# Simple synthesis of enantiomers of 6-hydroxyalkan-4-olides by stereoselective hydrogenation of methyl 4,6-dioxoalkanoates

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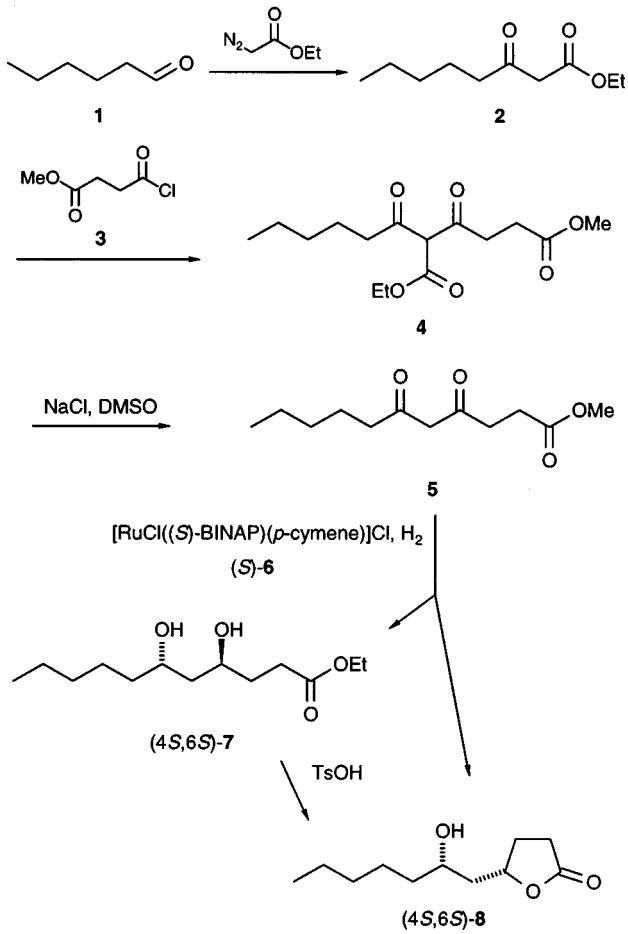
**A simple method for the synthesis of (*S*,*S*)- or (*R*,*R*)-6-hydroxyalkan-4-olides, components of the pheromonal secretion of the butterfly *Idea leuconoe*, in high ee by enantioselective hydrogenation of 4,6-diketo esters with a commercial available Ru–BINAP catalyst is described.**

During our studies on the pheromone system of males of the large danaine butterfly *Idea leuconoe*[1,2] we identified the previously unknown 6-hydroxyalkan-4-olides with chain-lengths between 10 and 13 carbon atoms. They seem to act synergistically with the other pheromone components and are probably involved in male–male interactions.[2] Therefore a synthesis of the pure enantiomers was needed to elucidate their absolute configuration and further investigate their ecological role.

High ee and dr of diols have been observed in Ru–BINAP catalyzed stereoselective hydrogenations of β-diketones.[3,4] We reasoned that 4,6-diketo esters might also be good substrates for such hydrogenations. Experiments with 3,5-diketo esters showed poor selectivity using the employed catalyst $[NH_2Et_2]^+$-$[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ between the diketo and the β-keto ester functionalities,[5] coupled with moderate enantioselectivity. In addition, the results could be interpreted as a preferred ligation of the ester group over the keto group.[5,6] On the other hand, small structural differences of the end groups are recognized by the catalyst, so that products with high dr and ee can be obtained, as has been shown by the hydrogenation of hexane-2,4-dione.[4] Therefore, the preferred reduction of the 4,6-diketo system in the presence of an ester group seemed to be possible. To the best of our knowledge, the only stable and commercially available chiral Ru–BINAP catalysts are [RuCl((*R*)-BINAP)(*p*-cymene)]Cl [(*R*)-**6**] and its (*S*)-enantiomer (Fluka). These catalysts have been regarded as ineffective below 60 °C in catalytic hydrogenations of dicarbonyl compounds.[6,7] Nevertheless, their application in the hydrogenation of allylic alcohols[8] and experience from our laboratories[9] showed that they can be effective catalysts in the reduction of β-keto esters at 80 °C and 40 bar hydrogen pressure, the upper limits of the equipment available to us. For example, hydrogenation of methyl 3-oxononanoate in the presence of (*S*)-**6** yielded methyl (*S*)-**3**-hydroxynonanoate in quantitative yield and 97.4% ee.

The major lactone in the secretion of *Idea leuconoe* is 6-hydroxyundecan-4-olide **8**. The 4,6-diketo ester required for its synthesis can be easily prepared starting from hexanal **1**. Reaction with ethyl diazoacetate yielded ethyl 3-oxooctanoate **2**,[10] which was acylated with 3-methoxycarbonylpropionyl chloride **3** (Scheme 1). Krapcho de-ethoxycarbonylation[11] of the product **4** then lead to the required precursor, methyl 4,6-dioxoundecanoate **5**. Hydrogenation at 40 bar $H_2$ and 80 °C in the presence of (*S*)-**6** for two days yielded a mixture of (*S*,*S*)-**8** and methyl (*S*,*S*)-4,6-dihydroxyundecanote **7**,† verified by chemical correlation as described below. The ester **7** could be smoothly transformed into (*S*,*S*)-**8** by column chromatography over silica, and subsequent treatment of the product with old $CHCl_3$ or TsOH. The dr and ee were determined by GC on a chiral phase (Lipodex E), which allowed separation of all enantiomers. The dr varied in different experiments between 95 and 99%, while the ee of the major enantiomer varied between 93 and 95%. The ee of the minor diastereomer could only be estimated to be between 0 and 20% because of the small amount isolated. Several lactones with chain lengths between $C_{10}$ and $C_{13}$ have been prepared with similar results by this method.

Finally, a chemical correlation was needed to see whether the stereochemical outcome of the reaction was as expected. Therefore, our synthesis of *rac*-6-hydroxydodecan-4-olide[1] was modified to obtain compounds with defined stereochemistry. Allylation of methyl 4-oxobutanoate with allyl(diisopinocampheyl)borane derived from (−)-α-pinene furnished (*S*)-hept-6-en-4-olide.[12] After ozonolysis, the labile and slowly epimerising aldehyde (*S*)-6-oxohexan-4-olide was alkylated with hexylmagnesium bromide, yielding a diastereomeric mixture of the hydroxy lactones, enriched in the (4*S*)-enantiomers. In a second experiment, *rac*-6-oxohexan-4-olide was alkylated using dihexylzinc in the presence of (1*R*,2*R*)-1,2-bis(trifluoromethylsulfonylamino)cyclohexane to yield a mixture enriched in the (6*S*)-enantiomers.[13] Gas chromatographic analysis of these mixtures and the racemate allowed unambiguous assignment of the (4*S*,6*S*)-configuration in the hydro-




**Scheme 1**

genation products obtained with (*S*)-**6**. The result is in accord with the enantioselective hydrogenations of β-diketones with Ru-BINAP catalysts described in the literature.[3,4] Obviously the alkyl and ester groups are clearly differentiated by the catalyst.

Work is in progress to expand the described methodology to other compounds and optimize it by using other catalysts. This method bears considerable potential for the synthesis of building blocks, because of the two stereocenters and three differentiated carbon atoms in an alkyl chain.

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## Notes and references

† *Synthesis* of (4*S*,6*S*)-6-hydroxyundecan-4-olide: A stainless steel autoclave lined with Teflon and equipped with a stirring bar was charged with 200 mg of methyl 4,6-dioxoundecanoate and 5 ml of absolute MeOH. The solution was freed from air by repeatedly applying and releasing nitrogen pressure.

Approximately 10 mg of the catalyst (*S*)-**6** was added maintaining a steady flow of nitrogen to minimize contact with air. Then the autoclave was closed, a pressure of 40 atm applied, and finally heated to 80 °C for two days. When all educt was consumed (TLC control), the autoclave was cooled, the solvent removed, the product taken up in $Et_2O$ and finally filtered over Celite. TLC control showed two spots, corresponding to **8** and **7**, which could be separated at this point by chromatography, if desired. Treatment of the crude mixture with a small amount of TsOH in $CH_2Cl_2$ transformed **7** into **8**. The product was then purified by chromatography over silica after removal of TsOH with saturated $NaHCO_3$ solution. Yield: 160 mg (91%); $[\alpha]_D^{22}$ +64.4 (*c* 1.30, $Et_2O$); $\delta_H$(500 MHz, $CDCl_3$) 0.89 (t, 3H, H-11, *J* 6.9), 1.25–1.52 (m, 8H, H-7–H-10), 1.68 (ddd, 1H, H5, $J_{4,5}$ 3.3, $J_{5,6}$ 9.8, $J_{5,5'}$ 14.5), 1.80 (ddd, 1H, H-5′, $J_{5',6}$ 2.6 $J_{4,5'}$ 9.5), 1.90 (ddt, 1H, H-3, $J_{3,4}$ 8.5, $J_{2,3}$ 9.5, $J_{3,3'}$ 12.5), 2.38 (m, 1H, H-3′, $J_{3',4}$ 6.5), 2.55 (m, 2H, H-2), 3.89 (m, 1H, H-6), 4.80 (dddd, 1H, H-4); $\delta_C$(100 MHz, $CDCl_3$) 13.98 (C-11), 22.58 (C-9), 25.14 (C-8), 28.52 (C-3), 28.86 (C-2), 31.70 (C-10), 38.02 (C-7), 43.16 (C-5), 68.54 (C-6), 78.10 (C-4), 177.09 (C-1).

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