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The Synthesis of Mono- and Sesqui-terpene Insect Pheromones

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The review presents a critical discussion of the available information on the syntheses of isoprenoid insect pheromones. Attention is concentrated on modern methods for the construction of molecules with a specified carbon skeleton. The efficiencies of the synthetic schemes are compared on the basis of the number of stages and the overall yields of the desired products. A systematic account of the data is given in terms of the types of pheromones.
The bibliography includes 179 references.

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I. INTRODUCTION

One of the most interesting and important fields in the modern science of life involves the study of insect pheromones. The term "pheromones" was proposed in 1959 [1] for chemical compounds "produced by living organisms, released into the environment, and inducing a specific response in individuals of the same biological species receiving them". Chemical signals ensuring intercommunications between insects may be individual compounds, but in most cases they are complex synergistic mixtures of substances whose biological activity can be reduced sharply following the removal of one of the components. The geometry and chirality of these components frequently exert a definite influence on the biological activity. The progress achieved recently in the determination of the absolute configurations of chiral pheromones has been possible by virtue of the employment of the most sophisticated methods of modern fine organic synthesis. Comparison of the spectroscopic characteristics and biological properties of the synthetic and natural specimens frequently permits a correct conclusion about the structure of the pheromone even in the presence of vanishingly small amounts of the latter.

Pheromones serve the most varied spheres in the vital activity of insects: sex and aggregation pheromones, fear pheromones, track pheromones, territorial markers, etc. are known. [2] The enormous interest by chemists and biologists in these copounds is associated not only and not so much with their purely scientific value as with the real possibility of their practical employment for the control of the size of the populations of harmful insects or as a method of fighting them by mass capture and, more rarely, by disorientation. At the present time there is a large number of reviews and monographs devoted to various questions concerning insect pheromones. [3-17] Correspondingly extensive factual data have accumulated on the syntheses of these compounds and are contained in a series of reviews, [13,18,19] which, being extremely extensive, nevertheless are not exhaustive, which has in turn led to the appearance of a series of small specialised reports on this topic. [20-23]

The present review is devoted to the synthesis of mono- and sesqui-terpene insect pheromones. Despite the fact that such data are partly contained in the communications noted above, there are no publications surveying the available information on this question. The present review contains data obtained mainly during the last ten years (up to July 1982 inclusive) and is concerned solely with regular and isomeric isoprenoid structures.

II. SEX AND AGGREGATION PHEROMONES

The sexual pheromones (SP) are produced by the insect in order to attract individuals of the opposite sex with the aim of subsequent coupling. Aggregation pheromones (AP) attract both sexes, which also as a rule precedes coupling. Since the purpose of the given group of substances is closely related to the propagation of the genus, they have in fact found extensive application in the protection of plants against insect pests and have therefore been studied at the present time on an extremely broad front.

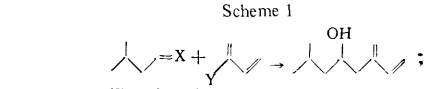
Among the isoprenoid SP, the main place is occupied perhaps by the monoterpenols found in certain insects of the family *Scolytidae*, which are dangerous forest pests.

1. Ipsenol

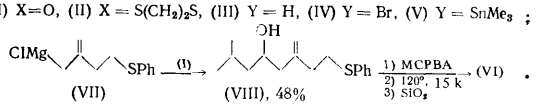
Ipsenol (VI) is a pheromone or a component of the pheromone mixture in many species of bark beetles of the genus *Ips* [24-29] and scolytid beetles of the genus *Pityokteines*. [30,31] In many instances only the *S*-(-)-enantiomer is biologically active. [28,31,32] Very many studies have been devoted to the synthesis of compound (VI). Here and henceforth we shall consider initially the preparation of the racemic product and then of the chiral derivative.

The majority of the methods of synthesis of compound (VI) are based on the construction of the whole C_{10} molecule from two C_5-synthones, one of which is isovaleraldehyde (I) or its dithioacetal (II) (Scheme 1).

Scheme 1



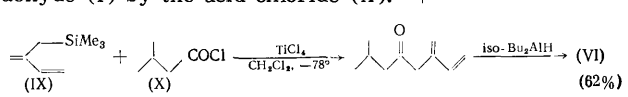
(I) X=O, (II) X = $S(CH_2)_2S$, (III) Y = H, (IV) Y = Br, (V) Y = $SnMe_3$;



Thus the deprotonation of the latter compound and subsequent alkylation with the bromide (IV) give rise to a product, which is converted into the required compound

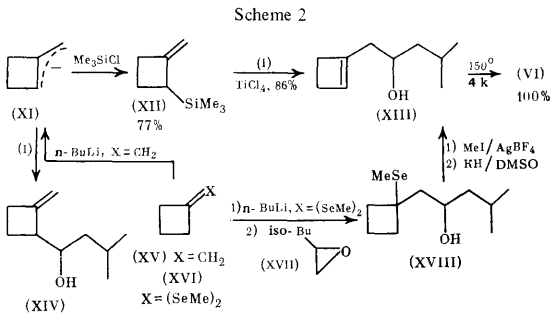
(VI) after the removal of the protecting dithio-group and hydride reduction.[24,33]

The bromide (IV) could not be converted into the magnesio- or lithio-derivative,[33] while the chloromagnesio-derivative (VII) could be very readily obtained from the corresponding chlorothioether, which made it possible to obtain the hydroxythioether (VIII), whose conversion with the aid of *m*-chloroperbenzoic acid (MCPBA) into the sulphoxide and the subsequent thermolysis of the latter yielded compound (VI) in an overall yield of 17%.[34] The single-stage synthesis of compound (VI), consisting in the Reformatskii condensation of compounds (I) and (IV) in the presence of zinc,[35] is extremely effective (yield 52%) and apparently the most appropriate method. The corresponding organozinc reagent could be conveniently generated *in situ* from tribromoisoprene.[36] The synthesis of compound (VI) with the aid of the ene reaction of compound (I) with isoprene (III), catalysed by Me_2AlCl, is also attractive by virtue of its simplicity and the ready availability of the starting materials.[37] However, the process is complicated by the concominant formation of the corresponding heterodiene condensation products. A single-stage synthesis of compound (VI) has also been achieved[38] using stannane (V). The use of the related silane (IX) gives an extremely low yield of compound (VI), but this limitation has been obviated by replacing the aldehyde (I) by the acid chloride (X).[39]†



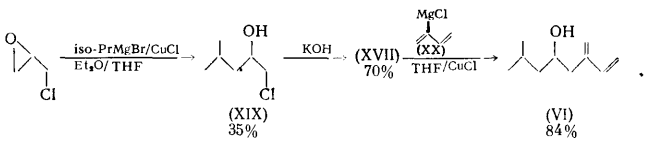
In one of the instances examined above, the 1,3-diene system is introduced into the molecules of compound (VI) in a "masked" form.[34] The same principle, but in a different version, underlies many syntheses of compounds (VI) based on cyclobutane derivatives (Scheme 2). Thus the ambident anion (XI), obtained by the deprotonation of methylenecyclobutane (XV), is converted in 80% yield into a mixture of the regioisomers (XIII) and (XIV) (~1 : 2) on treatment with the aldehyde (I); the thermolysis of cyclobutene (XIII) gives a quantitative yield of compound (VI):[40]

Scheme 2



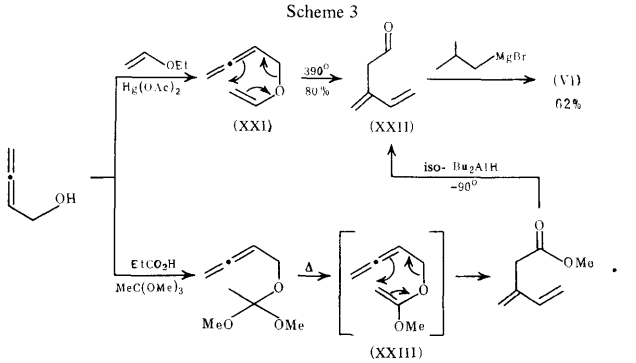
The isomer (XIV) remains a ballast compound under these conditions and its chromatographic separation is fairly difficult. A more effective procedure consists in the initial silylation of compound (XI) to give compound (XII), which subsequently reacts with compound (I) with total allyl rearrangement and gives rise to compound (XIII).[41] The third method of synthesis of this cyclobutene consists in the employment of the readily available *gem*-diselenide (XVI) as the C_4-synthone. Its metallation and treatment with the epoxide (XVII) (the C_6-synthone) lead to the hydroxyselenide (XVIII). The conversion of the latter into the dimethylselenonium derivative and its treatment with KH in dimethyl sulphoxide (DMSO) result in an exceptionally regiospecific formation of compound (XIII).[42] Overall, this method, being extremely laborious, is nevertheless characterised by a fairly high overall yield of compound (VI) (>50%).

The scheme involving the construction of the molecule of compound (VI) by coupling the epoxide (XVII) and buta-2-dienylmagnesium chloride (XX) as the C_6- and C_4-synthones respectively appears very simple and logical.[43] An extremely convenient method of synthesis of compound (XVII) proved to be the condensation of epichlorohydrin with isopropylmagnesium bromide in the presence of one equivalent of CuCl via the stage involving the formation of the intermediate chlorohydrin (XIX); the use of CuCl also makes it possible to increase significantly the yield of compound (VI) in the next stage:[44]



The same principle of the two-synthone approach is illustrated by Scheme 3. Here the key operation is the formation of the dienal (XXII) by the Claisen rearrangement of the vinylallenic ethers (XXI)[45] or (XXIII).[46] In both cases the overall yield of compound (VI) reaches 35%.

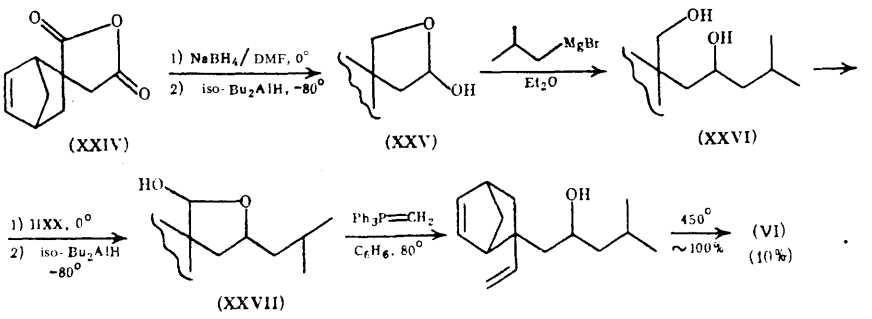
Scheme 3



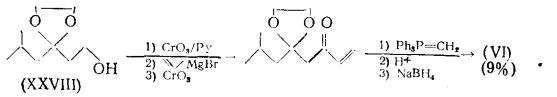
The synthesis of compound (VI) from itaconic anhydride in the form of its adduct (XXIV) with cyclopentadiene (Scheme 4) is somewhat less effective.[47] The main strategy reduces in this instance to the selective transformation of compound (XXIV) into the hemiacetal (XXV) and subsequently to the just as selective oxidation of the 1,4-glycol (XXVI) with the aid of pyridinium chlorochromate (PCC) to the lactol (XXVII). The methylenation of the latter and the retrodiene removal of the protection of the initial *exo*-methylene bond lead ultimately to compound (VI) in a very moderate yield:

†Here and henceforth the overall yields are indicated in brackets.

Scheme 4

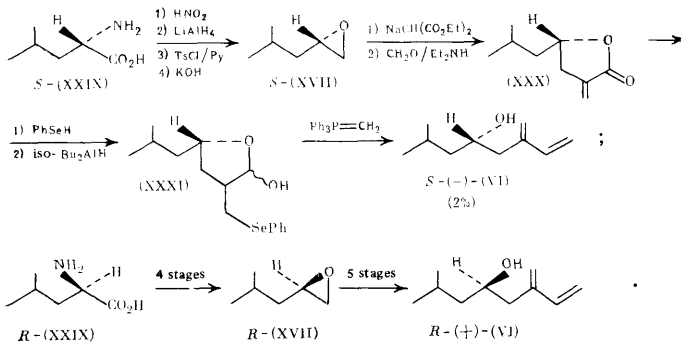


The overall yield in the six-stage synthesis of compound (VI) from the hydroxyacetal (XXVIII) with the aid of traditional methods for the increase in the length of the isoprenoid chain proved to be just as low: [48]



The synthesis of optically active compound (VI), which has been achieved in a low yield but which has made it possible to establish the absolute configuration of the pheromone, was undertaken from *S*-(+)-leucine (XXIX) (Scheme 5). Here the key product was the chiral epoxide *S*-(XVII) obtained in four stages. Its condensation with diethyl malonate and subsequent methylenation give rise to the lactone (XXX), which is transformed into the lactol (XXXI) after the protection of the *exo*-methylene double bond. Its Wittig methylenation, which takes place with the simultaneous removal of the phenyl selenide protecting group, leads to the natural product *S*-(-)-(VI). [49,50] The enantiomer *R*-(+)-(VI) has been obtained analogously from *R*-leucine (XXIX) via *R*-(XVII). [50]

Scheme 5



Subsequently both enantiomers (VI) were synthesised via a shorter pathway, using the method described above, [43] from the same chiral epoxides (XVII) and butadienylmagnesium chloride (XX) in an overall yield of ~50%. [51]

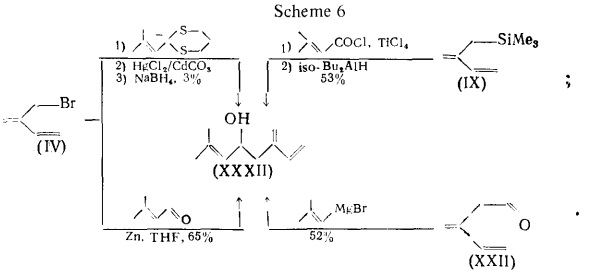
It is of interest to note that the biological action of the natural product *S*-(-)-(VI) is not inhibited by the presence of its optical isomer *R*-(+)-(VI), [28,31] at least for the bark beetle *Ips grandicollis* and the scolytid beetle *Pityokteines curvidens*. This fact permits one to hope for a possible practical application of compound (±)-(VI), which will thus remove the necessity for its enantioselective synthesis.

2. Ipsdienol

Like its dihydro-derivative (VI), ipsdienol (XXXII) is an aggregation-sex pheromone in many *Ips* [24-27,29,52-57] and *Pityokteines* [30,31] species and, in contrast to compound (VI), these functions can be fulfilled by both enantiomers of compound (XXXII) (see, for example, Vité et al. [32]).

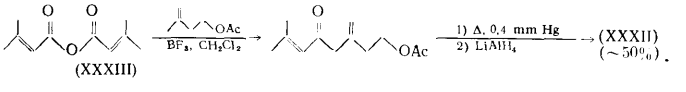
In conformity with the evident structural characteristics of this compound, the strategy used in many of its total syntheses proved to be analogous to that already considered for ipsenol (VI). Thus the two-synthone approaches ($C_5 + C_5$ or $C_4 + C_6$), represented in Scheme 6, are widely used:

Scheme 6



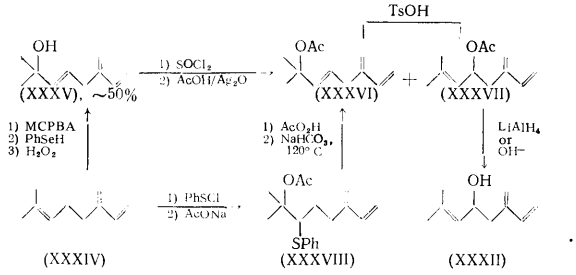
The extremely low overall yield of compound (XXXIII), initially obtained in three stages from the bromo-derivative (IV), can apparently be accounted for by the authors' [24,33] endeavour to confirm in the first place the structure of this pheromone. On the other hand, the simplicity and effectiveness of the synthesis of compound (XXXII) by the Reformatskii method [36,58] as well as the syntheses from the silane (IX) [39] and the aldehyde (XXII) [45,46] are evident.

The method based on the condensation of the anhydride (XXXIII) with isopentenyl acetate [59] proved to be fairly apt, despite the formation of up to 30% of regio-isomers as side products in the first stage:



A fundamentally different approach, directed in essence to the selective hydroxylation of myrcene (XXXIV), which possesses the fundamental structural features of the molecule of compound (XXXII), is illustrated in Scheme 7:

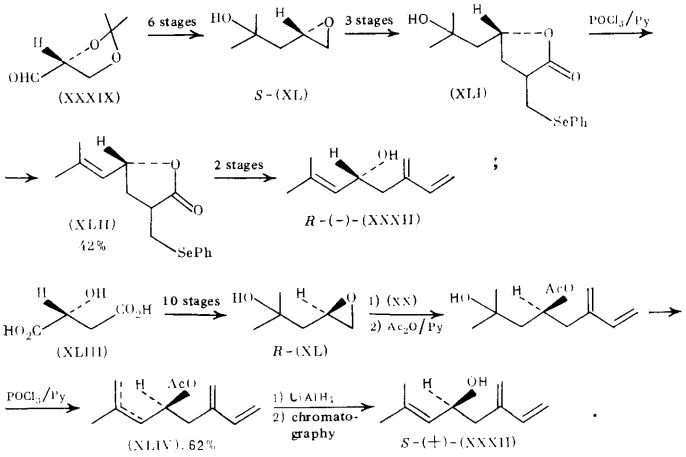
Scheme 7



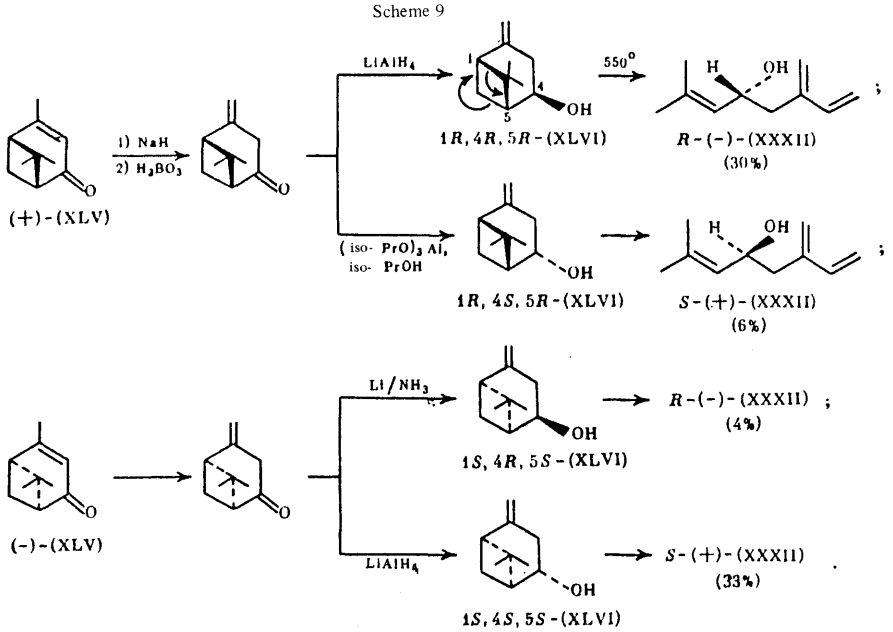
Thus the selective epoxidation of compound (XXXIV) with subsequent opening of the epoxide ring with the aid of PheH and treatment of the intermediate hydroxyselenide with H_2O_2 gives rise ultimately to amitinol (XXXV), which has proved to be the component of the aggregation pheromones (AP) of the bark beetles (see below). In view of its lack of resistance to the action of acids, the direct rearrangement of the tertiary alcohol (XXXV) proved difficult. An indirect procedure was therefore undertaken: the tertiary alcohol (XXXV) was converted into a mixture of the acetates (XXXVI) and (XXXVII); the latter was isolated from the mixture by the reductive cleavage with lithium tetrahydroaluminate to give the alcohols (XXXV) and (XXXII); and by the selective acetylation of the secondary alcohol (XXXII) with acetic anhydrides and the subsequent chromatography of the mixture of compounds (XXXV) and (XXXVII); the racemic secondary alcohol (XXXII) was obtained from the acetate (XXXVII) in an overall yield of ~10%. [60] A related approach consists in the selective conversion of compound (XXXIV) into the acetoxysulphide (XXXVIII) and the conversion of the latter into the acetate (XXXVII) via the sulphoxide and the tertiary acetate (XXXVI), which smoothly rearranges to compound (XXXVII). [The use of the rearrangement (XXXVI) → (XXXVII) would have probably halved the number of stages in the preceding synthesis.] The hydrolysis of compound (XXXVII) affords the required compound (XXXII) in an overall yield of ~25%. [61]

By analogy with the syntheses of the enantiomeric compounds (VI), the optically active isomers of compound (XXXII) have been obtained via the chiral hydroxyepoxides (XL) (Scheme 8). [51,62] Here compound *S*-(XL) was synthesised from a derivative of *R*-glyceraldehyde (XXXIX), which can be obtained in its turn from D-mannitol. The enantiomer *R*-(XL) was prepared from *R*-malic acid (XLIII). The conversion of the epoxide *S*-(XL) into the alcohol *R*-(XXXII) involves the formation of the selenide (XLI) at an intermediate stage (see Scheme 5). Its dehydration leads to the olefin (XLII), whose further transformation into the required compound *R*-(XXXII) was achieved analogously to the synthesis of compound (VI) via Scheme 5 in an overall yield of 0.2% with respect to compound (IX). The enantiomer *S*-(XXXII) was synthesised from the epoxide *R*-(XL), which was condensed by the method described above [43] with butadienylmagnesium chloride (XX). Successive acetylation of the secondary hydroxyl and dehydration lead to a ~1 : 1 mixture of the allyl isomers (XLIV). The absence of regioselectivity at the given stage is undoubtedly a significant disadvantage of the approach considered, because it requires the chromatographic isolation of compound *S*-(XXXII), formed after the reduction of the acetate in an overall yield of 0.03%.

Scheme 8



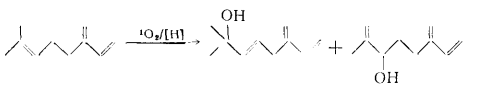
Scheme 9



An elegant method of synthesis of both enantiomers of compound (XXXII) is based on the four-stage transformation of the optically active verbenones (XLV) (Scheme 9). The β-verbenols (XLVI), obtained by the reduction of the corresponding non-conjugated ketones, were subjected to flash pyrolysis. As a result of the opening of the four-membered ring, the 1,5-diastereoisomers are then converted in pairs into the required compound (XXXII) in approximately identical yields, retaining the absolute configuration of the chiral centre C(4) in the molecule of compound (XLVI).[63] A disadvantage of this scheme is the comparative difficulty of obtaining the optically active verbenones (XLV).

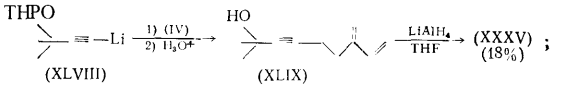
3. Amitinol

Yet another representative of the linear monoterpenols entering into the composition of the AP of the bark beetle of the genus *Ips* is amitinol (XXXV).[29,64] Apart from the synthesis described above (Scheme 7),[60,61,65] there exists yet another method of obtaining compound (XXXV) from myrcene, which consists in its reductive photochemical oxidation in the presence of $(H_2N)_2CS$ [66] or $n\text{-}Bu_4NBH_4$.[67] The regioisomer (XLVII) formed simultaneously can be separated chromatographically with comparative ease. The preparatively more convenient method employing $n\text{-}Bu_4NBH_4$ [67] is characterised by a somewhat lower yield of compound (XXXV):



(XXXIV) (XXXV) 40—50% (XLVII) 30—40%

A two-synthone ($C_5 + C_5$) scheme has also been described for the construction of amitinol from the bromo-derivative (IV) and the acetylide (XLVIII) with subsequent hydride reduction of the intermediate carbinol (XLIX).[45] However, one should note the moderate overall yield of compound (XXXV) in this instance:



(XLVIII) (XLIX)

THP = tetrahydropyranyl.

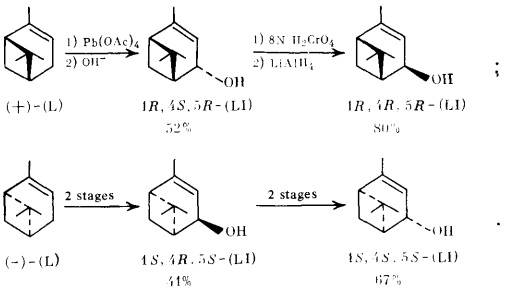
Finally, the pheromone (XXXV) has been recently identified[29] in one of the bark beetle species and has been obtained by the allyl isomerisation of ipsdienol on treatment with 3% HBF_4; the authors unjustifiably assumed that compound (XXXV) had not been synthesised previously.

4. Verbenols

The *cis*- and *trans*-verbenols (LI) have been found in the AP of many species of the *Ips* bark beetle and the timber beetles *Dendroctonus* [24–26,56,68–70] and in many instances the biological action of compounds (LI) can depend significantly on their enantiomeric purity;[26,32,71–73] mainly the 4*S*-(-)-*cis*- and 4*R*-(+)-*trans*-verbenols are active.

The syntheses of the racemic and chiral compounds (LI) are fairly isotypical and are based on standard and thoroughly investigated transformations of the α- and β-pinene derivatives.[24,33,63,74,75] In particular, the chiral compounds *trans*-(LI) have been obtained by the allyl oxidation of the corresponding α-pinene (L) enantiomers and *cis*-(LI) have been synthesised by the Jones oxidation of *trans*-(LI) to the verbenols (XLV) with a subsequent hydride reduction[74,75] (Scheme 10).

Scheme 10



(+)-(L) 1*R*,4*S*,5*R*-(LI) 52% 1*R*,4*R*,5*R*-(LI) 80%

(-)-(L) 1*S*,4*R*,5*S*-(LI) 41% 1*S*,4*S*,5*S*-(LI) 67%

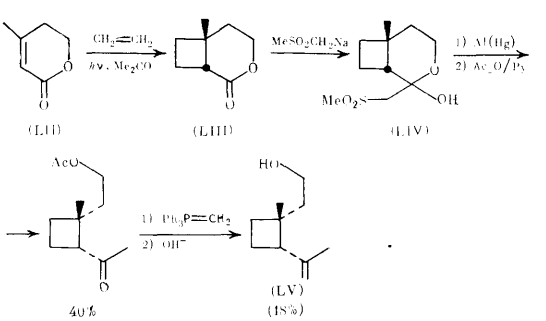
The partial racemisation occurring during the synthesis of the verbenols can be compensated by their conversion into the D-3β-acetoxyetienic esters and by the improvement of the optical purity of the latter as a result of crystallisation and the regeneration of the required alcohols with the aid of hydride reduction.[74,75]

5. Grandisol

The snout beetle *Anthonomus grandis* is one of the most dangerous pests on the cotton plant, "eating up", for example, 300 million dollars annually on American farms.[76] The aggregation-sexual pheromone "grandlure", produced by the males of this insect, consists of four components, the principal component being (+)-grandisol (LV).[77] Its enantiomer also exhibits a high biological activity,[78] which apparently eliminates the necessity for the chiral synthesis of compound (LV) for practical purposes.

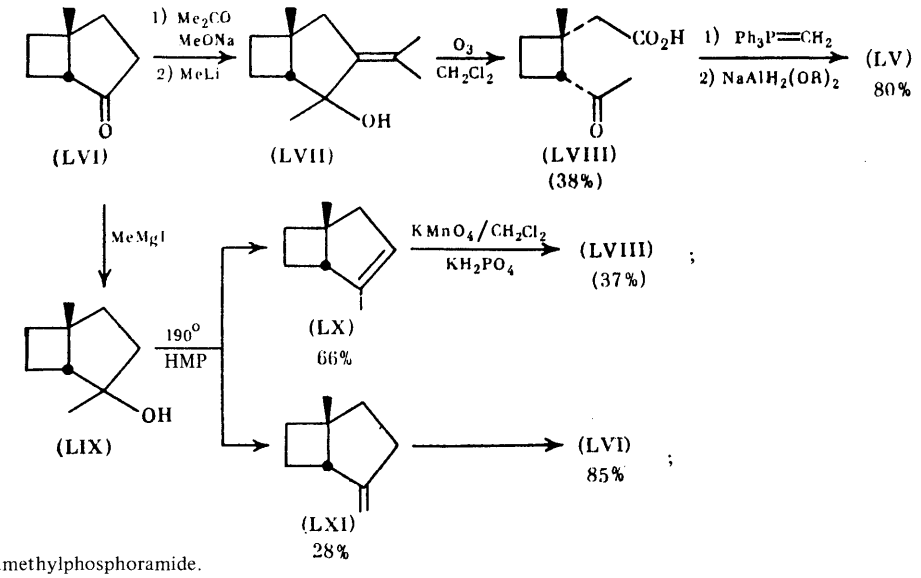
Numerous studies have been devoted to the synthesis of the racemate of compound (LV), evidently owing to the unusual nature of its cyclobutane structure and the growing need for this pheromone. Many methods for the construction of the molecule of compound (LV), developed prior to 1975, have been described in a review,[20] which effectively illustrates the evolution of the overall strategy in the synthesis of substances of this type. We shall therefore consider below only recently published and the most promising of the proposed schemes.

The key stage in the majority of the methods is the formation of the cyclobutane fragment of the molecule of compound (LV) and this is usually achieved by the photochemical [2 + 2]-cycloaddition. Thus the photoadduct (LIII) has been obtained from the lactone (LII) and ethylene; its treatment with the sodium derivative of dimethyl sulphone gives rise to the sulphone (LIV), which has been converted into grandisol by means of four simple operations:[79]



(LII) (LIII) (LIV) (LV) 40% (18%)

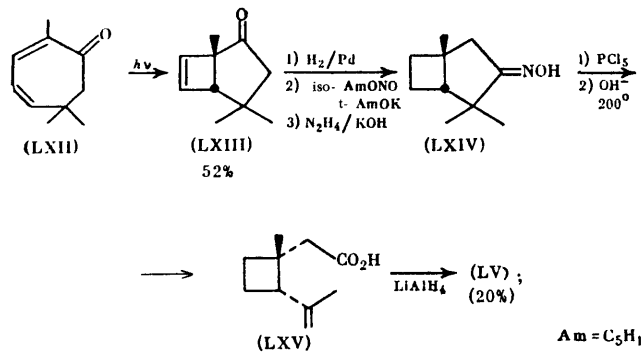
Scheme 11



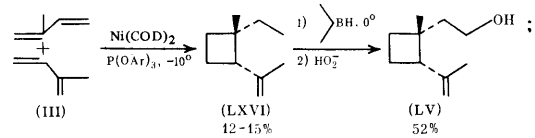
HMP = hexamethylphosphoramide.

The syntheses of compound (LV) based on the use of 3-methylcyclopentenone instead of the lactone (LII) (Scheme 11) can be regarded as just as successful. Here the main task is the specific transformation of the cyclopentane fragment of the photoadduct (LVI). In one instance this has been achieved by its conversion into the isopropylidene-carbinol (LVII) and subsequent ozonolysis to the ketoacid (LVIII) [80] and in another instance by the dehydration of the alcohol (LIX) to the olefins (LX) and (LXI). The oxidative cleavage of the first of these leads to the same ketoacid (LVIII) as above, while the cleavage of the second results in the formation of the initial ketone (LVI). [81]

A novel and extremely effective synthesis of compound (LV) is based on the intramolecular photocyclisation of the readily available eucarvone (LXII). The main difficulty in this approach consists in the shift of the carbonyl functional group in the intermediate (LXIII) to the neighbouring secondary carbon atom, which is achieved by hydrogenation and nitrosation. The subsequent reduction leads to the saturated oxime (LXIV). The Beckmann rearrangement of this kind and hydrolysis of the intermediate nitrile afford the acid (LXV), which is reduced to (±)-grandisol: [82]

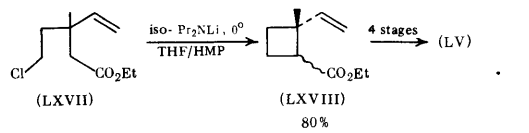


Apart from the photochemical methods, a whole series of fundamentally new approaches to the synthesis of compound (LV) have been described. The zerovalent nickel-catalysed cyclodimerisation of isoprene to the diene (LXVI) with subsequent selective "anti-Markovnikov" hydration of one of the C=C bonds must be regarded as the shortest of these, although its effectiveness is comparatively low: [83]



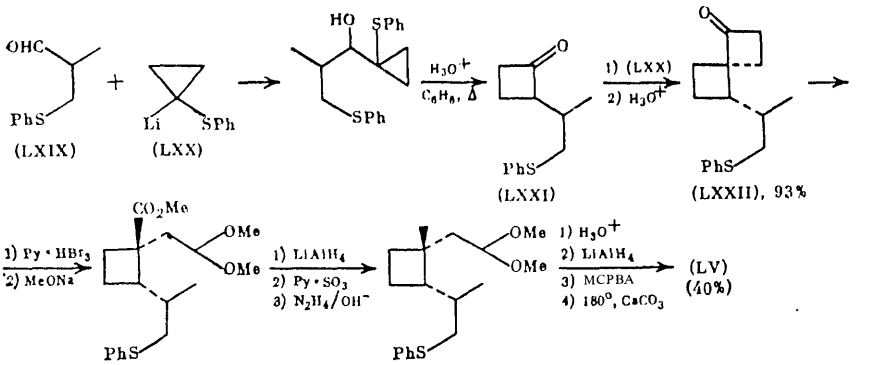
COD = cyclo-octadiene.

The construction of the cyclobutane skeleton of compound (LV) by the intramolecular cyclisation of suitable precursors with functional groups is usually associated with a low stereoselectivity of this key stage. Thus the smooth cyclisation of the δ-chloroether (LXVII) gives rise to a mixture of stereoisomers of compound (LXVIII) (*Z*/*E* ≅ 2:1); the subsequent conversion into compound (LV) entails a laborious operation involving their chromatographic separation. [84] The overall yield of compound (LV) was not indicated in the above study:

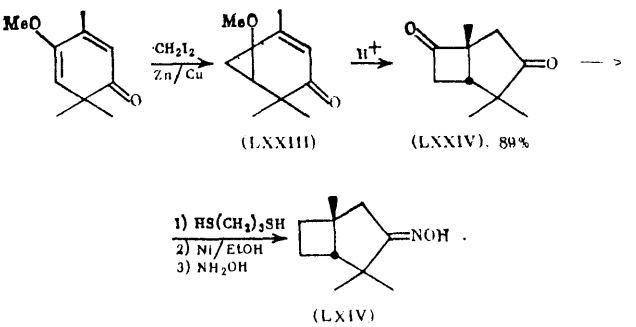


The cyclopropylcarbinyl rearrangement (CPCR) has served as an extremely effective procedure for the formation of the four-membered ring in the molecule of grandisol. The latter has been obtained (Scheme 12) in a very high yield and with a small admixture of the *E*-isomer (20%) from the thioaldehyde (LXIX) and the lithio-derivative (LXX) by the double application of the CPCR, which leads to the cyclobutanones (LXXI) and (LXXII). The required carbon skeleton was then obtained by the haloform cleavage of the spiro-heptanone (LXXII). The required product (LV) is then obtained by the reduction of the ester group to the methyl group and of the acetal group to the alcohol group, followed by the elimination of the elements of PhSH: [85,86]

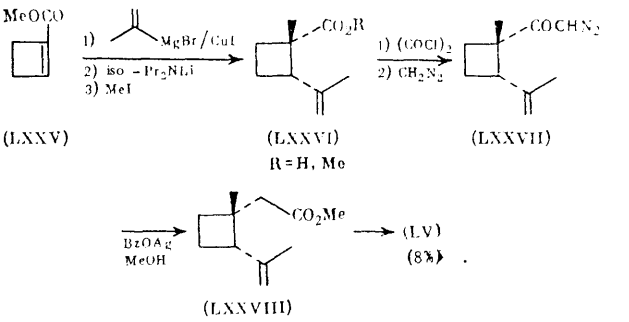
Scheme 12



An analogous principle underlies another approach leading to the geometrically pure compound (LV) in an overall yield of ~7%.[87] In this case the methoxybicycloketone (LXXIII) is subjected to the CPCR rearrangement and is transformed into the dione (LXXIV), which is then converted into the oxime (LXIV). The formation of compound (IV) from the oxime[82] was examined above:

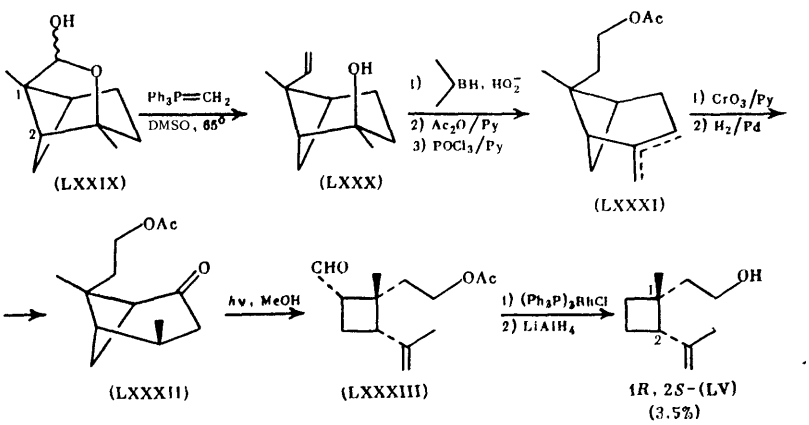


Among the syntheses of compound (LV) based on the use of cyclobutane precursors, mention should be made of the three-stage stereoselective transformation of the conjugated olefin (LXXV) into the ester (LXXVI). Its conversion into the diazoketone (LXXVII) and further into the ester (LXXVIII) makes it possible to obtain compound (LV) smoothly albeit in a low overall yield:[88]



The synthesis of (+)-grandisol (LV) is represented in Scheme 13. Its absolute 1*R*, 2*S*-configuration follows from the known configuration of the remote precursor (LXXIX), in the course of the transformation of which into the required compound the centres indicated are not involved.[89] The lactol (LXXIX), obtained in four stages from (-)-β-pinene, was converted by the Wittig reaction into the olefin (LXXX) and then by three simple operations into a mixture of the olefins (LXXXI). The allyl oxidation of this mixture with subsequent hydrogenation led to a satisfactory yield of the ketone (LXXXII). The Norrish photochemical cleavage of the latter, the deformylation of the aldehyde (LXXXIII) by means of Wilkinson's complex, and the removal of the acetate protecting group yield ultimately the optically pure 1*R*, 2*S*-(+)-grandisol, the biological and physicochemical properties of which correspond to those of the natural product.

Scheme 13



In another procedure (Scheme 14) both optical isomers of compound (LV) have been obtained from the racemic acid (LXXXIV), which can be readily synthesised from the cyclic photoadduct of ethylene with 3-ethoxycarbonylcyclopent-2-enone.[90] Quinine, cinchonine, or brucine salts of this acid have been separated and then converted in pairs into the isopropylidene derivatives (LVII) via stages involving the esters (LXXXV) and ketones (LVI). The conversion of compound (LVII) into the enantiomers of compound (LV) does not differ fundamentally from that considered in Scheme 11.

Naturally, neither of the enantioselective syntheses of compound (LV) is suitable for preparative purposes because of the large number of stages and the low overall yield, but the absolute configuration of this pheromone has been established with their aid.

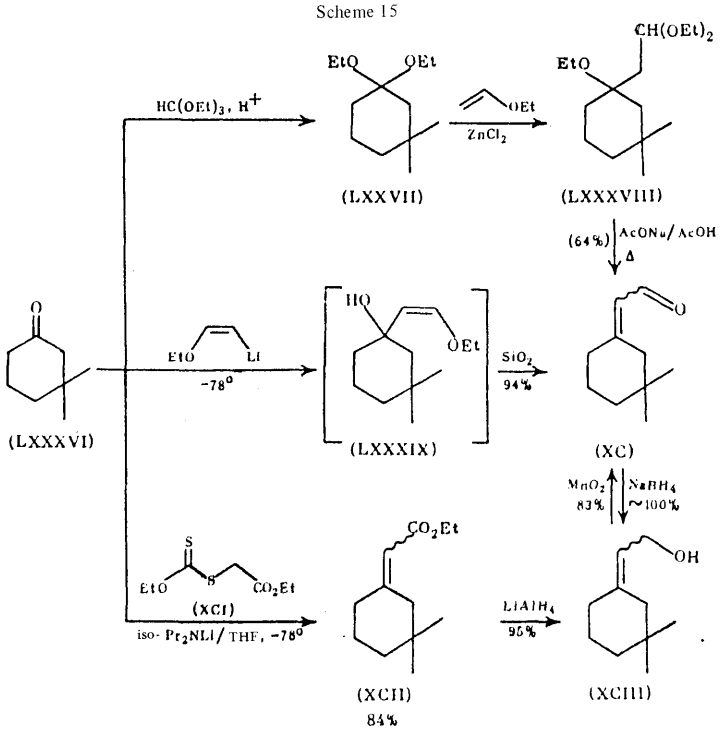
In conclusion one should mention the synthesis of 1*S*, 2*R*-(-)-(LV), carried out in order to investigate the biological properties of this enantiomer; this synthesis involves the separation of the quinine salts of the enantiomeric acids (LXV) obtained by the oxidation of compound (±)-(LV).[78]

From the wide variety of syntheses of compound (LV), one can apparently isolate the most promising syntheses based on the cyclodimerisation of isoprene[83] and the intramolecular photocyclisation of eucarvone.[82]

6. Cyclohexane Components of "Grandlure"

Apart from compound (LV), the cyclohexane monoterpenes *Z*,*E*-(XC) and *Z*-(XCIII) also enter into the composition of the AP of the cotton snout beetle. The methods of synthesis of these components of "grandlure" are fairly simple and have been largely considered in another review.[13] The majority of the procedures, including those published recently[91-93] (Scheme 15), are based on the employment of the readily available dimethylcyclohexanone (LXXXVI). The condensation of the acetal (LXXXVII) with ethyl vinyl ether gives a quantitative yield of the ethoxyacetal (LXXXVIII), which is subsequently converted into a mixture of the aldehydes (XC). The latter can be separated chromatographically and reduced to the corresponding isomers of the alcohols (XCIII).[91] The synthesis based on the condensation of the ketone (LXXXVI) with ethoxyvinyllithium must be included among the most effective methods. The resulting intermediate (LXXXIX) is smoothly converted into a 1:1 mixture of the isomers of compound (XC) in the course of chromatography of SiO_2.[92] A novel method of synthesis of αβ-unsaturated esters is characterised by high yields; the interaction of the carbanion derived from the dithiocarbonate (XCI) with the ketone (LXXXVI) leads to a ~1:1 mixture of the isomeric esters (XCII).[93] The latter can be reduced to the alcohols (XCIII), whose oxidation gives rise to the aldehydes (XC).[91]

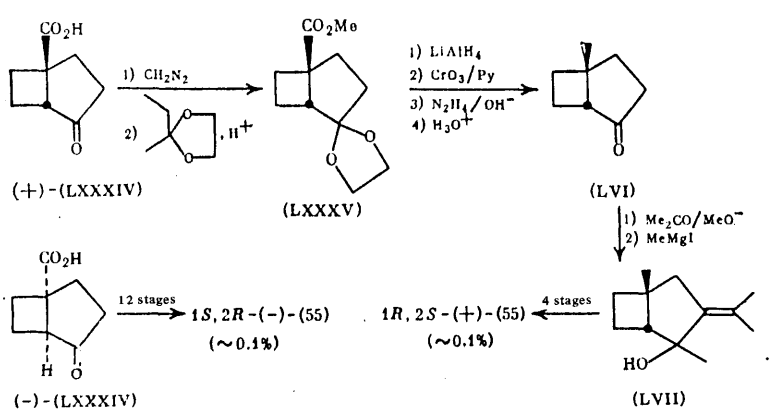
Scheme 15



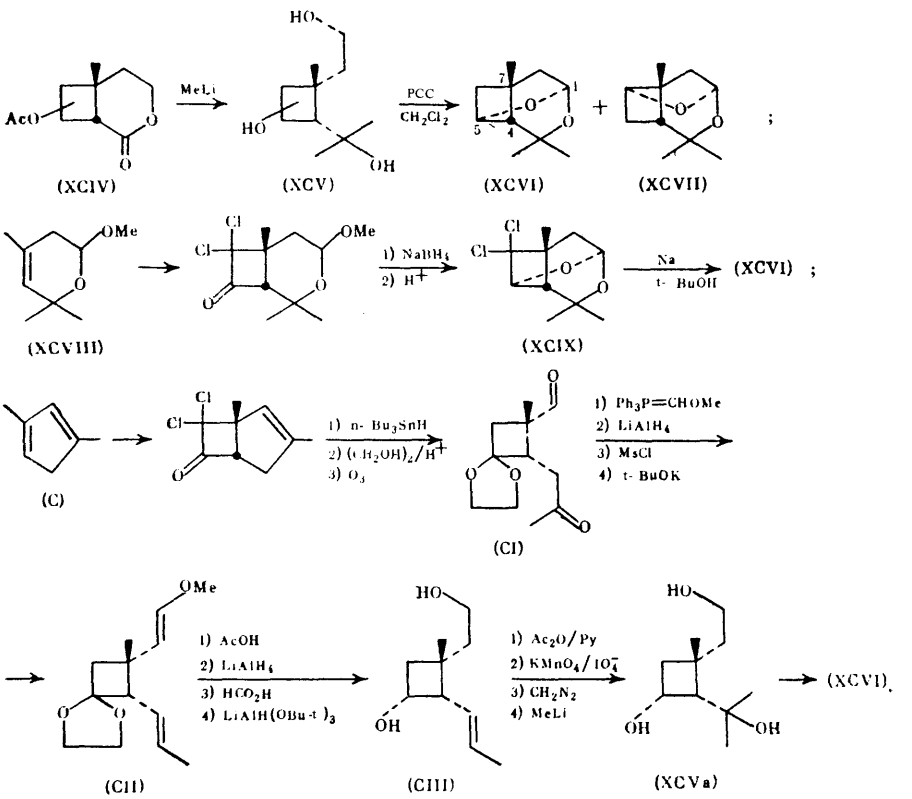
7. Lineatin

In contrast to the bark beetles of the genus *Ips*, in other representatives of this family (*Scolytidae*), namely the beetles *Trypodendron lineatum*, the AP, called lineatin, is produced by the females. It has been shown recently that the AP has the unusual dioxatricyclononane structure (XCVI).[94,95] It has also been established that the biological action of the natural (+)-isomer is not inhibited by its inactive optical isomer (-)-(XCVI).[96]

Scheme 14



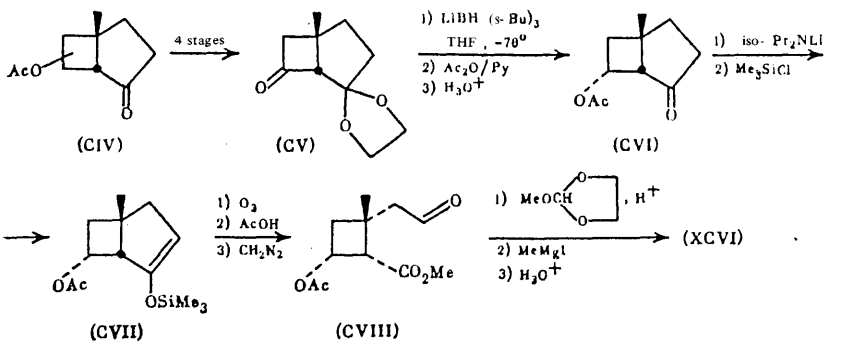
Scheme 16



In the first brief publication on the synthesis of compound (+)-(XCVI) three approaches, which must be regarded as extremely ineffective, are discussed at once. Nevertheless, they make it possible to establish unambiguously the structure of this pheromone[95] (Scheme 16). The cyclobutane fragment of the molecule of compound (XCVI) is then formed, as for compound (LV), by photocycloaddition. In one of the variants of the synthesis, when a mixture of the photoadducts (XCIV) of vinyl acetate and the lactone (LII) was employed, a mixture of the required compound (XCVI) and its regioisomer (XCVII), which can be separated chromatographically, was obtained via a stage involving the triols (XCV). In two other variants the transformation of the photoadducts of dichloroketen and the olefin (XCVIII) or the diene (C) led respectively to the acetals (XCIX) and (CI). The former was subsequently converted into compound (XCVI) by the reductive cleavage of the C–Cl bond, while the latter was converted by a multistage procedure, including the conversion into the vinyl ether (CII) and then into the diol (CIII). The latter was transformed in four stages into the required regioisomer of the triol (XCVa), whose oxidative cyclisation yielded the required compound (XCVI).

The approach involving the transformation of a 7:2 mixture of the photoadducts (CIV) of vinyl acetate and 3-methylcyclopent-2-enone [97] (Scheme 17) proved just as ineffective. Since it was found that the dominant regioisomer behaves as a ballast compound, the first four stages, including the chromatographic stage, reduced to the isolation of the required regioisomer in the form of the ketoacetal (CV). The latter is converted with the aid of a bulky reductant initially into the alcohol with the required *endo*-configuration and then into the ketoacetate (CVI) and the silyl ether (CVII). Its ozonolysis and treatment with acetic acid and then with diazomethane lead to the aldehyde (CVIII), which is transformed by three simple operations into the required compound (+)-(XCVI) in an overall yield of ~0.15%.

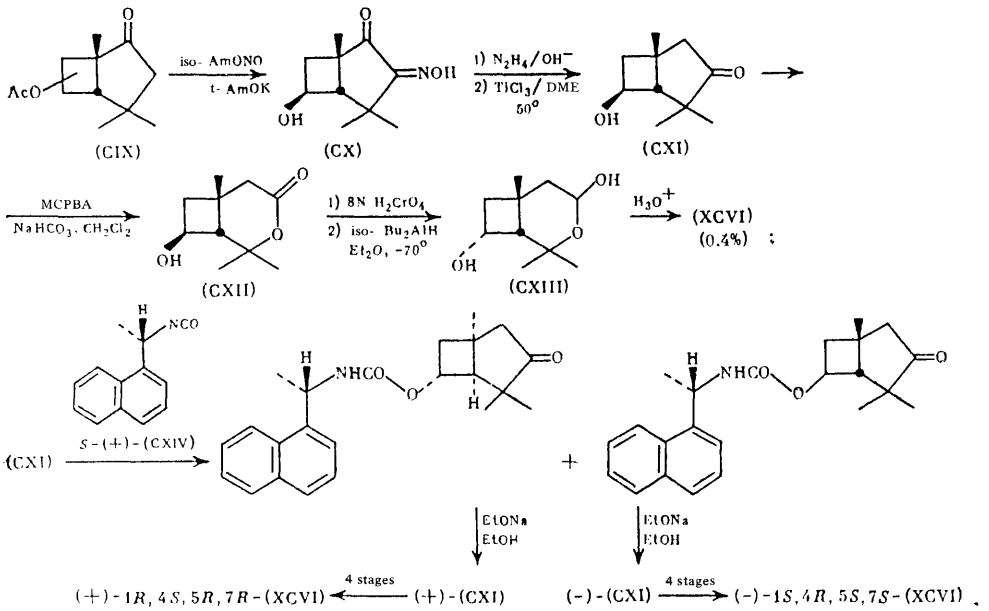
Scheme 17



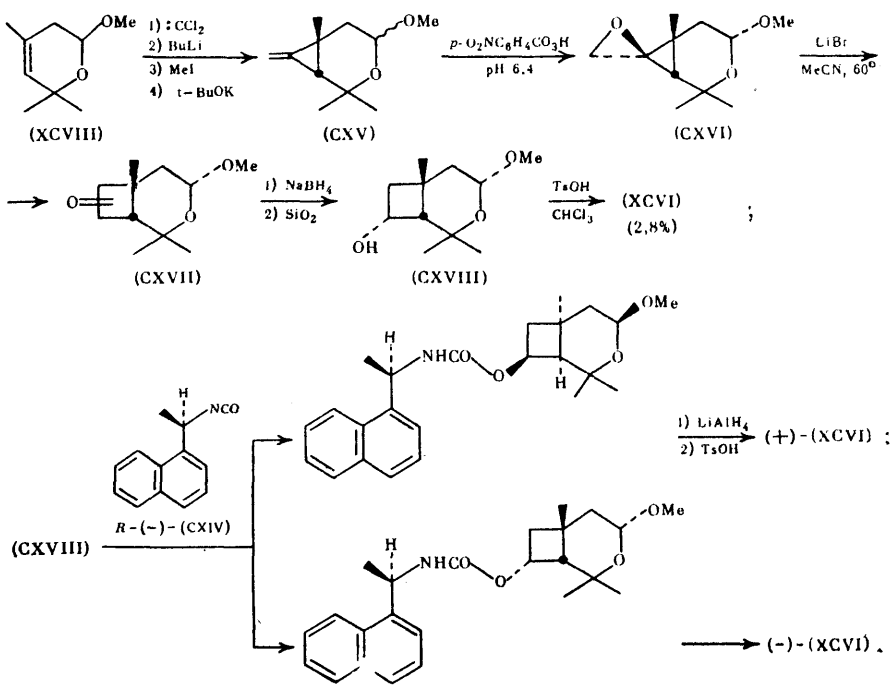
The synthesis of compound (±)-(XCVI) from the photoadducts of vinyl acetate and 2,4,4-trimethylcyclopent-2-enone, which is a mixture of the ketoacetates (CIX) in proportions of 3:2 with the required regioisomer predominating (Scheme 18), is significantly more successful. [98] In the first stage involving the "displacement" of the C=O group, the ballast isomer (CIX) is eliminated as a result of the retroaldol cleavage of the intermediate β-ketol and the oxime (CX) is converted in two stages into the ketoalcohol (CXI). The latter is transformed by the Baeyer–Villiger reaction into the lactone (CXII), whose conversion into the individual *endo*-isomer of the hydroxylactol (CXIII) is achieved by oxidation with subsequent reduction of the intermediate ketolactone with a bulky reagent. The acid-catalysed cyclisation of compound (CXIII) completes the sequence of reactions.

The synthesis of compound (±)-(XCVI) presented in Scheme 19 is even more effective. [99] The starting compound is the olefin (CXV), obtained in four stages from the dihydropyran (XCVIII). The conversion of this olefin into the epoxide (CXVI) and its subsequent rearrangement lead stereospecifically to the *endo*-isomers of the ketones (CXVII), the ratio amounting to 4:1 with the required isomer predominating. The latter is isolated chromatographically in the form of the alcohol (CXVIII) after the reduction of the mixture and is then cyclised to the required compound (XCVI).

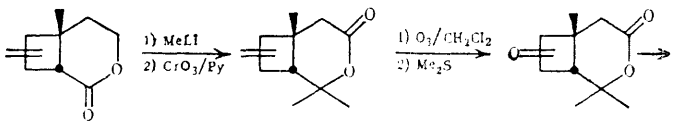
Scheme 18



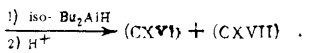
Scheme 19



The synthesis of the racemic compound (XCVI), based on the five-stage transformation of the photoadducts (CXIX) of an allene and the lactone (LII) (the mixture composition is 3:2 with the required isomer predominating) must be regarded as the most effective and shortest of the existing syntheses.[100] The conversion of the mixture of compounds (CXIX) into the olefins (CXX) and their subsequent ozonolysis afford the ketones (CXXI), which are converted, after reduction and cyclisation, into a ~2:1 mixture of the regioisomers (XCVI) and (XCVII). The required isomer (XCVI) is then isolated chromatographically in an overall yield of ~9%:



(CXIX) (CXX) 70% (CXXI) 69%



The method of synthesis of compounds (+)-(XCVI) via Scheme 20 [101] from the cyclic adducts of dichloroketen and isoprene, which are readily converted into the cyclobutanone (CXXII) in an overall yield of 39%, can also serve as a fairly effective preparative procedure. Condensation with acetone leads to the ketols (CXXIII), which are subjected to hydroboration, after reduction by a bulky reagent and protection of the secondary hydroxyl, with subsequent oxidation to the diols (CXXIV). The latter are transformed in two stages into the hydroxylactone (CXIIa), whose conversion into the required compound (XCVI) is analogous to that examined in Scheme 18.

The enantiomers of compound (XCVI) have been obtained by means of the chromatographic separation of the diastereoisomeric derivatives synthesised from the alcohol (CXI) and the *S*-(+)-isocyanate (CXIV) [98] (Scheme 18), from the alcohol (CXVIII) and compound *R*-(-)-(CXIV) [99] (Scheme 19), or from the alcohol (CXIIa) and the chiral hydroxylactone (CXXV), which can be obtained from *cis*-chrysanthemic acid[101] (Scheme 20). The subsequent regeneration of the optically active compounds (CXI), (CXVIII), or (CXIIa) and their transformation in the way described above lead to the enantiomers of compound (XCVI), among which the dextrorotary compound proved to be the natural product. X-Ray diffraction analysis of the diastereoisomers (CXXVI) made it possible to establish finally the absolute configurations of the pheromone and its optical isomer as 1*R*, 4*S*, 5*R*, 7*R* for (+)-(XCVI) and 1*S*, 4*R*, 5*S*, 7*S* for (-)-(XCVI).[101]

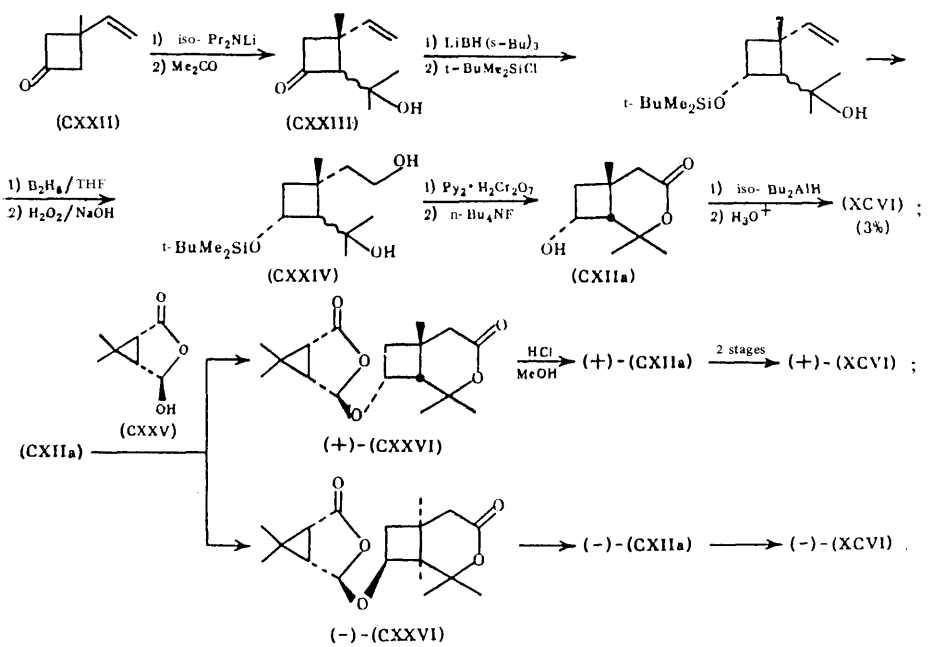
8. Periplanone B

The identification of the SP of the female of the American cockroach *Periplaneta americana* is an extremely complex chemical problem which has been recently solved successfully. As early as 1963, a structure was proposed for this pheromone[102] but it was subsequently disproved[103] and it was not until 13 years later that the structure of periplanone B (CXXX), one of the two main components of the pheromone mixture, was finally elucidated. It is a sesquiterpenoid of the germacrane series.[104-106]

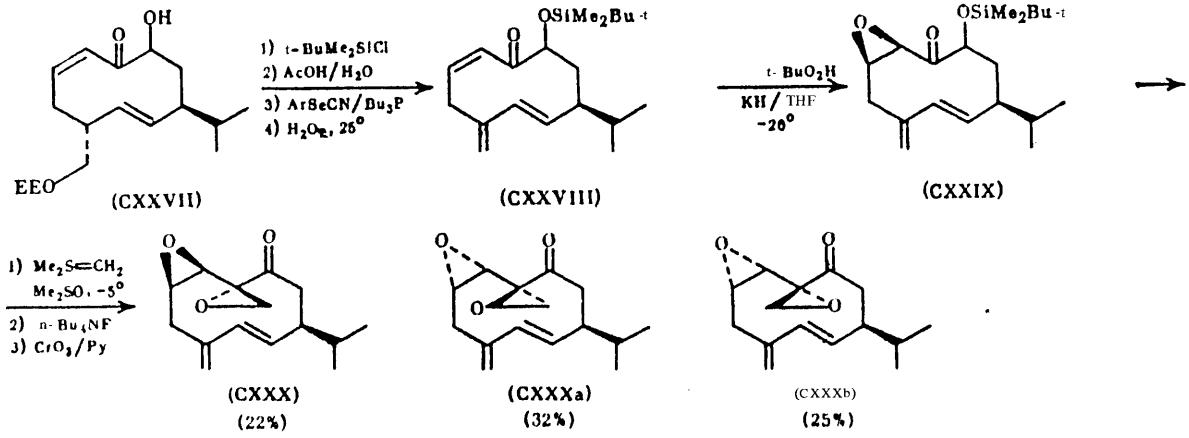
A very elegant, effective, and hitherto unique synthesis of this pheromone led to three of its four possible isomers and in addition made it possible to establish the relative configuration of periplanone B [107] (Scheme 21).

The norgermacrane ketodiol (CXXVII), containing the ethoxyethyl (EE) protecting group for one of its hydroxyls, was used as the starting compound. The silyl protection of the second hydroxyl and the liberation of the first with subsequent two-stage formation of the exo-methylene group

Scheme 20



Scheme 21



(CXXVII) (CXXVIII) (CXXIX)

(CXXX) (22%) (CXXXa) (32%) (CXXXb) (25%)

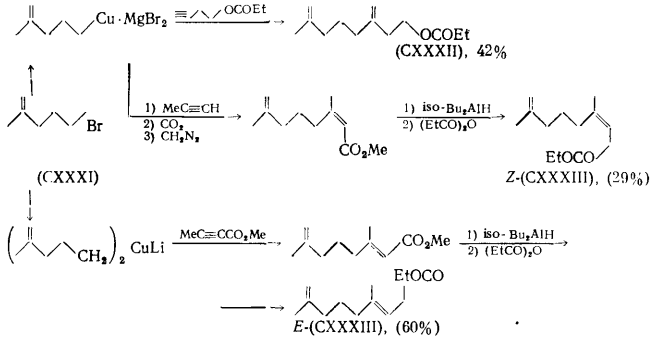
led smoothly to the triene (CXXVIII). Its selective epoxidation at the activated C=C bond yielded the epoxyketone (CXXIX). A second epoxide ring was introduced into this molecule by Corey's method. The subsequent removal of the silyl protecting group and oxidation of the resulting alcohol led to the required compound (CXXX), which exhibited a high biological activity and whose physicochemical properties were found to be identical with those of the natural specimen. The use of various methods for the introduction of the epoxide ring and a change in the sequence of the operations indicated made it possible to obtain in addition two products, (CXXXa) and (CXXXb), isomeric with periplanone B, which differ in the configurations of the two epoxide units.

9. The Pheromones of Scale Insects

Much attention has been devoted recently to the study of the pheromones of certain scale insects. Thus, a widely distributed pest on various trees, including fruit trees, namely the San Jose scale insect *Quadraspidiotus perniciosus* produces a SP whose components are the propionates of α-myrcenol (CXXXII), α-nerol *Z*-(CXXXIII), and α-geraniol *E*-(CXXXIII).[108-110]

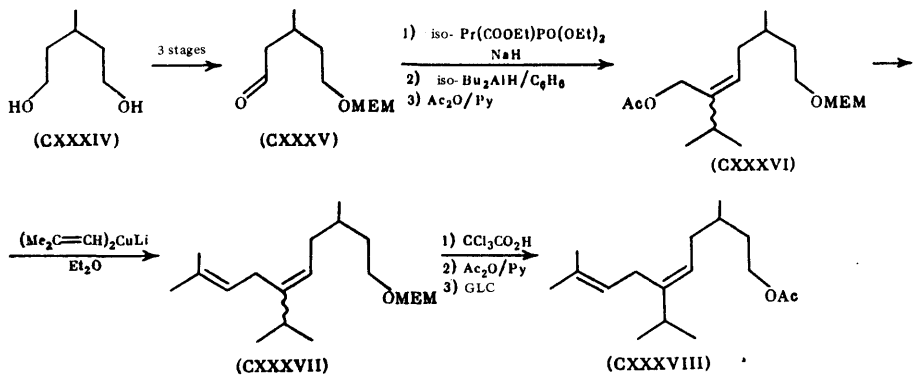
The key stage in the synthesis of each of the three components of this mixture is the addition of organocuprate derivatives of isohexenyl bromide (CXXXI) to substituted acetylenes (Scheme 22):[110,111]

Scheme 22



The SP of scale insects causing enormous damage, namely the yellow citrus scale insect *Aonidiella citrina* and the white plum scale insect *Pseudaulacaspic pentagona*, possess a more complex irregular sesquiterpene structure. The SP from the first of these insects, namely compound (CXXXVIII), has been obtained in an overall yield of 8% from the glycol (CXXXIV) in accordance with Scheme 23. This glycol was initially converted into the methoxyethoxymethyl (MEM) derivative of the aldehydoether (CXXXV). The conversion of the latter into the ethers (CXXXVI) and (CXXXVII) includes the Wittig–Horner addition of an olefin, which gives a mixture of isomers (*E*/*Z* ≅ 4:1), and substitution of type $S_{N}2$ using lithium diisobutenyl cuprate. The required compound *E*-(CXXXVIII) was isolated in the last stage by means of preparative gas–liquid chromatography (GLC).[112]

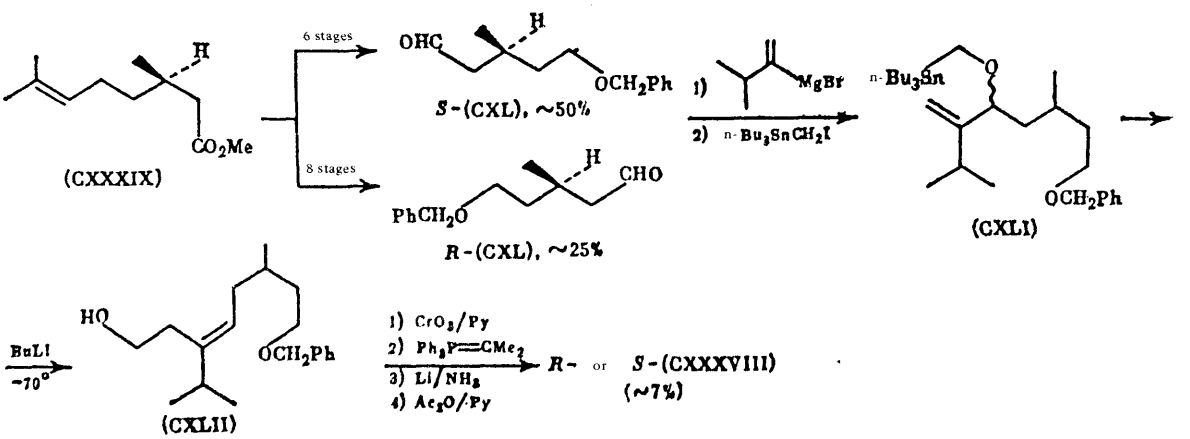
Scheme 23



(CXXXIV) (CXXXV) (CXXXVI)

(CXXXVII) (CXXXVIII)

Scheme 24

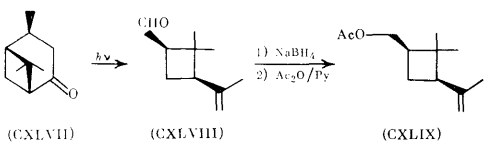


The chiral compounds (CXXXVIII), among which only the *S*-isomer proved to be biologically active, were synthesised (Scheme 24) from methyl *R*-(+)-citronellate (CXXIX) via the aldehydes *S*-(CXL) and *R*-(CXL). The conversion into the final compound (CXXXVIII) was achieved with the aid of the highly stereospecific 2,3-sigmatropic rearrangement of the stannanes (CXLI), leading to the *E*-isomers of compound (CXLII). The latter were converted into the (+)- and (-)-isomers of compound (CXXXVIII) in four fairly simple operations.[113]

Both enantiomers of the SP of the plum scale insect (CXLVI) were synthesised from the chiral aldehydes (CXLIII), which are readily available from the corresponding limonenes (Scheme 25).[114,115] The Corey–Yamamoto addition of an olefin to compound (CXLIII)[116] was first carried out using epoxyethane as the electrophile. The reaction apparently proceeds via the intermediate (CXLIV), giving rise to the trisubstituted homoallyl alcohols (CXLV) in a satisfactory yield and with exceptional stereospecificity (98% of the *Z*-isomer), the alcohol being subsequently converted into the required propionate (CXLVI). Comparison of the spectroscopic and biological properties of the synthetic and natural specimens showed that the latter has the 3*Z*, 6*R*-configuration.

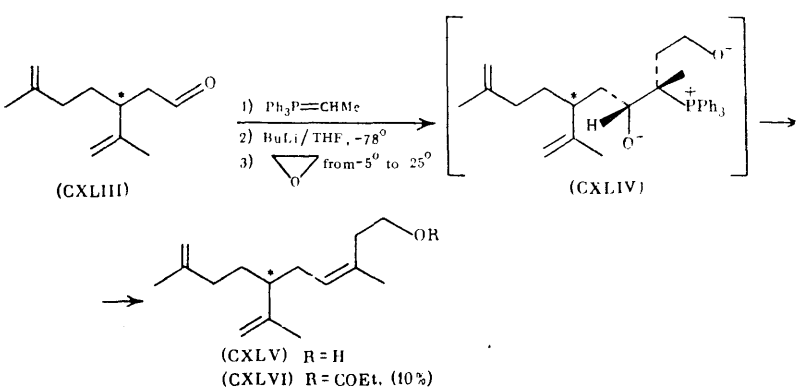
10. Other Sex Pheromones

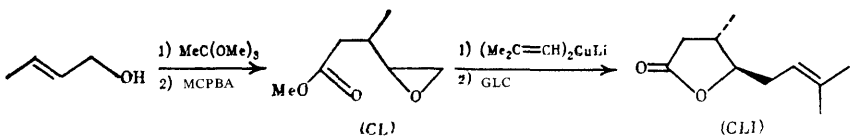
The citrus mealybug *Planococcus citri* is a citrus pest. Both enantiomers of its SP (CXLIX) have been recently synthesised by the photochemical cleavage of the corresponding *cis*-verbanones (CXLVII) (the yield was not indicated); the aldehydes formed in this process, for example, compound (CXLVIII), were then converted in two stages into the required acetates, among which the (+)-isomer (CXLIX) proved to be biologically active:[117]



The monoterpene lactone (CLI) has been identified as the SP of the pyralid Eldana saccharina—a sugar cane and maize pest. The synthesis of this compound, described without experimental details,[118] was achieved starting with crotyl alcohol via the epoxyester (CL); the required *trans*-isomer (CLI) was obtained by the addition of lithium di-isobutenyl cuprate:

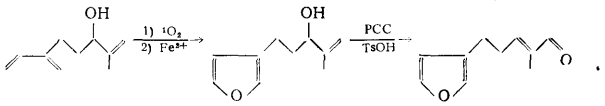
Scheme 25





(CL) (CLI)

Perillenal (CLII) is the SP of the pine sawfly *Neodiprion sertifer*, which causes significant damage to coniferous trees.[119] The pheromone (CLII) has been synthesised from the alcohol (XLVII), which can be obtained from myrcene (see above), by converting the 1,3-diene component of the molecule into a furan component and by oxidation with simultaneous allyl isomerisation of the alcoholic fragment:[67]



(XLVII) (CLII), 61% (CLII), 35%

It is noteworthy that compound (CLII) had been used earlier as an intermediate in the synthesis of perillene and dendrolasin (see Section IV, Scheme 32).

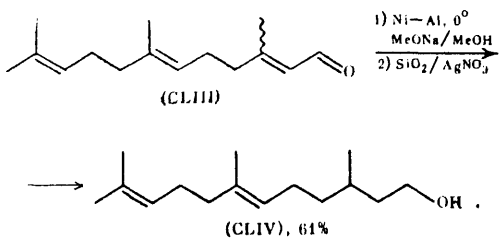
III. TRACK PHEROMONES AND TERRITORIAL MARKERS

Social insects widely employ chemical signals which determine the direction of the movement of separate individuals to the living quarters, a source of food, etc. Among substances controlling such behavioural responses, various linear and cyclic derivatives of the sesquiterpene and diterpene series have been discovered.

1. Terrestrol

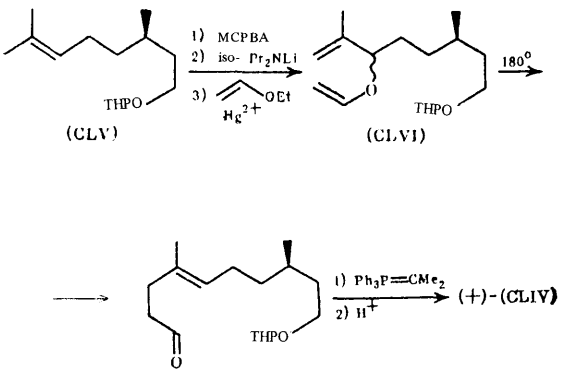
S-(-)-2,3-Dihydrofarnesol (terrestrol) (CLIV) is produced by the males of the bumble bee *Bombus terrestris* and a number of other species of this family of insects[120-123] and is used by them as a marker on the route covered by their movements.

The simplest synthesis of compound (±)-(CLIV) consists in the reduction of *Z*/*E*-farnesal (CLIII) (readily available from dehydronerolidol) in the presence of the Ni–Al alloy and methanolic alkali:[124]



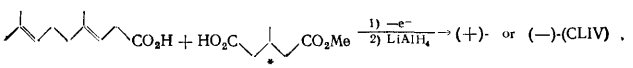
(CLIII) (CLIV), 61%

The synthesis of the optical isomers of compound (CLIV) has also been described. One of the syntheses is based on the ether (CLV) of *R*-(+)-citronellol, which is converted in the first three stages into a mixture of the diastereoisomers of the allyl vinyl ether (CLVI). Their subsequent Claisen rearrangement and combination with an olefin lead ultimately to *R*-(+)-(CLIV) in an overall yield of ~6%:[125]



(CLV) (CLVI)

In the second case both optical isomers have been obtained using homogeranic acid (CLVII) with the half-ester of D- or L-3-methylglutaric acid (CLVIII) in the key stage involving the Kolbe coelectrolysis:[126]



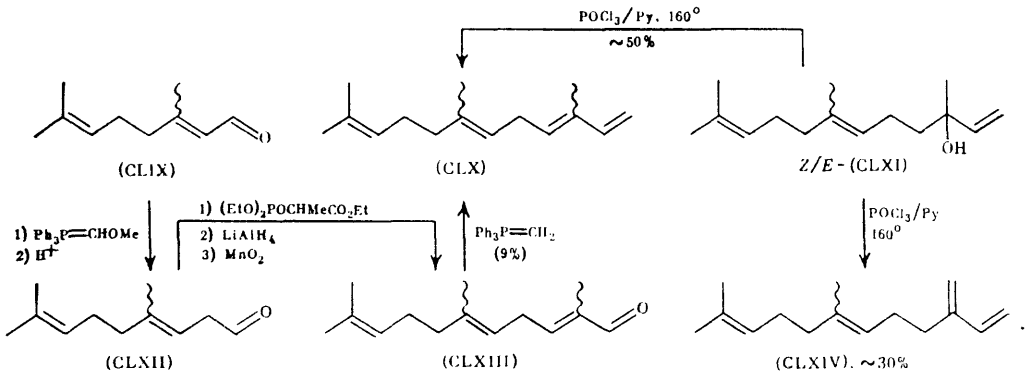
(CLVII) (CLVIII) ~(8%)

2. α-Farnesenes and Allofarnesenes

It has been shown recently that certain species of ants use various farnesene isomers, produced by the Dufur gland located in the rear part of the abdomen, as track pheromones and territorial markers. Thus *Z*,*E*-α-farnesene (CLX) has been detected in individual *Myrmica* species,[127] while the *E*,*E*-isomer of compound (CLX) [128] as well as *Z*,*Z*,*Z*-allofarnesene (CLXX) have been found in addition in the red ant *Solenopsis invicta*.[129,130]

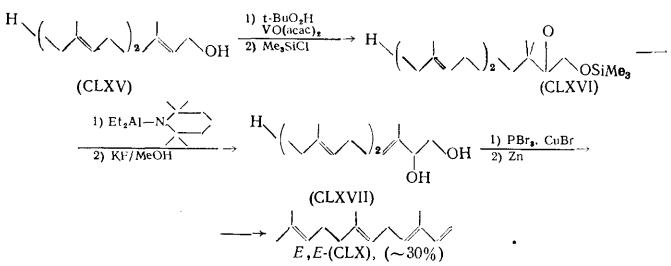
Some of these sesquiterpenes had been isolated still earlier from other natural sources and their synthesis, also giving rise to a series of possible regioisomers and stereoisomers, including β-farnesenes (CLXIV), has been achieved on the basis of citral (CLIX) and nerolidols (CLXI) (Scheme 26). The conversion of compound (CLIX) into the *Z*,*E*- and *E*,*E*-tetraenes (CLX) under consideration involves threefold combination with an olefin and the intermediate formation of the aldehydes (CLXII) and (CLXIII),[131] while vigorous dehydration of compound (CLXI) yields immediately all the isomers of the farnesenes (CLX) and (CLXIV) mentioned above.[128]

Scheme 26



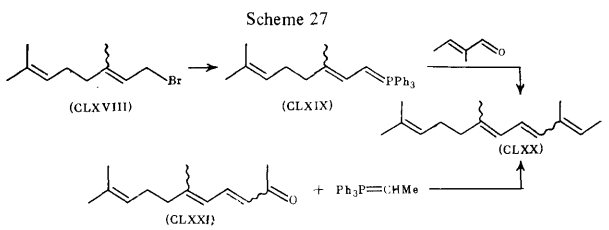
The low yields and the evident non-selectivity of the reactions considered above make it unlikely that the syntheses of α-farnesenes on the basis of the approaches described will be of much use.

The elegant synthesis of compound *E,E*-(CLX) from farnesol (CLXV), involving its selective epoxidation and rearrangement of the epoxide (CLXVI), is free from the above disadvantages. The diol (CLXVII) obtained in a high yield as a result was smoothly converted into the geometrically pure *E,E*-(CLX):[132]



Two approaches have been used (Scheme 27) in the syntheses of all the possible isomers of allofarnesene (CLXX), which made it possible to establish the configuration of the pheromone, which has the *Z,Z,Z*-geometry, as already mentioned.[130] The first synthesis involves the conversion of geranyl and neryl bromides (CLXVIII) into the corresponding phosphoranes (CLXIX) with subsequent addition of an olefinic group by these compounds to tiglic aldehyde, while the second synthesis involves an increase in the length of the isomeric pseudoionones (CLXXI) by a two-carbon fragment with the aid of ethylidenetriphenylphosphorane. It is difficult to estimate their effectiveness (the analysis has been carried out by GLC), but the simplicity of the chosen scheme is evident.

Scheme 27



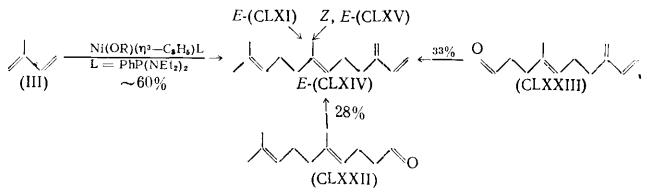
IV. FEAR PHEROMONES

Social insects widely employ chemical signals whose role reduces to warning of danger threatening members of the colony, which ultimately assists in the preservation of the species.

1. *E*-β-Farnesene

When attacked by a predator, many moth species instantly generate a mixture of substances with a protecting action and exhibiting simultaneously a repellant activity in relation to neighbouring members of the colony. The main component of this mixture is in many instances *E*-β-farnesene (CLXIV), which functions as a fear pheromone.[133–139] Special studies have shown that the *E*-geometry of the molecule of the given compound plays a decisive role in its function.[140,141]

The simplest pathway to compound *E*-(CLXIV) consists in the Ni(0)-catalysed trimerisation of isoprene.[142,143] Among other methods, mention should be made of the dehydration of nerolidol *E*-(CLXI)[128] and the six-stage transformation of farnesol *Z,E*-(CLXV),[132] which has been carried out in full conformity with the schemes for the synthesis of α-farnesenes discussed above. Finally, the synthesis of *E*-(CLXIV) from the relatively readily available C_{12}-aldehydes (CLXXII)[48,144] and (CLXXIII)[145] by standard procedures, involving the lengthening of the isoprenoid chain by a three-carbon fragment, has been described:

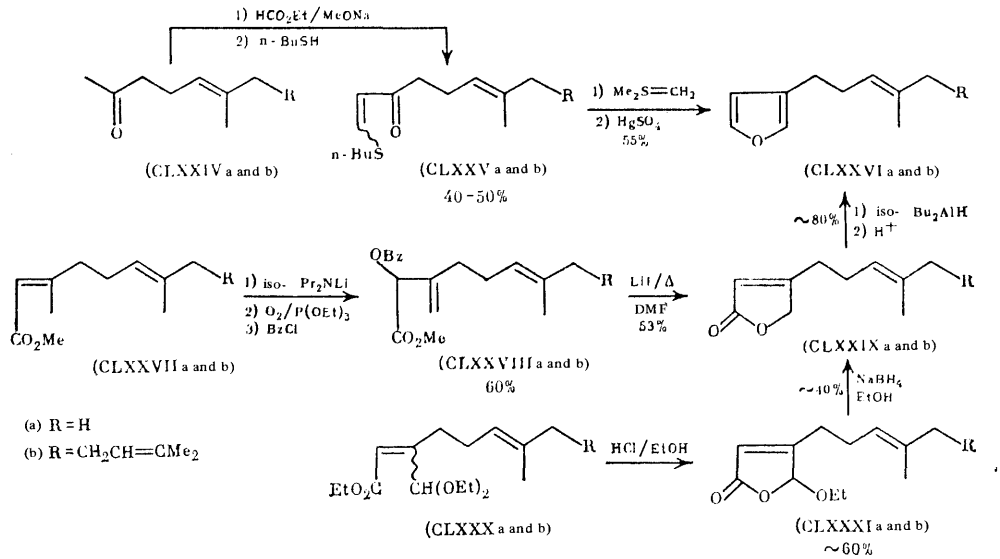


2. Perillene and Dendrolasin

Certain ant species produce perillene (CLXXVIa) and dendrolasin (CLXXVIb) as fear pheromones; these furanoterpenes can in addition fulfil protecting functions.[146,147]

A whole series of syntheses of both pheromones have now been described. One group of syntheses is based on the construction of a 3-substituted furan ring, while those in another begin with furan derivatives already synthesised

Scheme 28

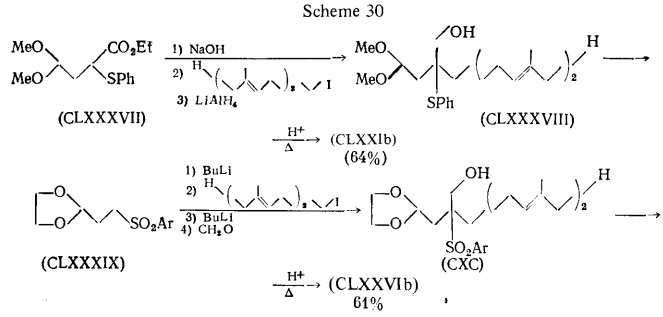


having a functional group at C(3). Thus formylation of methylheptanone (CLXXIVa) or geranylacetone (CLXXIVb) in accordance with Scheme 28 and the interaction of the corresponding thiovinyl ketones (CLXXV, a and b) with dimethylsulphonium methylide yield, after intramolecular cyclisation of the intermediate epoxides and the cleavage of the C–S bond, the required furanoterpenes (CLXXVI, a and b) in an overall yield of ~25%.[148] The conversion of the monoterpene esters (CLXXVIIa) and (CLXXXa) and the sesquiterpene esters (CLXXVIIb) and (CLXXXb) into the same products reduces to the formation of the corresponding furanones (CLXXIX, a and b) and includes the formation of the intermediate allyl benzoates (CLXXVIII, a and b)[149] or the hemiacetals (CLXXXI, a and b).[150] The conversion into the furans (CLXXVI) is carried out almost quantitatively by the acid treatment of the lactols arising on mild hydride reduction of the furanones (CLXXIX).

Other methods of synthesis of compound (CLXXVI) are presented in Scheme 29. According to one of them,[151] the aldehyde (CLXXXIII) is made to combine with an olefinic fragment by means of the phosphorane (CLXXXII), which is readily obtainable from maleic anhydride, to form the half-ester (CLXXXIV), which is transformed as a result of three simple operations into compound (CLXXIXa). In another method the condensation of the chlorozinc derivative (CLXXXVI) with the bromofuranone (CLXXXV), catalysed by a palladium complex, yields the required product (CLXXIXb) in a single stage.[152] Despite the evident effectiveness of both methods, the limited availability of the initial aldehyde (CLXXXIII) and the bromo-derivative (CLXXXV) must be emphasised.

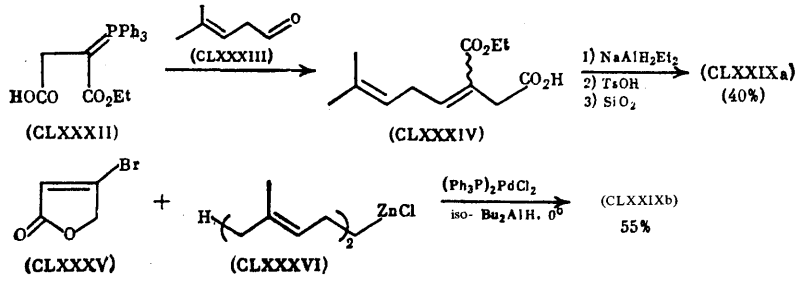
An approach to the synthesis of dendrolasin (CLXXVIb) based on the sulphur-containing acetals (CLXXXVII) and (CLXXXIX) (Scheme 30) is of definite interest. Their deprotonation and subsequent alkylation by homogeranyl iodide followed by the reduction of the ester group or condensation with formaldehyde lead to the corresponding primary alcohols (CLXXXVIII) and (CXC) in high yields. These alcohols are readily converted into the required product (CLXXVIb) by refluxing with toluene-*p*-sulphonic acid in benzene.[153]

Scheme 30



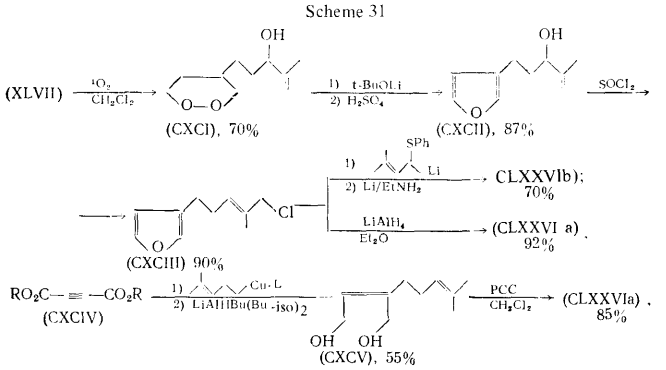
Among other methods for the formation of the hetero-aromatic ring of the pheromones (CLXXVI) based on linear precursors, mention must be made of those based on the photochemical oxidation of the 1,3-diene component of the alcohol (XLVII), which leads to the peroxide (CXCI),[66] and

Scheme 29



on the synthesis of the glycol (CXCV) from acetylenedicarboxylic ester (CXCIV) [154] (Scheme 31). The isomerisation of compound (CXCI) on treatment with a strong base and dehydration of the intermediate lactol afford the furan carbinol (CXCII) which is then converted into the allyl chloride (CXCIII). Its hydrogenolysis or the addition of a C_5 unit to it lead ultimately to compound (CLXXVIa) or (CLXXVIb) respectively. Perillene (CLXXVIa) has been obtained almost quantitatively in a single stage by oxidising the glycol (CXCV) with PCC.

Scheme 31

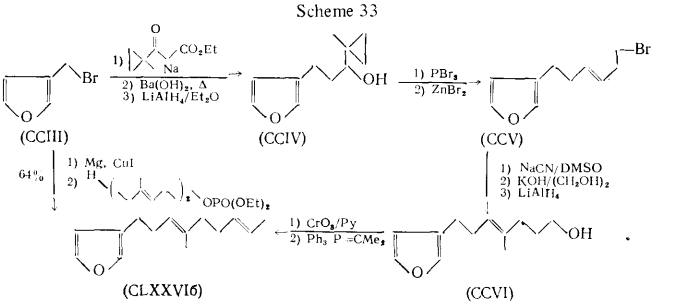


As already mentioned, the syntheses of compound (CLXXVI) in the second group begin with the furan C_5-synthones and reduce to the formation of the isoprenoid side chain. Scheme 32 illustrates one of the approaches using β-furylmethanol (CXCVII) with a Claisen type rearrangement as the key stage. Thus thermolysis of the vinyl ester (CXVI) gave a moderate yield of perillenal in the form of a mixture with $E/Z \cong 5:1$. Repetition of the above operations using the allyl alcohols (CXCIX) ($E/Z \cong 2:1$) led to the aldehyde (CCI) and both products, (CLII) and (CCI), were converted in accordance with the same scheme into the corresponding furanoterpenes (CLXXVI),[155] whose overall yields cannot be estimated. In another version[156] the alcohol (CXCVII) was converted into the aldehyde (CXCVIII) by increasing the length of the chain by a two-carbon fragment in a five-stage process. The aldehyde gave rise to the vinyl ether (CC) in two stages and thermolysis of the ether resulted in the formation of the aldehyde (CCII). The addition of an olefinic fragment to compounds (CXCVIII) and (CCII) by the Wittig method yields the required products (CLXXVIa) and (CLXXVIb) respectively.

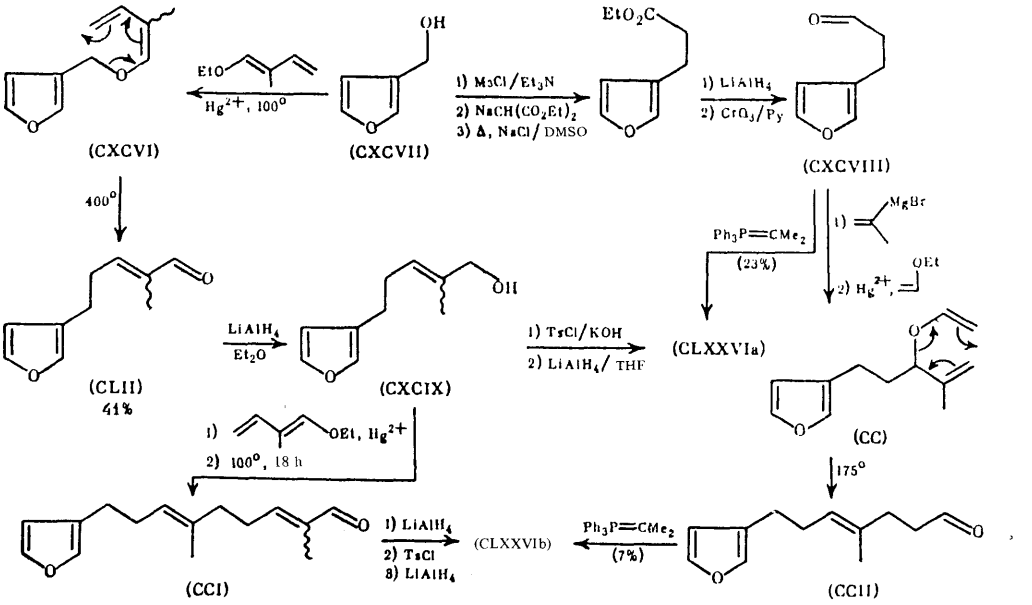
One of the first syntheses of dendrolasin (Scheme 33) is based on the conversion of the bromo-derivative (CCIII) into the cyclopropylcarbinol (CCIV). Its homoallyl rearrangement proceeds stereospecifically, giving rise to the bromo-derivative (CCV). The increase of the side chain of the latter by one carbon atom with formation of the alcohol (CCVI) as well as the conversion of the latter into compound (CLXXVIb) were achieved by standard methods, but the yields of the products in the overall scheme were not indicated in the study under discussion.[157]

The single-stage pathway to compound (CLXXVIb), starting with the same bromo-derivative (CCIII) and consisting in the CuI-catalysed condensation of the latter in the form of a Grignard reagent with geranyl diethyl phosphate, appears to be more effective.[158] The allyl regioisomer is formed simultaneously in 17% yield and is separated chromatographically from compound (CLXXVIb).

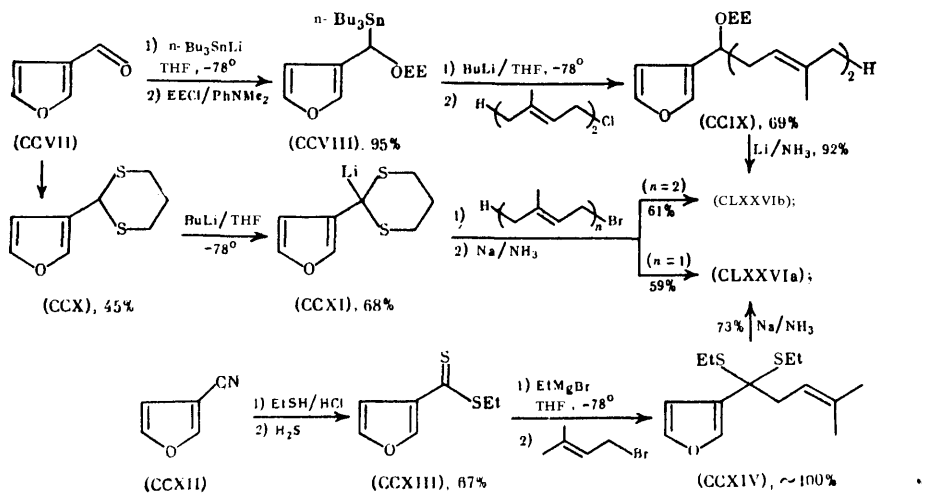
Scheme 33



Scheme 32



Scheme 34



A large group of syntheses of the pheromones (CLXXVI) begin with β-formylfuran (CCVII) and β-cyanofuran (CCXII) (Scheme 34). Thus stannylation of compound (CCVII) gives rise to a carbinol, which has been isolated in the form of the ethoxyethyl ether (CCVIII). Its metallation and alkylation lead to the derivative (CCIX), whose hydrogenolysis gives rise to dendrolasin in an overall yield of 60%.[159] The syntheses of compounds (CLXXVI) by the alkylation of the lithio-derivative (CCXI), the dithioacetal (CCX),[160] and the related magnesio-derivative, formed *in situ* on interaction of the thioether (CCXIII) with an excess of ethylmagnesium bromide,[161] proved to be just as effective. The reductive cleavage of the intermediate dithioacetals of the type (CCXIV) has been achieved in both cases without complications on treatment with sodium in liquid ammonia.

In conclusion, it must be emphasised that the present review covers data on the synthesis of only monoterpene and sesquiterpene pheromones. The methods of synthesis of certain linear and macrocyclic diterpenoids, identified as pheromones in various insect species, have not been included.

The data examined thus illustrate the abundance of the synthetic procedures, both traditional and most modern, which are used to construct the molecules of a wide variety of isoprenoid pheromones. In the immediate future one may expect a further improvement of such procedures as a result of the elucidation of the structures of new compounds and also in view of the constantly growing need for the synthesis of low-molecular-weight bioregulators belonging to this important class.

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During the preparation of the manuscript for the press, a number of publications concerning its individual sections have appeared. Thus the racemic ipsenol and ipsdienol have been obtained recently in high yields by the condensation of two C_5 fragments—of the silane (IX) with isovaleraldehyde and dimethylacrylic aldehyde respectively in the presence of Bu_4NF [162] or with the chlorides of isovaleric and dimethacrylic acids in the presence of $TiCl_4$.[163] The synthesis of the above pheromones as a result of the reaction of the bromo-derivative (IV), catalysed by the Zn/Ag couple, with the nitriles of the above acids is also effective.[164] The Kondakov acylation of isoprene by the chloride of dimethylacrylic acid using $EtAlCl_2$ as the catalyst affords, after the reduction of the intermediate ketone, ipsdienol in 12% yield.[165] Two extremely effective syntheses of compound (XXXII) from myrcene have also been published. In one case myrcene is epoxidised at the trisubstituted C=C bond with subsequent isomerisation of the epoxide on treatment with MeMgI,[166] while in the other case it is converted by a standard method[67] into amitinol, whose acetate isomerises on treatment with $HClO_4$.[167] Both enantiomers of compound (XXXII) were obtained in this process by the chiral reduction of ipsdienone, albeit in a low optical yield.[167]

The key stage in the six-stage syntheses of racemic derivatives of grandisol and lineatin has been the intramolecular cyclisation of 4-bromo-1-trimethylsilylbutyne[168] and 2,5,5-trimethylocta-1,6,7-trien-4-ol [169] respectively. The details of the synthesis of the racemic compound (XCVI) considered in Scheme 20 [101] and of both its enantiomers have been published recently.[170]

The pheromone (CXCIX) of the citrus mealybug has been synthesised non-stereospecifically by adding organocuprates to sulphonylbicyclobutanes.[171] On the other hand, two procedures for the preparation of eldanolide (CLI) from *S*-(+)-glutamic acid and the methyl ester of *R*-(+)-citronellic acid[173] respectively, which have made it possible to establish the 3*S*, 4*R*-configuration of the natural product, are characterised by a high enantioselectivity. Perillenal has been obtained by the allyl oxidation of perillene by SeO_2 in 42% yield.[174]

Farnesene *E*-(CLXIV) has been synthesised recently by the photolysis of 6*E*-farnesyl iodide in 80% yield;[175] the synthesis of this tetraene by the $ZnCl_2$-catalysed condensation of geranyl bromide *E*-(CLXVIII) with isoprenylstannane has been somewhat less successful.[176]

The key stage in the synthesis of perillene (yield not indicated) has been the radical cyclisation of a derivative of γ-dimethylallylpropargyl alcohol.[177] A further three approaches to β-prenylfurans (CLXXVI) from β-substituted furan C_5-synthones have also been published. Thus the reaction of the tosylate obtained from the alcohol (CXCVII) with lithium diprenyl cuprate[178] or of the bromo-derivative (CCIII) with a C_5 π-allylnickel complex[174] gives rise to perillene in 15% yield. On the other hand, a high yield of this compound as well as dendrolasin has been achieved by the Grignard reaction of the same bromo-derivative

(CCIII) with prenyl and geranyl diethyl phosphates respectively.[179]

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