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Lipase-catalyzed Kinetic Resolution of (±)-*trans*- and *cis*-2-Azidocycloalkanols

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The lipase-catalyzed kinetic resolution of *trans*- and *cis*-2-azidocycloalkanols and the preparation of enantiomerically pure *trans*- and *cis*-2-aminocycloalkanols are described.

Four kinds of lipases were screened for the acetylation of *trans*- and *cis*-2-azidocycloalkanols. Among them, *Pseudomonas* sp. lipases (lipase PS and lipase AK, Amamo Pharmaceutical Co.) showed the highest enantioselectivity. These products were converted to the corresponding 2-aminocycloalkanols to determine their enantiomeric excess (*ee*) and absolute configurations by HPLC and CD analyses, using (*S*)-TBMB carboxylic acid [(*S*)-2-*tert*-butyl-2-methyl-1,3-benzodioxole-4-carboxylic acid] as the chiral conversion reagent. The results of the CD analysis proved *N*,*O*-bis-(*S*)-TBMB carboxylated *cis*-2-aminocycloalkanols to adopt a predominantly *N*-equatorial conformation.

The partially resolved *trans*- and *cis*-2-aminocycloalkanols, except for *trans*-2-aminocyclopentanol, were recrystallized from ethyl acetate to give enantiomerically pure forms.

Key words: lipase-catalyzed kinetic resolution; 2-azidocycloalkanols; 2-aminocycloalkanols; CD detection; (*S*)-TBMB carboxylic acid

Chiral 2-amino alkanols have received wide attention in recent years for their diverse applications as versatile starting materials for constructing bioactive compounds such antibiotics,[1] alkaloids,[2] and enzyme inhibitors,[3] as chiral resolving reagents,[4] and as chiral auxiliaries for asymmetric syntheses.[5]

Despite the many synthetic methods for optically pure *trans*- and *cis*-2-aminocycloalkanols that have been reported,[6] it is still challenging to develop a new practical preparative method for these compounds. The most sophisticated chemical method for preparating *trans*-2-aminocycloalkanol so far would be the one reported by Overman and Sugai in 1985,[7] although, their method is not suited for practical preparation in respect of convenience and mass production. Moreover, an efficient chiral synthesis of *cis*-2-aminocycloalkanols has not been reported.

Since 2-aminocycloalkanols could be easily prepared from 2-azidocycloalkanols, it was considered that the lipase-catalyzed resolution[8] of racemic *trans*- and *cis*-2-azidocycloalkanols would be a practical method for mass preparation of enantiomerically pure *trans*- and *cis*-2-aminocycloalkanols.

We report here the enzymatic optical resolution of *trans*- and *cis*-2-azidocycloalkanols [(±)-*trans*-**1a**~**c** and (±)-*cis*-**1a**, **b**] and the preparation of optically pure *trans*- and *cis*-2-aminocycloalkanols from the resolved 2-azidocycloalkanols.

Results and Discussion

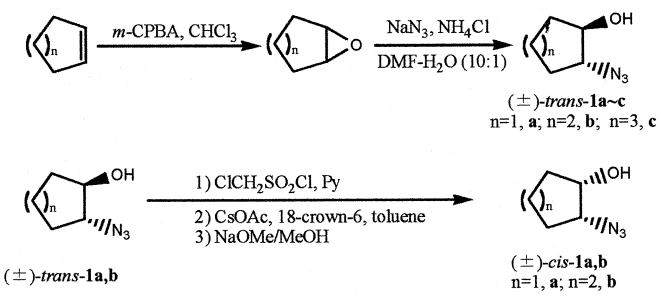
The *trans*-substrates [(±)-*trans*-**1a**~**c**] were prepared from the corresponding cycloalkenes by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA), and then by opening the epoxide with sodium azide to give *trans*-2-azidocycloalkanols. The *cis*-substrates [(±)-*cis*-**1a**, **b**] were prepared from the corresponding (±)-*trans*-**1a** and **1b** by using Nakata's inversion method for secondary alcohols.[9] (Scheme 1)

The lipase-catalyzed acetylation of (±)-*trans*-**1a**~**c** and (±)-*cis*-**1a**, **b** was carried out in vinyl acetate, which was also used as the acetylating reagent, for 20 hours [(±)-*trans*-**1a**~**c**], and for 4–10 hours [(±)-*cis*-**1a**, **b**] at 40°C with four kinds of lipases (Lipase PS and Lipase AK each derived from *Pseudomonas* sp, Lipase AY30 derived from *Candida rugosa*, and Lipase AP12 derived from *Aspergillus niger*). (Scheme 2)

The results are summarized in Tables 1 and 2.

The absolute configurations of the predominant isomers of all the *trans*-acetates (**2a**~**c**) and of the unreacted *trans*-2-azidocycloalkanols (**1a**~**c**) were determined by a CD analysis of the corresponding 2-aminocycloalkanols after *N*,*O*-bis-(*S*)-TBMB carboxylation. The *ee* values for the products were determined by HPLC of the *N*,*O*-bis-(*S*)-TBMB derivatives.

trans-Acetates **2a**~**c** were isolated by column chromatography and were deacetylated. The resulting *trans*-2-azidocycloalkanols and the remaining substrates were



Scheme 1. Preparation of 2-Azidocycloalkanols (±)-*trans*-**1a**~**c** and (±)-*cis*-**1a**, **b**.

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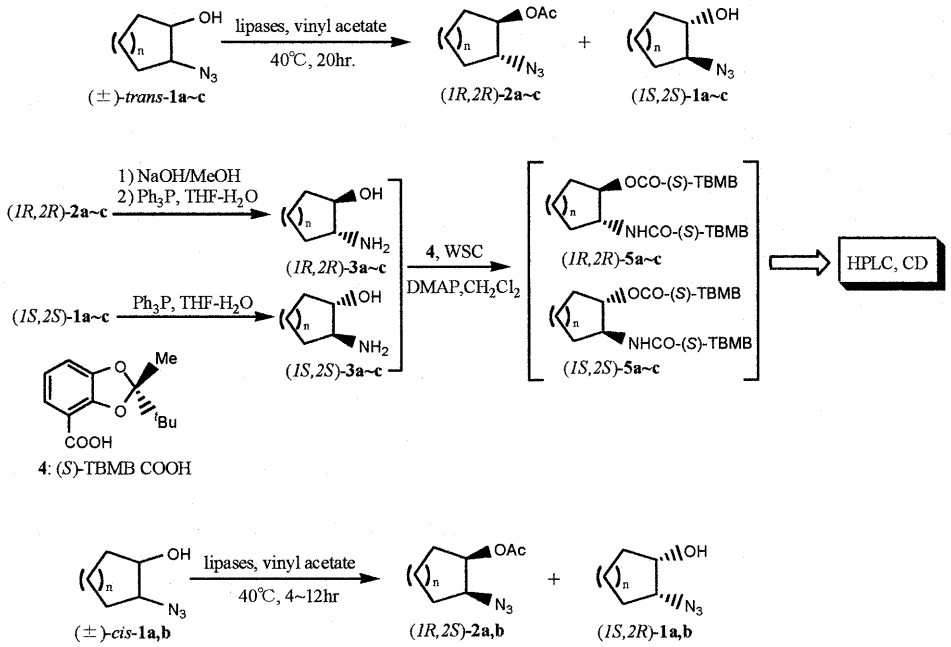


Scheme 2. Kinetic Resolution of (±)-*trans*-**1a**~**c** and (±)-*cis*-**1a**, **b**, Structure of (*S*)-TBMB Carboxylic Acid (**4**), and Chiral Conversion of *trans*-**3a**~**c** for the HPLC and CD Analyses.

Table 1. Kinetic Resolution of the (±)-*trans*-2-Azidocycloalkanols [(±)-*trans*-**1a**~**c**]

Entry	Substrate	Lipase	Time (hr)	(1*R*, 2*R*)-**2**		(1*S*, 2*S*)-**1**		E
				Yield (%)	%ee	Yield (%)	%ee	
1	*trans*-**1a**	Lipase PS	20	57	75.8	35	>99.9	
2	*trans*-**1a**	Lipase AK	20	46	90.0	43	97.9	87
3	*trans*-**1a**	Lipase AY30	20	68	0.54	30	39.4	1
4	*trans*-**1a**	Lipase AP12	20	32	77.6	62	48.4	13
5	*trans*-**1b**	Lipase PS	20	45	98.1	42	98.7	522
6	*trans*-**1b**	Lipase AK	20	44	96.0	40	98.9	253
7	*trans*-**1b**	Lipase AY30	20	24	92.3	65	50.3	41
8	*trans*-**1b**	Lipase AP12	20	7	95.7	78	24.5	58
9	*trans*-**1c**	Lipase PS	20	41	98.5	46	72.7	288
10	*trans*-**1c**	Lipase AK	20	45	98.6	41	99.4	815
11	*trans*-**1c**	Lipase AY30	20	32	86.0	51	54.2	23
12	*trans*-**1c**	Lipase AP12	20	5	87.4	79	12.6	17

Table 2. Kinetic Resolution of the (±)-*cis*-2-Azidocycloalkanols [(±)-*cis*-**1a**, **b**]

Entry	Substrate	Lipase	Time (hr)	(1*R*, 2*S*)-**2**		(1*S*, 2*R*)-**1**		E
				Yield (%)	%ee	Yield (%)	%ee	
1	*cis*-**1a**	Lipase PS	4	42	92.2	47	79.4	60
2	*cis*-**1a**	Lipase PS	12	49	87.2	36	88	42
3	*cis*-**1a**	Lipase AK	6	48	95.1	48	99	209
4	*cis*-**1a**	Lipase AK	12	48	87.3	43	99.3	82
5	*cis*-**1b**	Lipase PS	10	47	79.6	47	76.8	20
6	*cis*-**1b**	Lipase AK	10	47	98.8	48	95.2	622

submitted to a Staudinger azide reduction[10] to give the corresponding *trans*-2-aminocycloalkanols (**3a**~**c**), which were then labelled with (*S*)-TBMB carboxylic acid[11] (**4**) in the presence of water-soluble carbodiimide (WSC) to give the *N*,*O*-bis-(*S*)-TBMB carboxylated derivatives (**5a**~**c**), respectively, for submission to the HPLC and CD analyses.

The fluorescence-detected HPLC chromatograms of the *N*,*O*-bis-(*S*)-TBMB-carboxylated *trans*-2-aminocycloalkanols (**5a**~**c**) derived from racemic *trans*-2-aminocycloalcohols are shown in Fig. 1. As can be seen, all the chromatograms show 1:1 peaks of *trans*-**5a**~**c** to

indicate that no chiral discrimination during conversion had taken place. Thus, the optical purity of the 2-azidocycloalkanols could be determined by the HPLC method.

All the *N*,*O*-bis-(*S*)-TBMB-carboxyl derivatives of enantiomers of the *trans*-2-aminocycloalcohols gave symmetrical exciton CD spectra to indicate their absolute configurations. The CD spectra of (1*R*, 2*R*)- and (1*S*, 2*S*)-**5a**~**c** are shown in Fig. 2.

These results enabled the absolute configuration eluates of the first eluates from HPLC to be determined as 1*S*, 2*S*. The second eluates were determined to be of 1*R*, 2*R* configuration.

The absolute configurations of the main components of the *cis*-acetates (**2a, b**) and of the unreacted *cis*-2-azidocycloalkanols (**1a, b**) were determined to be 1*R*, 2*S* and 1*S*, 2*R*, respectively, by comparing with the HPLC chromatograms of *trans*-**5a** and **5b** after Walden-inversion of the secondary alcohol, reduction of the azido group, and conversion with **4**. (Scheme 3)

The CD spectra of the *N*,*O*-bis-(*S*)-TBMB-carboxylated *cis*-2-aminocycloalkanols (**5a, b**) were of the exciton type to show that *N*,*O*-bis-(*S*)-TBMB-carboxylated (1*R*, 2*S*)-**5a, b** exist mainly in a clockwise conformation, and the (1*S*, 2*R*)-isomers in an *anti*-clockwise one. (Fig. 3)

These results indicate that the equatorial preference of the TBMB-carboxylated amino group was stronger than that of the TBMB-carboxylated hydroxy group.

In general, the hydroxy group in an (*R*) configuration was preferentially acetylated by the lipases, except for the acetylation of *trans*-**1a** with Lipase AY30. Compared with *trans*-**1b** and *trans*-**1c**, *trans*-**1a** was more easily acetylated with any of the lipases. Fortunately, Lipase PS gave enantiomerically pure (1*S*, 2*S*)-2-azidocyclopentanol **3a**. Although Lipase AY30 and AP12 were not suitable for the kinetic resolution, the *Pseudomonas* sp. lipases showed sufficient reactivity and enantioselectivity.

The 2-aminocycloalkanols, except for *trans*-2-aminocyclopentanol **3a**, could be crystallized. These chiral 2-aminocycloalkanols were recrystallized from ethyl acetate to give enantiomerically pure compounds. The total yield of each enantiomerically pure 2-aminocycloalkanol starting from the corresponding 2-azidocycloalkanol was 22–29%.

In conclusion, we have demonstrated lipase-catalyzed

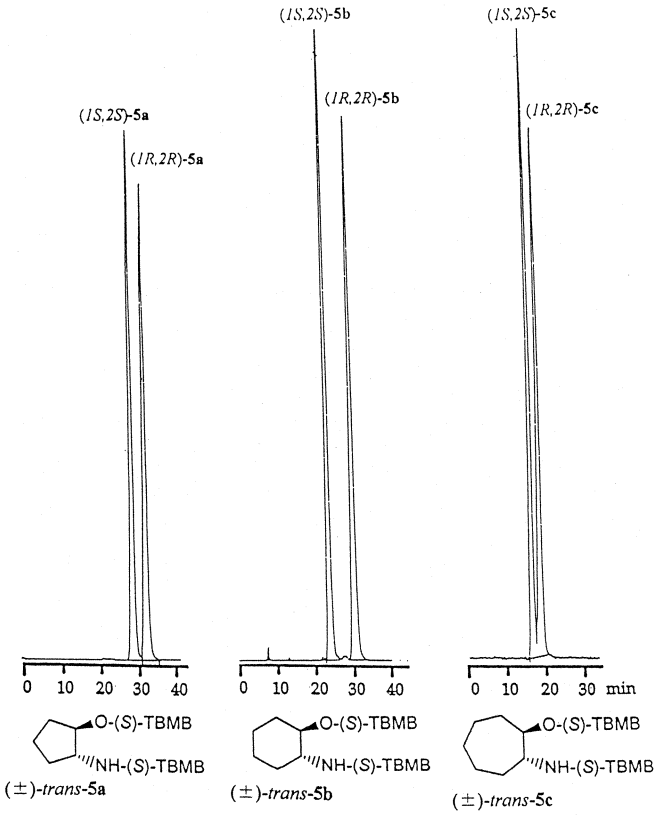
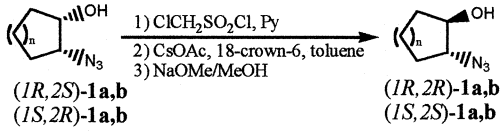


Fig. 1. HPLC Chromatograms of (±)-2-Aminocycloalkanol Derivatives *trans*-**5a**~**c**.

Conditions: mobile phase, *n*-hexane:THF=20:1; flow rate, 1 ml/min; column, TSK-GEL (TOSOH).



Scheme 3. Conversion of *cis*-**1a, b** to *trans*-**1a, b**.

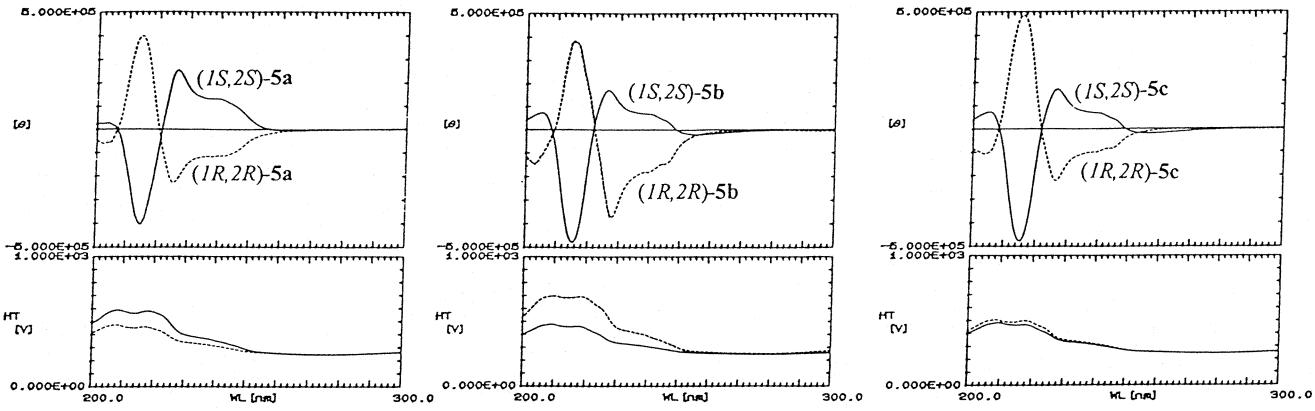


Fig. 2. CD Spectra for *trans*-**5a**~**c**.

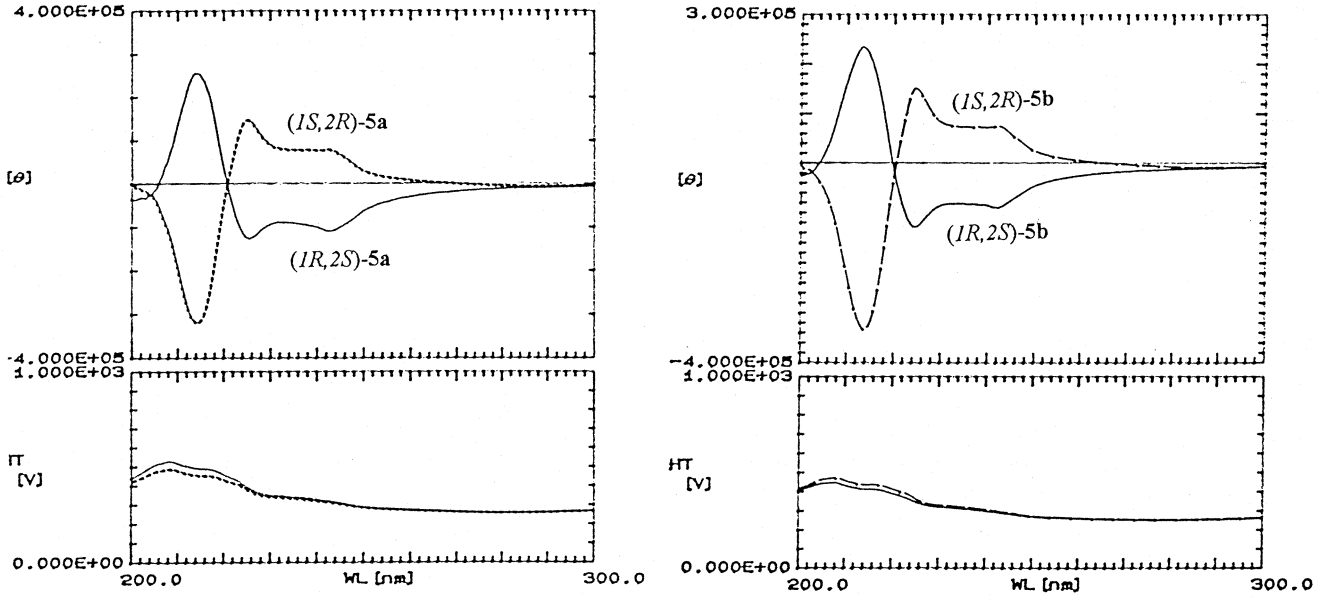


Fig. 3. CD Spectra for *cis*-**5a, b**.

kinetic resolution to be a powerful tool for obtaining optically pure *trans*- and *cis*-2-aminocycloalkanols. We also found *N,O*-bis-(*S*)-TBMB carboxylated *cis*-2-aminocycloalkanols [(1*R*, 2*S*)- and (1*S*, 2*R*)-**5a, b**] gave exciton-coupled CD spectra.

The prepared 2-aminocycloalcohols could be used as the backbone for fluorescent chiral conversion reagents to discriminate remote chirality.[12] Syntheses of the chiral conversion reagents from these 2-aminocycloalcohols are underway.

Experimental

Melting point (mp) data were recorded with Yanaco melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Varian Gemini 2000/300 instrument at 21–23°C in $CDCl_3$ with Me_4Si as an internal standard. MS spectra were obtained with a JEOL JMS-DX 303HF instrument, and IR spectra were measured with Nicolet Impact 410 apparatus. $[\alpha]_D$ values were measured with a JASCO DIP-4 spectrometer at 20°C. The HPLC system for measuring the fluorescence intensity consisted of a JASCO PU-980 liquid chromatographic pump, a 77251 injector with a 20-μl sample loop (Rheodyne), a TSK-GEL (TOSOH) separation column, a Toyo Soda FS-8000 fluorescence detector and Jasco-807IT recorder. CD spectra were obtained with a JASCO J-720 spectrometer, and silica gel column chromatography was conducted on Merck silica gel (Art. 7734).

(±)-trans-2-azidocyclopentanol [(±)-*trans*-**1a**]. To a solution of *m*-CPBA (14.00 g, 81.13 mmol) in $CHCl_3$ (300 ml) was added cyclopentene (5.00 g, 73.46 mmol). The reaction mixture was stirred for 12 hours at between 0°C and room temperature, quenched by adding sat. aq. NH_4Cl and then extracted with ether (300 ml). The combined extracts were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue (cyclohexene oxide) was submitted to the next process. To a solution of NaN_3 (10.00 g, 153.82 mmol) and NH_4Cl (5.00 g, 93.48 mmol) in DMF-H_2O (100 ml, 10:1, v/v) was added this residue. The mixture was stirred and refluxed for 3 hours, then extracted with ether (300 ml), dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane-ethyl acetate=10:1) to provide (±)-*trans*-**1a** (8.21 g, 64.64 mmol, 88% yield in two steps) as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 4.07 (m, 1H), 3.70 (m, 1H), 2.52 (s, 1H, -OH), 2.14–1.94 (m, 2H), 1.87–1.53 (m, 4H). HRMS *m/z*: calcd. for $C_5H_9ON_3$, 127.0745 (M^+); found, 127.0748 (M^+) (EI$^+$). IR (KBr disk) ν_{max} cm^{-1}: 3356 (-OH), 2100 (azide). *Anal.* Calcd. for $C_5H_9ON_3$: C, 47.22; H, 7.14; N, 33.06%. Found: C, 47.30; H, 7.15; N, 33.10%.

(±)-trans-2-azidocyclohexanol [(±)-*trans*-**1b**]. To a solution of NaN_3 (7.36 g, 113.18 mmol) and NH_4Cl (4.04 g, 75.45 mmol) in DMF-H_2O (100 ml, 10:1, v/v) was added commercially available cyclohexene oxide (7.40 g, 75.45 mmol). The mixture was stirred and refluxed for 3 hours, then extracted with ether (300 ml), dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane-ethyl acetate=5:1) to provide (±)-*trans*-**1b** (10.20 g, 72.29 mmol, 96% yield) as an oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.39 (m, 1H), 3.19(m, 1H), 2.44 (dd, 1H, -OH, J=3.2 Hz), 2.04 (m, 2H), 1.75 (m, 2H), 1.31 (m, 4H). HRMS *m/z*: calcd. for $C_6H_{11}ON_3$, 142.1019 (M^++H); found, 142.0990 (M^++H) (FAB$^+$). IR (KBr disk) ν_{max} cm^{-1}: 3370 (-OH), 2100 (azide). *Anal.* Calcd. for $C_6H_{11}ON_3$: C, 51.03; H, 7.86; N, 29.77%. Found: C, 51.06; H, 7.92; N, 29.66%.

(±)-trans-2-azidocycloheptanol [(±)-*trans*-**1c**]. (±)-*trans*-**1c** was prepared from cycloheptene with a 90%

yield in two steps according to the procedure described for (±)-*trans*-**1a** and obtained as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 3.52 (m, 1H), 3.70 (m, 1H), 2.31 (s, 1H, -OH), 1.98-1.84 (m, 2H), 1.79-1.40 (m, 8H). HRMS *m/z*: calcd. for $C_7H_{13}ON_3$, 155.1058 (M^+); found 155.1062 (M^+) (EI^+). IR (KBr disk) ν_{max} cm^{-1}: 3384 (-OH), 2100 (azide). *Anal.* Calcd. for $C_7H_{13}ON_3$: C, 54.16; H, 8.45; N, 27.08%. Found: C, 54.10; H, 8.42; N, 27.10%.

(±)-cis-2-azidocyclopentanol [(±)-*cis*-**1a**]. To a solution of (±)-*trans*-**1a** (3.15 g, 24.79 mmol) in pyridine (100 ml) was added chloromethanesulfonyl chloride (6.00 g, 40.27 mmol). The reaction mixture was stirred for 1 hour at 0°C and then extracted with ether. The combined extracts were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane-ethyl acetate=10:1) to provide chloromethanesulfonate (5.10 g, 21.29 mmol, 86% yield). To a solution of cesium acetate (1.20 g, 6.25 mmol) and 18-crown-6 (1.20 g, 4.54 mmol) in toluene (100 ml) was added this chloromethanesulfonate (1.00 g, 4.18 mmol). The mixture was stirred and refluxed for 2 hours, then extracted with ether (100 ml), dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane-ethyl acetate=10:1) to provide (±)-*trans*-2-azidocyclopentyl acetate. To a solution of NaOMe (50 mg) and MeOH (100 ml) was added this product. The reaction mixture was stirred for 2 hours at room temperature, then extracted with ether (100 ml), dried with $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane-ethyl acetate=10:1) to provide (±)-*cis*-**1a** (0.38 g, 3.01 mmol, 72% yield in two steps) as an oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 4.15 (m, 1H), 3.79 (m, 1H), 2.11 (s, 1H, -OH), 1.93 (m, 4H), 1.67 (m, 2H). HRMS *m/z*: calcd. for $C_5H_9ON_3$, 127.0745 (M^+); found, 127.0746 (M^+) (EI^+). IR (KBr disk) ν_{max} cm^{-1}: 3344 (-OH), 2100 (azide). *Anal.* Calcd. for $C_5H_9ON_3$: C, 47.22; H, 7.14; N, 33.06%. Found: C, 47.28; H, 7.16; N, 33.10%.

(±)-cis-2-azidocyclohexanol [(±)-*cis*-**1b**]. (±)-*cis*-**1b** was prepared from (±)-*trans*-**1b** in a 76% yield in three steps according to the procedure described for (±)-*cis*-**1a** and obtained as an oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.81 (ddd, 1H, J=3.0 Hz), 3.67 (ddd, 1H, J=3.0 Hz), 2.18 (s, 1H, -OH), 1.90 (m, 2H), 1.67 (m, 4H), 1.37 (m, 2H). HRMS *m/z*: calcd. for $C_6H_{11}ON_3$, 141.0901 (M^+); found, 141.0903 (M^+) (EI^+). IR (KBr disk) ν_{max} cm^{-1}: 3375 (-OH), 2100 (azide). *Anal.* Calcd. for $C_6H_{11}ON_3$: C, 51.03; H, 7.86; N, 29.77%. Found: C, 51.07; H, 7.82; N, 29.71%.

*Enantioselective acetylation of (±)-trans-***1a**~**c** *and (±)-cis-***1a, b** *with lipases. General method*: To a solution of (±)-*trans*-**1a** (1.50 g, 11.80 mmol) and vinyl acetate (30 ml) was added Lipase PS (1.00 g), and the reaction mixture was stirred for 20 hours at 40°C. The mixture was then filtered through Celite, and the filtrate was concentrated *in vacuo*. The crude product obtained was chromatographed on silica gel. Elution with hexane-ethyl acetate (10:1) gave acetate (1*R*, 2*R*)-**2a** (1.13 g, 6.68 mmol, 57% yield) and remaining substrate (1*S*, 2*S*)-**1a** (0.53 g, 4.17 mmol, 35% yield). (±)-*trans*-**1a** (10.80 g, 84.99 mmol) with Lipase AK gave (1*R*, 2*R*)-**2a** (6.68 g, 39.51 mmol, 46% yield) and (1*S*, 2*S*)-**1a** (4.64 g, 36.51 mmol, 43% yield). (±)-*trans*-**1a** (1.15 g, 9.05 mmol) with Lipase AY30 gave (1*R*, 2*R*)-**2a** (1.04 g, 6.15 mmol, 68% yield) and (1*S*, 2*S*)-**1a** (0.35 g, 2.75 mmol, 30% yield). (±)-*trans*-**1a** (1.32 g, 10.39 mmol) with Lipase AP12 gave (1*R*, 2*R*)-**2a** (0.57 g, 3.37 mmol, 32% yield) and (1*S*, 2*S*)-**1a** (0.82 g, 6.45 mmol, 62% yield). (±)-*trans*-**1b** (5.30 g, 37.56 mmol) with Lipase PS gave (1*R*, 2*R*)-**2b** (3.12 g, 17.04 mmol, 45% yield) and (1*S*, 2*S*)-**1b** (2.25 g, 15.95 mmol, 42% yield). (±)-*trans*-**1b** (4.00 g, 28.35 mmol) with Lipase AK gave (1*R*, 2*R*)-**2b** (2.30 g, 12.56 mmol, 44% yield) and (1*S*, 2*S*)-**1b** (1.60 g, 11.34 mmol, 40% yield). (±)-*trans*-**1b** (2.50 g, 17.72 mmol) with Lipase AY30 gave (1*R*, 2*R*)-**2b** (0.77 g, 4.21 mmol, 24% yield) and (1*S*, 2*S*)-**1b** (1.62 g, 11.48 mmol, 65% yield). (±)-*trans*-**1b** (2.50 g, 17.72 mmol) with Lipase AP12 gave (1*R*, 2*R*)-**2b** (0.24 g, 1.31 mmol, 7% yield) and (1*S*, 2*S*)-**1b** (1.94 g, 13.75 mmol, 78% yield). (±)-*trans*-**1c** (1.20 g, 7.74 mmol) with Lipase PS gave (1*R*, 2*R*)-**2c** (0.62 g, 3.15 mmol, 41% yield) and (1*S*, 2*S*)-**1c** (0.55 g, 3.55 mmol, 41% yield). (±)-*trans*-**1c** (14.00 g, 90.26 mmol) with Lipase AK gave (1*R*, 2*R*)-**2c** (7.94 g, 40.28 mmol, 45% yield) and (1*S*, 2*S*)-**1c** (5.78 g, 37.26 mmol, 41% yield). (±)-*trans*-**1c** (1.18 g, 7.61 mmol) with Lipase AY30 gave (1*R*, 2*R*)-**2c** (0.48 g, 2.44 mmol, 32% yield) and (1*S*, 2*S*)-**1c** (0.60 g, 3.87 mmol, 51% yield). (±)-*trans*-**1c** (1.30 g, 8.38 mmol) with Lipase AP12 gave (1*R*, 2*R*)-**2c** (0.08 g, 0.41 mmol, 5% yield) and (1*S*, 2*S*)-**1c** (1.03 g, 6.64 mmol, 79% yield). (±)-*cis*-**1a** (3.00 g, 23.61 mmol) with Lipase PS (4 hr reaction time) gave (1*R*, 2*S*)-**2a** (1.68 g, 9.94 mmol, 42% yield) and (1*S*, 2*R*)-**1a** (1.41 g, 11.10 mmol, 47% yield). (±)-*cis*-**1a** (0.70 g, 5.51 mmol) with Lipase PS (12 hr reaction time) gave (1*R*, 2*S*)-**2a** (0.46 g, 2.72 mmol, 49% yield) and (1*S*, 2*R*)-**1a** (0.25 g, 1.97 mmol, 36% yield). (±)-*cis*-**1a** (26.00 g, 204.60 mmol) with Lipase AK (6 hr reaction time) gave (1*R*, 2*S*)-**2a** (16.47 g, 97.42 mmol, 48% yield) and (1*S*, 2*R*)-**1a** (12.52 g, 98.53 mmol, 48% yield). (±)-*cis*-**1a** (0.67 g, 5.27 mmol) with Lipase AK (12 hr reaction time) gave (1*R*, 2*S*)-**2a** (0.43 g, 2.54 mmol, 48% yield) and (1*S*, 2*R*)-**1a** (0.29 g, 2.28 mmol, 43% yield). (±)-*cis*-**1b** (1.20 g, 8.51 mmol) with Lipase PS (10 hr reaction time) gave (1*R*, 2*S*)-**2b** (0.74 g, 4.04 mmol, 47% yield) and (1*S*, 2*R*)-**1b** (0.57 g, 4.04 mmol, 47% yield). (±)-*cis*-**1b** (1.70 g, 12.05 mmol) with Lipase AK (10 hr reaction time) gave (1*R*, 2*S*)-**2b** (1.04 g, 5.68 mmol, 47% yield) and (1*S*, 2*R*)-**1b** (0.82 g, 5.81 mmol, 48% yield).

Determination of the enantiomeric excess (ee) and the absolute configuration of acetylated **2a**~**c** *and remaining substrates* **1a**~**c**. *General method*: To a solution of NaOMe (20 mg) in MeOH (5 ml) was added (1*R*, 2*R*)-**2a** (0.82 g, 4.85 mmol), and the mixture was stirred for 1 hour at room temperature. The reaction mixture was washed with water to neutrality, extracted with $CHCl_3$, dried with $MgSO_4$, filtered, and concentrated *in vacuo*.

The residue was submitted to the next process. To a solution of Ph_3P (1.27 g, 4.84 mmol) in THF-H_2O (20 ml, 10:1, v/v) was added this residue. The reaction mixture was stirred for 12 hours at room temperature and then concentrated *in vacuo*. The residue obtained was chromatographed on silica gel. Elution with $CHCl_3$–MeOH–Et_3N (10:1:0.5) gave *trans*-2-amino cyclopentanol (1*R*, 2*R*)-**3a** (0.36 g, 3.56 mmol, 73% yield in two steps). (1*S*, 2*S*)-**3a** was prepared from (1*S*, 2*S*)-**1a** according to the procedures described for (1*R*, 2*R*)-**2a**, except for the deacetylation process. To a solution of WSC (20 mg, 0.10 mmol), DMAP (5 mg, 0.04 mmol), and (*S*)-TBMB carboxylic acid (50 mg, 0.21 mmol) in CH_2Cl_2 (5 ml) was added (1*R*, 2*R*)-**3a** (10 mg, 0.10 mmol). The mixture was stirred for 14 hours at room temperature, and then concentrated *in vacuo*. After being purified by preparative TLC, the sample of (1*R*, 2*R*)-**5a** was submitted to the HPLC and CD analyses.

(1R, 2R)-trans-2-aminocyclopentanol [(*1R, 2R*)-**3a**]. (1*R*, 2*R*)-**3a** was purified by preparative TLC to give the enantiomerically pure form as an oil. Which solidified with time, mp 82–83°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 3.75 (m, 1H), 3.03 (m, 1H), 2.34 (s, 3H, -OH, $-NH_2$), 2.00 (m, 2H), 1.70 (m, 2H), 1.54 (m, 1H), 1.19 (m, 1H). HRMS *m/z*: calcd. for $C_5H_{11}ON$, 101.0840 (M^+); found, 102.0922 ($M^+ + H$) (FAB^+). $[\alpha]_D^{20} = -30.59$ (*c*=0.78 in MeOH). *Anal.* Calcd. for $C_5H_{11}ON$: C, 59.36; H, 10.97; N, 13.85%. Found: C, 59.39; H, 10.92; N, 13.79%.

(1S, 2S)-trans-2-aminocyclopentanol [(*1S, 2S*)-**3a**]. (1*S*, 2*S*)-**3a** was purified by preparative TLC to give the enantiomerically pure form as an oil which solidified with time, mp 82–83°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 3.75 (m, 1H), 3.02 (m, 1H), 2.60 (s, 3H, -OH, $-NH_2$), 2.00 (m, 2H), 1.70 (m, 2H), 1.55 (m, 1H), 1.30 (m, 1H). HRMS *m/z*: calcd. for $C_5H_{11}ON$, 101.0840 (M^+); found, 102.0923 ($M^+ + H$) (FAB^+). $[\alpha]_D^{20} = +30.65$ (*c*=0.71 in MeOH). *Anal.* Calcd. for $C_5H_{11}ON$: C, 59.36; H, 10.97; N, 13.85%. Found: C, 59.35; H, 10.94; N, 13.82%.

(1R, 2R)-trans-2-aminocyclohexanol [(*1R, 2R*)-**3b**]. (1*R*, 2*R*)-**3b** was recrystallized from ethyl acetate in a 76% yield. The enantiomeric excess was determined as 100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 87°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 3.10 (m, 1H), 2.40 (m, 1H), 2.17 (s, 3H, -OH, $-NH_2$), 2.12–1.65 (m, 6H), 1.46–1.22 (m, 2H). HRMS *m/z*: calcd. for $C_6H_{13}ON$, 115.0996 (M^+); found, 115.0997 (M^+) (EI^+). $[\alpha]_D^{20} = -40.1$ (*c*=0.41 in MeOH). *Anal.* Calcd. for $C_6H_{13}ON$: C, 62.55; H, 11.38; N, 12.17%. Found: C, 62.60; H, 11.31; N, 12.08%.

(1S, 2S)-trans-2-aminocyclohexanol [(*1S, 2S*)-**3b**]. (1*S*, 2*S*)-**3b** was recrystallized from ethyl acetate in a 72% yield. The enantiomeric excess was determined as 100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 87°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 3.12 (m, 1H), 2.40 (m, 1H), 2.17 (s, 3H, -OH, $-NH_2$), 2.12–1.65 (m, 6H), 1.46–1.23 (m, 2H). HRMS *m/z*: calcd. for $C_6H_{13}ON$, 115.0996 (M^+); found, 115.0997 (M^+) (EI^+). $[\alpha]_D^{20} = +40.4$ (*c*=0.41 in MeOH). *Anal.* Calcd. for $C_6H_{13}ON$: C, 62.55; H, 11.38; N, 12.17%. Found: C, 62.32; H, 11.33; N, 12.12%.

(1R, 2R)-trans-2-aminocycloheptanol [(*1R, 2R*)-**3c**]. (1*R*, 2*R*)-**3c** was recrystallized from ethyl acetate in a 78% yield. The enantiomeric excess was determined as 100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 93°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 3.18 (m, 1H), 2.49 (m, 1H), 2.11 (s, 3H, -OH, $-NH_2$),1.92 (m, 1H), 1.74 (m, 1H), 1.64 (m, 2H), 1.56–1.36 (m, 6H). HRMS *m/z*: calcd. for $C_7H_{15}ON$, 129.1153 (M^+); found, 129.1156 (M^+) (EI^+). $[\alpha]_D^{20} = -17.20$ (*c*=0.77 in MeOH). *Anal.* Calcd. for $C_7H_{15}ON$: C, 65.06; H, 12.39; N, 10.85%. Found: C, 64.81; H, 12.26; N, 10.82%.

(1S, 2S)-trans-2-aminocycloheptanol [(*1S, 2S*)-**3c**]. (1*S*, 2*S*)-**3c** was recrystallized from ethyl acetate in a 76% yield. The enantiomeric excess was determined as 100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 93°C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 3.18 (m, 1H), 2.49 (m, 1H), 2.11 (s, 3H, -OH, $-NH_2$),1.92 (m, 1H), 1.77 (m, 1H), 1.65 (m, 2H), 1.58–1.36 (m, 6H). HRMS *m/z*: calcd. for $C_7H_{15}ON$, 129.1153 (M^+); found, 129.1155 (M^+) (EI^+). $[\alpha]_D^{20} = +17.19$ (*c*=0.63 in MeOH). *Anal.* Calcd. for $C_7H_{15}ON$: C, 65.06; H, 12.39; N, 10.85%. Found: C, 65.01; H, 12.36; N, 10.84%.

(1R, 2S)-cis-2-aminocyclopentanol [(*1R, 2S*)-**3a**]. (1*R*, 2*S*)-**3a** was recrystallized from ethyl acetate in a 78% yield. The enantiomeric excess was determined as 100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 74–76°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.90 (m, 1H), 3.23 (m, 1H), 2.34 (s, 3H, -OH, $-NH_2$), 1.84 (m, 3H), 1.71 (m, 1H), 1.53 (m, 1H), 1.43 (m, 1H). HRMS *m/z*: calcd. for $C_5H_{11}ON$, 101.0840 (M^+); found, 101.0841 (M^+) (EI^+). $[\alpha]_D^{20} = -15.56$ (*c*=0.36 in MeOH). *Anal.* Calcd. for $C_5H_{11}ON$: C, 59.36; H, 10.97; N, 13.85%. Found: C, 59.29; H, 10.92; N, 13.81%.

(1S, 2R)-cis-2-aminocyclopentanol [(*1S, 2R*)-**3a**]. (1*S*, 2*R*)-**3a** was recrystallized from ethyl acetate in a 82% yield. The enantiomeric excess was determined as 100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 74–76°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.90 (m, 1H), 3.23 (m, 1H), 2.34 (s, 3H, -OH, $-NH_2$), 1.84 (m, 3H), 1.71 (m, 1H), 1.53 (m, 1H), 1.43 (m, 1H). HRMS *m/z*: calcd. for $C_5H_{11}ON$, 101.0840 (M^+); found, 101.0839 (M^+) (EI^+). $[\alpha]_D^{20} = +15.48$ (*c*=0.40 in MeOH). *Anal.* Calcd. for $C_5H_{11}ON$: C, 59.36; H, 10.97; N, 13.85%. Found: C, 59.41; H, 10.91; N, 13.84%.

(1R, 2S)-cis-2-aminocyclohexanol [(*1R, 2S*)-**3b**]. (1*R*, 2*S*)-**3b** was recrystallized from ethyl acetate in a 79% yield. The enantiomeric excess was determined as

100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 73°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.69 (m, 1H), 2.90 (m, 1H), 1.84 (s, 3H, -OH, $-NH_2$), 1.79 (m, 1H), 1.54 (m, 5H), 1.34 (m, 2H). HRMS *m/z*: calcd. for $C_6H_{13}ON$, 115.0996 (M^+); found, 115.0997 (M^+) (EI^+). $[\alpha]_D^{20} = -26.23$ (*c*=0.41 in MeOH). *Anal.* Calcd. for $C_6H_{13}ON$: C, 62.55; H, 11.38; N, 12.17%. Found: C, 62.61; H, 11.42; N, 12.09%.

(1S, 2R)-cis-2-aminocyclohexanol [*(1S, 2R)*-**3b**]. (1*S*, 2*R*)-**3b** was recrystallized from ethyl acetate in a 74% yield. The enantiomeric excess was determined as 100% by an HPLC analysis, using (*S*)-TBMB carboxylic acid. mp 73°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 3.69 (m, 1H), 2.90 (m, 1H), 1.84 (s, 3H, -OH, $-NH_2$), 1.79 (m, 1H), 1.54 (m, 5H), 1.34 (m, 2H). HRMS *m/z*: calcd. for $C_6H_{13}ON$, 115.0996 (M^+); found, 115.0999 (M^+) (EI^+). $[\alpha]_D^{20} = +26.30$ (*c*=0.38 in MeOH). *Anal.* Calcd. for $C_6H_{13}ON$: C, 62.55; H, 11.38; N, 12.17%. Found: C, 62.51; H, 11.42; N, 12.16%.

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