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Enzymatic desymmetrization of a centrosymmetric diacetate

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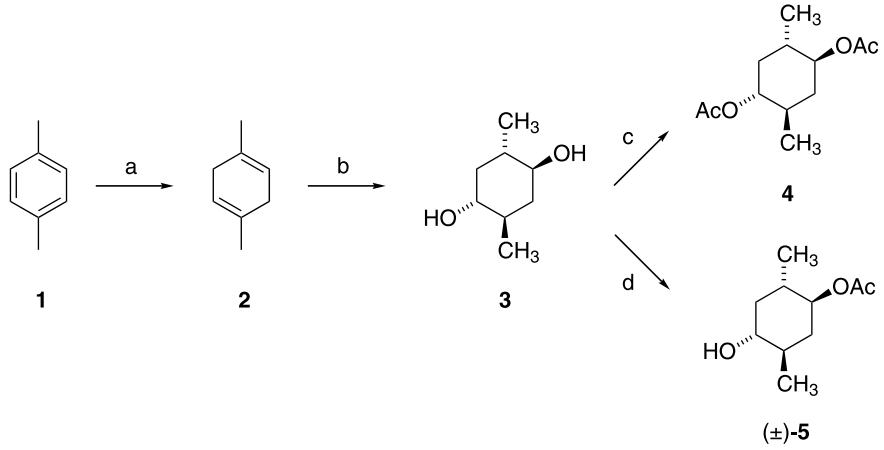
Abstract—An enantiomerically pure cyclohexanol was synthesized starting from *para*-xylene **1**. The key steps are a stereoselective twofold hydroboration and a pig liver esterase (PLE)-catalyzed desymmetrization of the centrosymmetric cyclohexanediacetate **4**.

1. Introduction

The desymmetrization of readily available *meso* compounds to yield enantiomerically enriched products has proven to be a valuable synthetic operation.[1] While this strategy has been widely applied to C_s symmetrical substrates, few examples of the desymmetrization of molecules belonging to the molecular point group C_i ($=S_2$), or other centrosymmetric substrates, have been described. As early as 1958, Prelog et al. reported the enantiotopos-selective reduction of a centrosymmetric decalin-dione using baker's yeast.[2] Very recently, the desymmetrization of a C_i-symmetrical bis-epoxide via metal-catalyzed epoxide hydrolysis was disclosed.[3] We now report a route to an enantiomerically pure cyclohexanol featuring an enzymatic hydrolysis of the corresponding centrosymmetric diacetate.

2. Results and discussion

Birch-reduction of *para*-xylene **1**[4] yielded 1,4-dimethylcyclohexa-1,4-diene **2**, which subsequently underwent hydroboration with excess 9-BBN-H. Oxidative workup gave the crystalline centrosymmetric diol **3** as the only isolated diastereomer and regioisomer in 39% overall yield. No C_2-symmetric diol was observed. Presumably, the high diastereoselectivity of the reaction results from preferential addition of the second borane molecule to the side opposite the bulky 9-BBN moiety in the



Scheme 1. Preparation of the centrosymmetric diacetate **4**. *Reagents and conditions*: (a) Na, NH_3, MeOH, THF; (b) i. 9-BBN (3 equiv.), THF, ii. H_2O_2, NaOH, 39%; (c) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 98%; (d) *n*-BuLi (1 equiv.), Ac_2O, 54%.

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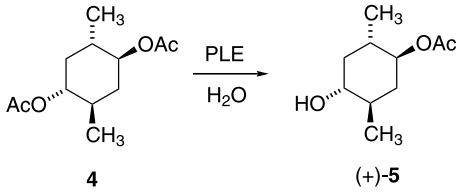
monoadduct. Upon treatment with Ac_2O in the presence of NEt_3 and DMAP, the diol **3** was converted into the diacetate **4** in 98% yield. Monodeprotonation of the diol **3** with *n*-BuLi (1 equiv.) followed by addition of Ac_2O, gave the racemic monoacetate **5** in 54% yield (Scheme 1).

Arguably, esterases such as pig liver esterase (PLE) have proven to be the most widely successful enzymes in asymmetric synthesis.[5] They are cheap, stable, do not require a coenzyme and tolerate a wide variety of substrates. The PLE-catalyzed hydrolysis of **4** gave rise to the enantiomerically pure cyclohexanediol monoacetate (+)-**5** in 95% yield and >99.5% e.e. (Table 1). Importantly, no further hydrolysis of the second acetate to afford **3** could be detected (by GC). This implies that the high e.e. does not result from kinetic resolution following the initial enantiotopos-discriminating hydrolysis.[6]

Table 1. Enzymatic hydrolysis of the diacetate **4**



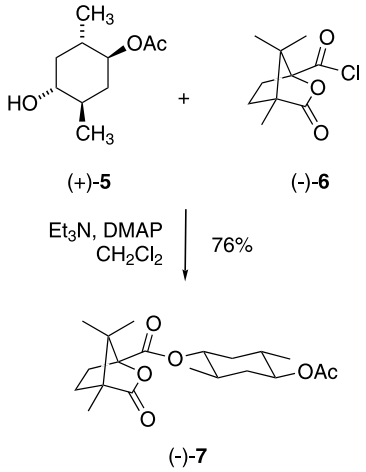
4 (+)-**5**

Entry	Additive	Conversion (%)[a]	React. time (h)	E.e.[b] (%)
1	–	100	20	>99.5
2	10% DMSO	100	17	>99.5

[a] Reaction was monitored by GC.
[b] ee was determined by chiral GC.

It has been reported that the presence of various organic cosolvents have a dramatic effect on the rate and selectivity of enzyme-catalyzed reactions.[7,8] However, we observed only moderate rate enhancement for the hydrolysis of **4** in the presence of 10% DMSO and no significant impact on the enantioselectivity (Table 1).

The absolute configuration of our enantiomerically pure monoacetate (+)-**5** was established by X-ray crystallography. Unfortunately, the *para*-bromo-benzoate of (+)-**5** did not yield high quality single crystals. Therefore, the camphanic acid ester derivative (–)-**7** was synthesized in 76% yield using standard conditions (Scheme 2). The latter was crystallized and analyzed by X-ray diffraction (Fig. 1).[9] The X-ray structure shows that the *pro*-(*R*)-acyl group is preferentially hydrolyzed by PLE. This is in accordance with the results of Schneider and Laumen, who examined the enzymatic hydrolysis of C_s-symmetric prochiral diesters.[10]



Scheme 2. Determination of the absolute configuration of (+)-**5**.

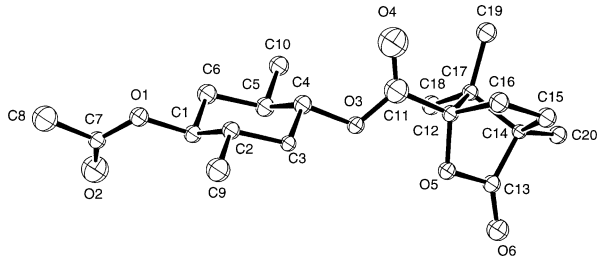


Figure 1. X-Ray structure of (–)-**7**.

3. Conclusion

In summary, we have achieved an asymmetric synthesis of the cyclohexanol (+)-**5** from readily available racemic starting materials in a highly enantioselective fashion. Our work demonstrates the usefulness of PLE for the desymmetrization of centrosymmetric diacetates. Studies on the scope and limitations of this methodology and its application to the total synthesis of natural products are underway and will be reported in due course.

4. Experimental

4.1. General

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. PLE was purchased from Sigma. Melting points were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C spectra were recorded on a Bruker DRX 500 or Bruker AMX 300. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Mass spectra were recorded on a VG ProSpec. Silica gel chromatography was carried out using ICN SiliTech 32–63 D 60 Å. Thin-layer chromatography (TLC) was performed with Merck Silica

Gel 60 plates. Elemental analysis was performed by the Microanalytical Laboratory operated by the UCB College of Chemistry. X-Ray analysis was performed on a Bruker SMART CCD area-detector diffractometer.

4.2. Compounds

4.2.1. 2,5-Dimethylcyclohexan-1,4-diol, 3. To a nitrogen-purged reaction flask containing a solution of 9-BBN in THF (0.5 M, 18 mL, 9.0 mmol, 3 equiv.) was added diene **2** (324 mg, 3 mmol, 1 equiv.). The solution was heated to reflux for 24 h. After cooling to 0°C, aqueous NaOH (2.5 M, 5 mL) and 30% aqueous H_2O_2 (5 mL) was added carefully. Upon complete addition, the mixture was heated to reflux for an additional hour, cooled to 0°C, and satd aq. NaCl (25 mL) and EtOAc (25 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×20 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography (hexanes/EtOAc, 1:2 v/v) to provide the desired diol **3** as a colorless solid (170 mg, 39%). Mp 156°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.03$ (d, $J=6.5$ Hz, 3H, CH_3), 1.45 (m, 2H), 1.51 (m, 2H), 1.93 (m, 1H), 3.20 (dd, $J=11.0$, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=18.1$, 38.5, 41.9, 75.3. MS (EI): 144 [M^+], 126 [M^+-H_2O] (90), 71 (50), 57 (100); IR (KBr): $\nu=3308$, 2923, 1453, 1033 cm^{-1}. Anal. calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 67.01; H, 11.53%.

4.2.2. 1,4-Diacetoxy-2,5-dimethylcyclohexane, 4. To an ice-cooled solution of diol **3** (200 mg, 1.4 mmol, 1 equiv.) in dry CH_2Cl_2 (20 mL) was added NEt_3 (870 μL, 6.24 mmol, 4.5 equiv.) followed by Ac_2O (590 μL, 6.24 mmol, 4.5 equiv.) and a trace of DMAP. After stirring at rt for 3 h (TLC) the solution was concentrated and the crude material purified by chromatography (hexanes/EtOAc, 1:1 v/v) to provide the diacetate **4** as a colorless solid (310 mg, 98%). Mp 96°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.90$ (d, $J=6.5$ Hz, 3H, CH_3), 1.14 (m, 2H), 1.70 (m, 1H), 2.04 (s, 3H, OAc), 4.41 (dd, $J=11.0$, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=17.8$, 21.1, 35.4, 37.8, 76.4, 170.8; MS (EI): 228 [M^+] (5), 169 [M^+–HOAc] (50), 108 (100); IR (KBr): $\nu=2957$, 1727, 1372, 1243, 1025 cm^{-1}. Anal. calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.30; H, 9.00%.

4.2.3. (+)-(1*R*,2*R*,4*S*,5*S*)-4-Acetoxy-2,5-dimethyl-1-cyclohexanol, (+)-5. A 3.2 M suspension of PLE in aq. $(NH_4)_2SO_4$ (140 μL, 2 U) followed by **4** (150 mg, 0.66 mmol, 1 equiv.) was added to aq. Tris–HCl (50 mL, pH 7.5) at rt. The reaction was monitored by GC analysis and TLC and terminated after complete conversion of the starting material. The mixture was then extracted with Et_2O (5×50 mL) and the combined organic layers were washed with brine, dried, and concentrated. Chromatography of the residue (Et_2O/*n*-pentane 1:1 v/v) gave (+)-**5** as a colorless oil (116 mg, 95%). $[\alpha]_D=48.0$ (*c* 0.42, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.90$ (d, $J=6.5$ Hz, 3H, CH_3), 1.14 (m, 2H), 1.70 (m, 1H), 2.04 (s, 3H, OAc), 4.41 (dd, $J=11.0$, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=17.8$, 21.1, 35.4, 37.8, 76.4, 170.8; MS (EI): 228 [M^+] (5), 169 [M^+–HOAc] (50), 108 (100); IR (KBr): $\nu=3428$, 2930, 1731, 1373, 1246, 1108, 1025 cm^{-1}. Anal. calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.25; H, 10.09%. The e.e. was determined by GC on a chiral column: HP 6850 Series GC system, HP 7683 Series Injector, detector: FID, 250°C, column: Astec 71023, β-cyclodextrin, 30.0 m×250 μm×0.25 μm, method: 90°C, 5 min; +5°C/min, 135°C, 70 min, −15°C/min. Retention time: 34.2 min.

4.2.4. (−)-Camphanic acid (4-acetoxy-2,5-dimethyl)-cyclohexyl ester, (−)-7. A solution of alcohol (+)-**5** (18.6 mg, 0.1 mmol, 1 equiv.), acid chloride (−)-**6** (26.0 mg, 0.12 mmol, 1.2 equiv.), and NEt_3 (21 μL, 0.15 mmol, 1.5 equiv.) in dry CH_2Cl_2 (5 mL) was stirred first at 0°C for 1 h, then at rt for 15 h. The solvent was evaporated, and the crude residue purified by chromatography (hexanes/EtOAc 1:1 v/v) to provide 27.8 mg (76%) ester (−)-**7** as a colorless solid. Mp 134°C; $[\alpha]_D=-8.7$ (*c* 0.85, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.92$ (d, $J=6.5$ Hz, 6H, $2CH_3$), 0.96 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.16 (m, 1H), 1.22 (m, 1H), 1.66–1.83 (m, 3H), 1.92 (ddd, $J=15.3$, 10.7, 4.6 Hz, 1H), 2.00–2.10 (m, 3H), 2.05 (s, 3H, CH_3), 2.40 (ddd, $J=14.9$, 10.7, 4.2 Hz, 1H), 4.42 (dt, $J=10.8$, 4.3 Hz, 1H), 4.56 (dt, $J=10.8$, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=9.7$, 16.8, 16.9, 17.8, 17.9, 29.0, 30.7, 35.2, 35.4, 37.7, 37.8, 54.1, 54.8, 76.2, 78.1, 91.1, 167.2, 170.8, 178.1; MS (FAB pos.): 367 [M+H$^+$] (25), 109 (100); IR (KBr): $\nu=2967$, 1789, 1729, 1451, 1375, 1243 cm^{-1}.

Acknowledgements

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9. X-Ray analysis for (−)-**7** (crystallized from CH_2Cl_2/hexanes). Empirical formula: $C_{20}H_{30}O_6$, colorless plates, crystal size: 23.0×0.16×0.06 mm, crystal system: triclinic, space group: $P1_1$, unit cell dimensions: $a=6.309(1)$, $b=6.668(1)$, $c=12.406(3)$ Å, $\alpha=96.895(3)$, $\beta=102.879(3)$, $\gamma=98.669(3)°$, $V=496.5(2)$ Å^3, $Z=1$, density = 1.226 g/cm^3, absorption coefficient = 0.89 cm^{-1}, $F(000)=198.0$; diffractometer used: Bruker SMART CCD, radiation: Mo-Kα ($\lambda=0.71069$ Å), $2\Theta_{max}=49.7°$, unique reflections: 925, $R_{int}=0.029$, $R=0.104$, $wR=0.111$, $R_{all}=0.169$, largest diff. peak: 0.70 and −0.55 e Å^{-3}. The crystallographic data for (−)-**7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CDCC 186333. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1 EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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