Enzymatic resolution of stereoisomers of 2-iodocyclohexanol

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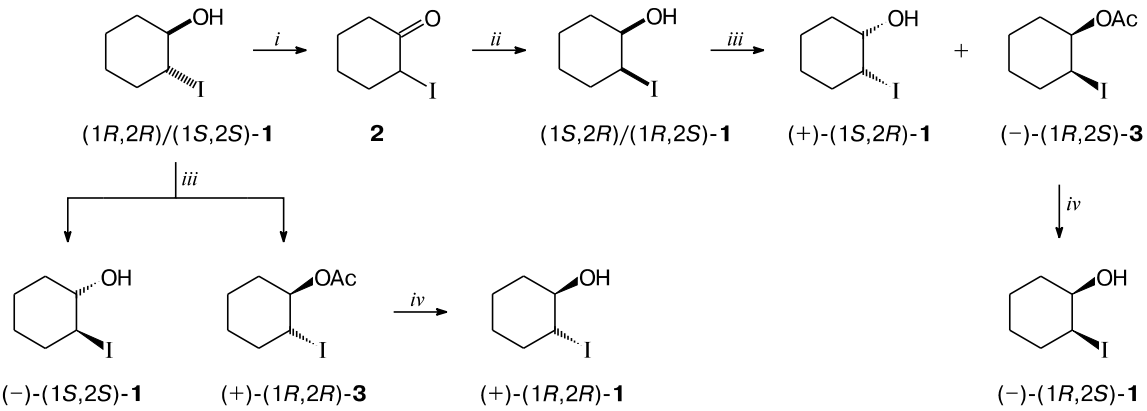
All four optically active stereoisomers of 2-iodocyclohexanol were synthesized. Their enantiomeric purity was determined upon derivatization with Mosher´s acid, absolute configuration have been established by chemical correlation.

Key words: stereoisomers of 2-iodocyclohexanol, kinetic separation, cyclohex-2-en-1-ol, chirality, lipase from *Burkholderia cepacia*.

Vicinal 2-substituted cycloalkanes find application in synthesis of various biologically active compounds, *e.g.*, precursors of prostaglandins and leukotrienes[1—4]. In the present work, the access to all possible enantiomerically pure stereoisomers of one compound of this type, namely, (1*S*,2*S*)-, (1*R*,2*R*)-, (1*S*,2*R*)-, and (1*R*,2*S*)-2-iodocyclohexanols, is described. *trans*-(1*S*,2*S*)-2-Iodocyclohexanol was reported earlier[5], whereas racemic (1*R**,2*S**)-2-iodocyclohexanol was not resolved. Our approach involves cyclohexene oxide as a starting compound, which upon treatment with lithium iodide was converted to racemic *trans*-2-iodocyclohexanol (**1**), which comprised (1*S*,2*S*)- and (1*R*,2*R*)-enantiomers (Scheme 1). Resulting racemic *trans*-**1** was oxidized according to Swern[6] to afford 2-iodocyclohexanone (**2**). Ketone **2** was reduced with sodium borohydride in methanol to obtain racemic *cis*-2-iodohexanol (1*R*,2*S*)/(1*S*,2*R*)-**1**, which was purified by recrystallization from hexane.

Enzymatic transesterification with vinyl acetate in the presence of lipase from *Burkholderia cepacia* (BCL), which was immobilized on diatomite, turned an effective tool in separating two individual enantiomers from racemic *cis*-**1**. The process was interrupted at 50% conversion of the starting racemic alcohol, the conversion rate being monitored by NMR. As a result, non-racemic alcohol (+)-(1*S*,2*R*)-**1** and acetate (−)-(1*R*,2*S*)-**3** with 98—99% enantiomeric excess (enantioselectivity factor $E > 100$) were obtained. Hydrolysis of acetate (−)-(1*R*,2*S*)-**3** in phosphate buffer at pH 7.2 in the presence of BCL gave corresponding optically active alcohol (−)-(1*R*,2*S*)-**1**. Additional low-temperature (−20 °C) recrystallization of these alcohols from hexane gave compounds (+)-(1*S*,2*R*)-**1** and (−)-(1*R*,2*S*)-**1**

Scheme 1



Reagents and conditions: *i*. $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; *ii*. $NaBH_4$, MeOH; *iii*. $AcOCH{=}CH_2$, lipase from *Burkholderia cepacia*, conversion ~50%; *iv*. H_2O, phosphate buffer, lipase from *Burkholderia cepacia*.

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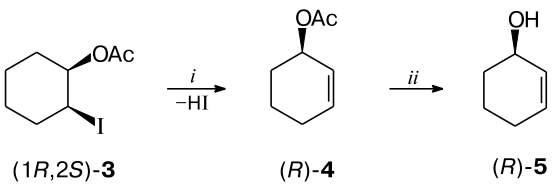
with *de* and *ee* ~99%. This result was confirmed by their standard derivatization[7,8] with Mosher´s (*R*)-acid chloride. In the ^{19}F NMR spectrum of derivatized enantiomer (1*R*,2*S*)-**1** only one signal at δ_F −72.21 was observed, whereas the spectrum of similar racemic esters *cis*-**1** contained two signals at δ_F −72.21 and −72.25. Accordingly, in the spectrum of the derivative of (1*S*,2*R*)-**1**, a single signal at δ_F −71.25 was observed. In the ^{1}H NMR spectrum of the Mosher´s derivative of alcohol (1*R*,2*S*)-**1**, a single signal of the methoxy group was observed at δ_H 3.60, whereas the spectrum of the racemate contained two signals at δ_H 3.60 and 3.57.

Similarly to racemate *cis*-**1**, acylation of racemic *trans*-cyclohexanol **1** with vinyl acetate in the presence of BCL under kinetically controlled conditions (50% conversion of the starting alcohol) gave alcohol (−)-(1*S*,2*S*)-**1** and acetate (+)-(1*R*,2*R*)-**3**, which were separated by column chromatography. Hydrolysis of acetate (+)-(1*R*,2*R*)-**3** in phosphate buffer at constant pH 7.2 resulted in second stereoisomer of *trans*-cyclohexanol (+)-(1*R*,2*R*)-**1**. Enantiomeric purity of alcohol (+)-(1*R*,2*R*)-**1** (*ee* > 98%) was assessed by NMR analysis of its Mosher´s derivarive. To this, the ^{1}H NMR spectrum of derivatized enantiomer (+)-(1*R*,2*R*)-**1** contained a single signal of the methoxy group at δ_H 3.59. Its ^{19}F NMR spectrum contained the single signal at δ_F −71.80 whereas the spectrum of the racemate consisted of signals at δ_F −71.79 and −71.81. Absolute configuration and optical purity of enantiomer (−)-(1*S*,2*S*)-**1** was confirmed by comparison of its optical rotation angle to the corresponding value of the earlier described compound[5].

For the more reliable determination of the absolute configuration, enantiomerically pure 1-acetoxy-2-iodocyclohexane (1*R*,2*S*)-**3** was dehydroiodinated to give optically active cyclohex-2-enyl acetate (*R*)-**4** (Scheme 2). This acetate was hydrolysed to give optically active cyclohex-2-en-1-ol (+)-(*R*)-**5**, whose absolute configuration was determined by comparison of its rotation angle to that of the earlier described compound[8]. Based on this, the absolute configuration of 2-iodocyclohexanols (1*R*,2*S*)-**1** and (1*S*,2*R*)-**1** was assessed by the chemical correlation method.

Scheme 2



(1*R*,2*S*)-**3** (*R*)-**4** (*R*)-**5**

Reagents and conditions: *i*. DBU, 70 °C, 12 h; *ii*. 1 *M* NaOH, MeOH; 20 °C, 18 h.

Experimental

^{1}H, ^{19}F, and ^{13}C NMR spectra were registered on a Bruker 170 Avance spectrometer operating at frequences of 500.07 (^{1}H) 376.29 (^{19}F) and 125.74 (^{13}C) MHz in $CDCl_3$, using hexamethyldisiloxane (^{1}H and ^{13}C) or fluorobenzene as internal standards (^{19}F). Thin layer chromatography was performed on silica gel coated aluminium plates (the thickness of the silica gel layer is 0.25 mm), visualization was performed by staining with anisaldehyde. Column chromatography was performed on silica gel Merck 60. Hexane, toluene, chloroform and dichloromethane were distilled over P_4O_{10} before use. Lipase from *Burkholderia cepacia* on diatomite was available from the Amano Pharmaceutical company (Japan), Mosher´s (*R*)-acid chloride ((*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride), oxalyl chloride, and dimethylsulfoxide were purchased from SigmaAldrich. Racemic *trans*-2-iodocyclohexanol **1** was obtained by reaction of cyclohexene oxide with lithium iodide[9,10].

2-Iodocyclohexanone (2). A solution of dimethylsulfoxide (3.6 mL, 50 mmol) in dichloromethane (10 mL) was added dropwise at stirring to cooled to −70 °C solution of oxalyl chloride (2 mL, 2.9 g, 23 mmol) in dichloromethane (40 mL). To the reaction mixture, *rac-trans*-2-iodocyclohexanol (4.5 g, 20 mmol) was added. After stirring for 30 min at −60 °C, triethylamine (15 mL) was added, and temperature was allowed to reach ~20 °C and then the mixture was poured into water (50 mL). The mixture was extracted with dichloromethane, the organic layer was dried with sodium sulfate, concentrated, and the residue was distilled *in vacuo*. Yield 65%, b.p. 110 °C (10 Torr). ^{1}H NMR, δ: 1.40 (m, 1 H, CH_2); 1.60 (m, 2 H, CH_3); 1.90 (m, 1 H, CH_2); 2.10—2.31 (m, 2 H, CH_2); 2.45 (m, 2 H, CH_2); 5.21 (m, 1 H, CHI).

***rac-cis*-2-Iodocyclohexanol (1*R*,2*S*)/(1*S*,2*R*)-1.** 2-Iodocyclohexanone (**2**) was reduced with sodium borohydride in methanol, yield 70%, m.p. 52—53 °C (from hexane). ^{1}H NMR, δ: 1.45 (m, 2 H, CH_2); 1.45—1.80 (m, 4 H, CH_3); 1.91 (m, 2 H, CH_2); 2.27 (m, 1 H, OH); 3.16 (m, 1 H, CHI); 4.71 (s, 1 H, C<u>H</u>OH). ^{13}C NMR, δ: 21.93 (s, CH_2); 24.48 (s, CH_3); 32.23 (s, CH_2); 34.12 (s, CH_2); 46.51 (s, CHI), 71.01 (s, CHOH). Found (%): C, 31.38; H, 4.50. $C_6H_{11}IO$. Calculated (%): C, 31.88; H, 4.90.

(1*S*,2*R*)-2-Iodocyclohexanol (1*S*,2*R*)-1. Racemate (1*R*,2*S*)/(1*S*,2*R*)-**1** (2.25 g, 10 mmol) was acylated with the excess of vinyl acetate (4 mL) in the presence of BCL (100 mg) upon stirring for 16 h at 24 °C. The solvent was evaporated and the residue was subjected to flash chromatography (silica gel, elution with hexane—chloroform, 1 : 1; then chloroform). The first fraction contained acetate (1*R*,2*S*)-**3** and the second fraction contained unreacted alcohol (1*S*,2*R*)-**1**, which was recrystallized from hexane. Yield 48%, m.p. 52 °C, $[\alpha]_D^{20}$ −31.4 (*c* 1, $CHCl_3$). ^{1}H NMR, δ: 1.45 (m, 2 H, CH_2); 1.60—1.80 (m, 4 H, CH_2); 1.80—1.91 (m, 2 H, CH_2); 2.28 (s, 1 H OH); 3.17 (s, 1 H, CHI); 4.72 (s, 1 H, C<u>H</u>OH). ^{13}C NMR, δ: 21.93 (s, C H_2); 24.48 (s, CH_2); 32.23 (s, CH_2); 34.12 (s, CH_2); 46.51 (s, CHI); 71.01 (s, CHOH).

(1*R*,2*S*)-1-Acetoxy-2-iodocyclohexane (1*R*,2*S*)-3. Yield 50%, b.p. 115 °C (10 Torr), $[\alpha]_D^{20}$ +62.5 (*c* 3, $CHCl_3$). ^{1}H NMR, δ: 1.40—1.65 (m, 4 H, CH_2); 1.85 (m, 1 H, CH_2); 2.00—2.10 (m, 4 H, CH_2); 2.15 (s, 3 H, CH_3); 2.45 (m, 1 H, OH); 4.05 (m, 1 H, CHI); 4.95 (m, 1 H, C<u>H</u>OAc). ^{13}C NMR, δ: 21.30 (s, CH_3); 22.40 (s, CH_2); 23.77 (s, CH_2); 29.30 (s, CH_2); 34.44 (s, CH_2); 36.04 (s, CHI); 72.95 (s, CHOH); 170.16 (s, C=O). Found (%): C, 35.68; H, 4.71. $C_8H_{13}IO_2$. Calculated (%): C, 35.84; H, 4.89.

(1*R*,2*S*)-2-Iodocyclohexanol (1*R*,2*S*)-1. Acetate (1*R*,2*S*)-**3** (10 mmol) was hydrolyzed in the presence of BCL (100 mg) in 0.05 *M* phosphate buffer (15 mL, 6.8 g of KH_2PO_4 in 1 L of distilled water), pH 7.2, the progress of the reaction was monitored by TLC, and the pH was maintained at 7.2 by addition of 1 *M* NaOH. Yield 60%, m.p. 50 °C (from hexane), $[\alpha]_D^{20}$ +31.14 (*c* 1, $CHCl_3$). ^{1}H NMR, δ: 1.46 (m, 2 H, CH_2); 1.60—1.80 (m, 4 H, CH_2); 1.80—1.90 (m, 2 H, CH_2); 2.27 (m, 1 H, OH); 3.16 (m, 1 H, CHI); 4.72 (s, 1 H, C<u>H</u>OH). ^{13}C NMR, δ: 21.93 (s, CH_2); 24.48 (s, CH_2); 32.23 (s, CH_2); 34.12 (s, CH_2); 46.51 (s, CHI); 71.01 (s, CHOH). Found (%): C, 31.77; H, 4.65. $C_6H_{11}IO$. Calculated (%): C, 31.88; H, 4.90.

(1*S*,2*S*)-2-Iodocyclohexanol (1*S*,2*S*)-1 was obtained similarly to (1*S*,2*R*)-**1** by enzymatic acylation of the racemic *trans*-**1**. Yield 49%, m.p. 46 °C (from hexane), $[\alpha]_D^{20}$ +34 (*c* 5, $CHCl_3$) (cf. Refs. 5, 11: $[\alpha]_D^{20}$ +33.1 (*c* 2.4, $CHCl_3$)). ^{1}H NMR, δ: 1.25—1.49 (m, 3 H, CH); 1.60 (m, 1 H, CH); 1.85 (m, 1 H, CH); 2.05—2.20 (m, 2 H, CH_2); 2.35 (s, 1 H, CH); 2.50 (d, 1 H, OH, J = 5.0 Hz); 3.65 (м, 1 H, CHI); 4.10 (m, 1 H, C<u>H</u>OH). ^{13}C NMR, δ: 24.50 (s, CH_2); 24.60 (s, CH_2); 34.01 (s, CH_2); 34.20 (s, CH_2); 38.60 (s, CHI); 75.81 (s, CHOH).

(1*R*,2*R*)-1-Acetoxy-2-iodocyclohexane (1*R*,2*R*)-3 was obtained by acylation of *rac*-*trans*-**1** similarly to (1*R*,2*S*)-**3**. Yield 50%, b.p. 115 °C (10 Torr), $[\alpha]_D^{20}$ −60.0 (*c* 3, $CHCl_3$) (cf. Ref. 11: $[\alpha]_D^{20}$ −47.1 (*c* 2.15, $CHCl_3$)). ^{1}H NMR, δ: 1.40—1.65 (m, 4 H, CH_2); 1.85 (m, 1 H, CH); 2.00—2.10 (m, 4 H, CH_2); 2.15 (s, 3 H, CH_3); 2.45 (m, 1 H, OH); 4.05 (m, 1 H, CHI); 4.95 (m, 1 H, CHOH). ^{13}C NMR, δ: 21.23 (s, CH_2); 23.56 (s, CH_2); 27.06 (s, CH_2); 31.57 (s, CH_2); 31.78 (s, CHI); 37.84 (s, CH_2); 77.00 (s, CHO); 169.60 (s, C=O). Found (%): C, 35.60; H, 4.85. $C_8H_{13}IO_2$. Calculated (%): C, 35.84; H, 4.89.

(1*R*,2*R*)-2-Iodocyclohexanol (1*R*,2*R*)-1 was obtained by hydrolysis of (1*R*,2*R*)-**3**, yield 48%, m.p. 46 °C (from hexane), $[\alpha]_D^{20}$ −34 (*c* 4, $CHCl_3$). ^{1}H NMR, δ: 1.25—1.49 (m, 3 H, CH); 1.60 (m, 1 H, CH); 1.85 (m, 1 H, CH); 2.05—2.20 (m, 2 H, CH); 2.35 (s, 1 H, CH); 2.50 (d, 1 H, OH, J = 5.0 Hz); 3.65 (m, 1 H, CHI); 4.10 (m, 1 H, C<u>H</u>OH). ^{13}C NMR, δ: 24.51 (s, CH_2); 24.60 (s, CH_2); 34.00 (s, CH_2); 34.21 (s, CH_2); 38.60 (s, CHI); 75.81 (s, CHOH).

(1*R*)-Cyclohex-2-enyl acetate (*R*)-4. A solution of (+)-(1*R*,2*S*)-1-acetoxy-2-iodocyclohexane (2 g, 7.5 mmol) (1*R*,2*S*)-**3** in DBU (5 ml) was heated at 70 °C for 12 h, diluted with diethyl ether, filtered, washed with diluted hydrochloric acid, $NaHCO_3$ (aq.), then concentrated and the residue was distilled under reduced pressure. Yield 50%, m.p. 60 °C (10 Torr); $[\alpha]_D^{20}$ +180 (*c* 3, $CHCl_3$) (*cf.* Ref. 11). ^{1}H NMR, δ: 2.02 (s, 3 H, CH_3); 2.29—1.63 (m, 6 H, CH_2); 5.73—5.67 (m, 1 H, OH); 5.99—5.92 (m, 1 H, CH=); 5.28—5.23 (m, 1 H, CH=).

(1*R*)-Cyclohex-2-en-1-ol (*R*)-5. To a solution of acetate (*R*)-**4** (0.57 g, 4.0 mmol) in methanol (1 mL), 1 *M* NaOH (8 mL) was added. The mixture was stirred at ~20 °C for ~18 h, and the product was extracted with dichloromethane. The extract was dried, the solvent was removed and the residue was distilled under reduced pressure. Yield 0.35 g (85%), colorless oil, b.p. 96—97 °C (75 Torr); $[\alpha]_D^{20}$ +123.5 (*c* 2, $CHCl_3$). ^{1}H NMR, δ: 2.11—1.39 (m, 7 H); 4.29—4.03 (m, 1 H, CHOH); 5.97—5.58 (m, 2 H, CH=).[9]

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