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PHOTOCHEMICAL APPROACH TO THE SYNTHESIS OF NATURAL PRODUCTS

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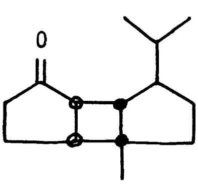
Abstract. The use of photochemical conversion of one molecule into an other as an approach to fine chemicals showing interest as new synthons, or as a key-step in multiple-steps synthesis of natural products is emphasized. The following topics are reviewed : photocycloaddition (photoannelation, ring-enlargement, access to grandisol, addition of allene to polycyclic enones), intramolecular cyclisation (electrocyclisation of benzylidene urethanes, photolytic cyclodehydrohalogenation, heteroatom directed photoarylation), molecular rearrangement of cross-conjugated cyclohexadienones, ring-opening of cyclanones and conjugated cyclohexadienones into terpenoids, formation and thermal decomposition of oxetanes, functional transformations.

The use of photochemistry as a tool either for a single transformation or as a key step in a multiple-steps sequence has received a large attention in the past ten years. It is not the goal of this article to review the industrial applications of photochemistry since this aspect has already been developped by eminent specialists[1] ; but rather to describe the synthetic approach towards fine chemicals using a photochemical transformation as a key step in a multiple-step reaction sequence. The principal reactions which will be dealt with are concerned with intermolecular photocycloaddition (oxetanes formation, photoannelation, ring-enlargement, access to grandisol, addition of allene to polycyclic enones), intramolecular cyclisation (α-diketones, benzylidene urethanes, cyclodehydrohalogenation and hetero-atom directed arylation) which has been used mainly to prepare alkaloids, molecular rearrangement of cross conjugated cyclohexadienones into bicyclo [3.1.0] hexenone intermediates, ring-opening of cyclanones according to the NORRISH type I reaction and of conjugated cyclohexadienones to form terpenoid-like compounds and, at last, functional transformations (such as elimination of blocking groups).

I INTERMOLECULAR PHOTOCYCLOADDITIONS.

The photochemical cycloaddition which forms four-membered ring compounds has been widely used to prepare natural products. In most cases, the light-induced reaction is only one step but the key of a multiple steps synthesis. Since four-membered ring compounds are of difficult access from ionic reactions, photochemistry appears to be the most suitable for their preparation. The few examples which follow demonstrate the variety of this type of reaction.

α- and β-bourbonenes (3 and 4 respectively) which are important components of *Geranium Bourbon* oil and *mentha piperita* have been obtained by three different methods[2-4], one of which[3] involves the photocycloaddition of 3-isopropyl-1-methylcyclopentene to cyclopentenone. The obtained adducts have correct *anti* conformation with the *cis*-fused junctions but the two head-to-head and head-to-tail isomers 1 and 2 are formed in almost equal proportions beside cyclopentenone dimers. Wittig's reaction transforms 1 in one step into β-bourbonene 4, while addition of methyllithium followed with acid-catalyzed dehydration of the intermediate alcohol leads with high yields to the mixture of α- and β-bourbonenes in which the α-isomer predominates.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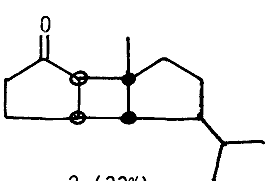
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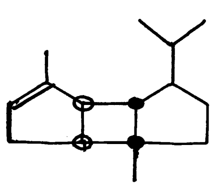
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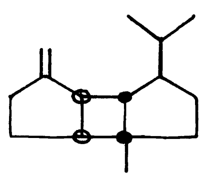
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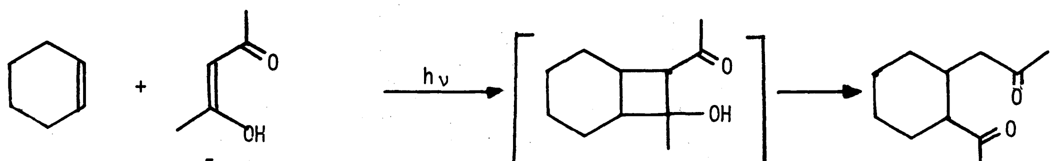
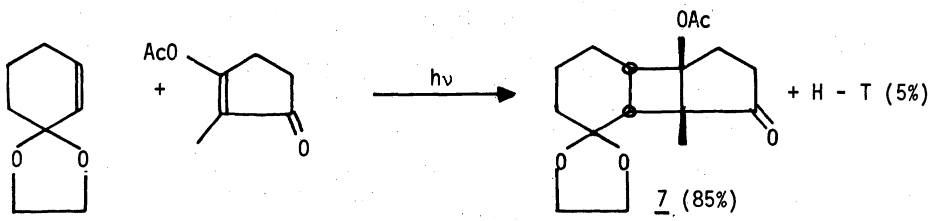
In several cases, the cyclobutane ring formed photochemically has suitable substituents which enable an easy ring-opening by chemical methods. This has been named photochemical annelation by P. de MAYO[5] after demonstration of the method[6,7] as synthetic tool for producing δ-diketones from enolizable β-diketones (for instance 5 → 6).



5 6

The chance was such that several synthesis based on the photoannelation have been carried out successfully (see further) before a limitation of the scope of the reaction was published[8] recently. Thus, 3-methylpentane-2,4-dione, 3-phenylpentane-2,4-dione, 1-phenylbutane-1,3-dione, methyl acetylacetate and ethyl benzoylacetate are found to be unreactive in the photochemical addition to cyclohexene.

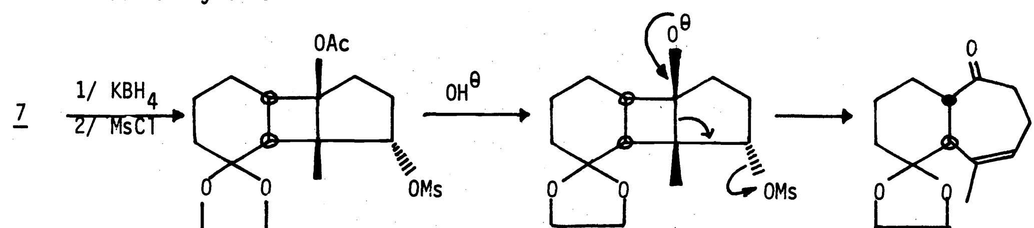
After the demonstration that cyclopentenone adds photochemically to cyclopentene[9], a mixed strategy which combines this photoaddition with the photoannelation has been used to synthesize β-himachalene **10** starting from the ethyleneketal of cyclohexenone and the enol acetate of 2-methyl cyclopenta-1,3-dione[10] :



+ H - T (5%)

7 (85%)

The main isomer 7 is transformed into the bicyclo [5.4.0] undecane structure 8 in three steps with 40% overall yields:



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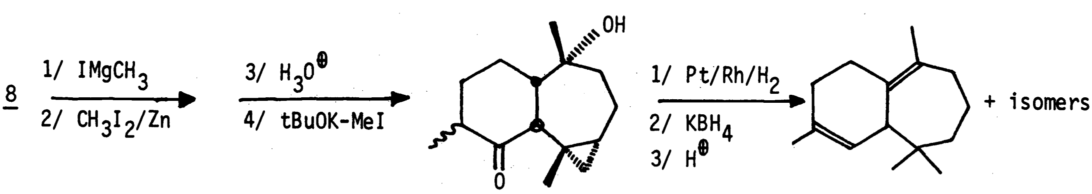
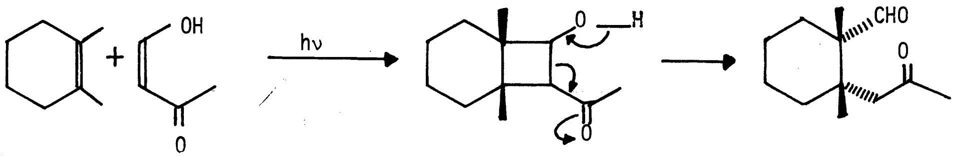
Transformation of the unsaturated ketone 8 into β-himachalene 10 involves the addition of methylmagnesium iodide to the free carbonyl function followed by the stereoselective addition, *cis* with respect to the hydroxy group, of a methylene group using SIMMONS-SMITH's procedure. The formed compound is then hydrolyzed to liberate the masked ketone which is methylated in α-position.



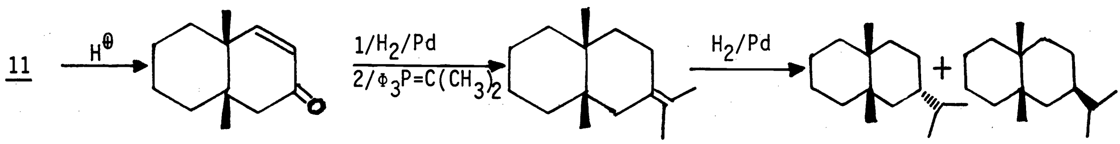
9 β-himachalene 10

Catalytical ring-opening of the cyclopropane ring in 9 followed by reduction of the carbonyl group and dehydration of the formed γ-diol leads to β-himachalene 10 as a mixture of isomers resulting from the different positions of the double bond in the 7-membered ring. *The photocycloaddition involves excitation of the unsaturated ketone which reacts from the lowest triplet state*[11] *and adds through an intermediate biradical, to the olefinic double bond.*

Addition of the enol form of acetylacetaldehyde to 1,2-dimethylcyclohexene[12] forms the cyclobutane adduct which undergoes spontaneous retro-aldolisation and yields efficiently ketoaldehyde 11. Cyclisation of the latter followed by hydrogenation, introduction of the isopropylidene group by Wittig's reaction and again hydrogenation leads to a 2 : 3 mixture of valerane 12 and isovalerane 13 :

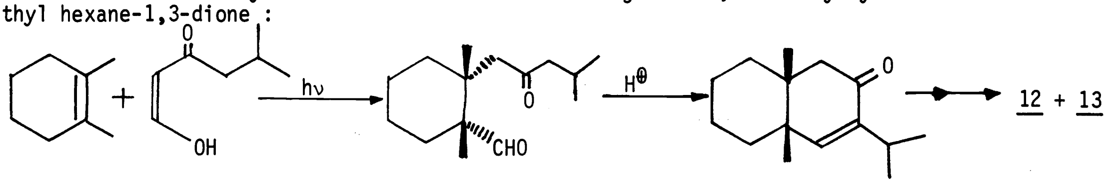


11 (100%)

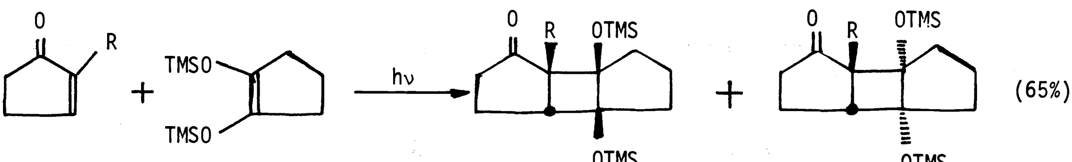


(86%) valerane 12 isovalerane 13

The same mixture of hydrocarbons is obtained starting from 1,2-dimethylcyclohexene and 5-methyl hexane-1,3-dione :

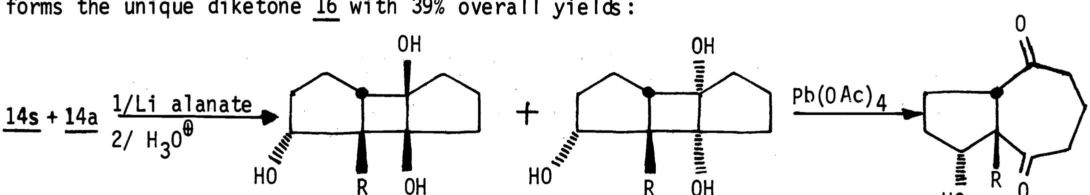


When the cyclobutane ring-opening is performed by chemical methods with a suitable substitution (oxidation of α-diols), then the photochemical reaction can be used to yield hydroazulenes[13] :



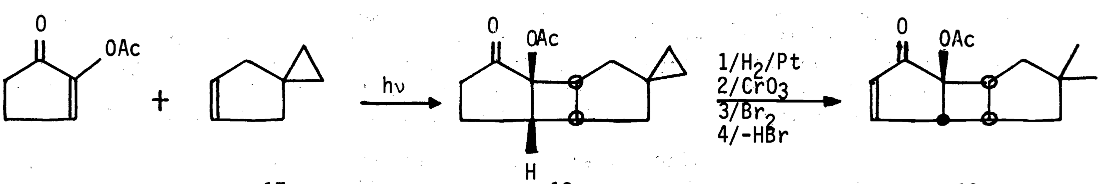
14s 14a

This cycloaddition seeks a new efficient synthetic route to two classes of hydroazulenic sesquiterpene lactones, namely guaïnolides and pseudoguainolides. The keto group of the adduct 14 is reduced with lithium alanate to the corresponding alcohol ; then, acid hydrolysis of the trimethylsilyl derivative leads to the mixture of triols 15. Lead tetracetate cleavage of 15 forms the unique diketone 16 with 39% overall yields:

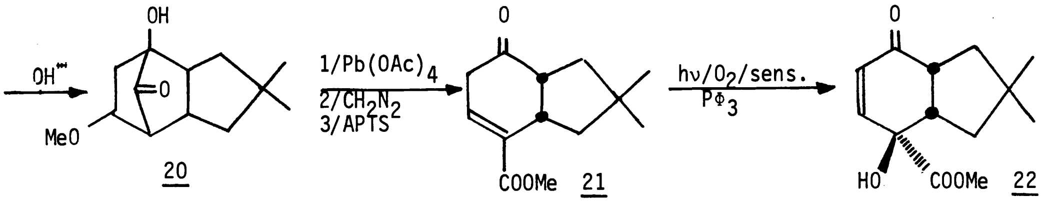


15s 15a 16

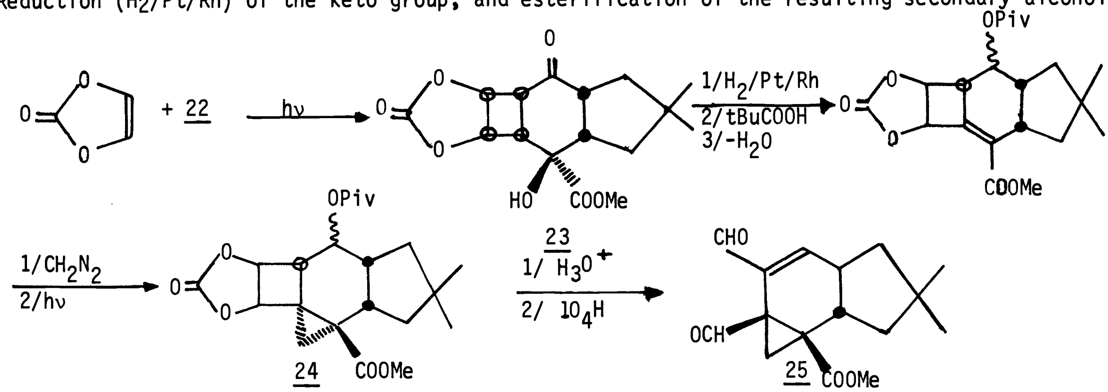
The preparation of the stereoisomer of methyl isomarasmate 25, using photochemical steps, is hardly an important synthetic pathway but shows the possibilities for cumulating several photochemical steps[14]. Thus, cycloaddition of the monoenol acetate of cyclopentane-1,2-dione to the spiro-olefin 17 forms the adduct 18 which is transformed in four steps into the unsaturated α-hydroxyketone acetate 19. Basic treatment of the latter forms the bridged compound 20 and the unsaturated keto-ester 21 by subsequent oxidation, esterification and methanol elimination. Rose bengale sensitized photoxidation of 21 gives the expected hydroperoxide which is reduced into 22 by Φ_3P.



17 18 19



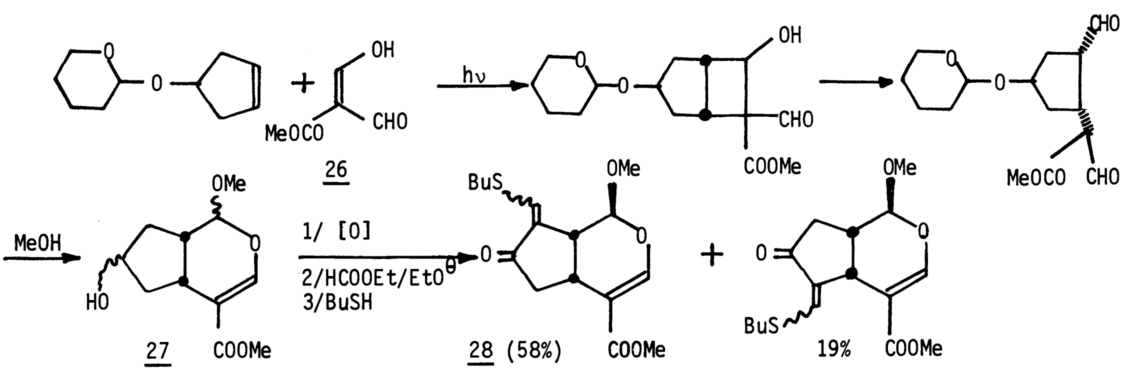
The obtained unsaturated keto-ester 22 adds photochemically to vinylcarbonate to form 23. Reduction (H_2/Pt/Rh) of the keto group, and esterification of the resulting secondary alcohol



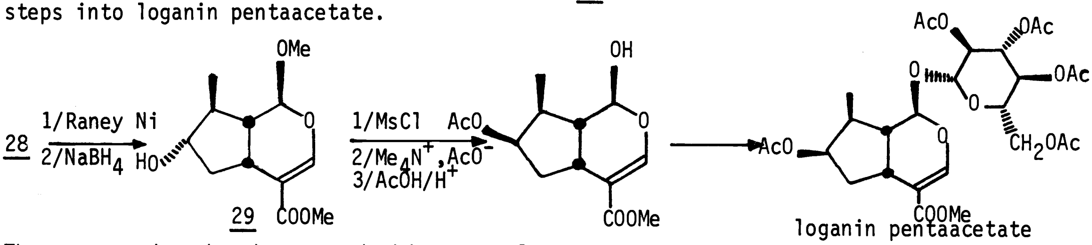
by pivalic acid forms the corresponding ester. The tertiary free hydroxy group is eliminated ($POCl_3$/pyridine) by trans-elimination and the resulting double bond is reacted with diazomethane to give a pyrazoline which eliminates N_2 under UV irradiation and leads to 24. Acid-catalized hydrolysis enables the transformation in the isomer of methyl isomarasmate 25 after periodate oxidation of the α-diol intermediate.

A new synthetic approach to synthons, or natural products, has been developped by BUCHI et al [15], and used by others[16-18], starting from the *methyl ester of 2-formylmalonaldehydic acid* 26. Photochemical addition of the enol form of 26 to an olefin follows the above-described photoannelation route in that spontaneous retroaldolisation occurs and gives a new dialdehydo-ester; cyclisation occurs then which leads to a dihydropyran. In a very recent work[8] on the photocycloaddition of 3-cyano-2,4-pentadione to cyclopentene or cyclohexene, it has been shown that the 1,3-dicarbonyl system requires an electronegative group to be reactive. As the photoaddition is easier in alcoholic solvents than in non-polar solvents, and since no addition occurs with olefins having ionization potentials lower than or equal to 8.6 eV, the photocycloaddition of 3-cyano-2,4-pentadione to olefins is believed to take place through an intermediate singlet excited complex. The cyclisation competes then with the electron transfer process in which the diketonitrile acts as an electron-acceptor and the olefin as a donor. With olefins having low ionization potential, the excited complex is considered to be dissociated into radical-ion pairs by electron-transfer. That such a mechanism occurs is shown by quenching experiments using vinyl ethers as quencher of the cycloaddition of the diketonitrile to cyclohexene : the quenching rate constant depends on the ionization potential of the quencher while piperylene (I_p = 8.7 eV) does not quench the photoaddition in a normal manner for a triplet quenching.

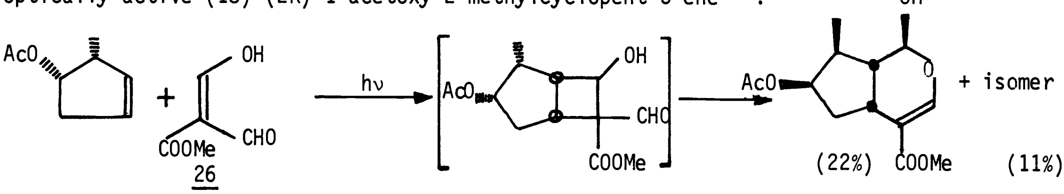
The cycloaddition starting from 26 has been used[15] to form the naturally occuring iridoid glucoside loganin which is a key intermediate in the biosynthetic pathway to the *Corynanthe, Aspidosperma, Iboga* and *Ipecacuanha* alkaloids : oxidation of the isomeric alcohols 27 gives the two isomeric



ketones, the one with the axially oriented methoxy group *cis* to the hydrogens of the cis-fused ring-junction being predominent (3 : 1). Its conversion into α-butylthiomethylene derivatives in which the expected isomers 28 dominate (58 : 19) is followed with desulphurization and then by sodium borohydride reduction to form alcohol 29 ; the latter is further transformed in four steps into loganin pentaacetate.

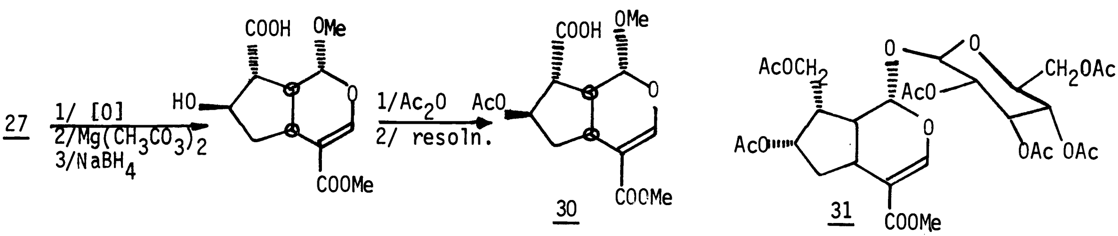


The same product has been reached by an analoguous photochemical step but starting from the optically active (1S) (2R) 1-acetoxy-2-methylcyclopent-3-ene[16] :

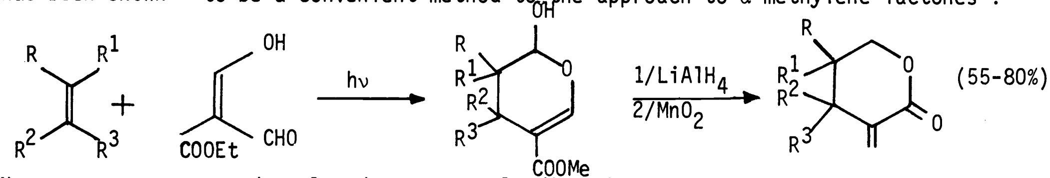


This last method has the advantage of suppressing the sequence 27 → 29 of the preceding method.

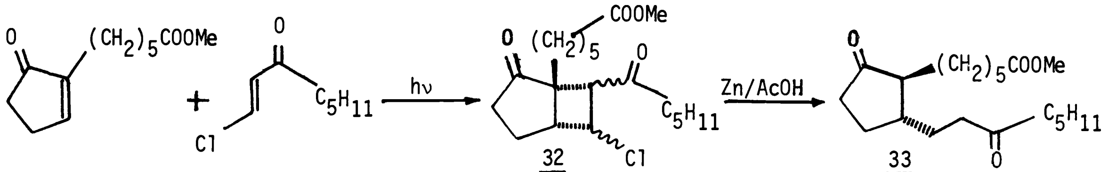
The same dialdehydo-ester 26 has been used to prepare[17] a modified loganin pentaacetate by introducing a hydroxymethyl group instead of the methyl group of intermediate 29. For this purpose, the ketone obtained by oxidation of 27 is selectively carbonated in α-position to the keto group using methylmagnesium carbonate at 135°. Reduction of the free keto group of the obtained compound by diborane is followed by the above-described method to reverse the configuration of the acetoxy group linked to the five-membered ring. The final steps are identical to those which have been used to prepare loganin pentaacetate. This methods leads now to compound 31.



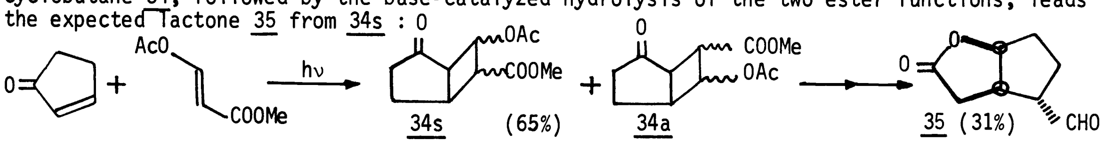
Recently, the photoaddition of the methyl ester of 2-formylmalonaldehydic acid 26 to olefins has been shown[18] to be a convenient method to the approach to α-methylene lactones :



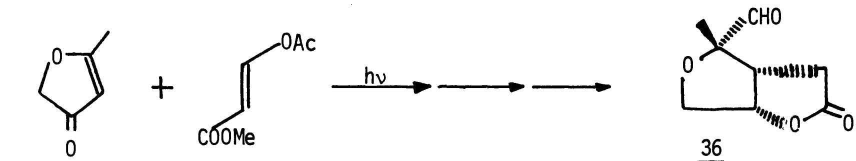
New routes to compounds related to prostaglandines have received some attention. For instance, prostanoic acid methyl ester can be reached[19] in two steps from 2-(7-carbomethoxyhexyl) cyclopent-2-en-1-one : photochemical addition to 1-chlorooct-1-en-3-one leads to the bicyclo [3.2.0] heptanone 32 in moderate yields (35%) which by reduction in acid medium gives the methyl ester



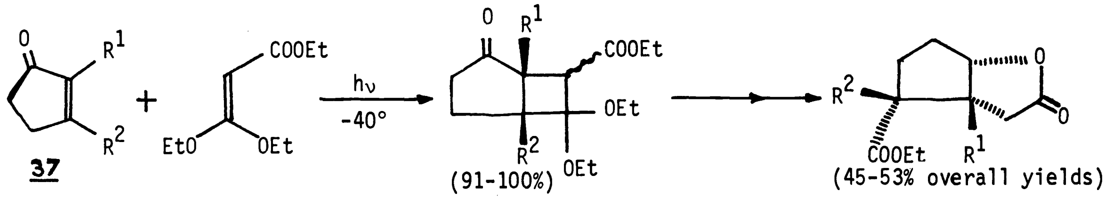
of prostanoic acid 33. With the same final objective the intermediate lactone 35, which is of interest on the route to 11-deoxyprostaglandines, has been prepared in a sequence which starts by the irradiation of cyclopentanone in the presence of the enol acetate of methyl 2-formylacetate[20]. Reduction (KBH_4) at low temperature (-40°) of the free carbonyl group of the formed cyclobutane 34, followed by the base-catalyzed hydrolysis of the two ester functions, leads to the expected lactone 35 from 34s :



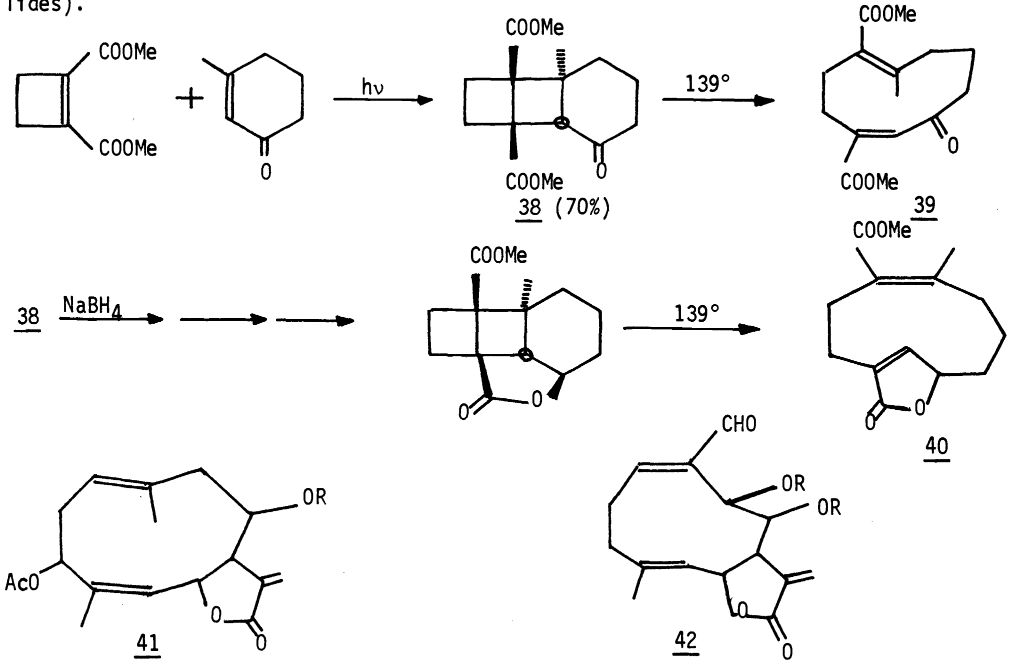
This reaction has been enlarged[20] to 36, the homologue of lactone 35 starting from 2-methyl-4-furanone :



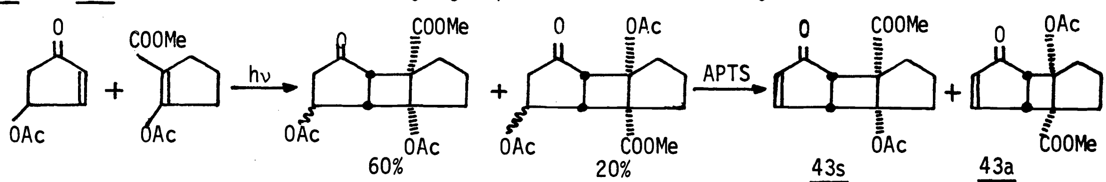
Closely related lactones have been obtained also from the cycloadducts formed by irradiation (366 nm) of cyclopentenones 37 in the presence of methyl β-oxysubstituted acrylate[21] :



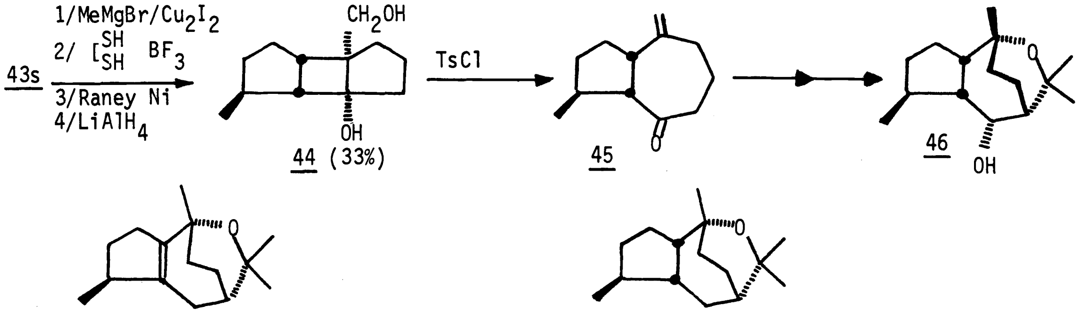
Photochemical addition of unsaturated esters to α,β-ethylenic cyclenones has been developped recently for the synthesis of large ring compounds ; the double bond of the ester is part of a ring and this limits the energy wastage which would occur by E - Z isomerization. The interest of the cycloaddition is increased when the molecule is symmetrical since only one adduct will be formed then; thus, 1,2 dicarbomethoxycyclobutene reacts with 3-methylcyclohex-2-en-1-one to form[22] the adduct 38 besides the dimer of the diester ; ring-opening of the cyclobutane is induced thermally and leads to the unsaturated diester 39 in which one double bond is E and the other Z. Further reduction ($NaBH_4$) of 38 forms a lactone-ester which decomposes thermally into the dienic compound 40 in which the two double bonds have now the opposite configuration. These two different pathways have been considered as a route to analogues of provincialine 41 (in the series of heliangolides) and to analogues of acanthospermal 42 (in the series of melampolides).



Access to the carbon skeleton of hydroazulenes has been approached[13] already and discussed above. A new synthetic route to compounds of this series has been described[23] recently. Thus, photochemical cycloaddition of 4-acetoxycyclopent-2-enone to the enol acetate of 2-carbomethoxycyclopentanone forms a 6 : 2 mixture of the *syn* and *anti* isomeric adducts which on elimination of one molecule of acetic acid lead to the tricyclo [5.3.0^{2,6}] dec-4-ene derivatives 43s and 43a ; 1,4-addition of a methyl group to the unsaturated system of the major isomer

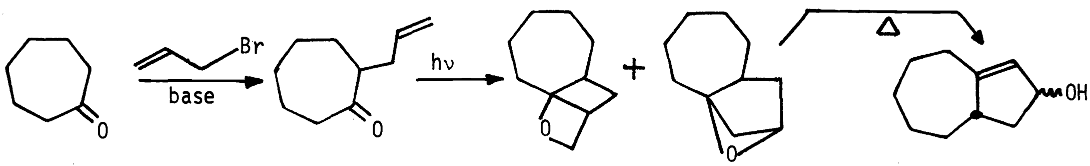


43s followed by hydrogenolysis of the carbonyl group and $LiAlH_4$ reduction of the two ester functions gives 44 ; breaking of the junction linkage at the level of the tertiary alcoholic function leads to 45 which is transformed into 46 in three steps and subsequently into dehydrokessane in one step or 5-epikessane in two steps.

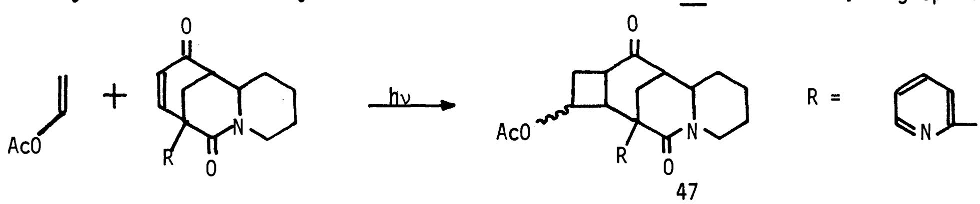


dehydrokessane 5-epikessane

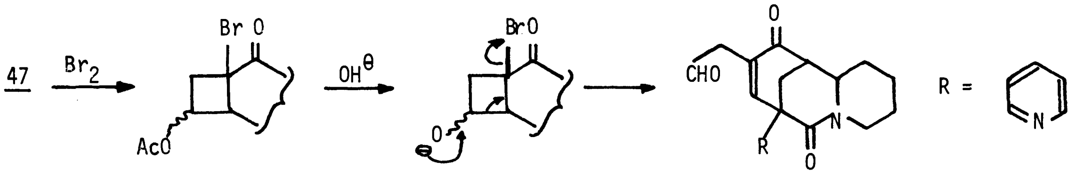
The hydroazulene skeleton also can be reached in three steps from cycloheptanone[24]:



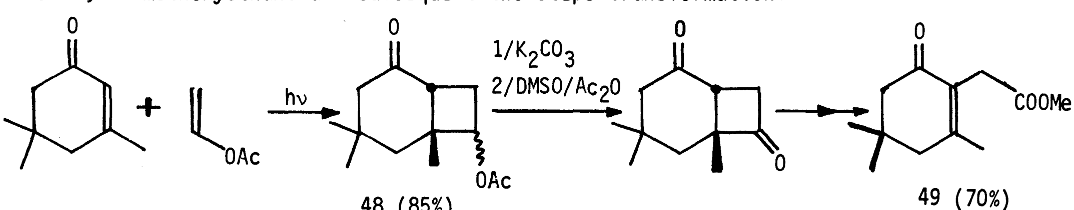
The cycloaddition of vinyl acetate to the double bond of an α,β-unsaturated ketone was reported[25] already in 1969 for the synthesis of the carbon skeleton 47 of *Ormosia* ; ring-opening of



the cyclobutane in 47 was induced by bromination in the α-position to the carbonyl group and base-catalyzed elimination of hydrobromic acid :

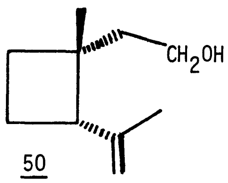


The disadvantage of this method is its limitation to ketones which can only give an enol with the double bond directed toward the cyclobutane ring. This ring-opening reaction has been ameliorated and generalized[26] after modification of the last chemical steps. Thus, treatment of ketoesters 48, which result from the photoaddition of vinyl acetate to isophorone, by potassium carbonate followed by oxidation of the alcoholic function and treatment with H_2O_2 leads to the expected ketoacid 49 ; a similar result is reached by irradiation of isophorone in the presence of 1,1-dimethoxyethane and subsequent two steps transformation.



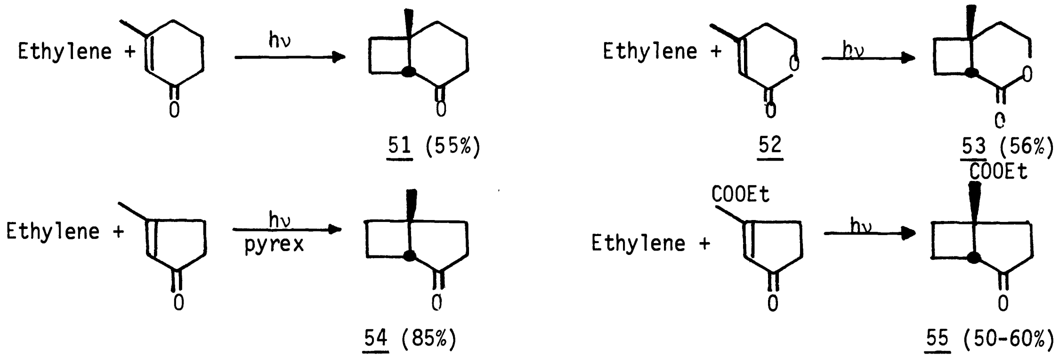
II GRANDISOL

One of the biggest "cheval de bataille" in the photochemical cyclobutane formation concerns the access to grandisol 50, one of the four pheromones of the male boll weevil *Anthonomus grandis* Boheman. One of them[27] starts with the photochemical cycloaddition of ethylene to 3-methylcy-

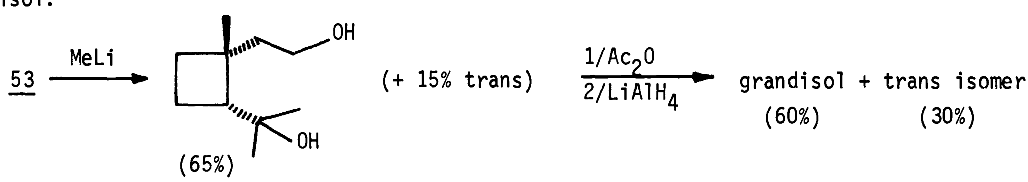


clohex-2-en-1-one[28] leading to the *cis*-fused bicyclo [4.2.0] octanone 51. A second one[28] adds ethylene to the unsaturated lactone 52 while a third one[29] takes advantage of the easy addition of ethylene to 3-methylcyclopent-2-en-1-one ; a fourth one[30] adds now ethylene to 3-carbethoxycyclopent-2-en-1-one to form the cycloadduct 55 the advantage of which is to contain an acid function and, thus, to make possible the resolution (although with difficulties) into its two enantiomers.

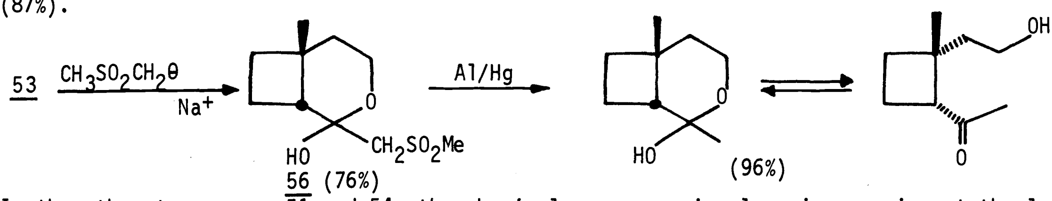
These photocycloadditions can be sensitized by acetone[31] or acetophenone[28a] and quenched by 1,3-pentadiene and, therefore, proceed through the triplet excited state of the carbonyl compound.



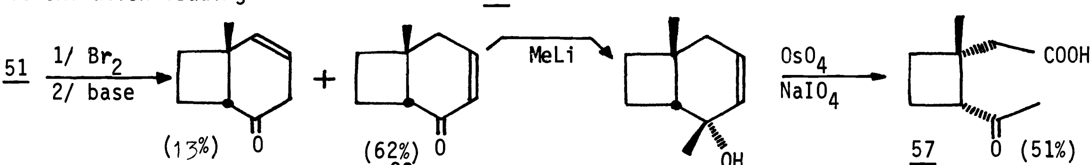
The subsequent sequences which enable the access to grandisol from these bicyclic compounds vary from one to the other. For instance, 53 is added[28a] to an excess of methyllithium ; the tertiary alcohol of the resulting diol is dehydrated while simultaneously the primary alcohol is transformed into the corresponding acetate ; subsequent reduction by $LiAlH_4$ leads to grandisol.



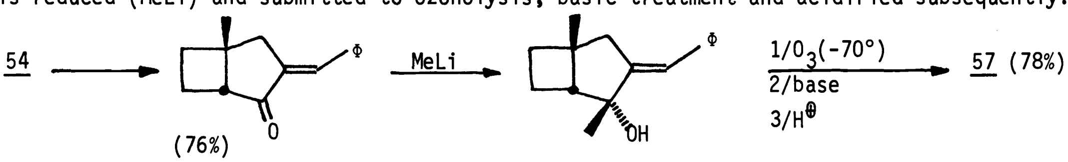
A variant[28b] is to transform 53 into the hemi-acetal 56 by addition of the sodium methylsulphonylcarbanion. Reduction (Al/Hg) of 56 leads to a second hemi-acetal which equilibrates with the δ-ketoalcohol form ; grandisol is obtained then in three steps by esterification of the primary alcohol (Ac_2O ; 45%), Wittig reaction ($\Phi_3P{=}CH_2$) and saponification of the ester (87%).



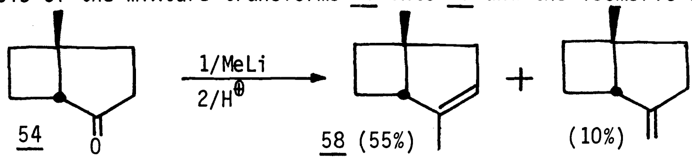
In the other two cases, 51 and 54, the chemical sequences involve ring-opening at the level of the carbonyl group. This is made possible by the creation of a double bond followed by reduction of the keto group ; the allylic alcohol obtained from 51 is submitted to hydroxylation and periodic oxidation leading to the δ-keto-acid 57.



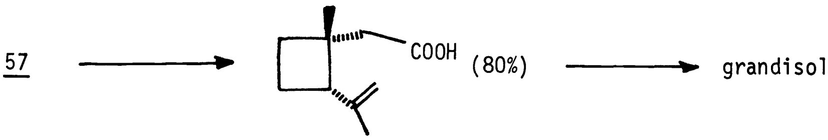
The same keto-acid 57 is obtained[29] from 54 by formation of the α-benzylidene derivative which is reduced (MeLi) and submitted to ozonolysis, basic treatment and acidified subsequently.



Another route to 57 involves reduction and dehydration of 54 followed by ozonolysis of the bicyclic olefin 58[32]. Formation of 58 is accompagnied with that of the exocyclic double bond. Ozonolysis of the mixture transforms **58 into** 57 and the isomeric olefin back to 54.

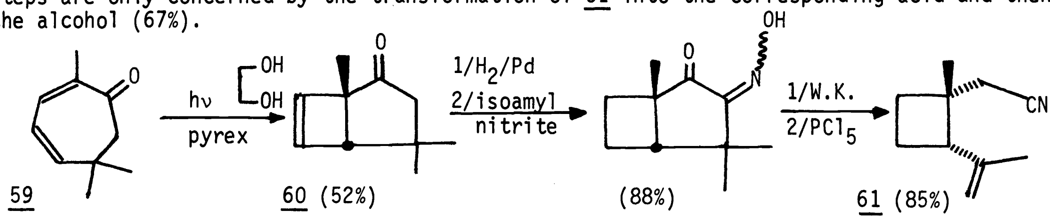


The δ-keto-acid 57 is transformed[27] in two steps into grandisol by Wittig's reaction ($\Phi_3P{=}CH_2$) at the level of the keto group, and reduction [$NaAlH_2(OEt)_2$] of the acid function.



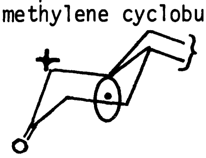
The δ-keto-ester 55 has been used to prepare the optically active 57. This access follows[30] a route very similar to the second one:formation of the α-isopropylidene derivative, reduction of the keto group by MeLi, epoxidation of the allylic alcohol and periodic oxidation of the epoxyalcohol.

A different access to grandisol has been opened[33] by photocyclisation of eucarvone 59 into the unsaturated bicyclic ketone 60 which is transformed into the corresponding α-keto-oxime. Wolff Kishner reduction, followed by ring-opening (PCl_5) gives the unsaturated nitrile 61 ; the last steps are only concerned by the transformation of 61 into the corresponding acid and then into the alcohol (67%).



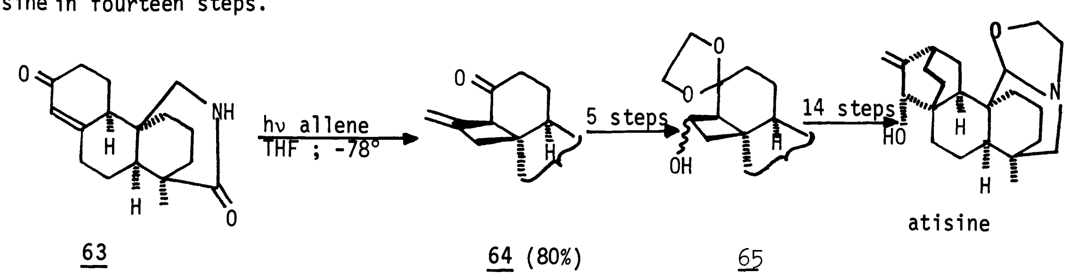
III PHOTOADDITION OF ALLENE TO UNSATURATED KETONES.

The photochemical addition of allene to α,β-unsaturated ketones has received a large attention in the synthesis of various alkaloids and related compounds. The reaction involves excitation of the carbonyl group which reacts from its triplet excited state[34]. According to SALEM *et al* [35] calculations and experimental results, one would expect the olefinic double bond to rotate partly and react rapidly with the ground-state allene molecule. Such an hypothesis could account to the high stereoselectivity observed in the cyclo-addition and to the geometrical configuration 62 depicted by WIESNER [34] to explain the attack at the level of the most stable intermediate. The addition leads to the methylene cyclobutane in which the exocyclic double bond has the

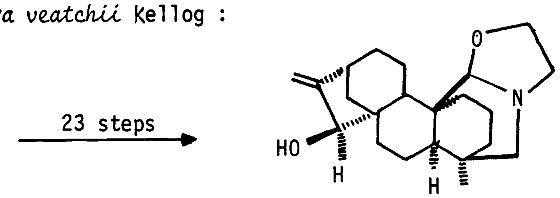


62

position which results from the bond formation between the carbon atom α to the carbonyl function and the central carbon atom of the allene moiety. In four different synthesis[36-39] the methylenecyclobutane is transformed into a cyclobutanol in three steps including acetalisation of the carbonyl group of the starting unsaturated α,β-ethylenic ketone. Thus, atisine, isolated from the roots of *Aconitum heterophyllum* Wall, has been prepared[33] by this way, starting from the α β-unsaturated ketone 63 to which allene is added photochemically ; the resulting methylenecyclobutane 64 is transformed into cyclobutanol 65 in five steps and further into atisine in fourteen steps.

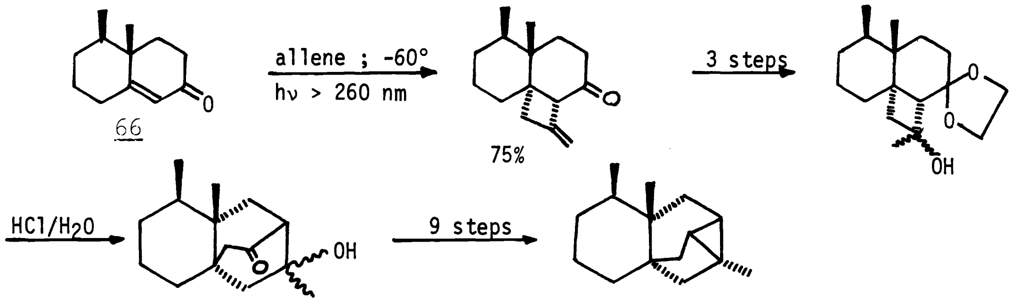


The same cycloadduct 64 has been used[40] to open an access to veatchine, an alkaloid isolated from *Garrya veatchii* Kellog :

64 

veatchine

Ishwarane, found in the roots of *Aristolochia indica* Linn and the petals of *cymbopetalum penduliforum* Baill, is prepared using[37] the same photochemical step from the bicyclic enone 66 :

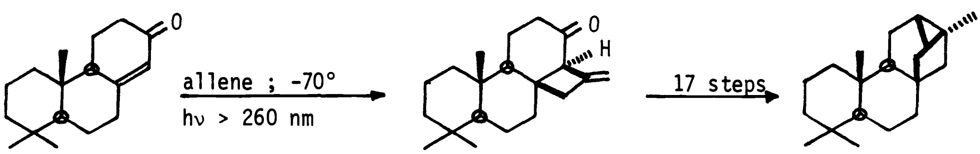


66

75%

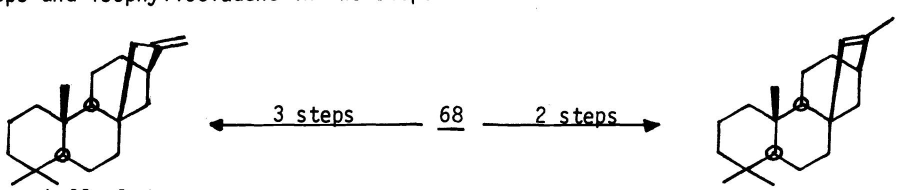
ishwarane

Trachylobane, isolated from *Sideritis canariensis Ait* (*labiatae*), has been reached[38] also by this method from the unsaturated ketone 67 :



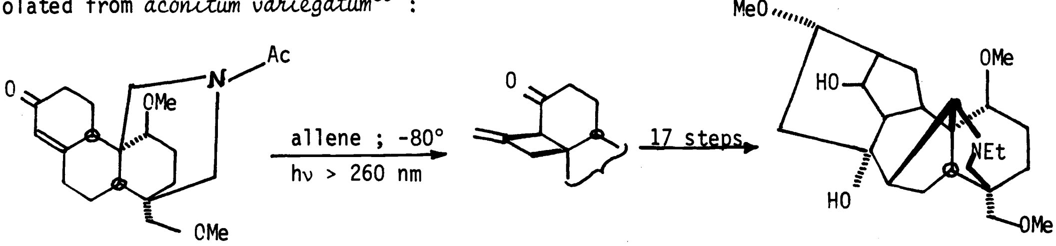
67 68 (70%) trachylobane

The same cycloadduct 68 has been taken as starting point in the synthesis of phyllocladene in three steps and isophyllocladene in two steps[41] :



phyllocladene isophyllocladene

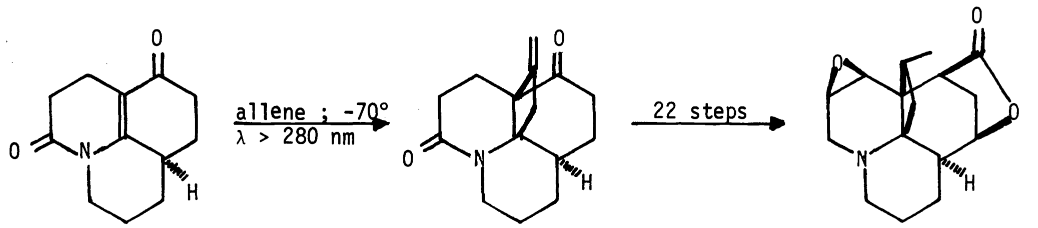
Similarly compound 69 has been taken as starting material to prepare talatisamine, an alkaloid isolated from *aconitum variegatum*[39] :



69 talatisamine

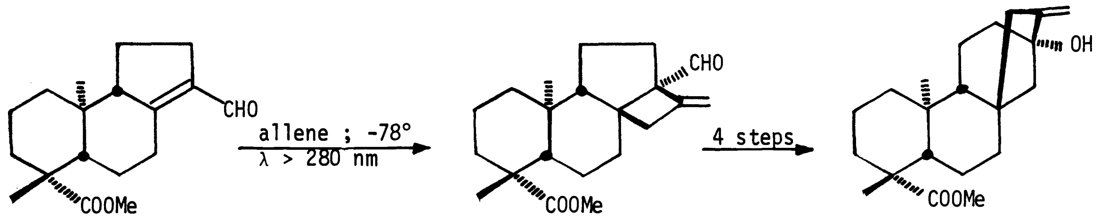
Three other synthesis of natural products start also from the photochemical cycloaddition of allene to an α,β-unsaturated ketone :

- annotidine, an alkaloid isolated from *Lycopodium annotinum* L. Lycopodiaceane, prepared[42] from 70 :



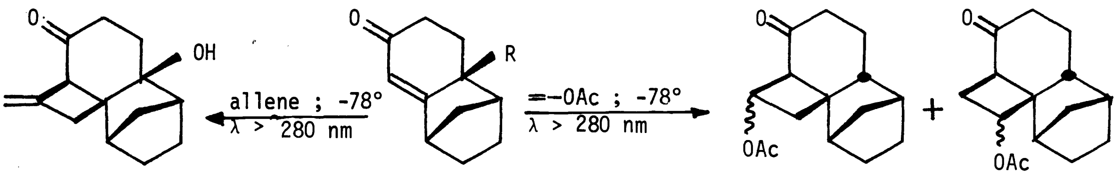
70 (54%) annotidine

- steviol, the aglucone from stevioside, isolated from the leaves and the stems of *Stevia rebaudiana* Bertoni, a paraguyan shrub, is prepared[43] from the unsaturated aldehyde 71 :



71 (42%) steviol

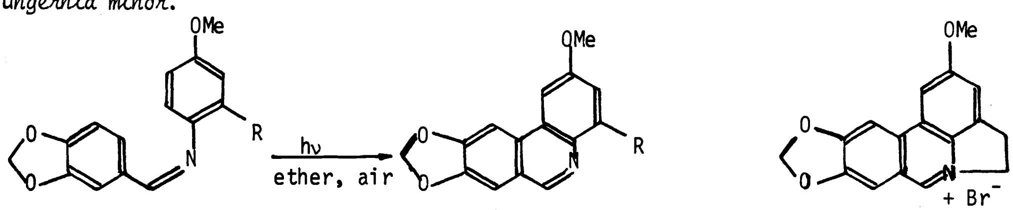
- an approach to chasmanine, an aconite alkaloid, built from two different variants starting from the unsaturated β-ketols 72 and 73[44] :



(87%) 72 (R=OH) 73 (R=H) ∿ 45% ∿ 45%

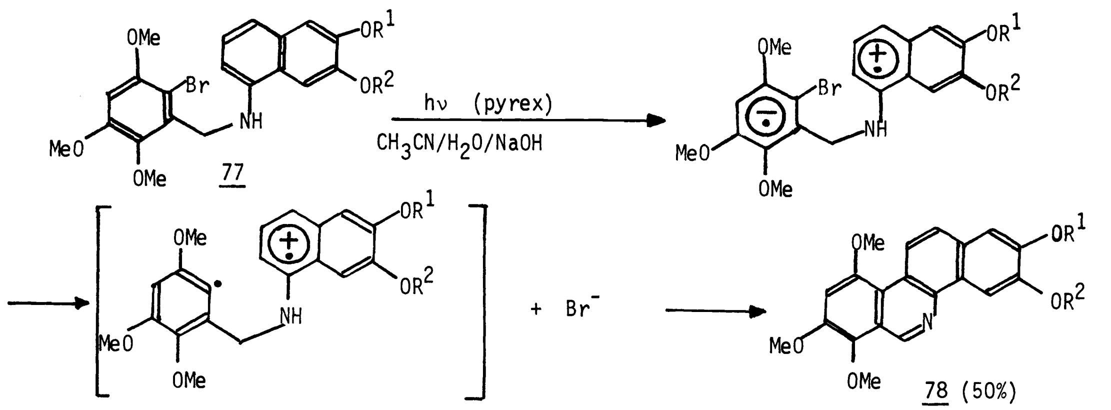
IV INTRAMOLECULAR CYCLISATION.

The cyclisation of stilbene-like aromatic compounds has been widely investigated and stereochemical evidences have been brought which suggest a conrotatory cyclisation from the excited singlet state[45]. Simple benzylideneanilines undergo the oxidative photocyclisation into phenanthridines but only in strong acid medium[46]. The presence of a group which interacts electronically with the benzylideneaniline system makes the cyclisation more favorable ; it occurs now even in neutral medium when methoxy groups or methylenedioxy substituents are present. Thus, this reaction has been used to cyclise Schiff bases into phenanthridine-type alkaloids[47] in neutral solution. For instance compounds 74 (R=H or COOEt) form the corresponding phenanthridines 75 by irradiation in ether solution. The obtained compound 75b is transformed easily into 76 which corresponds to the methyl derivative of ungeremine, an alkaloid isolated from *Ungernia minor*.

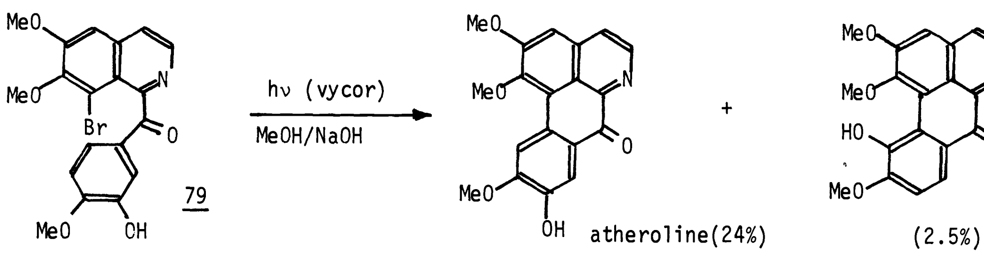


74 75a (R=H) 55% ; 75b ($R=CH_2COOEt$) 21% 76

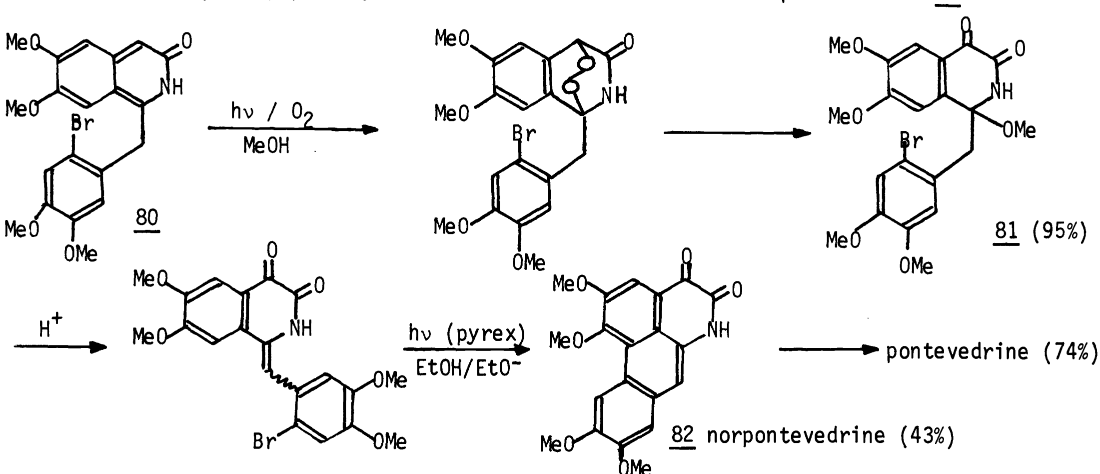
Cyclisation of an other type is related to the *photoaddition of aryl halides to aniline derivatives* through a postulated electron transfer process[48]. The yields are usually poor but can be improved by lowering the ionization potential of the electron-donor moiety. This cyclisation has been carried out with 77 where the α-naphtylamine moiety interacts intramolecularly with the trimethoxybromophenyl group under U.V. light and gives a complete charge-separation followed by the expulsion of a bromine anion and then cyclisation to form phenanthridine 78. The latter ($R^1R^2= -CH_2-CH_2-$) is easily transformed into the alkaloid chelilutine or, when $R^1=R^2=CH_3$, into sanguilutine.



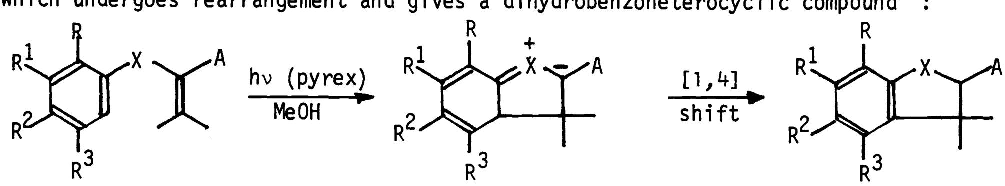
Similarly, a route to atheroline, an alkaloid isolated from *Atherosperma moschatum*, has been built[49] using the photolytic cyclodehydrohalogenation reaction[50] and starting from the phenolic 1-benzoylisoquinoline 79.



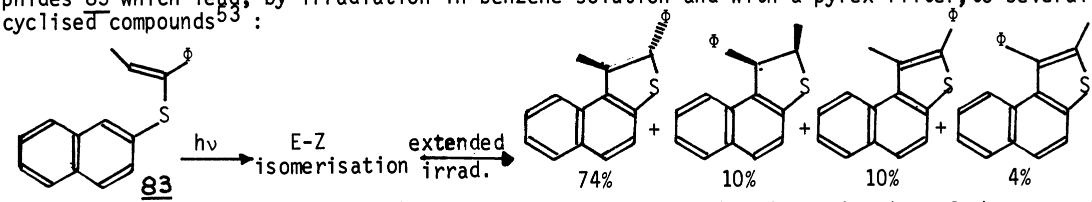
In the same series, this reaction opens an access to pontevedrine, a member of the group of 4,5-dioxoaporphine alkaloids which have been postulated to be directly related to the aristolactames and aristolochic acids the antitumor activity of which is well-known. The method uses[51] two photochemical steps, the one being a photoxidation reaction and the second the photolytic electrocyclisation of a bromo derivative. Thus, 80, is submitted to ultraviolet irradiation in an aerated methanol solution. The resulting diketo product 81 is treated with an acid medium and subsequently photocyclised in basic medium to form norpontevedrine 82 :



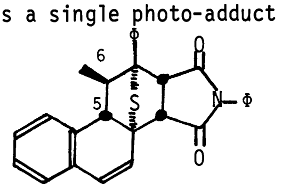
A conceptually new approach to the synthesis of fused heterocyclic compounds has been developped in the recent years by A. SCHULTZ and called *hetero-atom directed photoarylation*. The reaction can be applied to heteroatoms bounded on one side to an aromatic ring and on the other side to an ethylenic linkage activated by an electron-withdrawing group. The process occurs presumably via a conrotatory photocyclisation leading to an intermediate zwitterion which undergoes rearrangement and gives a dihydrobenzoheterocyclic compound :



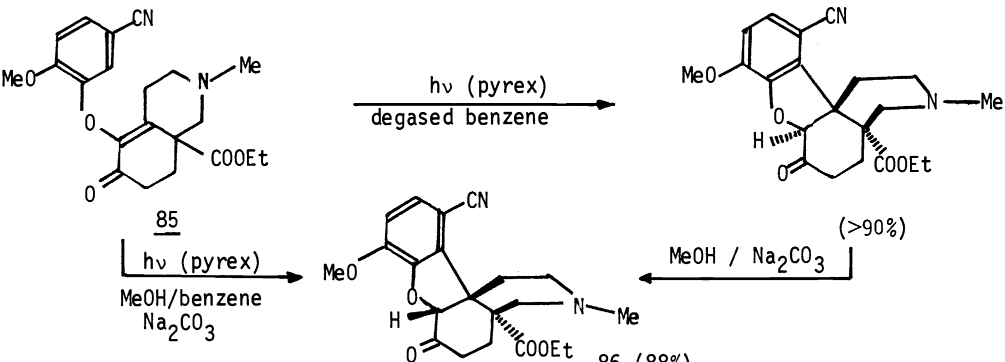
The chemical yields are usually over 80% when X is oxygen[52], sulphur[53] or an amino group[54] but only 60% when selenium[55]. The reaction has been well studied in the case of naphthyl vinyl sulphides 83 which lead, by irradiation in benzene solution and with a pyrex filter, to several cyclised compounds[53] :



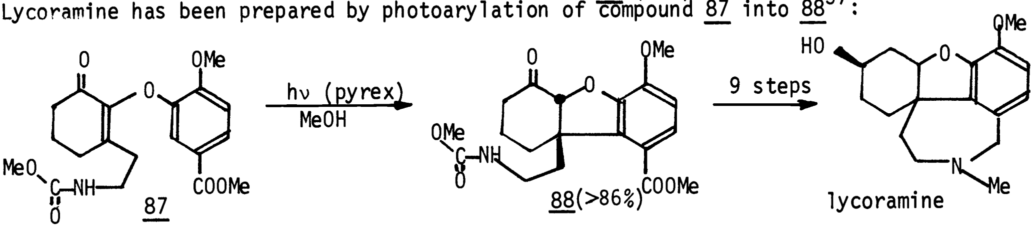
Sensitized reaction with Mischler's ketone results only in photoisomerisation of the exocyclic double bond. Irradiation of a degased solution of 83 in the presence of N-phenylsuccinimide gives a single photo-adduct 84. The fact that the two hydrogen atoms at C-5 and C-6 are in trans position is correctly interpreted in terms of a conrotary cyclisation from the excited singlet state ; as a consequence, the (1,4) hydrogen shift must be suprafacial. This photoarylation has been developped toward the preparation of compound 86 which looks like a promising route to morphine and codeine :



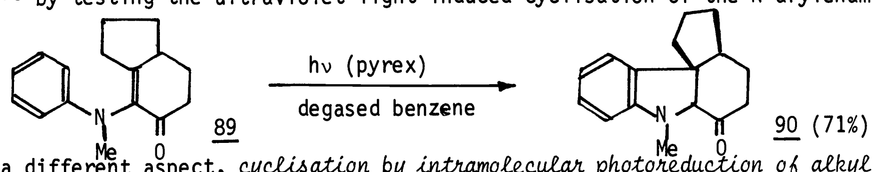
84 (55-60%)



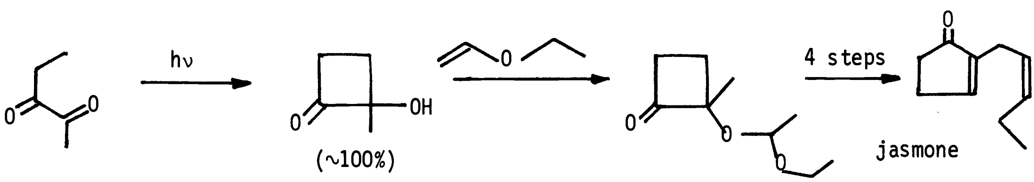
Lycoramine has been prepared by photoarylation of compound 87 into 88[57]:



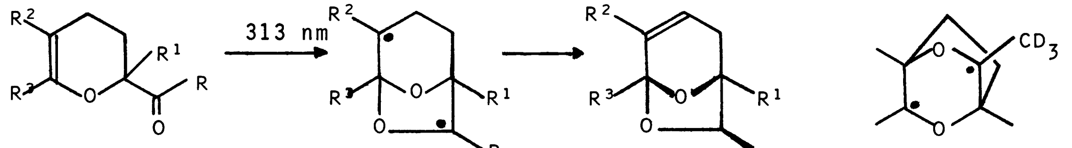
while a new approach to the Aspidosperma alkaloids vindorosine and vindoline has been undertaken[58] by testing the ultraviolet light-induced cyclisation of the N-arylenamine 89 into 90 :



In a different aspect, *cyclisation by intramolecular photoreduction of alkyl α-diketones* leads very efficiently to α-hydroxycyclobutanones. The reaction can be quenched by pyrene under a diffusion-controled process, indicating that the triplet excited state is responsible of the reaction[59]. Since the chemical yields of the cyclisation are high (over 90%) and the quantum efficiency of the order of 0.5, as soon as the abstracted γ-hydrogen is secondary or tertiary, the use of such a reaction in synthesis merits to be developped. One application is found in the litterature[60], based on this reaction for preparing γ-diketones, in an original route to jasmone.



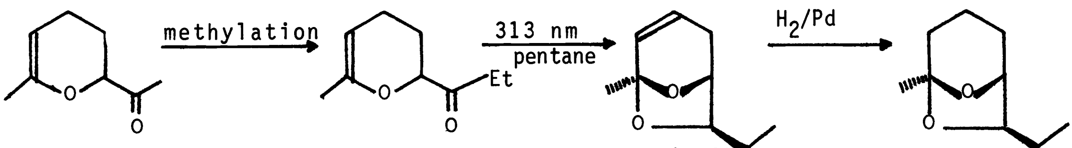
Selective irradiation of the carbonyl group of variously substituted 2-acyl-2,3-dihydro 4H pyrans 91 induces a bond formation between the carbon atom α to the oxygen of the vinyl ether part and the oxygen atom of the keto group[61]. The hypothetical biradical intermediate undergoes then hydrogen migration which shifts the original double bond to the position depicted on formula 92. That the attack of the oxygen occurs selectively at C-6 and not at C-5 is shown by deuterium labeling with 2-trideuterioacetyl-2,5,6-trimethyl 4H pyran. Attack of the oxygen at carbon C-5 would then give the symmetrical biradical intermediate 93 which either forms an oxetane by bond creation between the two radical sites or reverts to the starting material; in the latter case, one would also expect, because of the symmetry of the biradical, to get 2-acetyl-2,5-dimethyl-6-trideuteriomethyl 4H pyran. Since no such compound is detected when



91 92 93

the reaction is limited to 60% conversion, this attack can be legitimely disregarded. *The reaction occurs from the n,π* excited singlet state of the carbonyl group* as no quenching is observed with 2,5-dimethylhexa-2,4-diene. Also the reaction can be carried out with 253.7 nm light when using 1-methylnaphtalene as sensitizer of the carbonyl singlet state and quencher of the triplet state.

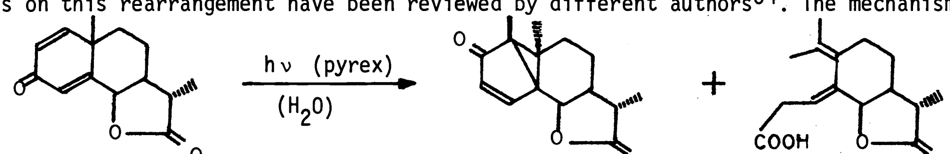
This reaction, which occurs also with 4-acylcyclohexenes[62], has been used to synthesize exo-Brevicomin, which is the principal component of the sex-attractant produced in the frass of the female western pine beetle, *Dendroctonus brevicomis*, boring in ponderosa pine. The DIELS-ALDER dimer of methyl vinyl ketone is alkylated by the imine procedure to form 2-propionyl-2,3-dihydro 4H pyran; irradiation of the latter forms 94 as sole product which is transformed further into exo-Brevicomin by catalytical reduction of the double bond. The exclusive exo configuration of the ethyl group makes this procedure very attractive compared to the acid-catalyzed cyclisation of the corresponding alcohol, which gives a mixture of the exo and endo isomers in *ca.* equal quantities.



94 (26%) exo-Brevicomin

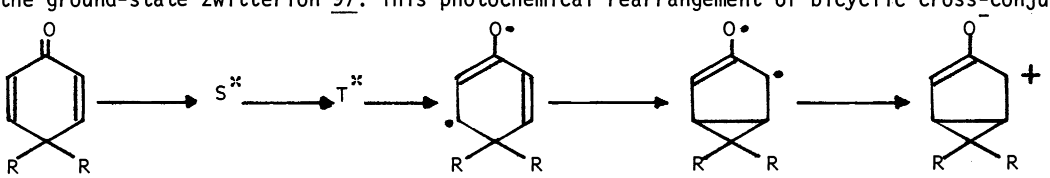
V MOLECULAR REARRANGEMENT.

This part of the review will be devoted mainly to the rearrangement of cross-conjugated cyclohexadienones. These molecules show deep-seated rearrangements when submitted to ultraviolet light irradiation in the 250-370 nm region. The most classical rearrangement is typified by the conversion of santonin into lumisantonin and into photosantonic acid. The extensive studies on this rearrangement have been reviewed by different authors[64]. The mechanism of the



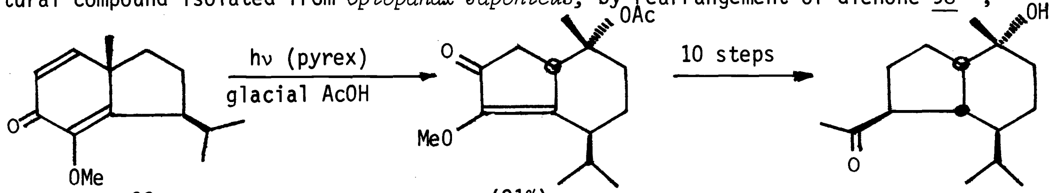
santonin lumisantonin

reaction, as described with the model compound 4,4-dialkyl-2,5-cyclohexadienone 95, involves excitation of the n,π* singlet state which intersystem-cross to the n,π* triplet state, bridging to 96, which is still an electronically excited molecule of the n,π* type, and crossing to the ground-state zwitterion 97. This photochemical rearrangement of bicyclic cross-conjugated cyclohexadienones has been used[65] to obtain the bicyclo [5.3.0] decane skeleton as the result of the reversible cyclopropylcarbinyl-allylcarbinyl "carbonium ion"-like rearrangement of zwitterion 97.



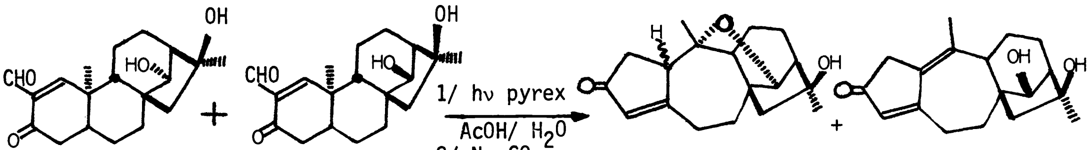
95 96 97

The most recent results in the series are concerned with the preparation of oplopanone, a natural compound isolated from *Oplopanax Japonicus*, by rearrangement of dienone 98[66],



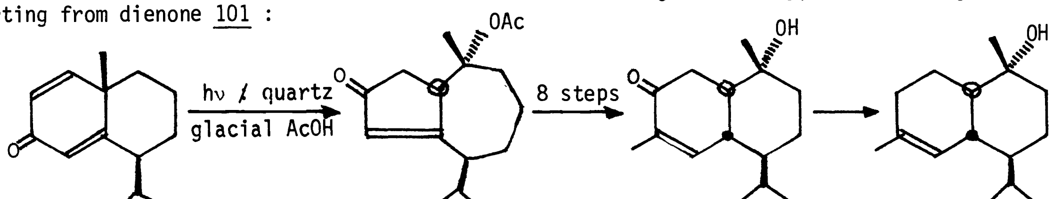
98 (91%) (d,l) oplopanone

and the first synthesis[67] of the 4,4-bisnorgrayanotoxin skeleton 100 from dienone 99, as a potential route to grayanotoxins obtained from *Leucothoe grayana* Max and showing insecticidal activity.



99α 99β 100α (overall yield: 35%) 100β

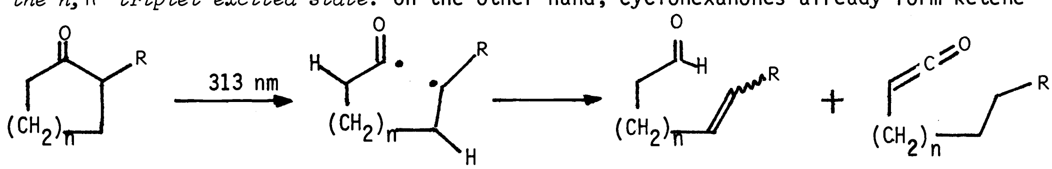
The access to 3-oxo-α-cadinol and to α-cadinol[68] also belongs to this type of rearrangement starting from dienone 101 :



101 (40%) 3-oxo-α-cadinol α-cadinol

VI PHOTOCHEMICAL RING-OPENING.

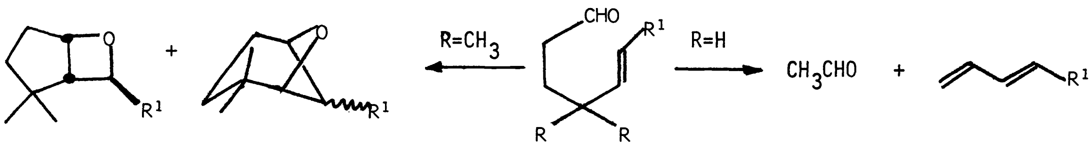
The photochemical NORRISH-type I reaction of cyclanones, which leads to unsaturated aldehydes can be taken as a mean to synthesize long-chain unsaturated products of the natural (or related) terpene series. This reaction has been well studied by different groups[69] and only the most striking features will be summarized here. The study is voluntarily limited to five and six membered ring ketones, since smaller and larger rings give also rise to different other reactions. The principal deactivation pathway of excited cyclopentanones is α-cleavage which forms γ,δ-unsaturated aldehydes with a chemical efficiency of the order of 90% and a quantum yield of about 0.3-0.4. Formation of a ketene is very inefficient for this type of ketones. *There has been speculation on the origin of the α-cleavage of cyclopentanones but recent results[70] obtained with 2-substituted cyclopentanones indicate clearly that this reaction occurs from the n,π* triplet excited state.* On the other hand, cyclohexanones already form ketene



with a non-neglegtible efficiency, and if the aldehyde/ketene ratio is of the order of 30 for the cyclopentanones, it is only 3 for the six-membered ring homologues. There are not yet sufficiently valuable explanations to account for this difference between the two series of cyclanones. *Anyhow, both processes occur from the excited triplet state.* When the cyclanone is α-substituted and if the substituent bears hydrogen atoms at the carbon γ to the carbonyl group, then hydrogen abstraction occurs at this level (NORRISH-type II reaction). This reaction which is typical of a n,π* excited state becomes more efficient as the energy of the γ-C-H bond to be broken is weakened and implies rather strict geometrical conditions : the hydrogen to be abstracted must lie in the plan of the carbonyl group[71], or very close to it. For this reason, the best geometrical conditions are found with cyclohexanones in which the α-substituent is equatorial; for instance, axial substituents on cyclohexanones do not undergo such γ-hydrogen abstraction[72] and the semi-axial position of the substituent makes the reaction very inefficient in the cyclopentanone series. *The intramolecular γ-hydrogen abstraction occurs only from the excited singlet state[73] in non-polar solvents and not from both singlet and triplet states as it is the case for aliphatic ketones[74]; nevertheless, both excited states are involved when the reaction is carried out in alcoholic solution.*

The presence of a double bond on the α-side chain, such as in 2-allylcyclanones, perturbs quite efficiently the normal course of the photochemical reaction scheme[75]; and the intersystem crossing from the excited singlet state to the triplet state of the same configuration is decreased by a factor which varies with the size of the ring and which can reach 20. As a consequence, almost no, if ever, aldehyde formation is observed in that case.

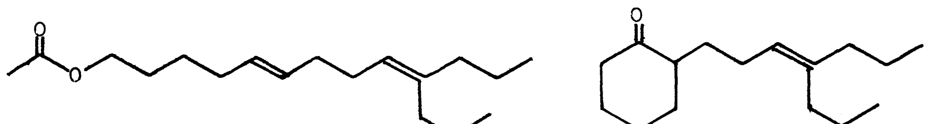
The aldehydes which are formed from the α-cleavage of the cyclanones absorb the light in the same region as the cyclanones themselves; depending on their origine, these aldehydes will evoluate very differently. Aldehydes which arise from cyclohexanones undergo an efficient NORRISH-type II reaction because of the low energy of the allylic γ-C-H bond. When no such hydrogens are available[76], or in the case of aldehydes which originate from the α-cleavage of cyclopentanones[77], the aldehydes are relatively stable and undergo, as main reactive pathway, isomerisation of the double bond and intramolecular PATERNO-BUCHI cycloaddition ; the first reaction originates from the excited triplet state, while the second comes from the excited singlet state.



Deactivation of the singlet state by γ-hydrogen abstraction or by the presence of a double bond on the side-chain is reflected in the sharp decrease of the singlet lifetime as well as of the fluorescence and intersystem crossing quantum yields. Because of the reversible γ-hydrogen abstraction and α-cleavage reactions, the intermediate biradicals do not collapse all to form the photoproducts but revert also to the starting ketone. The consequence is a more or less marked decrease in the products formation quantum yields.

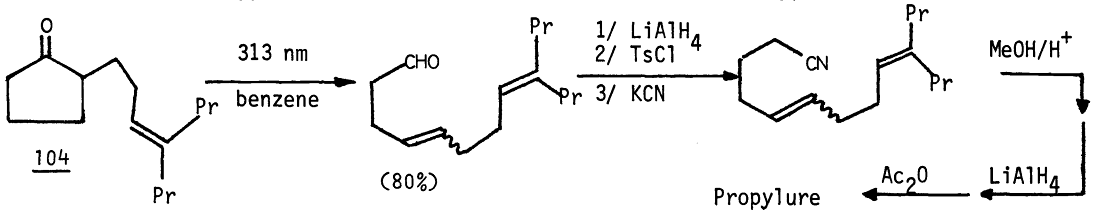
The potential synthetic application of α-cleavage of cyclopentanones has been explored in several directions. In all cases, the key photochemical step is followed by classical organic reactions to give the natural products, generally with overall yields higher than those obtained by other non-photochemical routes.

Access to Propylure, considered for a long time as the sexual pheromone of the pink bollworm moth, *Pectinophora gossypiella* Saunders, demonstrates clearly the difference in reactivity of cyclopentanones and cyclohexanones. Its structure has been demonstrated to correspond to the acetate of 10-*n*-propyl tetradeca-5(E),9-dien-1-ol, 102.



102 103

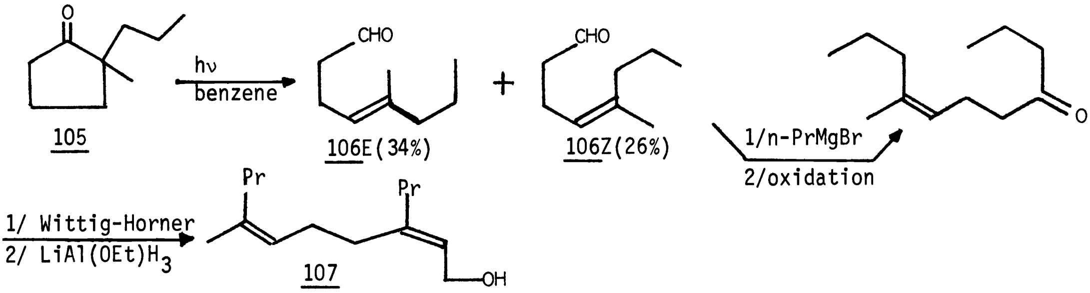
The effective sexual attractor was identified , short after our report[78] on the synthesis of Propylure, to be a mixture of the Z,Z and Z,E isomers of hexadeca-7,11-dien-1-ol acetate. However, this access is interesting to demonstrate the difference in reactivity with the ring-size. The 2-substituted cyclohexanone, 103, would have been the most suitable precursor to Propylure 102 as the unsaturated aldehydes formed by irradiation would have just to be reduced into the corresponding alcohols and esterified with acetyl chloride. Unfortunately, as expected, the photochemical behaviour of this cyclanone is oriented for the most part toward the abstraction of the allylic hydrogen atom and only traces (5-10%) of the δ,ε-unsaturated aldehydes are formed. As a consequence, the preparation of Propylure was started from the cyclopentanone homologue 104 which gives the aldehydes of the NORRISH-type I reaction, with *ca.*



104

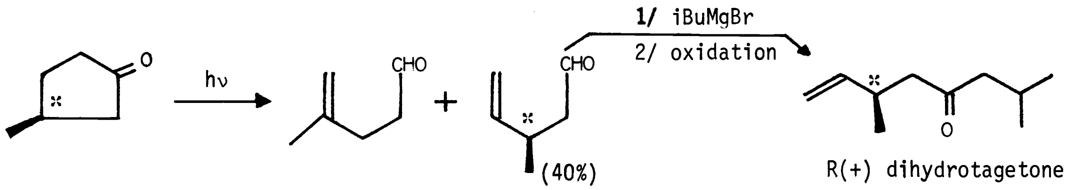
80% yields for over 80% conversion, as a mixture of the E and Z isomers in the ratio E/Z = 2. The subsequent sequences are mainly devoted to increase the chain by one carbon atom. This has been carried out by reduction ($LiAlH_4$) of the aldehydic function, tosylation of the formed alcohols and SN2 substitution of the tosylate by the cyanide ion; methanolysis of the resulting nitriles into the esters, reduction and finally esterification of the alcohols. Separation of the two isomeric acetates, 5-E and 5-Z, is achieved by column chromatography.

Access to the homoterpene 7-methyl-3-*n*-propyldeca-2(Z),6(Z)-dien-1-ol, 107, one of the pheromones isolated from the Codling moth, *Laspeyresia (carpocapsa) Pomonella,* takes advantage of the α-cleavage of the disubstituted cyclopentanone 105. This reaction, which occurs with a quantum yield of *ca.* 0.5, forms two isomeric aldehydes, 106E and 106Z, out of which the latter



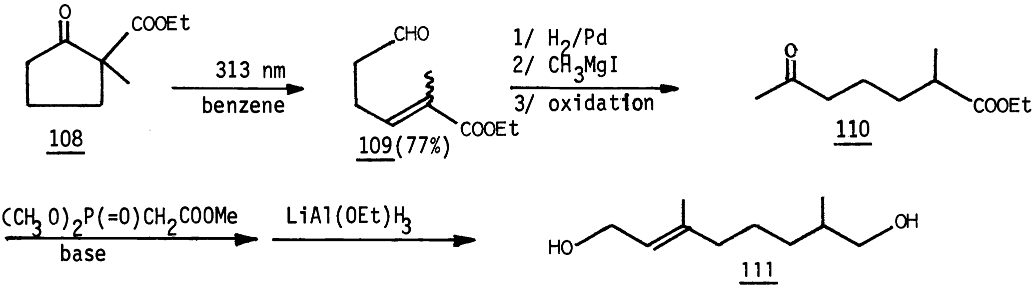
represents 42% of the mixture; the reaction is voluntarily limited to about 60-65% conversion to prevent from further photodecomposition. Transformation of the Z isomer into the pheromone 107 needs only four steps, three of which are almost quantitative. The only step which is less selective is the WITTIG-HORNER reaction with the stabilized ylid of trimethyl phosphonoacetate and which gives a mixture of E and Z isomers. Out of the four possible isomers for 107, the mixture of 106E + 106Z leads to the pheromone 107 with *ca.*27% yield.

The NORRISH-type I reaction has been used also to prepare optically active dihydrotagetone, one of the constituents of the essential oil *Tagetes Glandulifera* from the commercially available R(+) 3-methylcyclopentanone in three steps[80].



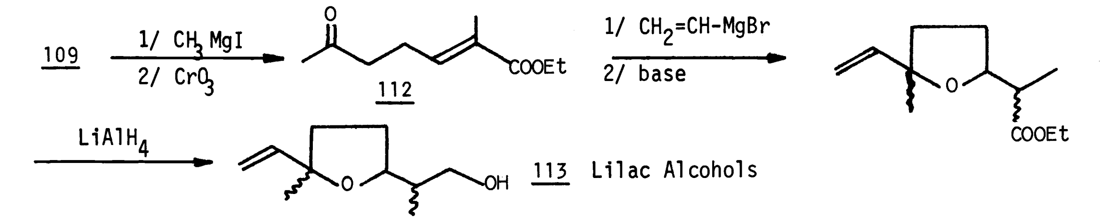
Introduction of a functional group in the α-position to the carbonyl group makes a very attractive series to extend the application of the NORRISH-type I reaction to the formation of bifunctional synthons. DIECKMANN ester and its 2-alkyl homologues seem reasonable starting materials for such an extension. Irradiation of 2-cyanocyclohexanone and 2-cyanocycloheptanone forms the aldehydes resulting from α-cleavage but the reaction gives also cyclisation products with substantial yields[81]. Based on what is already known on the difference in reactivity of cyclopentanones and cyclohexanones, one would expect the 5-membered ring ketone, DIECKMANN ester, and its 2-alkyl substituted derivatives, to be more suitable starting materials for the formation of aldehydes. Thus irradiation of DIECKMANN ester itself forms[82] the two expected unsaturated aldehydes with 78% yields and in the E:Z ratio of 78:22. The 2-methyl substituted homologue 108 gives the corresponding aldehydes with 77% chemical yields and 0.3 quantum yield.Compound 108 has been used to prepare two natural products.

Irradiation of 2-methyl-2-carbethoxy cyclopentanone 108 gives aldehydes 109 as a mixture of the E and Z isomers in the 1.6 ratio. Since no separation of the two aldehydes is needed for the subsequent steps, the reaction mixture can be distilled without special precaution. If separation is needed, this can be accomplished by carefull distillation. The unsaturated aldehydo-esters 109 are transformed into the saturated keto-ester 110 in three steps : catalytical reduction, selective GRIGNARD reaction at low temperature (-30°C) and chromic oxidation[83]. WITTIG-HORNER reaction of 110 with the stabilized ylid of trimethyl phosphonoacetate



in DMF solution is followed by the reduction of the two ester groups into 3,7-dimethyl oct-2(E)-en-1,8-diol 111 which has been characterized as one of the two major components of the hairpencil (brushlike glandular organs) of the *Danaus Chrysippus* (African Monarch) an old world member of the subfamily Danainae.

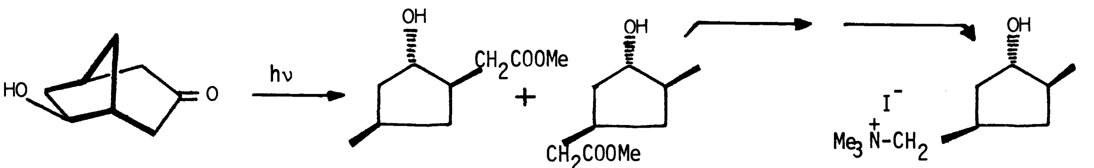
The other synthesis[84] involves the same first steps excepted the catalytical reduction. Irradiation of 108 to form the aldehydes 109 is now followed by the addition of methylmagnesium iodide and chromic oxidation to get the unsaturated keto-ester 112. Selective reaction of vinylmagnesium bromide with the keto group of 112 at low temperature and subsequent intramolecular Michael addition gives a tetrahydrofuran derivative which is further reduced into a mixture of four isomers of lilac alcohols 113.



113 Lilac Alcohols

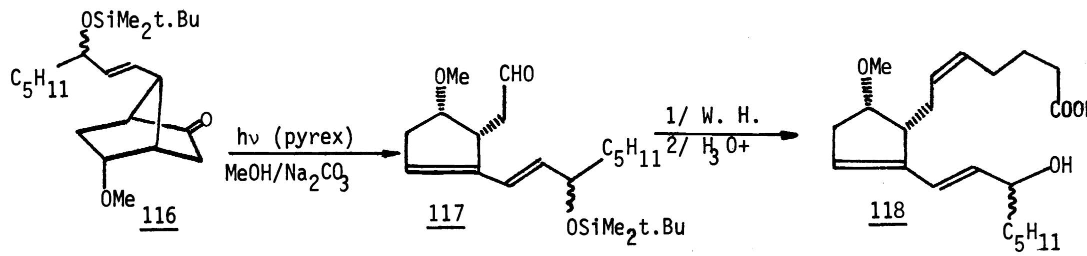
The photochemistry of bridged bicyclic compounds has been investigated and reviewed by P. YATES[85]. Depending on the substitution and on the size of the bicyclic ketone, the photoproducts can result from different pathways. We shall consider, here, only the synthetic aspect of such starting materials.

For instance 6-exo-hydroxy bicyclo[3.2.1.]octanone-3, 114, when irradiated in methanol solution gives the α-cleavage; the formed biradical evoluates efficiently toward the ketene, because of better stereoelectronic conditions compared to the formation of aldehydes; the ketene is further transformed into the mixture of the two hydroxy-esters 115a and 115b. Formation of the azide from 115b, thermal rearrangement into the isocyanate and hydrolysis in acid medium forms an amine which is quaternized into a muscarine isostere[86]. This can mimic the action of acetylcholine as a chemical transmitter of nerve impulses to smooth muscles.



114 115a 115b muscarine isostere

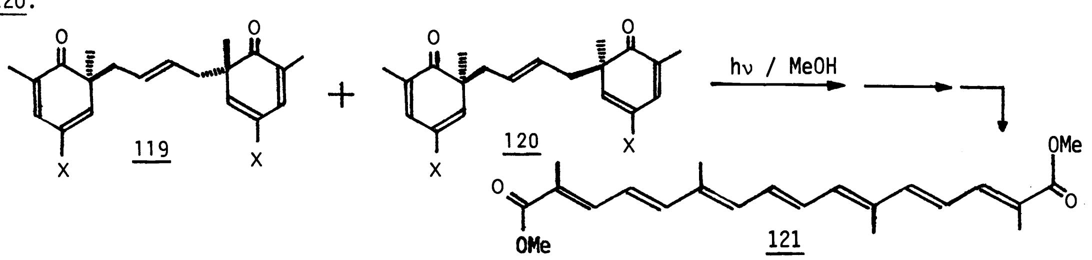
An entry to the 9α-hydroxy-9-deoxyprostaglandin-C_2 system has been demonstrated[87] recently using the Norrish type I reaction of a 7-substituted bicyclo[2.2.1]2-heptanone. The evolution of the biradical formed by α-cleavage at the level of the junction of the 2-keto system being principally the formation of aldehydes, the bridged ketone 116 gives the expected aldehyde 117 with 70% yield by irradiation in deoxygenated methanol containing a trace of potassium carbonate. The aldehydic function is smoothly transformed under WITTIG-HORNER conditions and



116 117 118

subsequent hydrolysis of the terbutyldimethylsilyl derivative affords the hydroxy acid 118.

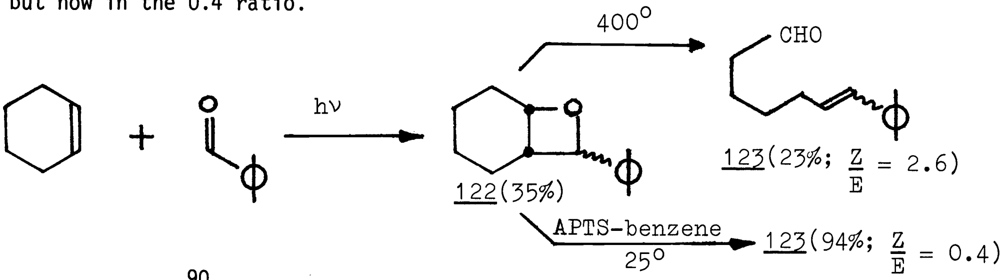
Although not a typical NORRISH-type I reaction, the ring-opening of conjugated cyclohexadienones to form ketenes would be noted; the use of this reaction to prepare the crocetin dimethyl ester 121 in three steps[88] has been accomplished by sunlight irradiation of ketones 119 and 120.



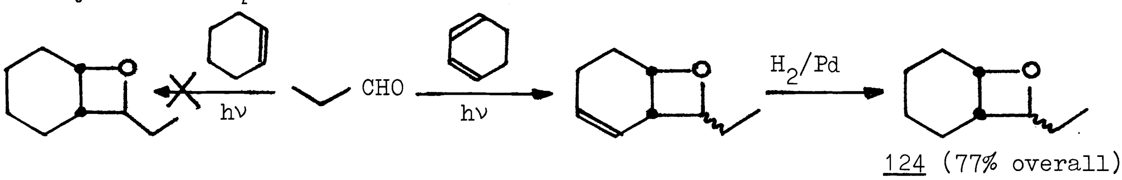
119 120 121

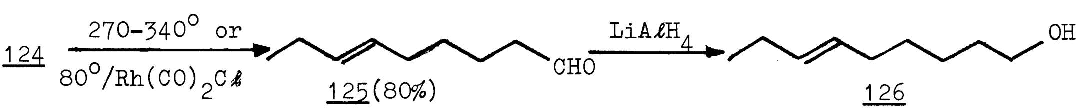
VII OXETANE FORMATION AND THERMAL CLEAVAGE

The formation of oxetanes by photochemical addition of a carbonyl group to a double bond is well-documented[89]. It is only recently that this reaction has been used to prepare unsaturated alcohols of interest as pheromones[90]. The reaction which had to be studied in detail was the ring-opening of the oxetane to an unsaturated aldehyde. This can be carried out by several methods. In one example, benzophenone was photo-added to cyclohexene. The obtained oxetane 122 can be cleaved thermally at 400° into the unsaturated aldehydes 123 as a mixture of the Z and E isomers in the 2.6 ratio or by acid-catalyzed ring opening into the same aldehydes but now in the 0.4 ratio.



In an other example[90], propanal was added photochemically to 1,3-cyclohexadiene after having observed the absence of oxetane formation with cyclohexene. The obtained unsaturated oxetane is hydrogenated and 124 is obtained with an overall yield of 77%. Thermal decomposition between 270° and 340° or chlorodicarbonylrhodium-catalyzed ring opening in refluxing benzene affords the unsaturated aldehyde 125 with over 80% yield. Reduction of the carbonyl group leads to non-6(E)-en-1-ol 126 which is the sex-attractant pheromone of the mediterranean fruit fly *Ceratitis Capitata.*





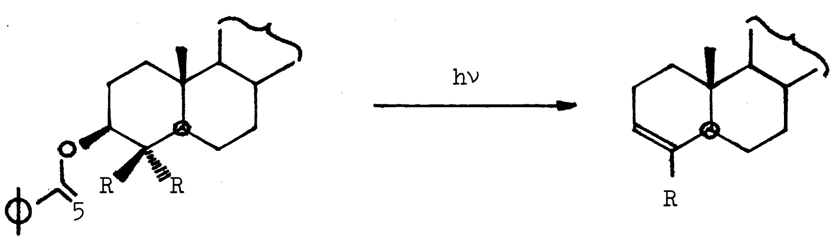
VIII FUNCTIONAL TRANSFORMATION

This part of the report will be made short and limited to hydroxyl functions. Hydroxyl groups can be blocked by different ways; usually, this enables different reactions to be carried out at other sites of plurifunctional molecules ; after the molecule being transformed, the blocked functional group can be recovered or modified.

For instance dehydration of alcohols can be carried out by transforming the hydroxylic function into an aromatic ester which contains a sulphur atom. Ultraviolet irradiation of the thioester at low temperature liberates the corresponding olefin with high yields[91].

$$Ar-CH_2-CH_2-O-\underset{\underset{S}{\|}}{C}-Ar \xrightarrow{h\nu\ -70°} Ar-CH=CH_2 \quad (90\%)$$

When carried out with steroids, the reaction occurs with high stereoselectivity and follows a cis-elimination; this can be opposed to the usual trans-elimination by an ionic mechanism.

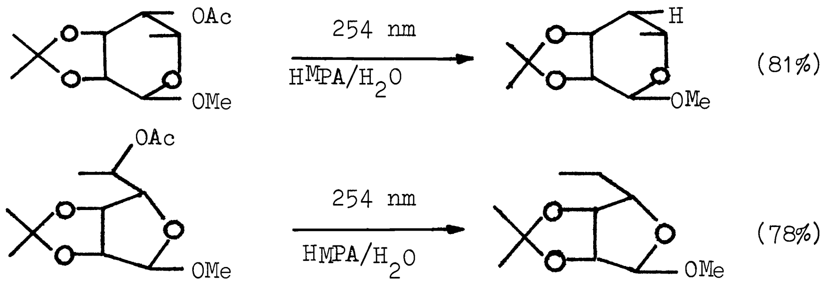


a R = H R' = D
b R = D R' = H

Another way to transform an alcoholic function is hydrogenolysis into the corresponding hydrocarbon. This has been shown to be effective by photoreduction of acetates in HMPA solution in the presence of small amounts of water. The reaction can be depicted as :

$$CH_3-\underset{\underset{O}{\|}}{C}-O-R \xrightarrow[254\ nm]{HMPA/H_2O} CH_3COOH + R-H$$

and several applications have been demonstrated in the sugar series[92] with differently protected hydroxylic groups. Thus :



There are some exceptions to this reaction and the alcoholic function can be liberated in certain special cases.

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