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Kinetic Resolution of *trans*-2-(1-Pyrazolyl)cyclohexan-1-ol Catalyzed by Lipase B from *Candida Antarctica*

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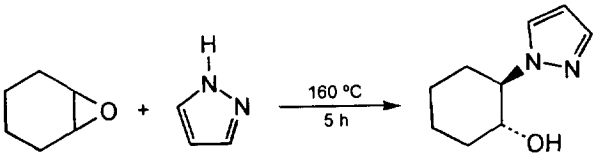
Abstract: The reaction of epoxycyclohexane with pyrazole gives *trans*-2-(1-pyrazolyl)cyclohexan-1-ol *rac*-**1** in high yields. *Rac*-**1** forms dimers in the solid state by linking one (1R,2R)- and one (1S,2S)-enantiomer via strong intermolecular H-bonds. In the presence of the immobilized lipase B of *candida antarctica* yeast, *rac*-**1** is acylated enantioselectively with isopropenylacetat acting as the acylating agent. Crystallisation of the reaction mixture gives enantiomerically pure (1S,2S)-**1**, which forms a helical structure in the solid state. The absolute configuration of this alcohol was examined by X-ray structure analysis of the esterification product with 5-oxo-(2R)-(trichloromethyl)-1,3-dioxolane-(4S)-acetylchloride **3** . Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Amino alcohols are widely used as ligands in main group and transition metal chemistry.[1] Chiral derivatives were found to be efficient ligands in different enantioselective reactions, e. g. the catalytic alkylation of aldehydes with dialkylzinc compounds.[2] In particular ligands with a rigid backbone give high enantiomeric excesses. In this paper we describe the synthesis of *trans*-2-(1-pyrazolyl)cyclohexan-1-ol **1** , a γ-amino alcohol with both functionalities attached at the stereogenic carbon centres of a conformationally well defined and rigid cycloalkane. As the lipase B of the *candida antarctica* yeast is known to be an efficient enzyme for the kinetic resolution of chiral cyclohexanols,[3] we applied its immobilised form for an enantioselective esterification of the racemic alcohol **1**.

RESULTS AND DISCUSSION

The reaction of pyrazole and epoxycyclohexane at high temperatures leads to *rac-trans*-2-(1-pyrazolyl)cyclohexan-1-ol (*rac*-**1**) in 80 % yield.



rac-**1**

^{1}H NMR investigations clearly proved the expected diequatorial arrangement of the substituents at the cyclohexane ring ($^3J_{H,H}$ = 9.2 Hz). Infrared measurements in toluene solution showed the presence of

intermolecular H-bridges depending on the concentration of the alcohol. With increasing concentrations of *rac*-**1** an absorption at 3408 cm^{-1} increases in intensity relative to an absorption at 3590 cm^{-1}. This observation is characteristic for an association process of alcohols via H-bridges. Ebulioscopic measurements confirmed a dependence of the degree of association from the solvent (40 °C; *n*-hexane: 42 % assoc., $CHCl_3$: 0 % assoc.).

In the solid state, *rac*-**1** forms dimers via H-bridges (O-H···N), each dimer contains one molecule of (1R,2R)- and (1S,2S)-**1**. No additional H-bridges are observed between these dimers (Figure 1).

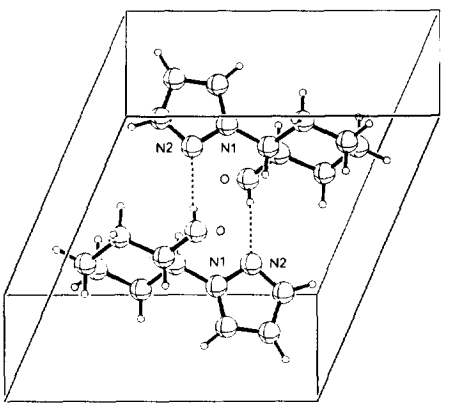
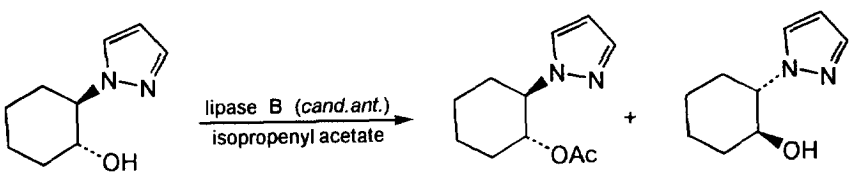


Figure 1. PLUTON plot of the dimeric structure of *rac*-**1**[4]

The kinetic resolution of *rac*-**1** was carried out with isopropenyl acetate as acylating agent in the presence of catalytic amounts of the immobilized lipase B from *candida antarctica*. We monitored the reaction by GC/MS and quenched it after 55 % conversion of the alcohol. Filtration of the solution and evaporation of the solvent (isopropenyl acetate) gave an oily mixture containing the ester **2** and the alcohol **1**, from which we obtained **1** in its enantiomerically pure form *en*-**1** (ee > 99 %) after three recrystallisations from *n*-hexane.



rac-**1** **2** *en*-**1**

Infrared spectroscopic investigations of *en*-**1** (in toluene) correspond with the IR-data of *rac*-**1**: two absorptions at 3590 and 3398 cm^{-1} are observed, the latter is shifted to lower wavenumbers ($\Delta\nu$ = 10 cm^{-1}), which indicates slightly weakened OH-bonds. Ebulioscopic measurements show a degree of association for *en*-**1** of 25 % in *n*-hexane (40 °C). We assume that the lower degree of association is responsible for the lower solubility of *en*-**1** and enables its separation and purification by crystallisation.

The solid state structure of *en*-**1** is again dominated by H-bridges (O-H···N), which are now generating an helical arrangement of the amino alcohol molecules instead of dimers (Figure 2).

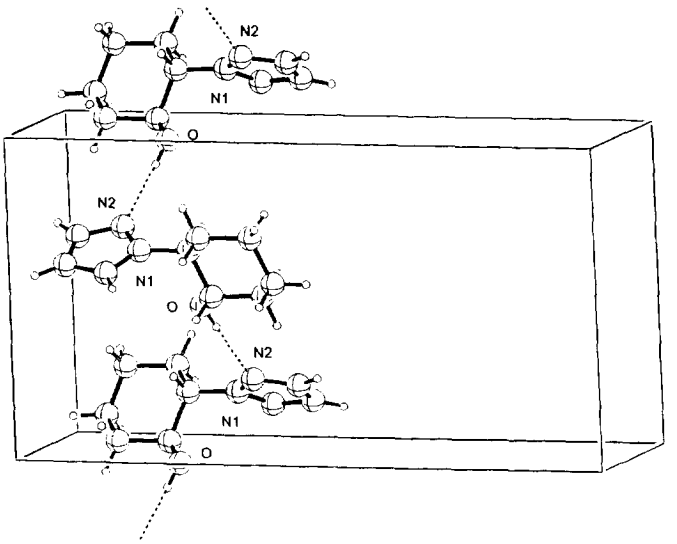
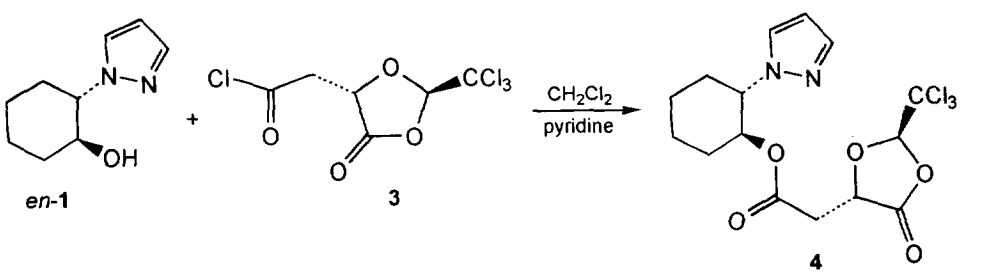


Figure 2. PLUTON plot of the helical structure of *en*-**1**[4]

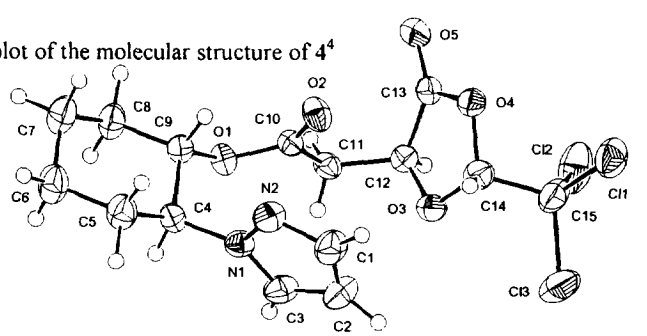
Both structures show almost the same intramolecular bond length and angles, only the torsion angles H-O-C-H (*rac*-**1**: -176 °, *en*-**1**: -75 °) are different. The determination of the absolute configuration of the esterification products was impossible from X-ray structure data of *en*-**1**.

Treatment of *en*-**1** with (1S)-(-)-camphanic chloride led to the corresponding camphanic acid ester, which did not give suitable crystals for X-ray structure analysis. We finally succeeded with a chiral acid chloride derived from malic acid: reaction of *en*-**1** with 5-oxo-(2R)-(trichloromethyl)-1,3-dioxolane-(4S)-acetylchloride **3** [5] led to the corresponding ester **4** in almost quantitative yield.



X-ray structure analysis now allowed the determination of the absolute configuration of the pyrazolylcyclohexanol fragment. Figure 3 shows the molecular structure of **4**.

Figure 3. PLATON plot of the molecular structure of **4**[4]



The absolute configurations of the four stereogenic centers of **4** are (4S), (9S), (12S), and (16R), which proves that (1R,2R)-**1** is esterified by the enzyme.

Similar results were obtained by the resolution of 2-methylcyclohexanol with S-ethyl thiooctanoate and *cis*-1,2-cyclohexanediol (desymmerization) with vinyl acetate in the presence of lipase B from *candida antarctica*.[3] The carbon atoms with the esterified alcohol moiety showed to be in a (R)-configuration. We are now going to examine complex formation between transition metals and the chiral γ-amino alcohol **1**, especially with regard to catalytic applications.

EXPERIMENTAL

Instruments: The NMR (Bruker DPX 400 and AMX 250), mass (gas chromatograph Hewlett-Packard HP 5890 Series II coupled with a mass selective detector HP 5971 A), and infrared spectra (Perkin-Elmer 1600 Series FTIR), and all elemental analyses were carried out at Anorganisch-chemisches Institut, Technische Universität München. For the determination of enantiomeric excesses we used a gaschromatograph (Chrompack CP 9000) equipped with a chiral capillary column (Macherey & Nagel, Lipodex D, 50 m). The numbering of the NMR data accords to the numbering scheme of figure 3. Lipase B from candida antarctica (SP 435) was purchased from Novo Nordisk A/S, Denmark.

***rac-trans*-2-(1-pyrazolyl)cyclohexan-1-ol *rac*-1**. Pyrazole (68 g, 1.0 mol) was dissolved in epoxycyclohexane (98 g, 1.0 mol) and the solution heated under reflux to 160 °C. After 5 hours the reaction mixture was cooled to room temperature and 800 ml *n*-hexane were added to the resulting oil. The mixture was then refluxed for 10 min. White crystals precipitated, which were separated by filtration, washed with cold *n*-hexane and dried under vacuo. Pure *rac*-**1** was obtained (133.0 g, 80% yield) as a white microcrystalline solid after Kugelrohr distillation. Crystals suitable for X-ray structure analysis were grown from *n*-hexane. Mp.: 67 °C. - Anal. Calcd for $C_9H_{14}N_2O$ (166.2): C 65.03, H 8.49, N 16.85, O 9.63. Found: C 64.96, H 8.49, N 16.84, O 9.71. - IR (KBr, cm^{-1}): ν = 3245 vs (ν_{OH}), 3107 m, 2932 s, 2857 m, 1468 m, 1402 m, 1297 m, 1187 m, 1074 s, 985 m, 758 s, 630 m. - ^1H NMR (250.13 MHz, 25 °C, $CDCl_3$): δ = 7.50 (d, $^3J_{1\text{-H, }2\text{-H}}$ = 2.0 Hz, 1-H), 7.43 (dd, $^3J_{2\text{-H, }3\text{-H}}$ = 2.0 Hz, $^3J_{1\text{-H, }3\text{-H}}$ = 0.6 Hz, 3-H), 6.20 (t, 2-H), 3.80 (m, 2H, $^3J_{4\text{-H,}9\text{-H}}$ = 9.2 Hz, 4-H, 9-H), 3.55 (d, $^3J_{OH,\ 9\text{-H}}$ = 2.0 Hz, OH), 2.11 - 1.26 (m, 8H, CH_2). - $^{13}C\{^1H\}$ NMR (62.9 MHz, 25 °C, $CDCl_3$): δ = 139.1 (C-1), 127.9 (C-3), 105.0 (C-2), 73.1 (C-9), 66.5 (C-4), 33.1 (C-8), 30.8 (C-5), 24.7 (C-6), 23.8 (C-7). - MS (EI): m/z (%) = 166 (5) [M^+], 95 (27) [$C_3H_3N_2C_2H_4^+$], 81 (100) [$C_3H_3N_2CH_2^+$], 69 (49) [$C_3H_5N_2^+$], 57 (10) [$C_3H_5O^+$], 55 (15) [$C_4H_7^+$], 41 (58) [$C_3H_5^+$], 31 (21) [CH_2OH^+].

(1R,2R)- and (1S,2S)-1. A mixture of rac-**1** (1.66 g, 10.0 mmol), isopropenylacetate (6.6 ml, 60.0 mmol) and the immobilized lipase B (80 mg) was stirred at 37 °C for 6 h. The reaction was quenched by filtration and 50 ml of *n*-hexane were added. The mixture was stirred 1 h and approx. 50 % of the solvent was removed in vacuo. 100 ml of *n*-hexane were added. Crude (1S,2S)-**1** (> 85 % ee by GC) precipitated as a white microcrystalline solid. After three recrystallisations from *n*-hexane, enantiomerically pure (1S,2S)-**1** was obtained (99 % ee by GC, 25 % yield). $[\alpha]_D^{25}$ = 32.5 (c = 1.00, toluene). The combined mother liquors, which contain (1R,2R)-acetate **2** and *rac*-**1**, were evaporized to dryness and the resulting oily residue was hydrolyzed with KOH in methanol. GC analysis showed an enentiomeric excess of (1R,2R)-**1** of 28 %.

Analytical data of *rac*-2. Anal. Calcd for $C_{11}H_{16}N_2O_2$ (208.1): C 63.44, H 7.74, N 13.45. Found: C 63.31, H 7.80, N 13.43. - IR (KBr, cm^{-1}): ν = 3450 s, 3129 s, 3112 s, 2940 vs, 2865 vs, 1732 vs ($\nu_{C=O}$), 1560 s, 1444 vs, 1400 vs, 1375 vs, 1292 vs, 1241 vs, 1196 vs, 1130 s, 1093 vs, 1039 vs, 954 vs, 752 vs. - ^{1}H NMR (400.13 MHz, 25 °C, $CDCl_3$): δ = 7.47 (d, $^3J_{1\text{-H, }2\text{-H}}$ = 2,1 Hz, 1-H), 7.37 (d, $^3J_{2\text{-H, }3\text{-H}}$ = 2.1 Hz, 3-H), 6.19 (t, 2H), 5.05 (dt, $^3J_{4\text{-H, }9\text{-H}} = {}^3J_{8\text{-H, }9\text{-Hb}}$ = 10.4 Hz, $^3J_{8\text{-H, }9\text{-Ha}}$ = 4.7 Hz, 9-H), 4.10 (ddd, $^3J_{4\text{-H, }9\text{-H}}$ = 10.2 Hz, $^3J_{4\text{-H, }5\text{-Hb}}$ = 4.3 Hz, $^3J_{4\text{-H, }5\text{-Ha}}$ = 12.2 Hz, 4-H), 1.82 (s, 3H, CH_3), 2.11 - 1.26 (m, 8H, CH_2). - $^{13}C\{^1H\}$ NMR (100.61 MHz, 25 °C, $CDCl_3$): δ = 169.3 (C=O)138.5 (C-1), 127.5 (C-3), 104.5 (C-2), 73.9 (C-9), 63.8 (C-4), 31.2 (C-8), 30.8 (C-5), 24.2 (C-6), 23.4 (C-7), 20.3 (CH_3). - MS (EI): m/z (%) = 208 (1) [M^+], 165 (2) [(M - C_2H_3O)$^+$], 148 (70) [(M - $C_2H_3O_2$)$^+$], 95 (15) [$C_3H_3N_2C_2H_4^+$], 81 (70) [$C_3H_3N_2CH_2^+$], 69 (61) [$C_5H_9^+$], 54 (14) [$C_4H_4^+$], 43 (100) [$C_2H_3O_2^+$], 41 (33) [$C_3H_5^+$].

Synthesis of 4. *(1S,2S)*-**1** (1.66 g, 10.0 mmol) and 5-oxo-(2R)-(trichloromethyl)-1,3-dioxolane-(4S)-acetylchloride **3** [5] (2.81 g, 10.0 mmol) were dissolved in 30 ml of abs. $CHCl_3$ at 0 °C. 2 ml of abs. pyridine were added dropwise over a period of 30 minutes. The mixture was stirred at room temp. for 3 d. 20 ml of brine were added, the aqueous solution was extracted with $CHCl_3$ (3x30 ml), the combined organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. After recrystallisation from CH_2Cl_2/*n*-hexane large colorless crystalls of **4** (1.65 g, 40%) were isolated. Mp: 170 °C. - $[\alpha]_D^{25}$ = 31.1 (c = 0.90, toluene). - Anal. Calcd for $C_{15}H_{17}Cl_3N_2O_5$ (411.67): C 43.76, H 4.16, Cl 25.84, N 6.81. Found: C 43.78, H 4.30, Cl 25.84, N 6.88. - IR (KBr, cm^{-1}): ν = 3134 vw, 3113 w, 2954 m, 2934 m, 2862 m, 1824 vs, 1738 vs ($2x\nu_{C=O}$), 1401 m, 1392 m, 1339 m, 1300 m, 1203 s, 1184 vs, 1122 m, 1080 m, 1040 s, 1022 s, 870 m, 854 m, 817 s (ν_{CCl3}), 755 s, 617 s. - ^{1}H NMR (400.13 MHz, 25 °C, $CDCl_3$): δ = 7.46 (d, $^3J_{1\text{-H, }2\text{-H}}$ = 2.0 Hz, 1-H), 7.37 (d, $^3J_{2\text{-H, }3\text{-H}}$ = 2.0 Hz, 3-H), 6.19 (t, 2-H), 5.63 (d, $^4J_{12\text{-H, }14\text{-H}}$ = 1.7 Hz, 14-H), 5.12 (dt, $^3J_{4\text{-H, }9\text{-H}} = {}^3J_{8\text{-Ha, }9\text{-H}}$ = 10.4 Hz, $^3J_{8\text{-Hb, }9\text{-H}}$ = 4.6 Hz, 9-H), 4.67 (dt, $^3J_{11\text{-Ha, }12\text{-H}} = {}^3J_{11\text{-Hb }12\text{-H}}$ = 3.8 Hz, $^4J_{12\text{-H, }14\text{-H}}$ = 1.7 Hz, 12-H), 4.08 (ddd, $^3J_{4\text{-H, }9\text{-H}}$, $^3J_{4\text{-H, }5\text{-Ha}}$ = 10.1, 12.3 Hz, $^3J_{4\text{-H, }5\text{-Hb}}$ = 4.3 Hz, 4-H), 2.80, 2.75 (2xdd, 2H, $^2J_{11\text{-Ha, }11\text{-Hb}}$ = 17.8 Hz, $^3J_{11\text{-Ha, }12\text{-H}}$ = 3.8 Hz, $^3J_{11\text{-Hb, }12\text{-H}}$ = 3.8 Hz, 11-Ha, 11-Hb), 2.16 - 1.33 (m, 8H, CH_2). - $^{13}C\{^1H\}$ NMR (100.25 MHz, 25 °C, $CDCl_3$): δ = 170.2 (C-13), 167.6 (C-10), 139.3 (C-1), 128.2 (C-3), 105.2 (C-14), 104.9 (C-2), 97.7 (C-15), 75.9 (C-9), 71.4 (C-12), 64.2 (C-4), 35.6 (C-11), 31.5 (C-8), 31.1 (C-5), 24.6 (C-6), 23.8 (C-7). - MS (EI): m/z (%) = 411 (1) [M^+], 376 (1) [(M - Cl)$^+$], 293 (1) [(M - CCl_3)$^+$], 193 (1) [$C_{10}H_{13}N_2O_2^+$], 165 (3) [($C_{10}H_{13}N_2O_2$ - CO)$^+$], 149 (42) [$C_9H_{13}N_2^+$], 148 (100) [$C_9H_{12}N_2^+$], 120 (13) [($C_9H_{12}N_2$ - N_2)$^+$], 95 (7) [$C_3H_3N_2C_2H_4^+$], 81 (63) [$C_3H_3N_2CH_2^+$], 69 (98) [$C_3H_4N_2^+$], 55 (10) [$C_4H_7^+$], 41 (19) [$C_3H_5^+$].

X-ray structure analyses. X-ray data were collected on a ENRAF NONIUS MACH3 (*rac*-**1**, *en*-**1**) and on a Stoe IPDS **4** . Structure solution was carried out with SHELXS-86[6a] (*rac*-**1**, *en*-**1**) and SIR-92[6b] **4** , structure refinement with SHELXL-92.[6c] All hydrogen atoms were located from difference-Fourier maps and refined with isotropic thermal parameters. Experimental data: *rac*-**1**: crystal system: monoclinic; space group: P21/c; a 9.771(3), b 9.7360(10), c 10.183(3) Å; α 90, β 112.100(10), γ 90 °; V 897.5(4) Å^3; Z 4; R 0.0439. *en*-**1**:crystal system: orthorhombic; space group: P212121; a 5.2810(10), b 9.4080(10), c 17.929(2) Å; α 90, β 90, γ 90 °; V 890.8 (2) Å^3; Z 4; R 0.0309. **4**: crystal system: orthorhombic; space group: P212121; a

5.6029(3), b 9.1036(8), c 35.613(2) Å; ; α 90, β 90, γ 90 °; V 1816.5(2) Å^3; Z 4; R 0.0366. Further details of the crystal structure investigations can be obtained either from the authors or the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (Germany).

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