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Summary of a PhD dissertation entitled:

Stereoselective reactions of enolate ions of butanodiacetal derivatives and their application in the synthesis of disparlure and monachalure

Pheromones constitute the most common group of compound used by organisms for chemical communication that evoke specific behavioral responses within species. They are usually mixtures of several compounds with one dominant component. In insects pheromones perform many functions, such as sexual attraction, alarm, defense, aggregation, marking of territory or trail. Many of them have chiral centers and usually these atoms determine their biological activity, and opposite stereoisomers may have quite different activities. Sometimes the opposite isomer has no biological activity but does not influence the perception of the pheromone. More frequently, however, even a small content of the unnatural isomer completely prevents the behavioral response. Stereoisomers may act as pheromones in different species or each may act on a different sex in the same species. All these phenomena require preparation of such chiral pheromones for biological studies and practical applications in optically pure form.

The Gypsy moth (*Lymantria dispar*) and the closely related nun moth (*Lymantria monacha*) utilize (+)-disparlure, an epoxy compound with two chiral centers at the epoxy ring ((7*R*,8*S*)-7,8-epoxy-2-methyloctadecane), as the main component of their sex pheromones. The pheromone blend of the nun moth also contains (–)-disparlure ((7*S*,8*R*)-7,8-epoxy-2-methyloctadecane), (+)-monachalure ((7*R*,8*S*)-*cis*-7,8-epoxyoctadecane), (-)-monachalure ((7*S*,8*R*)-*cis*-7,8-epoxyoctadecane) and their olefinic precursors. For Gypsy moth high optical purity of (+)-disparlure (>98% ee) is required to evoke male's sexual response and even small content of (–)-disparlure abolishes the biological activity.

Due to the great economic importance of the Gypsy moth and the nun moth, many synthetic routes for preparation of (+)- and (–)-disparlure have been developed to monitor and control their populations. These methods used various approaches to ensure the required configuration of asymmetric centers determining biological activity of these compounds. They included application natural chiral substrates, such as L-glutamic acid, D-glucose,

sorbitol, or enantioselective reactions, such as the Sharpless epoxidation, asymmetric dihydroxylation, chloroalliloboronation or organocatalysis.

The aim of this work was to develop a new synthetic procedure to obtain both isomers of disparlure and monachalure from butanediacetal derivatives of L-tartaric acid esters. Originally these compounds were intended for application in enzymatic reactions to determine specificity of epoxide hydrolases, which I identified in both the Gypsy moth and the nun moth and partially cloned in my Master's thesis research. However, development of several new synthetic approaches associated with stereoselective reactions of enolate ions of butanediacetal derivatives used as substrates and intermediates in the designed synthetic route redirected my research and limited the topic of my dissertation to pure organic synthesis.

The synthetic route started with generation of appropriate configurations on carbon atoms C_2 and C_3 of the butanodiacetal derivatives of L-tartaric acid. This goal was achieved by isomerization of the *trans* butanediacetal derivative with two thioethyl ester groups at carbon atoms C_2 and C_3 to the *cis* derivative. The substrate for this reaction was obtained by transesterification of a corresponding butanediacetal with two methyl ester groups. Results of the isomerization reaction strongly depended on the amount of the base, the time of existence of the enolate ion, the temperature, the proton source used for reprotonation, and the presence of additional substances that stabilize enolate ions (hexamethylphosphoramide and lithium chloride). Under best conditions, the ratio of the *cis* to *trans* isomers was 6.3:1, which represents a 4-fold improvement over the results reported previously in the literature. The *cis* isomer obtained in this reaction was used as a precursor for attachment of the alkyl chains of the pheromone molecules. However, selective reduction of one of the thioester groups in this compound gave a complex mixture, which could not be used in Wittig reactions. Therefore, a different approach was tried. During transesterification of the dimethyl ester derivative to the dithioester formation a small amount of a monothioester was observed. This compound could be an attractive substrate for the synthesis of isomers of disparlure and monachalure because it offers the possibility of applying selective reactions for different functional groups (ester and thioester) and avoiding protection reactions, which would significantly shorten the synthetic pathway. It was therefore prepared in large quantities and subjected to the same isomerization as the dithioester which under optimized conditions proceeded quantitatively. However, Witting reactions carried out with the aldehyde obtained by selective reduction of the thioester group gave unsatisfactory yields. The *trans* dithioester and the *trans* monothioester were therefore converted to a diol with one hydroxymethylene group in the axial position and one in the equatorial position – a common precursor used previously in the

synthesis of other natural products. Selective protection of the alcohol in the axial position and Swern oxidation of the alcohol in the equatorial position to an aldehyde provided the substrate for attaching the *n*-nonyl chain in Wittig reactions. Hydrogenation of the double bond, deprotection of the second alcohol group and its oxidation to the aldehyde, followed by attachment of 2-methylpentyl or *n*-pentyl chains provided precursors for (+)-disparlure and (+)-monachalure, respectively. Decomposition of the butanodiacetal rings gave *cis*-diols, which were used in epoxide ring-closure to give the final products in good yields. Their optical isomers were obtained by the same procedure by reversing the order of alkyl chain attachment (2-methylpentyl or *n*-pentyl first followed by *n*-nonyl).

This new synthetic pathway allowed preparation of both (+)- and (-)-disparlure and their analogues for application in biological and enzymatic studies of the Gypsy moth and nun moth. It may also be applied for preparation many other *cis*-epoxides. Significant improvement in the preparation of the *cis* butanediacetal derivative with two thioethyl ester groups will allow its wider application in the synthesis of other natural products. Preparation of a butanediacetal derivative with two different functional groups (one ester and one thioester) introduced a new substrate with attractive properties to stereoselective synthesis.

Doktorant

Promotor