Accordingly spiro annulation means the process involving the formation of a ring onto a pre-existing cyclic system leading to a spiro skeleton.(127)

Cyclic structures which incorporate conjoined rings can be regarded as members of a progression which begins (in a formal

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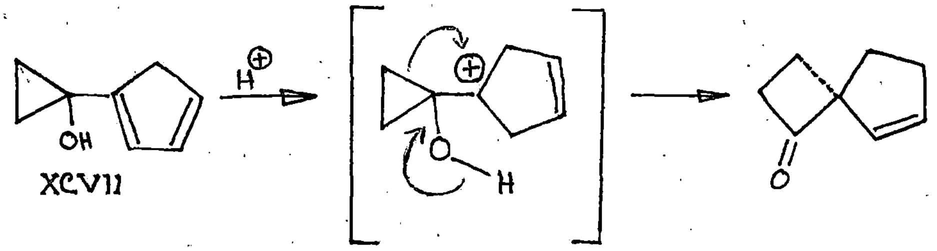
** There has been some discrepancy in the spelling of this word with two forms, annulation and annelation, being used, the latter some what more often than the former. However annulation is preferred by us. (Cf. Webster's Third New International Dictionary Unabridged.)

sense, the family of catenanes i.e. conjoined rings with no share atoms would be the first member of this series) with spiro cyclic systems (connected rings with one shared carbon) and extend through fused (two shared carbon) to bridged frames, incorporating three or more common atoms. Although a large number of methods of broad applicability exist for construction of fused and bridged ring skeletons, (126) relatively few general strategies are available for the elaboration of spiro cyclic structures. Recently considerable effort has been made to repair this deficiency and some developments along these lines have been published in three reviews (137,138 & 139). The first one (137) elaborates the intramolecular alkylation route to carbocyclic spiro compounds, the second (138) deals with the synthesis of spiro compounds via rearrangement routes and the discussions in the third review (139) has been concentrated towards the different types of cycloaddition reactions which are formally occuring in the spiro-annulation routes. The efforts of COX (56) and of HIROI (107) to accumulate the synthetic strategies on the preperation of carbocyclic spiro compounds also deserve mention. Here an attempt has been made to compliment the above efforts. The spiro annulation procedures, discovered so far (upto Dec. 1981) have been reviewed and divided into ten sections namely (i) Pinacol rearrangement route, (ii) Rearrangement of epoxy ketone, (iii) Cation olefin cyclization route, (iv) Thermolysis of olefin

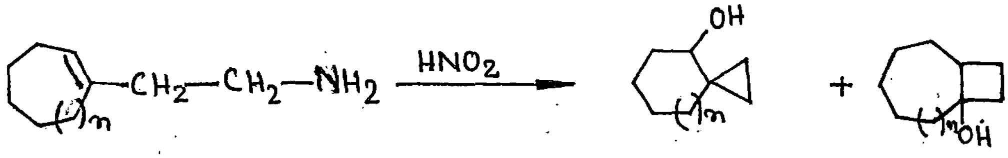
(v) Robinson's annulation and double Michael reaction route, (vi) Conversion of carbonyl carbon atom into a spiro center, (vii) Cyclo addition route, (viii) Preparation of spirane using organometallic reagents, (ix) Miscellaneous spiro annulation route, and (x) $Ar_{1-5}^{(-)}$ participation route.

PINACOL REARRANGEMENT ROUTE: WASSERMAN and CLAGETT(281) in 1966 prepared spiro (3.4) nona-5-ene-1-one (XCVIII) using ring expansion of cyclopentadienyl cyclopropanol (XCVII) e.g.,



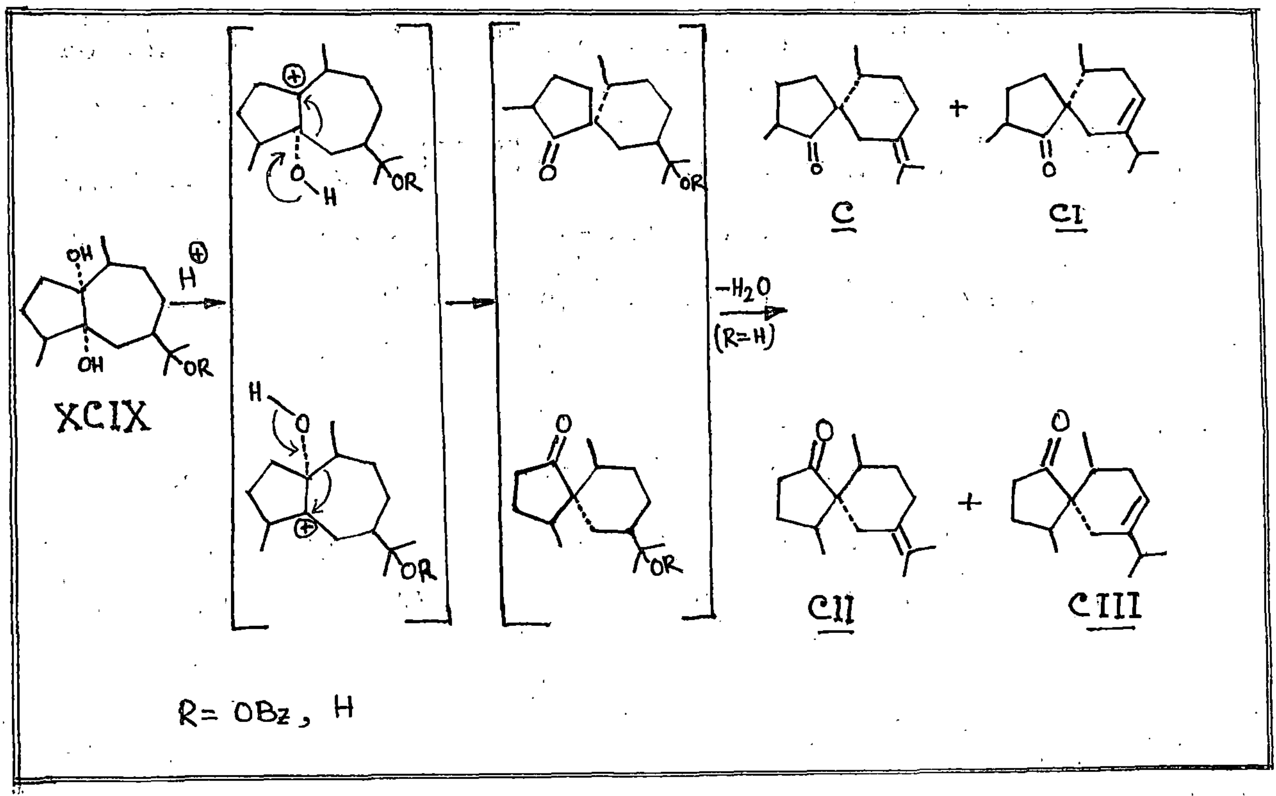
XCVII XCVIII

Nitrous acid deamination of cyclohepten-1-yl, cyclo octen-1-yl and cyclo-nonen-1-yl ethyl amines has been shown to give mixtures of spiro (2.6) nonan-4-ol, spiro (2.7) octan-4-ol, and spiro (2.8) undecane-4-ol respectively, together with the corresponding cyclobutanols(97).

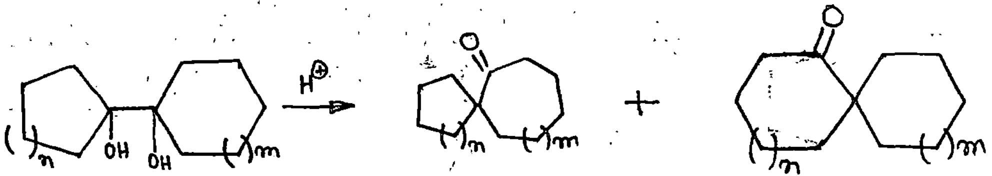


n = 1,2,3

Pinacol rearrangement of *cis*-dihydroxy guaiol (XCIX, R=H) and its mono benzoate (XCIX, R=OBz) has been shown to afford the (4.5) spiro decanes (C – CIII) via ring contraction (190), e.g.,

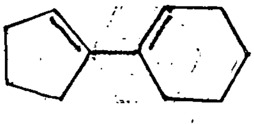


MUNDY *et. al.*, (187,188), examined the condition for the pinacol rearrangement route to spiro-annulations and found that on treatment with 25-92% sulphuric acid at 0°C the diol (CIV, n = 1, m = 1) gave mainly to spiro ketones (CV) and (CVI) resulting from ring enlargement rather than dehydration, with no secondary rearrangement of (CV) to (CVI). However, at 97°C (CV) gave (CVI) at all acid concentrations



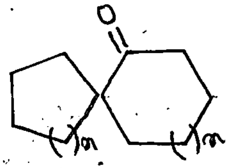
CIV CV CVI

The formation of the initial carbocation has been shown to be the major factor in determining the product composition. The order of cation formation is $C_7 > C_5 > C_6$ and hence in (CIV, n = 1, m = 1) formation of a C_5 carbocation is favoured over C_6 giving the spirenone (CV, n=m=1) as the major product(188). On carrying out the reaction at reflux temperature, the products consisted of the expected spiranones, but the diene (CVII) resulting from dehydration, made up a large portion of the product(242,243).



CVII

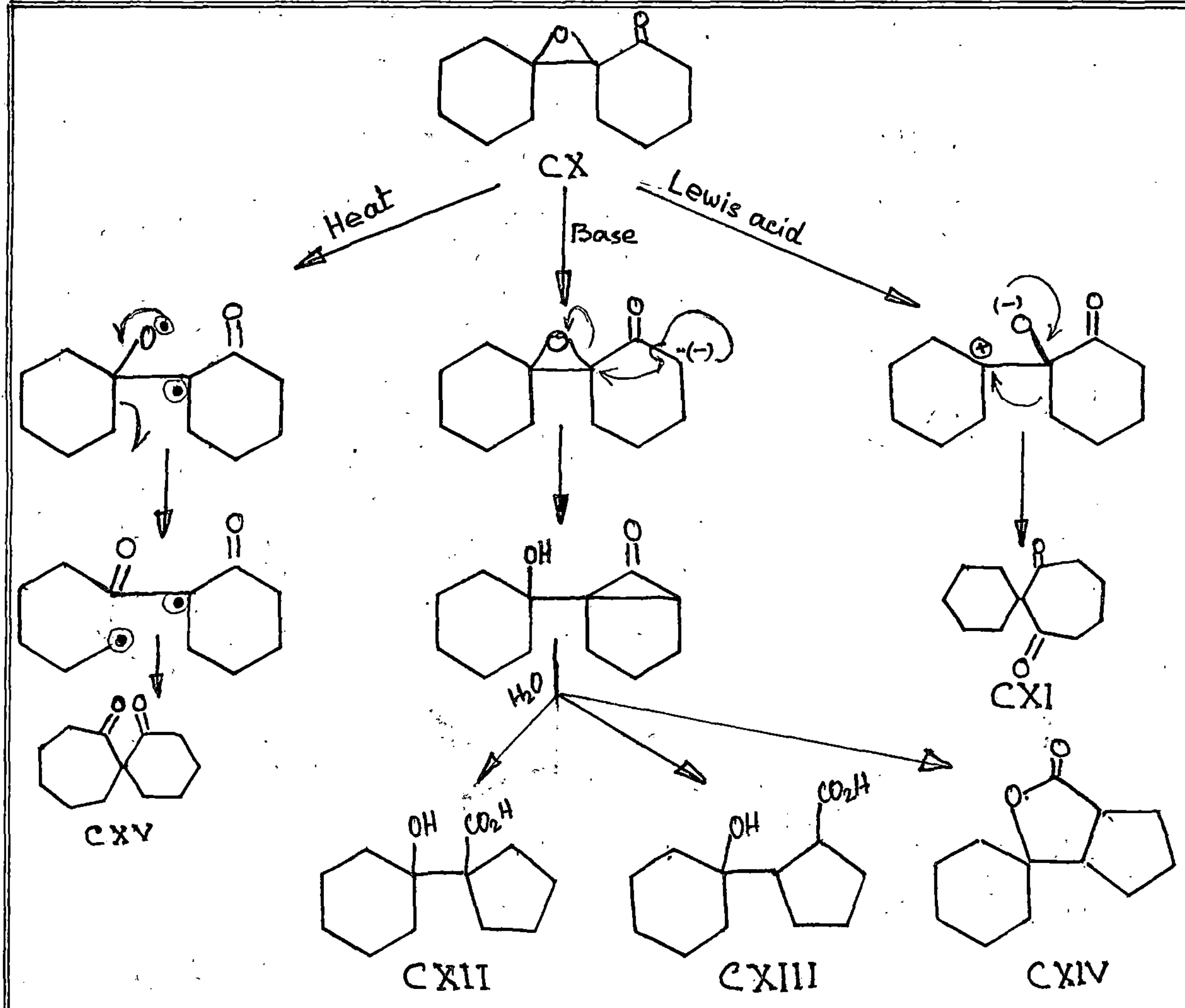
The application of gas phase pinacol rearrangement to spiro ketone synthesis has been reported by ALBEROLA, ESTEBAN, MARINAS and PEREZ-OSSORIO(1) who converted 1,1'-dihydroxy-1,1' dicyclo pentane and dicyclo hexane in the presence of gelatenous aluminium phosphate catalyst to the spiro ketones (CVIII) and (CIX) together with small amount of the conjugated diolefin formed by dehydration



CVIII, n = 1
CIX, n = 2

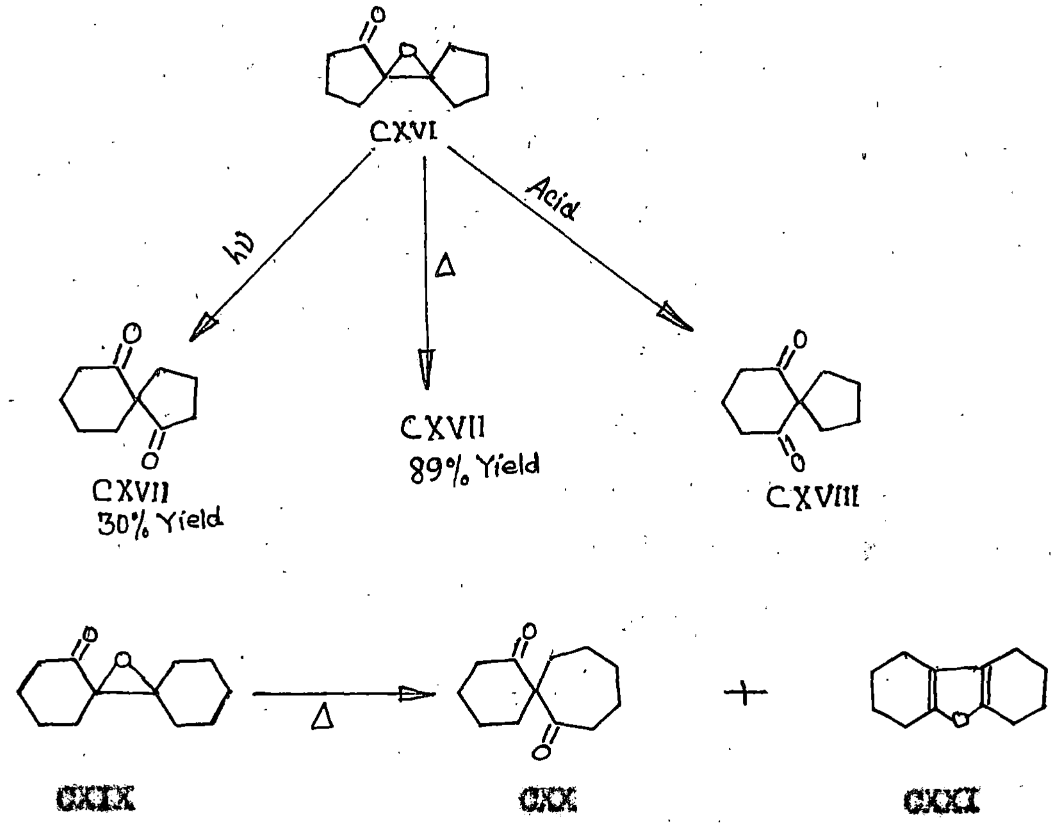
Optimal condition of temperature and W/F (g.catalyst/mol pinacol per hour) were 550° and 60 for (CVIII) and 350° and 120 for (CIX). Under these conditions the respective yields were 60% and 85% and 73% and 92% conversion of the starting material.

REARRANGEMENT OF EPOXY KETONE: The rearrangement of 1,1'-bicycloalkyl-2ones are interesting. Three different rearrangements of the epoxy ketone (CX) have been shown to occur under acidic, basic and thermal conditions(99). The acid catalyzed reaction to (CXI) presumably proceeds via a Wagner-Meerwein heterolytic route and the mechanism of base catalyzed decomposition of other cyclic *alpha*, *beta* epoxy ketones to *gamma* hydroxy acids and their lactones with concurrent ring contraction may follow Favorskii rearrangement as has been suggested for similar type of compounds by HOUSE and GILMORE (111). The isomerization to (CXV) on heating has been suggested to involve a radical reaction e.g.,

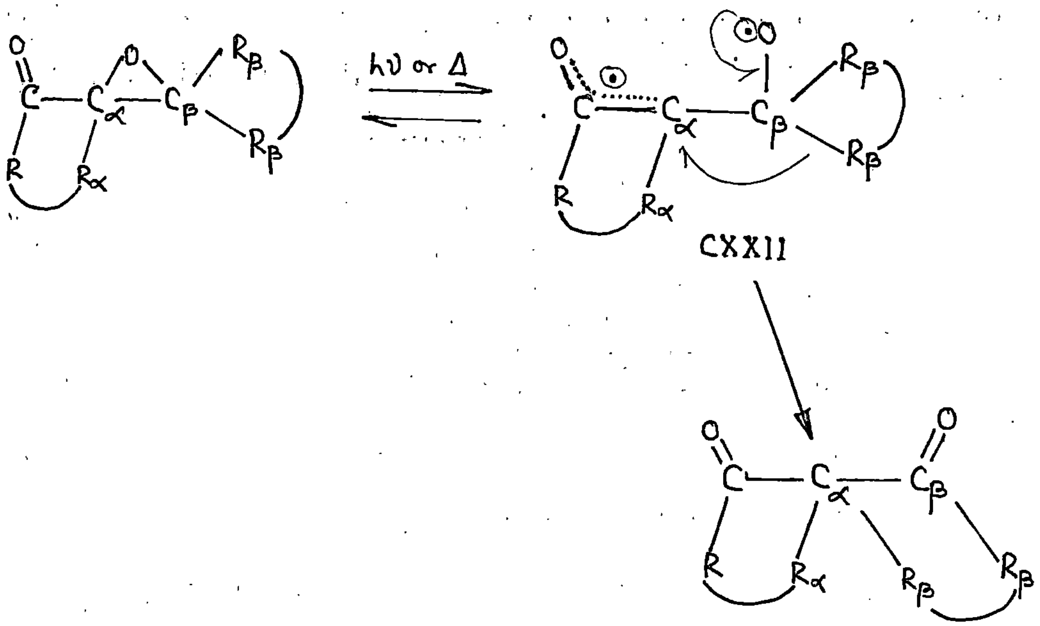


In an independant study (288), 2-cyclopentylidene cyclopentanone oxide (CXVI) and 2-cyclohexylidene cyclohexanone oxide (CXIX) were isomerized thermally and photochemically via

1,2-alkyl shift to spiro (4.5)-deca-1,6-dione (CXVII) and to spiro (5,6)-dodecane-1,7-dione (CXX) respectively. Acid catalyzed isomerization of (CXVI) was shown to proceed via 1,2 acyl shift to yield spiro (4.5) decane-6,10-dione (CXVIII). Thermolysis of (CXIX) also gave 1,2,3,4,6,7,8,9, Octahydro dibenzo furan in low yield.

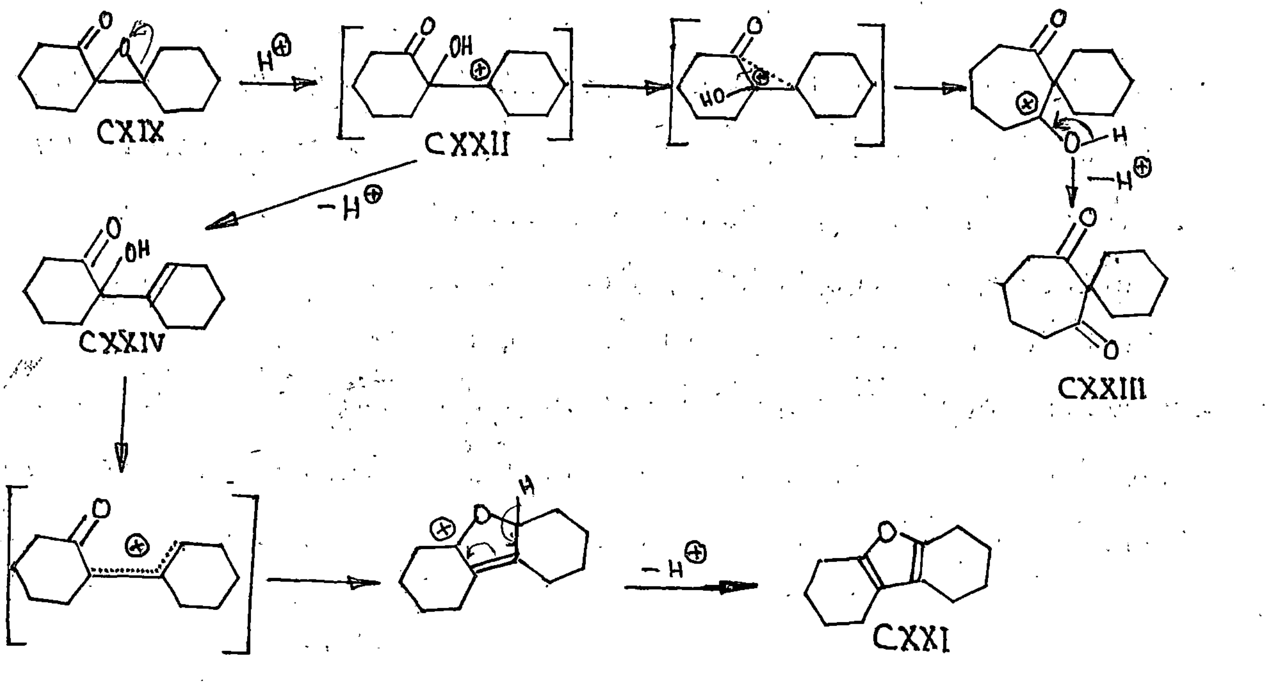


The thermolysis and photolysis reactions have been shown to proceed via the homolysis of the C_α— O bond as shown below:

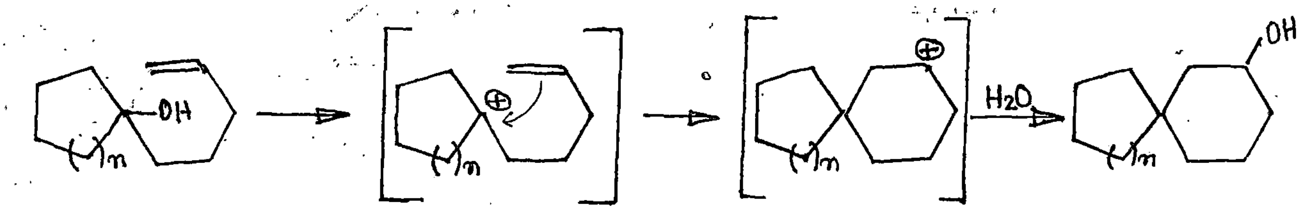


The carbonyl group can stabilize the radical charge at C_α as shown in structure (CXXII). Concurrently or at latter stage R_β migrates to C_α forming a carbonyl at C_β. However, the quantum yield data on the photolysis of optically active (CXVI)(297) exclude one common diradical intermediate of the type (CXXII) for three reaction paths involved (Photo isomerization and photo rearrangement to each isomer of the new product) in both the singlet and the triplet reactions. The quantum yield data require the rate of rearrangement is greater than the rate of rotation around the $C_\alpha - C_\beta$ bond in (CXXII) and that the rate difference is greater in singlet generated (CXXII) than in the triplet analog. Another possible explanation was that the $C_\alpha - C_\beta$ bond is cleaved followed by rotation which leads to recemization of (CXVI). In the formation of optically active (CXVII) it is R_β which is <u>cis</u> to the acyl group, migrates fastest in both singlet and triplet reaction.

The acid catalyzed reaction has been explained by a 1,2-acyl shift. Protonation of the epoxide (CXIX) should cause the $C_\beta - O$ bond to cleave, forming the hydroxy ketone (CXXII). The acyl migration in (CXXII) results in the formation of the diketone (CXXIII). However, if a proton is lost from (CXXII) to yield (CXXIV) followed by loss of water then 1,2,3,4,6,7,8,9-octa hydrodibenzofuran will be formed, e.g.,

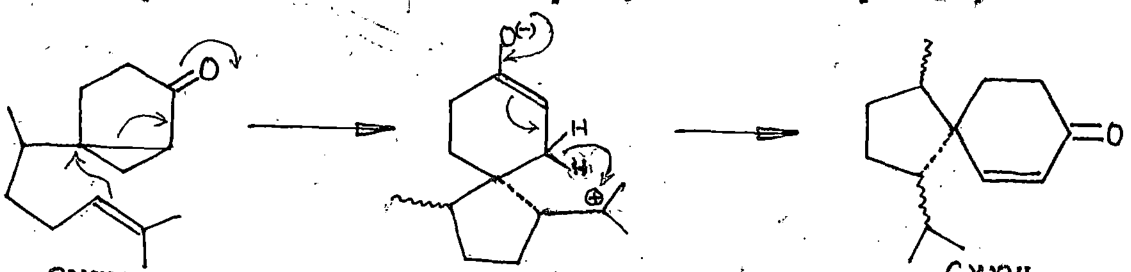


CATION OLEFIN CYCLIZATION ROUTE: The cation-olefin cyclization leading to spiro annulation has been reported by NOJIMA *et. al.* (200) who obtained spiro (5.5) undecan-2 ol and spiro (4.5) decane-7-ol in good yields by acetolysis of 1-pent-4-enyl cyclohexanol and 1-pent-4-enyl cyclopentanol respectively in the presence of p-toluenesulphonic acid or perchloric acid e.g.,



n = 1,2

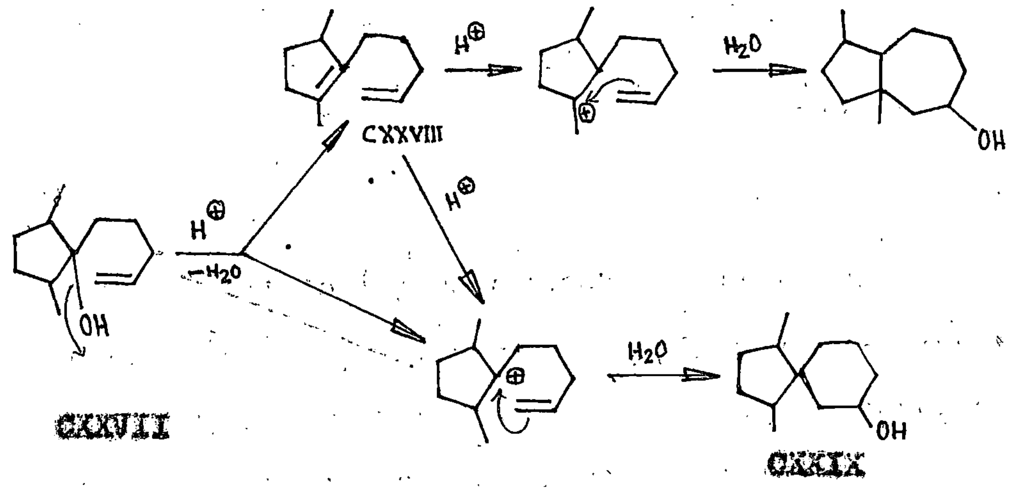
The cation-olefin cyclization route to spiro (4.5) decane system has been observed by COREY and BALANSON during their synthesis of (±) cedrene and (±) cedrol using a synchronous double annulation process (53). Thus while the diastereoisomers of the cyclopropyl ketone (CXXV) on treatment with acetyl methane sulphonate in methylene chloride gave (±) cerdrone and (±) epicedrone, their reaction with lewis acids in aprotic media gave mainly the spiro compound (CXXVI) through cation-olefin cyclization reaction followed by a rather uncommon 1,4 hydride shift, e.g.,



CXXV

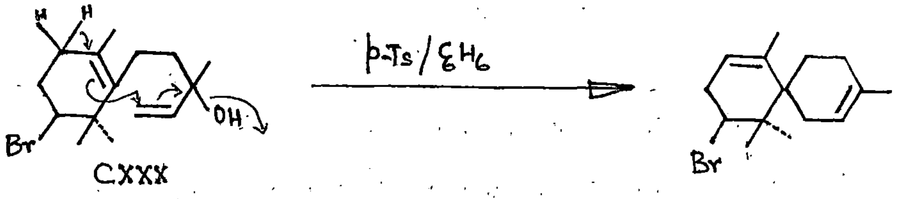
CXXVI

The acid catalyzed cyclization of 2,5-dimethyl-1-(4-pentenyl)-1-cyclopentanol (CXXVII) or -1-cyclopentene (CXXVIII) to the stereo isomeric spiro decanes (CXXIX) has been reported by WOLF *et. al.*,(291) and is believed to proceed as follows:

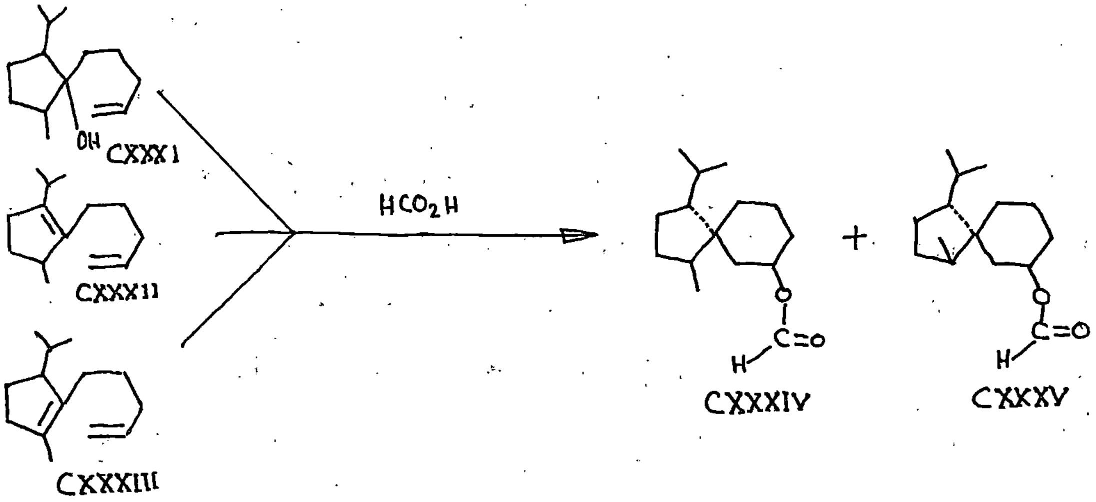


Latter, this acid catalyzed spiro annulation route has successfully been exploited in the synthesis of acorenone -B(292).

In a biometric approach to synthesize *Laurencia metabolites*(295) the synthesis of 10-bromo-*alpha*-chamigrene this acid catalyzed ene-reaction has been used. The annulation seems to be facilitated by the presence of allylic hydroxyl group in the alkyl side chain of the reacting species (CXXX).

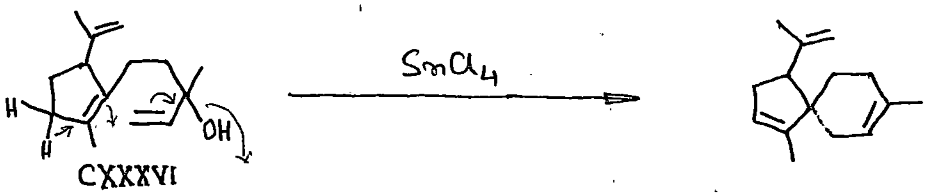


The formic-acid catalyzed spiro annulation resulting from cation-ene cyclization route has been reported by WOLF et. al.(293) who prepared the stereo isomeric (4.5) spiro decane-7-formylate (CXXXIV and CXXXV) from the cyclopentanol (CXXXI) or the olefines (CXXXII and CXXXIII) as follows:



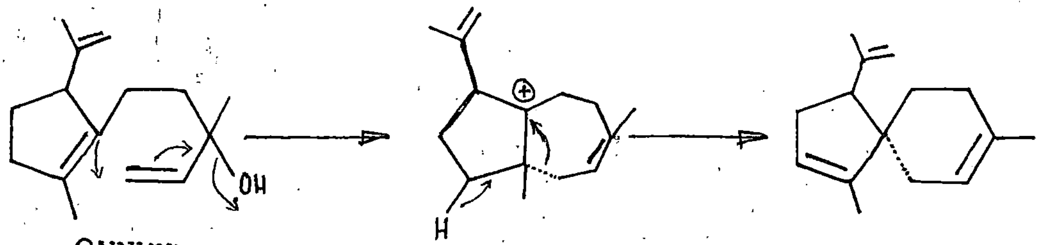
Later the process has been extended to the synthesis of (±) acorenone - B and (±) 4-epi-acorenone(294).

In synthesizing beta-acoratriene NAEGELI et. al.(192) used stannic chloride as the acid catalyst in cyclizing the alcohol (CXXXVI) through cation-ene spiro annulation route, e.g.,



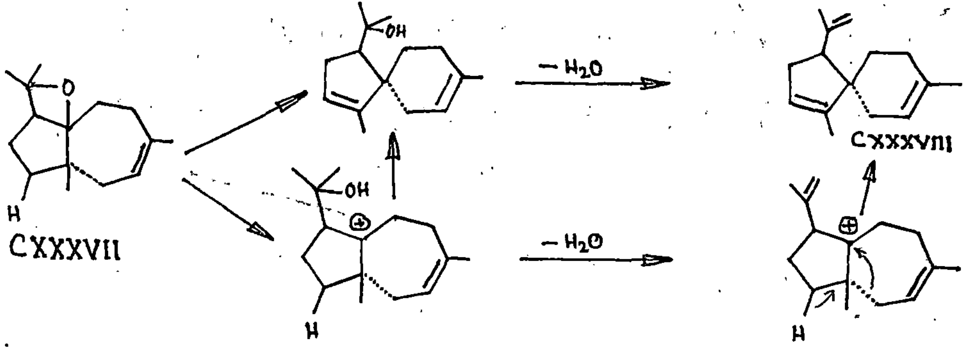
CXXXVI

The stereo selectivity of this cyclization is remarkable in that only the __beta__-isomer of acoratriene could be detected. This observation contrasts the results of biologically inspired studies of the cyclization of __gamma__-bisabolene where only the __alpha__ isomers were found to be formed (4). The intermediacy of a daucane structure in the cyclization of (CXXXVI) ~~e.g.~~, can account for this difference in behaviour. e.g.



CXXXVI

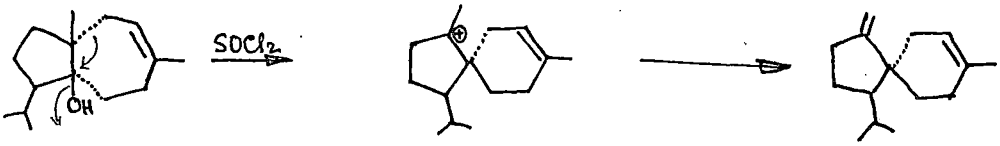
The daucane type sesquiterpene, carotol ether (CXXXVII) has been shown to undergo ring contraction on treatment with Lithium aluminium hydride-aluminium chloride as catalyst affording the __beta__-acoratriene (CXXXVIII) (67). The rearrangement may involve synchronous or stepwise hydrogen ion removal, methylene migration and C-O bond breaking, e.g.,



CXXXVII

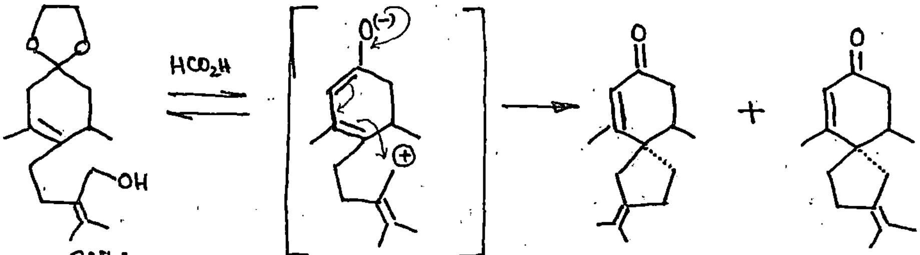
CXXXVIII

The rearrangement of carotol (CXXXIX) to the acoradiene (CXL) on treatment with thionyl chloride-the reaction which has been studied to determine the absolute configuration of accoradiene(305) may be taken as another example of the rearrangement of daucane skeleton to spiro (4.5) decane system involving Wagner-Meerwein 1,2 shift, e.g.,



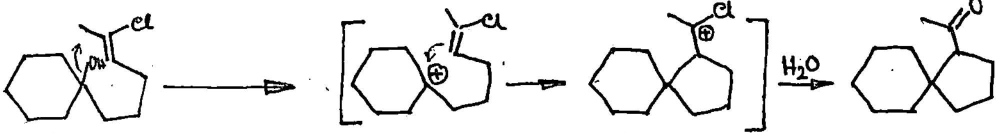
CXXXIX CXL

Intramolecular cationic cyclization of 3,5-dimethyl-4-(4-hydroxy-3-isopropylidene butyl) cyclo-hex-3-ene-1-one ethylene ketal (CXLI) has been shown to lead to the formation of *beta* vetivone, and 10 *epi-beta* vetivone(176).



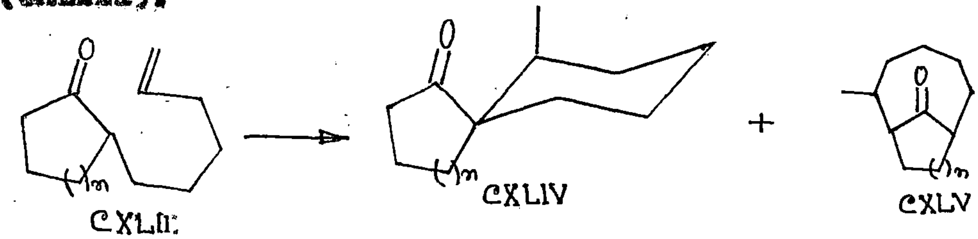
CXLI

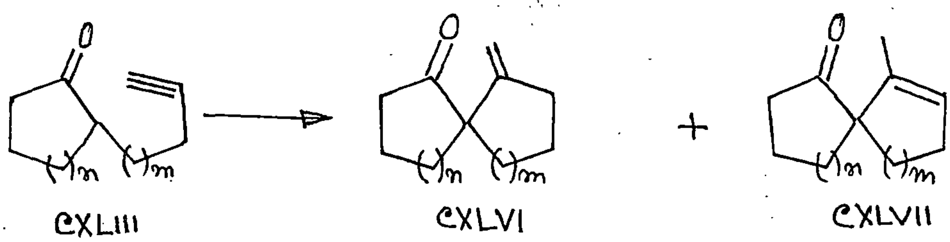
A beautiful cation initiated cyclization route to spiro (4.5) decane skeleton has been reported by LANSBURY(148) e.g.,



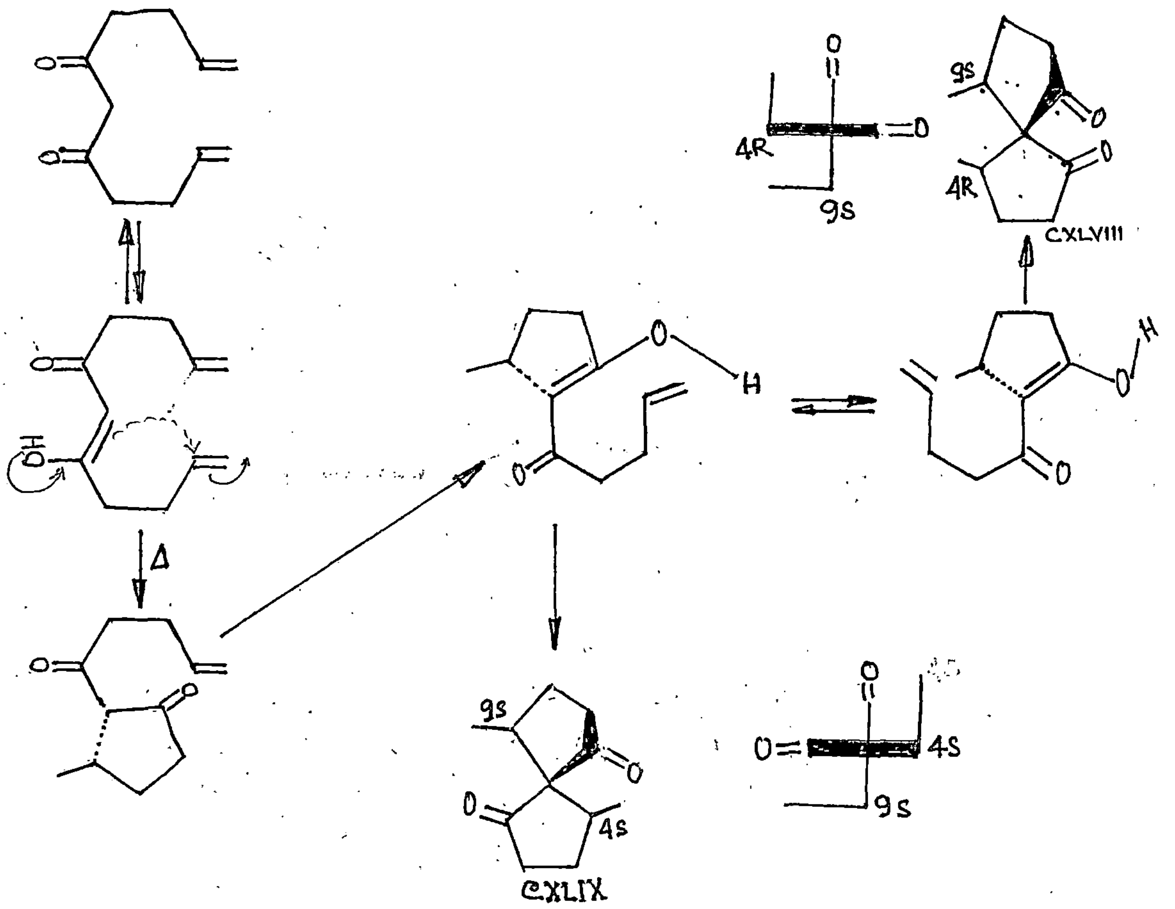
Unfortunately the stereo chemical aspects of such cyclizations have not yet been examined.

THERMOLYSIS OF OLEFIN: The thermolysis of cyclic ketones containing an unsaturated alkyl chain in the *alpha*-position has been studied by CONIA *et. al.*(163). Cycloalkanones (CXLII, n = 1,2) were thermally cyclized to the respective spiro alkanones (CXLIV, n = 1,2) and bicyclo alkanones (CXLV, n=1,2). Similarly a mixture of methylene spiro alkanones (CXLVI, n=1,2; m = 2,3) and methyl spiro alkanones (CXLVII, n = 1,2; m = 2,3) was obtained from the respective *alpha*-alkynyl cyclo alkanes (CXLIII).

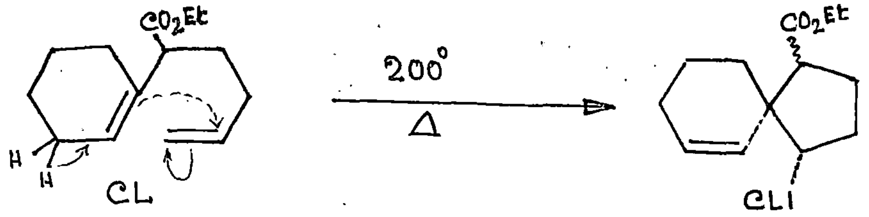




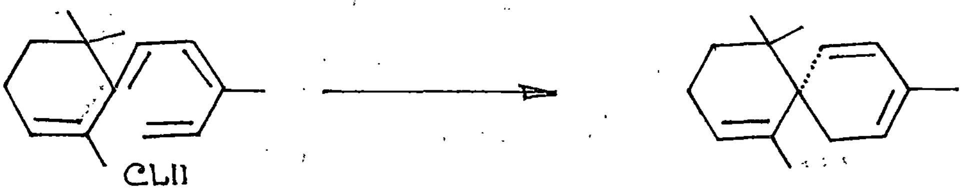
DROUIN, LEYENDECKER and CONIA (76) on their way to explore the thermal isomerization of some dienones and dienediones as a route to bi and polycyclic compounds prepared two spiro (4.4) nonane-1,6-diones (CXLVIII) and (CXLIX). The reaction path of their formation is depicted below:



The synthesis of beta acorenol and beta-acoradiene by OPPOLZER(206) involves thermal cyclization of ethyl-2-(1-cyclohexane-1-yl) 5-hexenoate (CL) to diastereomeric mixture of the spiro decane (CLI) e.g.,

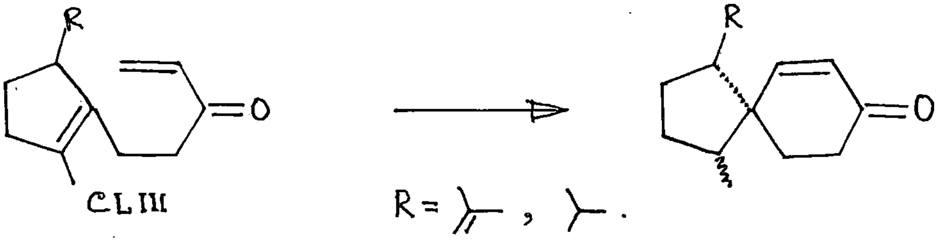


Later this intramolecular ene reaction has been applied in the synthesis of racemic acorenone-B(207) and in the synthesis of other members of the acorane family(208). Synthesis of racemic-alpha-chamigrene by FRATER[(83)] involved this thermal ene reaction of the dehydration product (CLII) of beta ionol as the spiro annulation route.

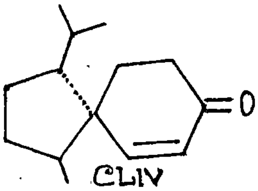


CLII

The spiro (4.5) decanone synthesis by HAEGELI[(191)] involved in the cyclization of the unsaturated ketone (CLIII) through ene type reaction e.g.,



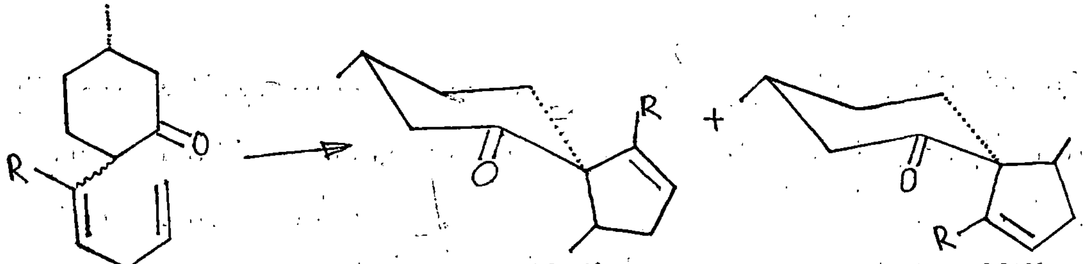
CLIII



CLIV

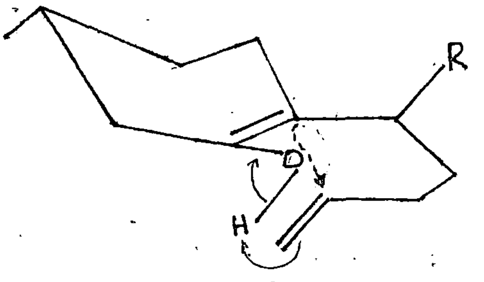
The synthetic endeavour also led to a missing spiro inverted acorenone (CLIV) which is yet to be found in nature.

Enones of the type (CLV) has been shown by CONIA[(60)] to undergo a thermal cyclization at temperature above 300° to give the spiro (4.5) decanones (CLVI) and (CLVII)

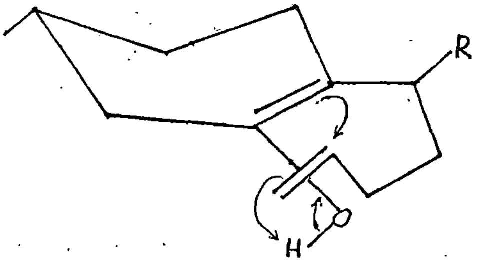


CLV CLVI CLVII

In the case where R = methyl, (CLVI) predominated slightly indicating a slight preference for the mode of cyclization depicted by (CLVIII) vs (CLIX)

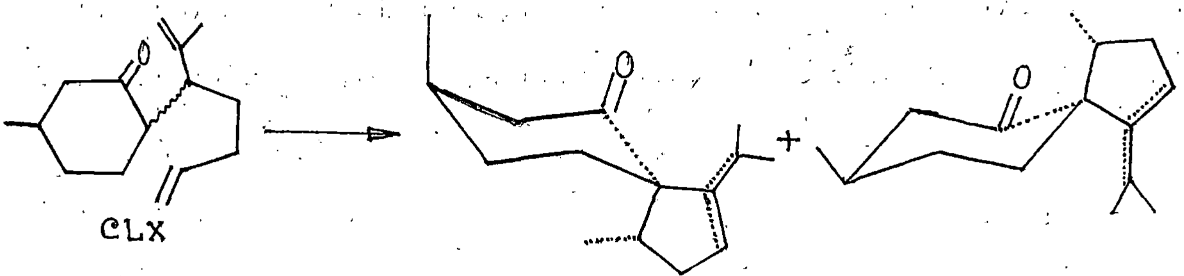


CLVIII



CLIX

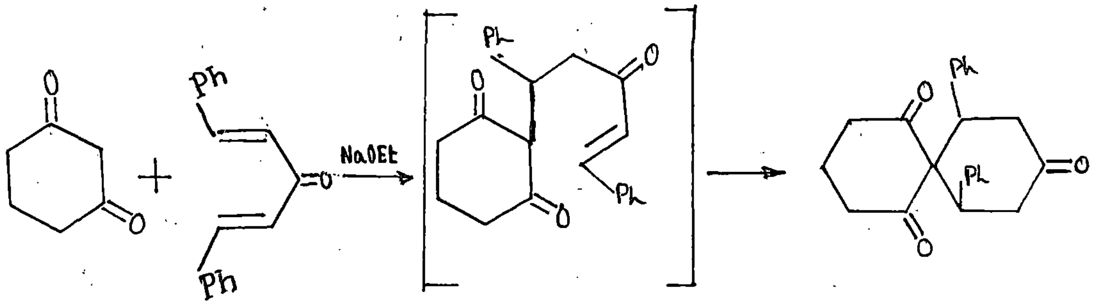
The synthesis of acorone by CONIA, DROUET and GORE(51) has been reported to involve the thermal spiro annulation in the crucial step where the dienone (CLX) yielded a mixture of spiro (4.5) decanones (CLXI) and (CLXII) upon thermolysis at 220° for 36 hours e.g.,



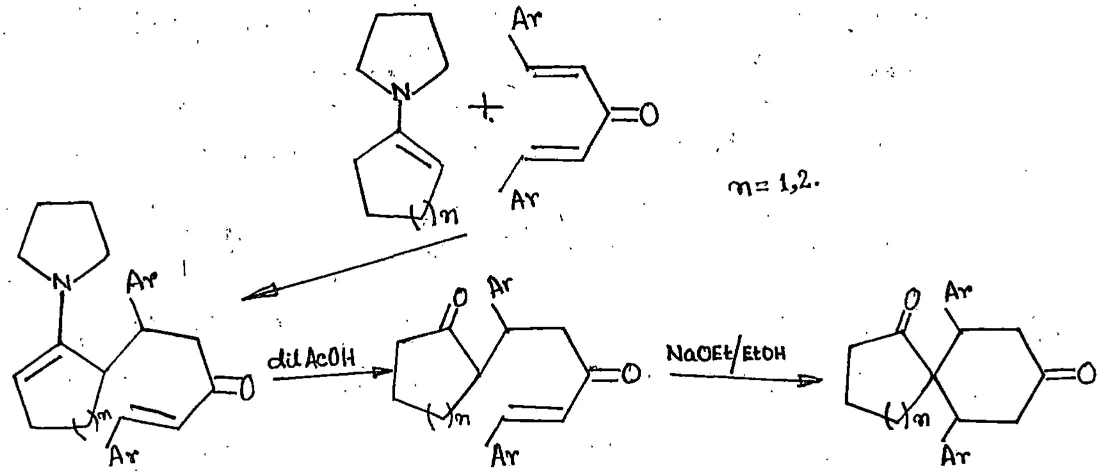
CLX CLXI CLXII

Interestingly, the desmethyl analog of the dienone (CLX) gave the desmethyl analog of enone (CLXI) containing only the exocyclic (isopropylidene) double bond isomer.

ROBINSON ANNULATION & DOUBLE MICHAEL ADDITION ROUTE: The double Michael reaction between a cyclo alkane 1,3-dione and an 1,4 diene-3-one leading to a spirane has been demonstrated by WYNBERG et al (69,70). Essentially the process involves normal Michael addition of the dienone to the activated methylene carbon atom of cyclo alka-1,3-dione followed by internal Michael addition of the alpha-beta unsaturated ketonic side chain on the same carbon atom e.g.,

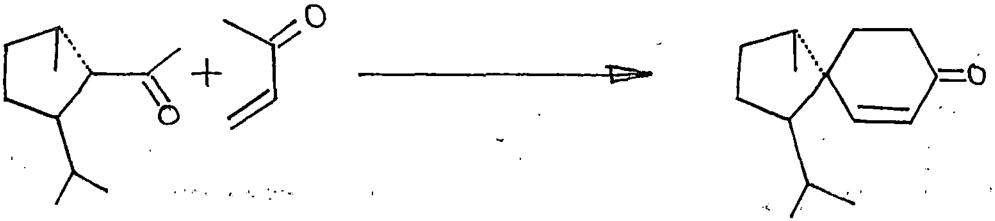


This method involving only one step in forming the spiro compound from the easily available chemicals is of potential importance as a synthetic tool. But when applied to monoketones the yields are very low and hence modification of the process became essential. Great improvement in yield was achieved by carrying out the stepwise addition of 1,4-diene-3-one using the pyrrolidine enamine of the ketone in the primary stage in place of the ketone itself. The Stork addition of the enamine to the dienone gave after hydrolysis the mono addition product which could be cyclized easily to the wanted spirane(6,71) e.g.,



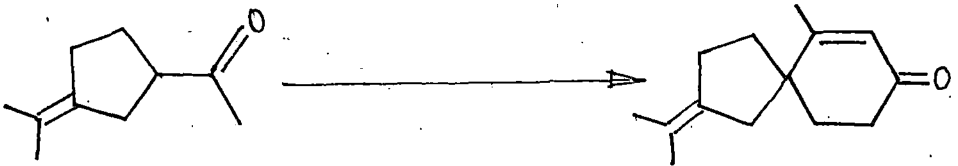
However, this reaction sequence accompanies with the possibility of the cyclization of the mono addition product on the other side of the carbonyl group in spite of on the substituted carbon atom, leading to the bridged compound, although the possibility is of only theoretical value and remains for future endeavour to be experimentally verified.

The application of Robinson's annulation reaction route to spiranes to the synthesis of (-) acorenone and (-) acorenone-B has been shown by PESARO and BACHMANN(215) who prepared the spiro enone (CLXIV) stereoselectively from the aldehyde (CLXIII) by treating it with methyl vinyl ketone in the presence of potassium hydroxide in dioxane.



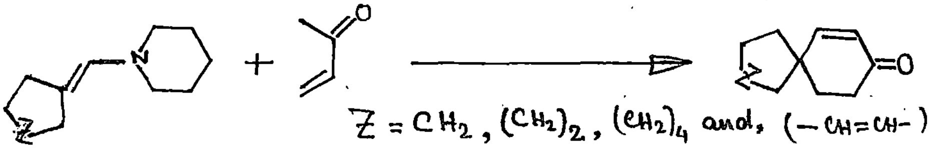
CLXIII CLXIV

Using the same reaction sequence, PESARO *et al.*(29) prepared the (4.5) spiro decenone (CLXVI) from the ketone (CLXV) in his *beta*-vetivone synthesis e.g.,



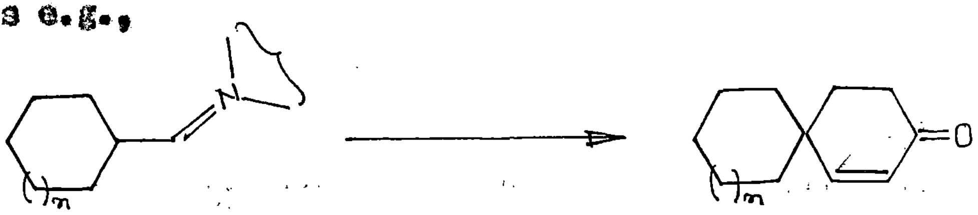
CLXV CLXVI

NATALE and HUTCHINS(196) converted the cyclic 1-carboxaldehyde enamines to the corresponding spiro cyclic compounds by heating the enamine with methyl vinyl ketone in the presence of acetic acid buffered with sodium acetate e.g.,



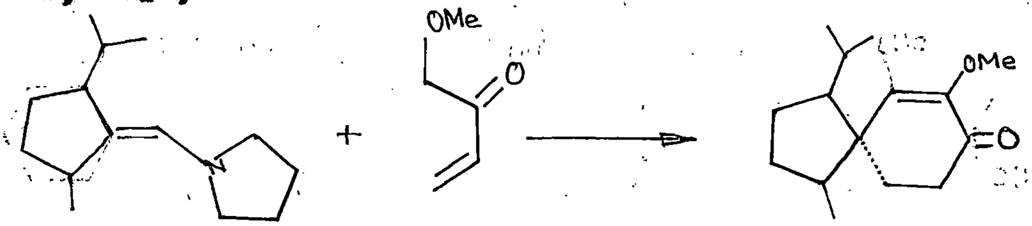
$Z = CH_2$, $(CH_2)_2$, $(CH_2)_4$ and, $(-CH=CH-)$.

A general and efficient approach to spiro cyclohexadienones using cycloalkane carboxaldehyde enamine and a Michael acceptor has been reported by KANE (129) who used the piperidine enamines of cycloalkane carboxaldehyde (CLXVII) and made it to react with methyl vinyl ketone to give the respective spiro ketones e.g.,



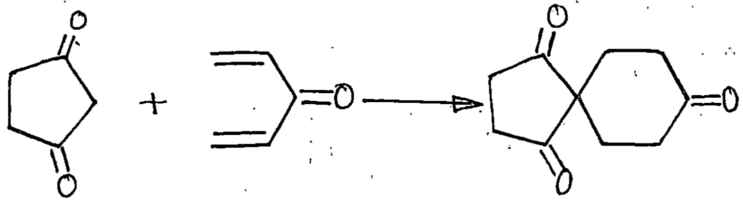
CLXVII   n = 0,1,2,3 & 6

In the spiro annulation step of a synthetic route to (-) acorenone and related compounds, LANGE, NEIDERT, ORROM and WALLACE (146) treated the pyrrolidine enamine of 2-isopropyl, 5-methyl cyclopentane carboxaldehyde (CLXVIII) with 1-methoxy-3-butene-2-one in the presence of acetic acid to obtain the spiran (CLXIX), e.g.,



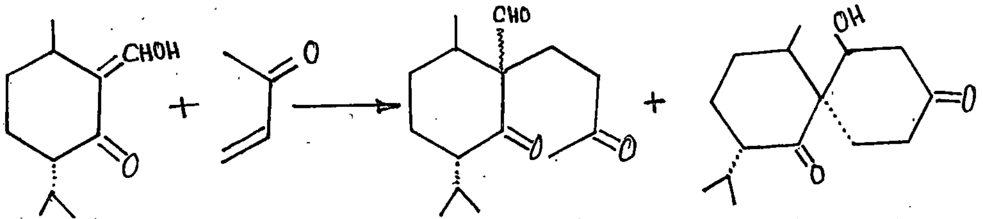
CLXVIII   CLXIX

HAMUNAKA, NAKAI and KURONO (96) demonstrated the double Michael addition route to spiro cyclic compounds in preparing spiro (4.5) deca-1,4,8,-trione (CLXX) the logical intermediate in their synthesis of dl -12,15, -ethylene -13,14 -dihydro postaglandin F -2-alpha methyl ester e.g.,



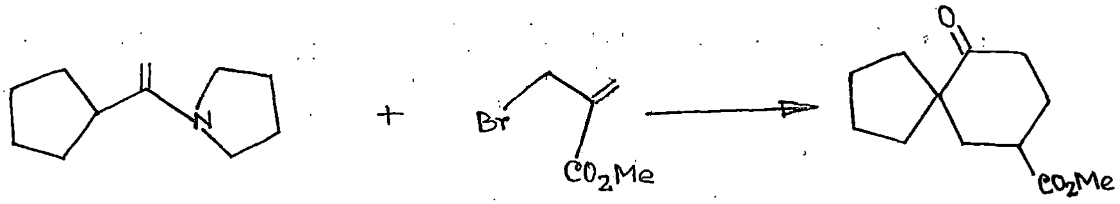
CLXX

JOSHI and LADWA (125) reported the formation of the spiran (CLXXIII) during the reaction between hydroxy methylene devivative (CLXXI) of menthone with methyl vinyl ketone along with the other non-annulated product (CLXXII). The spiro annulation has been assumed to occur through the intramolecular aldol type condensation of the Michael adduct (CLXXII) with the aldehyde function.



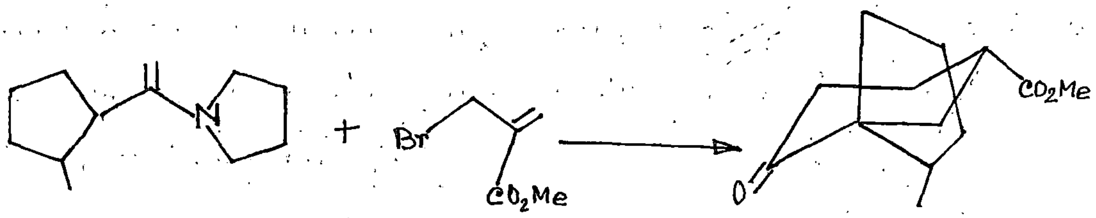
CLXXI CLXXII CLXXIII

The synthesis of spiro compounds can easily be effected from acetyl cyclo alkenes by using methyl-alpha-bromo methyl acrylate-a reagent which combines the properties of both allylic halides and alpha, beta unsaturated ester. Thus the methyl ester (CLXXV) gave the spiro annulated product (CLXXVI) when reacted with the enamine (CLXXIV) (77)



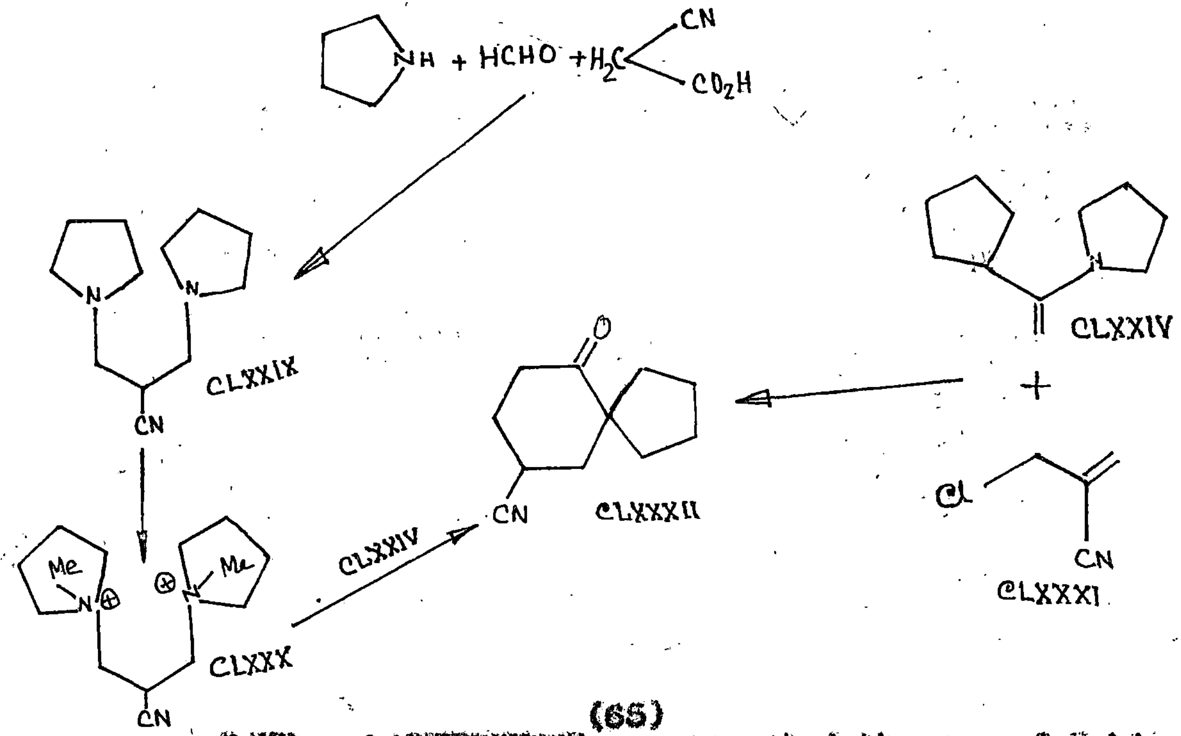
CLXXIV CLXXV CLXXVI

The occurrence of intramolecular Michael addition in this reaction from the less hindered side has been exemplified by condensing the enamine of 1 acetyl-2-methyl cyclopentane (CLXXVII) with the aforementioned acrylate (CLXXV) when the stereo chemistry of the product was shown to be as depicted in (CLXXVIII) (77).

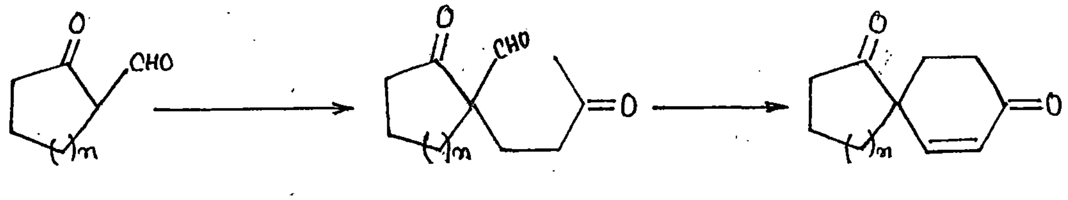


CLXXVII CLXXV CLXXVIII

The discouraging yield of spiro compound (CLXXXII) with <u>alpha</u>-(chloromethyl) acetonitrile (CLXXXI) (@ 30%) led them to develop a useful alternative. The bis-Mannich condensation (152) among cyanoacetic acid, pyrrolidine and formaldehyde with concomitant decarboxylation yielded 1,3-bis (pyrrolidino)-2-cyanopropane (CLXXIX). Reaction of this diaminonitrile (CLXXIX) with methyl-p-toluene sulphonate in refluxing acetonitrile gave the bis-quanternary salt (CLXXX) which on condensation with (CLXXIV) gave an appreciable yield of the spiro annulated product (CLXXXII)(77).



DAVE and **WHITEHURST**(65) reported the use of Robinson's annulation reaction in synthesizing the (n.4) spirane e.g., the adducts from methyl vinyl ketone and 2-hydroxy methylene derivative of cyclo-octanone and cyclo decanone (CLXXXIII) have been cyclized to spiro ketones (CLXXXIV) by way of distilling the adduct (CLXXXIII) from a little potassium hydroxide e.g.,

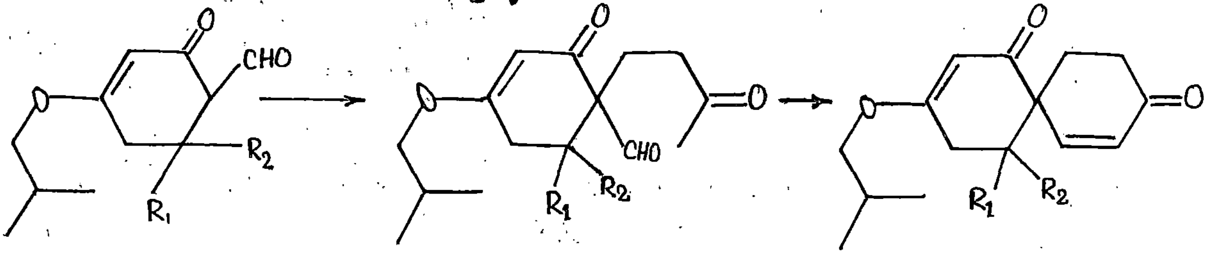


n= 4, 6.

CLXXXIII

CLXXXIV

De GROOT and JANSEN(68) treated the formyl cyclohexanone (CLXXXV) with methyl vinyl ketone in the presence of triethyl amine to give the adduct (CLXXXVI) which with pyrrolidine-acetic acid in methanol cyclized to give 80-90% of the spiro decane (CLXXXVII) e.g.,



CLXXXV CLXXXVI CLXXXVII

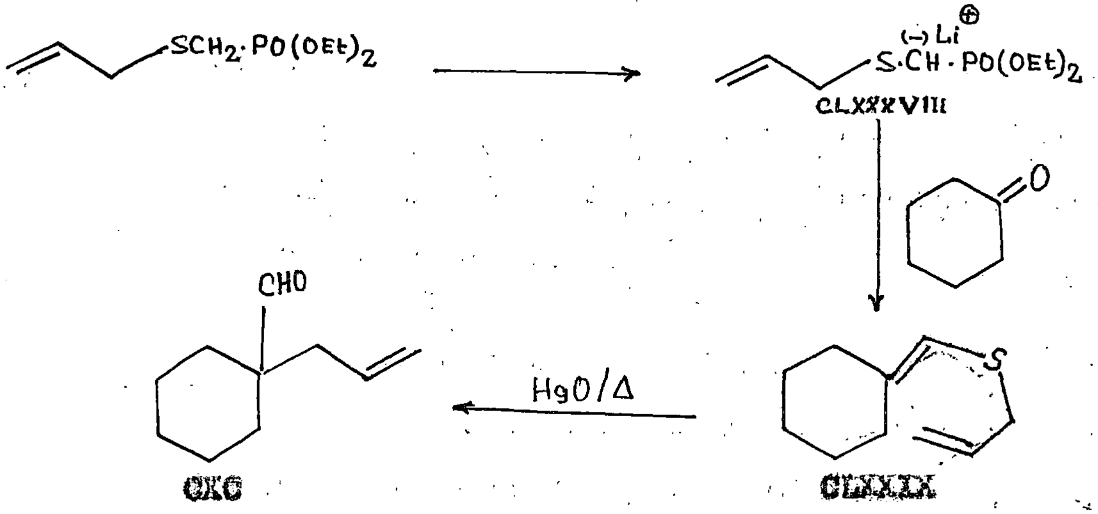
$R_1 = R_2 = H$, Me ; $R_1 = H$, $R_2 = Me$.

The high yield of the spiro compound (CLXXXVII) has been attributed to the following two facts:

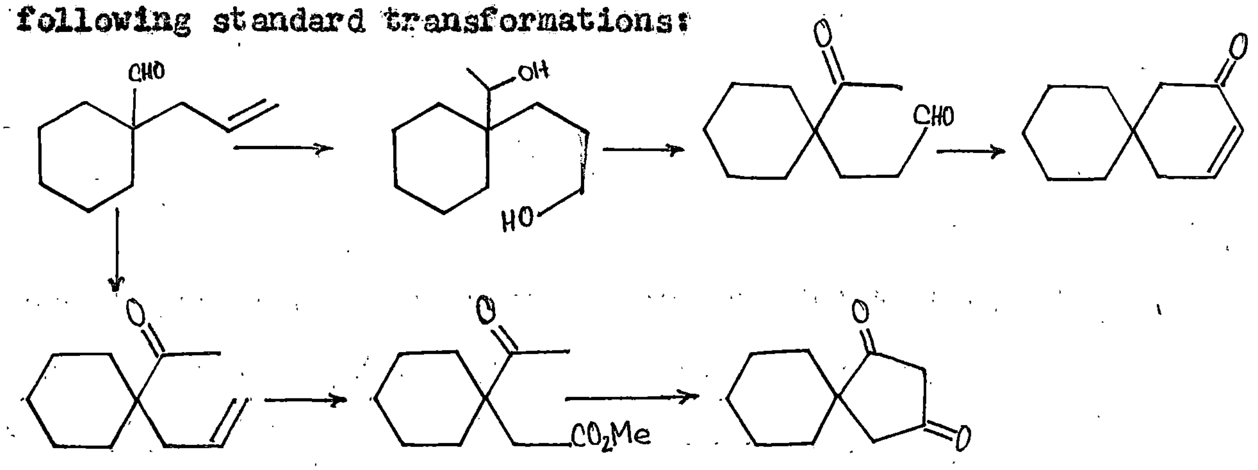
a) The reagent viz., pyrolidine-acetic acid in methanol used for the cyclization purpose is sufficiently efficient to avoid deformylation during the cyclization reaction and

b) the ring carbonyl function, being part of a vinylogous ester, is not sufficiently reactive to give rise to a condensation reaction.

CONVERSION OF CARBONYL CARBON ATOM INTO SPIRO CENTER : Since ketones are among the most accessible compounds in organic chemistry for the purpose of creating a quenternary carbon center, the procedure for geminal alkylation at a carbonyl carbon atom with functionally dissimilar substituent can well be regarded as a useful reaction sequence in the field of spiran synthesis. One such procedure was developed by COREY and SHULMAN (52). For example allyl thiomethyl phosphonate, prepared by Arbusov reaction gave after treatment with secondary butyl lithium an ylide (CLXXXVIII) which reacted with cyclohexanone to produce allyl vinyl sulphide (CLXXXIX). Treatment of the sulphide (CLXXXIX) with red mercuric oxide gave 1-allyl-1-cyclohexane carboxal-dehyde (CXC):

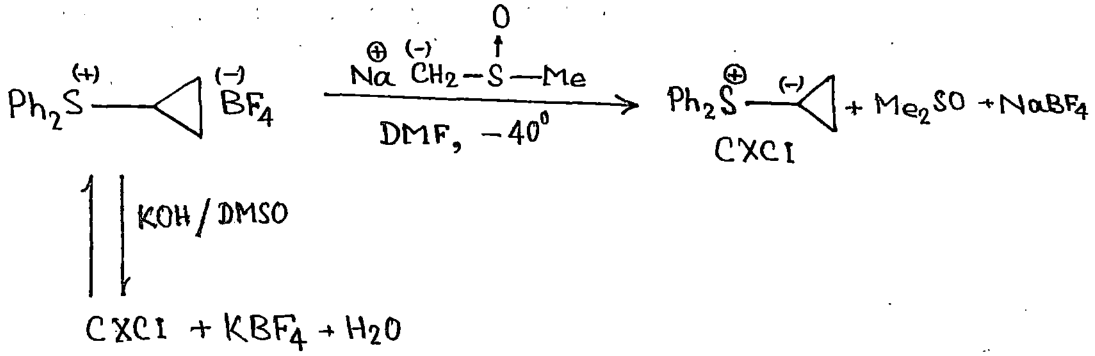


The utility of alpha-allyl alicyclic aldehydes in the synthesis of (4.5) and (5.5) spirans is illustrated by the following standard transformations:

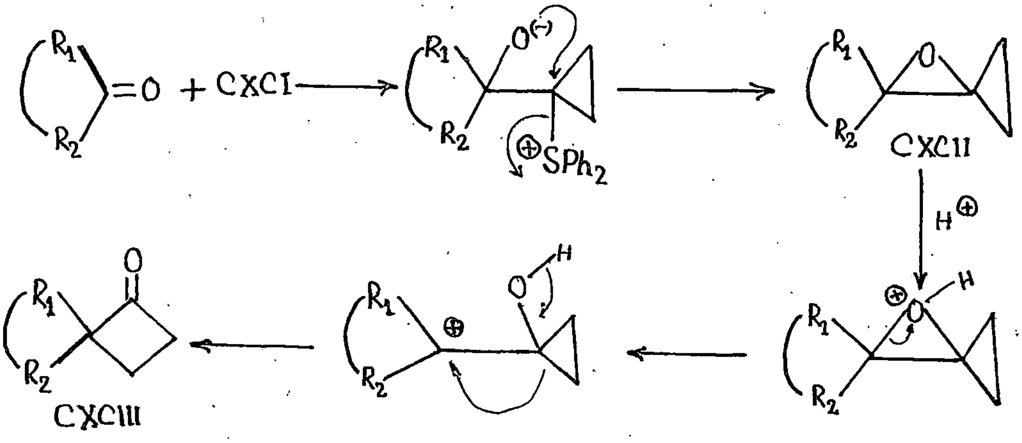


The synthesis of spiro (3.5) nonane-2-one by TROST *et al*(268), exemplifies the use of sulphur ylides in spiro annulation procedure.

The rearrangement of exaspiropentanes(270,271) prepared through the condensation of aldehydes and ketones with diphenyl suphonium cyclopropylide to cyclo butanone has been shown to give rise spiro annulation on the carbonyl carbon atom. The reagent diphenyl sulphonium cyclopropylide (CXCI) may be generated in two/different steps : irreversibly and reversibly. Irreversible generation of the ylide (CXCI) was sulphenyl carbanion in dimethyl formamide at -40°C and its reversible generation involves the utilization of powdered potassium hydroxide in dimethyl-Sulphoxide. The latter process led to higher yields of cyclobutanone with much less experimental difficulty(269).

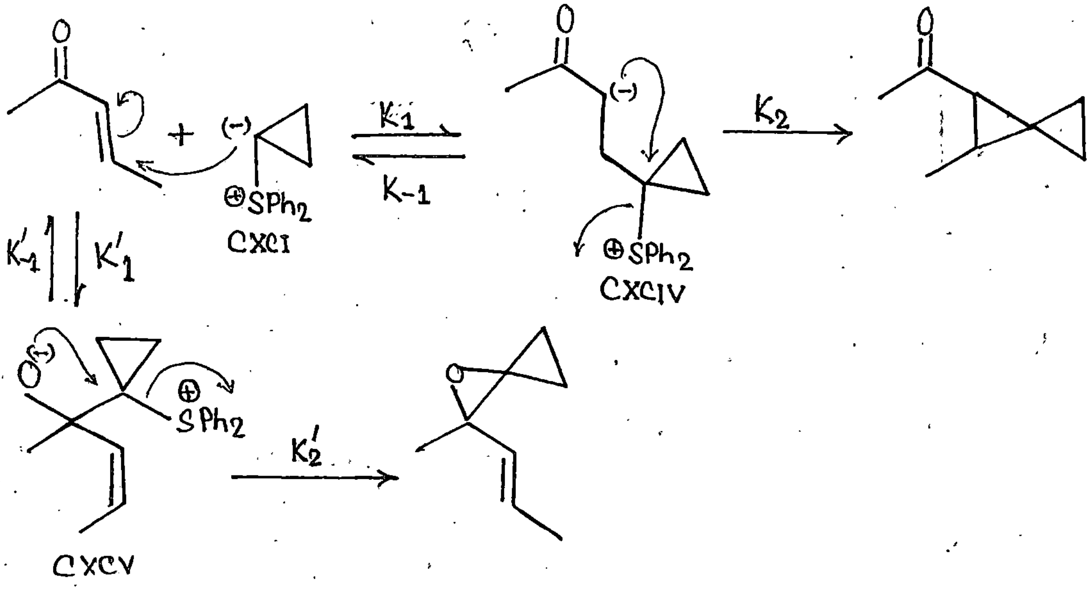


The condensation of this ylide (CXCI) with a carbonyl compound has been shown to proceed as ~~shown~~ below, leading to oxaspiro pentanes (CXCII) which undergo rearrangement to cyclobutanone (CXCIII) on acidic treatment.



The acid catalyzed rearrangement of oxaspiropentane (CXCII) when carried out with a protonic acid the anion of which can act as a base (e.g. hydrogen halides) some vinylcyclopropanol was found to accompany the product, cyclobutanone. Other methods e.g. use of lithium bromide and hexamethyl phosphorotriamide in benzene or lithium perchlorate in benzene may be employed to cause the rearrangement, under discussion, to occur quantitatively (225). The latter method is generally applicable since the non-aqueous, non-nucleophilic medium minimizes any alternative reaction.

The ambient nature of *alpha*, *beta*-unsaturated ketones towards sulphur ylide attack enabled cyclopropanation as well as epoxide formation to occur. The stability of the ylide carbanion and the rate of 1,3 elimination usually govern how the molecule will react with *alpha*, *beta*-unsaturated ketones. With highly reactive anions, they undergo carbonyl addition, whereas with stabilized anions they undergo conjugate addition. Alternatively, if the rate of 1,3 elimination in the betaine derived from carbonyl addition is slowed, again products from conjugate addition prevail. However, the *alpha*, *beta*-unsaturated carbonyl compound may also influence the course of reaction : either bulky substituents on the *beta* carbon or higher relative reactivity of the carbonyl (i.e. aldehyde > ketone > ester) leads to carbonyl addition (270). The above discussions have been rationalized as follows:

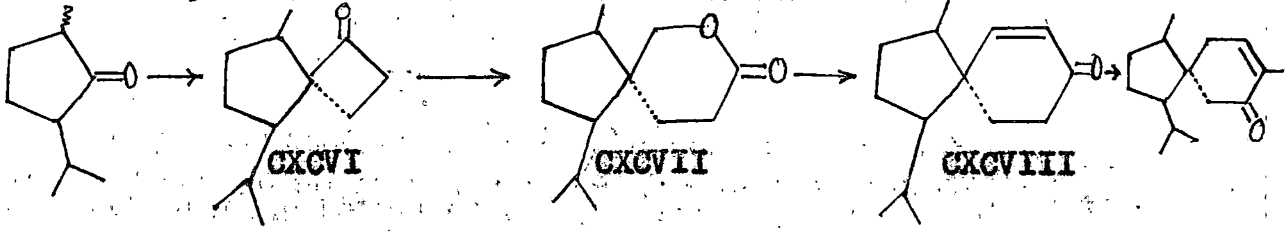


Utilizing the potassium hydroxide in dimethyl sulphoxide reversible ylide generation technique, the sensitive alpha-beta unsaturated esters have been spiro annulated likewise and the ester group was found to remain intact although use of excess base allowed the isolation of corresponding acids.

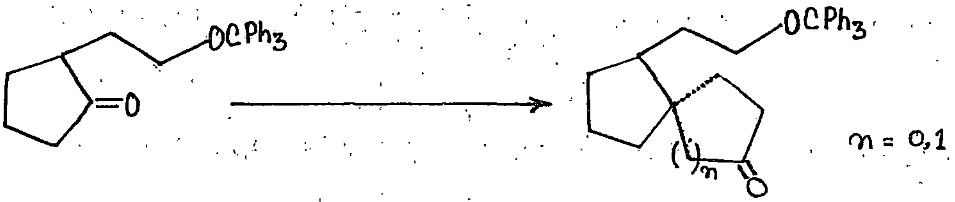
The stereochemical nature of this reaction has been studied by using methyl substituted cyclopropylide and has been shown that the ylide (CXCI) attacks the alpha, beta unsaturated carbonyl compound, as in simple carbonyl addition, with retention of configuration at the ylide carbon and subsequently loses diphenyl sulphide with inversion at the cyclopropyl ring. Whether a spiro pentane or an oxaspiro pentane is produced has been shown to depend upon the relative rate of betaine (CXCV) decomposition, K'_{-1} and K'_2 and/or 1,3 elimination, K_1 and K'_2. To produce an oxaspiropentane, betaine decomposition K'_2 must be fast relative to reversion, K'_{-1}. Conversely, if K'_{-1} is large relative to K'_2 the products are those of conjugate addition, the result of thermodynamic control. The decomposition pathway K'_{-1} will increase relative to K'_2 with ylides of increasing anionic stability. Furthermore, sulphonium ylides in which the rate of 1,3 elimination (K'_2) is decreased (e.g. cyclopropylides) also result in spiro pentane formation (270).

The synthetic use of the oxaspiropentanes have also been discussed by TROST and BOGDANOWICZ (271).

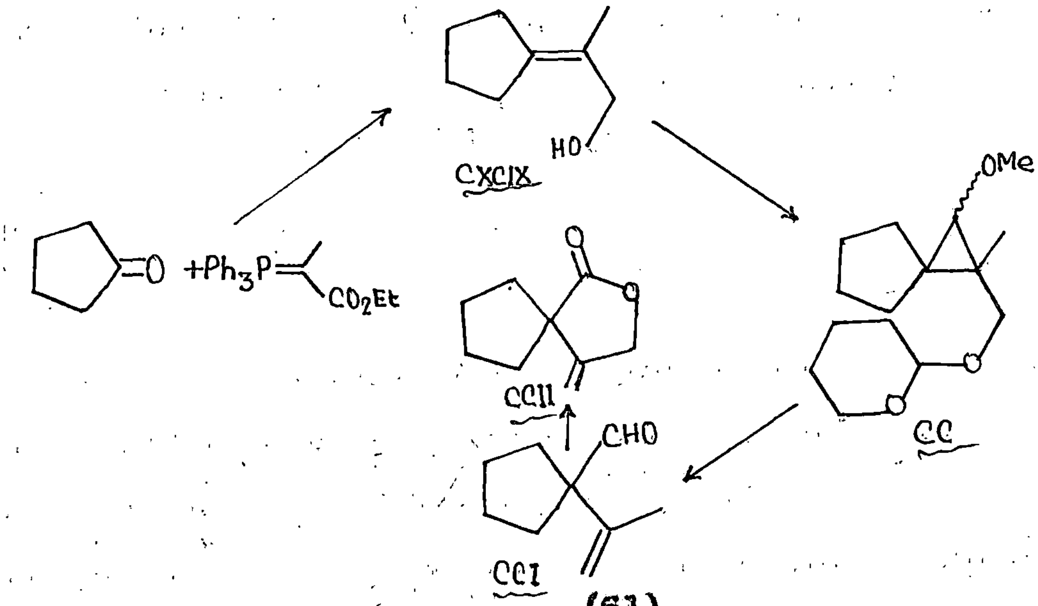
The total synthesis of acorenone - B by TROST, HIROI and HOLM (272) utilized the oxaspiro pentane as the intermediate. The synthesis also illustrates a new approach to secoalkylation and 1,2 alkylative carbonyl transposition. Spiro annulation of 2-isopropyl-5-methyl cyclopentane with cyclopropyldiphenyl sulphonium fluoroborate, followed by rearrangement of the oxaspiro pentane gave (Z,Z)-5 isopropyl-8-methyl spiro (3,4) octane-1-one (CXCVI). Formylation followed by acidic treatment effected cyclobutyl ring cleavage to an enol lactone (CXCVII) which constituted a net stereocontroled geminal alkylation with introduction of a one carbon and three carbon chain, differently functionalized. Standered methods converted the enol lactone (CXCVII) to 1-isopropyl-4-methyl spiro (4.5) dec-6-en-8-one (CXCVIII). Sulphinylation <u>alpha</u> to the ketone, addition of methyl lithium to the carbonyl group, dehydration to the enol thioether and hydrolysis completed 1,2 carbonyl transposition along with the introduction of a methyl group, and thus crossed the remaining hurdle to synthesize acorenone - B from (CXCVIII)


CXCVI CXCVII CXCVIII

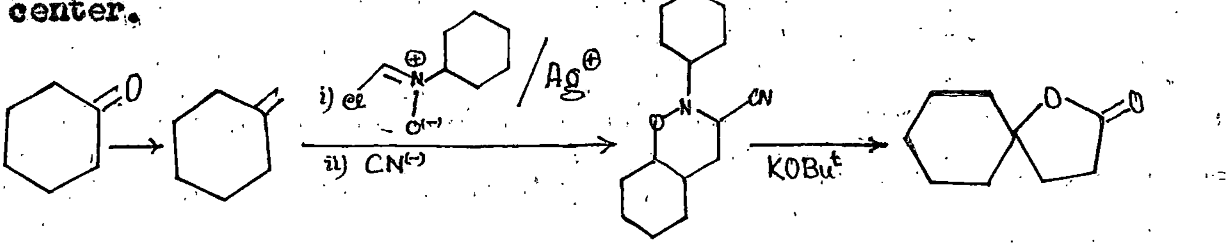
The development of a procedure for regio controlled ring expansion of cyclobutanone into a cyclopentanone during the synthetic approach by TROST et al (273) towards the synthesis of gibberellins provided a method for synthesizing spiro (n.4) systems in a stereo-chemically defined fashion and thus broadened the applicability of this method in spiran syntheses e.g.,



In an approach to synthesize Bakkenolide-A, CAMPBELL, CONSTANTINO, BROCKSOM and PETRAGNANI (40) prepared the oxaspirononane (CCII) through the sequence involving the reaction of cyclopentanone with ethyl-1-methyl-triphenyl phospholidene acetate followed by reduction to alcohol (CXCIX). The tetrahydropyranyl derivative of (CXCIX) on treatment with methoxy carbene followed by acid treatment gave the spiroheptane (CC). Oxidation followed by cyclization with N-bromo succinimide gave the oxaspirononane (CCII) e.g.,

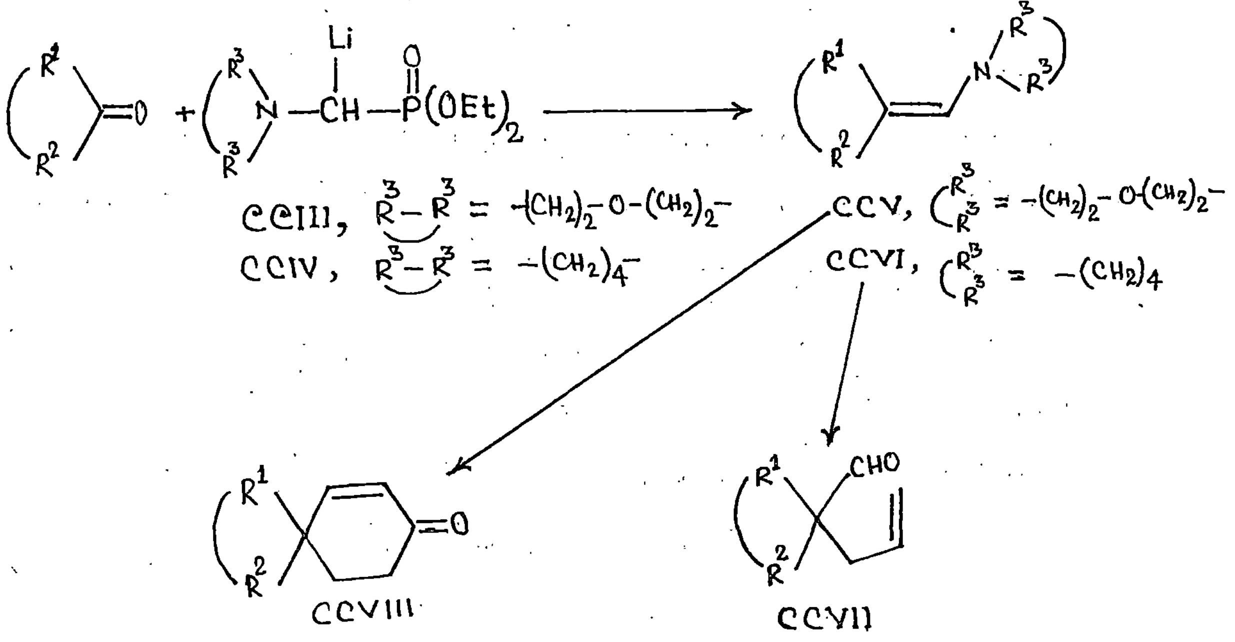


The effort of ESCHENMOSER et al (61) to convert cyclohexanone to spiro gamma butyro lactone by the use of chloro nitrone also exemplifies the conversion of carbonyl carbon atom to a spiro center.

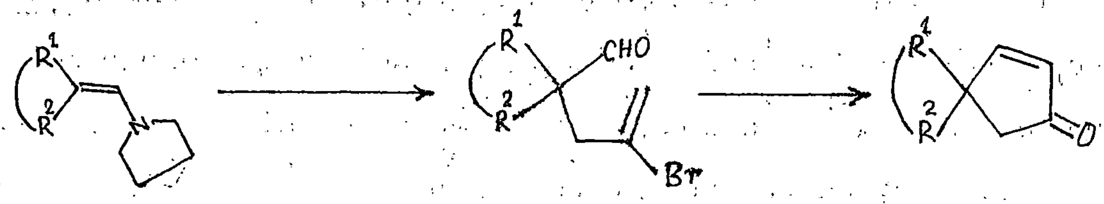


The procedure, developed for the geminal alkylation at a carbonyl carbon atom with functionally dissimilar substituents, by MARTIN et al (162,163), involves the conversion of a ketone into the morpholine or pyrrolidine enamine of homologous aldehyde with diethyl lithio morpholino (or pyrrolidinno) methyl phosphonate.

The inherent advantage of this procedure for carbonyl homologation is that the enamines (CCV) and (CCVI) which are useful functional derivatives of the corresponding aldehydes, are obtained directly. Furthermore, these enamines may be employed in subsequent reactions with electrophilic reagents without purification. For example, treatment of the pyrolidine enamine (CCVI) with allyl bromide gave the *alpha* allyl dialkyl aldehyde (CCVII) in good overall yields (162) and the reaction of the morpholino enamine (CCV) with methyl vinyl ketone followed by aldol cyclodehydration gave the 4,4 disubstituted 2-cyclohexenone (CCVIII) in moderate overall yields (163). The later procedure constitutes a facile method for the spiro annulation of six membered rings.

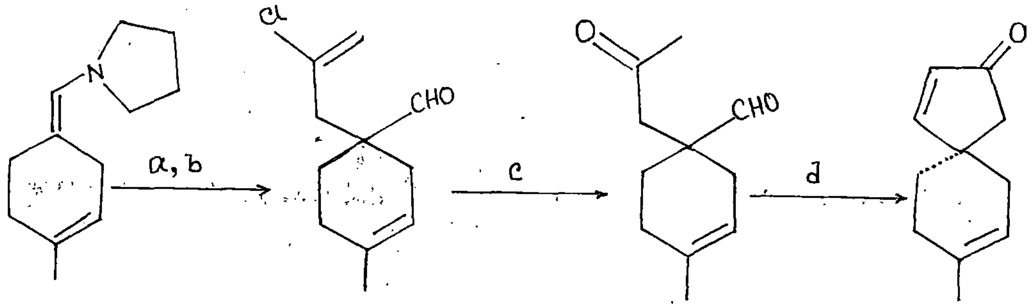


A strategy for the annulation of five membered rings using the same sequence of reactions was developed by the same school of synthetic chemists who modified their original procedure, mentioned above, and thereby converted the ketones to 4,4 disubstituted 2-cyclo pentenones. They treated the enamine (CCIX) with 2,3 dibromopropene and cyclised the resulting 2-(2-bromo-2-propenyl) aldehyde (CCX) with sulphuric acid at 0°C which after aqueous workup gave the desired 4,4 disubstituted 2-cyclo-pentanone (CCXI)(164) e.g.,



CCIX CCX CCXI

The application of this reaction sequence to cyclic ketones constitutes a new method for the spiro annulation of five membered rings which are suitably functionalized for further synthetic transformations. The stereo selective total synthesis of racemic acorene by MARTIN, <u>et al</u>(165), made use of a newly developed procedure for the cyclopentane ring annulation which commences, with the alkylation of the pyrrolidine enamine of 4-methyl-3-cyclohexane-1-carboxaldehyde (CCXII) with 3-iodo-2-chloro propene. Mercuric ion promoted hydrolysis of vinyl halide (CCXIII) thus produced gave the gamma-keto aldehyde (CCXIV), which underwent smooth, base catalyzed cyclization to the key intermediate, 8-methyl spiro (4.5) deca, 1,7-dien-3-one (CCXV).



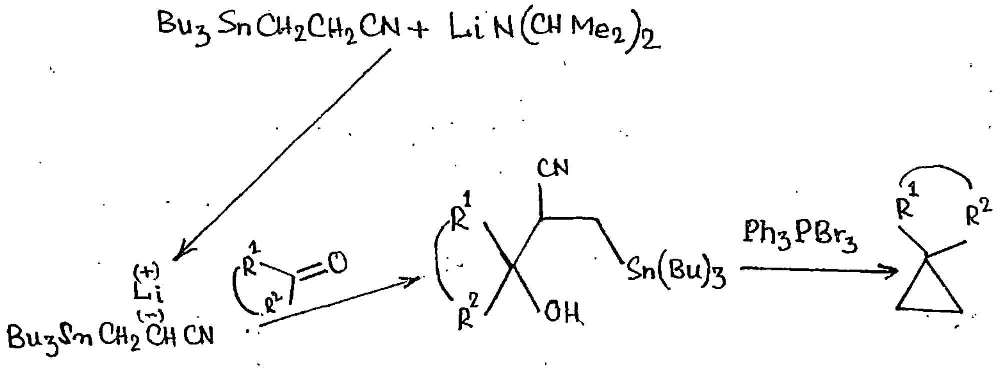
CCXII CCXIII CCXIV CCXV

a, $ICH_2CCl=CH_2/CH_3CN/\Delta$; b, H_2O ; c, $Hg(OAC)_2/BF_3.Et_2O/$ $HOAC$; d, 10% KOH/CH_3OH.

Mc CRAE and DOLBY(171) in their synthetic endeavour to racemic acorenone prepared the 1-(2-oxopropyl)-4-methyl-3-cyclohexene carboxaldehyde (CCXIV) from 4-methyl-3-cyclohexene carboxaldehyde-imine on alkylation with 1-trimethylsilyl-3-bromopropyne followed by mercuric ion promoted hydrolysis of the intermediate. The spiro annulation of the carboxaldehyde (CCXIV) was carried out as was done by MARTIN et al(165).

Lithiotributyl-(2-cyanoethyl) tin (CCXVI) prepared by the reaction between tributyl-(2-cyano ethyl) tin and lithio di-isopropyl amine, has been shown to react with aldehydes and ketones resulting in the formation of hydrine of the type (CCXVII).

([illegible]). On reaction with triphenyl phosphonium tribromide this was shown to give a *cis-trans* mixture of cyclopropanes (CCXVIII). When applied to cyclic ketones, the process gave the corresponding spiro (n.2) alkanes(265).

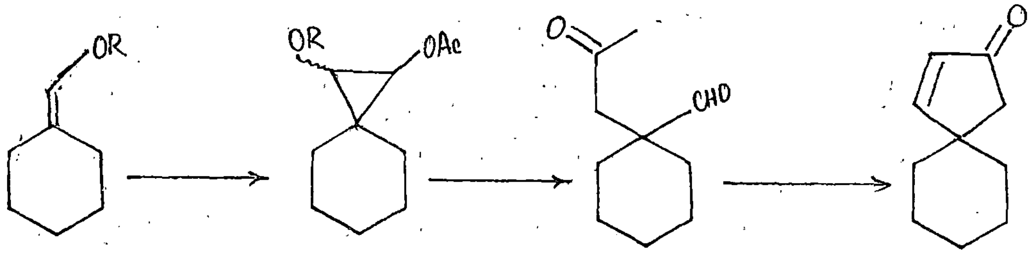


CCXVI CCXVII CCXVIII

<u>CYCLO ADDITION REACTION ROUTE</u>: Cyclo addition reactions which lead to the formation of spiro cyclic compounds have been reviewed by KRAPCHO(139). The addition of carbene intermediates to an unsaturated compound with exocyclic double bond results in the formation of spiro cyclic propanes. A number of methods for the generation of carbene intermediates have been described in the literature. In some cases the cycloadditions do not involve "free carbenes". The term "carbenoid" has often been used to describe complex carbenes or carbene-like intermediates. According to <u>WOODWARD</u> and <u>HOFFMANN</u> a singlet carbene with filled and vacant orbital can participate in a concerted, non-linear

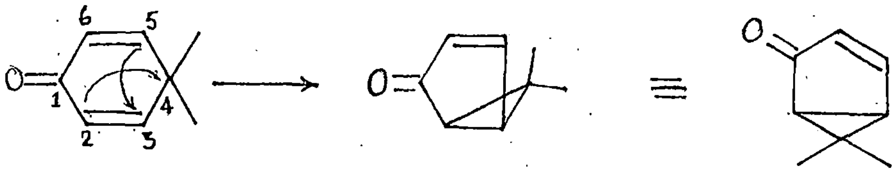
cheletropic mode of addition to a double bond ($\pi^{2s} + \omega^{2a}$). On the other hand the cyclo addition of a triplet appears to be stepwise(90,296).

KRAPCHO(139) has discussed the different processes involving carbene or carbenoid generation and their application to spirane synthesis. In the synthesis of racemic-<u>alpha</u>-Cuparenone and racemic-<u>beta</u>-vetivone ~~by~~ WENKERT <u>et al</u>(283) described the use of carbene addition reaction in geminal alkylation at a carbonyl carbon atom with two substituents possessing different functionalities. Through a series of reactions the geminal substituents were cyclized leading to a (4.5) spiro decane skeleton e.g.,

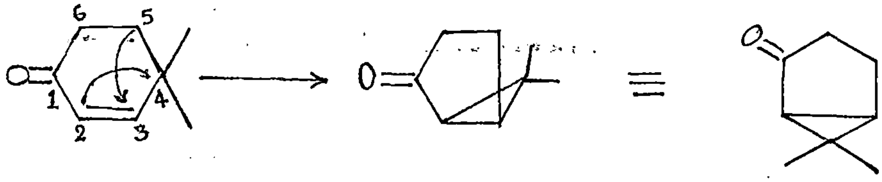


R = Me, Ac

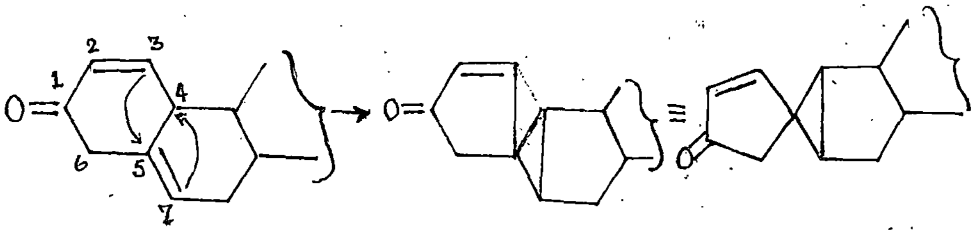
(2 + 2) Cycloadditions in the photo chemistry of cyclohexadienones and cyclohexenones may be of three types as depicted below:



Class A

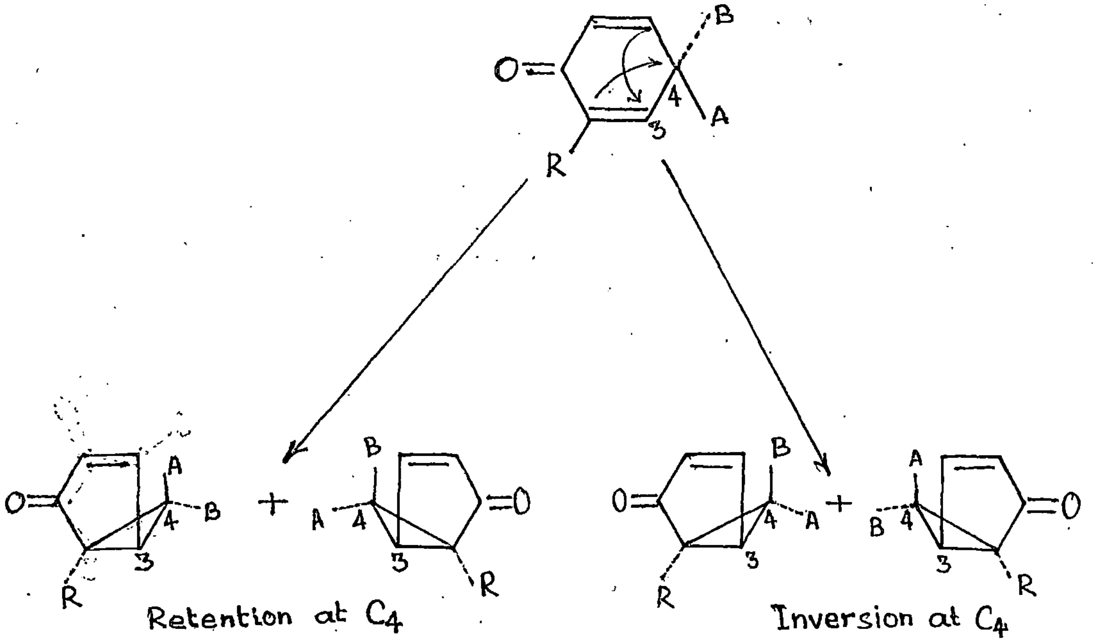


Class B



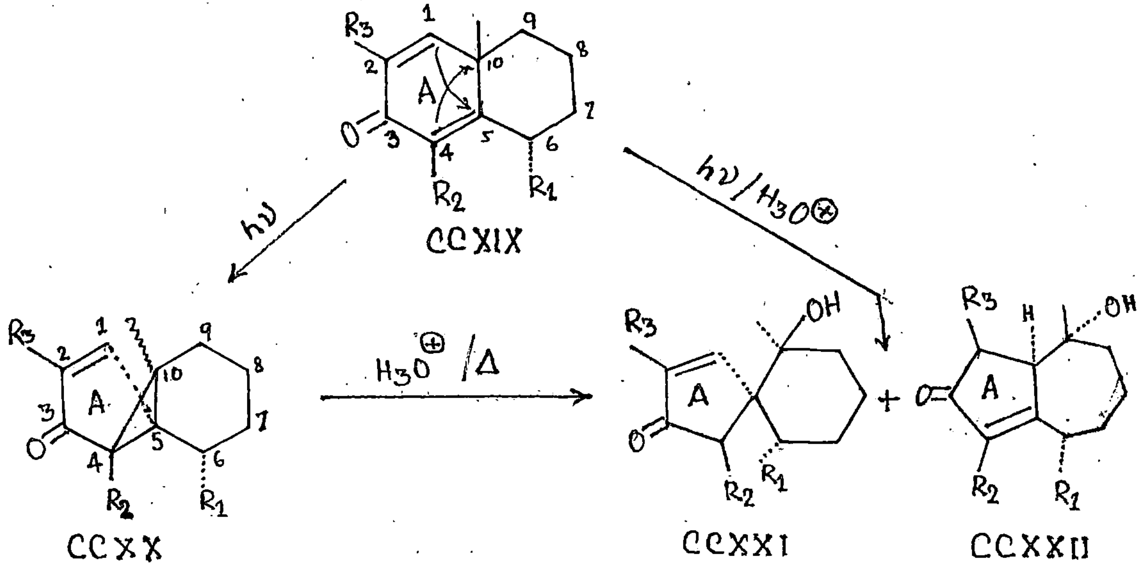
Class C

The concerted reaction in the classes A and B suprafacial participation of double bond 2,3 is a stereochemical impossibility, since it leads to trans fused three and five membered rings. Consequently these reactions must follow the ($\sigma^{2a} + \pi^{2a}$) course, which requires antarafacial addition at double bond 2,3 and inversion at C_4. In class C the special constraint present in classes A and B is absent and hence both ($\sigma^{2a} + \pi^{2a}$) and ($\sigma^{2s} + \pi^{2s}$) processes are feasible. In the case of cross conjugated cyclodienones (Class A) the inversion or retention at C-4 can each be performed in two distinct ways, depending on whether the addition at C_3 is on the top or bottom.



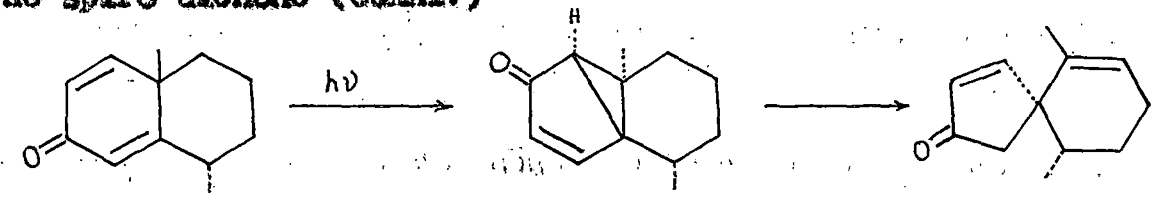
If A and B are different substituents these pathways become distinct, each with its own steric factors. It is thus likely that even a stereo specific process will yield two products in differing proportions. The products of inversion are diastereomeric, and enantiomeric to the products of retention.

Antara addition at the double bond and inversion at the migrating saturated carbon has been discussed (296) with the classic conversion of santonin into lumisantonin. KROPP (141), however, studied the photochemical rearrangements of substituted and unsubstituted cyclic 1,4-dien-3-ones and showed that the photochemical irradiation in neutral medium converts all the three naphthalenones (CCXIX, a,b,c), to the respective cyclopropyl ketones (CCXX, a,b,c) through a concerted antara addition of the double bond and inversion at the migrating saturated carbon atom. The study on the acid catalyzed cleavage of the cyclopropyl ketones (CCXX, a,b,c) revealed that the course of the reaction is remarkably influenced by the presence of A-ring substituents (140,141). The unsubstitued ketone (CCXX,a) gave predominantly spiro products accompanied by a small amount of the (5-7) fused ketone. The 2-methyl ketone (CCXX,b) gave exclusively spiro products. In constrast the 4-methyl analogue (CCXX,c) gave predominantly the (5-7) fused product accompanied by the spiro ketone in smaller quantity.



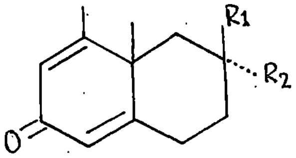
a, $R_2 = R_3 = H$, $R_1 = Me$
b, $R_1 = R_2 = H$, $R_3 = Me$
c, $R_1 = R_3 = H$, $R_2 = Me$

The first total synthesis of a spiro vetivane, beta vetivone, by MARSHALL and JOHNSON(155) employed the photochemical rearrangement of (CCXIX,a) in building up the spiro (4.5) decane with appropriate stereostructure and functionality which could easily be converted to that, required for beta vetivone. 6-beta methyl isomer of (CCXIX,a) has been irradiated by CAINE(36) in an analogous manner to obtain the lumiproduct (CCXXIII) which on treatment with sulphuric acid in acetic acid-acetic anhydride gave the spiro dienone (CCXXIV)

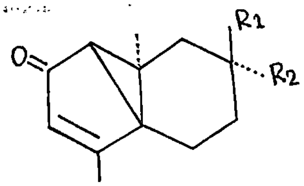


CCXIX a CCXXIII CCXXIV

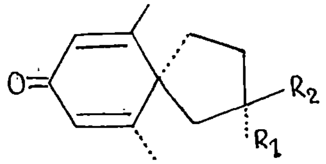
The photolytic interconversion of nootkatone and vetispirane sesquiterpene by CAINE et al(34,35) is charming. Irradiation of 3,4-dehydronootkatone (CCXXV,a) gave a lumiproduct which on further irradiation in 45% aqueous acetic acid gave the mixture of spiro ketone (CCXXVII,a), the bicycle dienone (CCXXVIII,a) and unconverted 3,4 dehydro nootkatone (CCXXV,a). Again dehydro alpha vetivone (CCXXV,b) on irradiation gave the lumiproduct (CCXXVI,b) which on further irradiation under the condition described for (CCXXVI,a) gave dehydro beta-vetivone (CCXXVII,b) as the exclusive product. On the other hand the irradiation of dehydro-rotunol (CCXXVII,a) gave a mixture of four possible diastereomeric compounds of the type (CCXXIX,a). Irradiation of this mixture in aqueous acetic acid gave a mixture of (CCXXV,a) and (CCXXVIII,a). Again dehydro *beta* vetivone (CCXXVII,b) gave on similar irradiation a mixture of two racemic diastereomeric mixtures of the type (CCXXIX,b) in the first stage and racemic dehydro *alpha* vetivone (CCXXV,b) on irradiation of the mixture in acetic acid medium, e.g.,



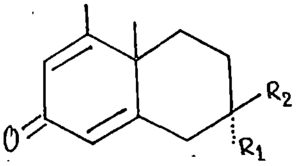
CCXXV



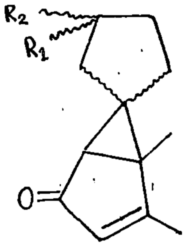
CCXXVI



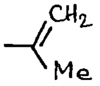
CCXXVII

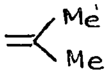


CCXXVIII

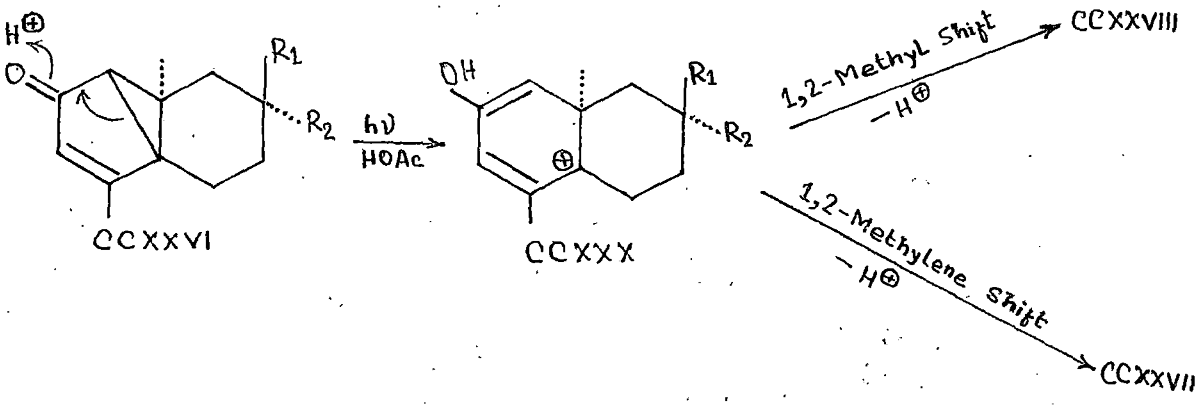


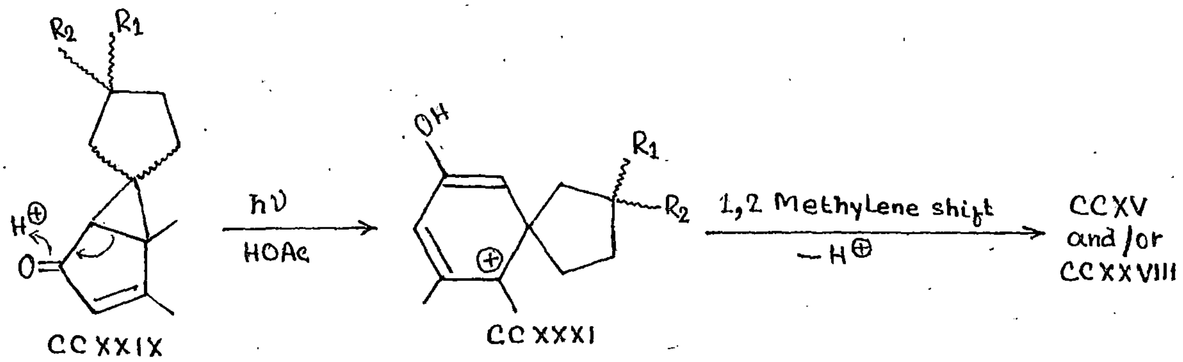
CCXXIX

a, R_1 = H ; R_2 = 

b, R_1R_2 = 

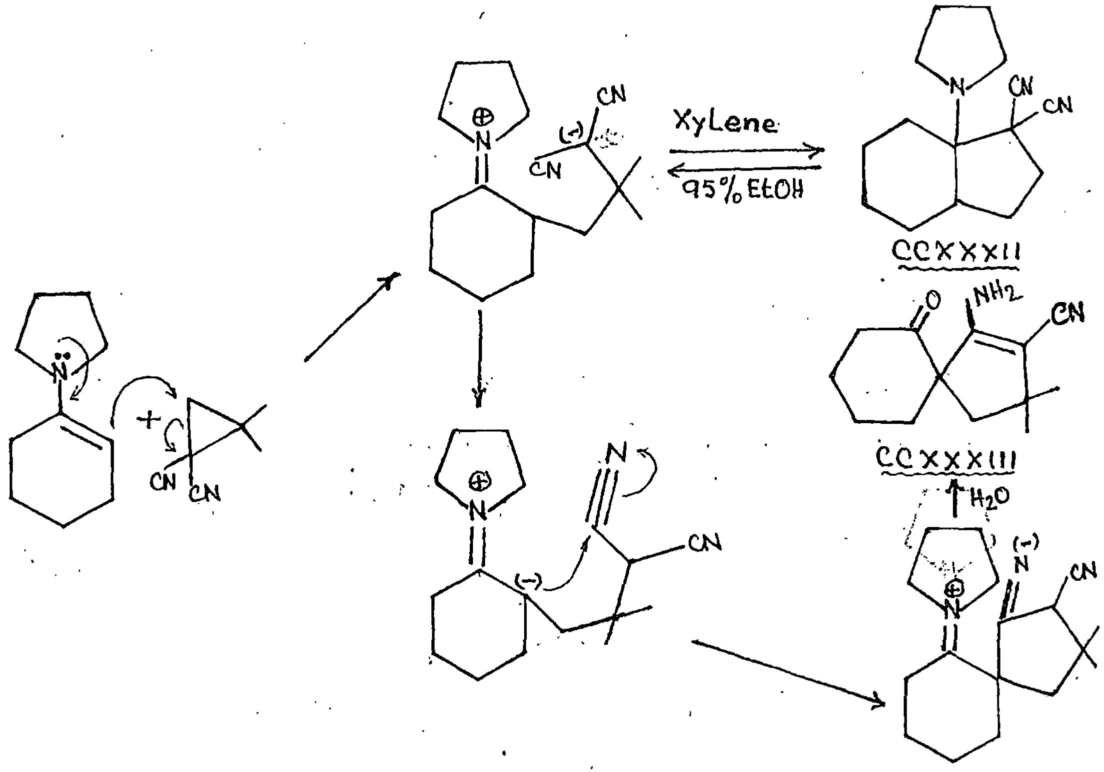
The irradiation of products (CCXXVI) and (CCXXIX) in protic solvents has been explained by the authors (34) by the formation of carbocation intermediates such as (CCXXX) and (CCXXXI) which can yield the observed photoproducts by appropriate 1,2-methyl or ring methylene shift to the positions para to the hydroxyl groups, e.g.,



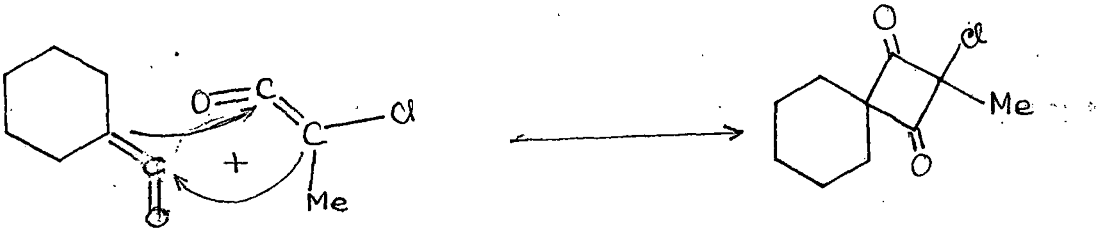


Direct formation of (CCXXVIII,a) from (CCXXVI,a) provided the first example of a 1,2-methyl shift in a photochemically generated species of this type.

The cycloaddition of N-pyrollidinyl cyclohexene to 1,1-dicyano, 2,2-dimethyl cyclopropane has been shown to proceed by an S_N2 route across the 1,3 bond to give the adduct (CCXXXII) which was shown to rearrange upon partial hydrolysis to a (4.5) spiro compound (CCXXXIII)(20).

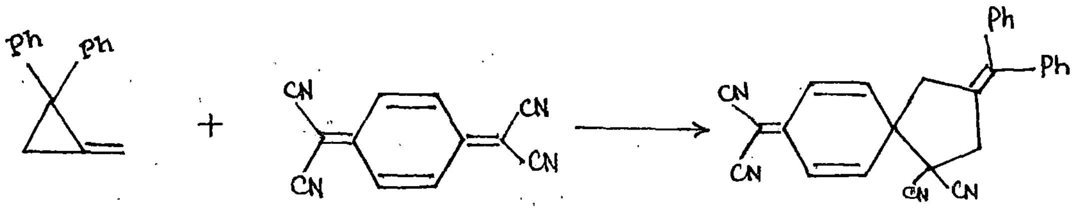


Orbital symmetry consideration of the cyclo additions involving 4 π – electrons indicate that the thermal ($\pi^{2s} + \pi^{2s}$) cycloaddition is forbidden but a concerted ($\pi^{2s} + \pi^{2a}$) is allowed. Orthogonal reactant approach as demanded by the latter process results in inefficient obital overlap (π – bond twisting) and the approach of the reactants can be hindered by steric interactions. A permissible approach of this type can be energitically unfavourable and stepwise mechanisms may occur via diradical or ionic intermediates. The situation may be explained by the mixed ketene dimerization between pentamethylene ketene (CCXXXIV) and alpha-methyl, alpha-chloroketene (CCXXXV) generated from cyclohexane carbonyl chloride and alpha chloropropionyl chloride respectively(27), e.g.,



CCXXXIV CCXXXV CCXXXVI

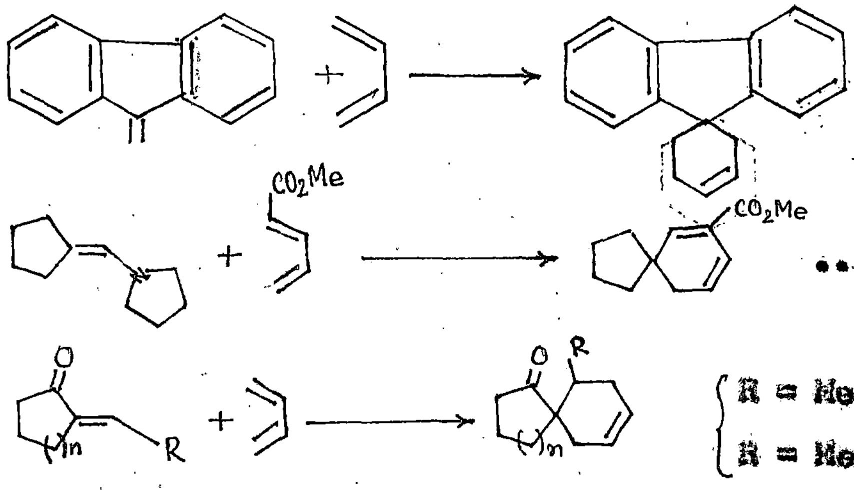
A ($\sigma^2 + \pi^2 + \pi^2$) type cyclo addition route to spiro (4.5) decene skeleton has been developed by NOYORI, HAYASHI and KATÔ(201) who obtained the spiro fused adduct (CCXXXIX) by heating an equimolecular mixture of 2,2-diphenyl methylene cyclopropane (CCXXXVII) and 7,7, 8,8-tetra cyano quino dimethane (TCNQ) (CCXXXVIII) in benzene, e.g.,



CCXXXVII CCXXXVIII CCXXXIX

The reaction has been shown to follow cycloaddition path solely. The possible concerted $[(\sigma^{2s} + \pi^{2s}) + \pi^{2s}]$ or $[(\sigma^{2a} + \pi^{2a}) + \pi^{2s}]$ process could explain most reasonably the cleanness of the reactions of this type. Rigorously, however, the alternative stepwise mechanism cannot be ruled out since the intriguing molecular structure of methylene cyclopropane in which the π and $C_2 - C_3$ bonds are perpendicular to one another, may prohibit sufficient orbital overlap for the transition states of concerted cycloaddition. Elucidation of the exact reaction mechanism awaits further theoretical and experimental scrutinies.

(4π + 2π) cycloaddition reactions (Diels-Alder reaction) is undoubtedly one of the most explored routes and generally leads to six-membered rings. A summetry allowed (π^{4s} + π^{2s}) route is possible and is the probable route for this cyclo addition to occur. Generally the process with unactivated dienophiles leads to low yields of the cyclo adduct although several interesting spiro systems have been prepared through this reaction e.g.,

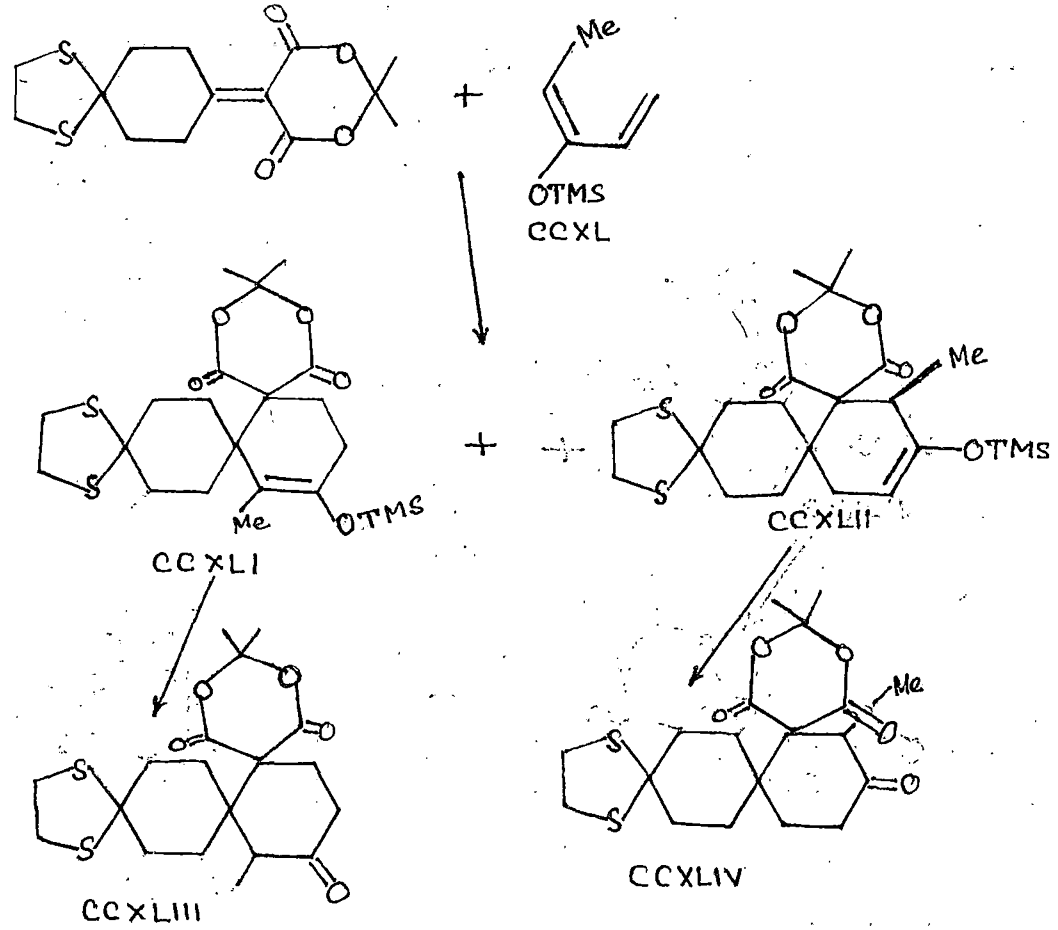


........(Ref. 277)

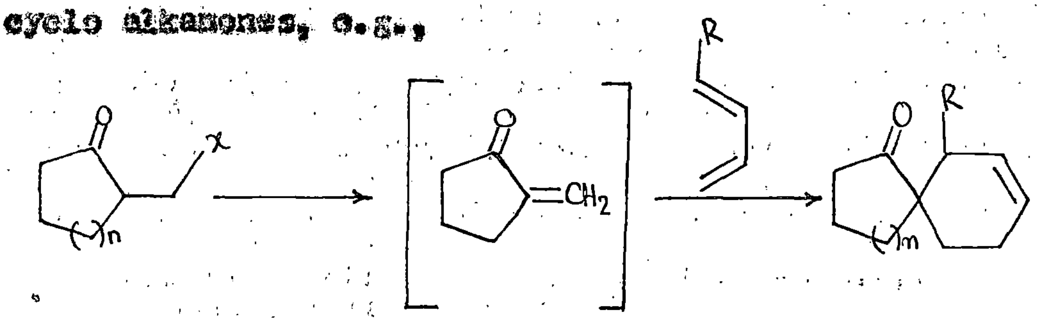
.........(Ref. 20)

R = Me, n = 1, (Ref. 91)
R = Me, Ph.; n=2,(Ref.178)

The synthesis of spiro cyclic compounds using (4+2) cyclo addition reaction by MOCK, HOLMES and RAPHEL(180) is interesting. They used the trimethyl silyl enol ether (CCXL) of pent -1-ene-3one as the diene and the easy hydrolytic removal of trimethyl silyl group in the resulting adducts (CCXLI) and (CCXLII) gave the respective carbonyl compounds (CCXLIII) and (CCXLIV) e.g.,



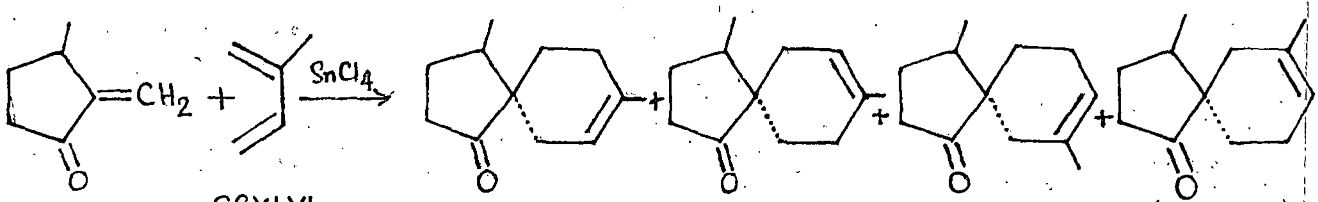
Unsubstituted alpha methylene cycloalkanones are generally, unstable but they can readily be prepared in situ and trapped with dienes. Mannich bases, alpha chloromethyl cycloalkanones, alpha-acetoxy methyl cyclo alkanones and alpha hydroxy methyl cycloalkanones can well be used as precursors of *alpha* methylene cyclo alkanones, e.g.,



x = -OH, -OAc, Halogen, -N<, etc.

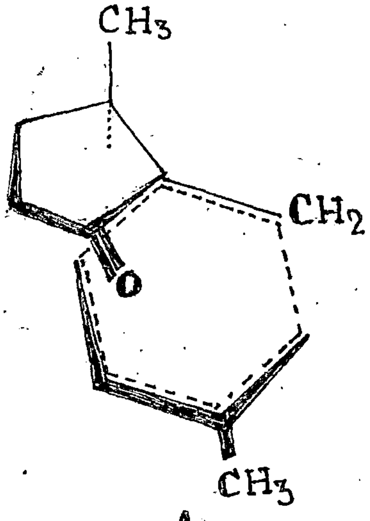
Examples of the in situ generation of *alpha*-methylene cycloalkanones and their reaction with added diene have been summarized by KRAPCHO(139).

The Diels-Alder reaction can be catalyzed by Lewis acids and the catalyzed reactions were shown to be highly stereospecific. The Lewis acid forms a complex with the polar substituents of the dienophile and accelerates the cycloaddition. The Lewis acid catalyzed Diels-Alder reaction has been utilized by MARX and NORMAN(161) in their synthesis of (-) acorenone and related spiro cyclic sesquiterpenes with the appropriately substituted diene (CCXLV) and dienophile (CCXLVI) in the crucial spiro annulation step and isolated all the four possible stereo isomeric products (CCXLVII to CCL).

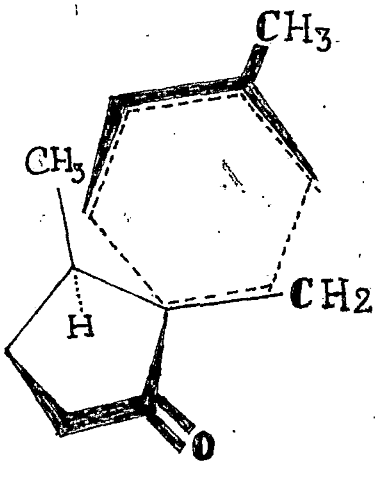


CCXLV CCXLVI CCXLVII CCXLVIII CCXLIX CCL

The relative abundance of these stereo isomers has been determined by revealing that the enone chromophore in the dienophile is essentially plannar with only the methyl group blocking one face partially from stereochemical approach of the diene. Thus the transition state <u>A</u> in which the isoprene attacks on the opposite face from the methyl group is favoured over the other (transition state <u>B</u>), leading to 'S' absolute configuration at the spiro center and thus giving rise to (CCXLVII) as the major product. The lesser major product must be (CCXLVIII) derived from transition state <u>B</u> and thus possesses the 'R' - configuration at the spiro centrer.

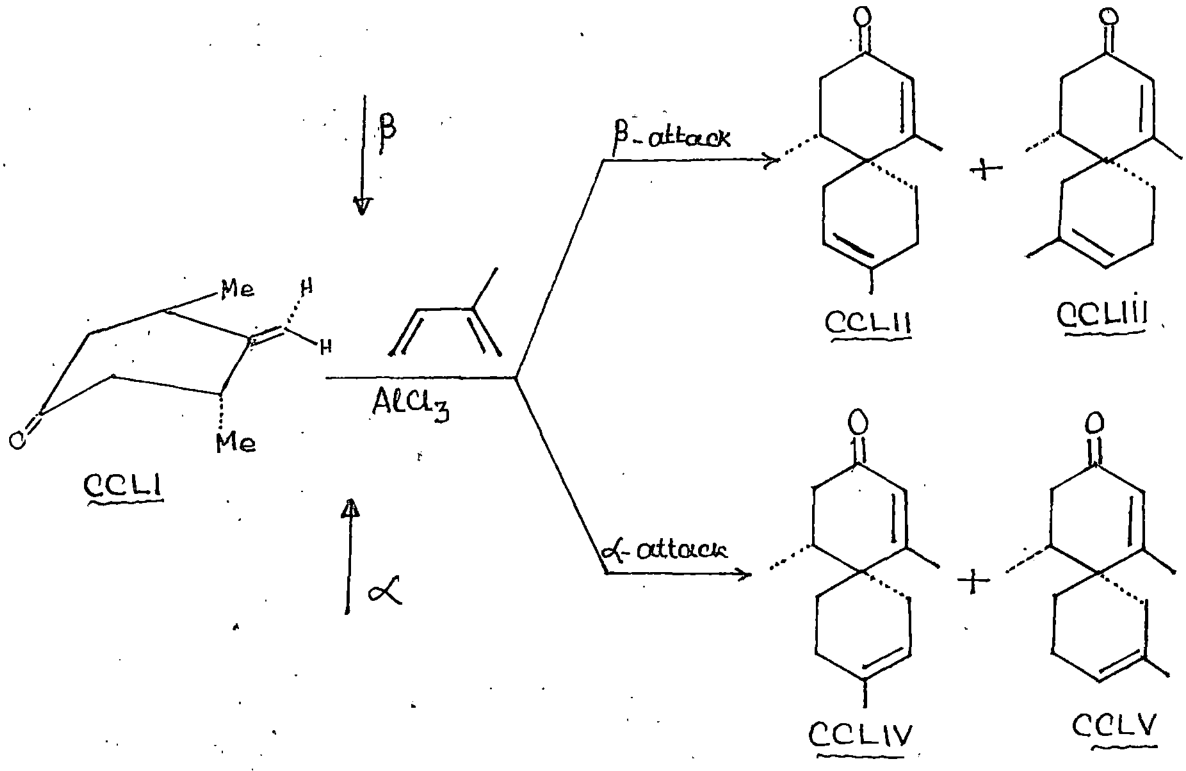


A



B

The acid catalyzed Diels-Alder reaction route to spiranes has also been exemplified by McCURRY and SINGH (177). In their reaction they used the cyclohexenone (CCLI) as dienophile and isoprene as diene, aluminium chloride as catalyst and chloroform as solvent. Out of the four possible products shown below, only two viz (CCLII) and (CCLIII) resulting from beta attack by the diene were obtained in 95:5 ratio. The experimental result can well be accounted for as was done by MARX and NORMAN (161).



CCLI

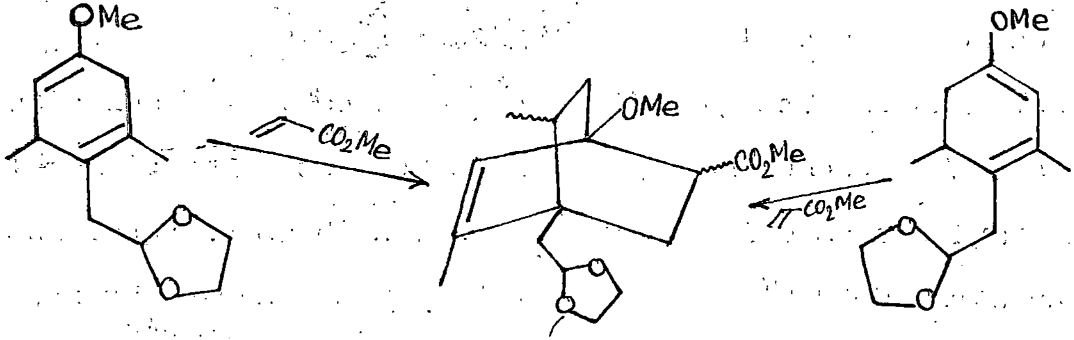
CCLII

CCLIII

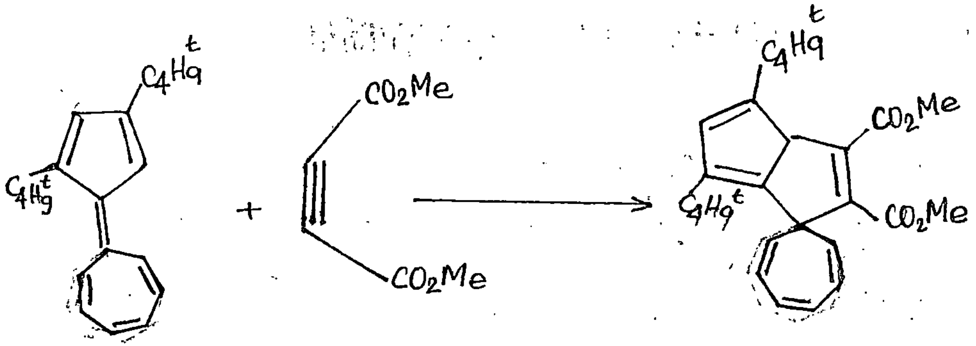
CCLIV

CCLV

One of the two major steps in the stereo selective synthesis of natural spiro vetivanes by MURAI, SATO and MASAMUNE (189) consists of the Diels-Alder reaction of substituted dihydro anisoles and methyl acrylate or its equivalents, e.g.,

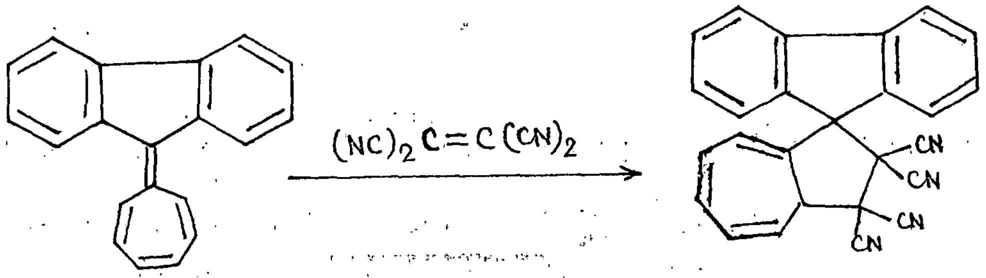


Since ($\pi^{6s} + \pi^{2s}$) process is thermally disallowed, a stepwise mechanism could operate in the cyclo addition reactions involving eight electrons. The reaction between sesquifulvalene (CCLVI) with dimethyl acetylene carboxylate to yield 1:1 adduct (CCLVII) was first reported to proceed through this type of cyclo addition. However, a more recent report indicates that the product is really a (4π + 2π) adduct (See Ref. 139).



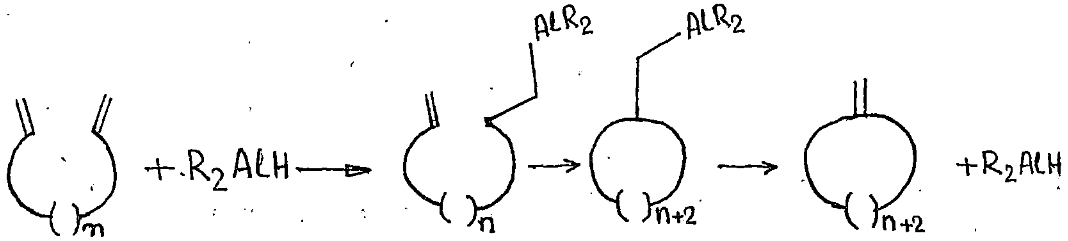
CCLVI CCLVII

The thermally allowed ($\pi^{8s} + \pi^{2s}$) route to spiro annulation is exemplified by the addition of (CCLVIII) with tetracyano ethylene affording the adduct (CCLIX). The reaction involves dipolar intermediates since they would be particularly stabilized (See Ref. 130).



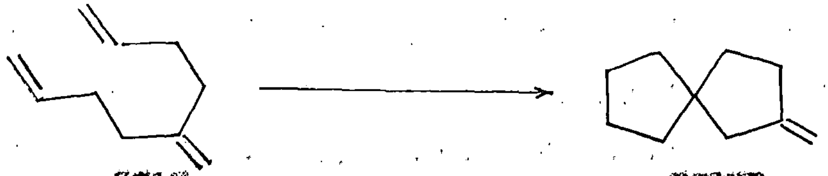
CCLVIII CCLIX

SPIRANES USING ORGANOMETALLIC REAGENTS: It was known for some time that insertion of a carbon-carbon double bond into an aluminium-carbon *sigma* bond can occur in an intramolecular fashion producing cyclic structure(306) e.g.,



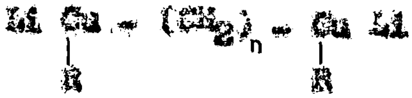
Since the insertion of a carbon-carbon double bond into an aluminium hydrogen bond readily takes place in a reversible process, only a catalytic amount of dialkyl aluminium hydride is required in such cyclization which is an advantage. This reaction has been exploited by CHUN and WILSON(47) in preparing 8-methylene spiro (4.4) nonane (CCLX) by treating 5-methylene

-1,8-nona diene (CCLX) with a catalytic amount of di-isobutyl aluminium hydride in mineral oil. In this case two double bonds undergo the intramolecular insertion reaction.



CCLX CCLXI

Another use of organometallic compounds in the synthesis of spiro compounds has been reported by WENDER and ECK (282) who used organobiscuprates in annulating halocycloalkenones. They utilized the findings of CASEY, MARTEN and BOGGS (43) that 3-acetoxy cyclohex-2-enone is converted upon reaction with lithium dimethyl cuprate into 3,3-dimethyl cyclohexanone. Accordingly WENDER and ECK used dilithio-bis-cuprate of the type (CCLXII) and found that the reaction of 3-acetoxycyclohex-2-enone with the reagent (CCLXII,a) proceeds with the cleavage of oxygen-acetyl bond to provide mainly cyclohexane-1,3-dione rather than the expected spiran.



$$\underset{R}{\mathrm{Li\ Cu}} - (CH_2)_n - \underset{R}{\mathrm{Cu\ Li}}$$

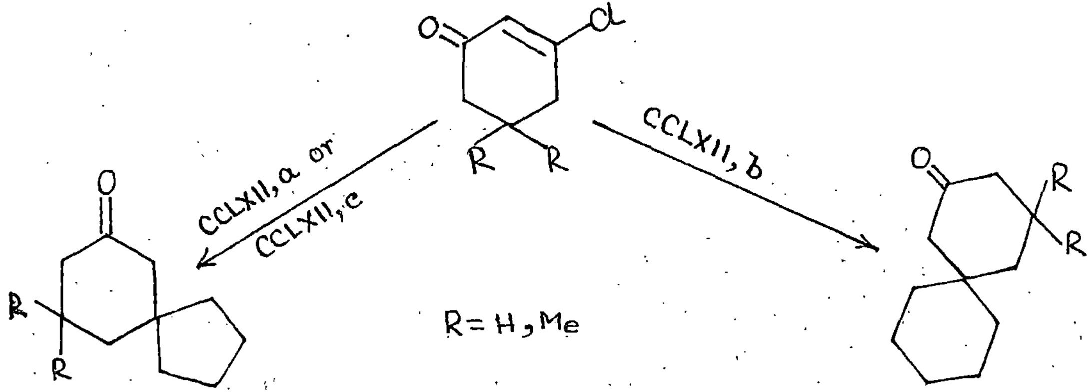
CCLXII

a, n = 4 ; R = SPh

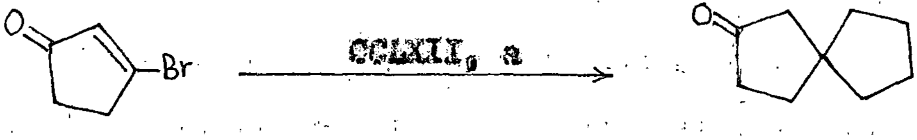
b, n = 5 ; R = SPh

c, n = 4 ; R = -(C ≡ C-Pr)

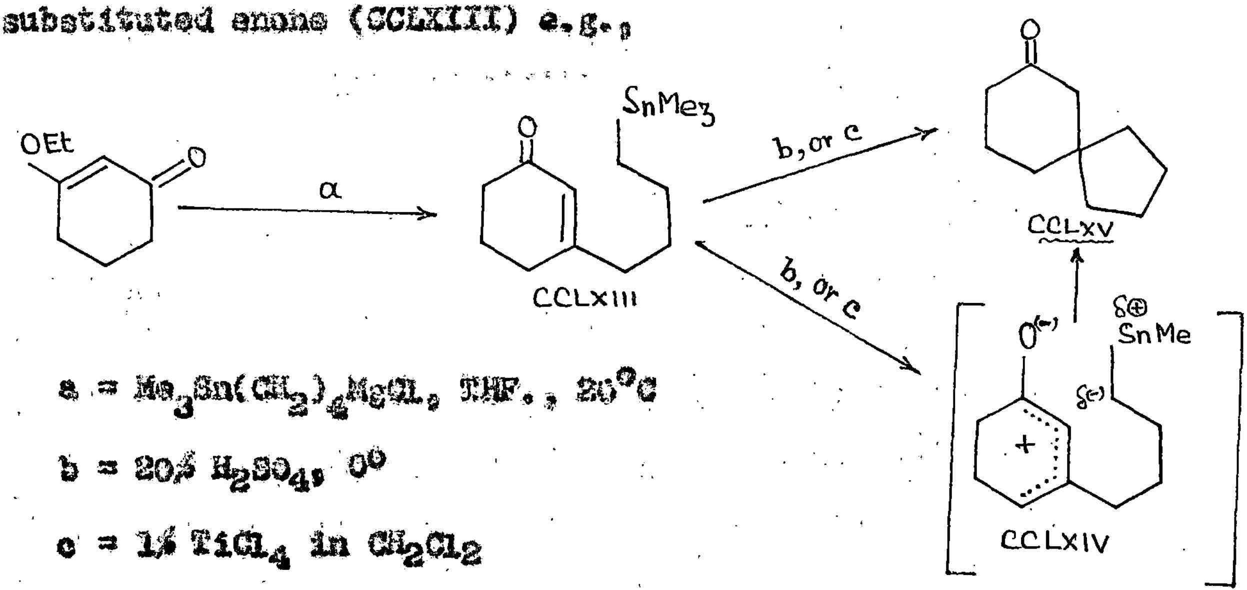
However, screening of the other 3-substituted enones eventually led them to observe that the readily available 3-chloro enones serve as suitable substrates for the desired spiro annulation procedure, e.g.,



Also they extended this spiro annulation strategy to bormoenones e.g.,



MACDONALD and MAHALINGAM (250) reported a method for effecting intramolecular conjugate addition to 2-cyclo-hexenone of unactivated carbon nucleophiles which proceeds through the mediation of novel-alkyl-tin (IV) chemistry. This method of cyclisation illustrates the use of carbon-tin *sigma* bond as a latent carbanionic nucleophile in the internal carbon-carbon bond formation. The cyclisation method employed activation of the *alpha-beta* enolic moiety with Lewis acid to engender a *beta*-electrophilic site (e.g. CCLXIV) which is sufficiently potent to react with a stereo-proximate carbon-tin-*sigma* bond. The ability of this method to create quaternary carbon-carbon bonds has been demonstrated by the formation of spiro cycle (CCLXV) from the *beta* substituted enone (CCLXIII) e.g.,



CCLXIII

CCLXV

CCLXIV

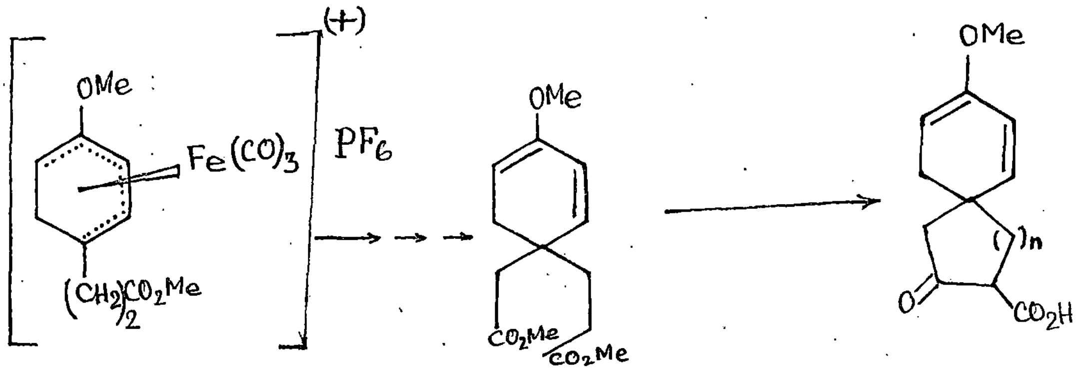
a = $Me_3Sn(CH_2)_4MgCl$, THF., 20°C

b = 20% H_2SO_4, 0°

c = 1% $TiCl_4$ in CH_2Cl_2

A synthetically useful feature of this approach to carbocyclization is that the weakly polarised nature of the carbon-tin *sigma* bond ($\overset{\delta(-)}{C} - \overset{\delta(+)}{Sn}$) ensures compatibility of the *alpha*-enone and tetra-alkyltin moieties until electrophilic activation.

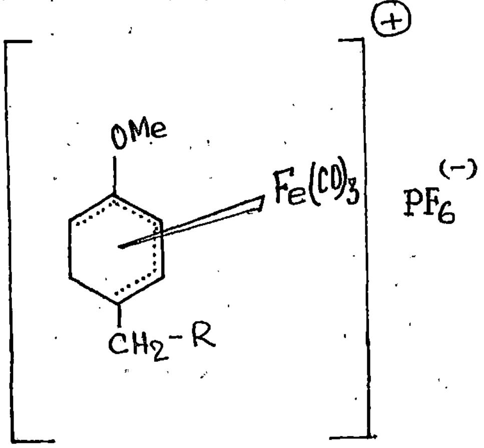
The attempt of PEARSON (212), directed towards the development of a spiro-annulation route gave the synthetic application of cyclohexadiene iron tricarbonyl complex to spirans. Thus the exospirodecadiene derivative (CCLXVIII, n = 1) was prepared in eight steps from p-methoxy cinnamic acid via the tricarbonyl iron complex (CCLXVI). The keystep in the reaction sequence was Dieckman cyclization of (CCLXVII) prepared from (CCLXVI) by sequential treatment with sodio-dimethyl malonate in T.H.F., trimethyl amine N-Oxide in benzene, and tretramethyl ammonium acetate in hot hexamethylphosphoramide (H.M.P.A). A similar series of reactions starting from 4-(p-methoxyphenyl) butyric acid led ultimately to methyl-3-methoxy-8-Oxospiro (5.5) undeca-1,3-diene-9-carboxylate (CCLXVIII, n = 2)

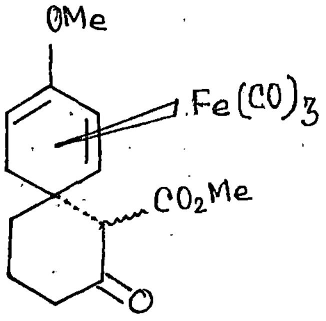


CCLXVI CCLXVII CCLXVIII

The attempted spiro cyclization of tricabonyl-[(dimethyl — 3-(4-methoxy cyclo hexa-2,4-dienylium) propyl malonate] iron hexafluorophosphate (CCLXIX) and the corresponding 3-oxo-pentanoate iron hexafluorophosphate (CCLXX) to the desired spiro (4.5) decane derivatives failed under a variety of mild conditions but, spiroannulation of tricarbonyl [methyl-6-(4-methoxy cyclohexa-2,4-dienylium)-3-oxohexanoate]-iron hexafluorophosphate (CCLXXI) occured smoothly and rapidly at

-78° to give the spiro (5,5) undecane (CCLXXII) as a mixture of diastereo isomers (213)





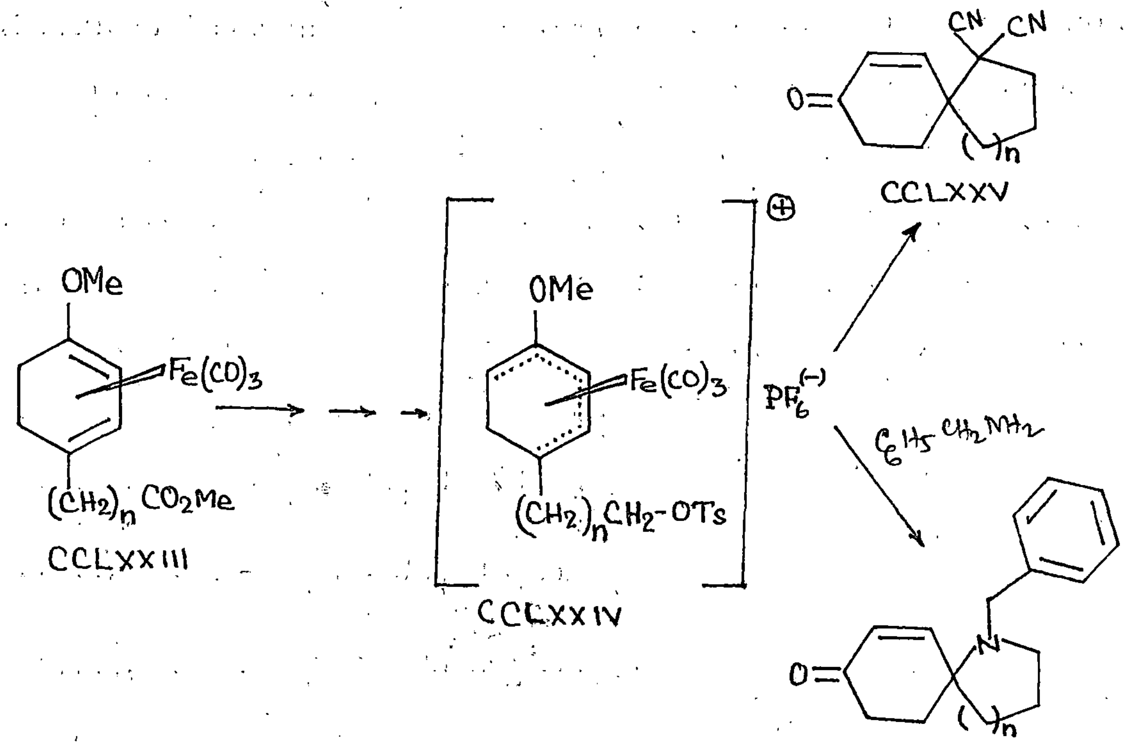
CCLXXII

CCLXIX, $R = -[CH_2 - CH_2 - CH(CO_2Me)_2]$

CCLXX, $R = -[CH_2 - CO - CH_2 - CO_2Me]$

CCLXXI, $R = -[CH_2 - CH_2 - CO - CH_2 - CO_2Me]$

The method was extended by PEARSON, HAM, and RESS (214) to the construction of azaspirocyclic compounds which, as envisaged by them, may have considerable potential in the synthesis of histrionicotoxin and cephalotaxus alkaloids. Thus the cyclohexadienylium complexes (CCLXXIV, n = 1,2) were prepared from the ester complexes (CCLXXIII, n = 1,2) by sequential reduction, tosylation and hydride abstraction. Reaction of (CCLXXIV, n = 1,2), with sodium malononitrile followed by demetalation and hydrolysis gave the spirocyclic enones (CCLXXV, n = 1,2) whereas reaction of (CCLXXIV, n = 1,2) with benzyl amine followed by demetalation and hydrolysis gave azaspirocyclic enones (CCLXXVI, n = 1,2)



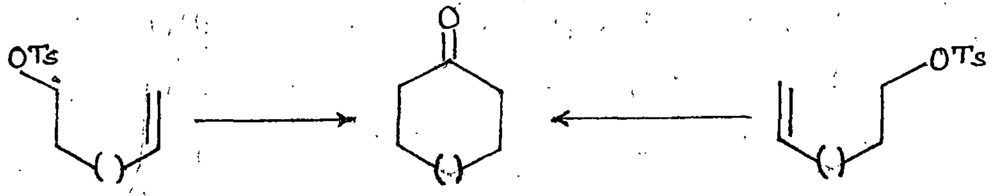
CCLXXIII

CCLXXIV

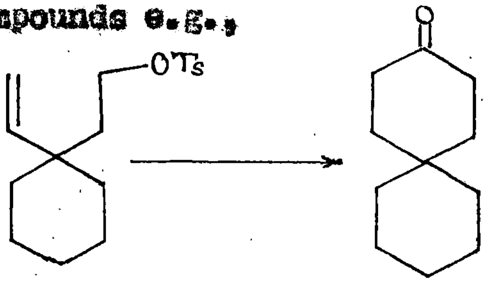
CCLXXV

CCLXXVI

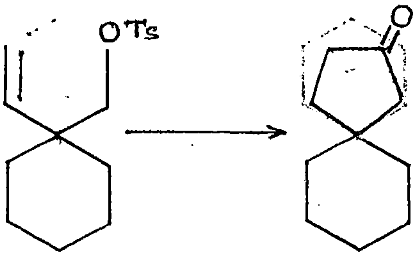
Cyclocarbonylation of olefinic tosylates with Collaman's reagent, disodium iron tetracarbonyl, was an effective method for the preparation of cyclopentanone and cyclohexanone (49,179,232). The potential value of the process stems from the fact that it allows chemists a fundamentally new and different way of preparing cycloalkanes. For planning purposes, one can dissect the cycloalkanone into two different olefinic tosylates which might serve as simple precursors to more complex targets e.g.,



By way of preparing (CCLXXVII) and (CCLXXVIII) McCURRY and ANDRUS (170) showed that the cyclo carbonylation reaction is an effedtive means of preparing five & six membered rings and also is a good method for the preparation of difficulty accessible spiro compounds e.g.,



CCLXXVII

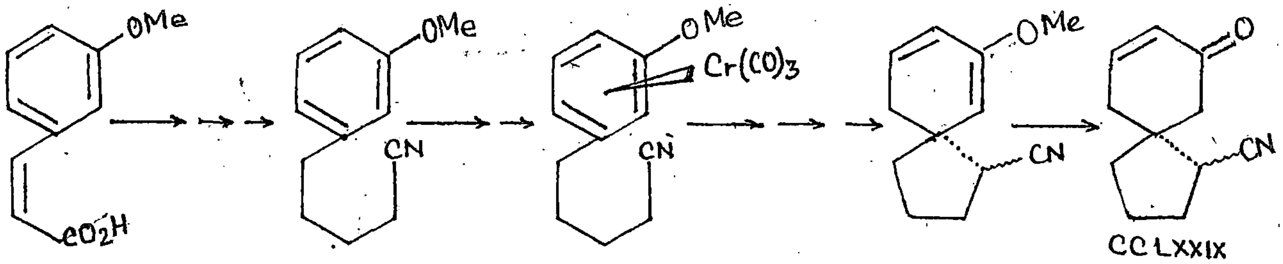


CCLXXVIII

The reaction has been shown to be limited to mono-substituted olefins. Attempted cyclocarbonylation of disubstituted olefins led only to aldehydes.

The spiro annulation strategy of SEMMELHACK, et al relies on the activating and meta-directing effects of the chromium tri-carbonyl group to introduce the spiro cyclopentane unit by nucleophilic addition to an anisole derivative (247,248,249).

A model sequence for this new approach to spiranes has been exemplified by the conversion of m-methoxy cinnamic acid to the spiro (4,5) cyclohexanone (CCLXXIX) which is definitely an intramolecular nucleophilic addition to the aromatic ring(248)

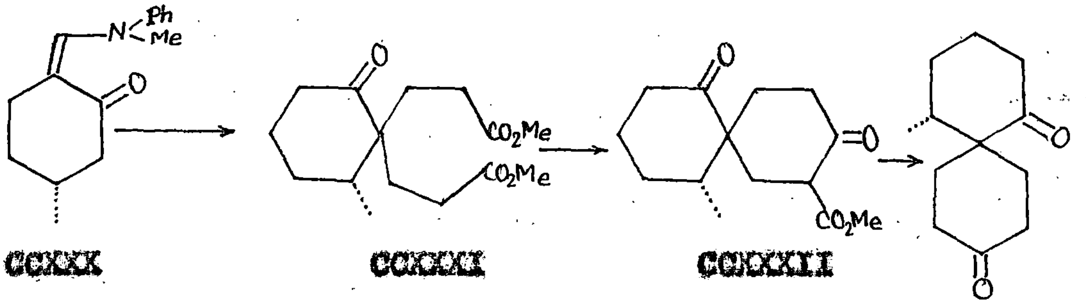


CCLXXIX

The method has also been applied by them in synthesizing acorenone and acorenone-B(249).

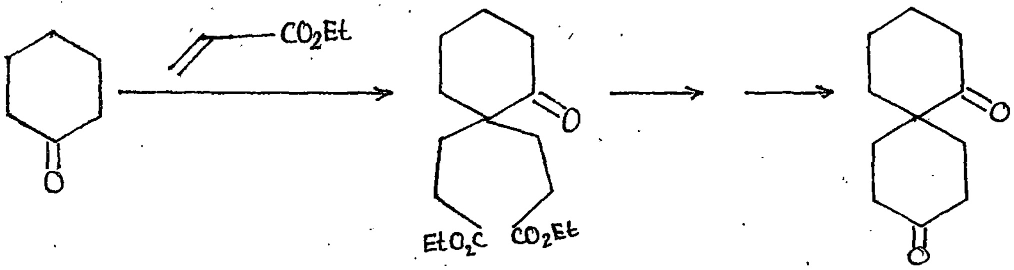
<u>MISC. SPIRO ANNULATION ROUTES:</u> The development of a method for geminal disubstitution on the <u>alpha</u> carbon atom of a cyclo alkanone followed by the application of Dickman cyclization route to spiro cyclic compounds has been reported by GUEST, HUGHES, RAMGE and SATTAR in their synthesis of (-) <u>alpha</u>-and (+) <u>beta</u> acorenol(95). The process involved the protection at C_6 of (+) - (3R)-methyl cyclo hexanone by formylation and subsequent formation of N-methyl amino derivative (CCXXX). Cyano ethylation followed by basic hydrolysis and subsequent esterification gave the keto ester (CCXXXI) which on cyclization using molecular sodium gave

the spiran (CCXXXII).



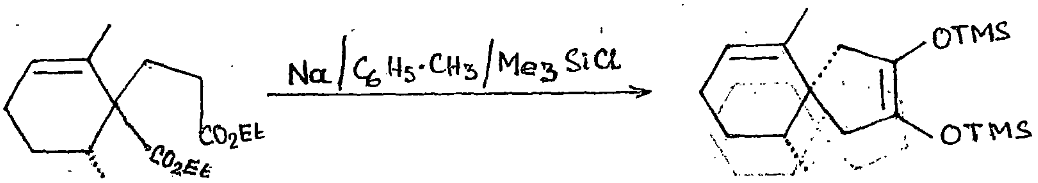
CCXXX CCXXXI CCXXXII

The reaction of cyclo hexanone with ethyl acrylate was reported to yield the keto ester (CCXXXIII) which on cyclization (16) gave spiro (5.5) undecane 1,9-dione (CCXXXIV).



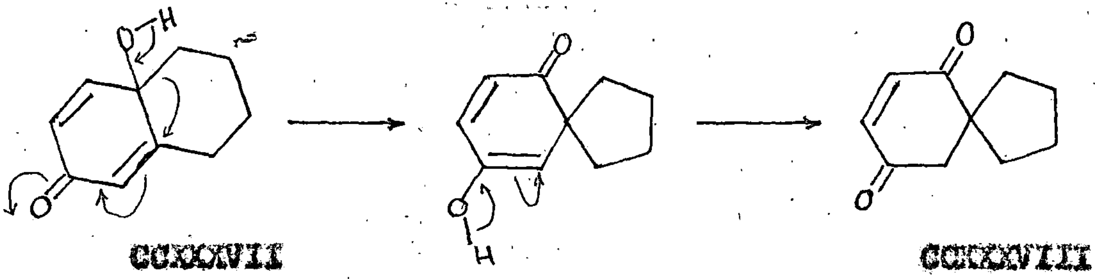
CCXXXIII CCXXXIV

The synthesis of spiro vetivanes by IIUKA, HAYASHI and MINAKATA (117) involved the acyloin intermediate (CCXXXVI) prepared by the cyclization of the diester (CCXXXV) e.g.,



CCXXXV CCXXXVI

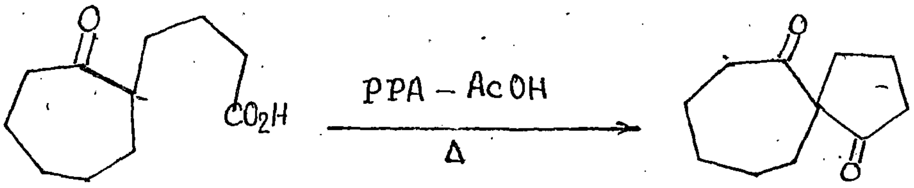
The dienone-phenol rearrangement route to (4.5) spiro decane skeleton is exemplified in the rearrangement of 6-hydroxy bicyclo (4.4.0) deca-1,4-dien-3-one (CCXXXVII) under the catalyzing influence of boron trifluoro etherate to spiro (4.5) dec-7-ene-6,9-dione (CCXXXVIII)(32).



CCXXXVII

CCXXXVIII

The synthesis of spiro (4.6) undecane-1-6-dione (CCXC) via an acid catalyzed intramolecular Claisen condensation of 4-(2' -oxocycloheptyl) butyric acid (CCLXXIX) has been described by WHEELER, JACKSON and YOUNG(284) e.g.,

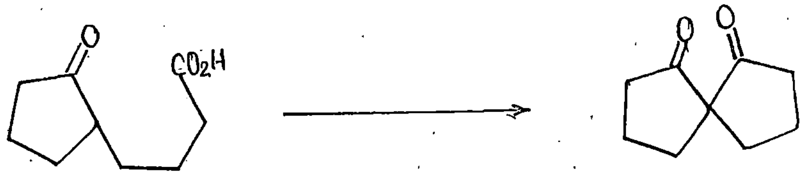


CCLXXIX

CCXC

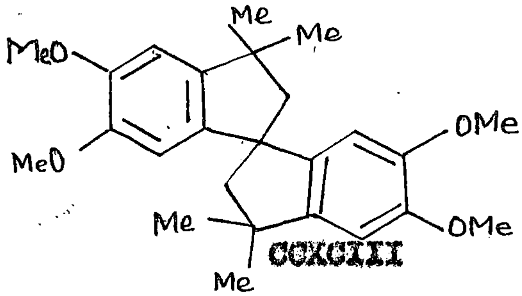
Actually the work is an extension of the observation made by GERLACH and MÜLLER (88,89) who reported that 4-(2'-oxocyclopentyl) butyric acid undergoes cyclization with polyphosphoric acid-acetic acid solution to afford an excellent yield of spiro (4.4) nonane-1,6-dione.

The cyclization of oxo acids, e.g. (CCXCI) to the cyclic-beta-diketone (CCXCII) has also been reported to be catalyzed by 2-naphthyl sulphonic acid (41).



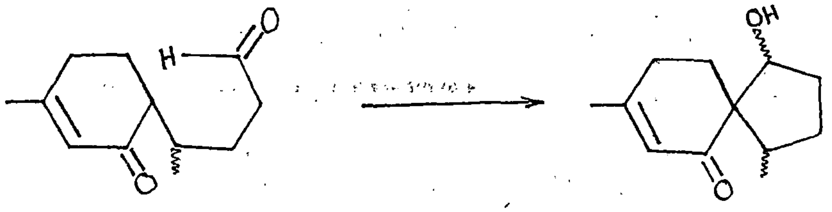
CCXCI CCXCII

The acid catalyzed condensation of phenolic ethers e.g. varatrole with carbonyl compounds e.g. acetone resulted in the formation of spiro annulated product (CCXCIII) (10).



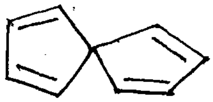
CCXCIII

The intramolecular aldol condensation of the keto-aldehyde (CCXCIV) to the spiro (4.5) decane derivative (CCXCV) has been reported by GOLDBERG and DRIEDING(91).

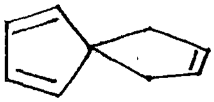


CCXCIV CCXCV

SEMMELHACK(246) has prepared spiro (4.4) nonatetraene (CCXCVI) by a relatively direct synthesis starting from allyl bromide and diethyl malonate. Also they have prepared nona (1,3,7) triene (CCXCVII) by a new route starting from cyclopentadienide anion and 4,5-di(bromomethyl) 2,2 dimethyl-1,3-dioxolane. Their report also contains a brief review of the use of cyclopentadienide anion in spirene synthesis.



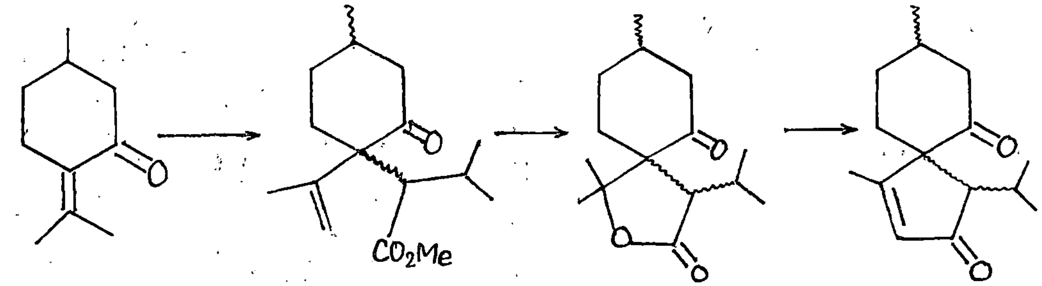
CCXCVI



CCXCVII

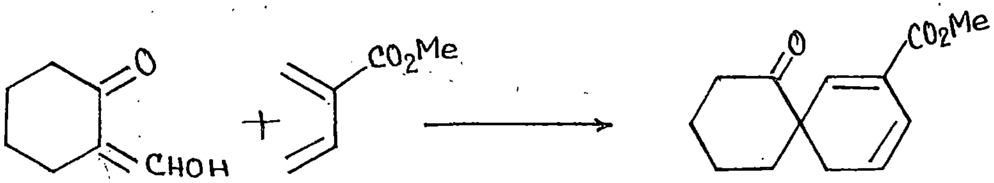
Another spiro annulating procedure of potential value has been developed by VISWANATH and KRISHNA RAO(277) on their way to synthesize acorenone skeleton by exploiting the gamma lactone-cyclopentenone transformation. Thus the spiro keto lactone

(CCC) was obtained from pulegone (CCXCVIII) by alkylation with methyl, alpha bromoisovalerate. Polyphosphoric acid treatment of (CCC) followed by equilibriation of the nonlactonic neutral product with sodium methoxide gave the bicyclic spiro enodione (CCCI) of the acorenone skeleton.



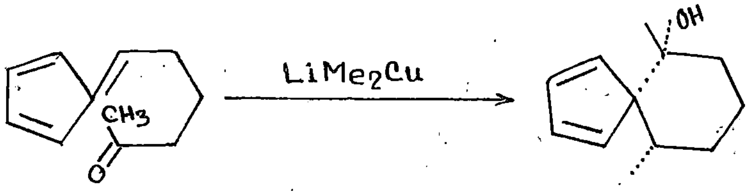
CCXCVIII CCXCIX CCC CCCI

The reaction of formyl hexanone and beta-vinyl acrylate in presence of DMSO (-) in DMSO has been shown to afford a mixture containing 40% of (CCCII). The reaction ~~may be deemed as a Lewis acid catalyzed cycloaddition reaction and~~ is a potentially important route to the functionalized spirane synthesis.(200)



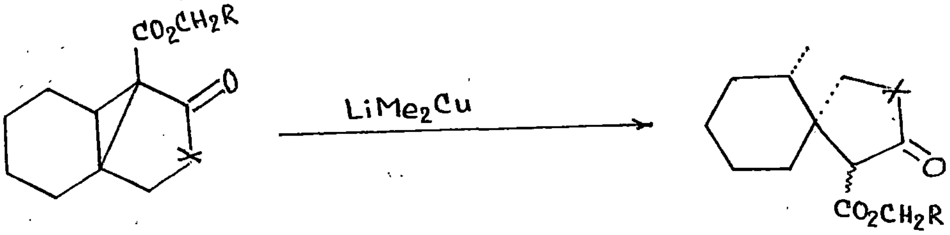
CCCII

Synchronous methyl addition to a carbonyl group and its cyclisation to the spiro cyclic carbinol (CCCIII) has been demonstrated by HÜNIG et al (31) through the use of lithium dimethyl cuprate in their synthesis of spiro vetivanes from fulvene, e.g.,



CCCIII

HEATHCOCK et al,(48) used lithium dimethyl cuprate in opening the cyclopropane ring of (CCCIV) to obtain the spirane (CCCV).



CCCIV

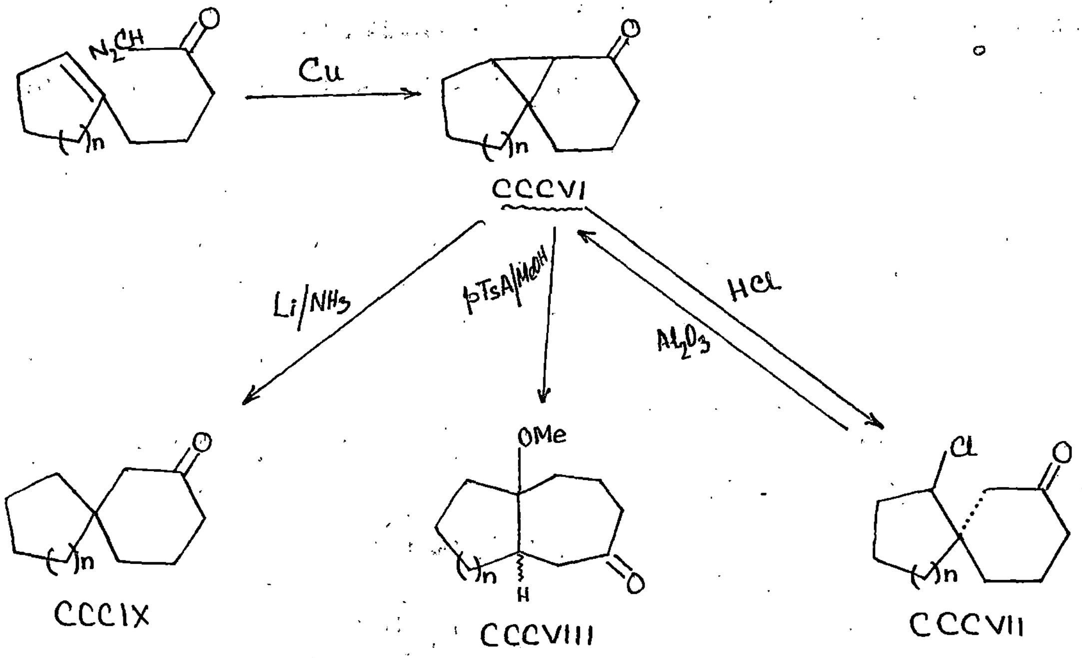
CCCV

$X = O, R = CH_3$

$X = CH_2, R = H$

WHITE(235,236,237) et. al described a method for the synthesis of spiro cyclic systems based on the intramolecular cyclo addition of a diazoketone followed by reductive scission of the peripheral bond in the cyclopropane. (±) Chamigrene, a spiro (5.5) undecane, was synthesized by them earlier by(235) this type of approach when the cyclopropane ring was opened by lithium and ammonia and the spirane (CCCIX) was formed. The cleavage was shown to be governed primarily by the stereo electronic factors(62,63).

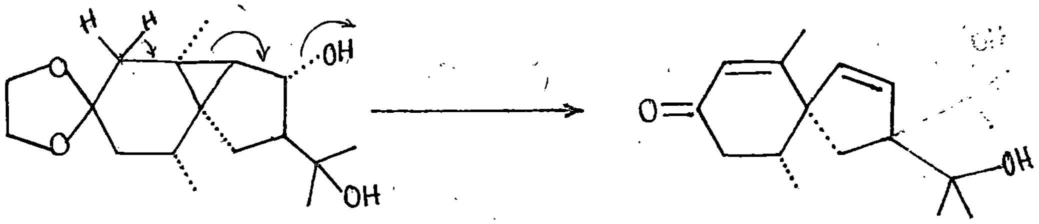
Fission of the cyclopropyl ring in (CCCVI) when carried out in a two phase system of concentrated hydrochloride acid and ether, they obtained a single spiro cyclic chloroketone whose structure was established as (CCCVII) whereas para toluene sulphonic acid catalyzed cleavage gave the fused product (CCCVIII) e.g.,



The methodology described above has been successfully applied by WHITE et.al (285) in synthesizing the spiro cyclic structure of (±) alpha-chamigrene, (-) acorenone-B and (-)-4-epi-acorenone-B .

DESLONGCHAMPS et. al (145,184) in their synthesis of

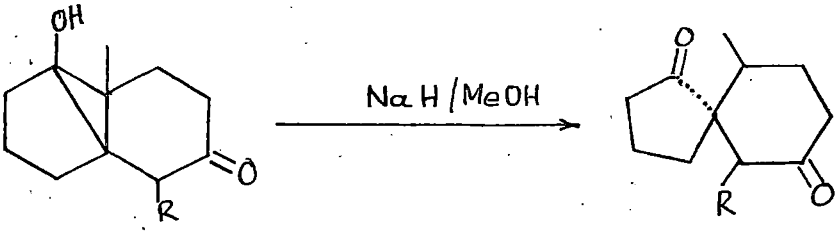
(±) — *epi* hinesol successfully exploited the principle that tricyclic structures like (CCCX), generated by the intramolecular addition of carbenoid to a cyclic ketone, can undergo cleavage of the exterior cyclopropane bond to yield the required skeleton as depicted in (CCCXI).



CCCX

CCCXI

Reductive opening of 1-methyl tricyclo $(4.4.0.0^{2,6})$ decane-3-one provides a general method of synthesis of spiro (4.5) decanone derivatives(37,62,220,224). A review on spiro annulation *via alpha* (cyclopropyl methylene) cycloalkanones has been published by PIERS and LAU(221). REUSCH *et. al*(224) reported that cyclopropanol (CCCXII) can be rearranged to spiro (4.5) dione (CCCXIII) with sodium hydride in methanol, e.g.,

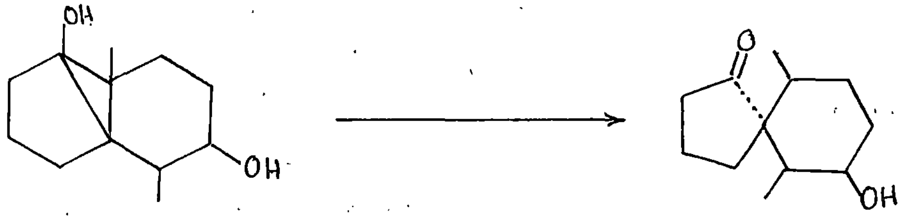


CCCXII

CCCXIII

$R = H, CH_3$

The synthesis of <u>beta</u>-betivone by SUBRHAMANIAN and REUSCH(261) employed the acid catalyzed ring opening of cyclopropanol (CCCXIV) in spiro skeleton formation step

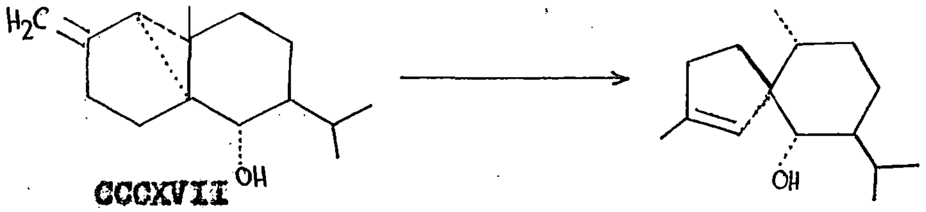


CCCXIV

Lithium-liquid ammonia cleavage of tricyclodecanone (CCCXV) by CAINE <u>et. al</u> showed that the opening of cyclopropane ring to the corresponding spiro ketone (CCCXVI) occurs exclusively with inversion of configuration at the <u>beta</u> carbon atom (C-1)(37) e.g.,

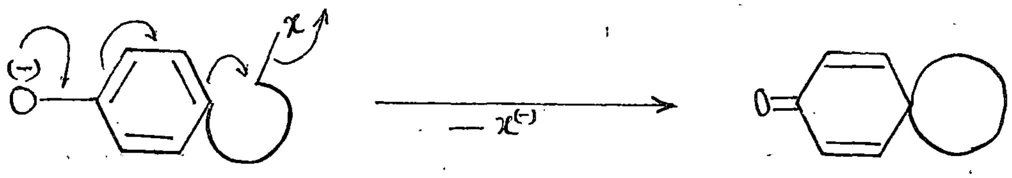
CCCXV CCCXVI

The synthesis of (-) axisonitrile-3 by CAINE and DEUTSCH(38) utilized the same cleavage reaction on the exomethylene compound of the type shown above, e.g.,



CCCXVII

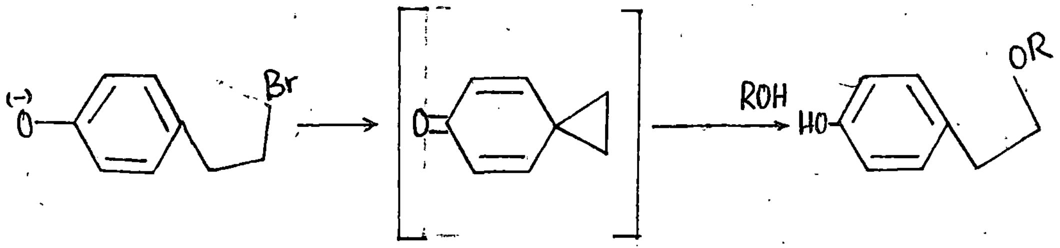
ARYL PARTICIPATION REACTION: It was found feasible to arrange for the formation of a dienone through aryl — participation reaction of a neighbouring phenoxide ion group through proper selection of the structure of a phenolic compound and the appropriate reaction environment. That means, if a suitably located electrophilic center can be created on the branch chain of a 4-alkyl phenolate ion, then in a suitable environment intramolecular alkylation on the phenolic ring may occur in its 4-position leading to a spiro dienone as product. The situation may be explained as,



Of course, the possibilities of the other competing reactions to occur cannot be overruled at the first instance.

The validity of the above idea has been reflected in the "Desaromatization reaction" of DREIDING(75) who obtained spiro (5.5) undeca-1,4-diene-3-one by heating a dilute solution of the potassium salt of 5-(p-hydroxy phenyl)-1-bromopentane; and in the work of BAIRD and WINSTEIN(14) who prepared spiro (4.5) deca-1,4-diene-3-one by treating the dilute solution of 4-(p-hydroxy phenyl)-1-butyl-p-bromobenzene sulphonate with a slight excess of potassium tert-butoxide in anhydrous tert-butanol. Both the schools used extremely dilute solution of the phenols in order to avoid the other competing intermolecular reactions.

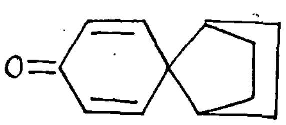
The aryl - participation reactions have been shown to be highly dependent on the nature of the solvent used as reaction medium. Uptil now *tert*-butanol has been shown to be the best for these reactions to occur. In general these reactions have been applied in preparing spiro (4.5) and spiro (5.5) skeleton (the $Ar_1^{(-)}-5$ and $Ar_1^{(-)}-6$ participation reactions) but the attempt to isolate the dienone (CCCXVIII) resulting from assisted alkylation of 2-(p-hydroxy phenyl) ethyl bromide was unsuccessful although there is evidence that the reaction proceeds through the dienone intermediate$^{(14)}$.



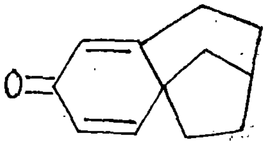
CCCXVIII

The ease of five or six membered ring annulation may be attributed to the lower ring strain associated with them. Using different nucleophiles in the alkyl side chain and applying different reaction conditions several other spiro dienones have been prepared by way of exploiting these $Ar_1^{(-)}$ - assisted intramolecular alkylation reaction.

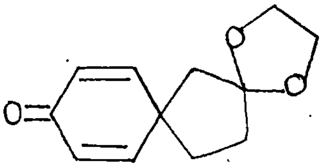
Examples are (CCCXIX)(17), (CCCXX)(167) and (CCCXXI)(73)



CCCXIX

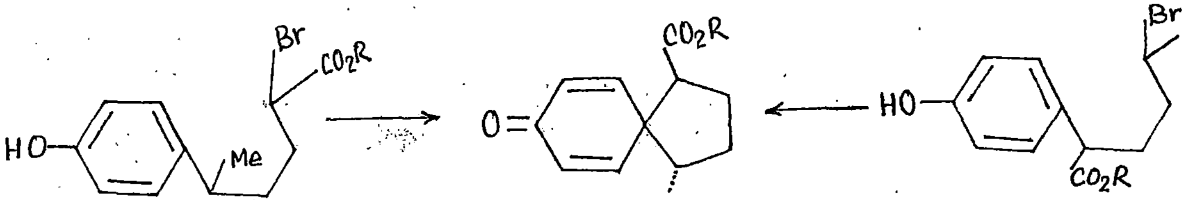


CCCXX



CCCXXI

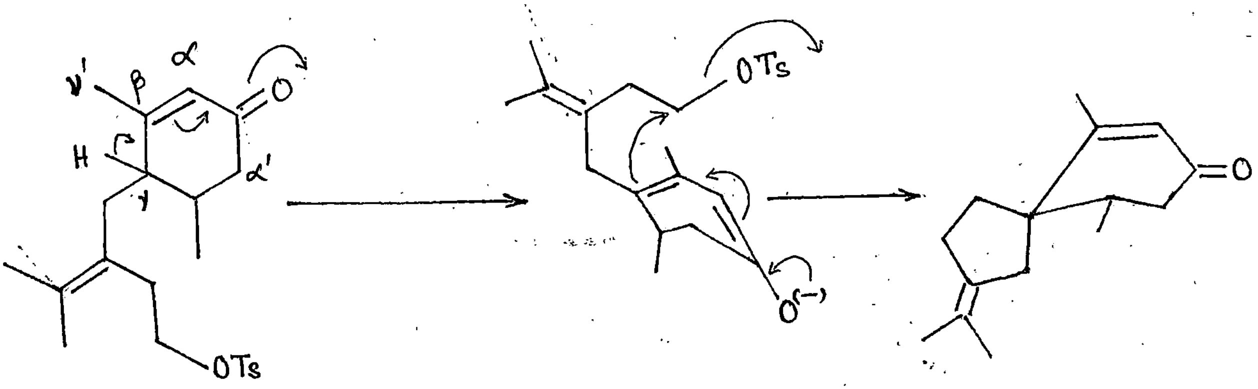
This reaction has been exploited in the synthesis of cedrene by two research groups working independently(54,59). Both of them employed phenolic bromo esters (CCCXXII) and (CCCXXIII) respectively, as key intermediates which afford the spiro (4.5) decane derivatives (CCCXXIV) (R = Me, Et) upon treatment with potassium tert-butoxide.



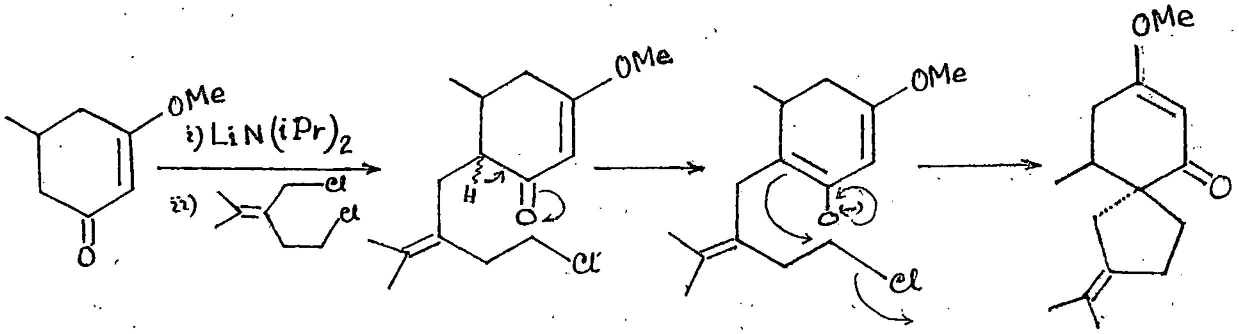
CCCXXII CCCXXIV CCCXXIII

R = Me, Et.

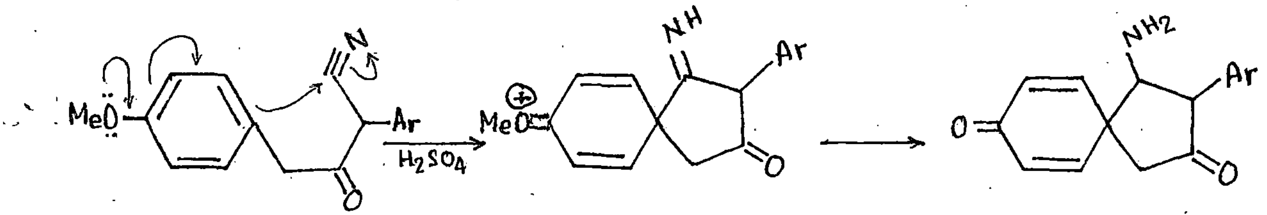
The application of spiro annulation via $Ar_1^{(-)}$-5- participation of alkyl phenols to the synthesis of terpenoids has been demonstrated by MUKHERJEE(186) and MASAMUNE(168). Recently TORII, UNEYAMA and OKAMOTO have synthesised(266,274) beta-vetivone using this tool of spiro annulation. The internal alkylation route to spiranes has successfully been applied by JOHNSON(126) to a non-aromatic system in his synthesis of racemic beta vetivone e.g.,



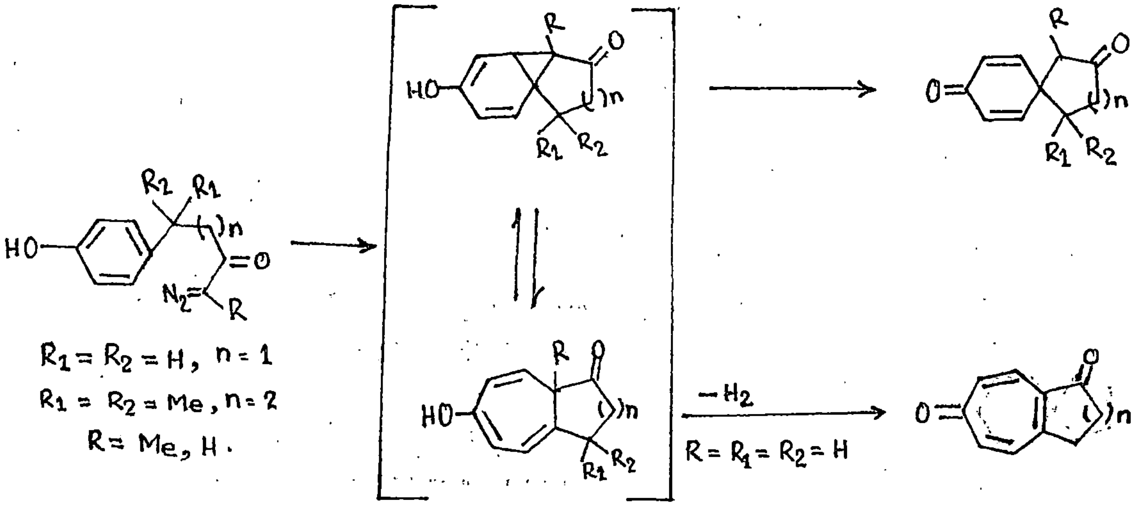
In the exceedingly elegant synthesis of <u>beta</u>-vetivone by STORK <u>et</u>. <u>al</u>., (258) the key step involved alkylation of the kinetic enolate of the enol ether of -4-methyl cyclohexane-1, 3-dione with 2-isopropylidine-1, 4-dichlorobutane. The presumed intermediate chloroketone evidently undergoes a highly stereoselective internal alkylation reaction upon treatment with strong base like lithium di-isopropyl amine.



A unique $\overset{(-)}{Ar_1}-5$ assisted intramolecular alkylation reaction resulting from the electrophilic attack of a nitrilium ion at the one position of 4-methoxy phenyl ring has been reported by GAJEWSKI(87). The nonoccurance of spiro cation rearrangement to the fused system or the non-formation of the unwanted products resulting from the possible competing intermolecular reactions were the added advantages

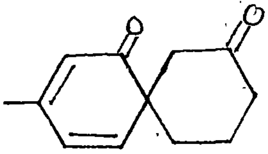


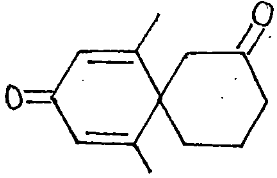
The cuprous ion catalyzed intramolecular cyclization of phenolic alpha-diazoketones in the synthesis of spiro (4.5) decane carbon frame work by IWATA et. al.(120) may be assumed to be another example of simple $\overset{(-)}{Ar_1}-5$ participation reaction at the first sight, assuming the diazogroup bearing carbon atom to act as the electrophilic center in the alkyl side chain, and thus fulfilling the required condition for $\overset{(-)}{Ar}$-participation to occur. Later studies showed that the reaction is not so simple as is assumed. The cyclization has been shown to proceed via norcaradiene derivatives and hence the aryl participation occurs, if at all does, during the opening of cyclopropane ring e.g.,



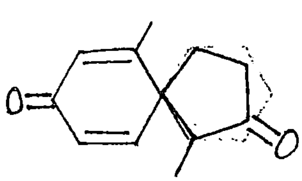
Based on this spiro annulation process, IWATA et. al. synthesized alpha chamigrene (122).

Similar intramolecular alkylation of phenolic diazocompounds has been carried out by BHATTACHARYA and SEN using boron triflouride etherate as catalyst (22,23). They prepared the spiro compounds (CCCXXV & CCCXXVI) (22) and (CCCXXVII) (23) from the corresponding diazoketo phenols.


CCCXXV



CCCXXVI

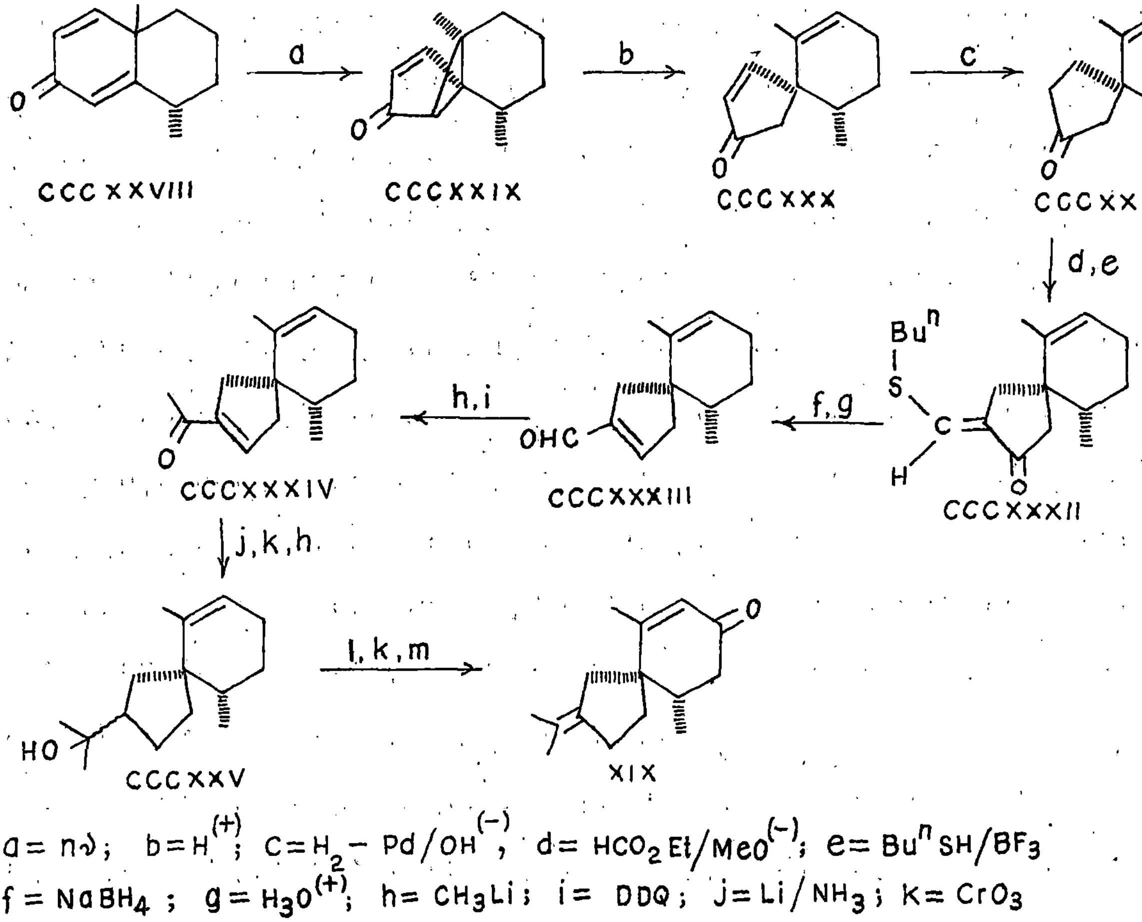


CCCXXVII

A good number of spiro annulation processes have earned their importance as synthetic tools in the synthesis of spiro sesquiterpenes.

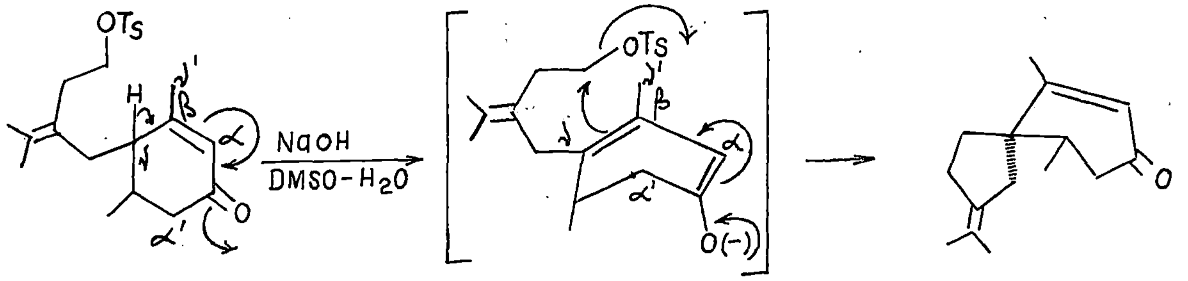
Uptil . now eighteen syntheses of *beta* vetivone has been reported in literature which are summarized below:

The first total synthesis of *beta* vetivone by MARSHALL and JOHNSON(155) employed the photochemical 2,5-cyclohexadienone rearrangement route to generate the spiro (4.5) decadienone (CCCXXX) from the appropriately substituted dienone (CCCXXVIII) via the cyclopropyl ketone (CCCXXIX). This route of preparing spiro (4.5) decanes by KROPP(140,141) has been discussed earlier. Selective reduction of the conjugated double bond afforded the enone (CCCXXXI). In order to introduce the iso-propylidene group at the proper position on the cyclopentane ring, the enone was condensed with ethyl formate when the condensation took place at the less hindered *alpha* position of this ketone to give a hydroxy methylene derivative which on subsequent treatment with butane thiol and boron trifluoride yielded the thioether (CCCXXXII). Sodium borohydride reduction of the oxo group in (CCCXXXII) followed by acid hydrolysis of the thio ether linkage and subsequent dehydration of the resulting alcohol led to the aldehyde (CCCXXXIII). The addition of methyl lithium to the aldehyde function of (CCCXXXIII) afforded a mixture of diastereomeric alcohols which on oxidation with 2,3 dicyano-5,6-dichloro-1,4 benzoquinone (DDQ) resulted in the conversion of secondary alcohol to the methyl ketone (CCCXXXIV). Selective reduction of the conjugated double bond in (CCCXXXIV) was accomplished by using lithium in ammonia-ethanol followed by the oxidation of the saturated alcohol distereomeric mixture to afford a nearly 1:1 mixture of two isomeric methyl ketones, differing in respect of the orientation of their respective acetyl substituents. Addition of methyl lithium afforded the corresponding alcohols (±) hinesol and (±) agarospirol (CCCXXXV). The conversion of the isomeric alcohols (CCCXXXV) to racemic beta vetivone was achieved along the route developed by YOSIOKA and KIMURA for the transformation of natural hinesol to (+)- beta vetivone (303)



$a = h\nu$; $b = H^{(+)}$; $c = H_2 - Pd/OH^{(-)}$; $d = HCO_2Et/MeO^{(-)}$; $e = Bu^nSH/BF_3$
$f = NaBH_4$; $g = H_3O^{(+)}$; $h = CH_3Li$; $i = DDQ$; $j = Li/NH_3$; $K = CrO_3$
$l = Ac_2O/NaOAc$; $m = BF_3$

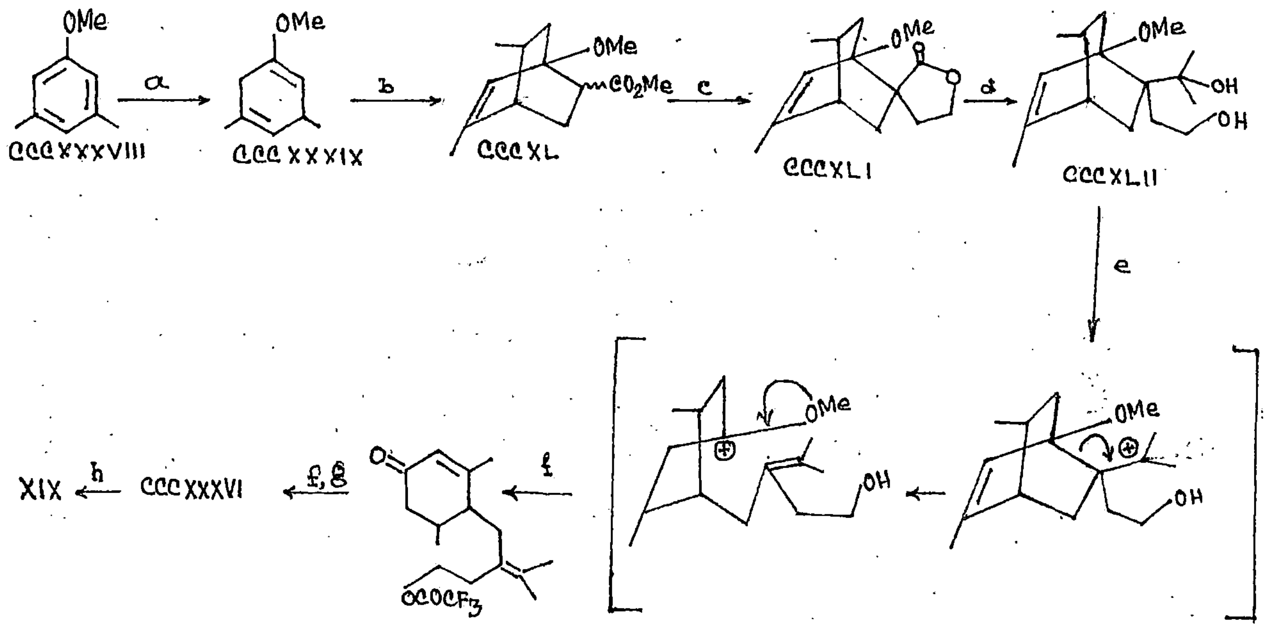
The second total synthesis of (±) **beta** vetivone by JOHNSON(126) involved the spiro annulation to the required (4.5) spiro skeleton in the final step by means of a stereo selective internal alkylation route, e.g.,



CCXXXVI CCCXXXVII XIX

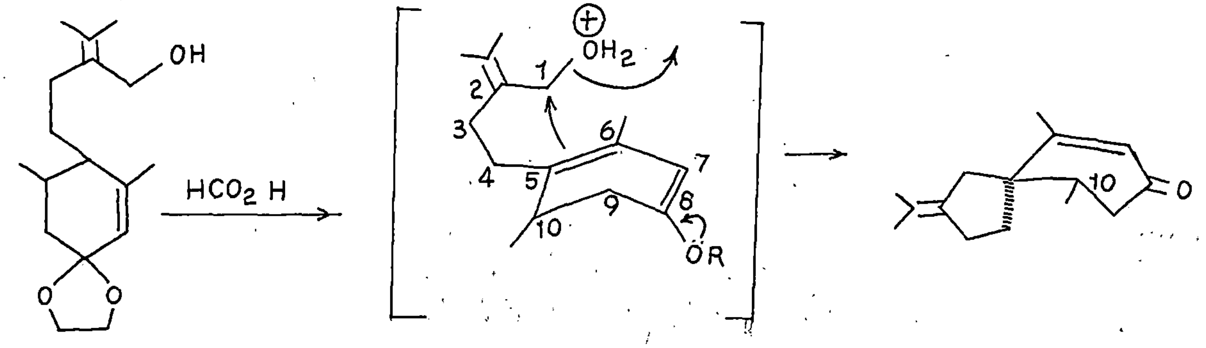
The enone (CCCXXXVI) could give rise to three different enolates which could, in turn, yield six different internal alkylation products, e.g. one from α'-alkylation, two from γ-alkylation, two from γ'-alkylation, and one from α-alkylation. After extensive experimentation, it was found that the use of sodium hydroxide in aqueous dimethyl sulphoxide could meet efficiently both the requirements, viz., preferential formation of the proper (gamma)-enolate as well as the stereo selective alkylation of this enolate to the ketone (CCCXXXVI) for being converted into racemic **beta**-vetivone (XIX). Presumably this particular basic solvent allowed the rapid equilibration of all possible enolates with the one depicted by (CCCXXXVII) being most prone to internal alkylation. The stereo chemistry of this step may be assumed to be controlled by the cyclohexyl methyl grouping, in so far as steric factor would favour the indicated arrangement.

The requisite enone (CCCXXXVI) was neatly prepared using 3:5 xylenol methyl ether (CCCXXXVIII) as the starting material. Birch reduction followed by Diels-Alder reaction of the product, the 1,4 diene (CCCXXXIX) with methyl acrylate afforded the stereo isomeric mixture of the adduct (CCCXL) in 2.5:1 ratio. Needless to say, the conversion required prior thermal isomerization of the diene (CCCXXXIX) to the 1,3 isomer, appropriate for Diels-Alder reaction to occur. The facile attack by ethylene oxide at the less hindered face of the ester enolate gave (CCCXLI) as the major component of the epimeric lactone mixture. Addition of methyl magnesium bromide to this lactone mixture gave the corresponding diol mixture (mainly CCCXLII) which underwent interesting fragmentation reaction(26) upon treatment with trifluoro acetic acid. Hydrolysis followed by esterification with p-toluene sulphonyl chloride afforded the desired enone (CCCXXXVI). The successful appropriate enolization followed by stereo controlled internal alkylation of (CCCXXXVI) completed the synthesis of (±) -*beta*-vetivone (XIX).



a = Li/NH$_3$; b = //‾CO$_2$Me / 140° ; c = ▷O/ Ph$_3$CLi ; d = MeMgBr ; e = CF$_3$CO$_2$H
f = NaHCO$_3$; g = p-TsCl ; h = NaOH/DMSO-H$_2$O.

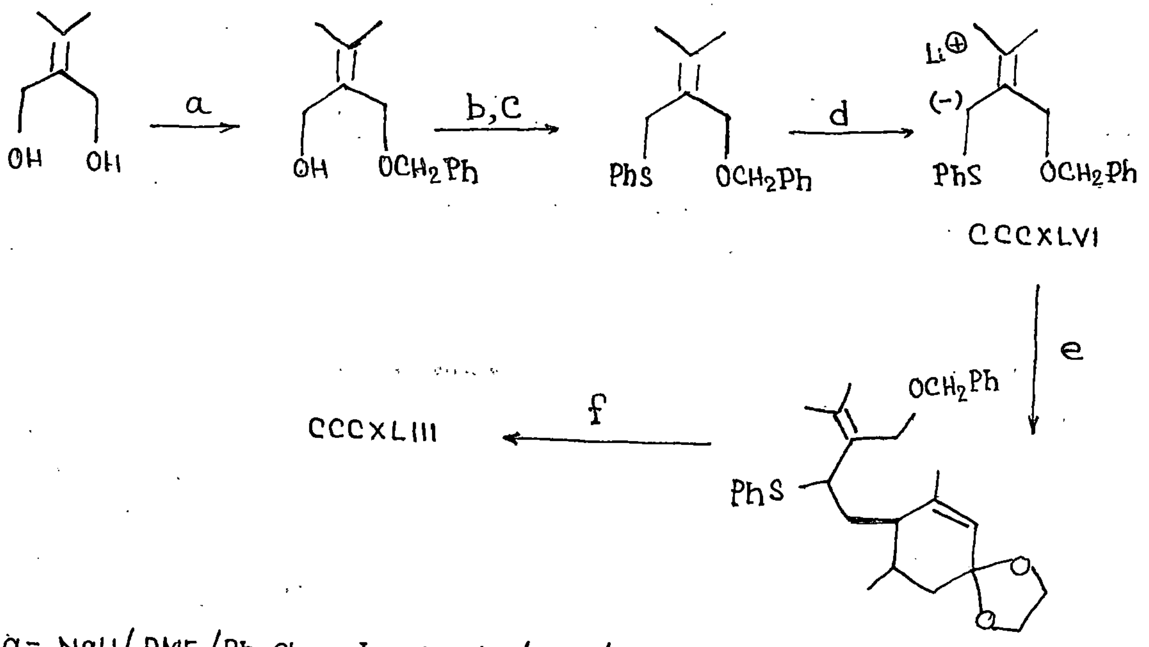
A related cationic cyclization route which resulted in the formation of (±) 10-*epi*-*beta* vetivone (CCCXLV) was reported by McCURRY *et. al.*(176). The final step in this case also involved the spiro annulation to (4.5) spiro decane skeleton as in the synthetic route developed by JOHNSON(126). The key annulation step in both the synthesis appears to be controlled by the stereochemical interactions which directed the formation of cyclopentane ring having *trans* geometry with respect to the adjacent methyl group e.g.,



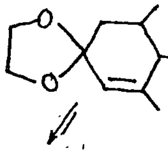
CCCXLIII CCCXLIV CCCXLV

Cf.(CCCXXXVI) ⟶ (XIX) in page 117)

The stereo selectivity of this spiro alkylation reaction has been described to be a result of "axial" alkylation in which the allylic carbon approaches the face of the molecule opposite the "pseudo axial" C_{10} methyl group. This is probably due to the lack of 1,3 axial-axial interaction and the minimization of Johnson-Mahlotra allylic 1,3 strain. Preparation of the penultimate intermediate (CCCXLIII) was effected through a convergent synthetic scheme involving alkylation of the lithio derivative with the indicated chloroketal (CCCXLVII). Reduction of the resulting product with lithium in ethyl amine effected hydrogenolysis of both the allylic sulphide and benzyl group to yield the alcohol (CCCXLIII)

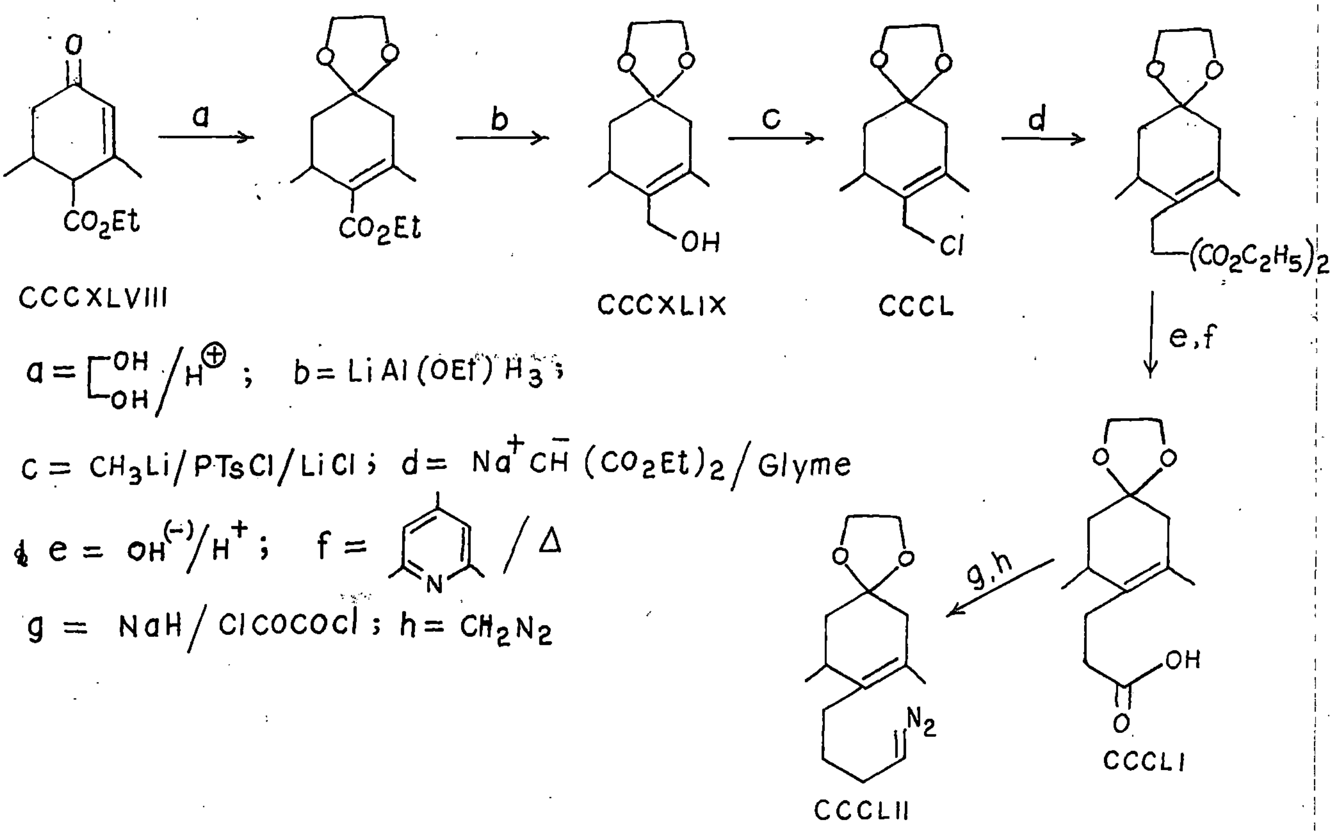


a = NaH/DME/Ph_2Cl; b = CH_3Li/TsCl/HMPA; c = LiSPh,

d = BuLi/DABCO; e =  , f = Li/EtNH_2/−78°C

CCCXLVII

A scheme for synthesizing <u>beta</u> betivone, closely related to that developed by DESLONG CHAMPS <u>et.</u> <u>al.</u>, for the synthesis of agarospirol (184) was conceived and executed by STORK and McCURRY (173,174). The effort utilized, as a route to spiro (4.5) decane skeleton, the copper catalyzed decomposition of the unsaturated diazoketone (CCCLII) prepared as follows:



CCCXLVIII CCCXLIX CCCL CCCLI CCCLII

$a = \left[{OH \atop OH}\right. / H^{\oplus}$; $b = LiAl(OEt)H_3$;

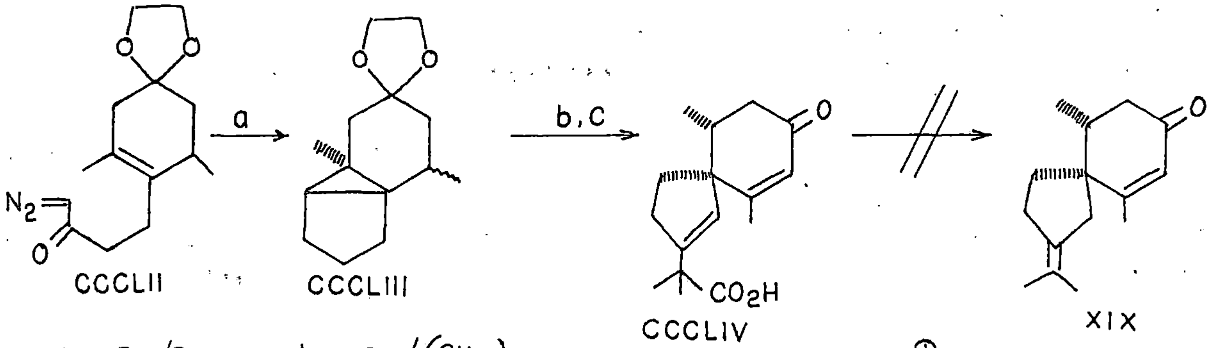
$c = CH_3Li/PTsCl/LiCl$; $d = Na^+\bar{C}H(CO_2Et)_2/$Glyme

$e = OH^{(-)}/H^+$; $f = \ / \Delta$

$g = NaH/ClCOCOCl$; $h = CH_2N_2$

The known compound (CCCXLVIII) was ketalized and then reduced with lithium monoethoxyaluminium hydride to afford the unsaturated alcohol (CCCXLIX). The unstable vinylogous beta-chloroketal (CCCL), prepared by using methyl lithium and para toluene sulphonyl chloride over lithium chloride, was submitted to malonic ester synthesis. The unsaturated ketal acid (CCCLI) was then converted to the diazoketone (CCCLII) via treatment of its acid chloride with an excess of diazomethane.

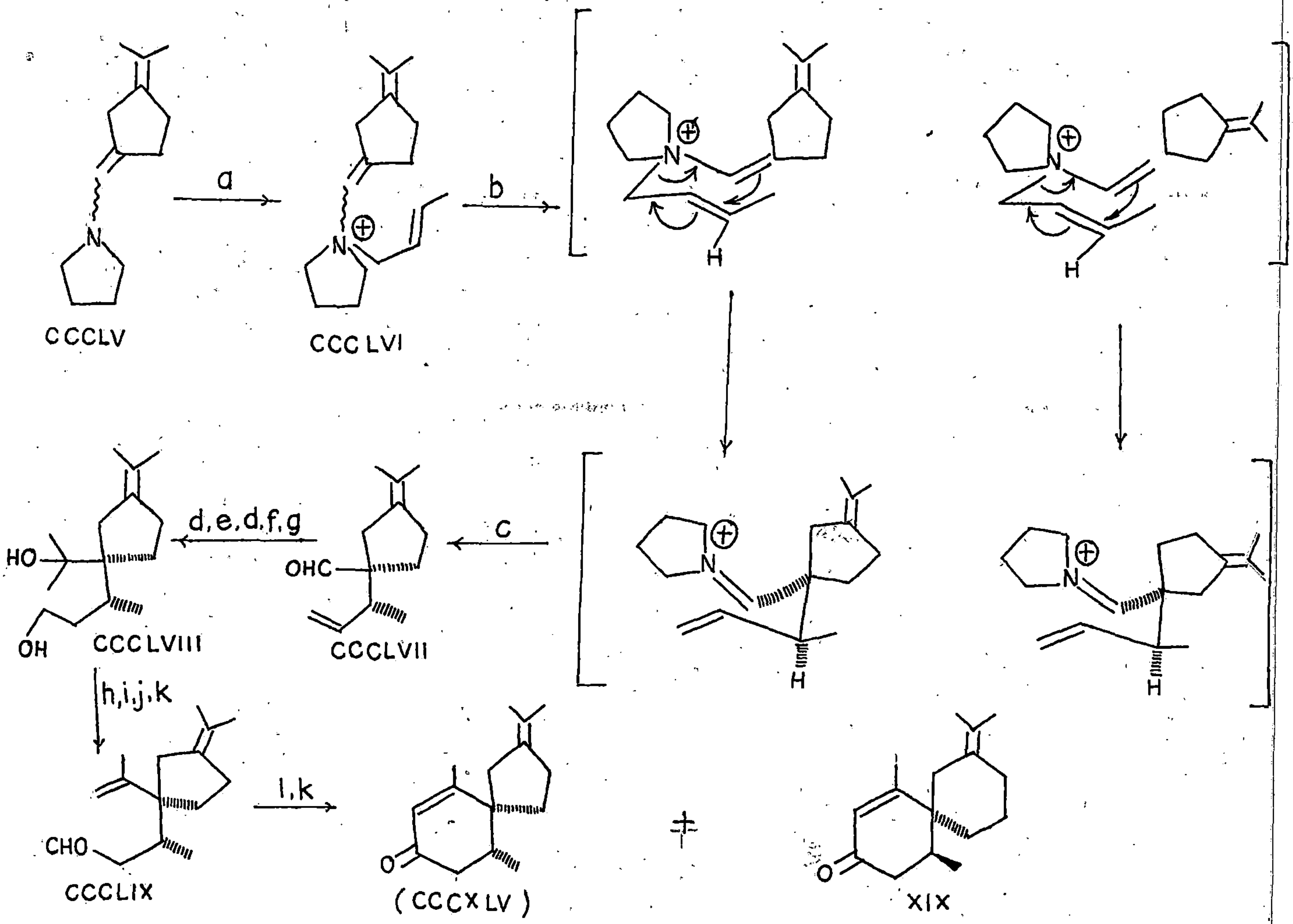
The intramolecular keto carbene insertion of (CCCLII) produced an epimeric mixture of the cyclopropyl ketone (CCCLIII) and the mixture was converted to the unsaturated acid via Reformatsky addition of ethyl-*alpha*-bromo isobutyrate followed by acidic cleavage of ketal and cyclopropane moieties and saponification of the ester grouping.



$a = Cu/C_6H_6$; $b = Zn/(CH_3)_2-C(Br)-CO_2Et$; $c = H^{\oplus}$

Unfortunately numerous attempts to effect decarboxylation of this *beta gamma* unsaturated acid were of no avail.

The second approach of STORK and McCURRY(173) involved aza-Claisen rearrangement of the ammonium intermediate (CCCLVI) prepared by alkylating the pyrollidine enamine (CCCLV) with crotyl bromide. The reaction was shown to proceed with 3,3 sigmatropic rearrangement of the quaternary salt and its steric course was reported to be governed by the orientation of the pyrollidine moiety as depicted below:



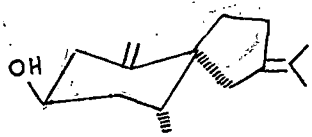
a= Br; b= Δ; C= H_2O; d= CH_3Li; e= NCS/$(CH_3)_2S$/Me_3N/-20°C
f= $(iso\ C_5H_{11})_2BH$; g= H_2O_2/NaOH, h= Ac_2O, i= $SOCl_2$/Py; j= NaOH;
k= Py, SO_3/DMSO; L= Silica gel.

Aldehyde (CCCLVII) appeared homogeneous by gas chromatography but the possibility that the stereoisomers could not be separated seemed likely. However, subsequent transformations involving addition of methyl lithium, oxidation to corresponding methyl ketone, repeated treatment with methyl lithium followed by terminal oxidation of the olefinic grouping with di-isoamyl borane yielded the diol (CCCLVIII). Selective acetylation of the

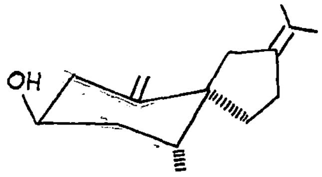
primary alcohol, dehydration of the tertiary alcohol followed by saponification and oxidation of the derived primary alcohol gave the unsaturated aldehyde (CCCLIX) which was cyclized to a mixture of epimeric methylene cyclohexanol upon treatment with silicagel. Oxidation with pyridine-sulphurtrioxide in dimethyl sulphoxide afforded (±)-10-*epi*-*beta*-vetivone (CCCXLV). The non isolation of the other possible isomer i.e. (±) *beta* vetivone (XIX) was apparently attributed to failure in crystallization.

Re-examination of the above reaction sequences by McCURRY *et. al.* (175) showed that the enamine (CCCLV) on treatment with *trans* Crotyl bromide furnished in 75% yield a 55:45 mixture of distereomers of (CCCLVII). Alternatively, when the enamine (CCCLV) was treated with *cis*-crotyl bromide the diastereomeric ratio was reversed suggesting that the 3,3 sigmatropic rearrangement of the quaternary salt is a highly stereo specific reaction.

The aldehyde (CCCLVII) (derived from *trans* Crotyl bromide) was converted to aldehyde (CCCLIX) following the methods described above. Acid catalyzed Prins reaction converted (CCCLIX) to a seperable mixture of diastereomeric spiro alcohols (CCCLX) and (CCCLXI) when exposed to a catalytic amount of stannic chloride in methylene chloride

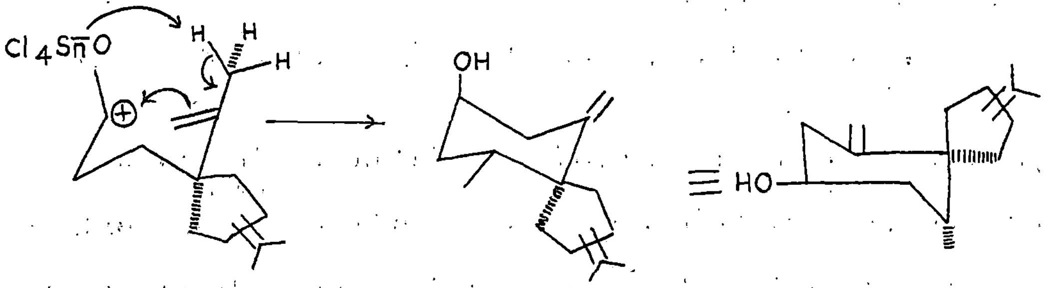


CCCLX



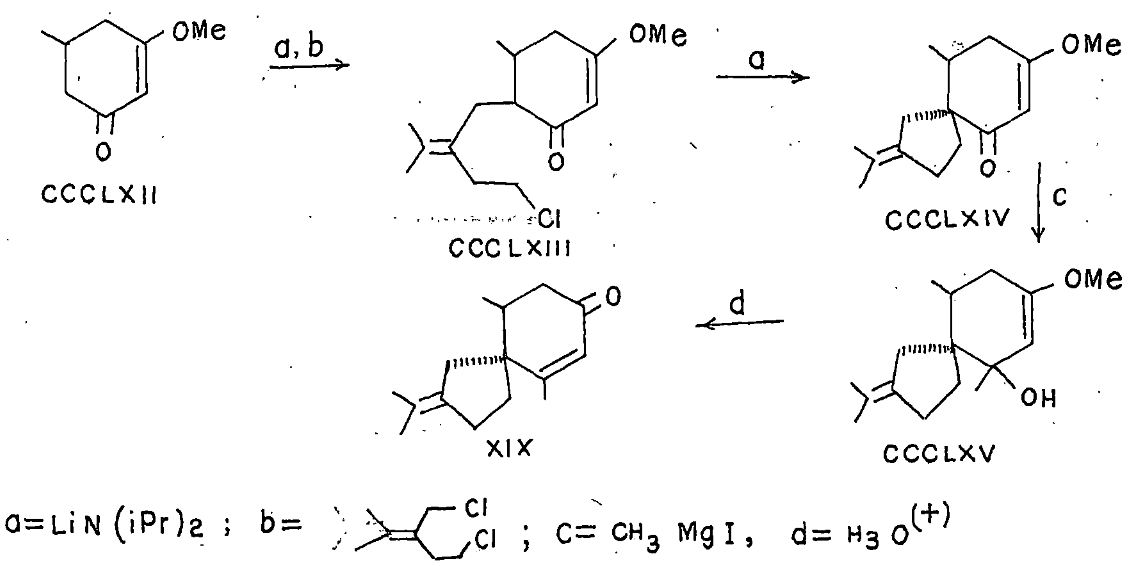
CCCLXI

Although there was formally the possibility of the formation of four diastereomeric dl pairs in the acid catalyzed Prins reaction, isomer (CCCLX) and (CCCLXI) accounted for over 97% of the reaction mixture. Both isomers possessed an equatorial alcohol function and an axial methyl group, which is compatible with the following reaction sequence:

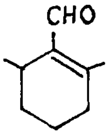


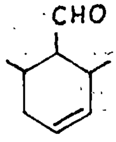
The oxidation of pure homo allylic alcohol (CCCLX) afforded (±) beta vetivone (XIX) and that of (CCCLXI) gave (±)-10-epi-beta-vetivone (CCCXLV).

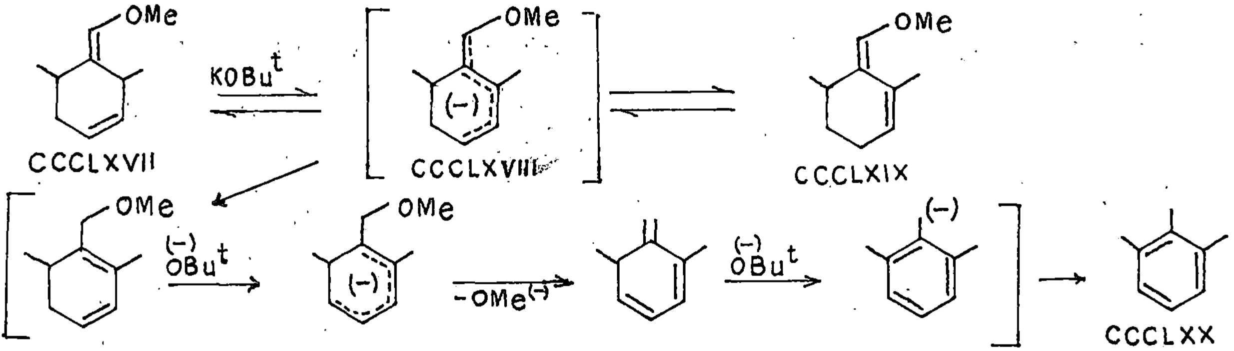
An exceedingly elegant synthesis of beta-vetivone was reported by STORK et. al.(258) The key intermediate involved alkylation of the kinetic enolate of the enol-ether of 5-methyl cyclohexane-1,3 dione (CCCLXII) with 2-isopropylidene-1,4-dichlorobutane. The presumed intermediate chloroketone (CCCLXIII) evidently undergoes a highly stereo selective cyclization reaction upon treatment with a strong base; none of the epimeric spiro (4.5) decane product was found to be formed. Addition of methyl magnesium iodide to the cyclized product afforded the alcohol (CCCLXV) which yielded racemic <u>beta</u>-vetivone (XIX) upon exposure to dilute acid.



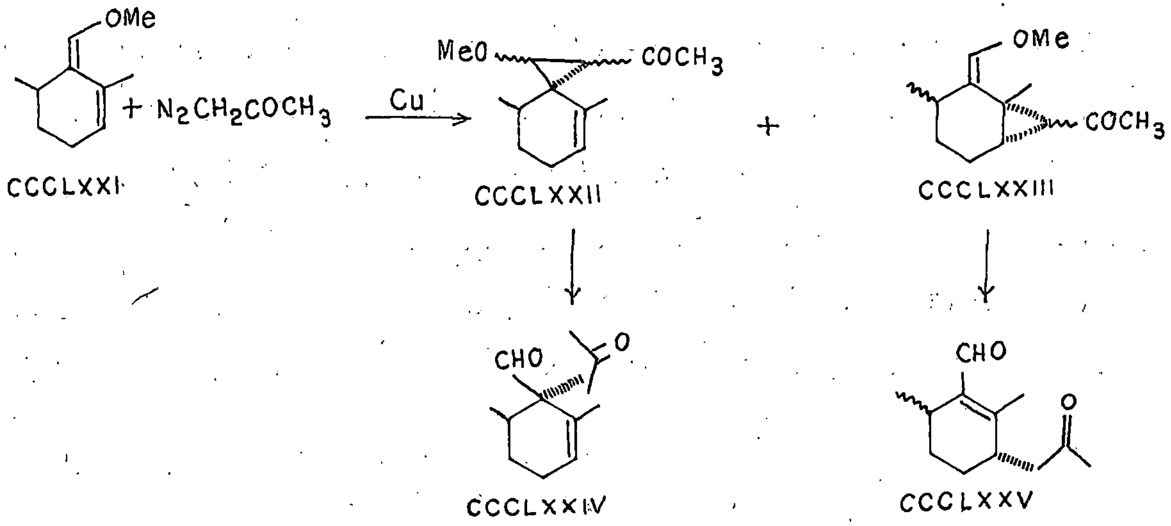
The application of a three step cyclopentanone synthesis scheme consisting of the cyclopropanation of enol derivatives with diazomethyl ketones, the liberation of <u>gamma</u> dicarbonyl compounds on acid hydrolysis of the resultant <u>beta</u>-oxycyclopropyl ketones, and intramolecular aldol condensation of the resultant 1,4-diketo system, to the synthesis of <u>beta</u>-vetivone has been described by SATHE(244) and WENKERT <u>et. al.</u>(283) . The required starting material for the purpose, the 2,6-dimethyl-1-cyclo hexene carboxaldehyde (CCCLXV) was not accessible and hence they started with its double bond isomer (CCCLXVI), the enol derivative (CCCLXVII) of which was subjected to equilibrium controlled strong base treatment to the stabilized pentadienyl anion (CCCLXVIII) and then to the conjugated dienyl ether (CCCLXIX). The occurrence of hemimesitylene (CCCLXX) as a side product indicated protonation of the intermediate anion (CCCLXVIII) to occur, even at the oxycarbon atom site, thereby deconjugating the enol ether system.


CCCLXV


CCCLXVI

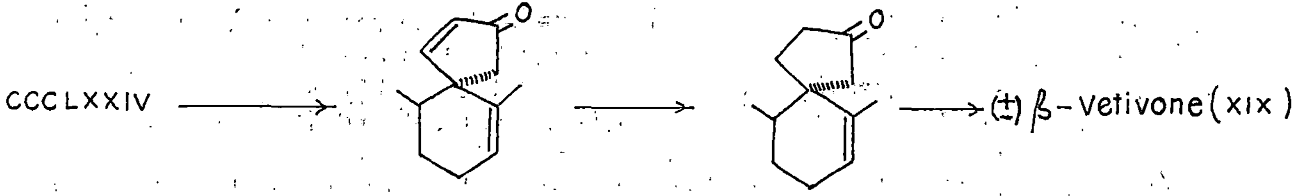


Copper catalyzed thermal decomposition of diazoacetone in diene (CCCLXXI) produced a difficultly separable mixture of cyclopropanones whose hydrolysate revealed to be a 1:3 combination of bicycles (CCCLXXII) (without stereochemical cannotations) and (CCCLXXIII) respectively. Acid catalyzed hydrolysis led to keto aldehydes (CCCLXXIV) and (CCCLXXV) respectively. The latter (CCCLXXV) was found to be a mixture of two stereo isomers whereas the former (CCCLXXIV) was a single entity e.g.



The stereochemical aspect of the reaction has been shown to be governed by the secondary methyl group.

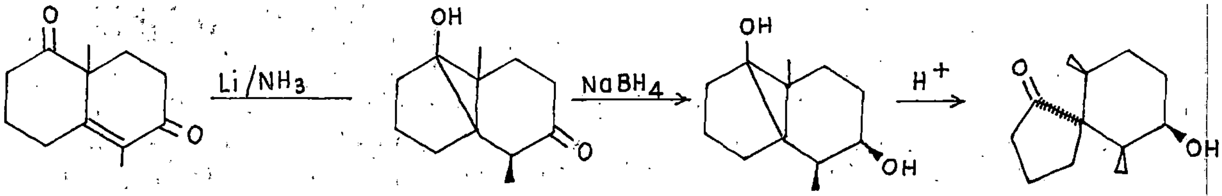
Base treatment converted the ketoaldehyde (CCCLXXIV) to the conjugated ketone (CCCLXXVI) whose hydrogenation in the presence of base furnished the spiro ketone (CCCLXXVII). The previous conversion of the spiro ketone (CCCLXXVII) to (±) -beta vetivone(154) made these reaction sequence a formal total synthesis of the sesquiterpene vetivone.



CCCLXXVI CCCLXXVII

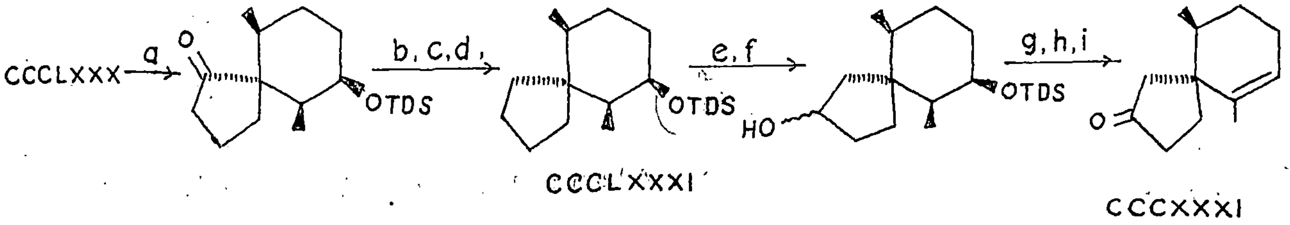
Using cyclopropanol ring opening reactions of 2-hydroxy tricyclo $(4.4.0.0^{2,6})$ decane-8-ones to spiro (4.5) decanes, an approach to synthesize beta-vetivone was explored by REUSCH and GRIMM(94). The 1,7-dimethyl-2-hydroxy tricyclo $(4.4.0.0^{2,6})$ decane-8-one was transformed through a series of step to a dienone which was reported to afford beta vetivone upon treatment with a copper modified grignard reagent.

SUBRAHMANIAN and REUSCH(261) reported a reaction sequence, described below, for the 1,2 transposition of carbonyl group in the cyclopentane ring of (CCCLXXX) to afford the spiro vetivone intermediate (CCCXXXI) which was prepared earlier by MARSHALL *et. al.*(155) in his *beta*-vetivone synthesis. Thus the effort may be treated as a partial synthesis of *beta*-vetivone. The tricyclic ketone (CCCLXXIX) prepared from the bicyclic ene-dione (CCCLXXVIII) on treatment with Lithium in ammonia, on sodium borohydride reduction followed by cyclopropyl ring opening with acid gave (CCCLXXX).



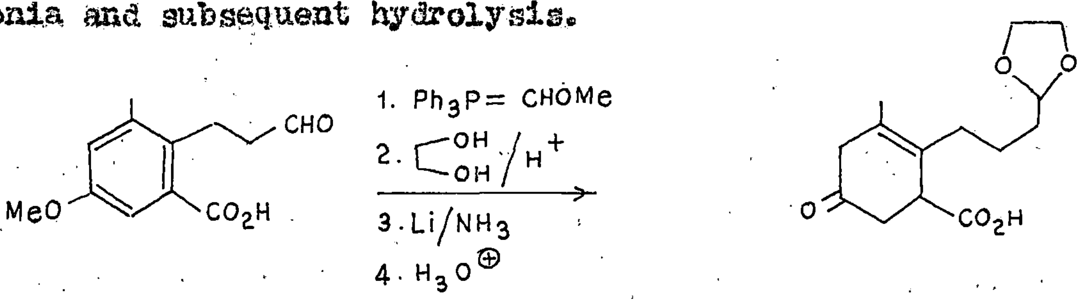
CCCLXXVIII CCCLXXIX CCCLXXX

The reduction of the carbonyl group with lithium aluminium hydride after protecting the hydroxyl group in the cyclohexane ring with tertiary butyl, dimethylsilylchloride, afforded a secondary alcohol which on subsequent dehydration through its chloride afforded the olefin (CCCLXXXI). Sequential hydroboration, Jones oxidation, removal of the protecting group and dehydration brought success to the effort in 1,2 transposition of carbonyl group of (CCCLXXX) by way of affording (CCCXXXI) - the required spiro vetivone intermediate.



a = $(CH_3)_3C\ Si(CH_3)_2\ Cl$/imidazole ; b = $LiAlH_4$; c = CH_3SO_2Cl ;
d = C_5H_5N/Δ ; e = Thexyl borane ; f = H_2O_2/NaOH ;
g = CrO_3/C_5H_5N ; h = H_3O^+ ; i = $C_7H_7\ SO_3H/C_6H_6/\Delta$

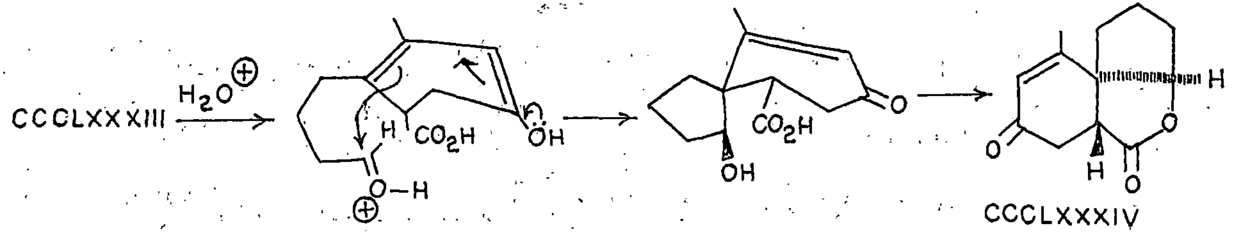
A valuable (4.5) spiro decane intermediate (CCCLXXXVIII) was prepared by YAMADA et. al. using (298) [illegible] cation cyclization reaction in the curcial step and utilized the intermediate, thus prepared, in synthesizing dl-beta vetivone, (298) dl-hinesol, dl-alpha, & dl-beta-vetisprine (299) and solavetivone (300). The appropriate cyclohexanone (CCCLXXXIII) for the purpose of cationic cyclization was prepared from the aldehyde (CCCLXXXII) through the reaction sequence involving Wittig reaction with methoxy methylene triphenyl phosphorane, acetalization followed by reduction with lithium - ammonia and subsequent hydrolysis.



CCCLXXXII

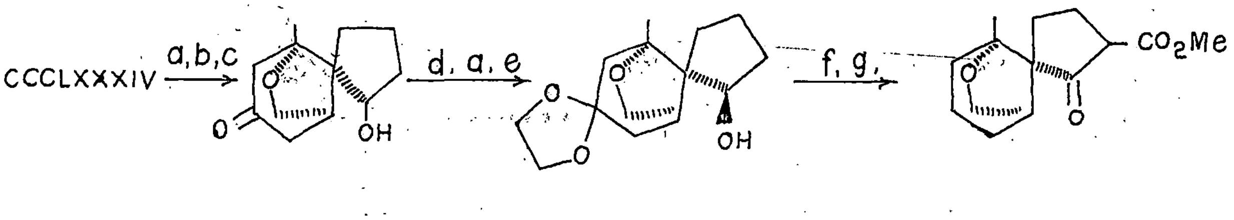
CCCLXXXIII

Under the acidic condition (6N HCl-DME, reflux, 4hr.) cationic cyclization of (CCCLXXXIII) took place to afford the lactone (CCCLXXXIV). During the course of this cyclization, the incoming carbon of the forming cyclopentanol ring attached the cyclohexadienol ring *cis* to the adjacent carboxylic acid grouping and thus creating a situation, suitable for lactonization, e.g.

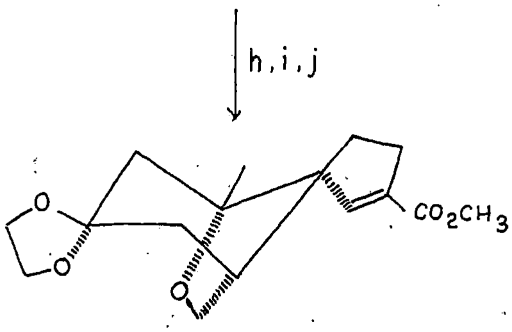


The exertion of *cis* directing effect of the carboxylic acid grouping may be compared with the *trans* directing effect of methyl substituent in the spiro annulation step (CCCXLIII → CCCXLV) in the synthesis of 10-*epi* *beta*-vetivone by McCURRY *et. al.*(176). Of course the cyclization of the unsaturated keto acetal (CCCLXXXIII) may be a reversible process whereas the cyclization of unsaturated ketal alcohol (CCCXLIII) is undoubtedly irreversible. In that event, lactonization may provide the driving force for the formation of the stereo isomer represented by structure (CCCLXXXIV). The lactone (CCCLXXXIV) was converted to the ketone (CCCLXXXV) by the sequence ketalization, reduction with lithium aluminium hydride and treatment with acid.

Acetylation, ketalization and hydrolysis converted the ketone (CCCLXXXV) to the ketal (CCCLXXXVI). Jones oxidation of (CCCLXXXVI) followed by carbomethoxylation gave the *beta* keto ester (CCCLXXXVII) which was converted to the desired (4.5) spiro decane intermediate, the unsaturated ester (CCCLXXXVIII), through the sequence, sodium borohydride reduction, mesylation, elimination of MesOH, e.g.,



CCCLXXXV CCCLXXXVI CCCLXXXVII



CCCLXXXVIII

a = $\left[\begin{matrix} OH \\ OH \end{matrix}\right. / H^+$; b = $LiAlH_4/THF$

c = 2NHCl/DMF ; d = Ac_2O/Py

e = KOH/MeOH ; f = CrO_3/Py

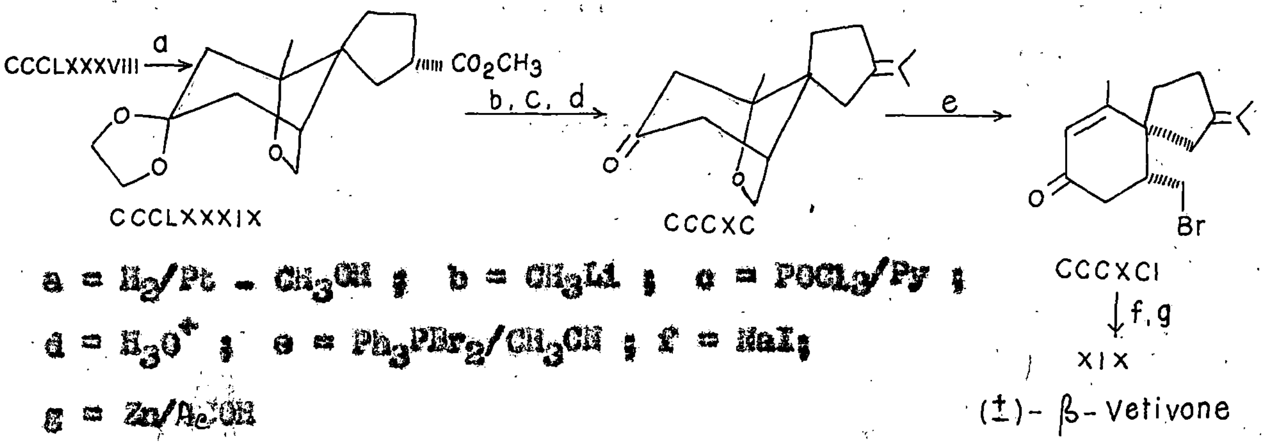
g = $(CH_3O)_2$ CO/NaH ; h = $NaBH_4$

i = MesCl/Py ; j = NaOMe/MeOH

The versatile intermediate (CCCLXXXVIII) was utilized in synthesizing of a number of spiro vetivenes mentioned earlier.

The utilization of (CCCLXXXVIII) in the synthesis of beta-vetivone involved the following reaction sequence:

Hydrogenation of the cyclopentene double bond expectedly took place from the less hindered face of (CCCLXXXVIII) to give the ester (CCCLXXXIX). Introduction of the isopropylidene grouping was effected through ~~of~~ methyl lithium followed by dehydration. Hydrolysis then afforded the keto ether (CCCXC). Ether cleavage with the triphenyl phosphine-bromine complex yielded the bromo ketone (CCCXCI). Hydrogenolysis of the related iodo ketone with zinc in acetic acid led to (±) --beta-vetivone (XIX).

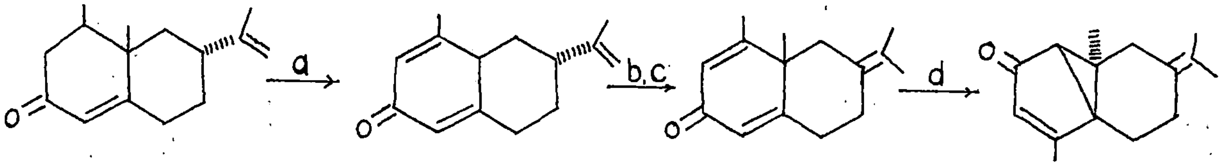


a = $H_2/Pt - CH_3OH$; b = CH_3Li ; c = $POCl_3/Py$;

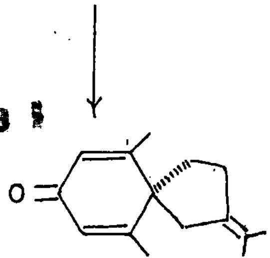
d = H_3O^+ ; e = Ph_3PBr_2/CH_3CN ; f = NaI;

g = Zn/AcOH

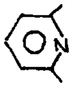
A synthesis of beta-vetivone and 10-epi-beta vetivone from nootkatone (CCCXCII) using photochemical spiro annulation route to (4.5) spiro decane skeleton has been described by CAINE and CHU(34). 3,4 dehydro nootkatone (CCCXCIII) prepared by oxidation of nootkatone (CCCXCII) with 2,3 dichloro-5,6-dicyano benzo-quinone (DDQ) on addition of hydrogen bromide to the isolated double bond followed by dehydrobromination gave dehydro-alpha-vetivone (CCCXCIV) which on irradiation in dioxane at 2537 Å gave the trycyclic ketone (CCCXCV). Irradiation of (CCCXCV) in 45% aqueous acetic acid using a 450-W Hanovia high pressure mercury lamp housed in a pyrex probe, gave dehydro-beta-vetivone (CCCXCVI) as the exclusive photo product, e.g.,



CCCXCII CCCXCIII CCCXCIV CCCXCV



CCCXCVI

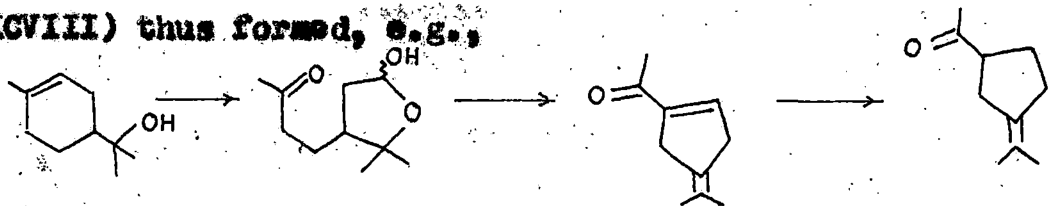
a = DDQ ; b = HBr ; c = $(nBu)_4 \overset{+}{N} \overset{-}{Br}$ /  $/CH_3COCH_3$;

d = hν /dioxane ; e = hν /ACOH - H_2O

Selective reduction of one double bond, affording racemic-beta-vetivone (XIX) and racemic 10-epi-beta-vetivone (CCCXLV) was carried out in two ways. Catalytic hydrogenation of (CCCXCVI) in ethyl alcohol at atmospheric pressure using 5% palladium on carbon as the catalyst gave approximately 60% of (XIX) and (CCCXLV) in 7:3 ratio while it chemical reduction with two equivalents of lithium in liquid ammonia containing one equivalent of tertiary butanol afforded a mixture of (XIX) and (CCCXLV) in @ 80% yield but the corresponding ratio of the products was just reverse.

$$\text{CCCXVI} \xrightarrow[\text{Li}/NH_3]{H_2/Pd(C)-EtOH \text{ or}} (\pm)\ \text{beta vetivone (XIX) and } (\pm)\ \text{10-epi-beta-Vetivone (CCCXLV)}$$

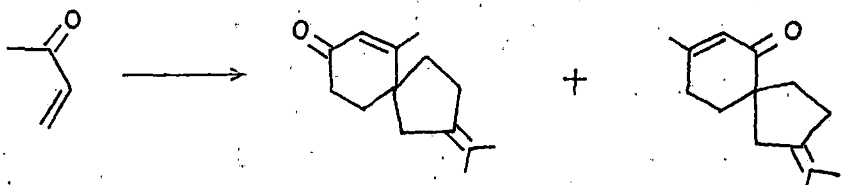
BOZZATO, BACHMANN and PESARO(29) synthesized racemic-beta-vetivone from racemic alpha-terpineol (CCCXCVII) using two different spiro annulation route viz, Robinson's annulation and the intramolecular acylation for building up the required (4.5) spiro decane skeleton. The logical starting material, the cyclopentyl ketone (CCCXCIX) was prepared from alpha terpineol by sequential ozonolysis, acid catalyzed rearrangement of the hemiacetal thus formed followed by steam distillation and subsequent hydrogenation of the conjugated double bond in the dienone (CCCXCVIII) thus formed, e.g.,



CCCXCVII CCCXCVIII CCCXCIX

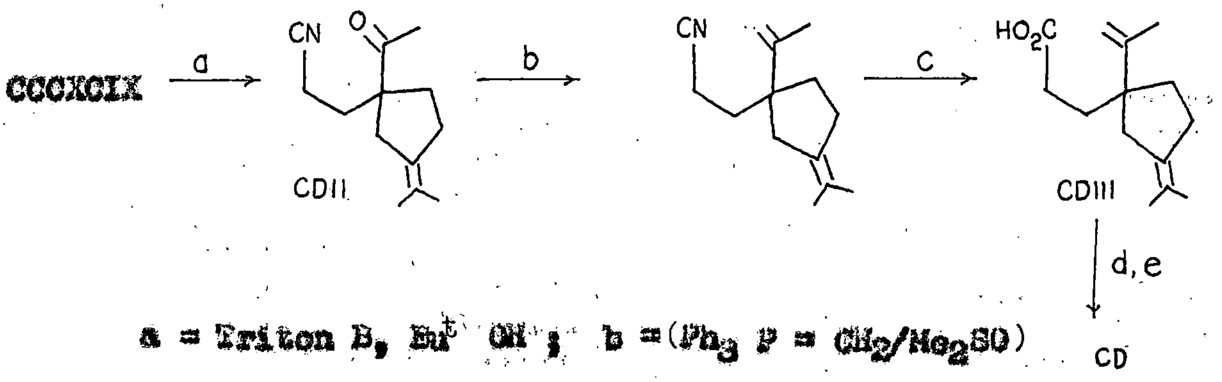
Robinson's annulation of the ketone (CCCXCIX) with methyl vinyl ketone afforded the spiro ketones (CD) and (CDI) in the unfavourable ratio 3:7

CCCXCIX +



CD CDI

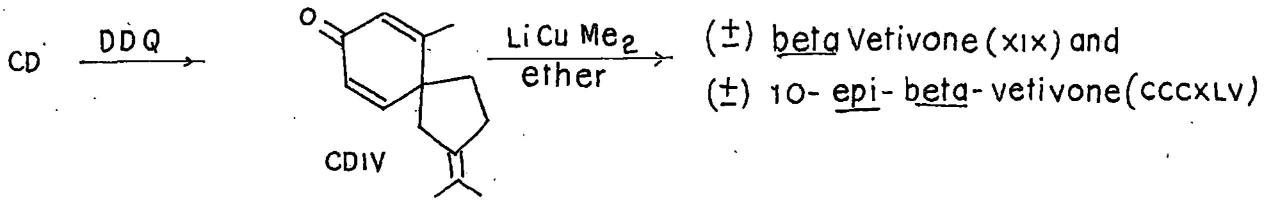
The alternative route to ketone (CD) comprised of the cyanoethylation of the ketone (CCCXCIX), Wittig reaction on the resulting cyanoketone (CDII), its basic hydrolysis to the acid (CDIII) and the conversion of the latter to the ketone (CD) by intramolecular acylation of the corresponding acid chloride, e.g.,



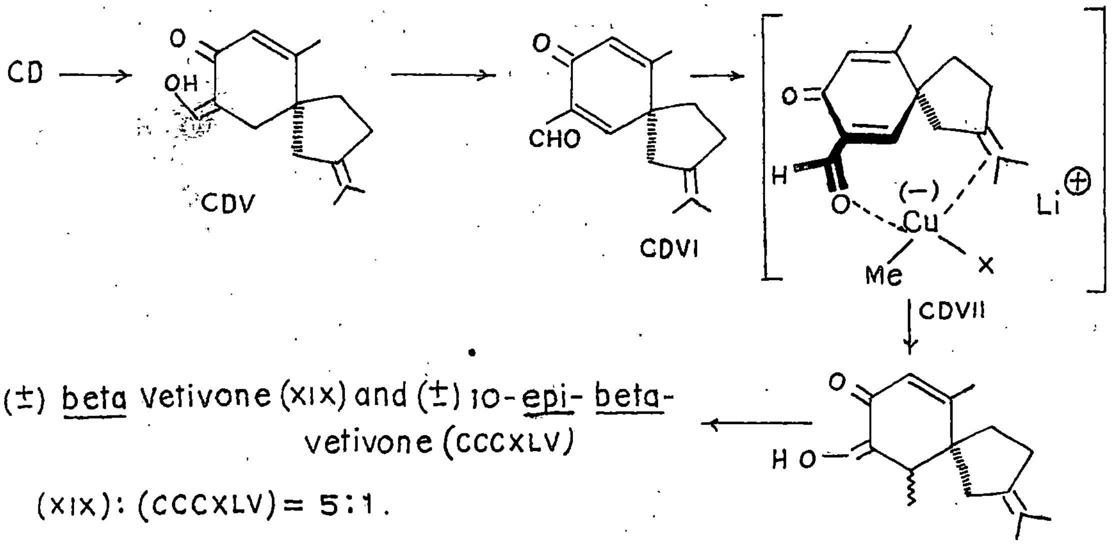
a = Triton B, Bu^t OH ; b = ($Ph_3P = CH_2/Me_2SO$)

c = $NaOH/C_2H_5OH - H_2O$; d = $(COCl)_2$; e = $SnCl_4/CS_2$

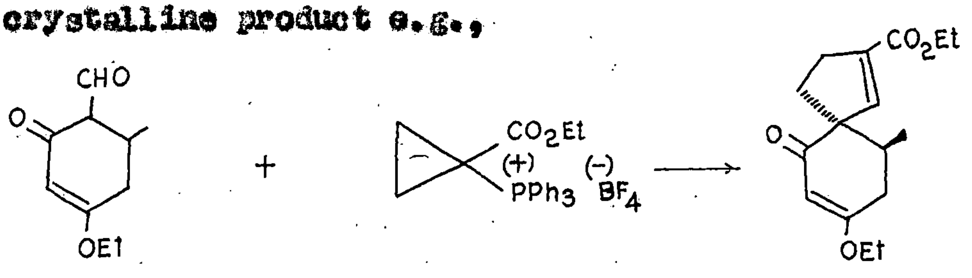
The DDQ dehydrogenation of ketone (CD) led to the dienone (CDIV) which by reaction with Lithium dimethyl cuprate gave a 1:1 mixture of recemic <u>beta</u>-vetivone (XIX) and its 10-methyl epimer (CCCXLV) which could be seperated by ~~[illegible]~~ chromatography over silica gel.



A fantastic improvement in the ratio of <u>beta</u>-vetivone and its 10-epimer as product was made by introducing a hydroxymethylene group in (CD) prior to its dehydrogenation with DDQ. The resulting hydroxymethylene derivative (CDV) on dehydrogenation gave the dienone (CDVI) which reacted stereo selectively with several methyl cuprates, possibly by preferential formation of an intermediate of the type (CDVII) involving the formyl group and the tetrasubstituted double bond of the dienone (CDVI) e.g., with lithium methyl bromocuprate di-isobutyl amine complex a 5:1 mixture of beta-vetivone (XIX) and 10-epi-beta-vetivone (CCCXLV) was obtained after deformylation.



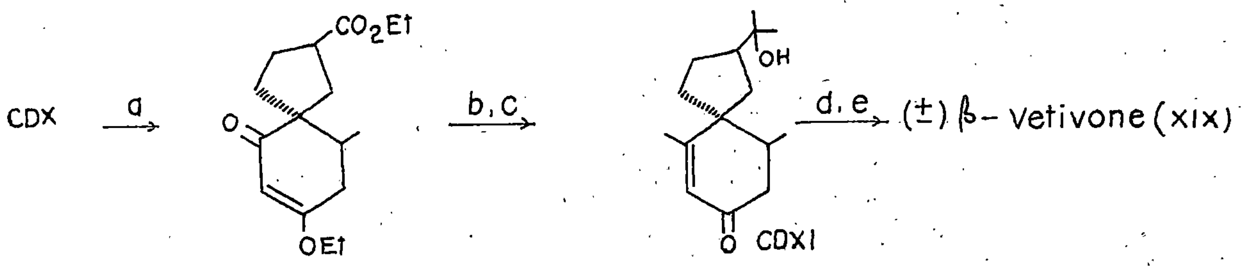
A total synthesis of spiro vetivane sesquiterpenes, dl-beta vetivone, dl-hinesol, dl-beta vetispinene and dl-alpha vetispirene from a common intermediate 2-carbethoxy-8-ethoxy-10 methyl spiro (4:5) deca-1, 7-dien-6-one (CDX) has been described by DAUBEN and HART (64) who exploited the general synthesis of spiro cycles through an extension of the synthesis of ethyl cyclopentene carboxylates by the closure of ylides derived from carbethoxy cyclopropyl triphenyl phosphonium tetrafluoroborate (CDIX) and beta-keto-esters or symmetrical 1:3 diketones. Thus the treatment of an HMPT solution of sodium enolate of formyl ketone (CDVIII), prepared from 3-ethoxy-5-methyl cyclohex-2-ene-1-one and ethyl formate, with (CDIX) produced the versatile intermediate (CDX) as a single crystalline product e.g.,



CDVIII CDIX CDX

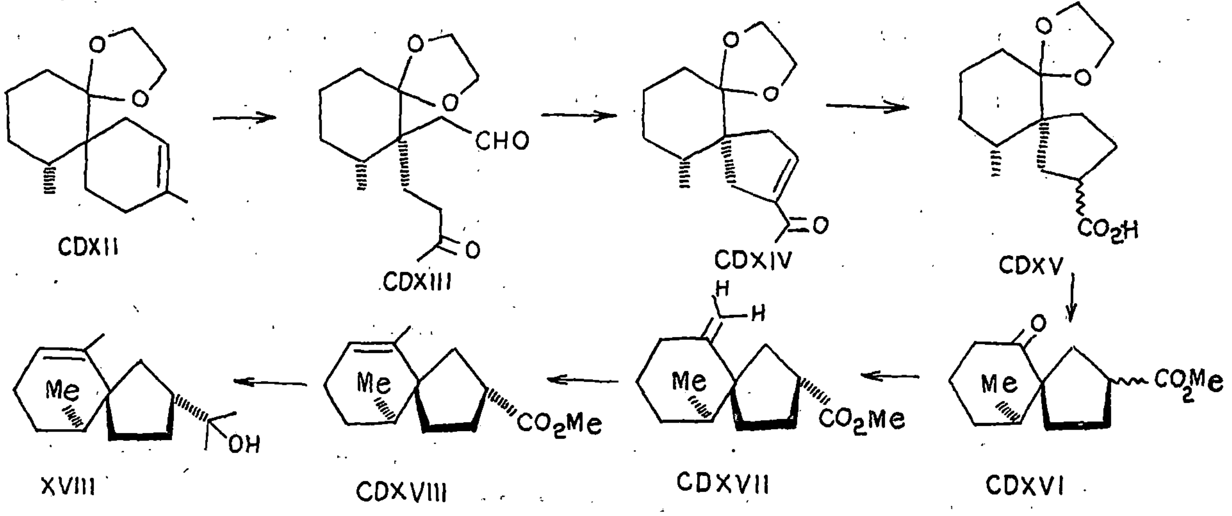
The stereoselectivity of the attack of the enolate on the activated cyclopropane most likely is due to the steric factors arising from the preferred pseudoaxial conformation of the incipient C-10 methyl group.

The conversion of the intermediate (CDX) into <u>dl-beta</u> vetivone involved the following reaction sequence : Selective hydrogenation of (CDX) in ethanol over palladium on charcoal followed by successive methylation with excess methyl lithium and 1.2N hydrochloric acid gave the crystalline ketol (CDXI). Acetylation followed by treatment with boron triflouride etherate converted the ketol (CDXI) into <u>dl-beta</u> vetivone, (XIX) e.g.,

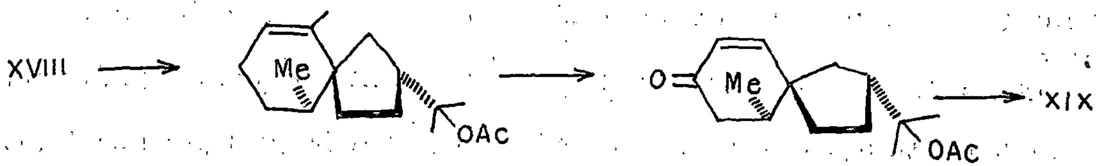


a = $H_2/Pd-C/EtOH$; b = CH_3Li ; c = 1.2.N·HCl. ; d = Ac_2O/H^+ ; e = BF_3, Et_2O .

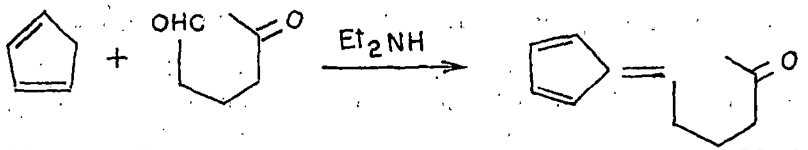
A stereospecific synthesis of (-)-agarospirol and its conversion to (-) *beta*-vetivone was reported by DIEGHTON, HUGHES and RAMAGE(66). They chose the spiro acetal (CDXII) as their starting compound which was prepared by RAMAGE *et. at.*(95) from (+)-3R-methyl cyclohexanone involving the Dieckmann cyclization of gem disbstituted esters of cyclic ketone. The procedure have been discussed earlier under the heading "spiro annulation through miscleneous routes, (Page 99). However, the spiro acetal (CDXII) on a ozonolysis followed by reductive cleavage afforded keto aldehyde (CDXIII) which was cyclized to the *alpha,beta* unsaturated ketone (CDXIV). Hydrogenation followed by haloform reaction produced the stereoisomeric mixture of acids (CDXV). Esterification followed by acidolytic cleavage of the acetal grouping afforded the seperable isomeric mixture of the keto ester (CDXVI). Wittig reaction on both the isomers of (CDXVI) gave the same methylenated product (CDXVII) which rearranged smoothly to the endocyclic olefin (CDXVIII). Treatment of (CDXVIII) with methyl lithium afforded (-) agaro spirol (XVIII) e.g.,



The (-) agarospirol (XVIII) was converted to (-) <u>beta</u> vetivone following the route of MARSHAL <u>et</u>. <u>al</u>.(155) e.g.

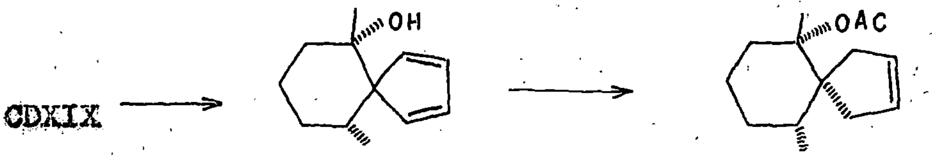


BÜCHI <u>et</u>. <u>al</u>.(31) synthesized recemic-<u>beta</u> vetivone from fulvene (CDXIX) prepared by condensing 5-oxo-hexanal with cyclopentadiene in the presence of diethyl amine e.g.,



CDXIX

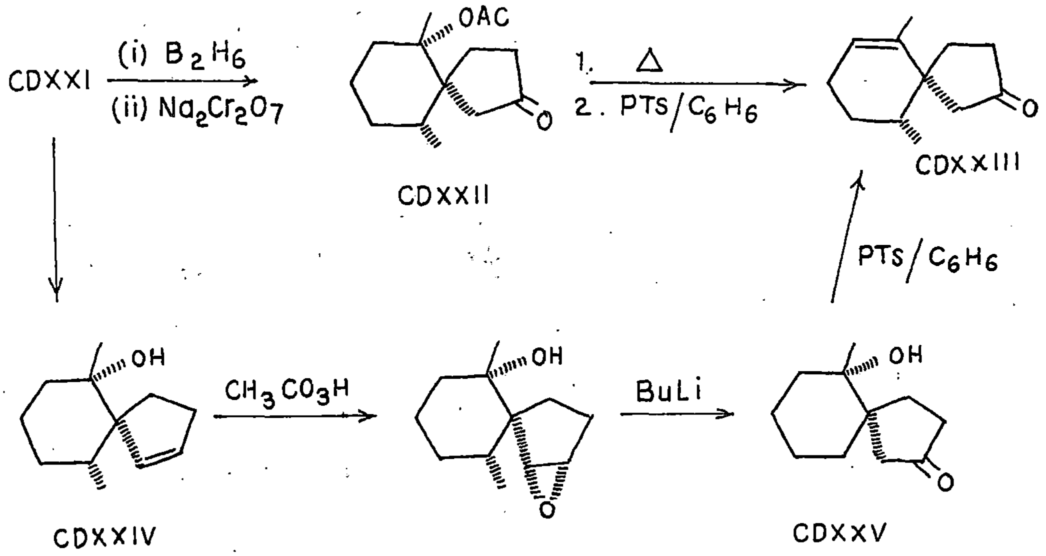
The addition of lithium dimethyl cuprate to fulvene (CDXIX) in ether produced the derived lithium cyclopentadienide which combined with the carbonyl group to form the cyclohexanol (CDXX) in preference to a cycloheptanol. Acetylation followed by regioselective reduction of one double bond with dimide (hydrazine, 30% hydrogen peroxide, ethanol) afforded a single dihydro compound (CDXXI) accompanied by a little tetrahydroproduct. . .



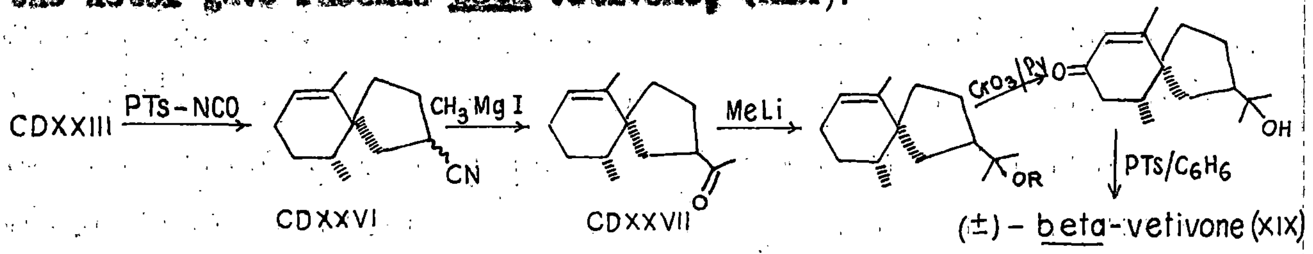
CDXX

CDXXI

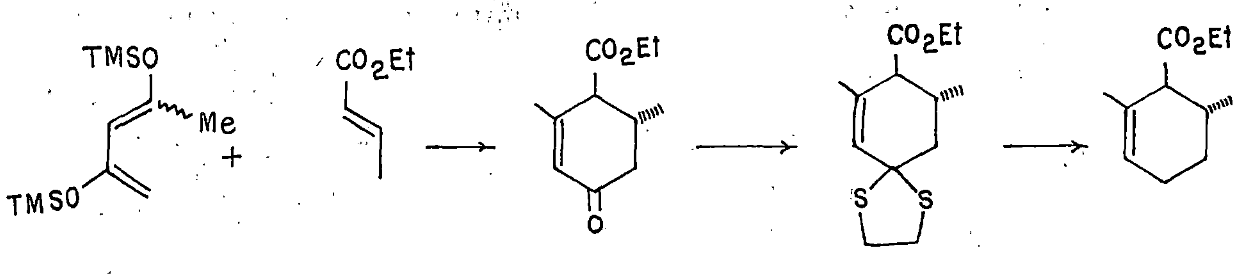
The olefin (CDXXI) was transformed to ketone (CDXXIII) in two ways. Treatment of the acetate (CDXXI) with diborane followed by oxidation of the resulting alcohol gave the acetoxy ketone (CDXXII) which on pyrolysis followed by equilibration of endo and exocyclic olefins yielded the more stable endo cyclic olefin (CDXXIII) containing $<10\%$ exocyclic isomer. In an alternative synthesis, the acetate (CDXXI) was hydrolyzed to alcohol (CDXXIV) which on epoxidation followed by treatment with butyl lithium in ether gave the ketone (CDXXV). Dehydration of (CDXXV) afforded the ketone (CDXXIII)



The spiro decenone (CDXXIII) was converted to a mixture of epimeric nitriles (CDXXVI) which was condensed with grignard reagent to afford the methyl ketone (CDXXVII). Methylation with methyl lithium followed by Jones oxidation and subsequent dehydration of the ketol gave racemic beta vetivone, (XIX).

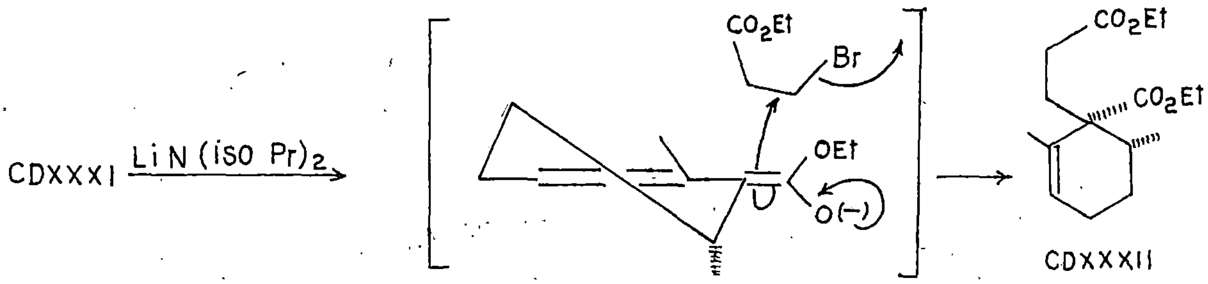


IBUKA, HAYASHI, MINAKATA, ITO and INUBUSHI(118) ~~have~~ reported a new synthesis of spiro vetivanes via spiro acyloin intermediate. The keto ester (CDXXIX) prepared by Diels-Alder reaction of 2,4-bis (trimethyl siloxy)-1,3 pentadiene (CDXXVIII) with ethyl chrotonate followed by hydrolysis, was treated with ethane dithiol to afford the dithioacetal (CDXXX) which on subsequent reduction with Raney nickel gave the beta-gamma-unsaturated ester (CDXXXI).

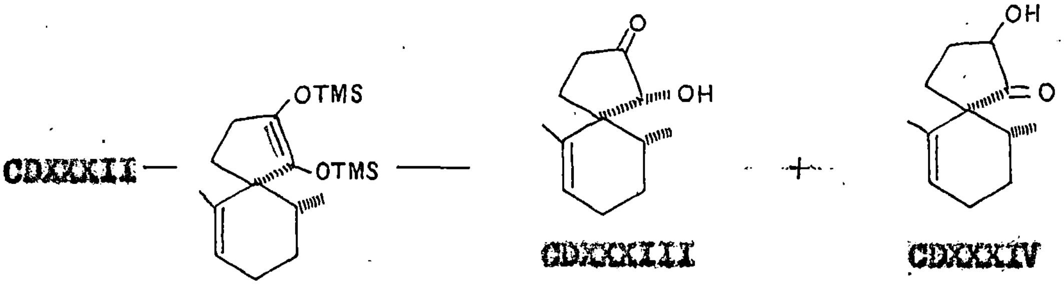


CDXXVIII CDXXIX CDXXX CDXXXI

Treatment of (CDXXXI) with lithium di-isopropyl amide and subsequent alkylation of the lithium enolate with ethyl-beta-bromopropionate provided the diester (CDXXXII) the stereochemistry of which was determined by the approach of the reagent from the less hindered face opposite to the pseudo axial C-10 methyl group in (CDXXXI) as shown below:

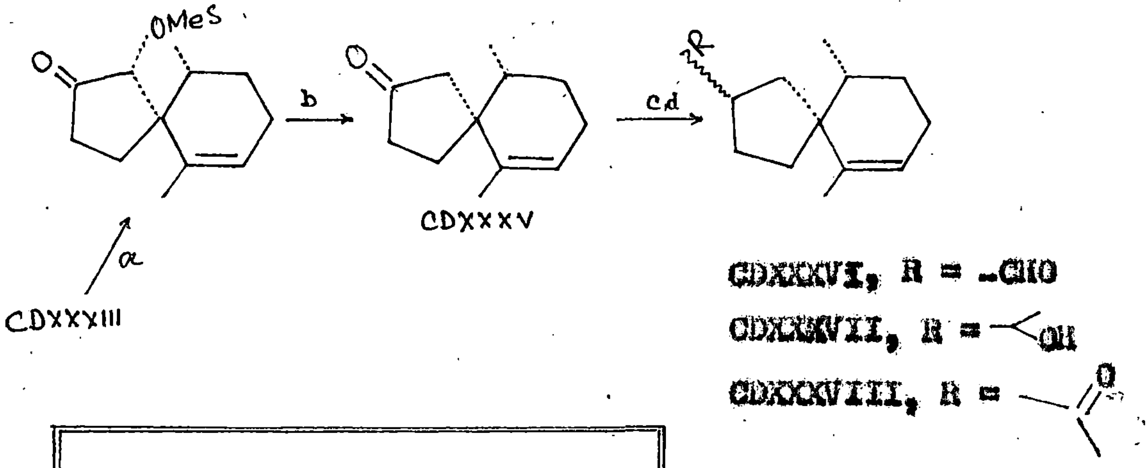


Acyloin condensation of (CDXXXII) with sodium and trimethyl chlorosilane followed by hydrolysis in THF containing 10% hydrochloric acid gave crystalline spiro acyloin (CDXXXIII) along with the isomeric (CDXXXIV)



Mesylation of (CDXXXIII) followed by reduction of the correspon-ding mesylate gave the spiro ketone (CDXXXV) which was converted to the epimeric mixture of aldehyde (CDXXXVI) through Wittig reac-tion with methoxy methylene triphenyl phosphorane followed by hydrolysis of the resulting enol methyl ether. The epimeric mixture of the aldehyde (CDXXXVI) was converted into a 3:2

mixture of (±) hinesol (LXXV) and (±) agarospirol (XVIII) by the conventional method via the alcohol (CDXXXVII) and the methyl ketone (CDXXXVIII). The epimeric mixture of (LXXV) and (XVIII) was readily converted to racemic beta-vetivone (XIX) according to the method of MARSHALL and JOHNSON (165)



CDXXXIII

CDXXXV

CDXXXVI, R = -CHO

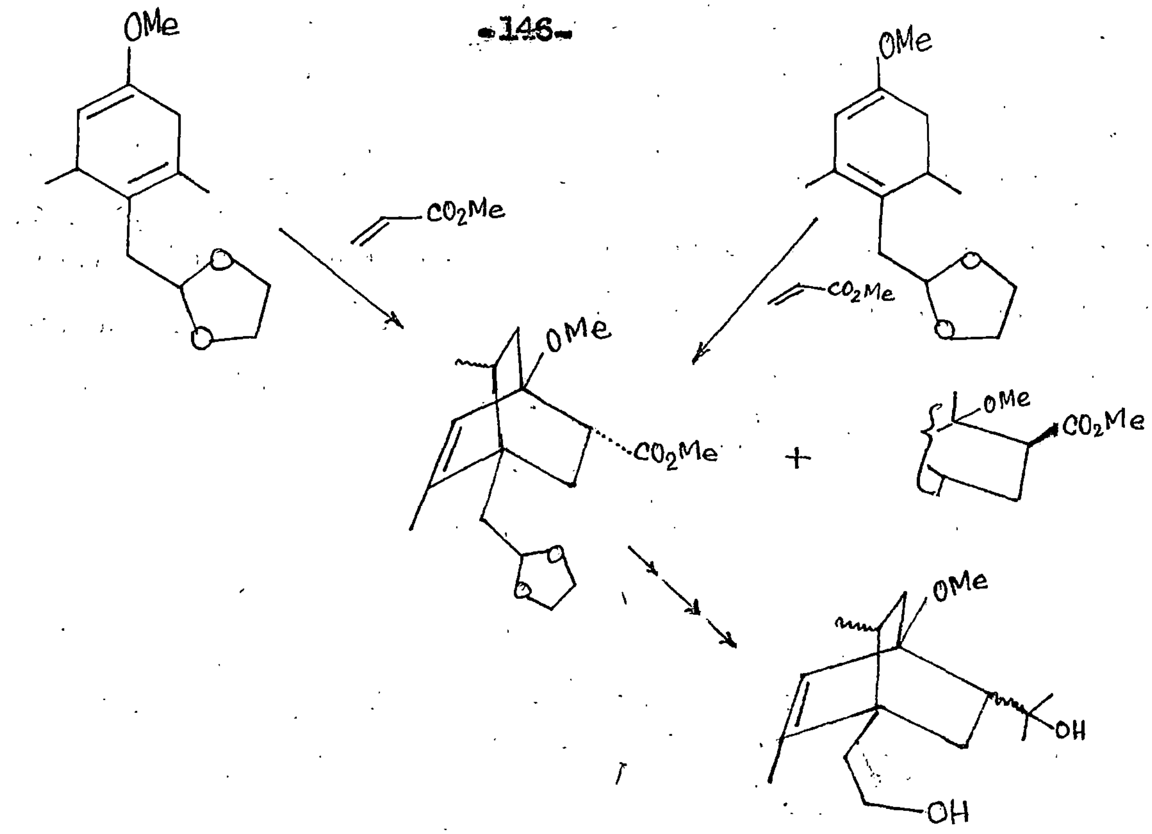
CDXXXVII, R =

CDXXXVIII, R =

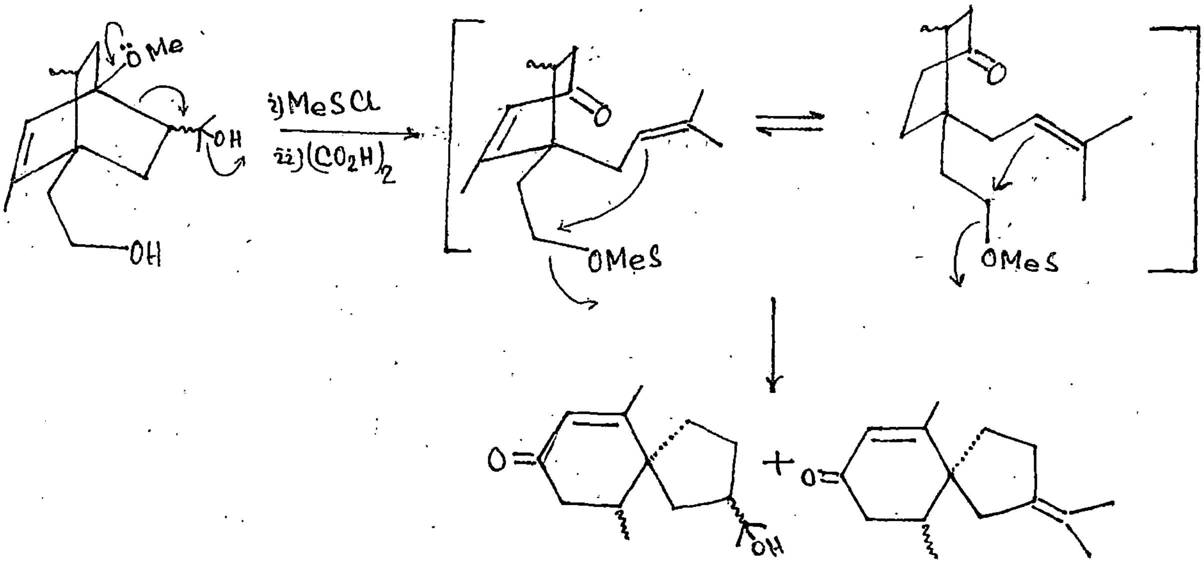
a, CH_3SO_2Cl/Py ; b, Zn/NH_4Cl ;
c, $Ph_3P = CHOMe$, d, 10% HCl

MURAI, SATO and MASAMUNE (189) have synthesized beta-vetivone, hinesol, beta vetispirane and solavetivone in a stereoselective fashion. Their approach consisted of two major steps:

1) the Diels-Alder reaction of the substituted dihydro anisoles and methyl acrylate or its equivalent followed by tranformation for the second key reaction,

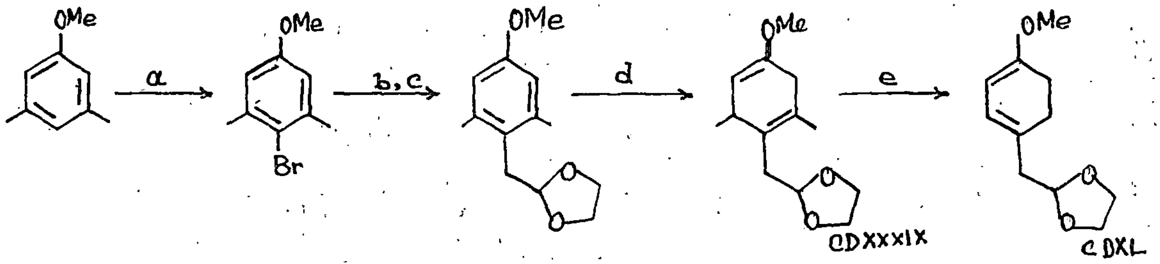


and (ii) acid cleavage of the resulting bicyclooctanes and subsequent π -cyclization, giving the spiro vetivanes practically in a single step,

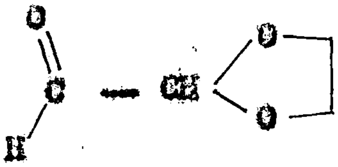


The relevant stereochemistry between C-4 and C-5 and between C_7 and C_5 was controlled in the first and second steps respectively as shown.

The preparation of the required dihydroanisoles (CDXXXIX) and (CDXL) from 3,5 dimethyl anisole involved the following steps:



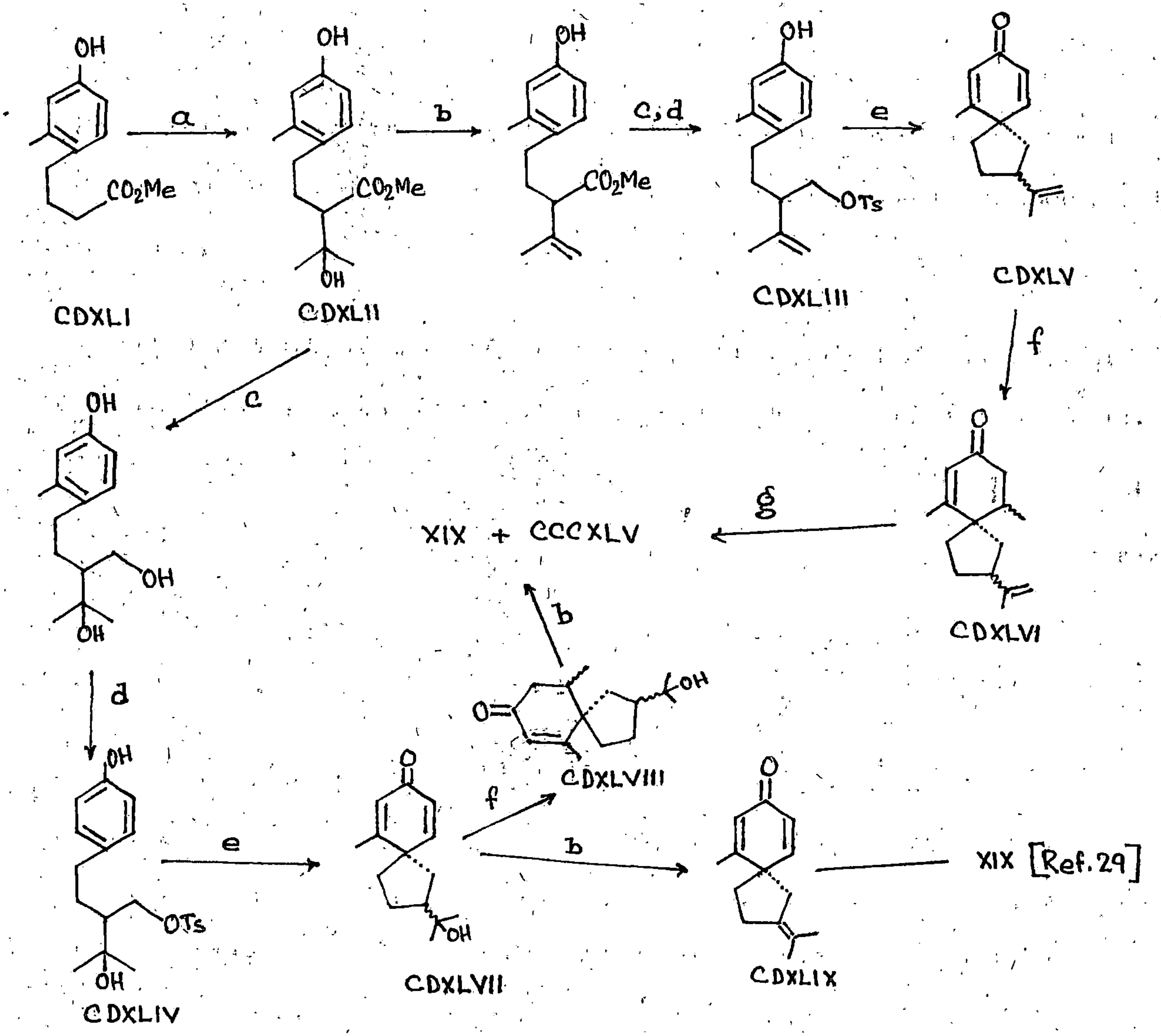
a = $Br_2/CCl_4/Fe$; b = Mg/Ether ; c =


$$HC(=O)-CH\left<{O \atop O}\right>$$

d = $Li/NH_3/THF$; e = $\Delta/140°$

Solavetivone and oxylubimin were also prepared by them in a similar manner.

The synthesis of (±) beta-vetivone and the related spiro vetivanes by TORII et.al. (266,274) is a complete departure from the other approaches, discussed above. It is the first synthesis of beta-vetivone making use of aryl participation reaction, discussed previously along with the other methods of spiro annulation procedures. Their approach is described below:



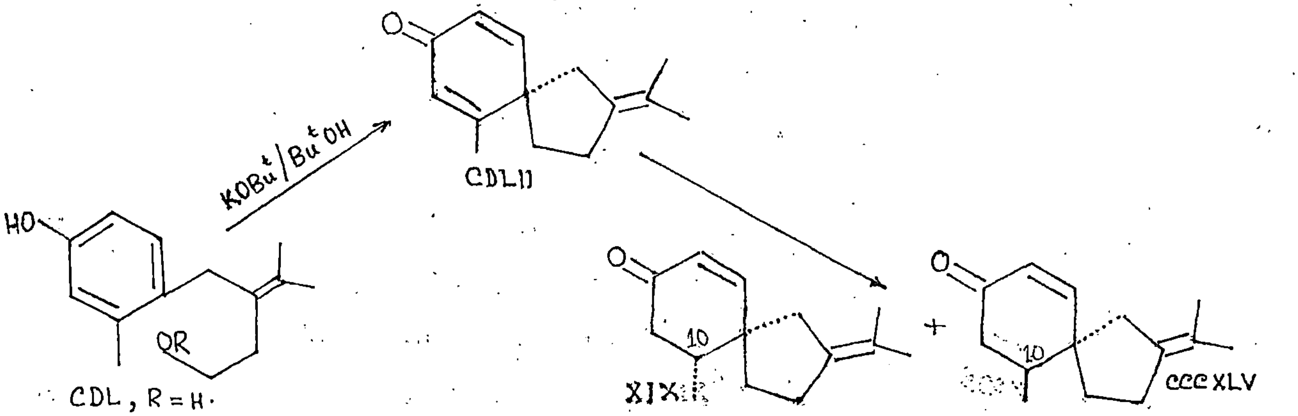
a = LDA/HMPA–THF/(1:10 v/v)/Me.CO.Me, -78°; b = $SOCl_2$/Py; c = LAH; d = pTsCl/Py
e = $KOBu^t/Bu^tOH$; f = $LiCuMe_2$; g = $RhCl_3$/EtOH

Methyl-4-(4'-hydroxy-2'-methyl phenyl) butanoate (CDXLI) which could readily be obtained from meta-cresyl methyl ether by way of succinoylation, Clemmensen reduction, demethylation and esterification was alkylated on treatment with lithium di-isopropyl-amide (LDA) followed by addition of acetone to methyl-3-hydroxy-2-[2-(4'-hydroxy-2'-methyl phenyl) ethyl]-3 methyl butanoate (CDXLII). Dehydration, reduction of the ester function and subsequent tosylation gave the tosylate (CDXLIII). Lithium aluminium hydride reduction of (CDXLII) followed by selective tosylation of the primary alcoholic function gave the hydroxy tosylate (CDXLIV). Treatment of (CDXLIII) with potassium *tert*-butoxide in *tert*-butanol gave the spiro dienone (CDXLV) which was methylated with lithium dimethyl cuprate (I) affording 2-isopropenyl-6, 10 dimethyl spiro (4.5) dec-6-en-8-one (CDXLVI) and this was isomerized to equimolar mixture of (±) *beta* vetivone (XIX) and (±) 10-*epi*-*beta*-vetivone (CCCXLV) on refluxing with rhodium trichloride in ethanol.

The hydroxy tosylate (CDXLIV) on treatment with potassium *tert*-butoxide in *tert*-butanol gave a minor quantity of the spiro dienone (CDXLVII) which was methylated to the C-10 epimers of the spiro dienone (CDXLVIII) which on dehydration with thionyl chloride afforded (±) *beta* vetivone (XIX) and (±)-10-*epi*-*beta* vetivone (CCCXLV) in 1:1 ratio. Initial dehydration of (CDXLVII) gave the spiranenone (CDXLIX) which was converted to (±)-*beta*-vetivone (XIX) by PESARO *et. al.*,(29) .

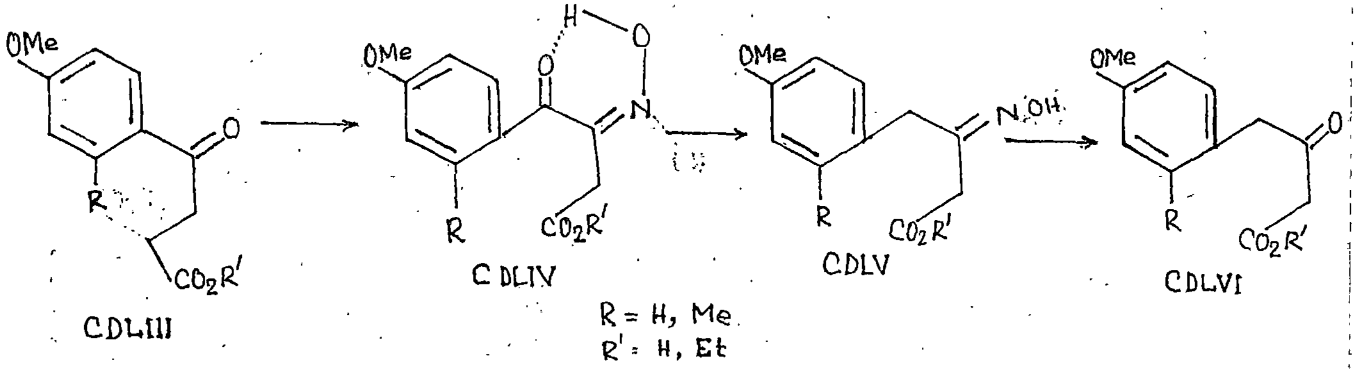
As has been discussed above, a good number of syntheses of *beta*-vetivone are reported in literature. More and more syntheses, differing in synthetic strategies are appearing in literature continuously. Uptil now only one synthesis of *beta*-vetivone and related compounds making use of $Ar^{(-)}_{1-5}$ participation reaction has been reported(266,274). One of the reasons why the application of aryl participation reactions, the novel route for construction of spiro (4.5) deca-1,4-dien-3-one, has not been much explored for the synthesis of vetivanes is presumably the difficulty in the synthesis of a suitable phenolic precursor having the appropriate functionalities making it a promising intermediate of high potential value. One of the attractive approaches to employ the Ar$_{1}^{(-)}$-5 participation reaction in the synthesis of beta-vetivone may involve the preparation of 2-isopropylidine-6-methyl spiro (4.5) deca-6,9-dien-8-one (CDLII) via base catalyzed annulation of the corresponding phenol (CDL) through WINSTEINS method(15).

The methylation of the spiro intermediate (CDLII) has been carried out by PESARO et. al.(29) which resulted in the formation of the mixture consisting of (±) beta-vetivone (XIX) and (±)-10-epi-beta-vetivone (CCCXLV)



CDL, R = H
CDLI, R = Ts

We wanted to make use of the carbonyl group of ethyl 3-(4'-methoxy-2'-methyl benzoyl)-propionate (CDLIII, R = Me, R' = Et) to introduce the iso-propylidene group. Of course, an initial transposition of the carbonyl group, employing any one of the methods described in literature(84,105,147,251) is necessary. Oximination(18,78,98,114) of the Keto ester (CDLIII, R = Me, R'=Et) followed by modified WOLFF-KISHNER(79,115) reduction was expected to give the *beta* oximino ester (CDLV, R = Me, R' = Et). Acid hydrolysis(79) or oxidative deoximination(9,33,108,161,194,204,205) of the oximino ester (CDLV, R = Me, R' = Et) would then give the desired 3-oxo-butanoate (CDLVI, R = Me, R' = Et).



CDLIII CDLIV CDLV CDLVI

Before embarking on the 1,2 transposition of carbonyl group in the actual synthetic scheme involving the derivatives of *meta* cresyl methyl ether it was thought that a detailed study of the reaction sequence using simpler systems would be rewarding and worthwhile. It was, therefore, decided to sunthesize ethyl-4-(4'-methoxy phenyl)-3-oxo-butanoate (CDLVI, R = H, R' = Et).

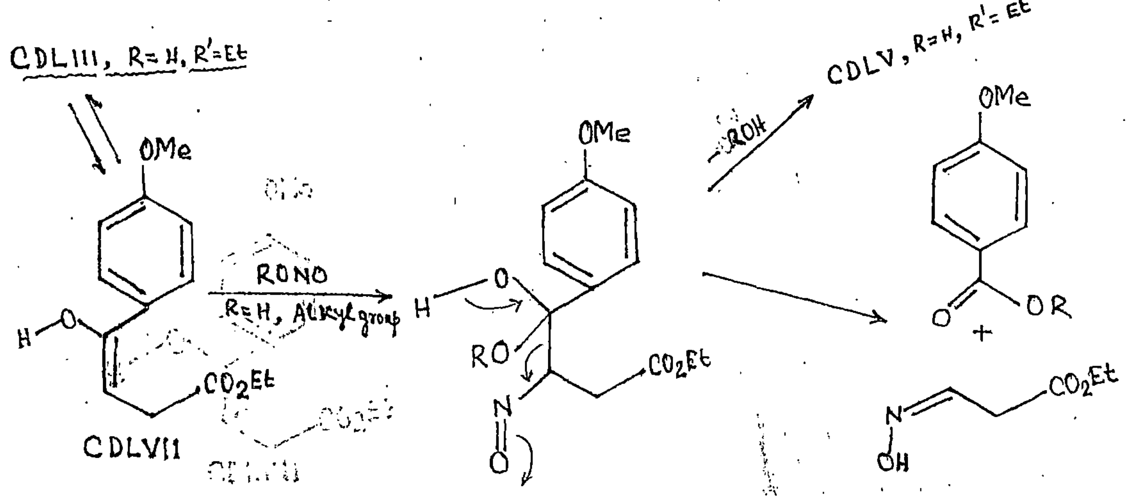
Succinoylation of anisole through standard procedure(113,223,267) afforded (4'-methoxy phenyl)-4-oxo-butanoic acid

(CDLIII, R = R' = H), m.p. 146° (Lit(227) recorded m.p. 146°) i.r. (nujol) : 2940 – 2560 cm^{-1}, 1720 cm^{-1}, 1685 cm^{-1}, 1660 cm^{-1}, 1420 cm^{-1}, 1260 cm^{-1} and 1240 cm^{-1} (Fig. I.R.1). Esterification of this acid with ethyl alcohol and sulphuric acid gave ethyl-4-(4'-methoxy phenyl)-4-oxo-butanoate (CDLIII, R = H, R' = Et) as a solid m.p. 46° ; i.r. (nujol) : 1720 cm^{-1}, 1670 cm^{-1}, 1658 cm^{-1}, 1648 cm^{-1}, 1420 cm^{-1}, 1260 cm^{-1} and 1235 cm^{-1} (broad) (Fig. I.R.-2). Treatment of this ester with isoamyl nitrite using sodium ethoxide as catalyst(78) gave the oximino ester (CDLIV, R = H, R' = Et) as a white solid m.p. (crude) 132 - 33° (decomp); i.r., (crude) (nujol); 3390 – 3340 cm^{-1} (broad); 2740 – 2600 cm^{-1}, 1700 cm^{-1} 1655 cm^{-1}, 1630 cm^{-1} (Fig. I.R.-3), in about 30% yield. Using other catalysts like potassium *tert* butoxide(18,114) or hydrogen chloride(98) only anisic acid could be isolated from the reaction mixture. With sulphuric acid as catalyst(18), simple hydrolysis of the keto-ester (CDLIII R = H, R' = Et) to the corresponding acid (CDLIII, R = R' = H) took place.

The oximino keto ester (CDLIV, R = H, R' = Et) was extremely sensitive to moisture and was found to decompose rapidly to anisic acid. However, on carrying out modified Wolff-Kishner reduction(79,116) with the crude oximino keto ester (CDLIV, R = H, R' = Et) resulted in the formation of the oximino ester (CDLV, R = H, R' = Et) as a yellow coloured solid, m.p. 118 - 120° i.r., (nujol): 3300 – 3280 cm^{-1} (broad), 1685 cm^{-1} and 1660 cm^{-1}

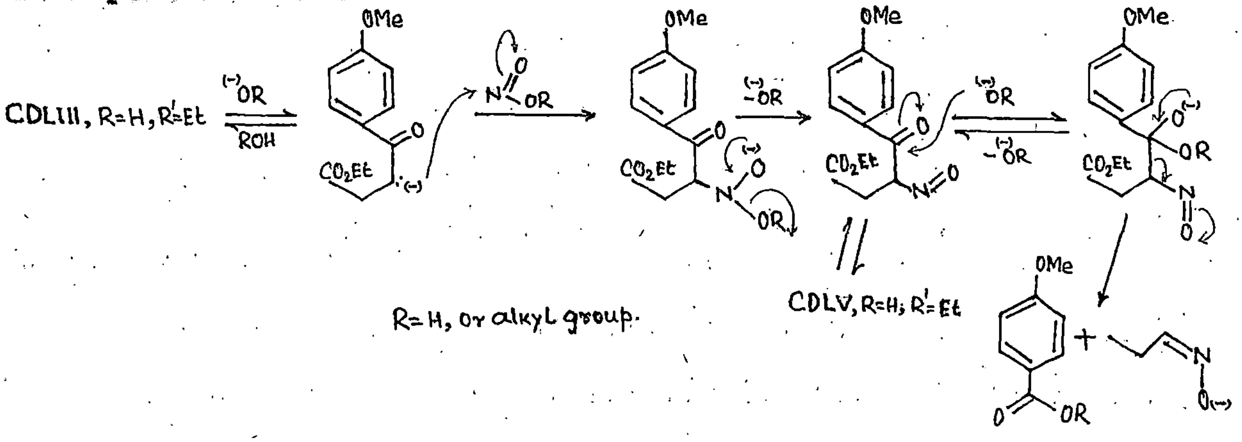
(Fig. I.R.-4) which on acid hydrolysis gave the beta keto acid (CDLVI, R = R' = H), m.p. (crude), 105 - 6° (decomp.). The beta keto acid (CDLVI, R = R' = H) was very unstable and could not be purified. Besides its instability, the low over all yield of 4-(4' methoxy phenyl)-3-oxo butanoic acid made us to search for an alternative reaction sequence for the purpose of synthesizing spiro (4.5) spiro decane sesquiterpenes.

The decomposition of the oximino keto ester needs some comment. The use of nitrosation in organic chemistry which involves a novel carbon-carbon bond cleavage was studied by ROGIC et. al.,$^{(135,228)}$ in detail and this type of carbon carbon bond cleavage through nitrosation has been termed by them as nitrosolysis. Accordingly, the decomposition of the aroyl propionic ester (CDLIII, R = H, R' = Et) to the aryl acid during nitrosation may well be assumed to proceed as follows:



The only requirement for this reaction to take place will be its ability to exist in the enolic form as depicted in (CDLVII). The usual tendency of aromatic ketones to enolize, of course in the possible cases, may be envisaged by their several reactions, described in the text books including the facile dehydration of beta-benzoyl propionic acid to phenyl- Δ^2 -crotono lactone.(227). The presence of electron releasing methoxyl group in the present case (CDLIII, R = H, R' = Et) in the para position of the aromatic nucleus may have some positive contribution to this type of enolization. This fact is supported by our observation that the keto ester (CDLIII, R = H, R' = Et) is completely inactive towards selenium dioxide oxidation and cannot be brominated with cuprous-bromide, but underwent addition reaction with bromine almost instanteneously in the acetic acid medium. For example no diketo compound (CDLVIII) was formed by selenium dioxide oxidation of (CDLIII, R = H, R' = Et).

The other possible pathway, as is depicted below may also be followed by the aforementioned fragmentation of the ketone (CDLIII, R = H, R' = Et) particularly when the nitrosation is carried out with basic catalysts e.g. potassium tert butoxide and sodium ethoxide, although the basicity of the employed base plays an important role.

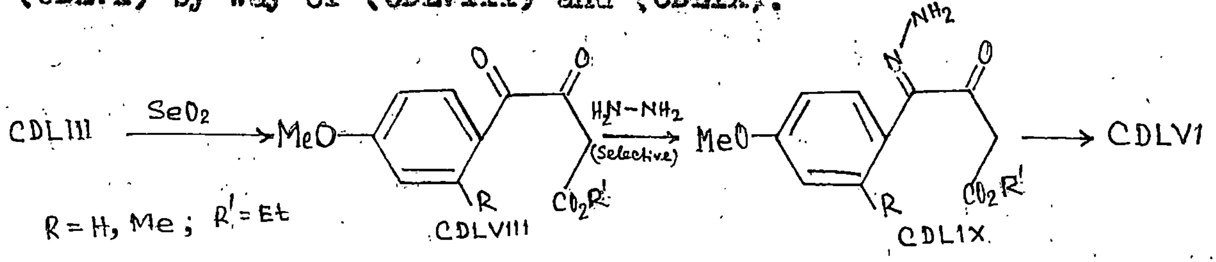


CDLIII, R=H, R'=Et

CDLV, R=H; R'=Et

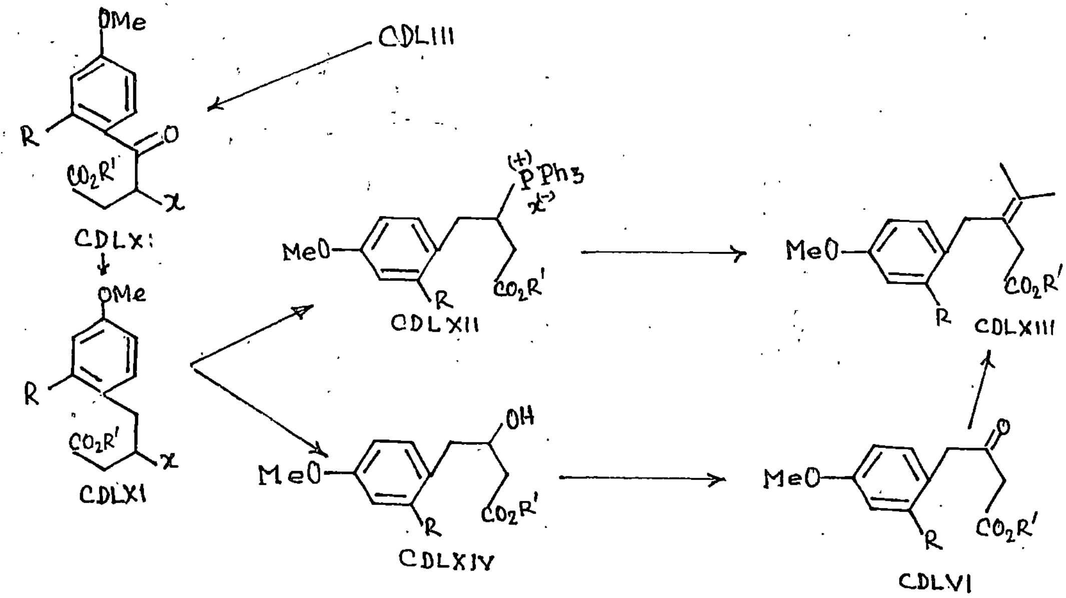
R= H, or alkyl group.

We did not therefore pursue the approach of converting (CDLIII) to (CDLVI) by way of (CDLVIII) and (CDLIX).



Our third and successful approach in this line involved the halogenation on the methylene carbon, alpha to the keto group of beta aroyl propionate (CDLIII) followed by reduction of the carbonyl group to afford the 3-bromo butenoate (CDLXI).

Treatment with triphenyl phosphine may easily convert (CDLXI) to the corresponding phosphorane (CDLXII) which is expected to undergo Wittig reaction with acetone to give the desired isopropylidine derivative (CDLXIII) which on demethylation and reduction of the ester group followed by tosylation would then afford the tosylate (CDLI) having the required potentiality to undergo $Ar_1^{(-)}$-5 assisted cyclization to afford the (4:5) spiro decane (CDLII), the key intermediate in the synthesis of beta vetivone.



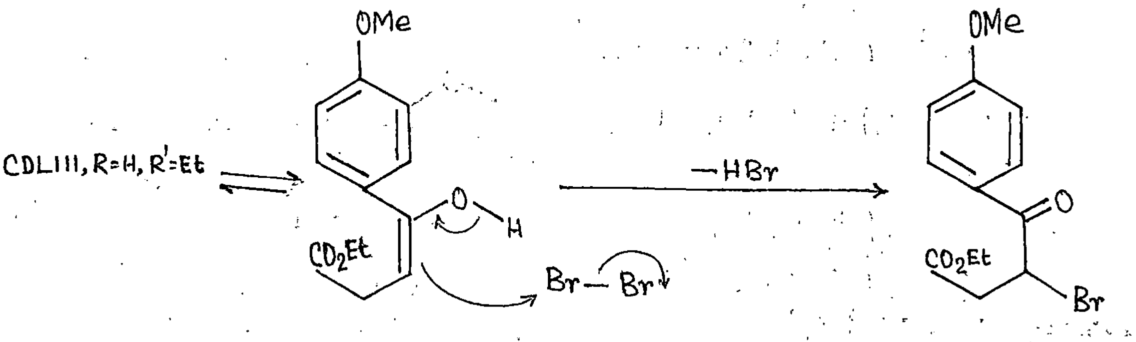
Alternatively the halide (CDLXI) can be hydrolyzed to the corresponding alcohol. Esterification would then give the alcohol ester (CDLXIV) which could easily oxidised to the *beta* keto ester (CDLVI).

There are a good number of methods for preparing *alpha* halo carbonyl compounds. Position specific preparation of *alpha* bromo ketones through bromination of lithium enolate by STOTTER and HILL (259), synthesis of *alpha*-halo carbonyl compounds using metal halides in the presence of a peroxide by INUKAI *et. al.* (118), regiospecific synthesis of bromo ketones through the bromination of ketones in the presence of epoxide by CALO *et. al.* (39), bromination of active hydrogen compounds with bromotrichloromethane and 1,8 diaza bicyclo (5.4.0) undec-7-ene by TANIGUCHI *et. al.* (109), the use of 5,5-dibromo-2,2 dimethyl-4,6-dioxo-1,3 dioxane prepared in two steps from malonic acid via Meldrum's acid in preparing *alpha* bromo ketones by BLOCH (25), the halogenation of carbonyl compounds through the reaction between the corresponding enamine with halogen by SEUFERT *et. al.* (250) and the use of anion exchange resins as halogen carriers in the halogenation of organic compounds by BONGINI *et. al.* (30) are some of the current developments in the field of the conversion of ketone to its *alpha* halo derivative.

The method developed by COREY and KNAPP (55) for *alpha* functionalization of ketones through its N,N-dimethyl hydrazone derivative or the use of N-bromo succinimide in *alpha* halogenation of ketones by MODARAI et. al.(182) are other important methods.

We attempted the conversion of beta-anisoyl propionate (CDLIII, R = H, R' = Et) to the corresponding halogen derivative (CDLX, R = H, R' = Et) making use of heterogeneous bromination with cuprous bromide-the method reported by KING et. al.(132). The attempt failed and no trace of the bromo keto ester (CDLX, R = H, R' = Et) was isolated from the reaction mixture. The starting material was recovered.

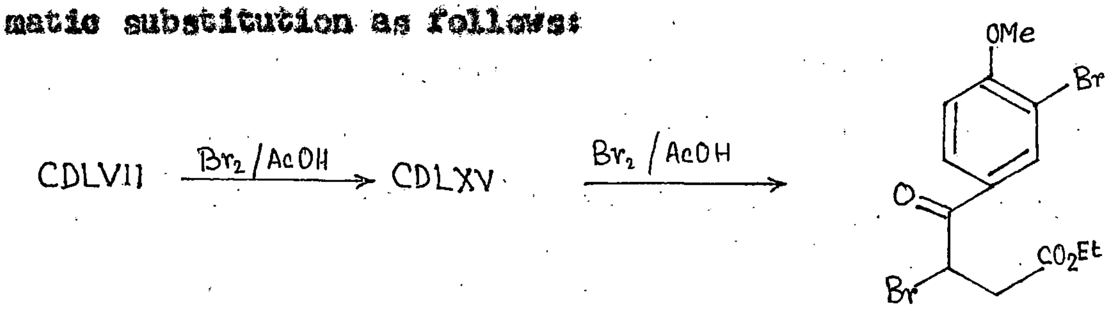
The non-reactivity of beta-anisoyl propionate towards bromination with cuprous bromide and its resistance towards oxidation with selenium dioxide may be attributed to the tendency of the keto ester to remain more in enol form than in keto form. Its colouration with neutral ferric chloride also indicated the presence of enolic hydroxyl group in the alcoholic solution of beta anisoyl propionate. A hypsochromic shift in the i.r. band for aromatic carbonyl of beta anisoyl propionate (CDLIII, R = H, R' = Et) by 20 cm^{-1} (Fig.I.R.2) from the normal absorption of aromatic carbonyls (1690 cm^{-1}) is in aggreement to our assumption. These observations led us to attempt the bromination of the keto ester (CDLIII, R = H, R' = Et) with bormine in acidic medium. The reaction was expected to proceed via the enol (CDLVII) as follows:



CDLVII

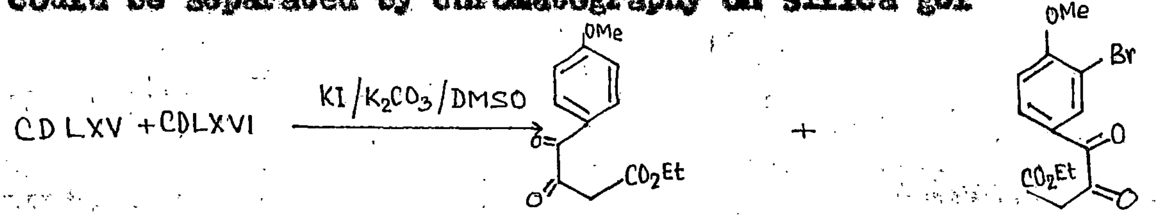
CDLXV

On treatment with bromine in acetic acid it was found that the reaction requires an initial initiation by way of warming up to 60°C. But once the reaction started, it proceeded at a fast rate through the sequential enol bromination followed by aromatic substitution as follows:



CDLXVI

The reaction could be controlled in the enol bromination stage by using one equivalent of bromine and by minimization of reaction period, although the product was always contaminated with the ring bromination product as was revealed the subsequent iodide catalyzed oxidation(19) of the brominated product with dimethyl suphoxide to the corresponding mixture of diketo compounds. They could be separated by chromatography on silica gel



CDLXVII CDLXVIII

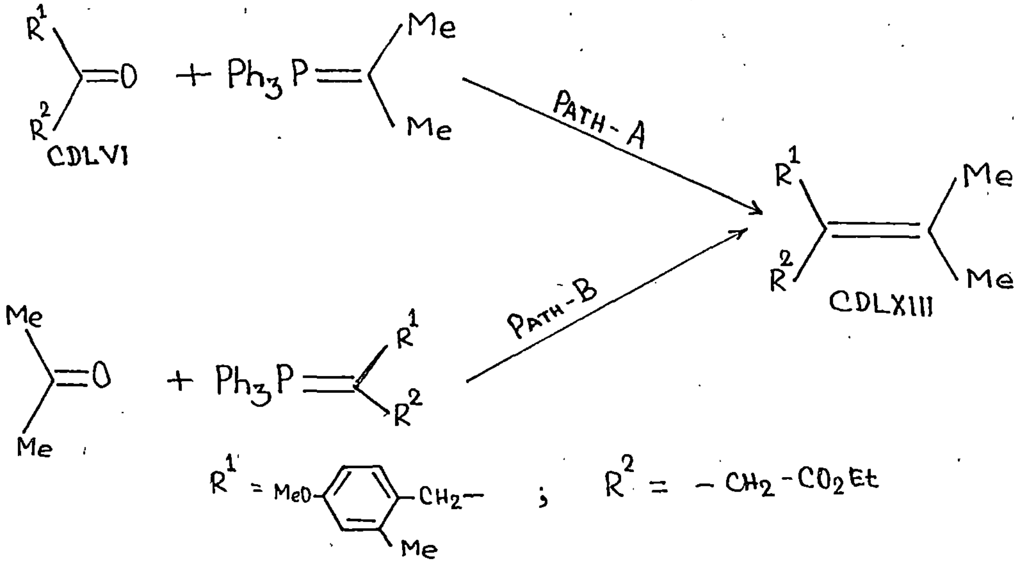
The light yellow crystalline diketone (CDLXVII), m.p. 97°, i.r. (nujol): 1730 cm^{-1}, 1715 cm^{-1}, 1665 cm^{-1}, 1625 cm^{-1} (Fig. I.R.6) was found to contain no halogen and could be oxidized to anisic acid m.p. 179-80°. The other product CDLXVIII which was found to consist of bromine and was oxidized in similar manner to 3-bromo-4-methoxy benzoic acid m.p. 218-219°.

As far as our synthetic scheme is concerned the separation of (CDLXVII) and (CDLXVIII) seems to be un-necessary because the nuclear bromine is expected to be removed during the proposed lithium aluminium hydride reduction of the ester group in the pen ultimate step of our synthetic strategy.

In view of the success in the preliminary studies we proceeded to construct the intermediate, succinoylation of meta-cresyl methyl ether as has been reported by PAPA, SCHWENK and HANKIN (209). The 3-(4'-methoxy 2'-methyl benzoyl) propionic acid (CDLIII, R = Me, R' = H), m.p. 136-37° was reported to be formed along with equal amounts of the corresponding demethylated product that melted after recrystallization from water at 179.5 - 180.5°. But no experimental details were given by them. However, we carried out the required succinoylation reaction using nitro benzene as solvent and found that while the 3-(4'-methoxy-2'-methyl benzoyl) propionic acid (CDLIII, R=Me, R' = H) obtained as precipitate on decomposing the rosy red reaction complex with hydrochloric acid, the other products remained in nitro benzene layer. The acid remained in nitro benzene layer were extracted with sodium hydroxide solution. Acidification gave the a solid m.p. 104 - 6° which probably is a mixture of (CDLIII, R=Me, R' = H) and the corresponding demethylated product. We did not attempt any separation or identification.

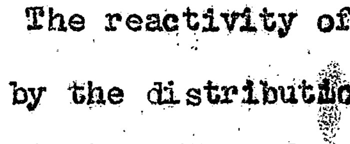
Esterification of 3-(4'-methoxy-2'-methyl benzoyl) propionic acid through the conventional ethyl alcohol-benzene-sulphuric acid method followed by continuous azeotropic separation of water from the reaction mixture gave the ethyl ester (CDLIII, R = Me, R' = Et) m.p. 49°, i.r. (nujol) : 1730 cm^{-1}, 1665 cm^{-1}, 1650 and 1640 cm^{-1}, 1420 cm^{-1}, 1240 cm^{-1} (Fig. I.R.-7). The keto ester on controlled bromination in acetic acid medium afforded a semi solid which on Clemmensen reduction with zinc amalgam(166) and subsequent chromatographic seperation afforded Ethyl-4(4'-methoxy-2'-methyl phenyl)-3-bromo butanoate (CDLXI, R = Me, R' = Et, x = Br) b.p. 200 - 04°/5 mm; 245 - 46°/7 mm i.r., (liquid film): 2970 cm^{-1}, 2930 cm^{-1}, 2860 cm^{-1}, 2830 cm^{-1}, 1730 - 1720 cm^{-1}

580 cm^{-1} (Fig. I.R.-8) and the corresponding carboxylic acid m.p. 75 - 76° which could easily be esterified to the ester (CDLXI, R = Me, R' = Et, X = Br) through alcohol-benzene-sulphuric acid method with continuous removal of water as azeotropic mixture. The use of the bormo ester (CDLXI, R = Me, R' = Et, X = Br) in the proposed Wittig reaction requires a comment. In principle the isopropylidine ester (CDLXIII) could be prepared by two different paths,

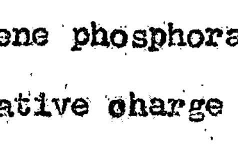


The use of first path (i.e. path A) requires the prior conversion of the bromo ester (CDLXI, R = Me, R' = Et, X = Br) to the corresponding keto ester (CDLVI). The reaction sequence required for the purpose would, besides involving more steps also makes use of beta keto ester. Hence path B was chosen to obtain the isopropylidino ester (CDLXIII) smoothly from the beta bromo ester (CDLXI, $R = Me$, $R^1 = Et$, $X = Br$). An illustration of the Path B, which starts from ketones has been shown by ANSELL and THOMAS(8).

The reactivity of an ylide is very much dependent on its structure. Unlike nitrogen, phosphorous is capable of being pentavalent, since it can expand its valency shell to ten electrons by inclusion of d-orbitals. Alkylidene phosphoranes can therefore be considered as resonance hybrids of two limiting structures, the ylide form (CDLXIX) and the ylene form (CDLXX), despite the fact that the protons in the phosphomium salts are under the influence of weaker repulsive coulomb forces than those in the ammonium salts (bond distances : P-C, 1.87 Å ; N-C, 1.47 Å). This greater tendency for the formation of phosphorous ylides reflects stabilization of the transition state by p-d orbital overlap.



CDLXIX

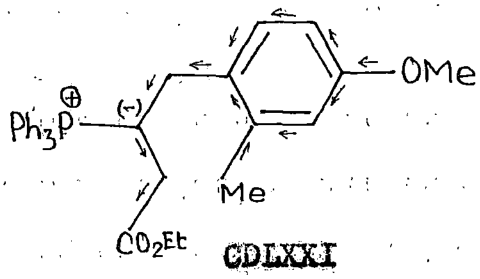


CDLXX

The reactivity of the alkylidene phosphoranes is determined by the distribution of the negative charge in the molecule, which in turn depends on the nature of the substituents (R_1)

and (R_2) in the alkylidene portion as well as of the groups (R) on phosphorous. Thus the nucleophilic character of the phosphorane is decreased and the stability of the phosphorane increased if the lone electron pair on the alpha carbon atom of the form (CDLXIX) is delocalized into groups (R_1) and (R_2). The groups (R) on phosphorous also influence the reactivity of the alkylidene phosphoranes since they may be capable of increasing or decreasing the d-orbital resonance with a consequent change in the relative importance of the form (CDLXX) in the resonance hybride. Decreased d-orbital resonance would result in greater importance of the ylide form (CDLXIX) and therefore increased reactivity of phosphorane. The larger the formal charge on phosphorous, the more important would be the ylene form (CDLXX). Electron withdrawing groups (R) on phosphorous will, other things being equal, increase the d-orbital resonance and therefore favour the ylene form (CDLXX) whereas electron-releasing group will increase the importance of the ylide form (CDLXIX). Thus alkylidene tri-substituted phosphoranes in which the formal positive charge on phosphorous is reduced by the inductive or other effect of the attached groups (R) would under otherwise equal conditions be more reactive than the alkylidene phosphoranes in which the groups attached to phosphorous has a opposite effect.

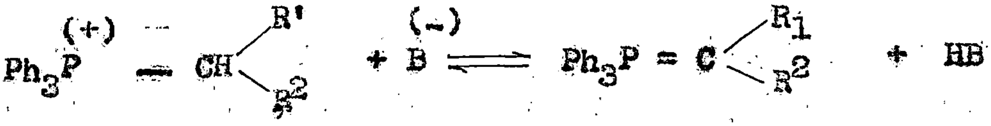
The substituents on the alkylidene portion of our proposed phosphorane have practically no effect on the alpha-carbon atom of the form (CDLXIX) since the -I effect of the ester group, being propagated through a methylene group to the alpha carbon atom, has a little effect on its nucleophilicity which may well be expected to be compensated by the electron releazing effect of para methoxy and ortho methyl groups in the aromatic ring, propagated to the alpha carbon atom via another methylene group e.g.



CDLXXI

The use of triphenyl phosphine in preparing such a phosphorane as (CDLXXI) would make this Wittig reagent to be moderately reactive so that its formation as well as its reaction with acetone would be smooth and is expected to remain free from additional difficulties.

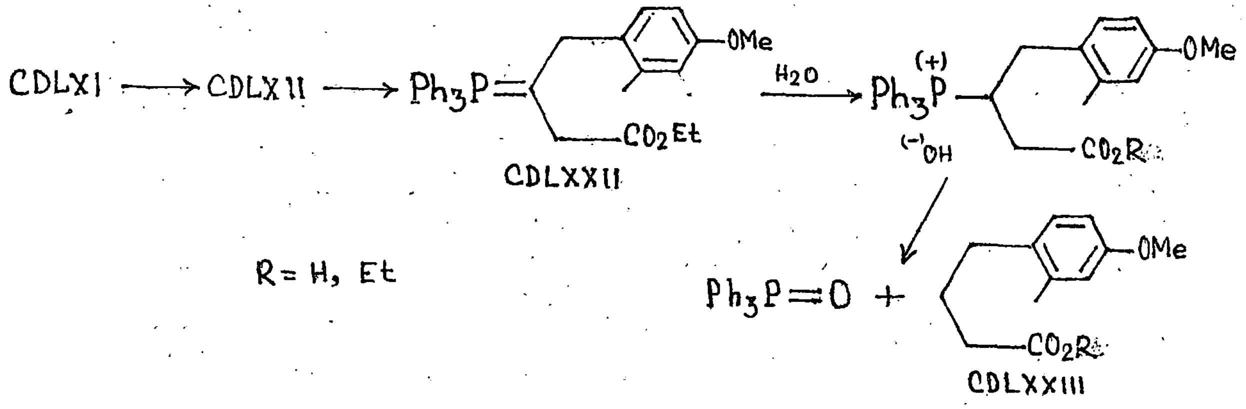
The Wittig reagents are usually prepared by the removal of a proton from the quaternary salts of phosphorous with a base in a, definitely reversible reaction



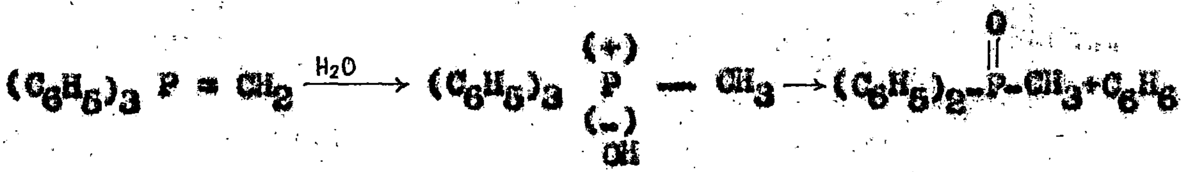
$$\overset{(+)}{Ph_3P} - CH\begin{matrix} R' \\ R^2 \end{matrix} + \overset{(-)}{B} \rightleftharpoons Ph_3P = C\begin{matrix} R_1 \\ R^2 \end{matrix} + HB$$

The choice of conditions depends entirely on the nature of the desired ylide. The most reactive phosphoranes which are normally air-and moisture sensitive, require to be prepared, an anhydrous medium, inert atmosphere and the use of organo metallic compounds as proton acceptor. The resonance stabilized ylides which are stable towards hydrolysis can be prepared by the action of alkali-metal hydroxides on aqueous solution of the phosphonium salt (119). These phosphoranes usually precipitate in crystalline form and can be dried in air. With sufficiently acidic phosphonium salts, weaker bases can also be used. The method of eleminating hydrogen bromide from triphenyl benzyl phosphonium bromide using metallic sodium has been reported by PARFENE'EV and SHAMSHURIN (211). Ethylidene triphenyl phosphorane was obtained in very good yield by the action of methyl sulphinyl carbanion on triphenyl ethyl phosphonium bromide in dimethyl sulfoxide (92).

Our attempt to prepare the phosphorane (CDLXXII) by treating the phosphonium salt (CDLXII), prepared by refluxing the bromo ester (CDLXI) with triphenyl phosphine in dry benzene, with metallic sodium (211) followed by addition of acetone resulted in the formation of 4-(4-methoxy, 2-methyl phenyl) butyric acid (CDLXXIII, R = H) probably due to the effect of moisture and thus indicates that the phosphorane (CDLXXII) is not that much unreactive as is expected from resonance stabilized phosphoranes.

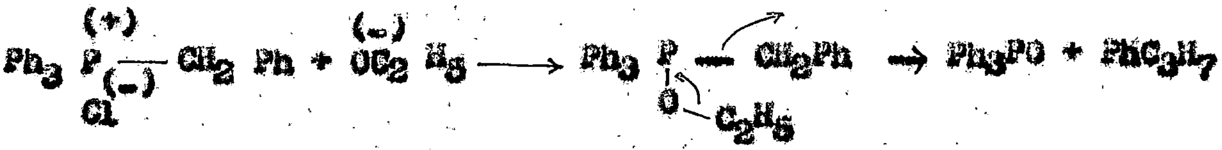


Similar hydrolysis of triphenyl methylene phosphorane was observed by FENTON and INGOLD (81) e.g.,



$$(C_6H_5)_3\,P=CH_2 \xrightarrow{H_2O} (C_6H_5)_3\,\overset{(+)}{\underset{\underset{OH}{(-)}}{P}}-CH_3 \rightarrow (C_6H_5)_2-\overset{\overset{O}{\|}}{P}-CH_3+C_6H_6$$

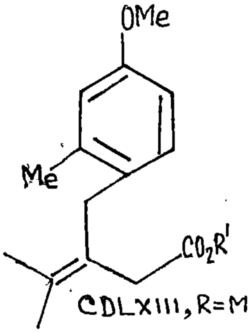
A simple method for the preparation of unstable ylides employs alkali metal alkoxides as proton acceptors, usually in the corresponding alcohols as solvent (290). The simplicity of this method is gaining more and more attention for it. Moreover the procedure permits preparation of unstable ylides directly in the presence of carbonyl compounds, thus minimizing side reactions. The only side reaction that generally occurs at elevated temperatures involves the attack of the base directly on phosphorous (106). e.g.,



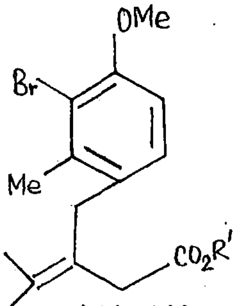
$$Ph_3\,\overset{(+)}{\underset{\underset{Cl}{(-)}}{P}}-CH_2\,Ph+\overset{(-)}{O}C_2\,H_5 \longrightarrow Ph_3\,\underset{\underset{O-C_2H_5}{|}}{P}-CH_2Ph \rightarrow Ph_3PO+PhC_3H_7$$

although the main reaction is the reversible removal of a proton from the alpha carbon atom.

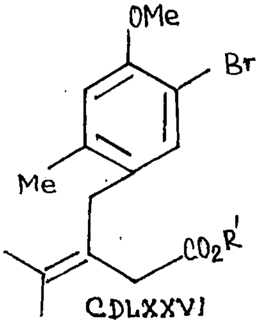
We prepared the phosphonium salt by refluxing a solution of the mixture of bromo ester (CDLXI, R = Me, R' = Et, X = Br) in dry benzene with a slight excess of triphenyl phosphine and subjected it to ethoxide treatment in two ways. In the first method benzene was removed as far as practicable by distillation under reduced pressure and the residue was treated with sodium ethoxide in super dry alcohol. The resultant reddish solution was treated with equivalent amount of acetone. Usual work up followed by chromatography over silica gel gave besides the unreacted triphenyl phospine, 3-iso-propylidino-4-(4'-methoxy-2'-methyl phenyl) butanoic acid (CDLXIII, R=Me, R'=H), m.p. 153 - 54°, i.r. (nujol): 3340 cm^{-1}, 3260-3030 cm^{-1} 1720 cm^{-1}, 1700 cm^{-1}, 1615 cm^{-1}, 1240 cm^{-1} (Fig. I.R.9). Esterification of this acid through ethyl alcohol-benzene-sulphuric acid resulted in the formation of the (CDLXIII, R=Me, R'=Et) m.p. 71 - 72°, i.r. (nujol): 3340 cm^{-1}, 1695 cm^{-1}, 1620 cm^{-1}, 1235 cm^{-1} (Fig. I.R.10). The second method involved the use of nitrogen atmosphere throughout the reaction period covering the formation of phosphonium salt ylide formation and its reaction with acetone. The other modification involved the use of dry benzene as solvent in place of ethanol and the use of solid sodium ethoxide as base. The result was same as in the first method in respect of the nature of products as well as the percentage of their yields. The use of bromo-ester (CDLXI, R=Me, R'=Et, X=Br) without purification in Wittig reaction resulted in the formation of the iso propylidino ester (CDLXIII, R=Me, R'=Et) and its nuclear bromo derivatives which could be seperated through chromatography. The mixture of the acids corresponding to the bromo derivatives (CDLXXV) and (CDLXXVI) was found to melt over a range 130°-135°C and was not separated on the assumption that both of them during reduction of their ester group to alcohol group with lithium aluminium hydride bromine will be replaced by hydrogen and both of them will lead to the same alcohol (CDLXXVII) as may be obtained from (CDLXIII, R=Me, R'=Et) on similar treatment.



CDLXIII, R=Me



CDLXXV

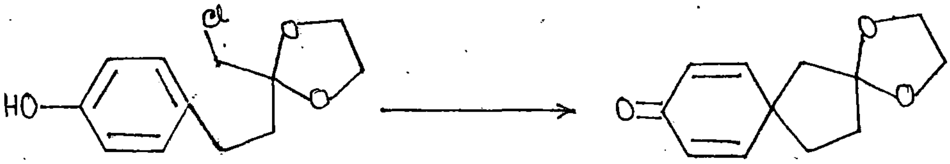


CDLXXVI

R' = H, Et.

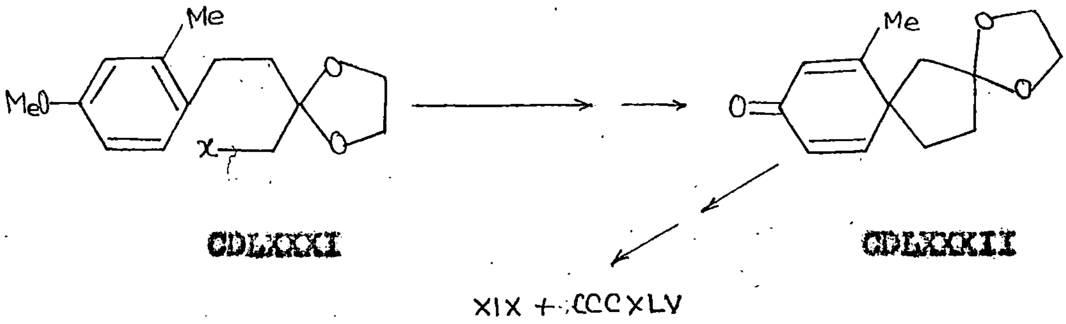
As the compounds (CDLXIII, R = Me, R' = Et), (CDLXXV) and (CDLXXVI) were obtained in very insufficient quantity it was not possible to complete the synthesis. More material is being synthesized to complete the synthesis.

In search of different routes to the spiro-dienone we turned our attention, in our second approach, to the $Ar_1^{(-)}$-5 participation method of DORLING and HARLEY-MASON(73) who spiro annulated 2-chloromethyl-2-(2-p-hydroxy phenyl ethyl) dioxolane (CDLXXIX), to the ethylene ketal of spiro (4:5)-deca 6:9-diene-2,8-dione (CDLXXX).



CDLXXIX CDLXXX

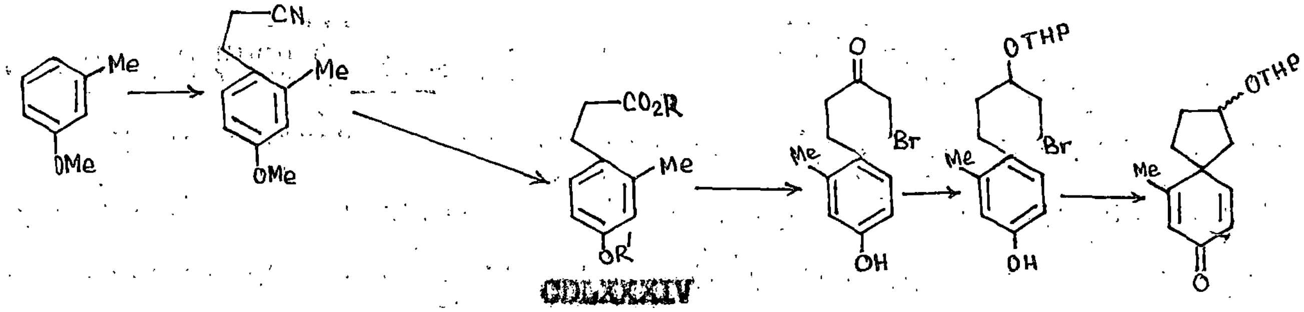
As has been discussed earlier the WINSTEIN's spiro annulation method(15) suffers from the limitation that on carrying out the reaction at higher concentrations the yield of spiro-dienone is very much reduced owing to intermolecular reactions. But in the case with the compound (CDLXXIX) the halogen atom is associated with high degree of steric hindrance to SN-2 displacement and has been tested by boiling (CDLXXIX) for several hours with concentrated alcoholic sodium hydroxide which resulted no liberation of chloride ion (73). This inertness of the halogen atom minimized the possibility of intermolecular reaction. However, the compound (CDLXXIX) on treatment with potassium tert butoxide in tertiary butanol in a steel autoclave at 180° gave the dien dione (CDLXXX). Changes in concentration was shown to have a little effect upon the yield of the spiro compound. Even more drastic conditions like pyrolysis of the dry sodium salt of compound (CDLXXIX), could conveniently be employed for the spiro annulation. Likewise the methyl derivative (CDLXXXI) may safely be assumed to spiro annulate to (CDLXXXII) which through a suitable series of reactions, involving the replacement of the C_2-oxo group by isopropylidene group in the five-membered ring and the introduction of methyl group at C_{10} of the six-membered ring, would give rise to beta vetivone (XIX) and/or its 10-epimer (CCCXLV) e.g.



CDLXXXI

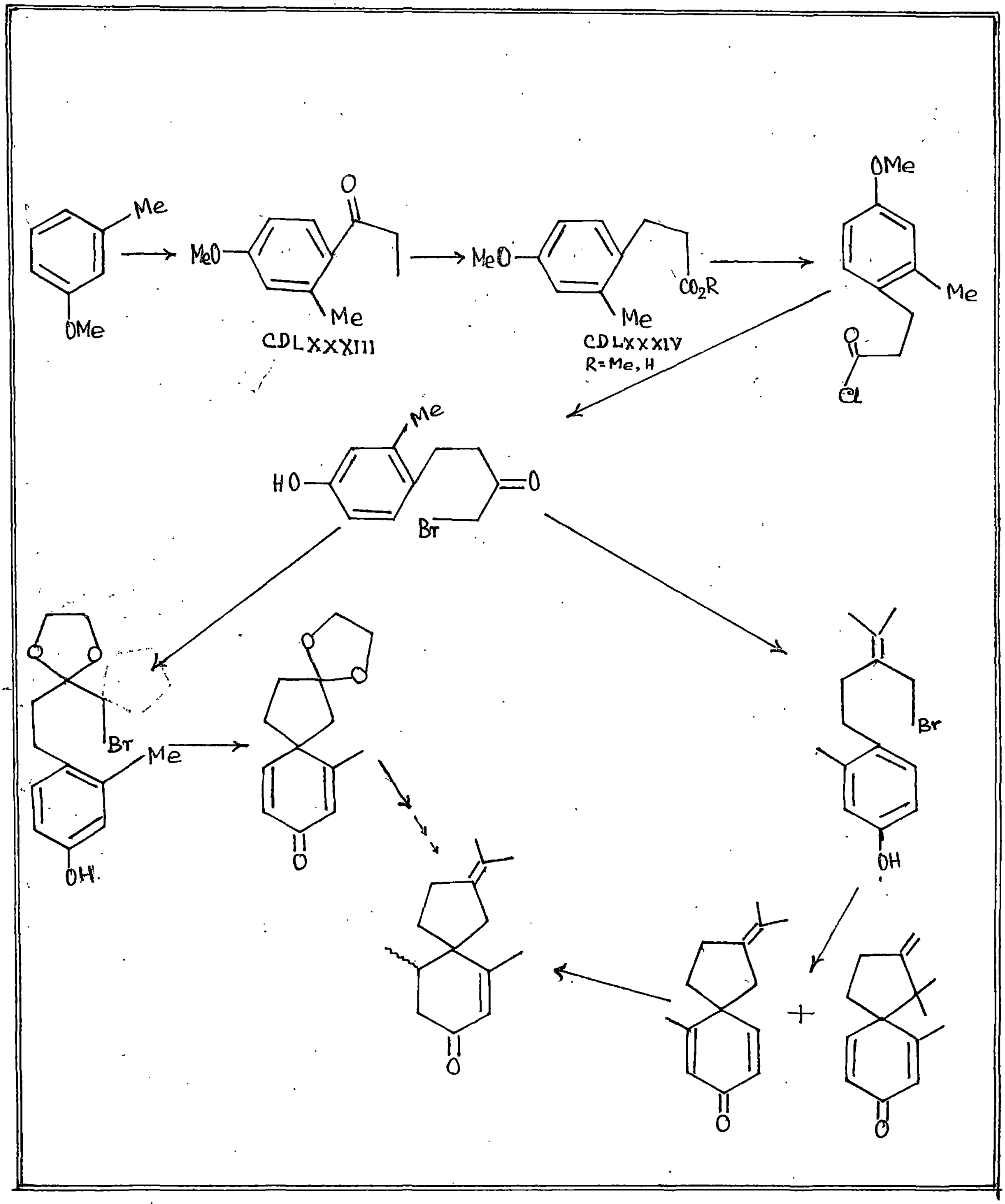
CDLXXXII

Mukharji and Sengupta (186) reported a synthesis of the spiran intermediate (A) by way of cyano ethylating meta-cresyl methyl ether followed by hydrolysis, demethylation, bromomethylation of the resulting acid (CDLXXXIV, R=R'=H), reduction of carbonyl group to the corresponding alcohol and spiro annulation of the resulting alcohol after protecting the hydroxyl function by preparing its tetra-hydro pyranyl ester e.g.

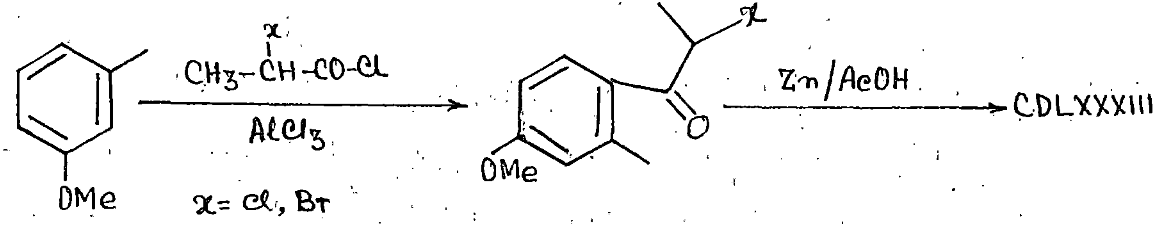


CDLXXXIV
R = Me, H
R' = Me, H

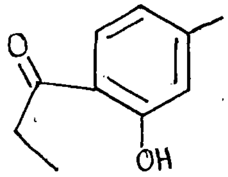
All their attempts to carry out a conjugate 1,4 addition on the spiro dienone (A) proved abortive. It seemed to us worth while to repeat their experiment so as to make a possible exploitation of the reaction sequence in synthesizing spiro vetivanes as shown below. Our effort differes from that of Mukharji et. al. (186) in respect of the preparation of 3-(4'-methoxy, 2'-methyl phenyl) propionic acid (CDLXXXIV, R=H). While Mukharji et. al., prepared this compound by cyanoethylation of meta cresyl methyl ether followed by hydrolysis of the resulting nitrile, our endeavour to obtain it was through Willgerodt reaction on 4'-methoxy-2'-methyl propiophenone (CDLXXXIII), prepared through Friedel-Crafts acylation reaction on meta cresyl methyl ether.


Me
OMe
MeO
O
Me
CDLXXXIII
MeO
CO$_2$R
Me
CDLXXXIV
R=Me, H
OMe
Me
O
Cl
Me
HO
O
Br
O
O
Br
Me
OH
O
O
O
Br
OH
O
O
O

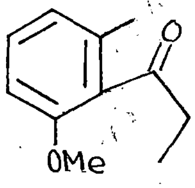
AUWERS(12) had prepared 4'-methoxy-2'-methyl propiophenone by Friedel Craft's reaction of *meta*-cresyl methyl ether with *alpha*-chloro (or *alpha* bromo) propionyl chloride followed by dehalogenation with Zinc-Acetic acid,



In addition to the methoxy propiophenone (CDLXXXIII) a small quantity of 2'-hydroxy-4'-methyl propiophenone (CDLXXXV) was isolated by him. It is significant to note that neither the methoxy derivative of (CDLXXXV) nor the isomeric 2'-methoxy-6'-methyl propiophenone (CDLXXXVI) was isolated by AUWERS.

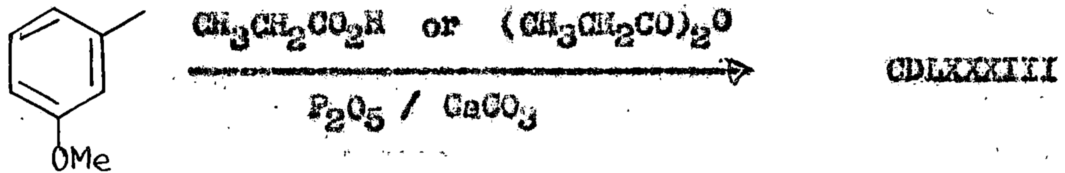


CDLXXXV

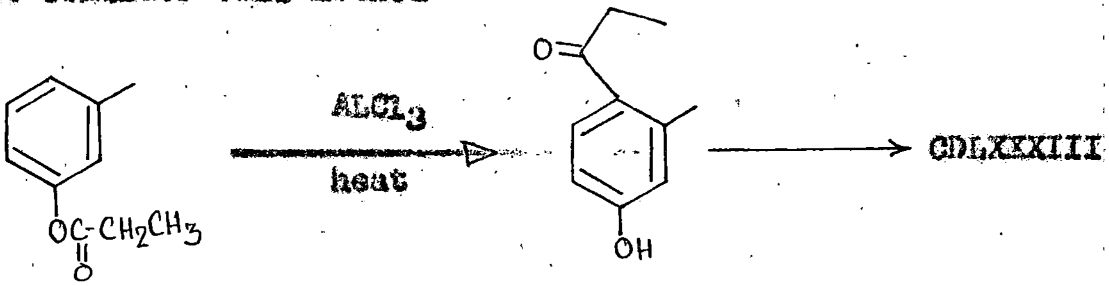


CDLXXXVI

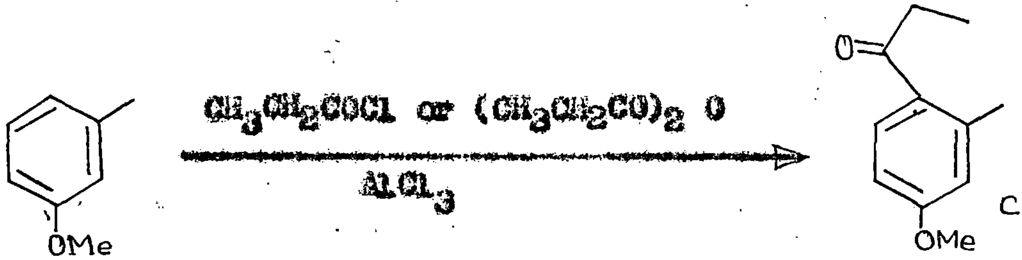
We considered some alternative methods for the preparation of the required compound (CDLXXXIII). Aryl ethers are so sensitive that acylation may occur in the presence of catalysts, less powerful than Aluminium Chloride even with free carboxylic acids as acytylating agents. KOSOLAPOFF(136) acetylated anisole by treating it with a mixture of glacial acetic acid and phosphoric anhydride. In view of the extreme simplicity of this procedure and the reported high yields we attempted to prepare (CDLXXXIII) by this method. On refluxing a mixture of meta cresyl methyl ether, phosphoric anhydride with continuous stirring in the presence of calcium carbonate for seventy five minutes, the compounds (CDLXXXIII) could be isolated after chromatography on silica gel in approximately ten percent yield. Use of propionic anhydride in place of propionic acid or increase in the reaction time did not materially affect the yield.



FRIES REARRANGEMENT (24) of phenolic esters could be one of the important methods of preparing of our desired propiophenone, but in view of the extremely poor yields, even in the simple case of phenyl acetate, the reported yield is about thirty percent, we did not consider this method

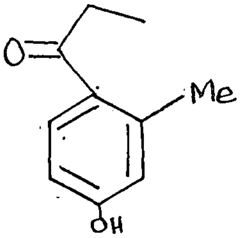


We therefore, considered the obvious but hitherto unreported Friedel-Craf~~f~~ts' acylation of meta cresyl methyl ether with propionyl chloride and propionic anhydride and found that this is the best preparative method for the desired 4'-methoxy-2'-methyl propiophenone (CDLXXXIII).

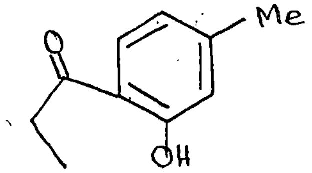


CDLXXXIII

In addition to the methoxy compound (CDLXXXIII) we could isolate 4'-hydroxy-2'-methyl propiophenone and (CDLXXXVII), and 2'-hydroxy-4'-methyl propiophenone (CDLXXXV). It has been found that the use of the aromatic substrate, propionyl chloride and anhydrous aluminium chloride in the molar ratio 1:1:2 gave the best yield. 4'-hydroxy compound (CDLXXXVII) could be almost quantitatively methylated to the 4'-methoxy compound (CDLXXXIII).



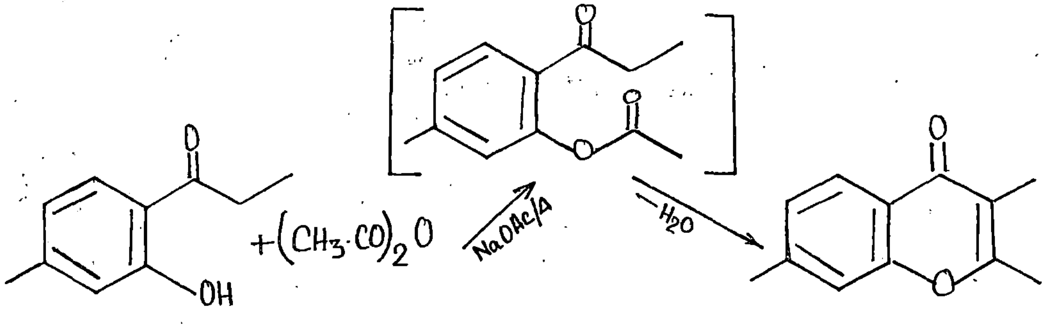
CDLXXXVII



CDLXXXV

4'-methoxy-2'-methyl propiophenone (CDLXXXIII) was identified through its melting point 43°(12), and by its oxidation to 4'-methoxy phthalic acid, m.p. 168 - 69°. The 2:4 dinitro phenyl hydrazone derivatives m.p. 142 - 43° and the oxime, m.p. 94 - 95°(12) have also been prepared i.r. (nujol): 1660 cm^{-1} (Fig. I.R. 11); p.m.r. (CCl_4), 1.03, 1.11 and 1.19 δ (3H, t, J = 7.5 Hz); 2.48 δ (3H, s); 2.65, 2.73, 2.81 and 2.90 δ (2H, q, J= 7.6 Hz); 3.78 δ (3H, s); 6.67 - 6.78 δ (2H, m); 7.58 and 7.67 δ (1H, d, J = 8.1 Hz) (Fig. p.m.r.-1).

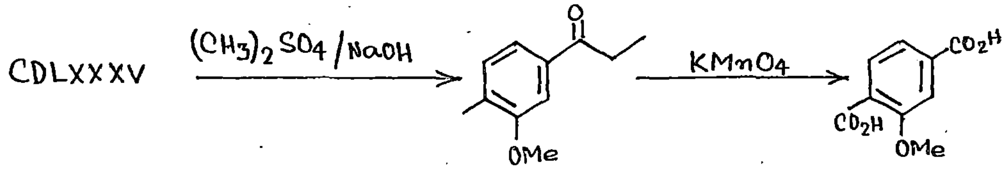
2'-hydroxy-4'-methyl propiophenone (CDLXXXV) was identified through its m.p. 42.5° and through the melting points of its 2:4 dinitrophenyl hydrazone derivative and oxime derivative which are 197 - 98° and 103 - 104° respectively(12) i.r. (nujol) : 3000-2800 cm^{-1} (merged with nujol band), 1640—1610 cm^{-1}, 1240 cm^{-1} (Fig. I.R. 13); p.m.r. ($CDCl_3$) : 1.15, 1.23 and 1.32 δ (3H, t, J = 7.5 Hz); 2.344 δ (3H, s.); 2.85, 2.93, 3.01 and 3.10 δ (2H, q, J = 7.5 Hz); 6.66 - 6.81 δ (2H, m); 7.62, 7.71 δ (1H, d, J = 8.1 Hz). (Fig. p.m.r.-2). Additional proof for its structure was obtained from its conversion to 2,3,7-trimethyl-1,4 benzopyrone (CDLXXXVIII), m.p. 85 - 86° following the method of ROBERTSON, WATERS and JONES(217a) e.g.



CDLXXXV

CDLXXXVIII

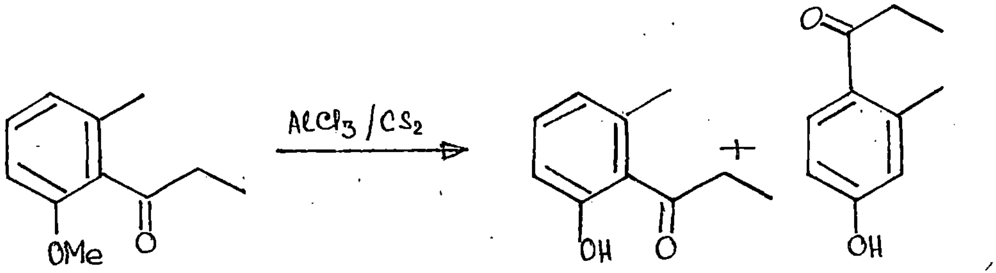
Further the hydroxy compound (CDLXXXV) was methylated to its methoxy derivative (CDLXXXIX) b.p. 85 - 87°/5 mm., 2,4-dinitrophenyl hydrazone, m.p. 167°. The chemical proof for the relative position of the substituents in (CDLXXXV) was obtained from its oxidation to methoxy terephthalic acid, m.p. 280°.



CDLXXXIX

The third product isolated from the Friedel - Craft's reaction was (CDLXXXVII) identified as 4'-hydroxy-2'-methyl propiophenone through its m.p. 117° (Lit., 114-15°) and its conversion to the methyl ether (CDLXXXIII). I.R. spectra of the hydroxy compound (CDLXXXVII) showed the following bands: 3200 cm^{-1}, 1645 cm^{-1} (Fig. I.R.-12).

The non-formation of 2'-methoxy-6'-methyl propiophenone (CDLXXXVI), the other possible product of the Friedel-Craft's reaction of <u>meta</u> cresyl methyl ether with propionyl chloride or with propionic anhydride may be attributed to steric factors. This is evident from the demethylation studies of ROBERTSON et.al.,(226) who found that the attempted demethylation of 2'-methoxy-6'-methyl propiophenone (CDLXXXVI) led to the formation of the normal demethylated product (CDXC) along with the unexpected 4'-hydroxy 2'-methyl propiophenone (CDLXXXVII) in the ratio 1:5.



CDLXXXVI CDXC CDLXXXVII

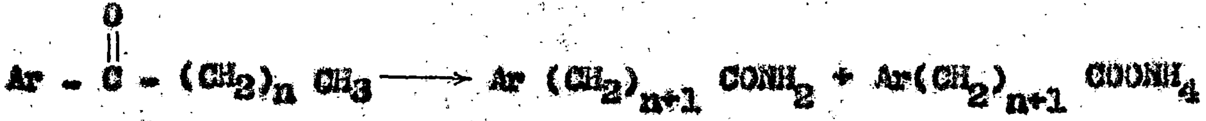
We also studied the demethylation of 4'-methoxy compound (CDLXXXIII) and the 2'-methoxy isomer (CDLXXXIX) and found that the later compound gave the 4'-hydroxy compound (CDLXXXVII) in significant amounts along with the normal demethylated product (CDLXXXV). Moreover the demethylation was faster as compared to that of 4'-methoxy analague (CDLXXXIII). The results are summarized in table I (Experimental section).

Two important conclusions regarding the reaction condition and the reactants' molecular ratio are obtained from the above studies on the demethylation of the methoxy compounds in respect of the preparation of our desired 4'-methoxy-2'-methyl propiophenone through the Friedel-Craft's acylation of <u>meta</u> cresyl methyl ether, mentioned earlier: ( ) The use of aromatic substrate and the catalyst, anhydrous aluminium chloride in the molar ratio 1:2 may enhance the yield of the 4'-hydroxy compound (CDLXXXVII). One mole of aluminium chloride will be utilized in the process of acylation of <u>meta</u> cresyl methyl ether leading to the three probable methoxy propiophenones (CDLXXXIII), (CDLXXXVI) & (CDLXXXIX) and the second molecule of the catalyst may lead to demethylation of the products with subsequent rearrangement in the possible cases [e.g. with compounds (CDLXXXVI) and (CDLXXXIX) to the 4'-hydroxy-2'-methyl propiophenone (CDLXXXVII), in approximately 84% from (CDLXXXIII), 34% from (CDLXXXIX) and cent percent from (CDLXXXVI)]. The second condition for this high yield of (CDLXXXVII), to occur, besides the use of the reactants in the said molecular ratio, is that the reaction mixture, after completion of the required duration for Friedel-Craff's acylation is to be refluxed for 24 hours. Thus the optimum yield of the

4'-hydroxy-2'-methyl propiophenone could be achieved and it can easily be methylated to the desired compound (CDLXXXIII). This prediction has actually been tested by carrying out the acylation reaction with different ratio of the reactants as is reflected from the table II (in the experiemental section).

The best yield of 4'-hydroxy-2'-methyl propiophenone (CDLXXXVII) was obtained by using meta cresyl methyl ether, propionyl chloride or propionic anhydride and anhydrous aluminium chrolide in the ratio 1:1:2, keeping the reaction mixture at rest for twenty four hours and then refluxing it for further twenty four hours (Expt. no. 4, Table II).

The conversion of the propiophenone (CDLXXXIII) into the aryl propionic acid (CDLXXXIV) was planned to be achieved through the WILLGERODT REACTION, — the name attributed to a group of closely related reactions which have as a common feature: the conversion of a carbonyl compound into an amide with the same number of carbon atoms. The original process involved the reaction of an appropriately substituted alkyl aryl ketone with an aqueous solution of yellow ammonium polysulphide at an elevated temperature to form an aryl substituted aliphatic acid amide, together with a small amount of the corresponding ammonium salt. The net result of the reaction have been shown to be the reduction of the carbonyl group and the oxidation of the terminal methyl group, e.g.

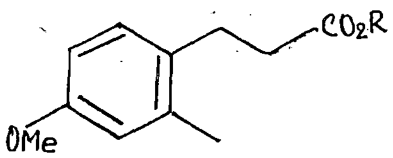


$$Ar - \overset{O}{\overset{\|}{C}} - (CH_2)_n\,CH_3 \longrightarrow Ar\,(CH_2)_{n+1}\,CONH_2 + Ar(CH_2)_{n+1}\,COONH_4$$

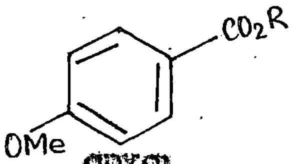
Although the WILLGERODT REACTION was known through standard references (110) it was used by a few workers only and remained a chemical curiosity until increasing interest in complex polynuclear systems led to a search for additional methods of synthesising aryl-substituted aliphatic acids of unequivocal structure. Interest in the reaction revived after its application to the preparation of 3-acenaphtyl acetic acid from 3-acetyl acenaphthene (81a). The requisite temperature was lowered to 160° by the use of purified dioxane to increase the mutual solubility of the ketone and aqueous ammonium polysulphide, and the yield of acid compared favourably with that realized by an alternative synthesis involving the ARNDT-EISTERT REACTION. The Willgerodt reaction in the presence of dioxane has been used by several investigators in the synthesis of a variety of aryl substituted aliphatic acids and amides (42).

The KINDLER variation (133,134) which promises to be more useful than the original Willgerodt procedure, consists in heating the ketone with approximately equimolecular amounts of sulphur and a dry amine instead of aqueous ammonium polysulphide. A thioamide is formed as the principal product and on hydrolysis with acid or alkali afford the carboxylic acid, usually in good yield. Generally a secondary aliphatic amine but some times a primary amine or even anhydrous ammonia is used. Morpholine is well suited to the Kindler version of WILLGERDT reaction (246). It is cheap, and its boiling point (128°) makes possible the use of open apparatus in place of an autoclave or bomb tube. Further this modified process generally lead to the higher yields of the desired acid or acid amide.

Our attempt to convert 4'-methoxy-2'-methyl propiophenone (CDLXXXIII) to 4'-methoxy-2'-methyl phenyl propionic acid (CDLXXXIV, R=H) through Kindler's modification of Willgerdt reaction showed that the reaction is highly dependant on the reaction temperature as well as on the ratio of the reactants used. The use of the ketone, morpholine and sulphur in the ratio of 1:3:2 followed by alkaline hydrolysis led to the formation of degraded aromatic acid (CDXCL) m.p. 176°, as a sole product on heating at 150-160°C for 20 hrs. Whereas by heating the 1:1:1 mixture of the same compounds as before at 130-140° through the same period of time (20 hrs.) followed by alkaline hydrolysis resulted in a mixture of acids (as is evident from the TLC of the methyl ester of the mixture), [redacted] the aromatic acid (CDXCL) and the propionic acid (CDLXXXIV).



CDLXXXIV



CDXCL

R = Me, H.

Further more the reaction temperature could be lowered and the reaction period could be minimized by using dry benzene as solvent when an 80% yield of the aromatic and was obtained after subsequent alkaline hydrolysis.

The acid mixture was separated into its constituent (CDXCI, R = H) and (CDLXXXIV, R = H) by esterifying the mixture with diazomethane followed by chromatography over silica gel. The separated esters (CDXCI, R = Me) and (CDLXXXIV, R = Me) were further purified through distillation. Methyl-3(4'-methoxy-2'-methyl Phenyl) propionate (CDLXXXIV, R = Me) had b.p. 155 - 6°/10 mm and was hydrolyzed with 10% ethanolic sodium hydroxide solution to the corresponding acid (CDLXXXIV, R = H), crystallized from water, m.p. 94 - 98° (Lit[186] m.p. 104°). In spite of repeated crystallisation the melting point did not improve. However satisfactory elemental analysis for the acid (CDLXXXIV, R = H) was obtained and its structure is supported by the following spectral data : i.r. (KBr) : 3040 - 2820 cm^{-1} (broad) 2910 cm^{-1}, 2700 - 2540 cm^{-1}, 1710 cm^{-1}, 1685 cm^{-1} (small band) (Fig. IR - 14) p.m.r ($CDCl_3$) : 2.35 δ(3H s); 2.46 - 2.73 δ (2H, m); 2.86 - 3.06 δ(2H, m); 3.83 δ (3H, s); 6.71 - 6.90 δ (2H,m); 7.11 and 7.20 δ (1H, d, J = 8.1 Hz), 10.31 δ (1H, broad); (Fig p.m.r. - 3)

Methyl - (4'-methoxy-2'-methyl) benzoate (CDXCI, R = Me), b.p. 160 - 170°/10 mm. was hydrolyzed through the same procedure as that with the propionic ester (CDLXXXIV, R = Me) to afford 4-methoxy benzoic acid (CDXCI, R = H), crystallised from benzene, m.p. 176°; i.r. (KBr): 2960 - 2780 cm^{-1} (broad), 2620 - 2500 cm^{-1}, 1690 cm^{-1}; p.m.r (DMSO d_6): 6.77 — 6.88 δ (2H, m) 7.84 and 7.93 δ (1H, d,

J = 8.1 Hz) (Fig p.m.r - 4). The other two bands at 2.51 δ and at 3.86 δ respectively were not assigned as the spectrum was taken using DMSO d_6 as solvent (c.f. Fig. p.m.r-4a). The bands due to aromatic hydrogens reveal 1,2,4 substitution pattern in the aromatic nucleous and the absence of methylene hydrogens are notable. In order to avoid difficulties in seperating the acid mixture (CDXCI and CDLXXXIV) through the method described above we felt the necessity of using g.l.c. technique in the said seperation. As we do not have g.l.c. facilities in our laboratory we are contacting sister laboratories abroad and hope to complete the synthesis in due course.