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Chemoenzymatic preparation of optically active β-amino-cyclohexanols and their application in the enantioselective addition of diethylzinc to benzaldehyde

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Abstract—Optically active vesamicol and other *trans*-2-(*N*,*N*-dialkylamino)cyclohexanols have been easily prepared in a two step sequence: opening of the oxirane ring of cyclohexene oxide with a secondary amine and subsequent resolution of the resulting racemic amino alcohol by transesterification catalyzed by *Pseudomonas cepacia* lipase. The utility of these β-aminocyclohexanols as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde has also been investigated.

1. Introduction

Enantiomerically pure β-amino alcohols play important roles both in the treatment of a wide variety of human diseases and disorders[1] and as chiral auxiliaries in asymmetric synthesis.[2] They are generally prepared from naturally occurring amino acids,[3] asymmetric amino hydroxylation of olefins[4] or via resolution of racemic β-amino alcohols, mainly, using optically active carboxylic or phosphoric acids.[5]

Enzymes are widely recognized as valuable tools for the synthesis of optically active compounds. Thus, lipase-catalyzed acylation or deacylation is one of the most efficient methods for the preparation of optically active amino alcohols.[6] Herein we apply this methodology to the resolution of some (±)-*trans*-2-(*N*,*N*-dialkylamino)cyclohexanols (Fig. 1), which are easily obtained by the ring opening of cyclohexene oxide. Some of these β-aminocyclohexanols, such as **3**, **4**, **5** (vesamicol) and **6**, were chosen for their importance as therapeutic agents. Ethers and esters derived from **3** and **4** are antiarrhythmic agents.[7] Vesamicol **5** and its analogue **6** show activity as anticholinergic,[8] with enantiomer (1*R*,2*R*)-**5** being 25-fold more potent than its counterpart.[9] Moreover, vesamicol also displays α-adrenoreceptor activity[10] and a high affinity for σ-receptors.[11]

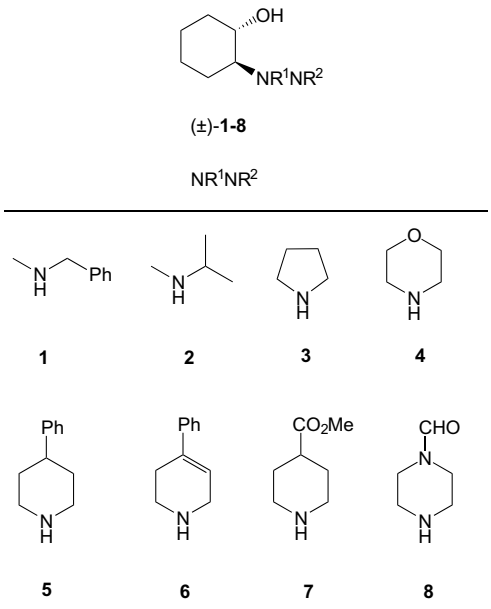

Figure 1.

Both enantiomers of vesamicol have previously been obtained by resolution of (±)-**5** using (−)-di-*p*-toluoyl-L-tartaric acid. However successive recrystallizations of the diastereomeric salts were required.[9] Compounds **1** and **4** can be obtained by asymmetric hydroboration of the corresponding enamine,[12] but resulting in very low enantiomeric excess, 27% and 21%, respectively, while compound **3** is obtained with high ee but low yield by

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the formation of diastereomeric borate complexes using chiral 1,1′-bi-2-naphthol and boric acid.[13] We believe that the lipase-catalyzed resolution could be an interesting alternative to these published methods.

On the other hand, our objective herein is also to investigate the utility of these optically active β-amino cyclohexanols as chiral ligands in the Et_2Zn addition to aldehydes. For this reason, we have included β-amino cyclohexanols **1** and **2** derived from acyclic amines, **7** and **8** that contain an additional functional group, which could be transformed to obtain other interesting compounds such as acids or polyamines.

2. Results and discussion

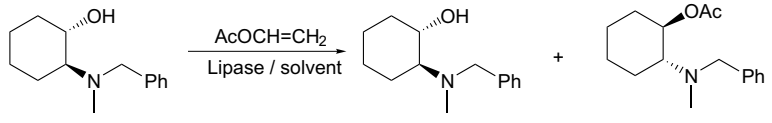
β-Amino alcohols (±)-**1**–**8** were obtained in very high yields by refluxing a mixture of the amine and cyclohexene oxide in ethanol.[14] The *trans*-configurations of the unpublished β-amino alcohols (±)-**2** and (±)-**7** were assigned by ^{1}H NMR from the coupling constants (J) values for H-1; in both cases two large J values of 9.7 Hz were observed, which is indicative of *trans*-diaxial arrangements between H-1 and H-2, and between H-1 and H-6ax. Similarly, the *trans*-configuration of (±)-**8** was established from the ^{1}H NMR spectrum of its acetyl derivative ($J_{1,2} = J_{1,6ax} = 10.4$ Hz).

2.1. Enzymatic resolution of (±)-1–8

In order to check the best reaction conditions for the resolution, compound (±)-**1** was used as a model substrate. Vinyl acetate and *tert*-butyl methyl ether[15] were selected as the acyl donor and the solvent, respectively, and the catalytic activity of several lipases tested (Table 1). Both lipase B from *Candida antarctica* (CAL-B) and lipase from *Pseudomonas cepacia* (PS-C) showed very high enantioselectivity (E[16] >200, entries 2 and 3), but the reaction rate with PS-C was notably higher than that with CAL-B. Although in these reactions anhydrous solvents and molecular sieves were used, partial lipase-catalyzed hydrolysis of vinyl acetate took place with the amino group being partially protonated by the resulting acetic acid. To investigate if this had some influence on the resolution process, we carried out the reactions in the presence of a basic additive such as triethylamine.[17] As it is shown, the use of this additive did not have a significant influence on the rate but the enantioselectivity of the CAL-B was lowered (entry 4). Other solvents were tested with lipase PS-C (entries 6–8), but in all cases rates, and enantioselectivities were poorer than with Bu^{t}OMe.

Resolutions of the other β-amino alcohols (±)-**2**–**8** were carried out under the optimal conditions found for (±)-**1**, with PS-C lipase, vinyl acetate and Bu^{t}OMe. In most cases, results obtained (Table 2) were excellent, with enantioselectivities being very high except for compound (±)-**2** (entry 2), for which the reaction occurred only with moderate enantioselectivity. Nevertheless, in all cases the produced esters were obtained with high yields and enantiomeric excesses (>92%). Moreover, in the resolution processes of vesamicol (±)-**5**, and its analogue (±)-**6** and (±)-**7** (entries 5–7), the conversion degrees attained were near to 50%, thus allowing us to obtain the remaining substrates with very high ee (>93%). With respect to the reaction rates, β-aminocyclohexanols **1**, **3**, **5**–**7** were transformed with similar rates, acetylations of **4** and **8** were slightly slower, and, newly, the poorer substrate was compound **2**, for which only 34% of conversion was achieved after a long reaction time (96 h, entry 2). The results obtained for **2** in comparison with

Table 1. Enzymatic transesterifications of (±)-**1**[a]

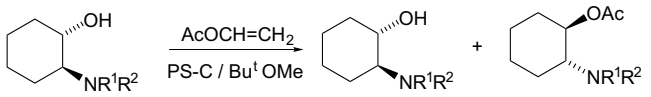


(±)-**1** (1*S*,2*S*)-**1** (1*R*,2*R*)-**9**

Entry	Enzyme	Solvent	Time (h)	c[b] (%)	Substrate, ee[c] (%)	Product, ee[c] (%)	E[d]
1	CAL-A	Bu^{t}OMe	96	No reaction			
2	CAL-B	Bu^{t}OMe	46	19	24	Enantiopure	>200
3	PS-C	Bu^{t}OMe	21	40	66	Enantiopure	>200
4	CAL-B[e]	Bu^{t}OMe	46	23	29	97	90
5	PS-C[e]	Bu^{t}OMe	21	42	72	Enantiopure	>200
6	PS-C	Hexane	21	39	59	92	45
7	PS-C	Acetonitrile	21	20	21	84	14
8	PS-C	Diethyl ether	21	28	38	98	126

[a] Reactions were conducted at 28 °C and 200 rpm.
[b] Conversion: $c = ee_s/(ee_s + ee_p)$.
[c] See text.
[d] Enantiomeric ratio calculated according to Ref. 16.
[e] Triethylamine (1.0 equiv) was used as an additive.

Table 2. Enzymatic transesterifications of (±)-**1**–**8**[a]



(±)-**1-8** (1*S*,2*S*)-**1-8** (1*R*,2*R*)-**9-16**

Entry	β-Amino alcohol	Time (h)	c[b] (%)	Substrate (1*S*,2*S*)-**1**–**8**		Product (1*R*,2*R*)-**9**–**16**		E[e]
				Yield[c] (%)	Ee[d] (%)	Yield[c] (%)	Ee[c] (%)	
1	(±)-**1**	21	40	58	66	36	>99	>200
2	(±)-**2**	96	34	50	47	33	92	38
3	(±)-**3**	26	45	44	78	43	96	117
4	(±)-**4**	34	43	52	74	39	Enantiopure	>200
5	(±)-**5**	29	49	49	95	43	Enantiopure	>200
6	(±)-**6**	26	48	51	93	44	Enantiopure	>200
7	(±)-**7**	25	49	47	95	42	Enantiopure	>200
8	(±)-**8**	33	41	58	70	41	>99	>200

[a] Reactions were conducted with PS-C, vinyl acetate (3.0 equiv) in Bu^{t}OMe at 28 °C and 200 rpm.
[b] Conversion: $c = ee_s/(ee_s + ee_p)$.
[c] Isolated yields.
[d] See text.
[e] Enantiomeric ratio calculated according to Ref. 16.

those obtained for the other substrates are indicative of the dramatic effect than the α-ramification of the alkyl group of the amine has on the activity of the lipase.

In the reactions of (±)-**3** and (±)-**5**, the stereochemical preference of the PS-C lipase was determined by establishing the absolute configuration of the remaining β-amino alcohols to be (1*S*,2*S*)-**3** and (1*S*,2*S*)-**5** after comparison of the specific rotations of **3** and the hydrochloride of **5** with those reported.[13,9] Furthermore, the configuration of the remaining (1*S*,2*S*)-**6** was established by its transformation into (1*S*,2*S*)-**5** by catalytic hydrogenation (H_2, Pd-black). In these cases, PS-C preferentially catalyzed the acetylation of the (1*R*,2*R*), following Kazlauskas' rule.[18] Taking into account the widely demonstrated enantiopreference of this lipase and the results obtained for **3**, **5** and **6**, we have tentatively assigned the (1*S*,2*S*) configuration for all the unreacted substrates (1*S*,2*S*)-**1**, **2**, **4**, **7**, **8**[19] and the (1*R*,2*R*)-configuration for the products (1*R*,2*R*)-**9**, **10**, **12**, **15**, **16**.

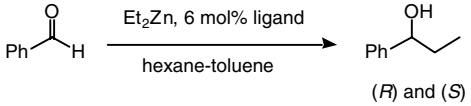
Enantiomeric excesses of the unreacted β-aminocyclohexanols **1**, **4**, **5** and **8** were determined by chiral HPLC (see Section 4.6 for the conditions of the analyses). For compounds **6** and **7**, direct analysis by HPLC was not possible. Thus, unsaturated compound **6** was transformed into **5** by catalytic hydrogenation and then analyzed by chiral HPLC. Compound **7** was treated with triphenylsilyl chloride and the resulting silyl derivative analyzed by chiral HPLC. All attempts to analyze compounds **2** and **3** or any of their derivatives (acetyl, benzoyl and triphenylsilyl derivatives) by chiral HPLC failed. For this reason ee of compound **2** was determined by ^{1}H NMR using (*R*)-(−)-α-methoxyphenylacetic acid as a chiral solvating agent.[21] Ee of **3** was determined by derivatization with (*S*)-MTPA-Cl[22] and further ^{19}F NMR analysis of the mixture of diastereomeric MTPA-esters.[23] To determine the enantiomeric excesses of esters (1*R*,2*R*)-**9**–**16**, these were previously hydrolyzed and the resulting alcohols analyzed as was pointed out before.

As indicated before the hydrogenation of (1*S*,2*S*)-**6** or its counterpart, (1*R*,2*R*)-**6** yields the corresponding optically active vesamicol **5** in very high yield (97%). This fact, along with the lower cost of the unsaturated piperidine used for the synthesis of (±)-**6** compared to the 4-phenylpiperidine required for the preparation of (±)-**5**, makes the resolution of (±)-**6** and the subsequent hydrogenation the most adequate to access optically active vesamicol.

2.2. Enantioselective addition of diethylzinc to benzaldehyde

Optically active acetyl derivatives (1*R*,2*R*)-**9**–**16** (Table 2, ee >92%) were hydrolyzed and the resulting amino alcohols (1*R*,2*R*)-**1**–**8** examined as chiral promoters in the addition of diethylzinc to benzaldehyde. Reactions were performed with 2.0 equiv of Et_2Zn in a mixture of hexane–toluene (2:1) and 6.0 mol% of β-aminocyclohexanol (1*R*,2*R*)-**1**–**8** at 20 °C following the procedure reported by Juaristi et al.[24] After 24 h of reaction, the benzaldehyde was completely consumed, and the product 1-phenylpropan-1-ol isolated in high yield (Table 3). Enantioselectivities achieved were moderate, the optimal results being obtained with aminoalcohols derived from cyclic amines. It is worthy of note the reversal of stereoinduction shown by these aminoalcohols. Thus, the *unlike* stereoinduction obtained in the alkylation with (1*R*,2*R*)-**2** [entry 2, (*S*)-1-phenylpropan-1-ol as the major enantiomer] is in line with the results obtained by Juaristi et al.[24] with the optically active (*S*,*S*,*S*)-2-[*N*-(α-methylbenzyl)amino]-cyclohexanol. However, a reverse stereoinduction was observed in the reactions with ligands derived from cyclic amines (1*R*,2*R*)-**3**–**8**, in all cases the (*R*)-1-phenylpropan-1-ol[25] being the major

Table 3. Enantioselective addition of Et_2Zn to benzaldehyde in the presence of ligands (1*R*,2*R*)-**1**–**8**[a]



Entry	Ligand	Yield (%)	Ee[b] (%)	Major enantiomer[c]
1	(1*R*,2*R*)-**1**	88	3	*R*
2	(1*R*,2*R*)-**2**	86	29	*S*
3	(1*R*,2*R*)-**3**	81	21	*R*
4	(1*R*,2*R*)-**4**	97	58	*R*
5	(1*R*,2*R*)-**5**	94	54	*R*
6	(1*R*,2*R*)-**6**	75	66	*R*
7	(1*R*,2*R*)-**7**	87	64	*R*
8	(1*R*,2*R*)-**8**	99	46	*R*

[a] (1*R*,2*R*)-**1**,**4**–**8**: ee >99%. (1*R*,2*R*)-**2**: ee=92%. (1*R*,2*R*)-**3**: ee=96%.
[b] Determined by chiral HPLC analysis (Chiralcel OD column, hexane–2-propanol 97:3, 0.8 mL/min), t_R = 14.7 (*R*) and 16.1 (*S*) min.
[c] Absolute configuration assigned from the sign of the specific rotation and from the elution order in HPLC analysis.

enantiomer (entries 3–8). These results indicate a strong influence of the substituents of the amine on the enantioselectivity, which would be exploited to prepare other interesting ligands.

3. Conclusion

P. cepacia lipase has shown to be an excellent catalyst in the acetylation of several *trans*-(±)-*N*,*N*-dialkylaminocyclohexanols with vinyl acetate. Between the substrates are included some biologically active β-amino alcohols such as vesamicol. In most cases the enantioselectivities of the enzymatic processes were very high allowing the isolation of both substrate and product with very high enantiomeric excesses. Furthermore, we have demonstrated the utility of the optically active amino cyclohexanols as ligands in the enantioselective addition of diethylzinc to benzaldehyde. In these reactions, enantioselectivities were moderate but the yields of the 1-phenylpropan-1-ol were high. Considering that some of the most efficient amino alcohols in this addition process bear a functional group susceptible to being transformed, that is, the methoxycarbonyl or formamide group, we can carry out some modifications on these substrates to give new and improved catalysts.

4. Experimental

4.1. General

Lipase B from *C. antarctica* (CAL-B), Novozym 435, was a gift from Novo Nordisk Co. and was employed without any previous treatment. CAL-A (Chirazyme L5, Lyo.) and lipase from *P. cepacia* (PS-C) were purchased from Roche and Amano Pharmaceutical Co., respectively. For the enzymatic reactions, commercial anhydrous *tert*-butyl methyl ether (99.8%) was used. IR spectra were recorded on an Infrared FT spectrophotometer using KBr pellets (for solids) or neat (for liquids). Chiral HPLC analyses were performed using Chiralcel OD, OD-H and OB-H columns (Daicel). ^{1}H, ^{13}C NMR and DEPT were recorded using AC-200 (^{1}H, 200 MHz and ^{13}C, 50.3 MHz), and AC-300 or DPX-300 (^{1}H, 300 MHz and ^{13}C, 75.5 MHz) spectrometers using $CDCl_3$ as solvent. Chemical shifts are given in delta (δ) values and the coupling constants (J) in hertz (Hz). ESI$^+$ was used to record mass spectra (MS). Microanalyses were performed on a Perkin–Elmer model 2400 instrument.

4.2. General procedure for the synthesis of (±)-*trans*-2-(*N*,*N*-dialkylamino)cyclohexanols 2, 7 and 8

To a solution of cyclohexene oxide (10 mmol) in deoxygenated ethanol (10 mL), the corresponding amine (15 mmol) was added. After 6 h to reflux (the reaction with *N*-methylpropan-2-amine was carried out in a sealed tube) the solvent was evaporated and the corresponding amino alcohol purified by distillation [**2**, 45 °C (0.5 Torr), 85% yield] or by flash chromatography [mixtures of ethyl acetate–methanol (6:1 for **7**, 90% yield, and 12:1 for **8**, 70% yield)].

4.3. Enzymatic transesterification of (±)-*trans*-2-(*N*,*N*-dialkylamino)cyclohexanols 1–8. General procedure

tert-Butyl methyl ether (12 mL) and vinyl acetate (6.0 mmol) were added to a mixture of the racemic amino alcohol (2.0 mmol), lipase (200 mg) and 4 Å molecular sieves (50 mg) under nitrogen atmosphere. The suspension was shaken at 28 °C and 200 rpm. Afterwards, the enzyme was filtered, washed with dichloromethane and the solvents evaporated. Both remaining amino alcohols and the corresponding amino ester present in the residue were separated by flash chromatography (hexane–ethyl acetate mixtures for the reactions of **1** and **4**–**7** or ethyl acetate–methanol mixtures for **2**, **3** and **8**).

4.3.1. (1*S*,2*S*)-2-(*N*-Benzyl-*N*-methylamino)cyclohexanol (1*S*,2*S*)-1. Yield: 58%. $[\alpha]_D^{20} = +33.5$ (*c* 1.1, $CHCl_3$) 66% ee. IR (neat) 3459 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.22–1.30 (m, 4H), 1.70–1.90 (m, 3H), 2.10–2.225 (m, 1H), 2.20 (s, 3H, N–CH_3), 2.39 (dt, 1H, J = 3.3 and 9.7 Hz, CH–N), 3.48 (d, 1H, J = 13.0 Hz, C*H*H–Ph), 3.40–3.54 (m, 1H), 3.74 (d, 1H, J = 13.0 Hz, CH*H*–Ph), 4.02 (br s, 1H, OH), 7.25–7.40 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 21.43 (CH_2), 23.98 (CH_2), 25.28 (CH_2), 33.09 (CH_2), 36.23 (CH_3), 57.89 (CH_2), 68.99 (CH), 69.09 (CH), 126.91 (CH), 128.19 (CH), 128.59 (CH), 139.20 (C); MS (ESI$^+$) m/z (rel. intensity): 220.1 [(M+H)$^+$, 100]. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.88; H, 9.56; N, 6.20.

4.3.2. (1*S*,2*S*)-2-(*N*-Isopropyl-*N*-methylamino)cyclohexanol (1*S*,2*S*)-2. Yield: 50%. $[\alpha]_D^{20} = +29.5$ (*c* 1.1, $CHCl_3$) 47% ee. IR (neat) 3442, 1082 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.97 (d, 3H, J = 6.5 Hz, CH_3), 0.99 (d, 3H,

$J = 6.5$ Hz, CH_3), 1.17 (m, 4H), 1.52–1.72 (m, 3H), 2.03 (m, 1H), 2.11 (s, 3H, N–CH_3), 2.25 (m, 1H), 2.82 (hept, 1H, $J = 6.5$ Hz, N–CH), 3.20 (dt, 1H, $J = 4.6$ and 9.8 Hz, C*H*–OH), 4.04 (s, 1H, OH); ^{13}C NMR (75.5 MHz): δ 20.12 (CH_3), 20.60 (CH_3), 23.97 (CH_2), 25.23 (CH_2), 25.48 (CH_2), 30.51 (CH_3), 32.90 (CH_2), 52.74 (CH), 66.02 (CH), 68.70 (CH); MS (ESI^+) m/z (rel. intensity): 172.1 [$(M+H)^+$, 100]. Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.06; H, 12.18; N, 8.35.

4.3.3. (1*S*,2*S*)-2-(Pyrrolidin-1-yl)cyclohexanol (1*S*,2*S*)-3. Yield: 44% $[\alpha]_D^{20} = +54.6$ (c 0.80, $CHCl_3$) 78% ee. Lit.[13] for (1*S*,2*S*)-(+)-**3**: $[\alpha]_D^{25} = +21.91$ (c 1.02, CH_2Cl_2) 36% ee. ^{1}H NMR (200 MHz): δ 1.17 (m, 4H), 1.68 (m, 7H), 2.05 (m, 1H), 2.30–2.70 (m, 5H), 3.29 (dt, 1H, $J = 4.5$ and 10.0 Hz, C*H*–OH), 3.98 (br s, 1H, OH); ^{13}C NMR data were in agreement with the literature.[13] MS (ESI^+) m/z (rel. intensity): 170.1 [$(M+H)^+$, 100].

4.3.4. (1*S*,2*S*)-2-(Morpholin-4-yl)cyclohexanol (1*S*,2*S*)-4. Yield: 52%. $[\alpha]_D^{20} = +53.6$ (c 1.1, $CHCl_3$) 74% ee. ^{1}H NMR (300 MHz): δ 0.98 (m, 4H), 1.40–1.66 (m, 3H), 1.80–2.00 (m, 2H), 2.19 (m, 2H), 2.48 (m, 2H), 3.14 (dt, 1H, $J = 4.7$ and 10.0 Hz, C*H*–OH), 3.47 (m, 4H, $2CH_2$–O) 3.58 (br s, 1H, OH); ^{13}C NMR data were in agreement with the literature.[12] MS (ESI^+) m/z (rel. intensity): 186.1 $(M+H)^+$, 100], 208.1 [$(M+Na)^+$, 6].

4.3.5. (1*S*,2*S*)-2-(4-Phenylpiperidin-1-yl)cyclohexanol (1*S*,2*S*)-5. Yield: 49%. Hydrochloride salt of (1*S*,2*S*)-**5**: $[\alpha]_D^{20} = +20.7$ (c 1.4, EtOH) 95% ee. Lit.[9] for (1*R*,2*R*)-(−)-**5**xHCl: $[\alpha]_D^{23} = -22.8$ (c 1.4, EtOH) enantiopure. ^{1}H NMR (300 MHz): δ 1.17–1.42 (m, 4H), 1.60–2.00 (m, 7H), 2.17–2.31 (m, 3H), 2.51 (m, 1H), 2.77 (m, 2H), 2.97 (m, 1H), 3.44 (dt, 1H, $J = 4.6$ and 9.6 Hz, C*H*–OH), 4.15 (br s, 1H, OH), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 22.06 (CH_2), 23.95 (CH_2), 25.46 (CH_2), 33.11 (CH_2), 33.81 (CH_2), 34.20 (CH_2), 42.83 (CH), 45.25 (CH_2), 53.29 (CH_2), 68.48 (CH), 70.46 (CH), 125.96 (CH), 126.65 (CH), 128.23 (CH), 146.13 (C); MS (ESI^+) m/z (rel. intensity): 260.2 [$(M+H)^+$, 100.

4.3.6. (1*S*,2*S*)-2-(4-Phenyl-1,2,5,6-tetrahydropyridin-1-yl)cyclohexanol (1*S*,2*S*)-6. Yield: 51%, mp 120–122 °C. $[\alpha]_D^{20} = +26.9$ (c 1.1, $CHCl_3$) 93% ee. IR (KBr) 3420, 1647, 1071 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.15–1.40 (m, 4H), 1.70–1.90 (m, 3H), 2.10–2.65 (m, 5H), 3.01 (m, 1H), 3.40–3.56 (m, 2H), 3.90 (br s, 1H, OH), 6.12 (t, 1H, $J = 3.6$ Hz), 7.20–7.45 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 21.81 (CH_2), 24.05 (CH_2), 25.46 (CH_2), 28.70 (CH_2), 33.18 (CH_2), 44.82 (CH_2), 48.55 (CH_2), 68.72 (CH), 69.31 (CH), 122.23 (CH), 124.66 (CH), 126.86 (CH), 128.19 (CH), 134.90 (C), 140.62 (C); MS (ESI^+) m/z (rel. intensity): 258.1 [$(M+H)^+$, 100]. Anal. Calcd for $C_{17}H_{23}NO$: C, 79,33; H, 9,01; N, 5,44. Found: C, 79.55; H, 8.89; N, 5.67.

4.3.7. (1*S*,2*S*)-2-(4-Methoxycarbonylpiperidin-1-yl)-cyclohexanol (1*S*,2*S*)-7. Yield: 47%, mp 51–53 °C. $[\alpha]_D^{20} = +44.0$ (c 1.1, $CHCl_3$) 95% ee. IR (KBr) 3491, 1729 cm^{-1}; ^{1}H NMR (200 MHz): δ 1.00–1.30 (m, 4H), 1.50–2.35 (m, 11H), 2.56–2.70 (m, 2H), 2.84 (dt, 1H, $J = 11.7$ and 3.5 Hz), 3.34 (dt, 1H, $J = 4.6$ and 9.7 Hz), 3.65 (s, 3H, OCH_3), 3.85 (br s, 1H, OH); ^{13}C NMR (50.3 MHz): δ 21.84 (CH_2), 23.64 (CH_2), 25.11 (CH_2), 28.40 (CH_2), 28.62 (CH_2), 32.85 (CH_2), 40.89 (CH), 44.68 (CH_2), 50.93 (CH_2), 51.18 (CH_3), 68.11 (CH), 70.21 (CH), 174.96 (C); MS (ESI^+) m/z (rel. intensity): 242.1 [$(M+H)^+$, 100], 264.1 [$(M+Na)^+$, 10]. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.89; H, 9.52; N, 5.99.

4.3.8. (1*S*,2*S*)-2-(4-Formylpiperazin-1-yl)cyclohexanol (1*S*,2*S*)-8. Yield: 58%, mp 56–58 °C. $[\alpha]_D^{20} = +32.9$ (c 0.93, $CHCl_3$) 70% ee. IR (KBr) 3454, 1674 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.19 (m, 4H), 1.75 (m, 3H), 2.00–2.50 (m, 4H), 2.69 (m, 2H), 3.20–3.70 (m, 6H including OH), 7.99 (s, 1H); ^{13}C NMR (75.5 MHz): δ 22.14 (CH_2), 23.60 (CH_2), 25.00 (CH_2), 32.85 (CH_2), 40.12 (CH_2), 45.82 (CH_2), 47.54 (CH_2), 48.78 (CH_2), 68.19 (CH), 70.26 (CH), 160.36 (CH); MS (ESI^+) m/z (rel. intensity): 213.1 [$(M+H)^+$, 38], 235.1 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62,23; H, 9,50; N, 13,20. Found: C, 62.05; H, 9.65; N, 13.36.

4.3.9. (1*R*,2*R*)-2-(*N*-Benzyl-*N*-methylamino)cyclohexyl acetate (1*R*,2*R*)-9. Yield: 36%. $[\alpha]_D^{20} = +2.0$ (c 0.65, $CHCl_3$) >99% ee. IR (neat) 1733, 1243 cm^{-1}; ^{1}H NMR (200 MHz): δ 1.15–1.50 (m, 4H), 1.60–2.20 [m + s, 4H + 3H (CH_3)], 2.23 (s, 3H, CH_3), 2.62 (dt, 1H, $J = 3.8$ and 10.8 Hz), AB system (δ_A 3.72, δ_B 3.61, $J_{A,B} = 13.5$ Hz, 2H), 4.96 (dt, 1H, $J = 4.7$ and 10.2 Hz, C*H*–OAc), 7.15–7.40 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 21.44 (CH_3), 24.25 (CH_2), 24.87 (CH_2), 25.05 (CH_2), 31.86 (CH_2), 36.80 (CH_3), 58.62 (CH_2), 65.17 (CH), 72.40 (CH), 126.50 (CH), 127.97 (CH), 128.26 (CH), 140.32 (C), 170.45 (C); MS (ESI^+) m/z (rel. intensity): Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5,36. Found: C, 73.42; H, 8.73; N, 5.48.

4.3.10. (1*R*,2*R*)-2-(*N*-Isopropyl-*N*-methylamino)cyclohexyl acetate (1*R*,2*R*)-10. Yield: 33%. $[\alpha]_D^{20} = -25.2$ (c 0.80, $CHCl_3$) 92% ee. IR (neat) 1733 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.95 (d, 3H, $J = 6.0$ Hz, CH_3), 0.97 (d, 3H, $J = 6.0$ Hz, CH_3), 1.10–1.40 (m, 4H), 1.60–1.80 (m, 3H), 1.90–2.05 [m+s, 1H+3H (CH_3)], 2.15 (s, 3H, N–CH_3), 2.50 (dt, 1H, $J = 3.6$ and 10.6 Hz), 2.82 (hept, 1H, $J = 6.5$ Hz, N–CH), 4.74 (dt, 1H, $J = 4.6$ and 10.1 Hz, C*H*–OAc); ^{13}C NMR (75.5 MHz): δ 20.46 (CH_3), 20.66 (CH_3), 21.34 (CH_3), 24.21 (CH_2), 25.08 (CH_2), 27.77 (CH_2), 31.43 (CH_3), 31.68 (CH_2), 52.49 (CH), 62.24 (CH), 72.19 (CH), 170.34 (C); MS (ESI^+) m/z (rel. intensity): 214.1 [$(M+H)^+$, 100], 172.1 [$(C_{10}H_{22}NO)^+$, 32]. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.80; H, 10.96; N, 6.44.

4.3.11. (1*R*,2*R*)-2-(Pyrrolidin-1-yl)cyclohexyl acetate (1*R*,2*R*)-11. Yield: 43%. $[\alpha]_D^{20} = -31.4$ (*c* 0.90, $CHCl_3$) 96% ee. IR (neat) 1736, 1241, 1040 cm^{-1}; ^1H NMR (200 MHz): δ 1.10–2.10 (m, 12H), 1.97 (s, 3H, CH_3), 2.36 (dt, 1H, $J = 3.5$ and 7.8 Hz), 2.52 (m, 4H), 4.84 (dt, 1H, $J = 3.8$ and 7.2 Hz, C*H*–OAc); ^{13}C NMR (50.3 MHz): δ 21.23 (CH_3), 22.53 (CH_2), 23.24 (CH_2), 25.92 (CH_2), 28.84 (CH_2), 49.75 (CH_2), 62.15 (CH), 72.93 (CH), 170.10 (C); MS (ESI^+) *m*/*z* (rel. intensity): 212.2 [$(M+H)^+$, 100], 170.2 [$(C_{10}H_{20}NO)^+$, 25]. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6,63. Found: C, 68.00; H, 10.26; N, 6.58.

4.3.12. (1*R*,2*R*)-2-(Morpholin-4-yl)cyclohexyl acetate (1*R*,2*R*)-12. Yield: 39%. $[\alpha]_D^{20} = -23.0$ (*c* 1.1, $CHCl_3$) enantiopure. IR (neat) 1733, 1241, 1117 cm^{-1}; ^1H NMR (300 MHz): δ 1.20–1.44 (m, 4H), 1.71–2.01 (m, 4H), 2.08 (s, 3H, CH_3), 2.32–2.50 (m, 3H), 2.69 (m, 2H), 3.61 (m, 4H, $2CH_2O$), 4.85 (dt, 1H, $J = 4.5$ and 10.2 Hz, C*H*–OAc); ^{13}C NMR (75.5 MHz): δ 21.34 (CH_3), 24.23 (CH_2), 24.54 (CH_2), 24.84 (CH_2), 31.70 (CH_2), 49.31 (CH_2), 67.35 (CH), 67.74 (CH_2), 71.50 (CH), 170.42 (C); MS (ESI^+) *m*/*z* (rel. intensity): 228.1 [$(M+H)^+$, 100], 250.0 [$(M+Na)^+$, 37]. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.35; H, 9.15; N, 6.35.

4.3.13. (1*R*,2*R*)-2-(4-Phenylpiperidin-1-yl)cyclohexyl acetate (1*R*,2*R*)-13. Yield: 43%. $[\alpha]_D^{20} = -19.2$ (*c* 1.0, $CHCl_3$) enantiopure. IR (nujol) 1725, 1244 cm^{-1}; ^1H NMR (200 MHz): δ 1.15–2.10 (m, 12H), 2.13 (s, 3H, CH_3), 2.30–2.68 (m, 4H), 2.83 (m, 1H), 2.99 (m, 1H), 4.93 (dt, 1H, $J = 4.7$ and 11.2 Hz, C*H*–OAc), 7.15–7.40 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 21.45 (CH_3), 24.32 (CH_2), 25.01 (CH_2), 31.89 (CH_2), 33.80 (CH_2), 34.64 (CH_2), 42.95 (CH), 48.51 (CH_2), 51.24 (CH_2), 67.33 (CH), 72.08 (CH), 125.83 (CH), 126.71 (CH), 128.17 (CH), 146.62 (C), 170.40 (C); MS (ESI^+) *m*/*z* (rel. intensity): 302.2 $(M+H)^+$, 100]. Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.50; H, 9.20; N, 4.72.

4.3.14. (1*R*,2*R*)-2-(4-Phenyl-1,2,5,6-tetrahydropyridin-1-yl)cyclohexyl acetate (1*R*,2*R*)-14. Yield: 44%, mp 70–72 °C. $[\alpha]_D^{20} = -23.4$ (*c* 1.0, $CHCl_3$) enantiopure. IR (KBr) 1720, 1250 cm^{-1}; ^1H NMR (300 MHz): δ 1.25–1.42 (m, 4H), 1.74–2.10 (m, 4H), 2.05 (s, 3H, CH_3), 2.40–2.75 (m, 4H), 2.94 (dt, 1H, $J = 10.8$ and 5.2 Hz), 3.34–3.44 (m, 2H), 4.99 (dt, 1H, $J = 4.5$ and 10.2 Hz, C*H*–OAc), 6.10 (br s, 1H), 7.20–7.45 (m, 5H, Ph); ^{13}C NMR (75.5 MHz): δ 21.40 (CH_3), 24.21 (CH_2), 24.90 (CH_2), 25.08 (CH_2), 28.73 (CH_2), 31.79 (CH_2), 45.21 (CH_2), 49.21 (CH_2), 65.69 (CH), 72.05 (CH), 122.48 (CH), 124.56 (CH), 126.62 (CH), 128.08 (CH), 134.64 (C), 140.80 (C), 170.47 (C); MS (ESI^+) *m*/*z* (rel. intensity): 300.1 [$(M+H)^+$, 30], 296.1 [$(C_{19}H_{22}NO_2)^+$, 100]. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.29; H, 8.58; N, 4.53.

4.3.15. (1*R*,2*R*)-2-(4-Methoxycarbonylpiperidin-1-yl)-cyclohexyl acetate (1*R*,2*R*)-15. Yield: 42%. $[\alpha]_D^{20} = -22.1$ (*c* 1.1, $CHCl_3$) enantiopure. IR (neat) 1736, 1241 cm^{-1}; ^1H NMR (300 MHz): δ 1.16–1.78 (m, 12H), 2.03 (s, 3H, CH_3), 2.14–2.24 (m, 2H), 2.31–2.46 (m, 2H), 2.67 (br d, 1H, $J = 10.1$ Hz), 2.87 (br d, 1H, $J = 9.8$ Hz), 3.64 (s, 3H, OCH_3), 4.82 (dt, 1H, $J = 4.6$ and 10.4 Hz); ^{13}C NMR (75.5 MHz): δ 21.23 (CH_3), 24.20 (CH_2), 24.60 (CH_2), 24.87 (CH_2), 28.93 (CH_2), 29.00 (CH_2), 31.74 (CH_2), 41.38 (CH), 47.22 (CH_2), 49.88 (CH_2), 51.30 (CH_3), 67.35 (CH), 71.62 (CH), 170.22 (C), 175.60 (C); MS (ESI^+) *m*/*z* (rel. intensity): 284.2 [$(M+H)^+$, 100], 306.2 [$(M+Na)^+$, 15]. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.69; H, 8.80; N, 4.80.

4.3.16. (1*R*,2*R*)-2-(4-Formylpiperazin-1-yl)cyclohexyl acetate (1*R*,2*R*)-16. Yield: 41%, mp 60–62 °C. $[\alpha]_D^{20} = -36.4$ (*c* 1.0, $CHCl_3$) >99% ee. IR (KBr) 1732, 1678 cm^{-1}; ^1H NMR (300 MHz): δ 1.15–1.35 (m, 4H), 1.65–2.10 (m, 4H), 2.02 (s, 3H, CH_3), 2.38–2.43 (m, 3H), 2.61–2.73 (m, 2H), 3.15–3.47 (m, 4H), 4.80 (dt, 1H, $J = 4.6$ and 10.4 Hz, C*H*–OAc), 7.95 (s, 1H); ^{13}C NMR (75.5 MHz): δ 21.18 (CH_3), 24.05 (CH_2), 24.51 (CH_2), 24.65 (CH_2), 31.57 (CH_2), 40.65 (CH_2), 46.29 (CH_2), 48.62 (CH_2), 48.93 (CH_2), 67.42 (CH), 71.23 (CH), 160.56 (CH), 170.25 (C); MS (ESI^+) *m*/*z* (rel. intensity): 255.1 [$(M+H)^+$, 26], 277.0 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.51; H, 8.61; N, 11.22.

4.4. Hydrogenation of (1*R*,2*R*)-6: synthesis of vesamicol

A suspension of (1*R*,2*R*)-**6** (32 mg, 0.13 mmol) and Pd–C (10%, 24 mg) in deoxygenated methanol (8.0 mL) was stirred for 12 h under a hydrogen atmosphere. The reaction mixture was filtered through Celite©, and the filtrate was evaporated to yield pure (1*R*,2*R*)-**5** (97%).

4.5. Triphenylsilyl derivative of (1*S*,2*S*)-7

To a solution of (1*S*,2*S*)-**7** (30 mg, 0.12 mmol) and imidazole (8.0 mg, 0.12 mmol) in anhydrous THF (5.0 mL) triphenylsilyl chloride (44 mg, 0.15 mmol) was added. After 24 h to room temperature, dichloromethane (10 mL) was added and the resulting organic solution washed with aq $NaHCO_3$ (2×10 mL) and water (10 mL). Evaporation of organic phase yielded crude (1*S*,2*S*)-**17**, which was purified by flash chromatography (hexane–AcOEt 8:1 as eluent). Yield: 60%. $[\alpha]_D^{20} = +8.2$ (*c* 1.2, $CHCl_3$) 95% ee. ^{13}C NMR (75.5 MHz): δ 23.20 (CH_2), 24.32 (CH_2), 24.81 (CH_2), 28.20 (CH_2), 28.59 (CH_2), 35.93 (CH_2), 41.51 (CH), 46.31 (CH_2), 50.29 (CH_2), 51.47 (CH_3), 69.27 (CH), 71.78 (CH), 127.57 (CH), 127.78 (CH), 129.76 (CH), 134.94 (C), 135.57 (CH), 175.70 (C); MS (ESI^+) *m*/*z* (rel. intensity): 500.2 [$(M+H)^+$, 100]. Anal. Calcd for $C_{31}H_{37}NO_3Si$: C, 74.51; H, 7.46; N, 2.80. Found: C, 74.67; H, 7.33; N, 2.95.

4.6. Chiral HPLC conditions for (±)-1, 4, 5, 8 and the silyl derivative (±)-17

Amino alcohol (±)-**1**: Chiralcel OD-H column (20 °C), hexane–propan-2-ol, 99:1, 0.4 mL/min, t_R 23.14 (1*S*,2*S*)

and 25.75 (1*R*,2*R*) min, $R_S = 1.9$. Amino alcohol (±)-**4**: Chiralcel OB-H column (20 °C), hexane–propan-2-ol, 99:1, 0.8 mL/min, t_R 10.75 (1*S*,2*S*) and 11.85 (1*R*,2*R*) min, $R_S = 1.3$. Amino alcohol (±)-**5**: Chiralcel OD column (20 °C), hexane–propan-2-ol, 99.4:0.6, 0.5 mL/min, t_R 27.44 (1*R*,2*R*) and 30.30 (1*S*,2*S*) min, $R_S = 1.5$. Amino alcohol (±)-**8**: Chiralcel OB-H column (35 °C), hexane–propan-2-ol, 90:10, 0.8 mL/min, t_R 21.11 (1*S*, 2*S*) and 24.87 (1*R*,2*R*) min, $R_S = 2.4$. Silyl derivative (±)-**17**: Chiralcel OD column (20 °C), hexane–propan-2-ol, 99.2:0.8, 0.3 mL/min, t_R 25.00 (1*R*,2*R*) and 25.75 (1*S*,2*S*) min, $R_S = 1.2$.

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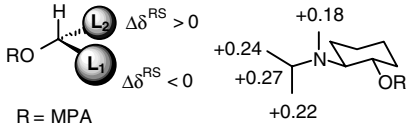
References and notes

1. Witiak, D. T.; Inbasekaran, M. N. In *Kirk-Othmer Encycl. Chem. Technol.*; Grayson, M., Ed.; 1982; pp 311–345.
2. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875; (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 34–48; (c) Tomioka, K. *Synthesis* **1990**, 541–549.
3. (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley-Interscience: New York, 1987; (b) Abico, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517–5518; (c) Drauz, K.; Schwarm, M.; Mckennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568–3571.
4. (a) Gontcharov, A. V.; Hong, L.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783–786; (b) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326–329; (c) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1308–1309, and references cited therein.
5. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; John Wiley: New York, 1981.
6. For some examples, see: (a) Luna, A.; Astorga, C.; Fülop, F.; Gotor, V. *Tetrahedron: Asymmetry* **1998**, *9*, 4483–4487; (b) Sekar, G.; Kamble, R. M.; Singh, V. K. *Tetrahedron: Asymmetry* **1999**, *10*, 3663–3666; (c) Luna, A.; Maestro, A.; Astorga, C.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 1969–1977; (d) Clariana, J.; García-Granda, S.; Gotor, V.; Gutiérrez-Fernández, A.; Luna, A.; Moreno-Mañas, M.; Vallribera, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4549–4557.
7. (a) Bain, A. I.; Beatch, G. N.; Longley, C. J.; Plouvier, B. M. C.; Sheng, T.; Walker, M. J. A.; Wall, R. A.; Yong, S. L.; Zhu, J.; Zolotoy, A. B. Patent 9 950 225, 1999; *Chem. Abstr*. **1999**, *131*, 257571; (b) MacLeod, B. A.; Walker, M. J. A.; Wall, R. A. U.S. Patent 5 637 583, 1997; *Chem. Abstr*. **1997**, *127*, 108837.
8. Marshall, I. G.; Parsons, S. M. *Trends Neurosci.* **1987**, *10*, 174–177.
9. Rogers, G. A.; Parsons, S. M.; Anderson, D. C.; Nilsson, L. M.; Bahr, B. A.; Kornreich, W. D.; Kaufman, R.; Jacobs, R. S.; Kirtman, B. *J. Med. Chem.* **1989**, *32*, 1217–1230.
10. Wannan, G.; Prior, C.; Marshall, I. G. *Eur. J. Pharmacol.* **1991**, *201*, 29–34.
11. Efange, S. M. N.; Mach, R. H.; Smith, C. R.; Khare, A. B.; Foulon, C.; Akella, S. K.; Childers, S. R.; Parsons, S. M. *Biochem. Pharmacol.* **1995**, *49*, 791–797.
12. Fisher, G. B.; Goralski, Ch. T.; Nicholson, L. W.; Hasha, D. L.; Zakett, D.; Singaram, B. *J. Org. Chem.* **1995**, *60*, 2026–2034.
13. Periasamy, M.; Kumar, N. S.; Sivakumar, S.; Rao, V. D.; Ramanathan, C. R.; Venkatraman, L. *J. Org. Chem.* **2001**, *66*, 3828–3833.
14. Mousseron, M.; Jullien, J.; Jolchine, Y. *Bull. Soc. Chim. Fr.* **1952**, *19*, 757–766.
15. García-Alles, L. F.; Gotor, V. *Biotechnol. Bioeng.* **1998**, *59*, 684–694.
16. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
17. Theil, F. *Tetrahedron* **2000**, *56*, 2905–2919.
18. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.
19. An attempt to determine the configuration of the remaining (1*S*,2*S*)-**2** by derivatization with (*R*)- and (*S*)-α-methoxy-phenylacetic acid (MPA) and ^{1}H NMR analysis of the corresponding MPA-esters derivatives was carried out.[20] From the signs of $\Delta\delta^{RS}$ (ppm) observed for the groups attached to the nitrogen (L_2 substituent), the (1*S*,2*S*) configuration for **2** can be deduced. However, signals corresponding to the L_1 substituent were not resolved and a complete analysis was not possible. Similar analyses were not carried out with the other amino alcohols because their ^{1}H NMR spectra were more complicated than that for (1*S*,2*S*)-**2**.



20. Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.
21. A 0.2 M solution of (±)-**2** and (*R*)-(−)- α-methoxyphenylacetic acid in $CDCl_3$ was directly prepared in a NMR tube and its ^{1}H NMR (200 MHz) spectrum recorded at room temperature. Two well resolved signals were observed for N–CH_3 group of (±)-**2** to 2.42 (1*S*,2*S*) and 2.35 (1*R*,2*R*) ppm.
22. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
23. ^{19}F NMR data for the diastereomeric MTPA-esters derived of (±)-**3**: δ −71.79 and −72.19 ppm ($CFCl_3$ as an external standard). For the MTPA-esters obtained from (1*S*,2*S*)-**3** a major signal to −72.19 was observed.
24. Sosa-Rivadeneyra, M.; Muñoz-Muñiz, O.; Anaya de Parrodi, C.; Quintero, L.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 2369–2375.
25. $[\alpha]_D^{20} = +30.7$ (*c* 2.00, hexane) 66% ee. Aldrich catalogue data for (*R*)-(+)-1-phenylpropan-1-ol: $[\alpha]_D^{20} = +48$ (*c* 2.25, hexane).