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Application of allylic substitutions in natural products synthesis*

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Abstract: Synthesis routes are described, allowing all known jasmonoids as well as their enantiomers to be synthesized in enantiomerically and diastereomerically pure form. The routes are based on a set of closely related lactones containing an electrophilic allylic moiety, which are accessible via asymmetric Pd-catalyzed allylic alkylation. Regio- and diastereoselective S_N2'-*anti*-reactions of the electrophilic lactones with organocopper compounds furnished 2,3-*cis*-disubstituted cyclopentenones, which were further transformed into the target compounds, i.e., 12-oxophytodienoic acid (12-OPDA) in excellent overall yields. The methodology also allowed iridoids and isoprostanes to be prepared. The configuration of an *Archaea* membrane lipid constituent containing cyclopentane rings was determined by total synthesis of a diol that was also obtained by degradation of the natural product.

Many natural products contain a five-membered ring as characteristic structural element. Prominent examples are steroids, prostaglandins, and carbanucleosides. While numerous syntheses of enantiomerically and diastereomerically pure compounds of these classes have been developed, there are areas that are less mature with respect to synthesis. In order to improve the situation in some of these areas, syntheses of jasmonoids and *Archaea* membrane lipids were devised.

JASMONOIDS

Plant defense (Fig. 1) against mechanical deformation, microbial infection or herbivore attack begins with liberation of linolenic acid, which is cyclized to yield the C_{18}-lipid 12-oxophytodienoic acid (12-OPDA) [1]. Hydrogenation followed by beta degradation gives rise to a series of two-carbon homologs down to *epi*-jasmonic acid. All these acids are apparently able to activate genes that produce proteins required for defense measures. For example, the attack of a caterpillar can activate this transduction cascade of the plant so as to produce volatiles that attract insects that are enemies of the caterpillar. In view of the analogy in the chemical structures of all these compounds, we were interested in a synthesis scheme that would provide access to all of the homologs. The methyl ester of *epi*-jasmonic acid, methyl *epi*-jasmonate, commands additional attention because it is a very important fragrance constituent.

The jasmonoids possess an epimerizable center on a *cis*-disubstituted cyclopentenone or cyclopentanone system. Many EPC-syntheses exist for methyl *epi*-jasmonate [2]. For the other octadecanoids, a broadly applicable, diastereoselective route to the racemic compounds has been worked out by Crombie and Mistry [3]. Asymmetric syntheses so far relied on enzyme-catalyzed reactions [4].

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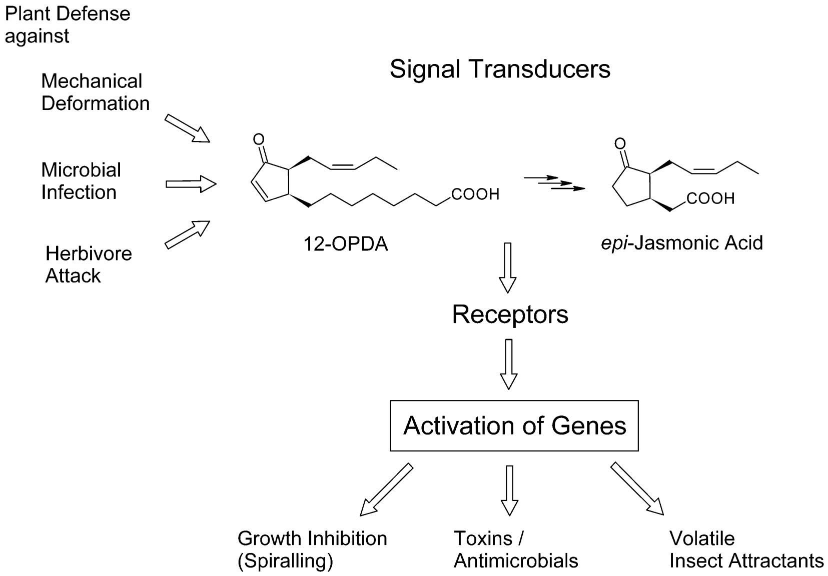
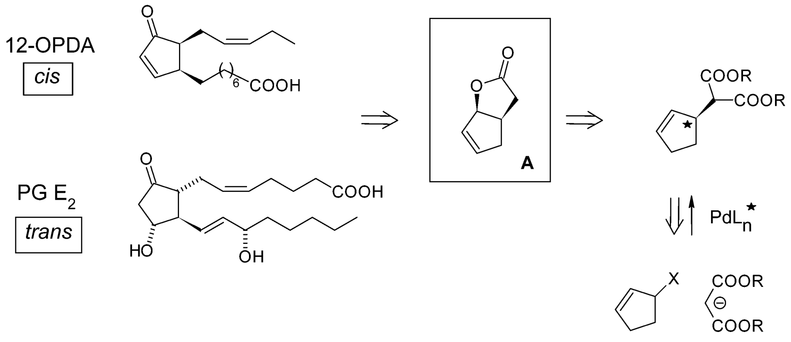


Fig. 1 Fundamental mechanisms of plant defense.

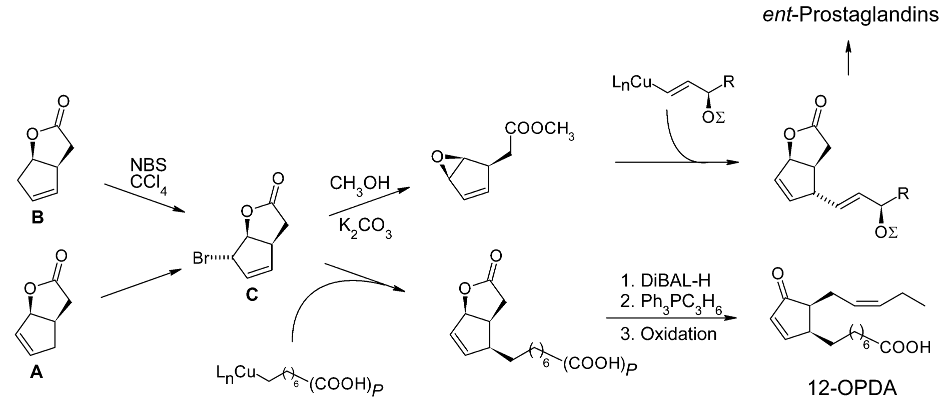
Our aim was to develop an enantioselective synthesis route on the basis of a metal-catalyzed enantioselective process that could be applied to all of the jasmonoids.

The jasmonoids obviously resemble prostaglandins, and our plan for their preparation was indeed inspired by prostaglandin chemistry. In Scheme 1, the formula of 12-OPDA with *cis*-configuration is compared with that of a typical prostaglandin, PG E_2, with *trans*-configuration of the C-appendages. We envisaged a possibility to derive both types of cyclopentanoids from a common precursor, the lactone **A**, for which we have devised a convenient synthesis on the basis of a Pd-catalyzed asymmetric allylic substitution by nucleophilic attack of malonate on cyclopentenyl derivatives (see below).



Scheme 1

Our starting point was a route to prostaglandins worked out by Glaxo chemists Newton and Roberts in the 1970s [5]. The route is described in Scheme 2 for *ent*-prostaglandins in order to compare it to that for the configurationally inverse jasmonoids. The Glaxo route relies on lactone **B**, which is an isomer of lactone **A**. Radical bromination with NBS preferentially gives *trans*-bromide **C**. Treatment of **C** with methanol and base transforms it into an epoxide. This is treated with an organocopper compound for introduction of the ω-side chain of the prostaglandins by a S_N2'-*anti* reaction. In general, the reaction of an organocopper reagent with an olefin with a leaving group in the allylic position proceeds with

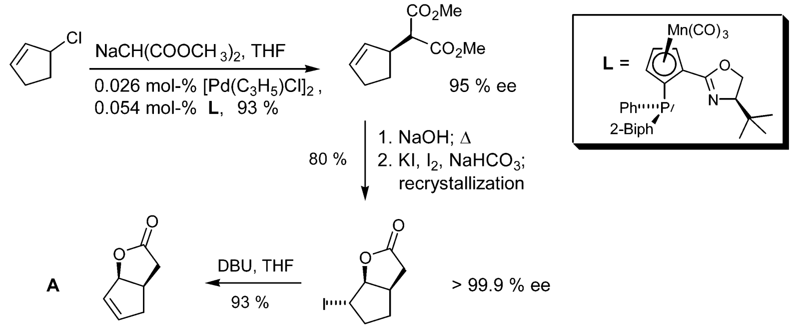


Scheme 2

preferred γ-attack, relative to the leaving group, from the direction *anti* to the leaving group. In the present case, this steric course leads to the *trans*-configuration of the two-carbon appendages, as required for prostaglandins.

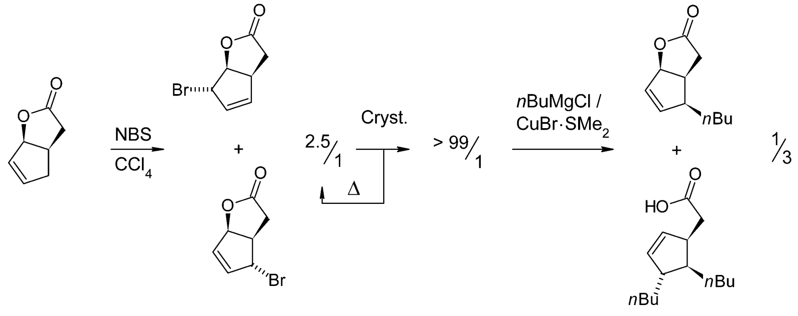
We have exploited the Glaxo strategy for our purpose on the basis of two considerations: (a) The bromide **C** is expected to be available from lactone **A**, which is accessible via allylic substitution, as readily as from lactone **B**. (b) Bromide **C** contains already an allylic system with a leaving group and, accordingly, might be reacted with an organocopper compound, again from the direction *anti* to the leaving bromide, i.e., from above, thus placing the new substituent *cis* to the C_2 side chain, as required for jasmonoids.

The synthesis of lactone **A** is described in Scheme 3 [6]. In order to increase the turnover frequency in the catalysis, we used cyclopentenyl chloride instead of the more common acetate or carbonate. Even with a molar ratio of Pd:substrate as low as 0.0012 enantiomeric excess of 95 % and almost quantitative yield were achieved. Standard saponification/decarboxylation and treatment with iodine gave an iodolactone, which could be obtained enantiomerically pure by recrystallization in a remarkably high overall yield of 80 %. Elimination with the base DBU furnished lactone **A** in very high yield.



Scheme 3

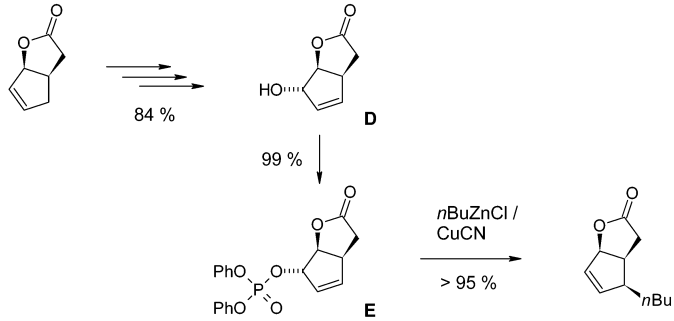
With a good supply of the crucial building block **A** in hand, we were able to start our plant hormone project as described in Scheme 4. At the outset, some difficulties were encountered. The radical bromination was indeed possible, however, the reaction was nonselective, furnishing isomeric bromides in a ratio of 2.5:1. In the racemic series, the major isomer can be isolated by recrystallization and the minor isomerized by heating and thus recycled [7]. The enantiomerically pure bromide is a low-melt-



Scheme 4

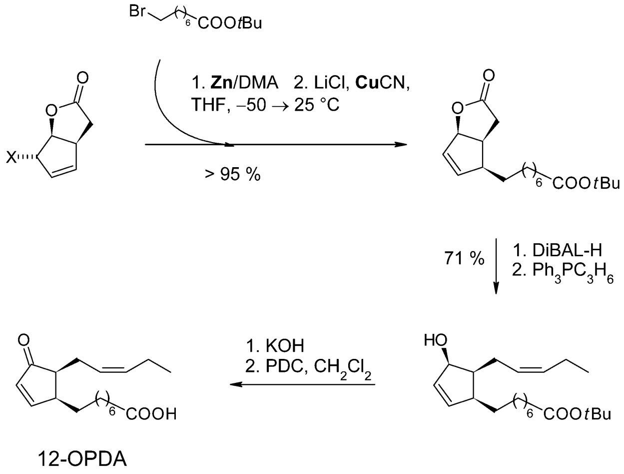
ing solid, however, so that tedious chromatographic separation of isomers was necessary. Next, the S_N2' reaction with an organocopper compound caused trouble. For example, the reaction of lactone **C** with butyl copper derived from butyl magnesium chloride, investigated as a model reaction, gave a mixture of the expected mono- and an undesirable disubstitution product. The latter arises because the monosubstitution product contains an allylic moiety with a carboxylate as leaving group and is, therefore, prone to be attacked to give a disubstitution product.

Both problems were solved as shown in Scheme 5. First, the bromide **C** was replaced by the corresponding hydroxylactone **D** as key intermediate. This compound is crystalline and can be obtained via a robust route involving osmium tetroxide catalyzed dihydroxylation, treatment of the resultant diol with HBr and elimination of HBr [8]. An advantageous aspect of lactone **D** is the possibility to introduce a tunable leaving group by modification of the OH group. In the present case, clean monosubstitution was generally obtained with the diphenyl phosphate in conjunction with a lower-order zinc cyanocuprate [9].



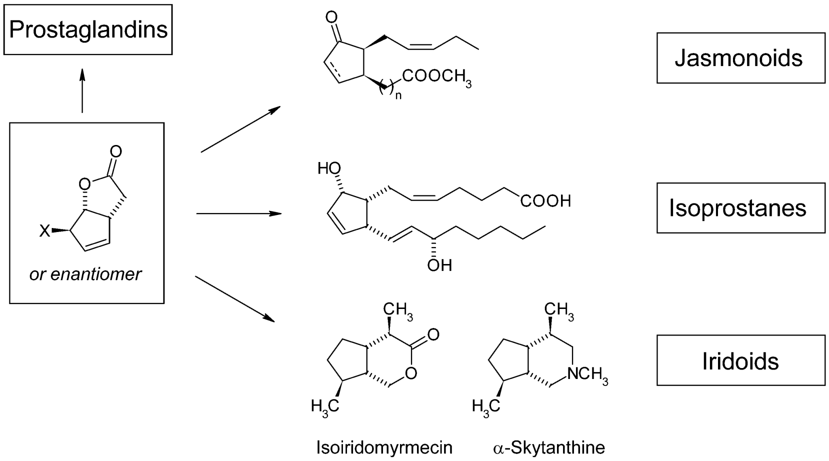
Scheme 5

Based on the methods described above, the synthesis of jasmonoids such as 12-OPDA was carried out (Scheme 6) [10], starting with the bromide **C** for racemic compounds and with the phosphate **E** or its enantiomer for enantiomerically pure targets. The organocopper compound was prepared from *t*-butyl ω-bromooctanoate, which was transformed into the zinc cyanocuprate using a procedure developed by Knochel [11]. With the mixed Zn/Cu reagent the reaction proceeded fast, yet it stopped at the desired stage to yield the substitution product in >95 % isolated yield. Further steps toward 12-OPDA followed standard procedures of prostaglandin chemistry. Biological activity of the methyl esters of the various enantiomerically pure synthetic jasmonoids and their corresponding reduced precursors was assessed in the *bryonia dioica* tendril coiling assay [12].



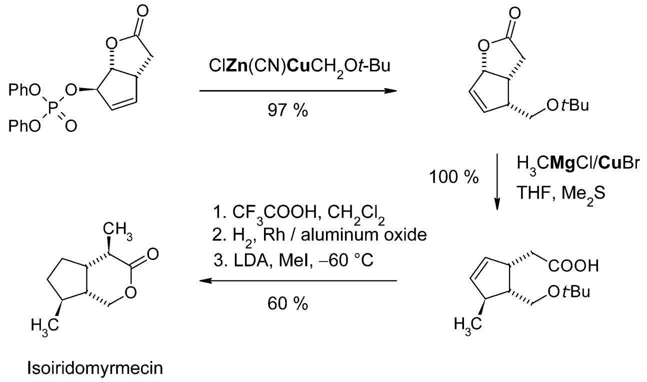
Scheme 6

The allylic phosphate **E** or, in the racemic series, the bromide **C** are useful intermediates, as demonstrated by the summary presented in Scheme 7. As described above, these compounds allow prostaglandins with *trans*-configuration and jasmonoids with *cis*-configuration of the carbon side chains to be prepared. Essentially the same route can be used to access isoprostanes, i.e., prostaglandin analogs with *cis*-configuration [13]. Remarkably, one can reach yet another large class of natural products, the iridoids. Iridoids are characterized by a methylated C_2 side chain and two additional C_1 substituents in *cis*, *trans*-configurations. As examples formulas of isoiridomyrmecin and of the alkaloid α-skytanthine are presented in Scheme 7.



Scheme 7

The route to access iridoids is described in Scheme 8, using isoiridomyrmecin as example. The *cis*-C_1-substituent was introduced by S_N2'-*anti* reaction with a Zn/Cu compound prepared from *t*-butyl methyl ether by treatment with KO*t*-Bu/*t*-BuLi [14] followed by addition of $ZnCl_2$ and CuCN•2LiCl. Then we made positive use of the previous problem of overreaction (cf. Scheme 4) by adding an organocopper reagent derived from methyl magnesium chloride to effect a second S_N2'-*anti* substitution [15]. The reaction proceeded cleanly to give the substitution product in quantitative yield. Further transformation to the target isoiridomyrmecin was carried out in standard manner [16].



Scheme 8

ARCHAEA MEMBRANE LIPIDS

The *Archaea* domain is composed of a variety of microorganisms that proliferate under extreme environmental conditions such as high acidity, high temperature, and/or high salt concentration [17]. *Archaea* are classified into three phenotypes on the basis of their living habitats: methanogens, halophiles, and thermoacidophiles. Among the distinctive features of the latter are their membranes. Figure 2 presents a survey of various types of *Archaea* membranes. Rather than the standard fatty acid esters, ethers of glycerol or higher sugars with branched alkyl groups, such as the phytanyl group, are encountered (cf. **F1**). There are also cyclic structures, 72-membered rings composed of methylated chains and glycerol (**F2**). The configurations of the methylated centers were determined by Heathcock and coworkers via a total synthesis of a diol also obtained by ether cleavage from the natural product [18]. However, the structures of the methylated chains do not fully characterize these types of compounds. As was first demonstrated by Gräther and Arigoni, there are several modes of binding to glycerol giving rise to regioisomers [19]. Recently, the synthesis of a macrocyclic glycerol tetraether lipid was accomplished by Eguchi et al. [20].

Compounds with up to eight five-membered rings were isolated from thermophilic *Archaea* (cf. **F3**–**F5**, Fig. 2). Configurations of these compounds were largely unknown at the outset of our work and, as a consequence, a stereoselective synthesis of a lipid of type **F3**–**F5** had not been undertaken. In Scheme 9, the formula of a specific example is given, a tetraether of glycerol with two identical chains. De Rosa et al. obtained various pure diols with five-membered rings, among them **H**, by degradation of natural ether lipids and determined their constitution by mass spectrometry and NMR [21]. Important features, revealed by ^{13}C NMR, are the C_2-symmetry of the structure of **H** and the *trans*-configuration of the rings, deduced by comparison of the ^{13}C NMR data with those of *cis*- and *trans*-1,3-dimethylcyclopentane. Further stereochemical features given in Scheme 9 were initially based on the speculation that **G** is formed from a tetraether of type **F2** by bond connection between carbon atoms of methyl and methylene groups, although the biosynthesis of **G** has not been elucidated in any detail [21b,22]. Very recently, pure tetraether **G** as well as an Arigoni–Gräther-type regioisomer were isolated by Damsté et al. from Arabian sea sediments and *Sulfolabus acidocaldarius*; the overall C_2-symmetry and the *trans*-configuration of the cyclopentanes were confirmed by an extensive NMR investigation [23].

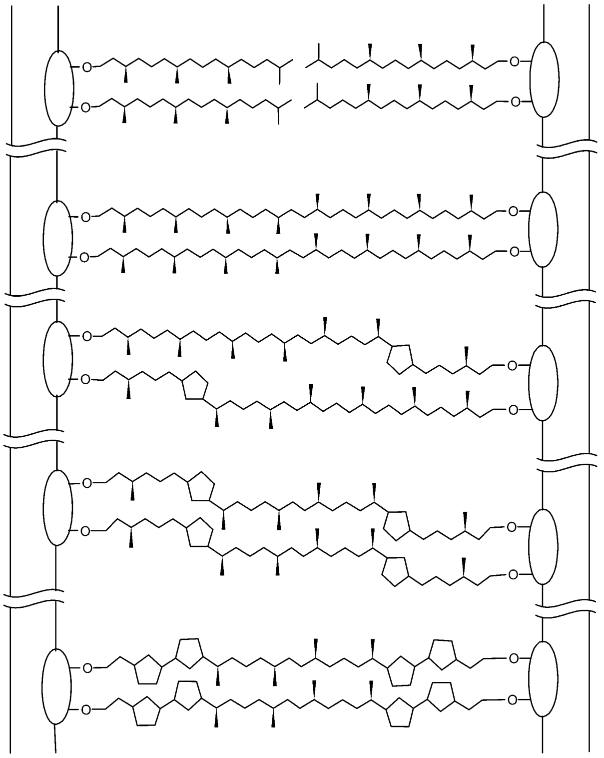
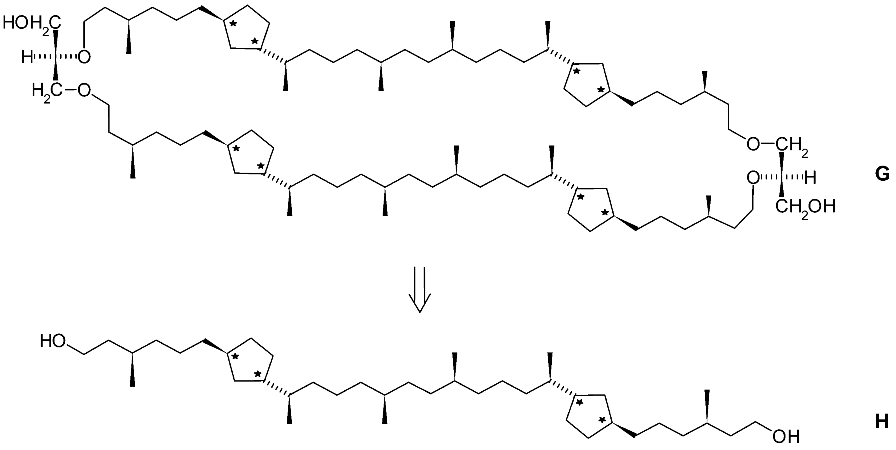
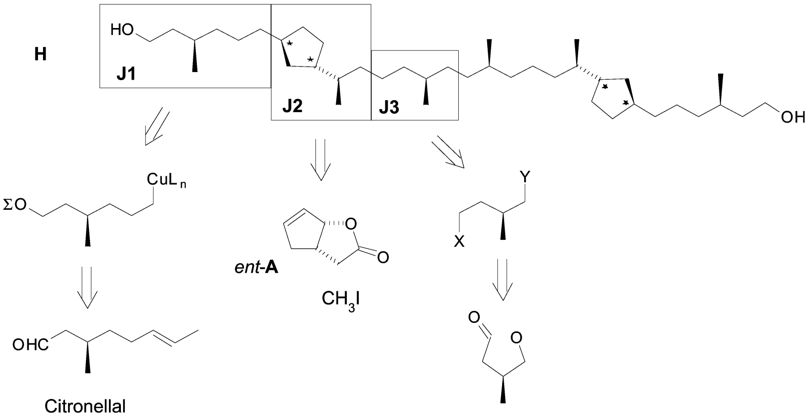


Fig. 2 Types of *Archaea* membrane lipids. Elipsoids represent glycerol or sugars.



Scheme 9

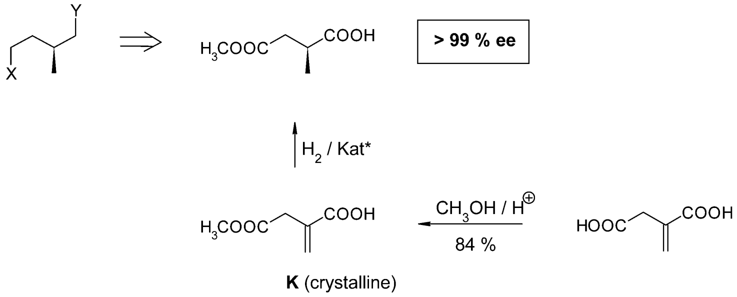
For the synthesis of diol **H**, the strategy that is described as retrosynthesis in Scheme 10 was conceived. Substructure **J2** was to be derived from lactone *ent*-**A** and a methylating agent via enolate alkylation. Substructure **J1** was anticipated to be readily available from citronellal by cleavage of the double bond and subsequent functional group manipulations. Citronellal is today available with >99 % ee by rhodium catalyzed enantioselective allylamine-enamine isomerization according to Noyori (Takasago process). For the connection of substructures **J1** and **J2** the venerable organocopper S_N2'-*anti* substitution was envisaged [15]. The hydroisoprene unit **J3** was to be derived from



Scheme 10

(*S*)-3-methylbutyrolactone. This compound is still advertised by some suppliers. In spite of that, it was not available, and we had to find another hydroisoprene equivalent.

Procedures for enantioselective preparation of hydroisoprene synthons have been developed in considerable variety in conjunction with total syntheses of α-tocopherol [24]. Astonishingly, the straightforward approach of asymmetric catalytic hydrogenation of a derivative of the readily available itaconic acid has not been fully developed (Scheme 11). A limiting requirement for such a procedure is the necessity to obtain the product with better than 99 % ee, because in a synthesis of **H** any enantiomeric impurity in the starting materials will transform into a diastereomeric impurity, removal of which would probably be very difficult. Checking the literature, we found a report by Baker of 1951 describing the preparation of methyl half ester **K** of itaconic acid in 84 % yield by simple acid-catalyzed esterification [25]. Bakers procedure allowed this compound to be prepared on a 100 g scale.



Scheme 11

While itaconic acid and its dimethyl ester have been widely used as benchmark substrates for asymmetric hydrogenation, half esters have only rarely been investigated. In Fig. 3, the state of the art in this area is reviewed. In the recent literature, we found two reports, from the Brown [26] and the Burk [27] group, on the hydrogenation of itaconic half esters. Respectable 95 % ee were achieved, but not the required >99 % ee. Of the numerous reports on hydrogenation of the diacid and the dimethyl ester, only the most recent are cited in Fig. 3 [28]. The Reetz ligand is the simplest and induces high catalytic activity. We prepared it and used it in the hydrogenation of the half ester **K**: 95 % ee. Better results were obtained with the potentially hemilabile analog **L2** that is described in Scheme 12.

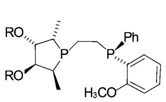
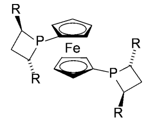
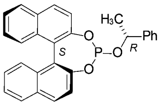
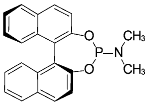
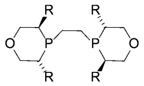
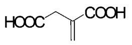
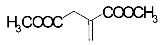
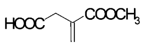
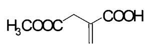
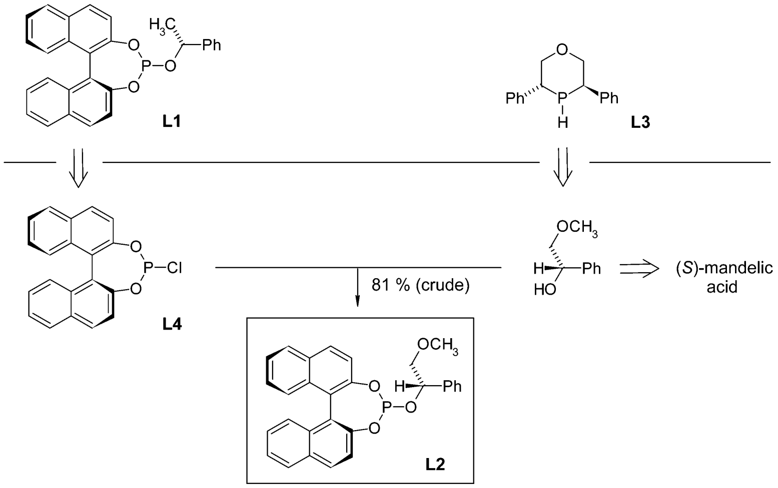
Rh	J. M. Brown 1999 	Behrens, Burk 2000 	Reetz 2000 	Feringa, de Vries 2000 	this group 2002 
	–	–		96.6	94
	85	98	99.6	94.4	
	94	–			
	95	95			

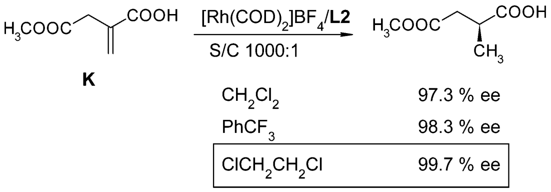
Fig. 3 Asymmetric catalytic hydrogenation of itaconic acid derivatives.



Scheme 12

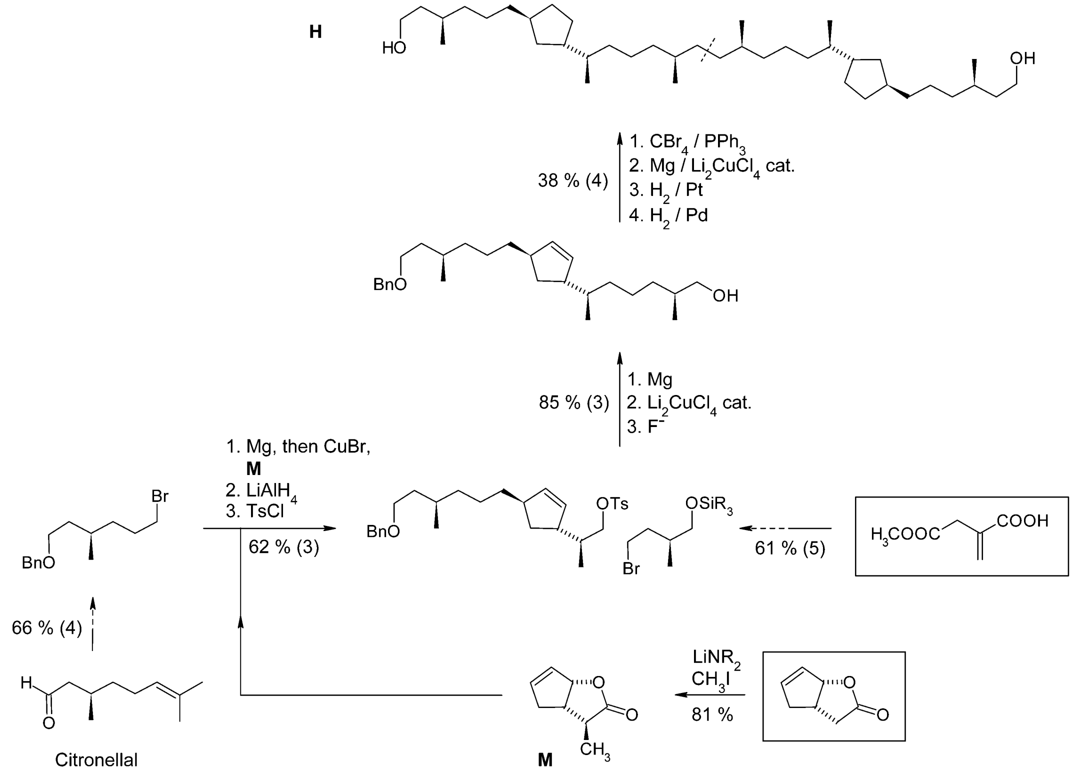
Ligand **L1** can be very easily prepared by reaction of 1-phenylethanol with phosphorous chloride **L4**, available by reaction of BINOL with PCl_3. In our work on oxaphosphinane ligands [28b], ligand **L3** was prepared from 1-phenylglycol, which was obtained by reduction of mandelic acid. Having the diol on the shelf, the monomethyl ether was prepared and reacted with phosphorus chloride **L4** to yield the phosphite **L2**.

Ligand **L2** was used in crude form in combination with $[Rh(COD)_2]BF_4$ as catalyst for the hydrogenation of half ester **K** (Scheme 13). Even with a substrate/catalyst ratio as high as 1000:1 excellent results were obtained. Crucial parameter to achieving the envisaged enantioselectivity >>99:1 was the polarity of the solvent [29].



Scheme 13

Based on these results, we were able to accomplish a total synthesis of diol **H** (Scheme 14) [30]. Particularly noteworthy is the fact that all the key intermediates were prepared with enantiomeric purities exceeding 99 % ee by reactions controlled by asymmetric catalysis. The compound obtained by total synthesis was compared with a sample obtained by degradation of a lipid isolated from *Archaea Sulfolabus acidocaldarius*. Both samples displayed identical NMR spectra and optical rotations.



Scheme 14

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