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Enzymatic resolution of 2-dialkylaminomethylcyclopentanols and -cycloheptanols

Enikő Forró and Ferenc Fülöp *

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, H-6701, Szeged, POB 121, Hungary

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Abstract

Extensive lipase screening was performed in relation to the asymmetric acetylation of *rac*-2-dialkylaminomethylcyclanols **1**–**5**. The lipase PS- and Novozym 435-catalysed resolutions of compounds **1**–**5** were based on asymmetric acylation of the secondary OH group at the *R*-stereogenic centre with various vinyl esters, in different organic media. High enantioselectivity (E>200) was observed when vinyl acetate was used as acylating agent, with diethyl ether or with diisopropyl ether as solvent. The reaction rates were markedly affected by the size of the alicyclic ring, and by the solvent.

1. Introduction

Many 1,2- and 1,3-amino alcohols have valuable pharmacological effects, and are also useful building blocks for the synthesis of various pharmaceutically important compounds. Earlier extensive investigations of alicyclic 1,2- and 1,3-amino alcohols[1–5] prompted us to continue our previous research on the resolution of 2-dialkylaminomethylcyclohexanols[6] with the enzymatic resolution of racemic *trans*-2-(1-piperidylmethyl)cyclopentanol **1**, *cis*- and *trans*-2-dimethylaminomethylcyclopentanol **2** and **3** and *cis*- and *trans*-2-dimethylaminomethylcycloheptanol **4** and **5** by using lipase-catalysed acylation in organic media (Scheme 1). Some of the racemates of the target compounds[7–11] have been transformed into *cis*- and *trans*-2-dialkylaminomethylcycloalkylcarbamates which display strong local anaesthetic activity.[11] *trans*-1-(*m*-Methoxyphenyl)-2-dimethylaminomethylcyclohexan-1-ol (Tramadol) exerts analgesic activity and is used to combat strong physical pain.[12] A number of Tramadol analogues have been synthesised and investigated pharmacologically. It was found that the *trans* isomers were more active than the *cis* derivatives, and the (+)-*trans* enantiomers were more active than the (−)-*trans* isomers.[13–15]

* Corresponding author. Tel: 36 62 455 564; fax: 36 62 420 604; e-mail: fulop@pharma.szote.u-szeged.hu

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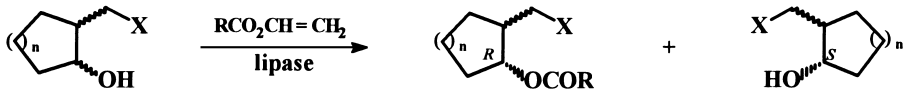


1-5 **1a-5a** **1b-5b**

1: n = 1, X = N⟨⟩, *trans*

2: n = 1, X = NMe_2, *cis*; **3**: n = 1, X = NMe_2, *trans*

4: n = 3, X = NMe_2, *cis*; **5**: n = 3, X = NMe_2, *trans*

Scheme 1.

2. Results and discussion

Lipase PS (*Pseudomonas cepacia*) is one of the most applicable enzymes for the resolution of secondary alcohols.[6,16–21] In previous work,[6] Novozym 435 (lipase from *Candida antarctica* B) also proved to be an excellent catalyst for the asymmetric acylation of 2-dialkylaminomethylcyclohexanols. Extensive lipase screening in diisopropyl ether indicated that for compound **1**, besides lipase PS- and Novozym 435, lipase AK (*Pseudomonas fluorescens*) was a promising catalyst, directing the acetylation to the *R*-stereocentre (Table 1). It turned out that the acetylation of **1** (0.1 M) in diisopropyl ether with vinyl acetate (0.2 M) at 25°C in the presence of lipase AK proceeded somewhat more slowly and less enantioselectively than when lipase PS or Novozym 435 was used (Table 1). It was observed that, under the above-mentioned conditions, lipase AY (*Candida rugosa*) directs the acetylation of **1** to the *S*-stereocentre, but with a low rate for the enzymatic reaction and with insufficient enantioselectivity for the products. The resolution conditions were subsequently optimised for the lipase PS- and Novozym 435-catalysed acylations by using **1** as a model compound.

Table 1
Lipase (30 mg ml^{-1})-catalysed acetylation of **1** (0.1 M) with vinyl acetate (0.2 M) in diisopropyl ether, at 25°C, after 1.5 h

Enzyme	Conversion (%)	$ee_{alcohol}$[a] (%)	ee_{ester}[b] (%)
lipase PS	35	51	94
lipase PS[c]	43	73	96
Novozym 435	43	73	95
lipase AK	28	35	89
lipase AY[d]	12	2	15

[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. [d]Reverse selectivity.

On the basis of previous experience with lipase PS and Novozym catalysis,[6,16–22] we have now examined several vinyl esters in the kinetic resolutions of **1**, using lipase PS and Novozym in diisopropyl ether (Table 2). It was found that the acylation of **1** in the presence of Novozym 435 (30 mg ml^{-1}) proceeded at a lower reaction rate with vinyl pivalate than with vinyl acetate; vinyl acetate displayed a better combination of activity and selectivity than that due to vinyl butyrate in the resolution of **1**

(Table 2). As a readily available and economical irreversible acyl donor (vinyl alcohol originating from vinyl acetate irreversibly tautomerises to acetaldehyde and prevents the back-reaction), vinyl acetate was used for the resolution of racemic **1**–**5**.

Table 2
Effects of various $RCO_2CH{=}CH_2$ (0.2 M) on the acylation of **1** (0.1 M) in the presence of Novozym 435 (30 mg ml^{-1}) or lipase PS[a] (50 mg ml^{-1}) in diisopropyl ether at 25°C

R	Enzyme	Time (h)	Conversion (%)	$ee_{alcohol}$[b] (%)	ee_{ester}[c] (%)
CH_3	Novozym	1	37	59	>99
	lipase PS	1	43	74	>99
$CH_3(CH_2)_2$	Novozym	1	49	91	94
	lipase PS	1	44	78	96
$(CH_3)_3C$	Novozym	30	46	86	>99
	lipase PS	30	44	77	>99

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

The nature of the solvent influences the activity and stability of the enzyme. Organic solvents can also have a marked effect on the enantioselectivity of enzymatic reactions. Ether solvents are generally preferable for work with lipase PS.[6,22] The Novozym 435 (30 mg ml^{-1})-catalysed acetylations of **1** (0.1 M) with vinyl acetate (0.2 M) at 25°C were performed in several organic solvents. Novozym 435, which was practically inactive for the reaction of *trans*-2-dimethylaminomethylcyclohexanol in acetone and tetrahydrofuran,[6] displayed high enantioselectivity in the case of **1** (Table 3). The reactions in toluene also exhibited high enantioselectivity, but with regard to the reaction rates, diethyl ether was finally chosen as the most favourable solvent for further studies, and led to excellent enantioselectivity (E>200).[23]

Table 3
Novozym 435 (30 mg ml^{-1})-catalysed acetylation of **1** (0.1 M) with vinyl acetate (0.2 M) in different organic solvents at 25°C

Solvent	log P[a]	Time (h)	Conversion (%)	$ee_{alcohol}$[b] (%)	ee_{ester}[c] (%)	E[d] (%)
Acetone	-0.23	2.5	41	65	92	47
Tetrahydrofuran	0.49	2.5	45	77	95	91
Diethyl ether	0.85	2	50	99	97	>200
Diisopropyl ether	1.90	2.5	48	87	96	139
Toluene	2.50	2.5	46	82	96	125

[a]P is the partition coefficient of the solvent between water and 1-octanol. [b]According to chiral GC after derivatization of the substrate with propionic anhydride. [c]According to chiral GC. [d]Enantiomeric ratio (E) = $\{\ln[(1-ee_{alc})/(1+ee_{alc}/ee_{ester})]\}/\{\ln[(1+ee_{alc})/(1+ee_{alc}/ee_{ester})]\}$.

The enzymatic reactions can also be controlled via the quantity of enzyme. Even though the enantioselectivity in the lipase PS- and Novozym 435-catalysed acetylations of alcohols **1**–**5** is generally excellent (usually E>200), the reactivity for the acetylation of **1** clearly passes through a maximum at a lipase PS content of ca. 50 mg ml^{-1}.

The results in Table 4 demonstrate that successful enantioselective acetylation of **1**–**5** is possible (with different reaction rates) when either lipase PS or Novozym 435 is used. It is important to note that the size of the cycloalkane ring has a clear effect on the rate of enantioselective acylation: the acetylation of the five-membered amino alcohols **1**–**3** proceeds more rapidly than that of the six-membered ones, and much more rapidly than that of the seven-membered amino alcohols **4** and **5**. It can also be concluded that the *trans* isomers react more rapidly than the *cis* counterparts.

Table 4
Activities of Novozym 435 (30 mg ml^{-1}) and lipase PS[a] (50 mg ml^{-1}) in the acetylation of **1**–**5** (0.1 M) with vinyl acetate (0.2 M) in diisopropyl ether at 25°C

Substrate	Enzyme	Time (h)	Conversion (%)	$ee_{alcohol}$[b] (%)	ee_{ester}[c] (%)	E (%)
1	Novozym	2	50	99	97	>200
	lipase PS	2	50	99	99	>200
2	Novozym	16	50	99	99	>200
	lipase PS	19	50	94	95	139
3	Novozym	2	50	98	98	>200
	lipase PS	2	50	97	93	121
4	Novozym	92	28	37	94	46
	lipase PS	92	36	53	96	83
5	Novozym	96	49	92	95	129
	lipase PS	96	50	95	95	>200

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

The amount of water present in the reaction mixture can influence biocatalysis in several ways. Moderate concentrations of water can often be added without loss of enzyme activity.[24] In order to decrease the rather long reaction time in the Novozym-catalysed resolution of **4** in diisopropyl ether (Table 4), some water was added. Even a small quantity of water (3%) destroyed the enantioselectivity, resulting in non-enzymatic acylation, leading to the racemic ester.

On the basis of the preliminary results on enzyme-catalysed acylations of the target compounds (Tables 1–4), gram-scale preparations of enantiomers of **1**–**5** were performed in diethyl ether or diisopropyl ether with lipase PS or Novozym as catalyst and vinyl acetate as acyl donor. The results are reported in Table 5 and in the Experimental.

Just as for the cyclohexanol derivatives,[6] the esters **1a**–**5a** produced by the (*R*)-selective acetylation of the cyclopentanols and cycloheptanols underwent spontaneous conversion to the corresponding alcohols **1c**–**5c** in methanol at room temperature, without loss of enantiopurity.

Table 5
Resolution of **1**–**5** in the presence of Novozym 435 (30 mg ml^{-1}) or lipase PS[a] (50 mg ml^{-1}) and vinyl acetate (0.2 M) in diethyl ether or diisopropyl ether at 25°C

Substrate	Enzyme	Time (h)	Conversion (%) E	Alcohol recovered (**1b-5b**) and (**1c-5c**,[b] second row)				Ester produced (**1a - 5a**)			
				Yield[c] (%)	Isomer	ee (%)	$[\alpha]_D^{20}$	Yield[c] (%)	Isomer	ee (%)	$[\alpha]_D^{20}$
1	lipase PS	1.5	50 E>200	56	*1S,2R* *1R,2S*	97.5[d] 97.0[d]	+26.0[e] −26.2[e]	65	*1R,2S*	95.3[f]	−36.6[e]
2	Novozym 435	16	50 E>200	38	*1S,2S* *1R,2R*	96.8[d] 98.0[d]	+15.0[g] −17.0[i]	60	*1R,2R*	98.7[f]	−37.8[h]
3	Novozym 435	2	50 E>200	83	*1S,2R* *1R,2S*	97.9[d] 97.5[d]	+59.2[j] −58.6[k]	96	*1R,2S*	99.0[f]	−55.4[e]
4	lipase PS	271	50 E>200	70	*1S,2S* *1R,2R*	96.1[d] 95.0[d]	+21.0[e] −20.0[l]	63	*1R,2R*	99.0[f]	−26.0[h]
5	lipase PS	144	49 E>200	59	*1S,2R* *1R,2S*	95.8[d] 99.0[d]	−26.1[e] +25.0[k]	94	*1R,2S*	>99.0[f]	−77.7[e]

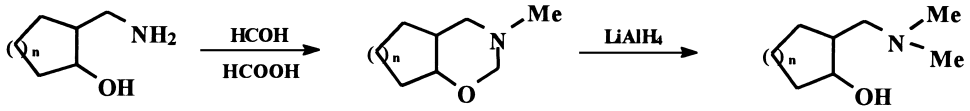
[a]Contains 20% (w/w) of lipase adsorbed on Celite in the presence of sucrose. [b]Obtained by hydrolysis of **1a-5a**. [c]Yield 100% at 50% conversion. [d]According to chiral GC after derivatization with propionic anhydride. [e]*c* = 1, MeOH.

2.1. *Absolute configurations*

The analysed chromatograms indicated that the corresponding enantiomers of compounds **1**–**5** react preferentially on lipase PS or Novozym 435 catalysis and similarly as in the case of 2-dialkylaminomethylcyclohexanols,[6] in accordance with the Kazlauskas model for the active site of lipases (a lipase distinguishes the two enantiomers on the basis of the sizes of the substituents R_{large} and R_{small} at the alcohol bearing 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)[25] the (1*S*,2*R*) configuration was proved for *trans*-2-dibenzylaminomethylcyclohexanol.[6] The (1*S*,2*S*) configuration is therefore accepted for the unreactive *cis*-cyclanols **2b** and **4b**, and the (1*S*,2*R*) configuration for the *trans* **1b**, **3b** and **5b** isomers.

2.2. *Synthesis of the racemic* cis- *and* trans-*2-dialkylaminomethylcyclanols*

Cyclopentanone or cycloheptanone was treated with an acidic mixture of piperidine or dimethylamine and formaldehyde, and the Mannich products were then reduced with $NaBH_4$, according to the literature.[7–10] From the diastereomeric mixtures, the rapidly eluting, major *trans* isomers were separated by column chromatography. The *cis* amino alcohols **2** and **4** were synthesised from the unsubstituted amino alcohols **6** and **7** (Scheme 2). *cis*-Amino alcohols **6**[26] and **7**[27] were transformed with a formaldehyde–formic acid mixture into *N*-methyltetrahydro-1,3-oxazines **8** and **9**, which were reduced with $LiAlH_4$ to the corresponding *cis*-**2** and *cis*-**4** (Scheme 2).



6 n = 1, *cis*
7 n = 3, *cis*

8 n = 1, *cis*
9 n = 3, *cis*

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

Scheme 2.

3. Experimental

3.1. Materials and methods

Vinyl acetate and vinyl pivalate were purchased from Aldrich Co., and vinyl butyrate from Tokyo Kasei Kogyo Co. 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.

The *trans*-2-dialkylaminomethylcyclanols **1**, **3** and **5** were prepared according to the literature.[7–10] From the *trans* isomer-rich diastereomeric mixtures, the rapidly eluting *trans* isomers were separated by column chromatography, **1** and **3** being eluted with toluene:methanol (2:1) and **5** with acetone.

3.2. Preparation of cis*-2-dimethylaminomethylcyclopentanol **2** and -cycloheptanol **4***

The *cis*-amino alcohols **6** and **7** (1.5 mmol) were heated under reflux with 36% aqueous formaldehyde solution (2 ml) and formic acid (2 ml). After 1 h, the mixture was poured onto 15 g ice, neutralised with Na_2CO_3, and extracted with chloroform (3×15 ml). The organic layer was dried (Na_2SO_4) and evaporated. The resulting crude oils **8** and **9** were reduced (without further purification) with $LiAlH_4$ (1 g) in boiling tetrahydrofuran (50 ml) for 2 h. The usual work-up afforded the corresponding *cis*-**2** (0.45 g) and *cis*-**4** (0.51 g). ^{1}H NMR data on **2** and **4** are similar to those on **2b**, **2c** and **4b**, **4c**, respectively.

3.3. General procedure for a typical small-scale experiment

The 2-dialkylaminomethylcyclanol **1**–**5** (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 these 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**–**5b**) and the produced ester (**1a**–**5a**) enantiomers were determined by gas chromatography on a Chrompack CP-Chirasil-DEX CB column (25 m).

3.4. Gram-scale resolution of trans*-2-(1-piperidylmethyl)cyclopentanol **1***

Racemic **1** (0.55 g, 3.0 mmol) and vinyl acetate (0.56 ml, 6.0 mmol) in diethyl ether (30 ml) were added to lipase PS (1.5 g, 50 mg ml^{-1}). The mixture was stirred at room temperature for 1.5 h. The reaction stopped at 50% conversion with 99% *ee* for the unreacted (1*S*,2*R*)-**1b** and 99% *ee* for the (1*R*,2*S*)-**1a**

produced. The enzyme was filtered off and the solvent was evaporated. The resolved products were separated on silica gel, elution being carried out with toluene:methanol (4:1) for **1a** (0.15 g oil, 0.84 mmol, *ee* 95.3%) and with methanol for **1b** (0.22 g oil, 0.98 mmol, *ee* 97.5%). Within 5 days, on standing in methanol at room temperature, the ester enantiomer **1a** underwent quantitative deacylation to give the corresponding alcohol **1c** (*ee* 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **1a**: 1.2–2.3 (17H, m, 8×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.3–2.4 (2H, dd, CH_2N), 4.8 (1H, m, C*H*OCOCH_3). Anal. calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 68.87; H, 10.21; N, 6.31.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **1b** and **1c**: 1.1–2.5 (17H, m, 8×CH_2 and remaining CH), 2.2 (1H, dd, CH_2N), 2.7 (1H, dd, *J*=12.3, 3.8 Hz, CH_2N), 3.7 (1H, m, C*H*OH), 5.1 (1H, brs, OH). Anal. calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found for **1b**: C, 72.67; H, 11.45; N, 7.96; found for **1c**: C, 72.40; H, 11.21; N, 7.36.

3.5. *Gram-scale resolution of* cis-*2-dimethylaminomethylcyclopentanol* ***2***

With the procedure described above, racemic **2** (0.42 g, 2.3 mmol) and vinyl acetate (0.40 ml, 4.3 mmol) in diethyl ether (25 ml) were added to Novozym 435 (0.75 g, 30 mg ml^{-1}); this afforded the unreacted (1*S*,2*S*)-**2b** (0.08 g oil, 0.56 mmol, *ee* 96.8%) and the ester (1*R*,2*R*)-**2a** (0.16 g oil, 0.87 mmol, *ee* 98.7%) in 16 h. Within 3–4 days, on standing in methanol at room temperature, the ester enantiomer **2a** underwent quantitative deacylation to give the corresponding alcohol **2c** (*ee* 97.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **2a**: 1.5–2.1 (7H, m, 3×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.3 (6H, s, 2×CH_3), 2.4 (1H, dd, *J*=12.4, 7.6 Hz, CH_2N), 2.5 (1H, dd, *J*=12.4, 6.0 Hz, CH_2N), 5.2 (H, m, C*H*OCOCH_3). Anal. calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.15; H, 10.20; N, 7.67.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **2b** and **2c**: 1.1–2.3 (7H, m, 3×CH_2 and remaining CH), 2.2–2.3 (2H, dd, CH_2N), 2.3 (6H, s, 2×CH_3), 4.3 (1H, m, C*H*OH). Anal. calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found for **2b**: C, 66.83; H, 11.90; N, 9.76; found for **2c**: C, 66.98; H, 11.89; N, 9.61.

3.6. *Gram-scale resolution of* trans-*2-dimethylaminomethylcyclopentanol* ***3***

With the procedure described above, racemic **3** (0.6 g, 4.2 mmol) and vinyl acetate (0.78 ml, 8.4 mmol) in diethyl ether (45 ml) in the presence of Novozym 435 (1.35 g, 30 mg ml^{-1}) afforded the unreacted (1*S*,2*R*)-**3b** (0.25 g oil, 1.7 mmol, *ee* 97.9%) and the ester (1*R*,2*S*)-**3a** (0.37 g oil, 2.0 mmol, *ee* 99.0%) in 2 h. Within 3−4 days, on standing in methanol at room temperature, the ester enantiomer **3a** underwent quantitative deacylation to give the corresponding alcohol **3c** (*ee* 97.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3a**: 1.2–2.3 (7H, m, 3×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.1 (1H, dd, CH_2N), 2.3 (6H, s, 2×CH_3), 2.3 (1H, dd, CH_2N), 4.8 (1H, m, C*H*OCOCH_3). Anal. calcd for $C_{11}H_{21}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.10; H, 10.24; N, 7.59.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **3b** and **3c**: 1.0–2.4 (6H, m, 3×CH_2 and remaining CH), 2.3 (6H, s, 2×CH_3), 1.9 (1H, dd, *J*=7.2, 3.8 Hz, CH_2N), 2.3 (1H, dd, CH_2N), 3.7 (1H, m, C*H*OH), 4.1 (1H, brs, OH). Anal. calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found for **3b**: C, 67.28; H, 12.15; N, 10.01; found for **3c**: C, 67.41; H, 12.02; N, 9.93.

3.7. Gram-scale resolution of cis-2-dimethylaminomethylcycloheptanol 4

With the procedure described above, racemic **4** (0.8 g, 4.7 mmol) and vinyl acetate (0.88 ml, 9.4 mmol) in diethyl ether (50 ml), in the presence of lipase PS (1.50 g, 50 mg ml^{-1}) afforded the unreacted (1*S*,2*S*)-**4b** (0.31 g oil, 1.45 mmol, *ee* 99%) and the ester (1*R*,2*R*)-**4a** (0.28 g oil, 1.6 mmol, *ee* 96.1%) in 271 h. Within 5 days, on standing in methanol at room temperature, the ester enantiomer **4a** underwent quantitative deacylation to give the corresponding alcohol **4c** (*ee* 97.5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4a**: 1.4–1.8 (10H, m, 5×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.1 (2H, dd, CH_2N), 2.2 (6H, s, 2×CH_3), 5.1 (H, m, C*H*OCOCH_3). Anal. calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.89; H, 11.00; N, 6.49.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **4b** and **4c**: 1.2–2.2 (11H, m, 5×CH_2 and remaining CH), 2.1 (1H, dd, CH_2N), 2.2 (6H, s, 2×CH_3), 2.6 (1H, dd, CH_2N), 3.9 (1H, m, C*H*OH), 5.7 (1H, brs, OH). Anal. calcd for $C_9H_{19}NO$: C, 70.12; H, 12.36; N, 8.18. Found for **4b**: C, 69.93; H, 12.20; N, 8.11; found for **4c**: C, 69.66; H, 12.17; N, 8.13.

3.8. Gram-scale resolution of trans-2-dimethylaminomethylcycloheptanol 5

With the procedure described above, racemic **5** (0.35 g, 2 mmol) and vinyl acetate (0.37 ml, 4 mmol) in diethyl ether (20 ml), in the presence of lipase PS (1.00 g, 50 mg ml^{-1}) afforded the unreacted (1*S*,2*R*)-**5b** (0.10 g oil, 0.60 mmol, *ee* 96.1%) and the ester (1*R*,2*S*)-**5a** (0.20 g oil, 0.96 mmol, *ee* 99%) in 271 h. Within 4–5 days, on standing in methanol at room temperature, the ester enantiomer **5a** underwent quantitative deacylation to give the corresponding alcohol **5c** (*ee* 96.6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **5a**: 1.2–2.1 (11H, m, 5×CH_2 and remaining CH), 2.0 (3H, s, CH_3), 2.0–2.1 (2H, dd, CH_2N), 2.2 (6H, s, 2×CH_3), 4.6 (H, m, C*H*OCOCH_3). Anal. calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.28; H, 10.89; N, 6.55.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) for **5b** and **5c**: 1.1–1.8 (11H, m, 5×CH_2 and remaining CH), 2.1 (1H, dd, *J*=12.3, 2.9 Hz, CH_2N), 2.2 (6H, s, 2×CH_3), 2.5 (1H, dd, CH_2N), 3.5 (1H, m, C*H*OH). Anal. calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found for **5b**: C, 70.02; H, 12.44; N, 8.18; found for **5c**: C, 69.86; H, 12.30; N, 8.11.

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