Over the past years chiral cyanohydrins (α-hydroxynitriles) have become a versatile source for a variety of chiral building blocks. Several classes have already been synthesized, including β-hydroxy-α-amino acids [1], α-hydroxy-β-amino acids [2], α-hydroxy ketones [3] and β-hydroxy nitrones [4]. Although chiral α-hydroxy aldehydes are interesting compounds, their synthesis from chiral cyanohydrins has always been difficult. Some examples of the synthesis of chiral α-hydroxy aldehydes have been published but the results, both in yield and optical purity, seem to be contradictory [5]. This poster describes the first results of the synthesis of O-protected chiral α-hydroxy aldehydes and their subsequent use in the Horner-Wittig reaction.

The synthesis and application of chiral cyanohydrins is a major interest in our group. In recent years a simple system has been developed by which these cyanohydrins can be prepared in excellent enantiomeric purity by the addition of HCN to aldehydes in a reaction catalyzed by the enzyme R-hydroxynitrile lyase (R-Hnl), as present in almonds [E.C. 4.1.2.10] (Figure 1). As source of the enzyme both almond meal (ground and defatted almonds) and the purified enzyme can be used (Figure 2).
The cyanohydrins obtained are known to possess the R-configuration, provided that the hydroxyl substituent has priority over substituent R. A wide variety of substrates can be employed in the R-Hnl catalyzed reaction. These include aromatic, heterocyclic, and saturated as well as α,β-unsaturated and ω-unsaturated aliphatic aldehydes. The reaction proceeds in good yield and provides the target compounds in excellent enantiomeric purity (Scheme 1). For the route described here benzaldehyde, the enzymes natural substrate, was used.

![Scheme 1](image1.png)

**Scheme 1.** Synthesis of chiral cyanohydrins under catalysis of R-Hnl (R=Ph).

Since cyanohydrins are unstable under basic or reductive conditions a protecting group at the oxygen atom has to be introduced. Both silyl ethers and tetrahydropyranyl (THP) ethers turned out to be satisfactory protecting groups in the conversion described here. After protection the nitrile moiety could be reduced with diisobutylaluminum hydride (DIBAL-H). The aluminum complex originally formed was decomposed by the addition of acid. The formed O-protected chiral α-hydroxy aldehyde was then used in a Horner-Wittig reaction with (carbethoxymethyl)-diphenylphosphine oxide, thus forming a chiral γ-hydroxy-α,β-unsaturated ester (Scheme 2).

![Scheme 2](image2.png)
This reaction proceeded in a yield of 86% and the product formed had an enantiomeric purity of 96% as determined by HPLC [6]. NMR spectroscopy showed that the conversion had proceeded with complete or almost complete E-selectivity [7]. The results indicate that this is a good and reliable method for the synthesis of this class of compounds. The reaction also proceeds well starting from aliphatic and \( \omega \)-unsaturated chiral cyanohydrins (R=propyl or 3-butenyl). The scope of this transformation, as well as its extension to other Horner-Wittig reagents, is presently under investigation.

References:

6. The enantiomeric purity was determined by HPLC using a *Daicel* Chiralcel OD-column (flow = 1 ml/min, \( \lambda = 254 \) nm). As eluent a mixture of hexane and 2-propanol was used (95 / 5).
7. E-selectivity was determined by NMR spectroscopy (*Bruker* DPX-200 instrument) and was based on the coupling constant of the hydrogen atoms at the newly formed double bond. The found value of 15 Hz is typical of an E double bond. No peaks belonging to the Z isomer could be found.

More information about this subject and other projects of our group can be found on our homepage:

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