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Enzymatic resolution of (±)-2-(N_β-*t*-butoxycarbonyl-N_α-methylhydrazino)cycloalkanols

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Abstract

Racemates of *cis*- and *trans*-2-(N_β-*t*-butoxycarbonyl-N_α-methylhydrazino)cyclopentanols and -cyclohexanols **1**–**4** were resolved through lipase PS- or Novozym 435-catalysed asymmetric acylation of the secondary OH group at the (*R*)-stereogenic centre. High enantioselectivity (*E* >200) was observed when vinyl acetate or vinyl butyrate was used in diisopropyl ether, resulting in the enantiopure hydrazino esters **1a**–**4a** and hydrazino alcohols **1b**–**4b**. Methanolysis of the esters **1a**–**4a** afforded the corresponding 2-hydrazinocycloalkanols **1c**–**4c** (ee usually >95%).

1. Introduction

Many 1,2- and 1,3-aminoalcohols and their derivatives are known to be useful building blocks for the synthesis of various pharmaceutically important compounds.[1–5] We have recently described the enzymatic resolution of several 2-substituted cycloalkanols,[6–8] e.g. aminoalcohols or aminoalcohol precursors. Chiral hydrazinoalcohols derived from 1,2-aminoalcohols are also important synthons in enantioselective syntheses, e.g. the reactions of various aromatic aldehydes with chiral hydrazine prepared from (*R*)-(−)-2-aminobutanol were reported by Bataille et al.: the enantioselective addition of organometals to chiral hydrazones, followed by catalytic hydrogenolysis, afforded the corresponding chiral α-phenylalkanamines.[9,10]

The primary focus of this work was to find the optimum conditions for the enzymatic resolution of *cis*- and *trans*-2-(N_β-*t*-butoxycarbonyl-N_α-methylhydrazino)cycloalkanols by using lipase-catalysed acylation (Scheme 1). To the best of our knowledge, the enzymatic resolution of hydrazino alcohols has not been described previously.

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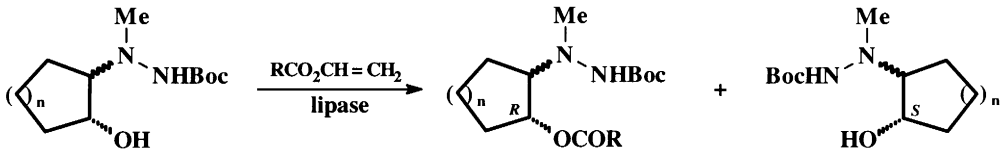


1-4 **1a-4a** **1b-4b**

1 n=1, *cis*; **2** n=1, *trans*; **3** n=2, *cis*; **4** n=2, *trans*

Scheme 1.

2. Results and discussion

Lipase PS (*Pseudomonas cepacia*) and Novozym 435 (lipase from *Candida antarctica* B) are the most commonly used enzymes for the resolution of secondary alcohols.[6–8,11–13] Extensive lipase screening for compound **2** in diisopropyl ether indicated that, besides lipase PS and Novozym 435, lipase AK (*Pseudomonas fluorescens*) is also a promising catalyst for acetylation (Table 1). On the basis of previous experience with lipase PS and Novozym 435 catalysis,[6–8] diisopropyl ether was used as solvent and vinyl acetate as irreversible acyl transfer reagent throughout the work (vinyl alcohol undergoes irreversible tautomerisation to acetaldehyde). Lipase AY does not exhibit any selectivity in the acetylation of **2**, yielding nearly racemic products, and porcine pancreatic lipase (PPL) even catalysed the acetylation selectively, the reaction rate being very slow (Table 1). The acetylation of **1** catalysed by lipase PS, Novozym 435 and lipase AK displayed a similarly high enantioselectivity (enantiomeric ratio E >200)[14] as in the case of **2** (Table 1). Because of certain technical peak-separation problems in the chromatograms in the case of **1** (the acetate and possible underivatised alcohol peaks partially overlap), the acylation of **1** with vinyl butyrate was also investigated. The lipase PS- and lipase AK-catalysed butyrylation reactions of **1** (Table 1, rows 4 and 10) proceeded more rapidly than the acetylations, while, surprisingly, a slower reaction was observed in the Novozym 435-catalysed butyrylation of **1** (row 7).

Although the enzymatic reactions can also be controlled via the amount of enzyme,[7,8] the effect is less pronounced in the case of the lipase PS-catalysed acetylation of **1** (Table 1, rows 2 and 3).

Gram-scale preparations of the enantiomers of **1**–**4** were performed in diisopropyl ether with lipase PS or Novozym 435 as catalyst and vinyl acetate or vinyl butyrate as acyl donor. The results are reported in Table 2 and in the Experimental section.

It is important to note that, in good agreement with our previous observation,[8] the size of the cycloalkane ring had a clear effect on the rate of enantioselective acylation: the acetylation of the five-membered aminoalcohols (**1** and **2**) proceeded more rapidly than that of the six-membered ones (**3** and **4**). Some doubts arose about the possibilities for the resolution of *cis*-2-(N_β-*t*-butoxycarbonyl-N_α-methylhydrazino)cyclohexanol **3** because of the rather long reaction time needed to reach the theoretical 50% conversion, due to the probable steric hindrance; in spite of the long reaction time, the products were characterised by an excellent enantiomeric excess (Table 2, row 5) at 50% conversion.

The esters **1a**–**4a** produced by the (*R*)-selective acetylation of the cyclopentanols and cyclohexanols were alcoholised[15] to the corresponding alcohols **1c**–**4c** in K_2CO_3/MeOH, at room temperature, without loss of enantiopurity (Scheme 2).

2.1. Absolute configurations

The analysed chromatograms indicated that the corresponding enantiomers of **1**–**4** reacted preferentially on lipase PS or Novozym 435 catalysis, in accordance with the Kazlauskas model for the active site

Table 1
Lipase-catalysed (i: 30 mg ml^{-1}, ii: 50 mg ml^{-1}) acylation of **1** and **2** (0.1 M) with vinyl acetate (VA) or vinyl butyrate (VB, 0.2 M) in diisopropyl ether, at 25°C

Enzyme	Substrate	Acyl donor	Time (h)	Conv. (%)	$ee_{alcohol}$[a] (%)	ee_{ester}[b] (%)	E
lipase PS[c] (i)	**2**	VA	14	47	84	96	130
	1	VA	27	42	73	99	>200
lipase PS[c] (ii)	**1**	VA	27	45	80	99	>200
	1	VB	18	47	87	99	>200
Novozym 435 (i)	**2**	VA	14	48	89	96	147
	1	VA	19	50	95	96	>200
	1	VB	27	42	72	98	>200
lipase AK (i)	**2**	VA	14	47	79	89	41
	1	VA	27	16	19	99	>200
	1	VB	18	21	27	99	>200
lipase AY (i)	**2**	VA	14	60	6	4	1
PPL (i)	**2**	VA	14	10	11	99	>200

[a]According to chiral GC after derivatization of the substrate with propionic anhydride. [b]According to chiral GC. [c]Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose.

Table 2
Enzyme-catalysed resolution of **1**–**4** in the presence of Novozym 435 (30 mg ml^{-1}) or lipase PS[a] (50 mg ml^{-1}) and vinyl acetate (VA, 0.2 M) or vinyl butyrate (VB, 0.2–0.4 M) in diisopropyl ether, at 25°C

	Enzyme / Acyl donor	Time (h)	Conv. (%) / E	Alcohol recovered (**1b-4b**) and (**1c-4c**[b], sec. row) Yield[c] (%)	Isomer	ee (%)	$[\alpha]_D^{20}$	Ester produced (**1a-4a**) Yield[c] (%)	Isomer	ee (%)	$[\alpha]_D^{20}$
1	lipase PS	23	50	54	*1S,2R*	99.0[d]	−20.5[e]	93	*1R,2S*	99.0[f]	−28.5[e]
	VB		>200		*1R,2S*	99.0[d]	+20.2[e]				
2	Novozym	7	52	63	*1S,2S*	99.0[d]	+30.2[e]	89	*1R,2R*	91.3[f]	−49.5[e]
	VA		111		*1R,2R*	94.5[d]	−28.4[g]				
3	lipase PS	335	50	89	*1S,2R*	97.9[d]	−3.4[h]	86	*1R,2S*	99.7[f]	−31.5[i]
	VA		>200		*1R,2S*	99.0[d]	+3.8[h]				
4	Novozym	168	50	44	*1S,2S*	98.6[d]	+34.0[e]	40	*1R,2R*	98.9[f]	−40.5[e]
	VA		>200		*1R,2R*	95.9[d]	−31.5[e]				

[a]Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose. [b]Obtained by hydrolysis of **1a**–**4a**. [c]Yield 100% at 50% conversion. [d]According to chiral GC after derivatization with propionic anhydride. [e](c = 0.5, MeOH). [f]According to chiral GC. [g](c = 0.68, MeOH). [h](c = 0.53, MeOH). [i](c = 0.55, MeOH).

of lipases (a lipase distinguishes the two enantiomers on the basis of the sizes of the substituents R_{large} and R_{small} at the alcoholic stereocentre [$R_{small}CH(OH)R_{large}$]: the more reactive enantiomer involves the (*R*) absolute configuration when the Cahn–Ingold–Prelog priority of group R_{large} is higher than that of group R_{small} and H is behind the plane).[16,17] The validity of this was proved in the case of *trans*-2-(N_β-*t*-

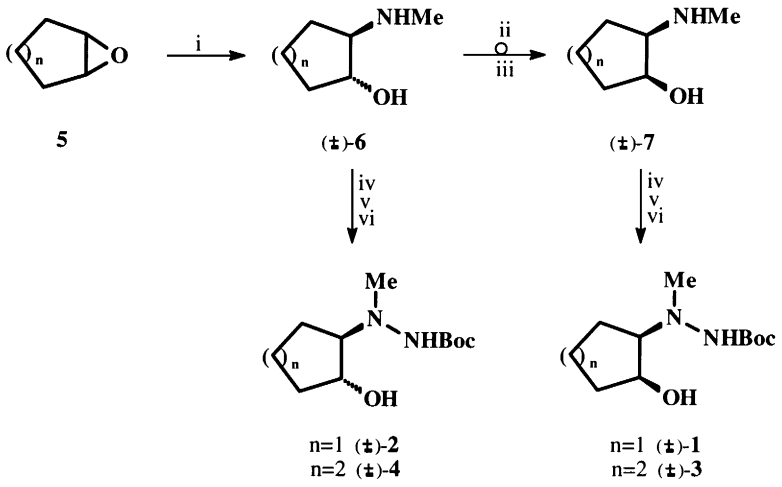
Scheme 2.

butoxycarbonyl-N_α-methylhydrazino)cyclohexanol **4**. For this purpose, the enantiomer **4b** was reduced catalytically to the corresponding *trans*-2-methylaminocyclohexanol hydrochloride. The value of $[\alpha]_D^{20}$ +34.0 (*c* 0.2, H_2O; ee 91%) for the reduced product and the literature value for the (1*R*,2*R*)-*trans*-2-methylaminocyclohexanol hydrochloride[18] ($[\alpha]_D^{20}$ −56 (*c* 1, H_2O)) indicate the (*R*) selectivity for the enzymatic acylation. Therefore, the (1*R*,2*S*) configuration is established for the esters of *cis* cyclanols (**1a** and **3a**), and the (1*R*,2*R*) configuration for the *trans* (**2a** and **4a**) counterparts.

3. Experimental

3.1. Materials and methods

The racemic *trans*-2-methylaminocyclopentanol and -cyclohexanol **6** were prepared from the corresponding epoxides **5** by methylamine ring opening.[19] The *trans* aminoalcohols **6** were inverted to the racemic *cis* counterparts by acetylation, followed by thionyl chloride oxazolidine formation and hydrolysis (Scheme 3), as described earlier.[20]



Scheme 3. (i) NH_2Me; (ii) Ac_2O, $SOCl_2$; (iii) NaOH; (iv) $NaNO_2$, AcOH, H_2O, 0–5°C; (v) $LiAlH_4$, THF; (vi) Boc_2O, rt

Vinyl acetate was purchased from Aldrich Co., and vinyl butyrate from Fluka. Lipase PS and lipase AK were obtained from Amano Pharmaceuticals, and Novozym 435 as an immobilised preparation from Novo Nordisk. Before use, lipase PS (5 g) was dissolved in Tris–HCl buffer (0.02 M; pH 7.8) in the presence of sucrose (3 g), followed by adsorption on Celite (17 g) (Sigma). The lipase preparation thus obtained contained 20% (w/w) of lipase.

3.2. General method for preparation of the racemic cis- and trans-2-(N$_\beta$-t-butoxycarbonyl-N$_\alpha$-methylhydrazino)cyclopentanols (**1** and **2**) and -cyclohexanols (**3** and **4**)

To a stirred solution of the hydrochloride salt of **6** or **7** (33.8 mmol) in 20 ml of water were added dropwise $NaNO_2$ (4.35 g, 63 mmol), dissolved in 5 ml of water, and acetic acid (2.94 g, 49 mmol) at 0°C. The mixture was stirred for 5 h at 0–5°C, and was then extracted with ethyl acetate (3×50 ml). The organic phase was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and evaporated to dryness. The resulting oil was dissolved in 20 ml of dry THF and was added dropwise to a stirred mixture of $LiAlH_4$ (3.65 g, 96 mmol) and dry THF (80 ml) at 0°C. After stirring and refluxing for 1.5 h (the end of the reduction was detected by means of TLC), the mixture was decomposed with 7 ml of water under ice cooling. The inorganic material was filtered off and washed with THF. After drying and evaporation, the pale-yellow oily hydrazino alcohol was obtained. To the solution of the crude hydrazino alcohol in 40 ml of dioxane, 20 ml of water and 20 ml of a 1 M NaOH solution of di-*t*-butyl dicarbonate (4.8 g, 22 mmol) dissolved in 10 ml of 1,4-dioxane were added dropwise at 0°C. The solution was stirred for 4 h at room temperature, the dioxane was evaporated off and the aqueous solution was acidified (pH=2.5) by treatment with 10% sulphuric acid solution. The solution was extracted with ethyl acetate (3×50 ml), and the organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. The resulting yellow crystalline product was recrystallised from diisopropyl ether.

Compound (±)-**1** (yield: 35%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.46 (9H, s, 3×CH_3), 1.62–1.96 (6H, m, 3×CH_2), 2.62 (3H, s, CH_3), 2.68 [1H, m, C*H*N(Me)(NHBoc)], 3.9–4.0 (1H, b s, NH), 4.01 (1H, m, C*H*OH), 5.57 (1H, b s, OH); anal. calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16; found: C, 57.54; H, 9.13; N, 12.43; mp: 111–113°C.

Compound (±)-**2** (yield: 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.39–1.98 (6H, m, 3×CH_2), 1.46 (9H, s, 3×CH_3), 2.61 (3H, s, CH_3), 2.88 [1H, dd, *J*=14.6, 7.0 Hz, C*H*N(Me)(NHBoc)], 3.0 (1H, b s, NH), 3.89 (1H, dd, *J*=14.2, 6.9 Hz, C*H*OH), 5.48 (1H, b s, OH); anal. calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16; found: C, 57.54; H, 9.48; N, 12.27; mp: 149–151°C.

Compound (±)-**3** (yield: 32%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.10–2.40 (8H, m, 4×CH_2), 1.46 (9H, s, 3×CH_3), 2.61 (3H, s, CH_3), 2.61 [1H, m, C*H*N(Me)(NHBoc)], 3.97 (1H, m, C*H*OH), 5.45 (1H, b s, OH); anal. calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.90; N, 11.47; found: C, 58.76; H, 9.63; N, 11.75; mp: 122–123°C.

Compound (±)-**4** (yield: 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.20–2.40 (9H, m, 4×CH_2 and remaining CH), 1.46 (9H, s, 3×CH_3), 2.62 (3H, s, CH_3), 3.25 (1H, m, C*H*OH), 4.65 (1H, b s, NH), 5.35 (1H, b s, OH); anal. calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.90; N, 11.47; found: C, 58.39; H, 9.66; N, 11.77; mp: 135–137°C.

3.3. General procedure for a typical small-scale experiment

The 2-(*N*$_\beta$-*t*-butoxycarbonyl-*N*$_\alpha$-methylhydrazino)cycloalkanol **1**–**4** (0.1 M solution) in an organic solvent (3 ml) was added to lipase PS (50 mg ml^{-1}) or Novozym 435 (30 mg ml^{-1}). A vinyl ester (0.2 M in the reaction mixture) was added. The mixture was shaken at 25°C. The progress of the reaction was followed by taking samples (0.1 ml) from the reaction mixture at intervals and analysing them by gas chromatography. The unreacted alcohol in the sample was derivatised with propionic anhydride in the presence of 4-dimethylaminopyridine and pyridine before the gas chromatographic analysis. The ee values of the unreacted alcohol (**1b**–**4b**) and the produced ester enantiomers (**1a**–**4a**) were determined by gas chromatography on a Chrompack CP-Chirasil-DEX CB column (25 m).

3.4. Gram-scale resolution of (±)-cis-2-(N$_\beta$-t-butoxycarbonyl-N$_\alpha$-methylhydrazino)cyclopentanol **1**

Following the procedure described above, racemic **1** (0.5 g, 2.2 mmol) and vinyl butyrate (0.36 ml, 4.4 mmol) in diisopropyl ether (30 ml) were added to lipase PS (1.5 g, 50 mg ml^{-1}); this afforded the unreacted (1*S*,2*R*)-**1b** (0.13 g, 0.58 mmol; $[\alpha]_D^{20}$ −20.5 (*c* 0.5, MeOH); mp 117–118°C; ee 99%) and the ester (1*R*,2*S*)-**1a** (0.31 g oil, 1.03 mmol; $[\alpha]_D^{20}$ −28.5 (*c* 0.5, MeOH); ee 99%) in 23 h. Within 3–4 h, on stirring in K_2CO_3/methanol at room temperature, the ester enantiomer **1a** underwent quantitative deacylation, resulting in the corresponding alcohol (1*R*,2*S*)-**1c** ($[\alpha]_D^{20}$ +20.2 (*c* 0.5, MeOH); mp 117–118°C; ee 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **1a**: 0.95 (3H, t, CH_3), 0.95–1.85 (6H, m, 3×CH_2), 1.44 (9H, s, 3×CH_3), 2.3 (4H, m 2×CH_2), 2.71 (3H, s, CH_3), 3.5 [1H, m, C*H*N(Me)(NHBoc)], 5.20 (1H, m, C*H*OCOPr), 6.7 (1H, b s, NH); anal. calcd for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.40; N, 9.33; found: C, 59.81; H, 9.20; N, 9.66.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **1b** and **1c** are similar to those for (±)-**1**; anal. calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16; found for **1b**: C, 57.17; H, 9.60; N, 12.11; found for **1c**: C, 57.51; H, 9.58; N, 12.09.

3.5. Gram-scale resolution of (±)-trans-2-(N$_\beta$-t-butoxycarbonyl-N$_\alpha$-methylhydrazino)cyclopentanol **2**

Following the procedure described above, the reaction of racemic **2** (0.38 g, 1.65 mmol) and vinyl acetate (0.20 ml, 3.3 mmol) in diisopropyl ether (50 ml) in the presence of Novozym 435 (1.5 g, 30 mg ml^{-1}) afforded the unreacted (1*S*,2*S*)-**2b** (0.12 g oil, 0.52 mmol; $[\alpha]_D^{20}$ +30.2 (*c* 0.5, MeOH); ee 99%) and the ester (1*R*,2*R*)-**2a** (0.19 g oil, 0.70 mmol; $[\alpha]_D^{20}$ −49.5 (*c* 0.5, MeOH); ee 91.3%) in 7 h. Within 3−4 h, on stirring in K_2CO_3/methanol at room temperature, the ester enantiomer **2a** underwent quantitative deacylation, resulting in the corresponding alcohol (1*R*,2*R*)-**2c** ($[\alpha]_D^{20}$ −28.4 (*c* 0.68, MeOH); mp 149–151°C; ee 94.5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **2a**: 1.44 (9H, s, 3×CH_3), 1.55–2.0 (6H, m, 3×CH_2), 2.0 (3H, s, CH_3), 2.6 (3H, s, CH_3), 3.18 [1H, m, C*H*N(Me)(NHBoc)], 5.1 (1H, m, C*H*OCOCH_3), 5.65 (1H, b s, NH); anal. calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29; found: C, 58.01; H, 9.13; N, 10.59).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **2b** and **2c** are similar to those for (±)-**2**; anal. calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16; found for **2b**: C, 57.11; H, 9.33; N, 12.24; found for **2c**: C, 56.97; H, 9.51; N, 12.15.

3.6. Gram-scale resolution of (±)-cis-2-(N$_\beta$-t-butoxycarbonyl-N$_\alpha$-methylhydrazino)cyclohexanol **3**

Following the procedure described above, the reaction of racemic **3** (0.5 g, 2.03 mmol) and vinyl acetate (0.49 ml, 8.1 mmol) in diisopropyl ether (40 ml), in the presence of lipase PS (2.0 g, 50 mg ml^{-1}), afforded the unreacted (1*S*,2*R*)-**3b** (0.25 g, 1.02 mmol; $[\alpha]_D^{20}$ −3.4 (*c* 0.53, MeOH); mp 125–126°C; ee 97.9%) and the ester (1*R*,2*S*)-**3a** (0.23 g oil, 0.81 mmol; $[\alpha]_D^{20}$ −31.5 (*c* 0.55, MeOH); ee >99%) in 335 h. Within 3–4 h, on stirring in K_2CO_3/methanol at room temperature, the ester enantiomer **3a** underwent quantitative deacylation, resulting in the corresponding alcohol (1*R*,2*S*)-**3c** ($[\alpha]_D^{20}$ +3.8 (*c* 0.53, MeOH); mp 123–125°C; ee >99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3a**: 1.25–1.96 (8H, m, 4×CH_2), 1.44 (9H, s, 3×CH_3), 2.09 (3H, s, CH_3), 2.64 (3H, s, CH_3), 2.81 [1H, m, C*H*N(Me)(NHBoc)], 5.3 (1H, m, C*H*OCOCH_3), 5.95 (1H, b s, NH); anal. calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78; found: C, 58.87; H, 9.09; N, 9.77.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **3b** and **3c** are similar to those for (±)-**3**; anal. calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.90; N, 11.47; found for **3b**: C, 59.02; H, 9.60; N, 11.40; found for **3c**: C, 59.10; H, 9.81; N, 11.19.

3.7. *Gram-scale resolution of (±)-*trans*-2-(*N$_\beta$*-t-butoxycarbonyl-*N$_\alpha$*-methylhydrazino)cyclohexanol **4***

Following the procedure described above, racemic **4** (1.5 g, 6.1 mmol) and vinyl acetate (0.74 ml, 12.2 mmol) in diisopropyl ether (70 ml), in the presence of Novozym 435 (2.1 g, 30 mg ml^{-1}), afforded the unreacted (1*S*,2*S*)-**4b** (0.31 g, 1.26 mmol; $[\alpha]_D^{20}$ +34.0 (*c* 0.5, MeOH); mp 131–132°C; ee 98.6%) and the ester (1*R*,2*R*)-**4a** (0.34 g oil, 1.19 mmol; $[\alpha]_D^{20}$ −40.5 (*c* 0.5, MeOH); ee 98.9%) in 168 h. Within 3–4 h, on stirring in K_2CO_3/methanol at room temperature, the ester enantiomer **4a** underwent quantitative deacylation, resulting in the corresponding alcohol (1*R*,2*R*)-**4c** ($[\alpha]_D^{20}$ −31.5 (*c* 0.5, MeOH); mp 128–129°C; ee 95.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4a**: 1.2–2.0 (8H, m, 4×CH_2), 1.44 (9H, s, 3×CH_3), 2.0 (3H, s, CH_3), 2.6 (3H, s, CH_3), 2.7 [1H, m, C*H*N(Me)(NHBoc)], 4.8 (1H, m, C*H*OCOCH_3), 5.8 (1H, b s, NH); anal. calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78; found: C, 59.03; H, 8.89; N, 9.55.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **4b** and **4c** are similar to those for (±)-**4**; anal. calcd for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.90; N, 11.47; found for **4b**: C, 59.12; H, 9.81; N, 11.21; found for **4c**: C, 58.84; H, 9.82; N, 11.30.

3.8. *General method for the methanolysis of **1a**–**4a** to the corresponding alcohol enantiomers **1c**–**4c***

A mixture of 1 mmol of **1a**–**4a** and K_2CO_3 (0.33 g, 2.4 mmol) in 25 ml of methanol was stirred for 4 h at room temperature.[15] After evaporation, the residue was dissolved in 20 ml of water and extracted with diethyl ether (3×30 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness and the product (**1c**–**4c**) was recrystallised from diisopropyl ether.

3.9. *Transformation of **4b** to (+)-(1*S*,2*S*)-2-methylaminocyclohexanol hydrochloride (+)-**6**·HCl (*n*=2)*

To a solution of **4b** (0.10 g) in 1 ml of CH_2Cl_2, TFA (5 ml) was added at room temperature.[15] After stirring for 25 min at room temperature, 150 ml of ice-cooled water was added and the mixture was extracted with diethyl ether (2×30 ml). The water phase was basified (pH=10) and extracted with $CHCl_3$ (4×30 ml), and the combined organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. The residual yellow oil was dissolved in 25 ml of methanol and hydrogenolysed in the presence of 0.05 g of Raney-Ni catalyst under hydrogen (1 bar) in an ultrasonic bath at room temperature for 2 h.[21] After filtration and evaporation, the hydrochloride salt was prepared with ethanol containing 22% of dry hydrogen chloride. The product was transferred together with racemic (±)-**6**·HCl (*n*=2; in the presence of 4-dimethylaminopyridine and pyridine) to a chiral column and accepted as one enantiomer of the racemic (±)-**6**. Since the sign of rotation of our synthetic product ($[\alpha]_D^{20}$ +34.0 (*c* 0.2, H_2O; ee 91%)) is opposite to that of the literature ($[\alpha]_D^{20}$ −56 (*c* 1, H_2O) for (1*R*,2*R*)-*trans*-2-methylaminocyclohexanol hydrochloride[18]), its absolute stereochemistry can be assigned as (+)-(1*S*,2*S*)-2-methylaminocyclohexanol hydrochloride.

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