# Synthesis of (1*S*,4*R*)-(−)-4-Hydroxy-2-cyclopentenyl Acetate by a Highly Enantioselective Enzyme-Catalyzed Transesterification in Organic Solvents[1]

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(1*S*,4*R*)-(−)-4-Hydroxy-2-cyclopentenyl acetate (**2**), a versatile intermediate in prostaglandin syntheses, was readily prepared by an efficient enzyme-catalyzed enantioselective monoacetylation of *cis*-2-cyclopenten-1,4-diol (**1**) with 2,2,2-trichloroethyl acetate in the organic solvent system triethylamine/tetrahydrofuran. The chemical yield reached nearly 50%. The enantiomeric excess of the crude product was 95%. It could be raised to more than 99% by a single recrystallization. Commercially available pancreatin, a crude enzyme preparation from porcine pancreas, was used as biocatalyst.

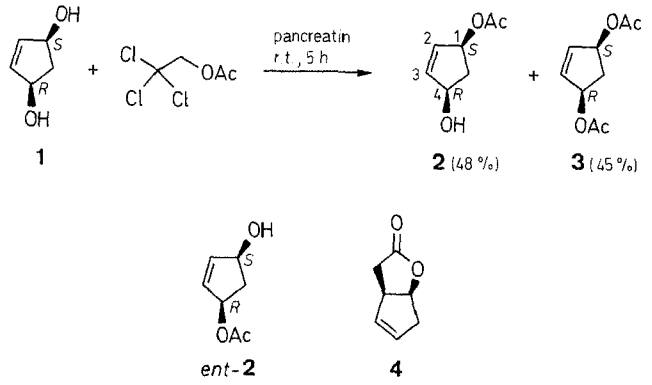
The enantiomerically pure (1*S*,4*R*)-(−)-4-hydroxy-2-cyclopentenyl acetate (**2**) belongs to a group of 1,4-disubstituted 2-cyclopentenes, which are attractive starting materials for the synthesis of prostaglandins[2-5] and other cyclopentanoid natural products.[6] Several approaches to prepare **2**[3,7-10] as well as *ent*-**2**[11-13] from the *meso*-compound **3** by an enantioselective microbial or enzymatic hydrolysis of the *R*- or *S*-acetoxy group have already been described. In principle, both compounds can be transformed via Claisen orthoester rearrangement into the enantiomerically pure lactone **4**, an important intermediate of many prostaglandin syntheses.[14] However, **2** is the preferred enantiomer, since it requires the lower number of reaction steps.[13]

Presently much attention has been focussed on the enzyme-catalyzed processes in organic solvents.[15-19] Following this direction, we have found a very efficient alternative to the above

mentioned procedures to convert the *meso*-diol **1**[20,21] into the monoacetate **2** by transesterification with 2,2,2-trichloroethyl acetate catalyzed by pancreatin in various organic solvents.

When the diol **1** is reacted in a mixture of dry tetrahydrofuran and triethylamine at ambient temperature for 5 hours with an excess of 2,2,2-trichloroethyl acetate in the presence of pancreatin, the starting material is completely converted into a mixture of the monoacetate **2** and the diacetate **3**.

The desired monoacetate **2** is isolated in 48% yield with an enantiomeric excess of 95% by flash chromatography on silica gel. The enantiomeric excess is increased to more than 99% by a single recrystallization from ether/*n*-hexane. The separated diacetate **3** can be hydrolyzed to the diol **1** and recycled.




In the absence of triethylamine the transesterification proceeds very slowly. Solvents like 1,4-dioxane or toluene are also suitable, but with respect to solubility problems and reaction rate, tetrahydrofuran proved to be the solvent of choice.

The described enzyme-catalyzed process was carried out in a multigram scale and represents a significant improvement for the synthesis of the enantiomerically pure prostaglandin intermediate **4**.

THF was dried with sodium wire. $Et_3N$ was distilled from and stored over KOH. Pancreatin, qualified as 6×NF, is a mixture of crude porcine pancreatic enzymes with protease, amylase, and lipase activities. The product, purchased from Fa. Belger, Kleinmachnow, GDR, had a water content of 5.4% (Karl-Fischer-titration) and a lipase activity of 820 U/g (triolein as substrate). The $^1$H-NMR spectrum was recorded at 100 MHz on a Tesla BS-567 spectrometer. Optical rotations were measured with the photoelectric polarimeter Polamat A (Carl Zeiss Jena) at 546 and 578 nm and extrapolated to 589 nm. Differential scanning microcalorimetry (DSC)[22,23] was performed on a DSC-1B (Perkin-Elmer). The enantiomeric excess (e.e.) was calculated on the basis of the optical rotation and of DSC measurements. Melting points were determined on a Boëtius micro melting point apparatus and are corrected. TLC was carried out on silica gel 60 $F_{254}$ (E. Merck) using EtOAc/*n*-hexane (2:1). For visualization, the plates were treated with 5% $H_2SO_4$ in EtOH and heated to 150°C.

**(1*S*,4*R*)-(−)-4-Hydroxy-2-cyclopentenyl Acetate (2):**
$Et_3N$ (5 mL, 36 mmol), 2,2,2-trichloroethyl acetate (50 mL, 365 mmol), and pancreatin (25 g) are added to a solution of *cis*-2-cyclopentene-1,4-diol (**1**)[20,21] (5 g, 50 mmol) in THF (125 mL). After stirring at ambient temperature for 5 h, the suspension is filtered through celite. The filter cake is washed with EtOAc (3×20 mL). Then solvents and excess of 2,2,2-trichloroethyl acetate are distilled off under reduced pressure. The residue is purified by flash chromatography on silica gel (140 g, 25×4 cm, 0.063–0.04 mm) using *n*-hexane/EtOAc (2:1 and 1:1) as eluent. First diacetate **3** (4.1 g, 45%; colourless liquid; $R_f$ 0.75) is eluted, then monoacetate **2**. The TLC homogeneous product solidifies immediately after evaporation of the solvent affording colourless crystalline material; yield: 3.4 g (48%); mp 39–47°C; $[\alpha]_D^{20}$ −62.7° (*c* = 1.0, $CHCl_3$); e.e.: 95%. A single recrystallization from ether/*n*-hexane gives rise to enantiomerically pure **2**; $R_f$ 0.43; mp 46–48°C; $[\alpha]_D^{20}$ −66.3° (*c* = 1, $CHCl_3$); e.e.: 99% (calculated from the optical rotation) and 99.7% (calculated from DSC measurements), respectively [Lit.[9] mp 49–50°C; $[\alpha]_D^{20}$ −66° (*c* = 0.63, $CHCl_3$), e.e.: 98%; Lit.[12] $[\alpha]_D^{20}$ +66.3° for *ent*-**2** (*c* = 1.63, $CHCl_3$), e.e.: 99%); Lit.[11] $[\alpha]_D^{22}$ +75.0° for *ent*-**2** (*c* = 1.16, $CHCl_3$), e.e. ~100%].

$^1$H-NMR ($CDCl_3$/TMS): $\delta$ = 1.58 (dt, 1 H, *J* = 15, 4 Hz, $H_a$ of $CH_2$); 1.86 (s, 1 H, OH, exchangeable with $D_2O$); 1.99 (s, 3 H, $CH_3$); 2.74 (dt, 1 H, *J* = 15, 8 Hz, $H_b$ of $CH_2$); 4.65 (m, 1 H, CHOH); 5.42 (m, 1 H, HCOAc); 5.98 (dd, 2 H, *J* = 15, 6 Hz, CH=CH).

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