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Enzyme-catalysed kinetic resolution of *N,O*-diacetyl derivatives of cyclic 1,3-amino alcohols

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Abstract—Racemates of *N,O*-diacetyl derivatives of *cis*- and *trans*-2-aminomethylcyclopentanols **5** and **6** and *cis*- and *trans*-2-aminomethylcyclohexanols **7** and **8** were resolved through lipase-catalysed asymmetric *O*-deacylation at the (1*R*) stereogenic centre. The gram-scale resolutions of **5**–**8** were carried out with ethanol in di-*iso*-propyl ether in the presence of Novozym 435. The unreacted *N,O*-diacetyl compounds **5a**–**8a** were transformed to the corresponding alcohols **5c**–**8c** without loss of enantiopurity.

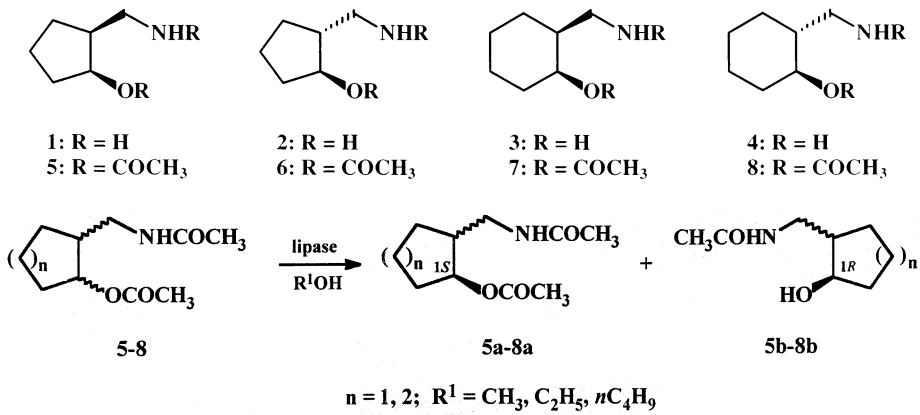
1. Introduction

Many 1,2- and 1,3-amino alcohols play important roles in the synthesis of pharmacologically active compounds.[1–4] For this reason, and because of the wide variety of their possible transformations and applications,[5–8] their preparation in enantiomerically pure form is very important.

On the basis of our earlier studies on the resolution of cyclic 1,3-amino alcohols,[9,10] we decided to investigate the enzyme-catalysed kinetic resolution of *cis*- and *trans*-2-aminomethylcyclopentanols and *cis*- and *trans*-2-aminomethylcyclohexanols **1**–**4**. Since these compounds have two functional groups, there are several possibilities for their resolution. For example, asymmetric acylation of the alcohol function of the *N*-protected compound is practical,[11,12] because the hydroxy group is attached directly to the stereogenic centre. Another efficient method is to prepare the *N,O*-diacetyl derivative and investigate the enzyme-catalysed *O*-deacylation in the presence of water[13] or alcohol.[14]

2. Results and discussion

The aim of our present work was to establish appropriate conditions for the resolution of **5**–**8** (Scheme 1). In order to find the optimal conditions for the gram-scale resolutions of these compounds, the effects of enzyme, alcohol, solvent and temperature on the enantioselectiv-



Scheme 1.

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ity ratio (E) and the reaction rate were investigated. The excellent result reported for the resolution of the *N*,*O*-diacetyl derivative of *cis*-1-amino-2-indanol through lipase-catalysed *O*-deacylation in organic media[14] prompted us to start our experiments with Novozym 435 at 45°C. The model compound for preliminary experiments was (±)-*trans*-*N*,*O*-diacetyl-2-aminomethylcyclohexanol **8**.

Good enantioselectivity, but a very low reaction rate, was observed when (±)-**8** was deacetylated in *n*-BuOH in the presence of Novozym 435 (50 mg mL^{-1}) and the mixture was shaken at 45°C (Table 1, row 1). In order to decrease the reaction time, the Novozym-catalysed alcoholysis of **8** with *n*-BuOH was tested in several solvents: tetrahydrofuran, dioxan and di-*iso*-propyl ether (Table 1, rows 2–4). The fastest reaction was observed in di-*iso*-propyl ether. Besides Novozym 435 (lipase from *Candida antartica* B), lipase PS (*Pseudomonas cepacia*), as the enzyme most commonly used for the resolution of secondary alcohols,[15–18] was tested under the same conditions (*iso*-Pr_2O:*n*-BuOH = 1:1, at 45°C). Surprisingly, there was no reaction after 72 h.

The rate of the enzymatic reaction could be increased by increasing the amount of Novozym from 50 mg mL^{-1} to 100 mg mL^{-1} (Table 1, rows 4 and 5). In efforts to further decrease the reaction time, the deacetylation agent *n*-BuOH was replaced with either EtOH or MeOH. The data presented in Table 1 (rows 5–7), reveal that EtOH was the most favourable acetyl acceptor for acceleration of the alcoholysis.

On increasing the temperature from 45 to 50°C, the reaction rate was increased without a drop in enantioselectivity (Table 1, rows 6 and 8). When the ratio of organic solvent:alcohol was changed from 1:1 to 4:1, a significant increase occurred in the reaction time (Table 1, rows 8 and 9).

Since the ideal working temperature for Novozym 435 is 60°C, some preliminary experiments were carried out at this temperature. The reaction rate increased slightly, with no change in the E value (Table 1, rows 8 and 10). When the amount of ethanol was decreased to 4 μL mL^{-1} (about 6–7 equiv. for the substrate), the reaction time decreased markedly (Table 1, rows 12 and 13). For reasons of economy, the amount of enzyme was decreased (Table 1, rows 13–15); under the same reaction conditions, the same good results were obtained with 50 mg mL^{-1} of enzyme as with 100 mg mL^{-1}.

In conclusion, the best results for the enzymatic resolution of **8** were observed with Novozym 435 (50 mg mL^{-1}) in di-*iso*-propyl ether solvent and performing the reaction at 60°C with ethanol as the acetyl acceptor. When small-scale resolutions of **5**–**7** were carried out under these conditions, to our surprise a low E value (after 1 h, conv. = 50%, $e.e._s$ = 77%, $e.e._p$ = 77%, E = 17) was observed in the case of **6**. In order to obtain **6a** and **6b** with higher e.e., the enzymatic reaction was stopped at 28% conversion ($e.e._{\mathbf{6a}}$ = 92%), and the unreacted enantiomerically enriched substrate was then subjected to a further enzymatic resolution. This second resolution was overrun and afforded the enantiopure **6b** ($e.e._{\mathbf{6b}}$ = 92%).

On the basis of the preliminary results, gram-scale resolution of **5**–**8** were performed in di-*iso*-propyl ether with Novozym 435 in the presence of ethanol, at 60°C. The results are reported in Table 2 and in Section 3.

The unreacted *N*,*O*-diacetyl enantiomers **5a**–**8a** were alcoholysed to the corresponding alcohols **5c**–**8c** in K_2CO_3/MeOH at room temperature without loss of enantiopurity (Scheme 2).

The size of the cycloalkane ring had a marked effect on the rate of enantioselective deacylation: the five-mem-

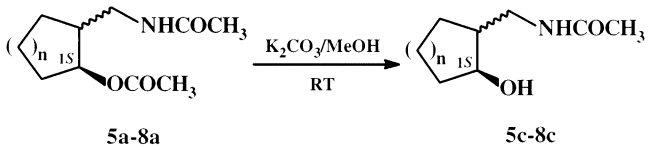
Table 1. Novozym 435-catalysed deacylation of **8** (0.1 M) in the presence of different alcohols in organic media at different temperatures

Temp. (°C)	Novozym 435 (mg mL^{-1})	Solvent	Time (h)	Conv. (%)	$E.e._s$ (%)	$E.e._p$ (%)	E	Row
45	50	*n*-BuOH	504	25	32	>99	>200	1
45	50	THF:*n*-BuOH (1:1)	398	44	78	>99	>200	2
45	50	Dioxan:*n*-BuOH (1:1)	398	43	74	>99	>200	3
45	50	*iso*-Pr_2O:*n*-BuOH (1:1)	120	33	50	>99	>200	4
45	100	*iso*-Pr_2O:*n*-BuOH (1:1)	96	40	67	>99	>200	5
			20	14	16	>99	>200	
45	100	*iso*-Pr_2O:EtOH (1:1)	20	27	37	>99	>200	6
45	100	*iso*-Pr_2O:MeOH (1:1)	96	22	27	>99	>200	7
50	100	*iso*-Pr_2O:EtOH (1:1)	22	38	60	>99	>200	8
50	100	*iso*-Pr_2O:EtOH (4:1)	22	48	92	>99	>200	9
60	100	*iso*-Pr_2O:EtOH (1:1)	21	38	60	>99	>200	10
60	75	*iso*-Pr_2O:EtOH (1:1)	19	34	51	>99	>200	11
60	75	*iso*-Pr_2O:EtOH (4:1)	16	43	75	>99	>200	12
60	75	*iso*-Pr_2O:EtOH (24:1)	7	49	95	>99	>200	13
60	50	*iso*-Pr_2O:EtOH (24:1)	7	49	94	>99	>200	14
60	25	*iso*-Pr_2O:EtOH (24:1)	7	26	34	>99	>200	15

Table 2. Novozym 435 (50 mg mL^{-1})-catalysed deacylation of **5**–**8** (0.1 M) in the presence of ethanol (0.04 μL mL^{-1}) in di-*iso*-propyl ether at 60°C

	Time (h)	Conv. (%)	E.e.$_{\mathbf{5a–8a}}$ (%)	Isomer **5a**–**8a**	Yield[a] (%)	$[\alpha]_D^{25}$	E.e.$_{\mathbf{5b–8b}}$ (%)	Isomer **5b**–**8b**	Yield[a] (%)	$[\alpha]_D^{25}$	*E*
5	28	51	98	1*S*,2*S*	88	+55.9[b]	96	1*R*,2*R*	83	−5.1[b]	>200
6	Resolution in two steps		97	1*S*,2*R*	23	+29.6[c]	92	1*R*,2*S*	30	−34.5[d]	
7	624	50	92	1*S*,2*S*	87	+49.5[b]	92	1*R*,2*R*	91	−9.8[b]	78
8	9	50	98	1*S*,2*R*	95	+39.9[b]	99	1*R*,2*S*	86	−9.1[b]	>200

[a] Yield 100% at 50% conversion.
[b] $c=0.8$, MeOH.
[c] $c=1.0$, MeOH.
[d] $c=0.95$, MeOH.



5a-8a 5c-8c

Scheme 2.

bered amino alcohol derivatives **5** and **6** reacted faster than the six-membered derivatives, **7** and **8**. It was also observed that the *trans* isomers **6** and **8** deacetylated faster than the *cis* isomers **5** and **7**.

2.1. Absolute configurations

On the basis of the Kazlauskas model for the active site of the lipases,[19,20] 1*R*-selectivity was predicted for the Novozym 435-catalysed deacetylation of **5**–**8**. The validity of this was proved in the case of **8b**, which was hydrolysed to the corresponding enantiomeric amino alcohol hydrochloride. The value of $[\alpha]_D^{25} = -26.7$ (*c* 1.0, H_2O) obtained for the amino alcohol hydrochloride, and the literature value for the (1*R*,2*S*)-*trans*-aminomethylcyclohexanol hydrochloride $[\alpha]_D^{25} = -27.1$ (*c* 2, H_2O),[21] indicate the *R* selectivity of the enzyme, in accordance with the Kazlauskas model. The (1*R*,2*S*) configuration is therefore accepted for the produced *trans* isomers **6b** and **8b**, and the (1*R*,2*R*) configuration for the produced *cis* isomers **5b** and **7b**.

3. Experimental

3.1. Materials and methods

The *cis*-2-aminomethylcycloalkanols **1** and **3** were obtained by reduction of the corresponding 5,6-dihydro-4*H*-1,3-oxazines.[22] The reduction of *trans*-2-cyanocycloalkanols resulted in the *trans*-2-aminomethylcyclanols **2** and **4**.[21] *n*-Butanol was purchased from Aldrich Co., and methanol and ethanol from Reanal. Lipase PS was 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 preparations thus obtained contained 20% (w/w) of lipase. All the solvents were of the highest analytical grade. For column chromatography, Merck silica gel 60/63–200 mesh was used.

The e.e. values of the unreacted *N*,*O*-diacetyl analogues **5a**–**8a** and the produced alcohols **5b**–**8b** were determined by gas chromatography on a Chrompack CP-Chirasil-DEX CB column (25 m). The produced alcohols **5b**–**8b** in the samples were derivatised with propionic anhydride in the presence of 4-dimethylaminopyridine and pyridine before the gas chromatographic analysis.

Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. Melting points were determined on a Kofler apparatus.

3.2. Preparation of *N*,*O*-diacetyl derivative of (±)-*cis*-2-aminocyclopentanol (±)-5

cis-2-Aminocyclopentanol **1** (1 g, 8.68 mmol) was dissolved in pyridine (3 mL), and acetic anhydride (3.5 mL) was added. The solution was stirred at rt for one night, and toluene (10 mL) was then added to the mixture (in order to facilitate evaporation of pyridine). The residue was chromatographed on silica. Elution with toluene:acetone (9:1) afforded an oil of **5** (1.13 g, 5.68 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33–1.90 (6H, m, 3×CH_2), 1.96 (3H, s, CH_3), 2.03–2.06 (1H, m, H-2), 2.07 (3H, m, CH_3), 2.69–2.76 (1H, m, CH_2NHCOCH$_3$), 3.65–3.72 (1H, m, CH_2NHCOCH$_3$), 5.23–5.25 (1H, m, H-1), 6.08 (1H, br, NH). Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.03; H, 8.78; N, 7.09%.

3.3. Preparation of *N*,*O*-diacetyl derivative of (±)-*trans*-2-aminocyclopentanol (±)-6

Using the procedure described above, *trans*-2-aminocyclopentanol **2** (1.4 g, 12.17 mmol) afforded (±)-**6** as a colourless oil (1.81 g, 9.13 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.18–2.08 (7H, m, 3×CH_2 and H-2), 1.99 (3H, s, CH_3), 2.05 (3H, s, CH_3), 3.02–3.06 (1H, m, CH_2NHCOCH$_3$), 3.27–3.32 (1H, m, CH_2NHCOCH$_3$), 4.81–4.84 (1H, m, H-1), 6.75 (1H, br, NH). Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.65; H, 8.41; N, 6.93%.

3.4. Preparation of *N*,*O*-diacetyl derivative of (±)-*cis*-2-aminocyclohexanol (±)-7

With the procedure described above, *cis*-2-aminocyclohexanol **3** (1 g, 7.74 mmol) afforded white crystals of (±)-**7** (1.32 g, 6.19 mmol); mp 73–76°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26–1.84 (9H, m, 4×CH_2 and H-2), 1.97 (3H, s, CH_3), 2.11 (3H, m, CH_3), 2.51–2.57 (1H, m, CH_2NHCOCH$_3$), 3.43–3.50 (1H, m, CH_2NHCOCH$_3$), 5.12–5.13 (1H, m, H-1), 6.15 (1H, br, NH). Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.65; H, 8.79; N, 6.73%.

3.5. Preparation of *N*,*O*-diacetyl derivative of (±)-*trans*-2-aminocyclohexanol (±)-8

With the procedure described above, *trans*-2-aminocyclohexanol **4** (1 g, 7.74 mmol) afforded white crystals of (±)-**8** (1.28 g, 6.01 mmol; mp 94–97°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.12–1.96 (9H, m, 4×CH_2 and H-2), 1.96 (3H, s, CH_3), 2.08 (3H, m, CH_3), 2.93–2.96 (1H, m, CH_2NHCOCH$_3$), 3.51–3.56 (1H, m, CH_2NHCOCH$_3$), 4.56–4.61 (1H, m, H-1), 5.85 (1H, br, NH). Anal. calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.23; H, 8.83; N, 6.46%.

3.6. General procedure for a typical small-scale experiment

Lipase PS (50 mg mL^{-1}) or Novozym 435 (25, 50, 75 or 100 mg mL^{-1}) was added to the appropriate *N*,*O*-diacetyl derivative **5**–**8** (0.1 M solution) in organic solvent: R^1OH (1 mL) and the mixture was shaken at 30, 45, 50 or 60°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.

3.7. Gram-scale resolution of (±)-5

(±)-**5** (0.7 g, 3.52 mmol) was dissolved in di-*iso*-propyl ether (34 mL), Novozym 435 (1.76 g, 50 mg mL^{-1}) and ethanol (1.40 mL) were added, and the mixture was shaken at 60°C for 28 h. The enzyme was filtered off at 51% conversion, and the solvent was evaporated. The residue was chromatographed on silica, with elution with toluene:acetone (9:1) affording the (1*S*,2*S*)-*N*,*O*-diacetyl and (1*R*,2*R*)-*N*-acetyl compounds.

(1*S*,2*S*)-**5a** was isolated as a colourless oil (0.31 g, 1.56 mmol); $[\alpha]_D^{25}=+55.9$ (*c* 0.8, MeOH); e.e. = 98%). The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **5a** are similar to those for (±)-**5**. Anal. found: C, 59.92; H, 8.45; N, 6.81%.

The produced (1*R*,2*R*)-**5b** was obtained as a white crystalline product (0.23 g, 1.46 mmol); $[\alpha]_D^{25}=-5.1$ (*c* 0.8, MeOH); e.e. = 96%; mp 91–94°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.45–1.87 (7H, m, 3×CH_2 and H-2), 2.01 (3H, s, CH_3), 3.01–3.06 (1H, m, CH_2NHCOCH$_3$), 3.58–3.66 (1H, m, CH_2NHCOCH$_3$), 4.03–4.05 (2H, m, H-1 and OH), 6.05 (1H, br, NH). Anal. calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.38; H, 9.45; N, 8.77%.

On stirring in K_2CO_3/MeOH at rt, *N*,*O*-diacetyl (1*S*,2*S*)-**5a** underwent quantitative deacylation within 3–4 h, resulting in the corresponding alcohol (1*S*,2*S*)-**5c** ($[\alpha]_D^{25}=+5.5$ (*c* 0.63, MeOH); e.e. = 98%; mp 97–100°C). The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **5c** are similar to those for **5b**. Anal. found: C, 61.35; H, 9.53; N, 8.79%.

3.8. Gram-scale resolution of (±)-6

Following the procedure described above, the reaction of (±)-**6** (1.42 g, 7.03 mmol) and ethanol (2.86 mL) in di-*iso*-propyl ether (68.9 mL) in the presence of Novozym 435 (3.55 g, 50 mg mL^{-1}) at 60°C afforded the unreacted (1*S*,2*R*)-**6a** as a colourless oil (0.78 g, 3.92 mmol; e.e. = 35%) and *N*-acetyl (1*R*,2*S*)-**6b** (0.20 g, 1.27 mmol; $[\alpha]_D^{25}=-34.5$ (*c* 0.95, MeOH); e.e. = 92%) in 40 min.

The unreacted **6a** (0.78 g, 3.92 mmol; e.e. = 35%) was subjected to a second enzymatic resolution. The reaction in di-*iso*-propyl ether (38.8 mL) with ethanol (1.6 mL) and Novozym 435 (2 g, 50 mg mL^{-1}) at 60°C afforded the unreacted (1*S*,2*R*)-**6a** as an oil (0.21 g, 1.05 mmol; $[\alpha]_D^{25}=+29.6$ (*c* 1.0, MeOH); e.e. = 97%) in 2.5 h.

The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **6a** are similar to those for (±)-**6**. Anal. found: C, 60.45; H, 8.68; N, 7.13%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **6b**: 1.23–1.97 (7H, m, 3×CH_2 and H-2), 1.99 (3H, s, CH_3), 2.63 (1H, s, OH), 3.11–3.13 (1H, m, CH_2NHCOCH$_3$), 3.41–3.46 (1H, m, CH_2NHCOCH$_3$), 3.84–3.86 (1H, m, H-1), 6.29 (1H, br, NH). Anal. calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.01; H, 9.53; N, 8.98%.

On stirring in K_2CO_3/MeOH at rt, *N*,*O*-diacetyl (1*S*,2*R*)-**6a** underwent quantitative deacylation within 3–4 h, resulting in the corresponding alcohol (1*S*,2*R*)-**6c** ($[\alpha]_D^{25}=+36.3$ (*c* 0.5, MeOH), e.e. = 97%). The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **6c** are similar to those for **6b**. Anal. found: C, 59.93; H, 9.70; N, 8.83%.

3.9. Gram-scale resolution of 7

Following the procedure described in Section 3.7, the reaction of (±)-**7** (0.6 g, 2.82 mmol) and ethanol (1.12 mL) in di-*iso*-propyl ether (27 mL) in the presence of Novozym 435 (2.82 g, 100 mg mL^{-1}) at 60°C afforded the unreacted (1*S*,2*S*)-**7a** (0.26 g, 1.22 mmol; $[\alpha]_D^{25}=+49.5$ (*c* 0.8, MeOH); e.e. = 92%; mp 63–65°C) and *N*-acetyl (1*R*,2*R*)-**7b** (0.22, 1.29 mmol; $[\alpha]_D^{25}=-9.8$ (*c* 0.8, MeOH); e.e. = 92%; mp 53–55°C) in 26 days.

The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **7a** are similar to those for (±)-**7**. Anal. found: C, 61.69; H, 8.83; N, 6.75%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **7b**: 1.25–1.91 (9H, m, 4×CH_2 and H-2), 2.01 (3H, m, CH_3), 2.82–2.85 (1H, m, CH_2NHCOCH$_3$), 3.47–3.57 (2H, m, OH and CH_2NHCOCH$_3$), 3.78–3.81 (1H, m, H-1), 5.89 (1H, m, NH). Anal. calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.41; H, 10.13; N, 8.32%.

On stirring in K_2CO_3/MeOH at rt, *N*,*O*-diacetyl (1*S*,2*S*)-**7a** underwent quantitative deacylation within 3–4 h, resulting in the corresponding alcohol (1*S*,2*S*)-**7c** ($[\alpha]_D^{25}=+10$ (*c* 0.70, MeOH); e.e. = 92%; mp 55–57°C). The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **7c** are similar to those for **7b**. Anal. found: C, 62.92; H, 10.09; N, 8.27%.

3.10. Gram-scale resolution of 8

Following the procedure described in Section 3.7, the reaction of (±)-**8** (0.6 g, 2.82 mmol) and ethanol (1.12 mL) in di-*iso*-propyl ether (27 mL) in the presence of Novozym 435 (1.41 g, 50 mg mL^{-1}) at 60°C afforded the unreacted (1*S*,2*R*)-**8a** (0.28 g, 1.33 mmol; $[\alpha]_D^{25}=+39.9$ (*c* 0.8, MeOH); e.e. = 98%; mp 117–119°C) and *N*-acetyl (1*R*,2*S*)-**8b** (0.21, 1.21 mmol; $[\alpha]_D^{25}=-9.1$ (*c* 0.8, MeOH); e.e. = 99%; mp 94–95°C) in 9 h.

The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **8a** are similar to those for (±)-**8**. Anal. found: C, 62.13; H, 8.87; N, 6.69%.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **8b**: 1.06–1.98 (9H, m, 4×CH_2 and H-2), 2.01 (3H, m, CH_3), 2.79–2.85 (1H, m, CH_2NHCOCH$_3$), 3.15–3.22 (1H, m, CH_2NHCOCH$_3$), 3.77–3.92 (2H, m, OH and H-1), 6.13 (1H, m, NH). Anal. calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.97; H, 10.11; N, 8.03%.

On stirring in K_2CO_3/MeOH at rt, the (1*S*,2*R*)-*N*,*O*-diacetyl compound **8a** underwent quantitative deacylation within 3–4 h, resulting in the corresponding alcohol (1*S*,2*R*)-**8c** ($[\alpha]_D^{25}=+9.5$ (*c* 0.98, MeOH); e.e.= 98%; mp 88–90°C). The ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) data for **8c** are similar to those for **8b**. Anal. found: C, 63.22; H, 10.09; N, 8.12%.

3.11. Preparation of (1*R*,2*S*)-*trans*-2-aminocyclohexanol hydrochloride

(1*R*,2*S*)-**8b** (0.2 g, 1.17 mmol) was dissolved in 6N HCl (3 mL). The solution was stirred under reflux for 5 h, and the solvent was then evaporated down. Recrystallisation of the crude product from ethanol/diethyl ether afforded white crystals of (1*R*,2*S*)-**4**·HCl (0.15 g, 9.06 mmol; $[\alpha]_D^{25}=-26.7$ (*c* 1.0, H_2O); e.e.=99%; mp 150°C). ^{1}H NMR (400 MHz, D_2O) δ (ppm) data for (1*R*,2*S*)-**4**·HCl: 1.04–1.94 (9H, 4×CH_2 and H-2), 2.91–2.96 (1H, CH_2NH_2), 3.16–3.21 (1H, CH_2NH_2), 3.43–3.44 (1H, m, H-1). Anal. calcd for $C_7H_{16}ClNO$: C, 50.75; H, 9.74; Cl, 21.40; N, 8.45. Found: C, 50.86; H, 9.69; Cl, 21.33; N, 8.41%.

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