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An improved procedure for the lipase-catalysed kinetic resolution of *endo-endo-cis*-bicyclo[3.3.0]octane-2,6-diol — synthesis of potential C_2-symmetric enantiomerically pure bidentate auxiliaries

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Abstract: An improved procedure for the kinetic resolution of *endo-endo-cis*-bicyclo[3.3.0]octane-2,6-diol *rac*-**1** by transesterification with vinyl acetate catalysed by lipase from *Pseudomonas cepacia* in an organic solvent which yields both enantiomers with an enantiomeric excess of >95% is described. The configuration at both stereogenic centres bearing hydroxy groups has been inverted by treatment of the corresponding mesylates with caesium acetate in the presence of 18-crown-6 to afford, after deacetylation, the corresponding enantiomerically pure diastereoisomeric *exo-exo-cis*-diols. © 1997 Elsevier Science Ltd

endo-endo-cis-Bicyclo[3.3.0]octane-2,6-diol *rac*-**1** has been used as a versatile starting material for the synthesis of racemic prostaglandins.[1] Biocatalytic separation of the enantiomers of *rac*-**1** was achieved either by esterase-catalysed enantiomer-selective hydrolysis of its diacetate with *Plexaura homomalla* Esper[2] or by pancreatin-catalysed enantiomer-selective transesterification of *rac*-**1** with 2,2,2-trichloroethyl acetate in tetrahydrofuran/triethyl amine.[3] The hydrolytic way exhibits some disadvantages such as moderate selectivity, very low substrate concentration and time-consuming product isolation. Thus, only the slow reacting enantiomer could be isolated with an ee of 88% in 41% chemical yield.[2] Some of these problems could be overcome by using the pancreatin-catalysed transesterification.[3] However, it was not possible to separate the racemate in one step affording both enantiomers with ees >95% due to the moderate selectivity of the enzyme. At 30–35% conversion the faster reacting enantiomer was isolated as its diacetate (1*S*,2*R*,5*S*,6*R*)-**3** with an ee of 97–99% besides unconverted diol (1*R*,2*S*,5*R*,6*S*)-**1** with an ee of 55–68% and a small amount of the monoacetate (1*S*,2*R*,5*S*,6*R*)-**2** with an ee of ca. 40%. However, a higher degree of conversion caused a decrease of the ee of the faster reacting enantiomer. Therefore, the slower reacting diol (1*R*,2*S*,5*R*,6*S*)-**1** could be obtained only after a second enantiomer-selective transesterification of the enantiomerically enriched fraction.

Furthermore, the enantiomers of *rac*-**1** have been separated *via* formation of diastereoisomeric esters of (−)-menthyloxyacetic acid followed by chromatographic separation and recrystallisation.[4]

In addition to its versatility as starting material for prostaglandins, these C_2-symmetric diols in enantiomerically form should be potential chiral auxiliaries e.g. as ligands for enantiomerically pure reagents or catalysts like other molecules with C_2-symmetry.[5] In order to obtain both enantiomers of *rac*-**1** more efficiently and in larger quantities the existing procedures had to be improved. Finally, simultaneous inversion at both stereogenic centres bearing hydroxy groups to afford the diastereosiomers of *rac*-**1** was envisaged.

The aim to obtain both enantiomers of *rac*-**1** with ees of >95% prompted us to reinvestigate the lipase-catalysed kinetic resolution of *rac*-**1** in order to improve the previously described procedure.[3] The usefulness of lipase-catalysed reactions to prepare enantiomerically pure building blocks is well demonstrated[6] and the outcome of the reactions can be improved by variation of the reaction conditions,

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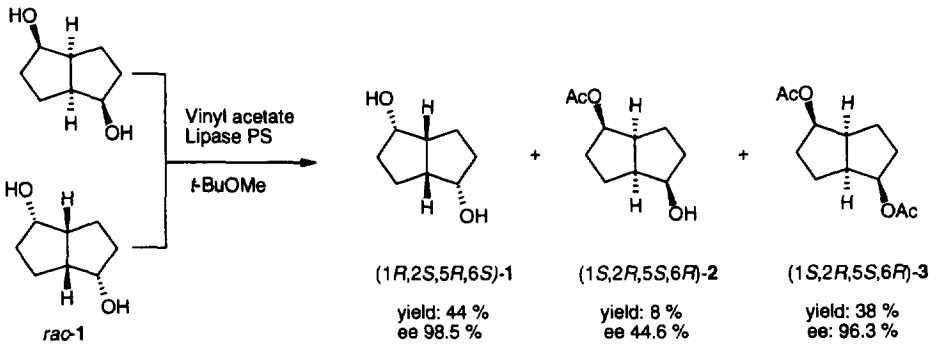
for example enzyme or solvent engineering. Due to our experience in resolutions of further diols with lipase from *Pseudomonas cepacia* (lipase PS from Amano)[7] we have chosen this enzyme showing very high substrate flexibility combined with high selectivity and here we report an improvement of the previously described resolution of *rac*-**1**.[3]

Treatment of a solution of the racemic diol *rac*-**1** in solvents such as *tert*-butyl methyl ether or tetrahydrofuran with vinyl acetate and lipase from *Pseudomonas cepacia* (lipase PS from Amano) yielded, according to Scheme 1 in a sequential reaction (Figure 1), the slow reacting unconverted diol (1*R*,2*S*,5*R*,6*S*)-**1** in a yield of 44% with an ee of 98.5% and the diacetate (1*S*,2*R*,5*S*,6*R*)-**3** in a yield of 38% with an ee of 96.3%. The monoacetate (1*S*,2*R*,5*S*,6*R*)-**2** was isolated as the minor product in a yield of 8% with an ee of 44.6%.



Scheme 1.

The aim to epimerise the enantiomerically highly enriched diol (1*R*,2*S*,5*R*,6*S*)-**1** into its *exo-exo*-diastereoisomer (1*R*,2*R*,5*R*,6*R*)-**6** was achieved *via* mesylation of the diol and subsequent nucleophilic substitution with caesium acetate. The epimerisation of several sulfonates including methane sulfonates derived from secondary monohydroxy compounds by reaction with caesium salts has been demonstrated.[8] Therefore, the diol (1*R*,2*S*,5*R*,6*S*)-**1** was transformed into its dimesylate (1*R*,2*S*,5*R*,6*S*)-**4** which was recrystallised to become enantiomerically pure as demonstrated after the

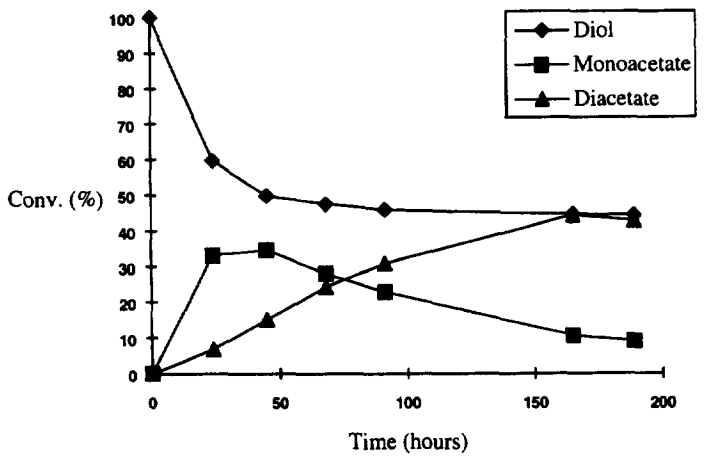
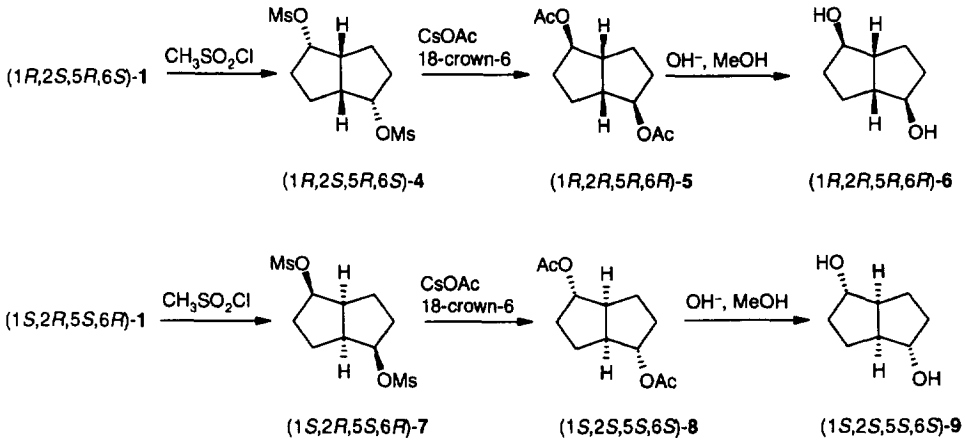


Figure 1. Time course for the transesterification of *rac*-**1** with vinyl acetate in *tert*-butyl methyl ether in the presence of lipase from *Pseudomonas cepacia*.

next step (see below). The latter compound was treated with anhydrous caesium acetate in toluene in the presence of 18-crown-6 to furnish the diacetate (1*R*,2*R*,5*R*,6*R*)-**5** in 63% yield with an ee of >99% as shown by HPLC[9] in a smooth reaction under simultaneous inversion at both stereogenic centres bearing the mesyl groups. The *exo-exo*-stereochemistry of (1*R*,2*R*,5*R*,6*R*)-**5** was confirmed by its ^{13}C NMR-spectrum which shows only six signals for twelve carbon atoms due to the C_2-symmetry of the molecule. Finally, deacetylation of (1*R*,2*R*,5*R*,6*R*)-**5** with methanol in the presence of a strong basic ion-exchange resin afforded the *exo-exo*-diol (1*R*,2*R*,5*R*,6*R*)-**6** in almost quantitative yield (Scheme 2).



Scheme 2.

The mesylation–substitution procedure proceeding under inversion described for one enantiomeric series was applied onto the enantiomeric *endo-endo*-diol (1*S*,2*R*,5*S*,6*R*)-**1**. The latter diol was obtained from the diacetate (1*S*,2*R*,5*S*,6*R*)-**3** by saponification with methanol in the presence of a strong basic ion-exchange resin and was finally converted into the *exo-exo*-diol (1*S*,2*S*,5*S*,6*S*)-**6** (Scheme 2).

In conclusion the lipase-catalysed kinetic resolution of the C_2-symmetric racemic diol *rac*-**1** has been improved so that both enantiomers can be obtained with ees >95% in one step using vinyl acetate in *tert*-butyl methyl ether in the presence of lipase from *Pseudomonas cepacia*. The configuration at the stereogenic centres in 2- and 6-positions of the enantiomerically pure *endo-endo*-diols could be inverted to afford the corresponding *exo-exo*-diastereoisomers. These transformations represent a chemo-enzymatic access to novel potential enantiomerically pure C_2-symmetric diols which should be useful as chiral auxiliaries such as ligands for novel chiral catalysts or reagents.

Experimental

All reactions, except those which were monitored by HPLC, were followed by TLC on glass plates coated with a 0.25 mm layer of silica gel. Compounds were visualised with a 3.5% solution of molybdatophosphoric acid in ethanol and/or by UV light. HPLC was carried out on a Merck-Hitachi system consisting of L-6200A Pump, Differential Refractometer RI-71 and Chromato-Integrator D-2500. Flash chromatography was performed with silica gel 60 (0.040–0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ if not otherwise indicated on the Varian instruments UNITYplus-500 or -300 at 500 or 300 and 125 or 75 MHz, respectively. Mass spectra were recorded on the Autospec VG. Optical rotations were measured on a Perkin–Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}.

(1R,2S,5R,6S)-Bicyclo[3.3.0]octane-2,6-diol (1R,2S,5R,6S)-1 and (1S,2R,5S,6R)-bicyclo[3.3.0]-octane-2,6-diyl diacetate (1S,2R,5S,6R)-3 by kinetic resolution

A solution of the diol *rac*-**1** (4.0 g, 28.5 mmol) in *tert*-butyl methyl ether (80 mL) was treated with vinyl acetate (18.4 mL), lipase PS (0.80 g) and stirred at room temperature under HPLC monitoring on Lichrosorb Si60® [100×4 mm, 7 µm, *n*-heptane/ethyl acetate (3:1), 1 mL/min, RI-detection] for 190 h. The reaction mixture was filtered through a pad of Celite® and separated by flash chromatography on silica (500 g, 20×7 cm) with *n*-hexane/ethyl acetate (2:1) to afford in the order of elution the diacetate (1*S*,2*R*,5*S*,6*R*)-**3** (2.45 g, 38%), the monoacetate (1*S*,2*R*,5*S*,6*R*)-**2** (0.43 g, 8%) and the diol (1*R*,2*S*,5*R*,6*S*)-**1** (1.78 g, 44%). (1*S*,2*R*,5*S*,6*R*)-**3**: $[\alpha]_D^{20}$ +104.3 (*c* 1.0, $CHCl_3$) {Ref.[3] $[\alpha]_D^{25}$ +113.1 (*c* 2.26, $CHCl_3$) for ee >99%}. (1*R*,2*S*,5*R*,6*S*)-**1**: $[\alpha]_D^{20}$ +42.5 (*c* 1.0, $CHCl_3$) {Ref.[3] $[\alpha]_D^{25}$ +44.0 (*c* 2.122, $CHCl_3$) for ee 90%}.

The ee of the products was determined as follows: (1*S*,2*R*,5*S*,6*R*)-**3** and (1*S*,2*R*,5*S*,6*R*)-**2** were deacetylated by reaction with methanol in the presence of the strong basic ion-exchange resin Dowex® 1×2-100 (OH^--form). The ee of the diols were determined by HPLC[10] and found to be 96.3% for the diacetate (1*S*,2*R*,5*S*,6*R*)-**3**, 44.6% for the monoacetate (1*S*,2*R*,5*S*,6*R*)-**2** and 98.5% for the diol (1*R*,2*S*,5*R*,6*S*)-**1**.

(1R,2S,5R,6S)-Bicyclo[3.3.0]octane-2,6-diyl bismethane sulfonate (1R,2S,5R,6S)-4

A solution of the diol (1*R*,2*S*,5*R*,6*S*)-**1** in dry dichloromethane (10 mL) and pyridine (2 mL) was treated dropwise under ice-cooling with methane sulfonyl chloride (1.83 g, 16.1 mmol). The reaction mixture was warmed up to room temperature, stirred for 6 h, washed with a saturated aqueous solution of $NaHCO_3$ (2×5 mL) and water (2×5 mL). The organic phase was dried with Na_2SO_4 and evaporated to dryness by co-distillation with toluene. Recrystallisation of the solid residue from ethanol afforded pure dimesylate (1*R*,2*S*,5*R*,6*S*)-**4** (1.34 g, 72%) with an ee >99% as determined after the next step (see below).

M.p. 77–79°C (ethanol); ^1H NMR: δ=1.64–1.78 (m, 2 H), 1.82–2.04 (m, 6 H), 2.78 (m, 2 H), 3.04 (s, 6 H), 5.06 (m, 2 H); ^{13}C NMR: δ=22.75, 33.11, 38.34, 45.20, 83.74; MS (CI, NH_3): *m/z*=316 (M^++NH_4, 100%); $[\alpha]_D^{20}$ +66.5 (*c* 1.0, MeOH); calc. C 40.25, H 6.08, S 21.49, found C 40.28, H 6.24, S 21.70.

(1R,2R,5R,6R)-Bicyclo[3.3.0]octane-2,6-diyl diacetate (1R,2R,5R,6R)-5

A solution of the dimesylate (1*R*,2*S*,5*R*,6*S*)-**4** (1.4 g, 4.7 mmol) in toluene (35 mL) was treated with anhydrous caesium acetate (2.70 g, 14.2 mmol), 18-crown-6 (0.620 g, 2.35 mmol) and stirred at 110°C for 14 h. The solvent was removed under reduced pressure and the residue was dissolved in water (20 mL). The aqueous mixture was extracted with ethyl acetate (3×20 mL). The organic extracts were dried with Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by flash-chromatography on silica (50 g, 20×2.2 cm) with *n*-hexane/ethyl acetate (10:1) to afford the diacetate (1*R*,2*R*,5*R*,6*R*)-**5** (0.664 g, 63%) in enantiomerically pure form as determined by HPLC.[9] B. p. 150°C (1 Pa, Kugelrohr); ^1H NMR: δ=1.38–1.46 (m, 2 H), 1.64–1.71 (m, 2 H), 1.78–1.86 (m, 2 H), 1.97–2.08 (m, 2 H), 2.02, (s, 6 H), 2.75 (m, 2 H), 4.82 (m, 2 H); ^{13}C NMR: δ=21.33, 27.96, 31.47, 48.28, 82.09, 170.92; MS (FAB, magic bullet): *m/z*=453 (2 M^++H, 15%), 227 (M^++H, 15%), 167 (100%); $[\alpha]_D^{20}$ +27.7 (*c* 1.0, $CHCl_3$); calc. C 63.69, H 8.02, found C 63.78, 8.07 H.

(1R,2R,5R,6R)-Bicyclo[3.3.0]octane-2,6-diol (1R,2R,5R,6R)-6

A solution of the diacetate (1*R*,2*R*,5*R*,6*R*)-**5** (0.452 g, 2 mmol) in methanol (30 mL) was treated with Dowex® 1×2-100 (OH^--form, 1 g) and stirred at room temperature for 24 h. The ion-exchange resin was filtered off, the solvent was removed under reduced pressure to furnish the diol (1*R*,2*R*,5*R*,6*R*)-**6** (0.28 g, 99%). M.p. 91–92°C (ethyl acetate); ^1H NMR: δ=1.25–1.33 (m, 2 H), 1.35 (s, 2 H), 1.55–1.63 (m, 2 H), 1.67–1.75 (m, 2 H), 1.98–2.07 (m, 2 H), 2.48 (m, 2 H), 3.92 (m, 2 H); ^{13}C NMR ($C_2D_2Cl_4$):

δ=27.57, 34.20, 51.03, 79.88; MS (FAB, magic bullet): *m/z*=285 (2 M^++H, 10%), 133 (100%); $[\alpha]_D^{20}$ +37.0 (*c* 1.0, $CHCl_3$); calc. C 67.57, H 9.92, found C 67.55, H 9.91.

(1S,2R,5S,6R)-Bicyclo[3.3.0]octane-2,6-diol (1S,2R,5S,6R)-1

A solution of the diacetate (1*S*,2*R*,5*S*,6*R*)-**3** (1.5 g, 6.7 mmol) in methanol (150 mL) was treated with Dowex® 1×2-100 (OH^--form, 2 g) and stirred for 24 h at room temperature. The ion-exchange resin was filtered off and washed twice with methanol. The combined filtrates were evaporated to dryness under reduced pressure to furnish the diol (1*S*,2*R*,5*S*,6*R*)-**1** (0.862 g, 92%). $[\alpha]_D^{20}$ −41.6 (*c* 1.0, $CHCl_3$).

The enantiomers of the second series have been prepared as described above.

(1S,2R,5S,6R)-Bicyclo[3.3.0]octane-2,6-diyl bismethane sulfonate (1S,2R,5S,6R)-7

M.p. 77–79°C, (ethanol), $[\alpha]_D^{20}$ −66.8 (c 1.0, MeOH).

(1S,2S,5S,6S)-Bicyclo[3.3.0]octane-2,6-diyl diacetate (1S,2S,5S,6S)-8

$[\alpha]_D^{20}$ −28.5 (*c* 1.0, $CHCl_3$).

(1S,2S,5S,6S)-Bicyclo[3.3.0]octane-2,6-diol (1S,2S,5S,6S)-9

M.p. 91–92°C (ethyl acetate), $[\alpha]_D^{20}$ −37.1 (*c* 1.0, $CHCl_3$).

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9. Chromatographic data: stationary phase: Chiralcel OJ® (250×4.6 mm); mobile phase: *n*-heptane/ethanol (99:1); flow rate: 1 mL/min; temperature: 22°C; detection: RI; first eluted: (1*R*,2*R*,5*R*,6*R*)-**5**: R_{t1}=10.10 min, k'_1=2.61, second eluted (1*S*,2*S*,5*S*,6*S*)-**5**: R_{t1}=11.40 min, k'_2=3.07; k'_2/k'_1=1.18, Res.=5.6.
10. Chromatographic data: stationary phase: Chiralpak AD® (250×4.6 mm); mobile phase: *n*-heptane/ethanol (9:1); flow rate: 1 mL/min; temperature: 22°C; detection: RI; first eluted: (1*S*,2*R*,5*S*,6*R*)-**1**: R_{t1}=7.86 min, k'_1=1.80, second eluted (1*R*,2*S*,5*R*,6*S*)-**1**: R_{t1}=8.75 min, k'_2=2.12; k'_2/k'_1=1.18, Res.=4.7.

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