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Synthetic and chemical studies on pheromones of some forest pest insects

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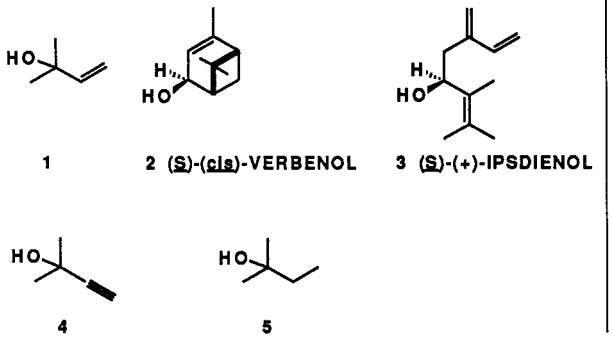
Abstract - Recent studies on pheromones and related chemical signals of some forest pest insects (*Ips typographgus, Pityogenes chalcographus* and *Neodiprion sertifer*) are presented. Synthetic strategies and separation procedures which provide products of very high isomeric and enantiomeric purities are emphasized. Analytical methods for the determination of the enantiomeric compositions of monoterpene hydrocarbons are presented. These methods have been applied for studies of the transformation of a host-plant constituent, (-)- α-pinene, to an essential pheromone constituent, (4 *S*)-*cis*-verbenol, in the hind guts of *Ips typographus*. - The application of a highly enantioselective method for α-alkylation of alkanoic acids and ketones using a chiral auxiliary of pyrrolidine type is presented. Convenient synthetic procedures based on the use of hydrolytic enzymes have been developed for the preparation of these chiral auxiliaries.

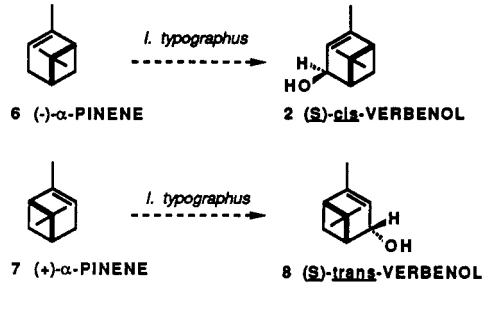
As part of an investigation of forest pest insects, which at present is carried out in Sweden in collaboration with biologists and forest entomologists, we have encountered a number of problems, which have required the development of new synthetic methods as well as of advanced chromatographic techniques. In the present paper some results regarding pheromones and related chemical signals of two bark beetles (*Ips typographus* and *Pityogenes chalcographus*) and of the red pine saw-fly (*Neodiprion sertifer*) will be presented.

The spruce bark beetle, *I. typographus*, is responsible for considerable damage on forest plantations of Norway spruce, *Picea abies* (L.) Karst. 2-Methyl-3-buten-2-ol (**1**), (*S*)-*cis*-verbenol (**2**) and (*R*)-ipsdienol (**3**) have been identified as components of the aggregation pheromone of this insect (Scheme 1).[1-4] A mixture of these components is used as a commercial lure for mass trapping of the beetle. In collaboration with a Czechoslovakian research group we have recently found that 2-methyl-3-buten-2-ol (**1**) can be replaced by the corresponding acetylenic analogue **4** in baits for trapping *Ips typographus*.[5,6] The saturated derivative **5** also exhibits a similar biological activity. These findings are unusual in pheromone chemistry. To our knowledge, there are no previous cases in which an essential bark beetle pheromone component can be effectively replaced by a synthetic analogue.

Scheme 1



Scheme 2



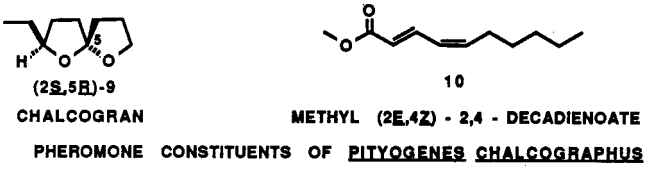
Studies on pheromones and related chemical signals require efficient analytical methods for the determination of enantiomeric compositions. Such methods are also useful for the analysis of semiochemicals since the chirality and enantiomeric composition are important parameters for biological activity. We have developed methods for the de-termination of the enantiomeric composition of monoterpene hydrocarbons.[7,8]

(-)-α-Pinene (**6**) is known to be an essential host compound for the spruce bark beetle, since it is converted in the beetle to *cis*-verbenol (**2**), which is an important constituent of the aggregation pheromone of the beetle (Scheme 2). Thus, the presence of (-)-α-pinene (**6**) in the wood oil of the host tree, *Picea abies*, is important for the beetle. (+)-α-Pinene (**7**), on the other hand, is converted in the beetle to *trans*-verbenol (**8**), which is not an aggregation pheromone constituent. The biological significance of *trans*-verbenol (**8**) is still not settled.

We have shown that the enantiomeric composition of α-pinene varied considerably between spruce trees of different genetic origin. There was also a strong correlation between the chirality of α-pinene in a host tree and the *cis/trans* ratio of verbenols produced by the bark beetles which infested the tree.[7] We are at present investigating the genetic importance of the enantiomeric composition of alpha-pinene in Norway spruce. There may be a possibility to find clones which only produces (+)-α-pinene and therefore should be more resistant to spruce bark beetle attacks.

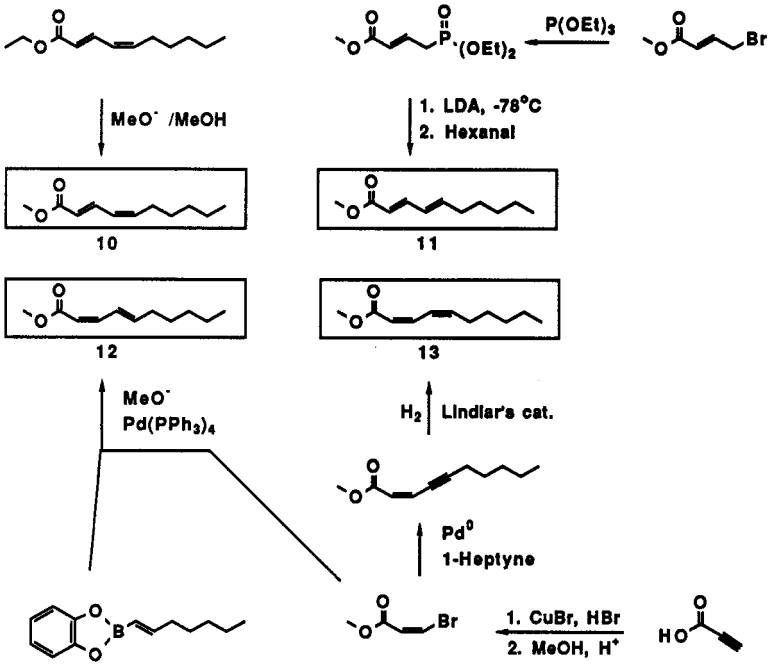
During our studies of another bark beetle, *Pityogenes chalcographus*, we were confronted with the problem of preparing long-chain pheromones of diene nature. This insect shows only low attraction towards the previously known pheromone component chalcogran (**9**, Scheme 3). However, methyl (2*E*,4*Z*)-2,4-decadienoate (**10**) has now been identified as an additional pheromone component. Adding this diene ester (**10**) to chalcogran (**9**) causes a 35-fold increase in trap catches of the beetle.[9]

Scheme 3



There are several syntheses of 2,4-dienoic acids reported in the literature.[10] However, none of the methods provide isomerically pure products. Since the behavioral response usually is very sensitive to changes in the stereoisomeric composition of a pheromone, we developed synthetic procedures in order to obtain all four isomers of methyl 2,4- decadienoate (**10**-**13**). Our synthetic strategies are outlined in Scheme 4.[10]

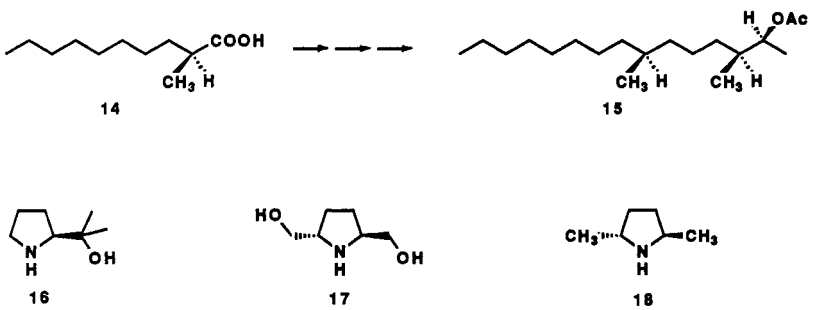
Scheme 4



Crystallization of urea inclusion complexes were used in the final purification procedures. All four isomers of chalcogran were also prepared in a pure state.[11] The biological tests showed that only the (2*E*,4*Z*)-isomer **10** of the diene esters was active together with chalcogran and that the (2*S*,5*R*)-isomer of chalcogran was the most active isomer. There was no synergistic or inhibitory effects of the inactive or less active isomers.

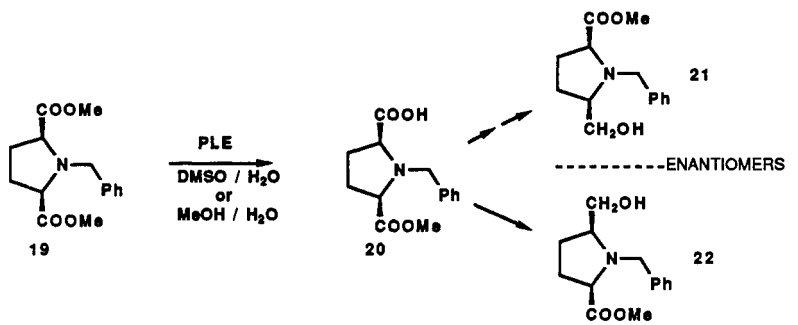
The chiral specificity of the pheromone constituents of the red pine saw-fly (*Neodiprion sertifer*) is most interesting and urged for efficient and selective synthetic procedures.[12,13,14] The need for enantiomerically pure 2-methyldecanoic acid (**14**) as a starting material for a synthesis of an essential pheromone component of this insect (diprinyl acetate, **15**) initiated studies on asymmetric alkylations.[13]

Scheme 5



We have developed methods of preparing optically pure 2-alkylalkanoic acids based on α-alkylations using proline derived chiral auxiliaries.[13] An efficient reagent is the dimethyl substituted prolinol derivative **16** (Scheme 5), but reagents with C2-symmetry such as *trans*-2,5-disubstituted pyrrolidine derivatives (*eg* **17** and **18**, Scheme 5) are also most useful in this context. Enzyme catalyzed reactions are suitable for the preparation of chiral auxiliaries and synthons of this type.[15,16,17]

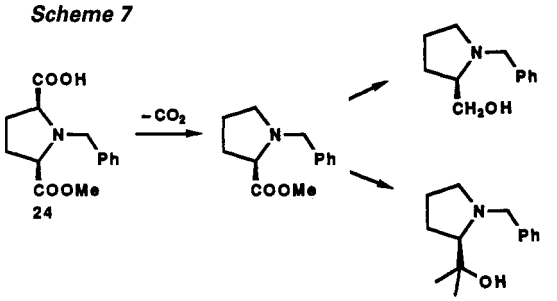
Scheme 6



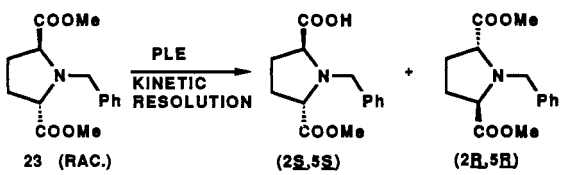
The PLE catalyzed hydrolysis of the *cis*-diester **19**, which is a readily available starting material, affords the chiral monoester **20** (Scheme 6). The product is obtained optically pure, when the enzymatic reaction is carried out in 25 % aqueous dimethyl sulphoxide (DMSO) or in 10 % aqueous methanol. This is an illustrative example which demonstrates that there are drastic solvent effects on the enantioselectivity in enzyme catalyzed reactions.[16]

A limiting factor in the use of enzymes for asymmetric organic syntheses is that only one enantiomer of the desired product can be produced. This disadvantage can sometimes be overcome. Thus the monoester **20** can be transformed to either enantiomer of the carbomethoxy prolinol (**21** and **22**), which are versatile starting materials *eg* for pyrrolidine alkaloids. The monoester **20** can also be transformed into derivatives of the "unnatural" (R)-proline series (Scheme 7).[17]

Scheme 7



Scheme 8



Studies on the enzymatic hydrolysis of the racemic trans-diesters **23** are at present carried out in our laboratory (Scheme 8). Successful kinetic resolutions have been performed, which opens the way to the syntheses of powerful chiral auxiliaries of C2-symmetry.

The intention of my presentation is to stress the significance of advanced research efforts in organic chemistry for successful research on biologically related problems and in natural product chemistry. The development of synthetic methods and separation procedures which provide products of high isomeric and enantiomeric purities are most important.

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