

## DSM Science & Technology Awards 2003

Name	Anja Hoffmann – Röder
University	University of Dortmund (D)
Department	Department of Organic Chemistry II
PhD Supervisor	Prof. Dr. N. Krause

Dr. Anja Hoffmann-Röder

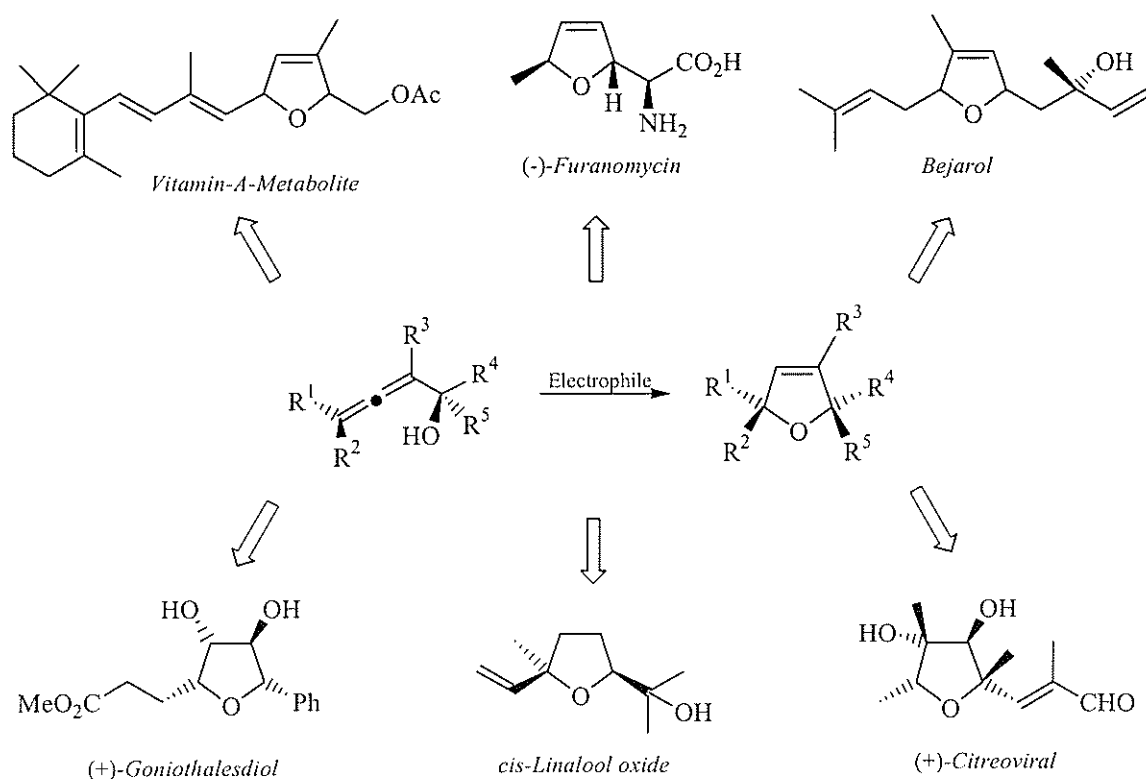
Summary of the Ph.D. Thesis

## From Functionalised $\alpha$ -Hydroxyallenes to 2,5-Dihydrofurans: Stereoselective Syntheses with Copper, Silver and Gold

Date of the Ph.D. Examination: January 29, 2003

Although often being regarded as chemical curiosities, allenes have emerged over the past years as valuable synthetic precursors for the construction of complex target molecules. This development has certainly been stimulated by the increasing number of natural products and pharmacologically active compounds comprising an allenic entity, but might also be attributed to the high reactivity and (upon proper substitution) inherent axial chirality of these interesting molecules. Consequently, a number of procedures for the synthesis of functionalised allenes have been reported to date.

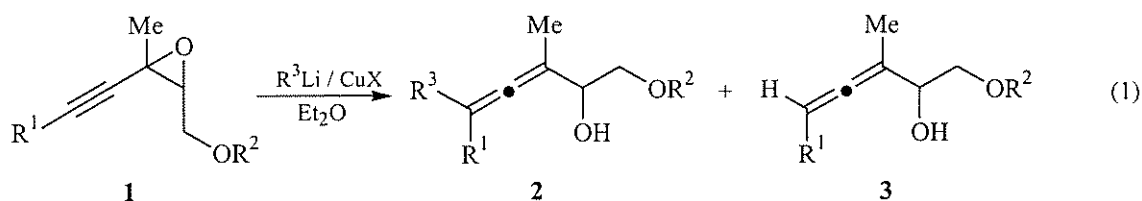
With regard to natural product synthesis,  $\alpha$ -hydroxyallenes have proven to be particularly useful intermediates since they can be readily transformed into 2,5-dihydrofurans by electrophilically induced cycloisomerisation. The resulting 2,5-dihydrofurans (or corresponding tetrahydrofurans) represent again important structural motifs of a wide variety of different natural products and other interesting target molecules (Scheme 1).



Scheme 1:  $\alpha$ -Hydroxyallenes as key intermediates in Natural Product Synthesis.

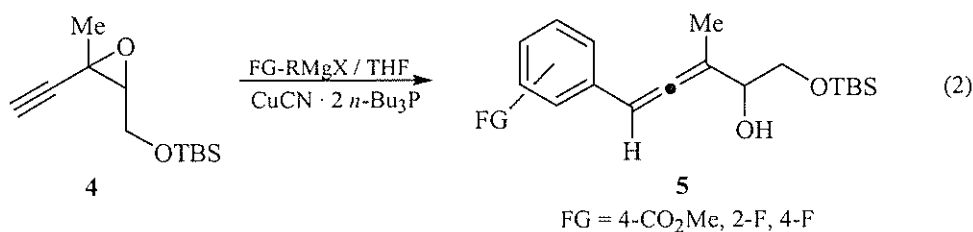
Probably the most versatile approach for the generation of  $\alpha$ -hydroxyallenes relies upon the  $S_N2'$ -substitution of propargylic oxiranes with organocuprates. Although this reaction has already been known for several years, its application in target-oriented synthesis has been limited so far. Thus, the objective of this Ph.D. thesis was to demonstrate the synthetic utility of  $\alpha$ -hydroxyallenes as key intermediates in the synthesis of natural products comprising a 2,5-dihydrofuran moiety as central structural element.

Since  $S_N2'$ -substitution reactions of functionalised propargylic oxiranes have been investigated only scarcely so far, the scope of this reaction was initially with simple (unfunctionalised) lithium dialkylcuprates and epoxides of type **1** as a test substrate (eq. 1).

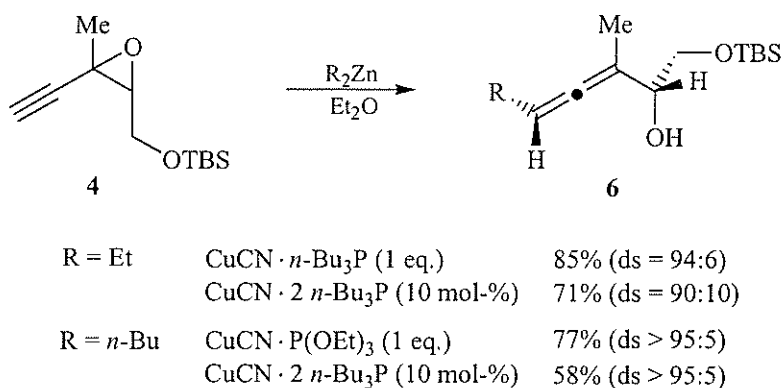


Interestingly, depending upon the substrate and the reaction conditions (copper salt, solvent, additives), the substitution did not always proceed as expected but furnished (in particular with lithium di-*n*-alkylcyanocuprates) often significant amounts of the “formal hydrolysis” product **3**. The formation of this latter compound was attributed to the hydrolysis of a rather stable copper(III) intermediate (inhibited reductive elimination step); consequently, **3** could be isolated as the major product at low temperature using short reaction times. However, the desired substitution product **2** can be obtained predominately by using tributylphosphine *n*-Bu<sub>3</sub>P as an additive, which also proved to be advantageous for high diastereoselectivities, most probably by preventing a racemisation of the allenic entity.

Unfortunately, the product distribution (reduction vs. substitution product) of the  $S_N2'$ -substitution reactions of propargylic oxiranes with lithium cyanocuprates often shows a strong influence of the substrate structure (e.g., the presence of further functionalities like free hydroxyl groups) and therefore must be optimised for each system. This capricious behaviour of lithium cuprates, as well as their reduced compatibility with functional groups, led to the use of magnesium cuprates in this reaction. Indeed, in the presence of copper cyanide and tributylphosphine or triethylphosphite as a donor ligand, a clean and highly diastereoselective conversion of oxiranes **1** into the desired substitution products **2** was achieved. Gratifyingly, the method could also be applied to Knochel’s functionalised Grignard reagents, giving an access to  $\alpha$ -hydroxyallenes **5** bearing an additional ester or fluoro group (eq. 2).

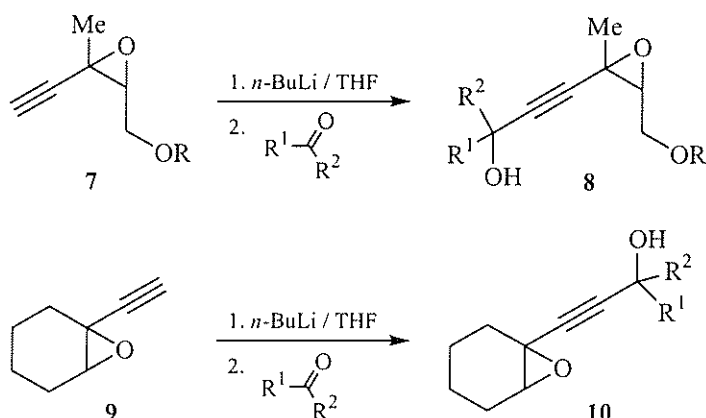


As a third method for the synthesis of  $\alpha$ -hydroxyallenes, the use of dialkylzinc reagents in copper-promoted  $S_N2'$ -substitution reactions of propargylic oxiranes was examined. It was found that these transformations proceed without any side reactions to furnish the desired allenes with high diastereoselectivities in the presence of phosphines or phosphites. Furthermore, they can also be carried out with *catalytic amounts* of CuCN and *n*-Bu<sub>3</sub>P (Scheme 2). In an analogous fashion, organozinc halides like *i*-PrZnCl can be employed as the nucleophile in these  $S_N2'$ -substitutions, which opens up new opportunities for the introduction of functionalised groups into  $\alpha$ -hydroxyallenes.



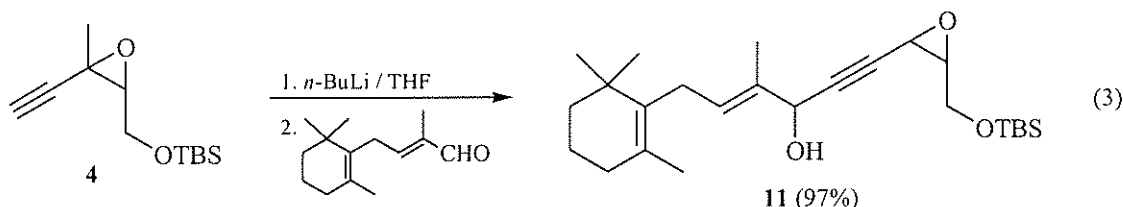
*Scheme 2:*  $S_N2'$ -substitution of propargylic oxirane **4** with dialkylzinc reagents in the presence of stoichiometric or catalytic amount of CuCN and a donor ligand.

The starting materials for these reactions, the propargylic oxiranes of type **1**, are usually synthesised by epoxidation of the corresponding enynes with peracids or peroxides. In order to introduce a high degree of complexity at a rather early stage of longer synthetic sequences, the deprotonation of terminal propargylic epoxides and addition of the acetylides thus formed to aldehydes and ketones was examined. By using non-nucleophilic bases like LDA, but also with the more nucleophilic *n*-Butyllithium, high yields of the desired hydroxy-substituted propargylic oxiranes **8** and **10**, respectively, were obtained without competing side reactions at the epoxide ring (Scheme 3).

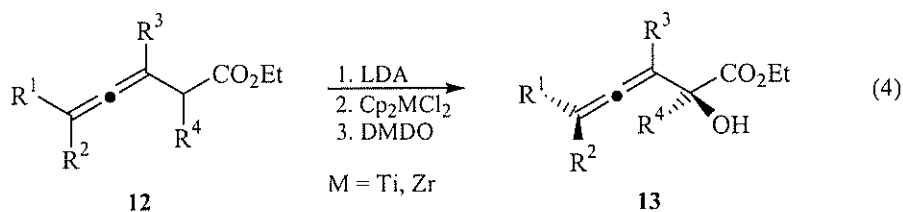


*Scheme 3:* Formation of functionalised propargylic oxiranes **8/10** by deprotonation of substrates **7/9** and addition to carbonyl compounds.

This method does not only tolerate various functional groups like hydroxy groups, halides, silyl ethers and C-C double bonds in the starting epoxides and carbonyl compounds, but it also opens up a convenient access to multiply unsaturated propargylic oxiranes, e.g., the retinoid **11** (eq. 3). Compounds of this type cannot be prepared by the traditional method of addition and subsequent epoxidation since the presence of chemically very similar double bonds would give rise to the formation of complex mixtures in the epoxidation step.



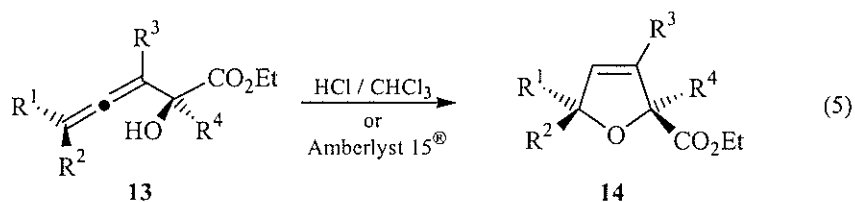
As an alternative route to  $\alpha$ -hydroxyallenes **13** bearing an additional ester function, the enolate oxidation of  $\beta$ -allenic esters **12** with dimethyl dioxirane (DMDO) was developed in this work (eq. 4). Target molecules of type **13** are hardly accessible by the  $S_N2'$ -substitution of propargylic oxiranes mentioned above. The starting  $\beta$ -allenic esters **12** (which can be prepared conveniently by 1,6-addition of organocuprates to 2-en-4-ynoates) are first deprotonated with a suitable non-nucleophilic base (e.g., LDA), and the lithium enolates thus formed are transmetalated with titanocene or zirconocene dichloride prior to the chemo- and diastereoselective oxidation with DMDO.



It was found that both the diastereoselectivity and the chemical yield depend strongly on the steric properties of the starting allene **12**. Whereas high diastereoselectivities of up to 90% ds were achieved when the substituents  $R^1$  and  $R^2$  differ strongly in size, the conversion of the starting material (and consequently the chemical yield of the product **13**) was often unsatisfactory. Here, the application of lithium or potassium hexamethyldisilazide as the base, and in particular the use of the more reactive zirconium enolates proved to be advantageous and allowed the preparation of the  $\alpha$ -hydroxyallenes **13** in fair to high yields.

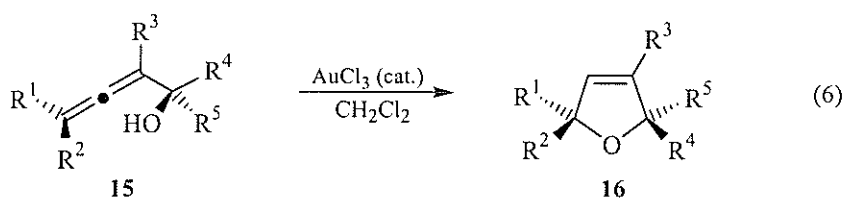
For the electrophilically induced cycloisomerisation of  $\alpha$ -hydroxyallenes to 2,5-dihydrofurans, the use of silver nitrate in aqueous media has been established by Marshall and is still the most frequently employed method. Under these conditions, however, reasonably high reaction rates often require the presence of *stoichiometric amounts* of the silver salt. In the course of this work, three new, complimentary procedures could be developed. Thus, the 2-hydroxy-3,4-dienoates **13** formed in the enolate oxidation mentioned above can be

cycloisomerised into the corresponding 2,5-dihydrofurancarboxylates **14** with excellent yields and complete chirality transfer by treatment with an anhydrous solution of hydrogen chloride in chloroform (eq. 5).

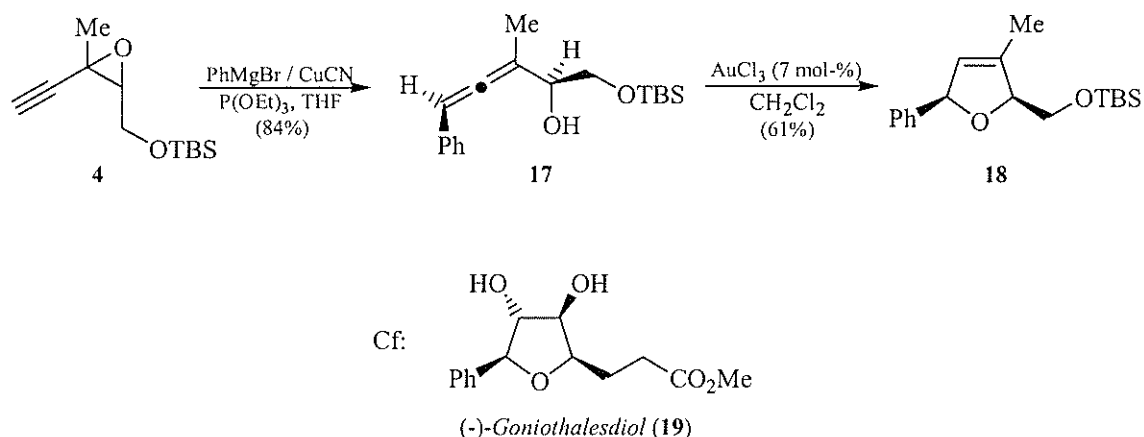


Even more convenient is the use of the acidic cation exchange resin Amberlyst 15<sup>®</sup> which induced a rapid cyclisation of allenes **13** into dihydrofurans **14** in refluxing dichloromethane and allowed the isolation of the products without aqueous workup. These cyclisations take place so smoothly that a purification of the crude product is often unnecessary.

For more sensitive  $\alpha$ -hydroxyallenes (e.g., those which bear an acid-sensitive silyl protecting group), a new gold-catalysed cyclisation method was established. Thus, treatment of substrates **15** with 1-10 mol-% of gold(III)-chloride in dichloromethane led to the formation of the desired 2,5-dihydrofurans **16** which was usually complete within a few hours at room temperature (eq. 6). The reaction is compatible with the presence of many functional groups and may well become the standard method for the conversion of  $\alpha$ -hydroxyallenes into 2,5-dihydrofurans since it proceeds selectively and rapidly with catalyst loadings as low as 1 mol-%.

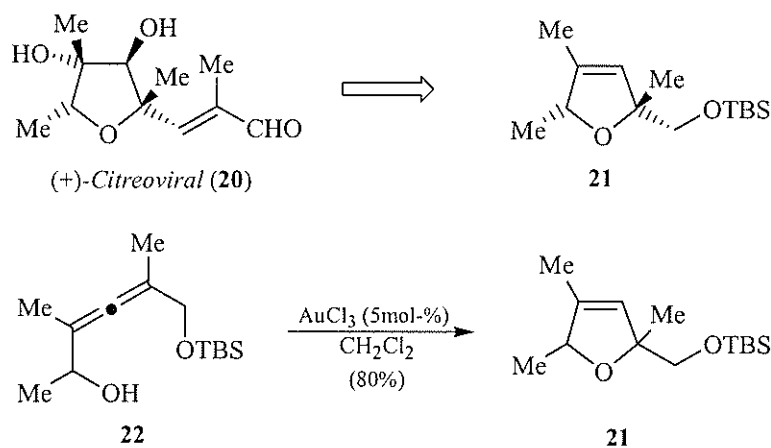


In the final part of the Ph.D. thesis, the application of the newly developed methods towards the synthesis of natural products with a 2,5-dihydrofuran or tetrahydrofuran structure was examined. For example, a methyl analogue of the cytotoxic natural product *goniothalesdiol* (**19**) should be accessible from the 2,5-dihydrofuran **18** which was prepared starting from the propargylic oxirane **4** by copper-promoted  $S_N2'$ -substitution reaction with phenylmagnesium bromide and subsequent gold-catalysed cycloisomerisation of the  $\alpha$ -hydroxyallene **17** (Scheme 4).



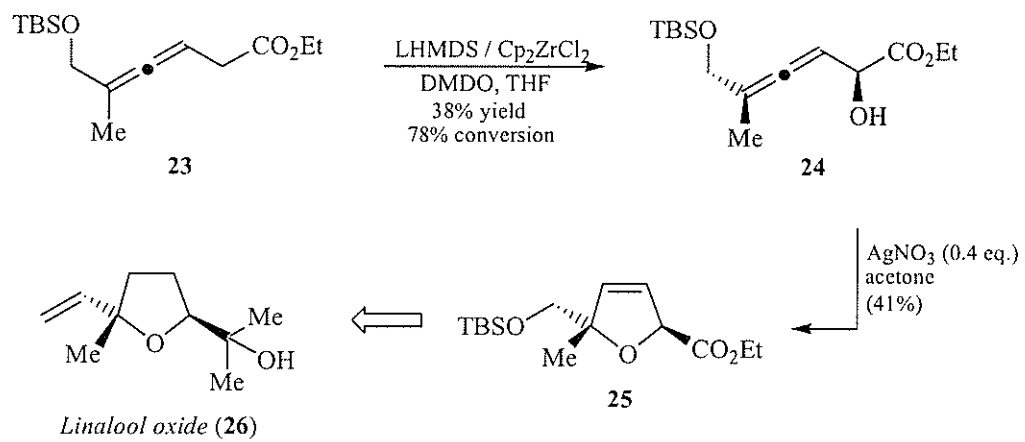
Scheme 4: Synthesis of 2,5-dihydrofuran **18**, a precursor for a methyl analogue of *goniothalesdiol* (**19**).

A formal synthesis of the racemic mycotoxin metabolite *citreoviral* (**20**) was completed and took advantage of the gold-catalysed cyclisation of the hydroxyallene **22** to the 2,5-dihydrofuran **21** (Scheme 5). The conversion of the latter into *citreoviral* had been established earlier by Marshall and coworkers.



Scheme 5: Formal synthesis of *citreoviral* (**20**) by gold-catalysed cyclisation of  $\alpha$ -hydroxyallene **22** to 2,5-dihydrofuran **21**.

Finally, a precursor for the natural flavouring compound *linalool oxide* (**26**) was synthesised by enolate oxidation and subsequent cyclisation. DMDO oxidation of the zirconium enolate formed from 3,4-dienoate **23** by treatment with lithium hexamethyldisilazide and zirconocene dichloride gave the  $\alpha$ -hydroxyallene **24** which could be cyclised to the 2,5-dihydrofuran **25** with silver nitrate (0.4 eq.) in acetone (Scheme 6). Both steps are not yet optimised, and a different protecting group at the primary hydroxy group of **25** may be necessary in order to achieve a gold-catalysed cyclisation.



Scheme 6: Synthesis of 2,5-dihydrofuran **25**, a precursor for *linalool oxide* (**26**).