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CHIRAL CYCLOPENTANOID BUILDING BLOCKS BY ASYMMETRIC ENZYMATIC HYDROLYSIS

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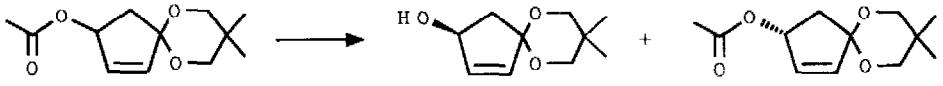
Summary: As chiral building block for the synthesis of natural cyclopentanoid substances, an optically pure and stable ketal of 4-hydroxycyclopent-2-en-1-one was prepared by enantioselective enzymatic hydrolysis of the corresponding racemic acetate.

As an useful starting material for the preparation of cyclopentanoid natural compounds - e.g. prostaglandins - chiral 4-hydroxycyclopent-2-en-1-one gains high importance.[1] Various successful attempts have been made, to prepare optically active cyclopentanoid precursors by enzymatic hydrolysis, starting from 3,5-diacetoxycyclopent-1-ene.[2-6]
Here we report a different approach to achieve both enantiomers of a suited cyclopentanoid precursor[7-8] in high optical purity by asymmetric enzymatic hydrolysis. Since the chiral 4-hydroxycyclopent-2-en-1-one is susceptible to racemization, the racemic ketal of 4-acetoxycyclopent-2-en-1-one 1 was chosen for an enantioselective hydrolysis.[9] Incubation with a commercially available hydrolytic enzyme[10] yields the (S)-alcohol 2 in high optical purity whereas the (R)-ketal 3 remains unhydrolyzed (Scheme 1).[11] Alcohol 2 was easily converted into the corresponding acetate, subsequent selective hydrolysis of the ketal yielded pure 4-(S)-acetoxycyclopentenone without any racemization.



1 2 3

Scheme 1.

In a typical experiment two Erlenmeyer-flasks - each filled with 500 ml of 0.2 m potassium phosphate buffer solution (pH 7.0), 600 mg racemic acetate 1 and 2.5 g lipase (Amano Pharm. Co., Type P) - were incubated for 16 hour on a rotary-shaker at 27°C with 120 rpm. After incubation the buffer solutions were pooled and extracted with 500 ml dichloromethane for three times. The pooled organic phases were dried over Na_2SO_4, filtrated and concentrated to a volume of about 3 ml. The crude residue was fractionated by chromatography on Si-60

columns (Type: "Lobar"; Merck,Darmstadt) with a n-hexane/ethyl acetate gradient (changing from 0 to 20% ethyl acetate). The hydrolysis yielded 170 mg S-alcohol {42% yield; ee >95%; $[\alpha]_D^{21}$ -54.0° (c=1.0, $CHCl_3$)} and 433 mg R-acetate {86% yield; ee >95%; $[\alpha]_D^{21}$ +73.2° (c=1.0, $CHCl_3$)}.

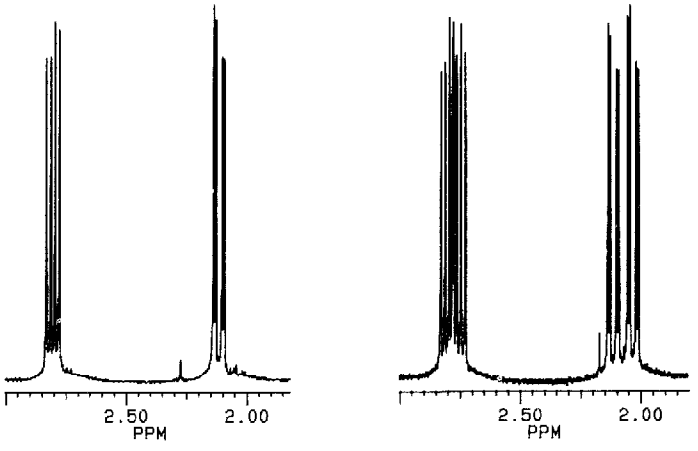


Fig.1
Part of ^1H NMR spectrum (400 MHz, $CDCl_3$) of the MTPA-ester of

a) the chiral alcohol 2

b) the corresponding racemic alcohol

The enantiomeric excess was calculated from the ^1H NMR spectrum of the diastereomeric MTPA-esters (Fig.1).[12]

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