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Supporting Information

Highly Efficient Synthesis of Enantiopure Diacetylated C_2-Symmetric Diols by Ruthenium and Enzyme-Catalyzed DYKAT

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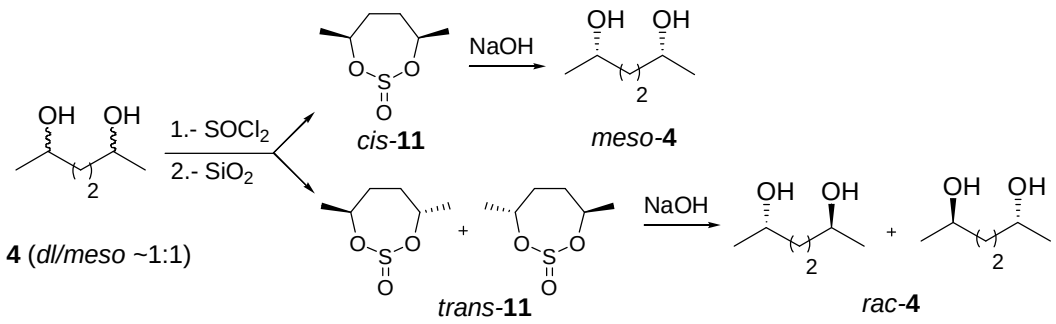
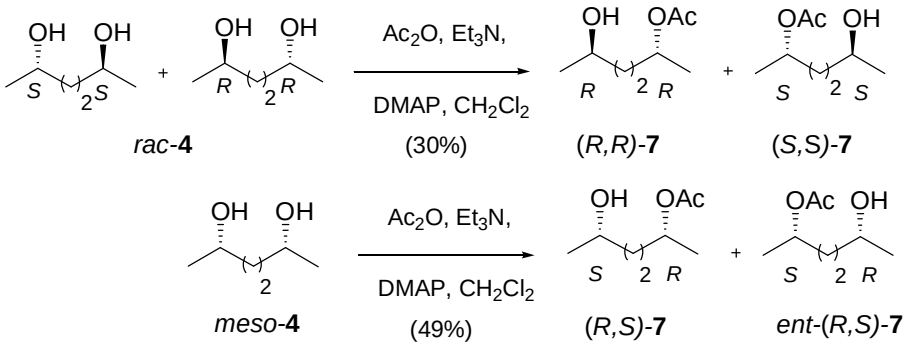
General Methods. NMR spectra were recorded at 23 °C on the following spectrometers: Varian Unity-400 (400 MHz in ^{1}H and 100 MHz in ^{13}C), and Varian Unity-300 (300 MHz in ^{1}H and 75 MHz in ^{13}C) with chloroform (7.26 ppm ^{1}H, 77.0 ppm ^{13}C) as an internal reference. All the ^{13}C were proton-decoupled. Optical purity was determined on a Varian 3800 analytical GC equipped with a CP-Chirasil-Dex CB column. Solvents were purified and dried using standard procedures. Thin layer chromatography was carried out using TLC aluminum sheets of silica gel (Merck 60-F_{254}). Chromatography purifications were carried out using flash grade silica gel (Merck 60, 35-70 μm) with distilled solvents. Extractive work-up refers to partitioning of the crude reaction between an organic solvent and water, phase separation, drying (Na_2SO_4 or $MgSO_4$), and evaporation under reduced pressure. All reactions were carried out under an argon atmosphere unless otherwise noted. *p*-Chlorophenyl acetate[1] was prepared according to literature procedures. The *ee* of diols was determined on the diacetate by chiral GC (unless otherwise noted: CP-Chirasil-Dex column, constant flow: 1.8 mL/min, hydrogen carrier gas. Temperature program: 70 °C for 3 min, then up to 140 °C with 2 °C/min; then up to 180 °C with 100 °C/ min and keep for 10 min).

***rac*-2,5-Hexanediol (*rac*-4) and *meso*-2,5-Hexanediol (*meso*-4).**



Commercial *dl/meso*-2,5-hexanediol **4** (*dl/meso* ≈ 1:1) was converted into cyclic sulfites **10** according to a literature procedure.[2] After 1h at room temperature the reaction mixture was concentrated on silica. Flash chromatography (pentane/Et_2O 10:1) gave pure fractions of *cis*-**11** and *trans*-**11** as confirmed by ^1H NMR.[**Fehler! Textmarke nicht definiert.**] Sulfite *cis*-**11** (2.74 g, 16.7 mmol) was refluxed in 2M NaOH (60 mL) for 1 h and the reaction mixture was allowed to cool to room temperature. The solution was saturated with solid NaCl and extracted with EtOAc. The combined organic phases were pre-adsorbed onto silica and the solvent was removed in vacuo. Purification by chromatography (SiO_2, pentane/EtOAc 1:1 to 0:1) gave *meso*-**4** (1.76 g, 89%) as white crystals. Its NMR spectra were in agreement with those previously reported.[3] Similarly, sulfite *trans*-**11** (1.6 g, 9.75 mmol) was refluxed in 2M NaOH (35 mL) for 1 h and the reaction mixture was allowed to cool to room temperature. The solution was saturated with solid NaCl and extracted with EtOAc. The combined organic phases were concentrated under reduced pressure and purified by chromatography (SiO_2, pentane/EtOAc 1:1 to 0:1) to yield *rac*-**4** (1.04 g, 90%) as white crystals. Its NMR spectra were in agreement with those previously reported.[**Fehler! Textmarke nicht definiert.**]

General procedure for the chemical mono-acylation of diols. Synthesis of racemic mixtures of monoacetates (7).

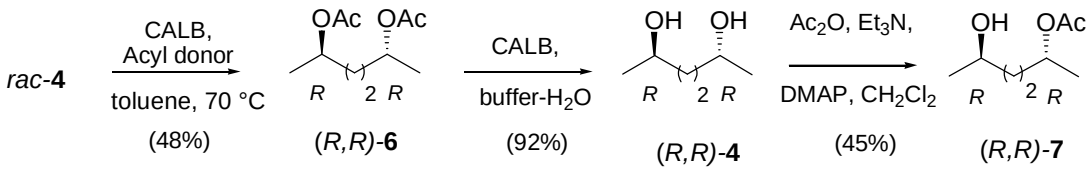


To a stirred solution of *rac*-**4** (600 mg, 5.1 mmol), DMAP (6.2 mg, 0.05 mmol), and Et_3N (516 mg, 5.1 mmol) in CH_2Cl_2 (10 mL)

at room temperature was added Ac_2O (417 mg, 4.08 mmol). The reaction mixture was stirred at room temperature for 2 h, and then poured into 1M HCl (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with aqueous Na_2CO_3, water and brine. Drying ($MgSO_4$) followed by flash chromatography (SiO_2, pentane/EtOAc 2:1) furnished a racemic mixture of (*R,R*)-**7** (GC, R_t = 20.40 min) and (*S,S*)-**7** (GC, R_t = 16.72 min) as a colorless oil (230 mg, 30 %).[4] The NMR spectra were in agreement with those previously reported.[5]

Similarly, chemical acylation of *meso*-**4** afforded a racemic mixture of monoacetates (*R,S*)-**7** (GC, R_t = 19.80 min) and *ent*-(*R,S*)-**7** (GC, R_t = 17.18 min) (49 % yield).[**Fehler! Textmarke nicht definiert.**] The NMR spectra were in agreement with those previously reported.[**Fehler! Textmarke nicht definiert.**]

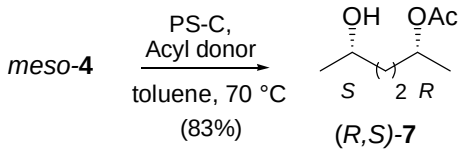
(2*R*,5*R*)-5-Acetoxy-2-hexanol ((*R,R*)-7)



To a stirred solution of *rac*-**4** (600 mg, 5.1 mmol) and *p*-chlorophenyl acetate (1.7 g, 10.2 mmol) in toluene (17 mL) was added CALB (153 mg). The flask was evacuated and filled with argon before it was sealed and then heated in an oil bath at 70 °C. The reaction mixture was stirred for 3 h and then allowed to cool to room temperature. The enzyme was filtered off, and the solvent was evaporated. Purification by flash chromatography (SiO_2, pentane/EtOAc 5:2) furnished diacetate (*R,R*)-**6** as a yellowish oil (495 mg, 48 %). A mixture of (*R,R*)-**6** (495 mg, 2.44 mmol) and CALB (73.2 mg) in a 0.1 M phosphate buffer pH 7.5 (15 mL) was stirred at room temperature overnight. The solution was filtered and the

enzyme was washed with EtOAc. The organic phase was separated, and the aqueous was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, pentane/EtOAc 5:2) furnished diacetate (*R,R*)-**4** as a white solid (265 mg, 92 %). Following the general procedure, (*R,R*)-**4** was chemically acetylated to yield (*R,R*)-**7** (GC, R_t = 20.40 min) (45%).[**Fehler! Textmarke nicht definiert.**]

(2*S*,5*R*)-5-Acetoxy-2-hexanol ((*R,S*)-7).



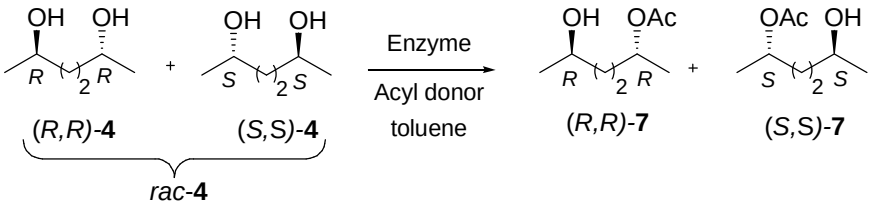
To a stirred solution of *meso*-**4** (200 mg, 1.7 mmol) and *p*-chlorophenyl acetate (577 mg, 3.4 mmol) in toluene (6 mL) was added PS-C “Amano II” (50 mg). The flask was evacuated and filled with argon before it was sealed and then heated in an oil bath at 70 °C. The reaction mixture was stirred for 3 h and then allowed to cool to room temperature. The enzyme was filtered off and washed with EtOAc. The combined organic layers were purified by flash chromatography (SiO_2, pentane/EtOAc 1:1) to furnish monoacetate (*R,S*)-**7** (GC, R_t = 19.80 min) as a colorless oil (225 mg, 83 %).[**Fehler! Textmarke nicht definiert.**]

5-Hydroxy-hexan-2-one (8).

To a solution of acetonyl acetone (8 g, 70.1 mmol) in isopropanol (80 mL) under an argon atmosphere was added $NaBH_4$ (666 mg, 17.6 mmol) at 0 °C.. The reaction mixture was stirred for 4 h at room temperature. Aqueous HCl (10%) was added slowly until the pH was adjusted to 6.5. The white solid obtained was filtered off and the filtrate was evaporated. After purification by column chromatography

(SiO_2, 2:1 pentane/EtOAc) 5-hydroxy-hexan-2-one (**8**) was obtained as a colorless oil (1.2 g, 15%):[6] ^{1}H NMR (400 MHz, $CDCl_3$) *d* 3.79 (br s, 1H), 2.59 (t, *J* = 6.9 Hz, 1H), 2.57 (t, *J* = 6.9 Hz, 1H), 2.16 (s, 3H), 1.81-1.61 (m, 2H), 1.2 (d, *J* = 6.0 Hz, 3 H). Traces of tetrahydro-2,5-dimethyl-2-furanol were detected by ^{1}H NMR.

Kinetic resolution of a racemic mixture of (*R*,*R*)-4 and (*S*,*S*)-4.

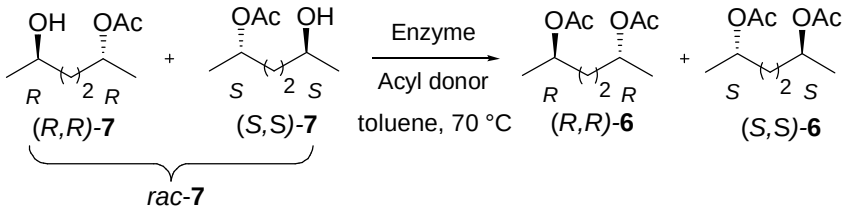


PS-C-Catalyzed KR: To a solution of racemic monoacetate (*R,R*)-**7**/(*S,S*)-**7** (30 mg, 0.19 mmol) and *p*-chlorophenyl acetate (95 mg, 0.56 mmol) in toluene (0.5 mL) was added 5.6 mg of PS-C "Amano II". The flask was evacuated and filled with argon and stirred at 70 °C (oil bath temperature). After 22 min, the enzyme was filtered off. GC analysis showed a mixure of diol, monoacetate and diacetate. The diols were separated from the mixture of monoacetates and diacetates, which were collected together, by silica gel chromatography (SiO_2, pentane/EtOAc 5:2 → 0:1). The *ee* of the diol (18% *ee*) was measured after chemical acylation to the diacetates. The monoacetate/diacetate fraction was analyzed by GC, and showed a 1.9:1 mixture of (*R,R*)-**7** in >99% *ee* and diacetate (*R,R*)-**6** in >99% *ee*.

CALB-Catalyzed KR: Similarly, to a solution of racemic monoacetate (*R,R*)-**7**/(*S,S*)-**7** (142 mg, 1.20 mmol) and *p*-chlorophenyl acetate (614 mg, 3.60 mmol) in toluene (3 mL) was added 36 mg of CALB. The flask was evacuated and filled with argon and stirred at room temperature. After 2.5 min, the enzyme was filtered off. GC analysis showed a mixture of diol,

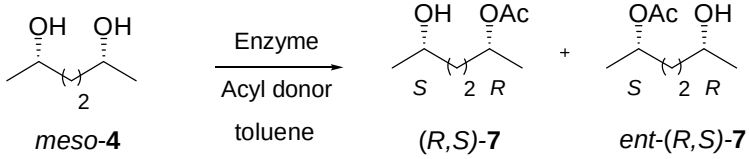
monoacetate and diacetate which were separated by chromatography (SiO_2, pentane/EtOAc 5:2 → 0:1). The *ee* of the diol (8% *ee*) was measured after chemical acylation to the diacetates. The *ee* of the monoacetate fraction was >99%, and the *ee* of the diacetate fraction was >99%. The monoacetate/diacetate ratio was not determined.

Kinetic resolution of racemic monoacetate (*R*,*R*)-7/(*S*,*S*)-7.



To a solution of racemic monoacetate (*R*,*R*)-**7**/(*S*,*S*)-**7** (30 mg, 0.19 mmol) and *p*-chlorophenyl acetate (95 mg, 0.56 mmol) in toluene (0.6 mL) was added 5.6 mg of the appropriate enzyme (CALB or PS-C "Amano II"). The flask was evacuated and filled with argon and stirred at 70 °C (oil bath temperature). After 30 minutes the enzyme was filtered off. GC analysis showed a mixture of monoacetates and diacetates.

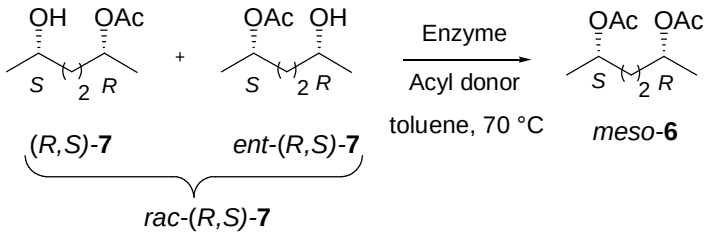
General procedure for the desymmetrization of *meso*-4.



To a solution of *meso*-**4** (30 mg, 0.25 mmol) and *p*-chlorophenyl acetate (130 mg, 0.76 mmol) in toluene (0.6 mL) was added 7.6

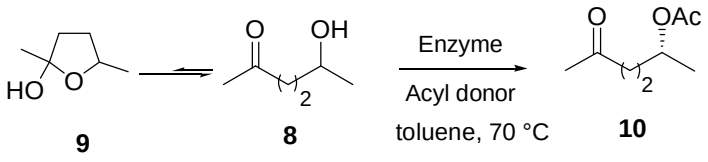
mg of the appropriate enzyme (CALB or PS-C “Amano II”). The flask was evacuated and filled with argon and stirred at room temperature in the case of CALB, and at 70 °C (oil bath temperature) in the case of PS-C. After 15 minutes the enzyme was filtered off. Formation of diacetate was not detected; GC analysis showed a mixture of only monoacetate and diol in each case. The conversion was determined by ^{1}H NMR spectroscopy, and the *ee* of the product was determined by GC analysis.

General procedure for the kinetic resolution of racemic monoacetate(*R,S*)-7/*ent*-(*R,S*)-7.



To a solution of racemic monoacetate (*R,R*)-**7**/(*S,S*)-**7** (15 mg, 0.09 mmol) and *p*-chlorophenyl acetate (42 mg, 0.25 mmol) in toluene (0.3 mL) was added 3 mg of the appropriate enzyme (CALB or PS-C “Amano II”). The flask was evacuated and filled with argon and stirred at at 70 °C (oil bath temperature). After 30 minutes the enzyme was filtered off. The conversion was determined by ^{1}H NMR spectroscopy, and the *ee* of the remaining starting material was determined by GC analysis.

Kinetic resolution of 5-Hydroxy-hexan-2-one (8).



To a solution of 5-hydroxy-hexan-2-one (**8**) (25 mg, 0.22 mmol) and *p*-chlorophenyl acetate (73 mg, 0.43 mmol) in toluene (0.5 mL) was added 6.4 mg of the appropriate enzyme (CALB or PS-C

"Amano II"). The flask was evacuated and filled with argon and stirred at 70 °C (oil bath temperature). After 30 minutes the enzyme was filtered off. The conversion was determined by ^{1}H NMR, and the *ee* of the product (**10**) was determined by GC. **10**: ^{1}H NMR (400 MHz, $CDCl_3$) *d* 4.89 (sext, *J* = 6.8 Hz, 2H), 2.47 (t, *J* = 6.8 Hz, 2H), 2.15 (s, 3H), 2.02 (s, 3H), 1.87-1.78 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 3H).

General procedure for the DYKAT of 2,5-hexanediol (4):

A solution of *t*-BuOK (0.5 M in THF; 100 µL, 0.05 mmol) was added to a 10 mL Schlenk flask. The THF was carefully removed under vacuum and the flask filled with argon. PS-C "Amano II" (80 mg), Na_2CO_3 (106 mg, 1 mmol) and Ru-catalyst **2** (32 mg, 0.05 mmol) were quickly added. The Schlenk flask was evacuated and filled with argon. After addition of toluene (2 mL) the mixture turned dark orange. After 6 min 2,5-hexanediol (**4**) (123 µL, 1 mmol) was added, and after 4 min isopropenyl acetate (330 µL, 3 mmol) was added. The reaction mixture was stirred for 6 h at 50 °C, and then filtered, concentrated, and analyzed: >99% yield, *R,R/meso* = 92:8, >99% *ee* (chiral GC, CP-Chirasil-Dex column). Purification by column chromatography (SiO_2; pentane/diethyl ether 98:2) afforded (*R,R*)-2,5-diacetoxyhexane as a colorless oil (193 mg, 95% yield, *R,R/meso* = 92:8, >99% *ee* (chiral GC, CP-Chirasil-Dex column)). The NMR spectra were in agreement with those previously reported in the literature.[Fehler! Textmarke nicht definiert.]

DYKAT of 2,4-pentanediol (3)

Ruthenium complex **2** (32 mg, 0.05 mmol), CALB (6 mg) and Na_2CO_3 (106 mg, 1 mmol) were placed in a Schlenk flask. The flask was evacuated and filled with argon and then toluene (2 mL) was added. Addition of *t*-BuOK (0.5 M in THF; 180 µL, 0.09 mmol) to

the yellow suspension resulted in a color change to orange. The mixture was then stirred for 6 min, and then 2,4-pentanediol (110 μL, 1 mmol) was added. On the addition of the diol the mixture turned red. After 4 min isopropenyl acetate (330 μL, 3 mmol) was added and the flask was placed in an oil bath at 50 °C. After 20 h the reaction mixture was filtered and analyzed: 96% yield, *R,R/meso* = 97:3[7] (achiral GC, CP-Sil 8 CB column, constant column flow: 1.8 mL/min, hydrogen carrier gas. Temperature program: 50 °C for 2 min, then up to 180 °C with 5 °C/min; then up to 300 °C with 80 °C/ min and keep for 5 min. Retention times: (*R,R*)-**5** = 12.32, *meso*-**5** = 13.36 min), >99% *ee* (chiral GC, CP-Chirasil-Dex column, constant flow: 1.8 mL/min, hydrogen carrier gas. Temperature program: 90 °C for 3 min, then up to 115 °C with 3 °C/min; then up to 200 °C with 80 °C/ min and keep for 8 min. Retention times: (*R,R*)-**5** = 6.67, *meso*-**5** = 7.96 min).

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[2] G. Caron, R. J. Kazlauskas, *Tetrahedron: Asymmetry* **1994**, *5*, 657-664.
[3] H. Ikeda, E. Sato, T. Sugai, H. Ohta, *Tetrahedron* **1996**, *52*, 8113-8122.
[4] The reaction mixture contained also diacetate (**6**) and unreacted racemic diol (**4**).
[5] M. Edin, J.-E. Bäckvall, *J. Org. Chem.* **2003**, *68*, 2216–2222.
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