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Cyclic *trans*-β-amino alcohols: preparation and enzymatic kinetic resolution

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ABSTRACT

Enantioenriched cyclic β-amino alcohols, *trans*-2-aminocyclohexanols (ee, >99%), *trans*-2-aminocyclopentanols (ee, >99%), *trans*-1-amino-2-indanols (ee, >99%) and *trans*-2-amino-1-indanols (ee, ~98%) were prepared in high yields via an *Arthrobacter* sp. Lipase/PLAP catalyzed kinetic resolution of racemic phthalimido acetates. The addition of toluene as a co-solvent dramatically improved the hydrolysis and enantioselectivity, whereas for indanols, substrate immobilization on Celite improved the efficacy of the kinetic resolution.

1. Introduction

The recurrent vicinal amino alcohol moiety is an important component of a large variety of natural products and biologically active molecules.[1] In particular, chiral cyclic 1,2-amino alcohols are the vital structural components of a large number of pharmaceuticals,[2] peptide nucleic acids (PNA),[3] as a part of key enzymes in the human immunodeficiency virus (HIV) protease inhibitors,[4] and as metabolites of aminoindane in the urine of rabbits and rats[5] (Fig. 1). They have also been used as potent chiral ligands[6] and chiral auxiliaries in asymmetric transformations[7] including carbonyl reductions,[8] aldol reactions,[9] diethylzinc addition to aldehydes[7e,6a], and Diels–Alder reactions.[10]

Due to their vast chemical, biological, and economical importance, numerous efforts have been directed toward the development of efficient methods for their synthesis in enantiomerically pure form. Optically active cyclic β-amino alcohols are generally obtained via the resolution of racemic compounds such as salts of chiral acids.[11] Reactions such as Friedel–Crafts cyclization of (−)- and (+)-phenylalanine,[12] ring opening of *meso*-epoxides by TMS-azide in the presence of chiral metal catalysts followed by reduction,[13] asymmetric epoxidation and dihydroxylation of prochiral olefins,[14] and kinetic resolution[15] are frequently used for their synthesis. The literature review contains a number of attempts to prepare both the enantiomers of 2-aminocycloalkanols, however the high enantiopurity (>99%) of products and ease of handling still remain a major challenge.

The biocatalytic resolution methods mostly employ stereoselective transesterifications. Pioneering work by Gotor et al. over the last two decades has contributed significantly in the area of enzyme catalyzed kinetic resolution of cycloalkanols and indanols.

Thus, Maestro et al.[16] reported the transesterfication of *N*-protected *trans*-2-aminocyclohexanol (ee 87%, yield 48%, 14 h) and *trans*-2-aminocyclopentanol (ee 99%, yield 49%, 5 days) respectively using *Candida antarctica* lipase (CAL). Gonzalez-Sabin et al.[7f] have used the transesterfication of *trans*-2-(*N*,*N*-dialkylamino)cyclohexanols with the lipase PS-C for the preparation of enantioriched *trans*-2-(*N*,*N*-dialkylamino)cyclohexanols (ee 95%, yield 45%, 29 h). The synthesis of optically active *trans*-2-azidocyclohexenol (ee 98.7%, yield 42%, 20 h) and *trans*-2-azidocyclopentanol (ee 97.9%, yield 43%, 20 h) was reported by Ami et al.[15k] via the transesterfication of racemic *trans*-azidocycloalkanols with various lipases (Fig. 2). Honig et al.[15q] have reported the hydrolysis of *N*-protected cyclohexanol acetates by different lipases with a maximum enantioselectivity of 90%. Takada et al.[15r] also employed enzymatic hydrolyis for (±)-*trans*-2-aminocyclohexanol and obtained the product in 97–99% enantiomeric purity after 48% conversion.

Thus, lipase catalyzed transacylation has been the preferred method for the preparation of optically active amino alcohols for obvious reasons.[17] The enzymatic hydrolysis methodology has scarcely been reported for the preparation of optically active 2-amino cycloalkanols and 1/2-aminoindanols. The low reactivity and selectivity of the substrates, difficulties in processing of the hydrolyzed products and the increased inhibition of hydrolases during the product formation are some of the possible explanations.[18]

In the past we have been working on the kinetic resolution of several bioactive molecules, including drug intermediates, through enzymatic hydrolysis using whole cells, and successfully generated the products with high enantiopurity. In this respect one of the indigenous microbial strains bearing *Arthrobacter* sp. lipase (ABL) (MTCC No. 5125)[19] has proven to be highly enantioselective on a broad range of substrates, in particular secondary alcohols.[20] We therefore envisaged using an enzymatic hydrolysis methodology

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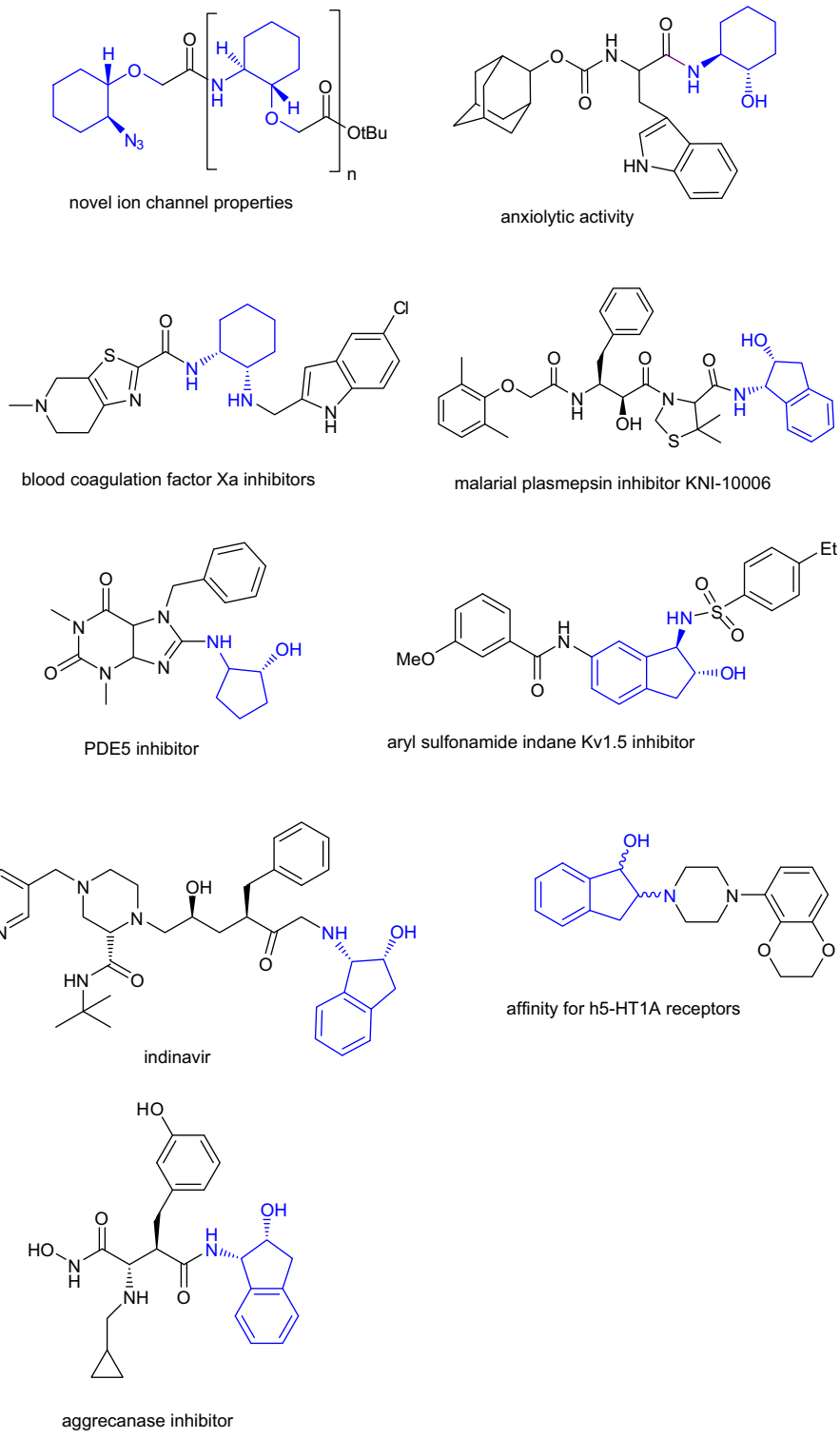


Figure 1. Bioactive molecules containing vicinal aminocycloalkanols.

with *Arthrobacter* sp. lipase in the kinetic resolution of racemic 2-amino cycloalkanols and 1/2-aminoindanols. In these experiments we also successfully employed PLAP (pig liver acetone powder)[21] in the kinetic resolution of one of the amino indanol derivatives, where all other biocatalysts failed.

Herein we have used phthalimide protected amino alcohols which proved to be very effective during the enantioselective hydrolysis of racemic acetates. In addition to providing easy manoeuvrability and recovery of the substrate/product, tagging with a phthalimide moiety also facilitated the separation and detection of the racemates during liquid chromatography; improved miscibility with organic solvents, and also minimized enzyme inhibition by the product.

Herein we report the synthesis of both enantiomers of cyclic *trans*-aminoalcohols, that is, *trans*-2-aminocyclopentanols/hexanols and *trans*-1/2-aminoindanols in high enantiomeric purities and yields using the whole cells of *Arthrobacter* sp. Lipase and PLAP.

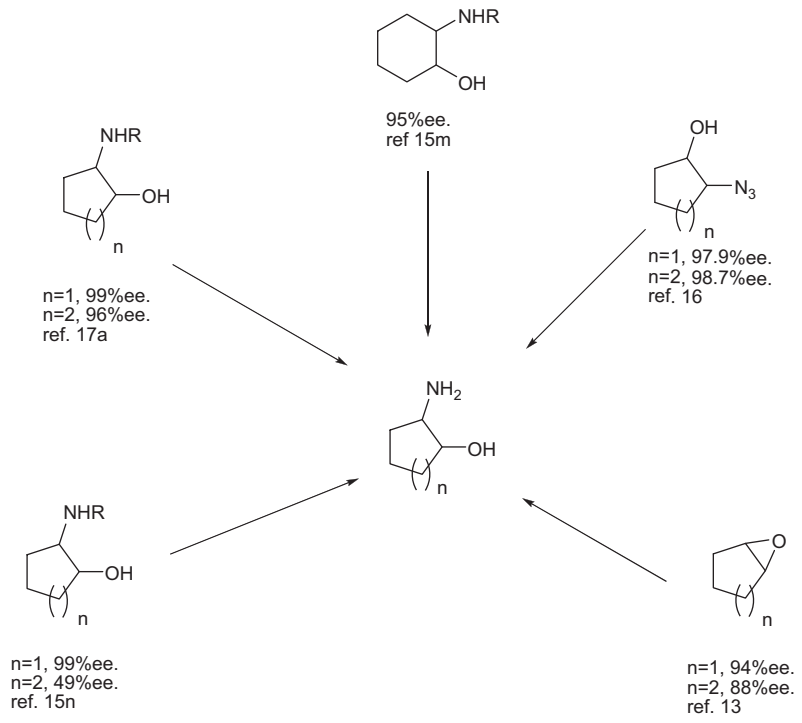
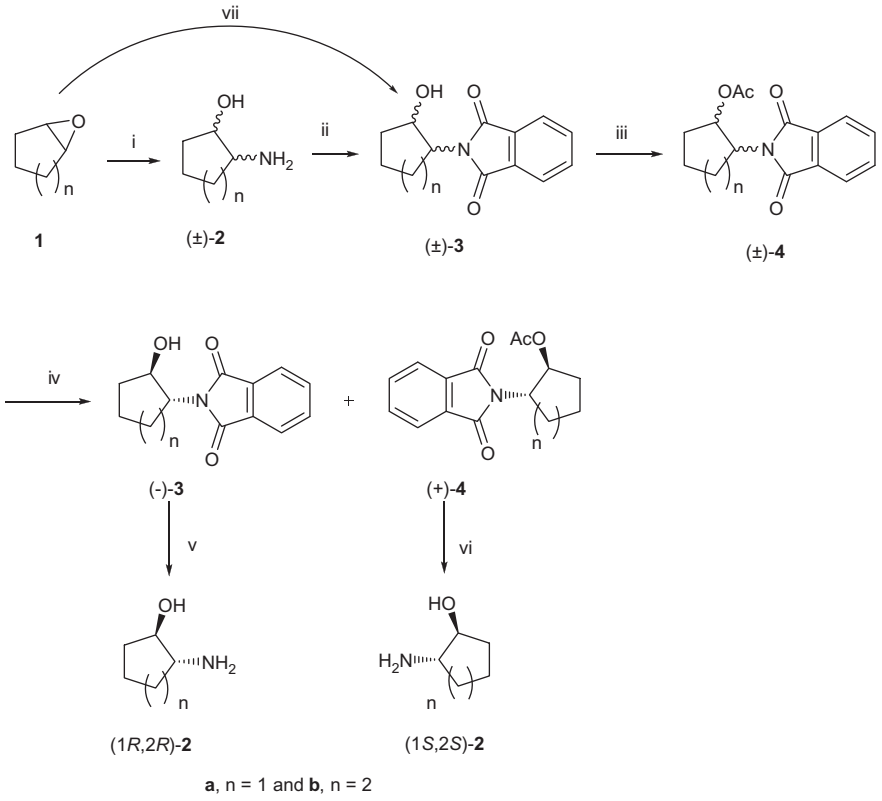


Figure 2. Literature routes for the preparation of enantiomerically enriched cycloalkanols.

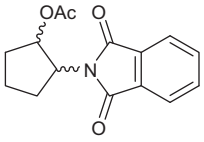
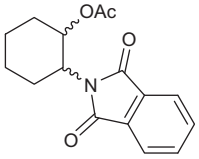
2. Results and discussion

Our initial attempts to synthesize racemic *trans*-2-phthalimidocyclopentanol **3a** and *trans*-2-phthalimidocyclohexanol **3b** via epoxide ring opening directly in the presence of phthalimide were only partially successful as the reaction required 5–6 days. Alternatively, both substrates were synthesised in two steps in 12 h and a 90% yield via epoxide ring opening with ammonia, followed by



Scheme 1. Reagents and conditions: (i) 10% NH_3 in MeOH, 60 °C; (ii) phthalic anhydride, Et_3N, toluene, reflux; (iii) Ac_2O, DMAP, CH_2Cl_2; (iv) *Arthrobacter* sp. lipase, 10% toluene in phosphate buffer, pH 7.0; (v,vi) Hydrazine hydrate, H_2O, 60 °C, 3 h; (vii) Phthalimide, pyridine, DMF or 2-propanol, reflux, 5–6 days.

Table 1
Effect of co-solvents on *Arthrobacter* sp. lipase catalyzed hydrolysis of **4a** and **4b** at 20 g/L concn

Entry	Substrate	Co-solvent[a]	Concn[b] (%)	Time (h)	ee_p[b] (%)	ee_s (%)	E[c]
1		Nil	25.4	17	41	15.6	2.6
2		DMSO	35.3	17	83	45	17
3		DMF	38	17	99	61	375
4		THF	NR	17	—	—	—
5		Dioxane	15	17	>99	17.6	355
6		CH_3CN	NR	17	—	—	—
7		*n*-Butanol	42	17	>99	72.4	1826
8	(±)-**4a**	**Toluene**	**50**	**20**	**>99**	**>99**	**>2000**
9		Nil	NR	24	—	—	—
10		DMSO	15.6	60	99	18.5	185
11		DMF	NR	60	—	—	—
12		THF	NR	60	—	—	—
13		Dioxane	7.5	60	>99	8.0	162
14		CH_3CN	NR	60	—	—	—
15		*n*-Butanol	NR	60	—	—	—
17	(±)-**4b**	**Toluene**	**50**	**66**	**>99**	**>99**	**>2000**

All reactions were carried out on a shaker at 250 rpm. Substrate/Enzyme 1:2 ratio (w/w).
[a] 10% (v/v) Co-solvent used with respect to buffer.
[b] Conversion and ee were calculated from chiral HPLC.
[c] E was determined by using $E = [\ln(1-\text{convn}(1+\text{eep})]/[\ln(1-\text{convn}(1-\text{eep})]$,[22] NR = No reaction.

refluxing with phthalic anhydride in toluene using triethylamine as a catalyst**.** After converting the racemic *trans*-2-phthalimidocycloalkanol into the corresponding acetate, the enantioselective hydrolysis was performed using *Arthrobacter* sp. lipase (Scheme 1).

Initially, the kinetic hydrolysis of phthalimido acetates **4a** and **4b** was carried out in an aqueous phosphate buffer (0.1 M, pH 7.0); however, the rate of hydrolysis was found to be quite slow with low enantioselectivity (ee ~41% and 0% respectively). The addition of an organic solvent in the aqueous phase dramatically improved the hydrolysis as well as enantioselectivity. Both nonpolar as well as polar solvents in a ratio ranging from 5% to 30% (v/v) in the buffer were used; toluene (10% v/v) was found to be the optimal co-solvent of choice (Table 1).

The efficacy of the *Arthrobacter* sp. lipase for the hydrolysis of (±)-**4a** was compared with other commercially available lipases. From the results (Table 2) it is apparent that ABL was better than most of the commercial lipases.

Table 2
Screening of different lipases for the hydrolysis of (±)-**4a** in toluene as a co-solvent

S. No.	Lipase	Concn (%)	Time (h)	ee_p (%)	ee_s (%)
1	ABL	41	15	>99	69.5
2	PSL	3	15	>99	3
3	AA	NR	15	—	—
4	CAL-B	9	15	>99	9.8
5	MM	NR	15	—	—
6	CRL	NR	15	—	—

All reactions were carried out on a shaker at 250 rpm. Substrate/Enzyme 1:2 ratio (w/w). 10% (v/v) co-solvent used with respect to buffer, Conversion and ee were calculated from chiral HPLC, E was determined by using $E = [\ln(1-\text{convn}(1+\text{eep})]/[\ln(1-\text{convn}(1-\text{eep})]$, NR = No reaction, ABL = *Arthrobacter* sp. lipase, PSL = *Pseudomonas* sp. lipase, AA = *Amono acylase*, CAL-B = *Candida antarctica* lipase-B, MM = *Mucor miehei*, CRL = *Candida rugosa* lipase.

In order to optimize the yields, the kinetic resolution studies were carried out at various concentrations ranging from 20 to 80 g/L. It was found that *Arthrobacter* sp. lipase was quite effective up to 80 g/L. The enantioselectivity remained unchanged (>99%) in concentrations up to 80 g/L, however, as expected, the rate of hydrolysis decreased with higher concentrations (Fig. 3). From the time-space yield calculations, it was established that 80 g/L for **4a** and 40 g/L for **4b** were the optimum concentrations for the kinetic resolution. At optimum concentrations, the average rate of the product formation was calculated as 1.48 g/L/h for **4a** and 0.29 g/L/h for **4b**.

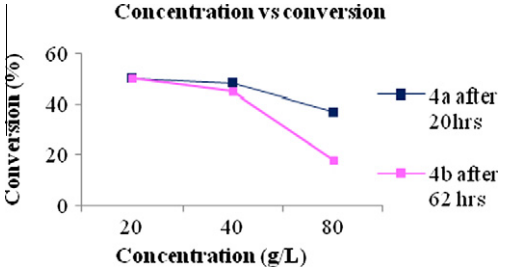


Figure 3. Concentration v/s conversion of **4a** and **4b** in toluene/buffer using *Arthrobacter* sp. lipase.

Encouraged by the efficacy of *Arthrobacter* sp. lipase for the kinetic resolution of 2-phthalimidocycloalkanols, we next examined its versatility in the kinetic resolution of racemic *trans*-1-phthalimido-2-indanol **8** and *trans*-2-phthalimido-1-indanol **13**. Similar to amino alkanols, amino indanols are also essential components of many bioactive compounds and organo-catalysts.[7a] Although several publications and reviews[7a] have appeared reporting the synthesis of enantiomerically pure *cis*-1-amino-2-indanol and *cis*-2-amino-1-indanol, there are only a few successful attempts toward the synthesis of optically active *trans*-1-amino-2-indanol and *trans*-2-amino-1-indanol including chemo-enzymatic methods. A chemo-enzymatic methodology by Luna et al.[17c] reported on the transesterfication of *N*-benzyloxycarbonyl derivatives using *Pseudomonas cepacia* lipase to produce optically active *trans*-1-amino-2-indanol (ee 99%, yield 50%, 3 days) and *trans*-2-amino-1-indanol (ee 20%, yield 17%, 10 days) respectively. Mitrohikine et al.[15d] reported the enantioselective lipase catalyzed transesterfication of 2-azido-1-indanols with CAL-A (ee 99%, yield 34%, 10 days) (Fig. 4).

The *trans*-amino indanol derivatives are known to be slow to react and most of the biotransformation reactions require several days to complete with unsatisfactory yields. Therefore, enzymatic hydolysis has not been attempted for their kinetic resolution.

Herein we report the synthesis of enantioenriched *trans*-aminoindanols in high yields using the phthalimide protection strategy and enzymatic deacylation of *trans*-indanacetates. In both examples, the use of co-solvents and immobilization of the substrate on a Celite surface, led to a significantly improved enantioselectivity and a reduction of the reaction time.

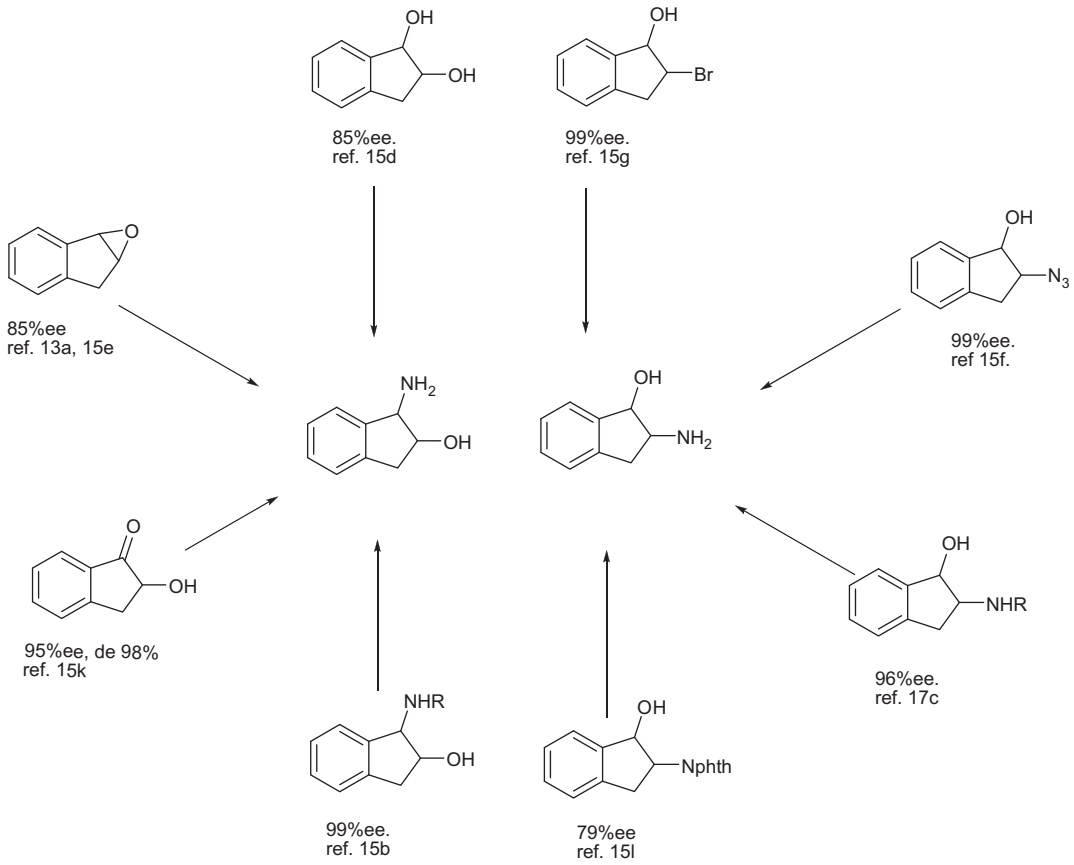
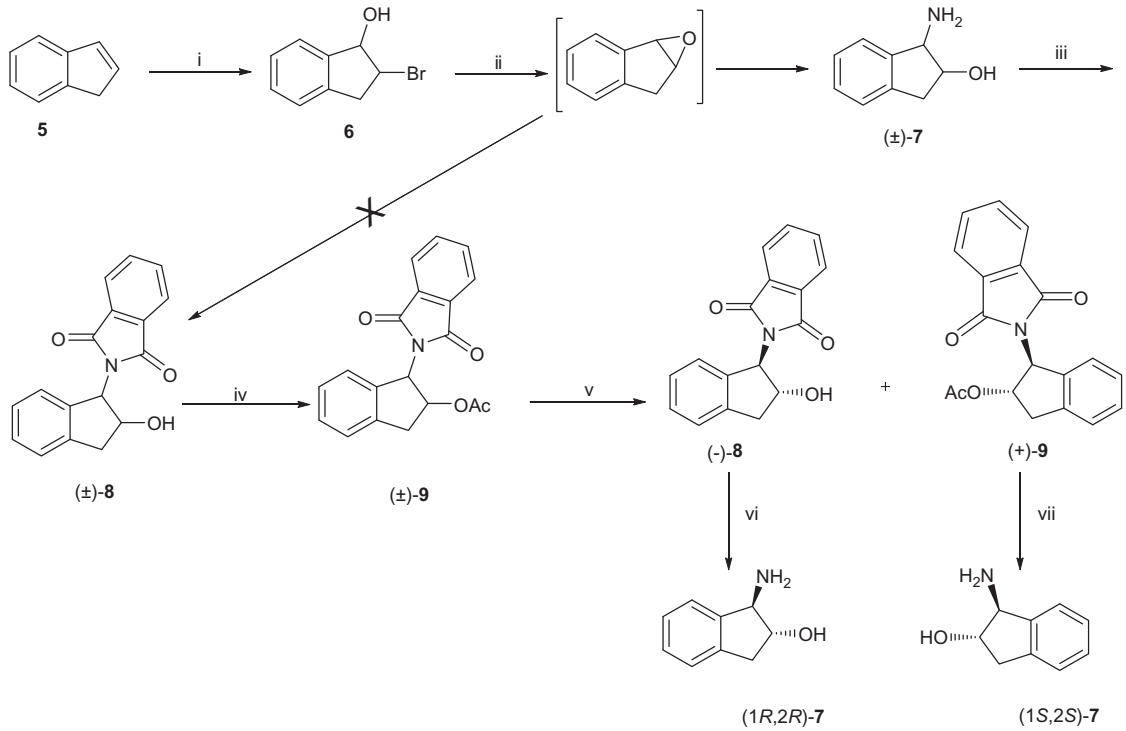
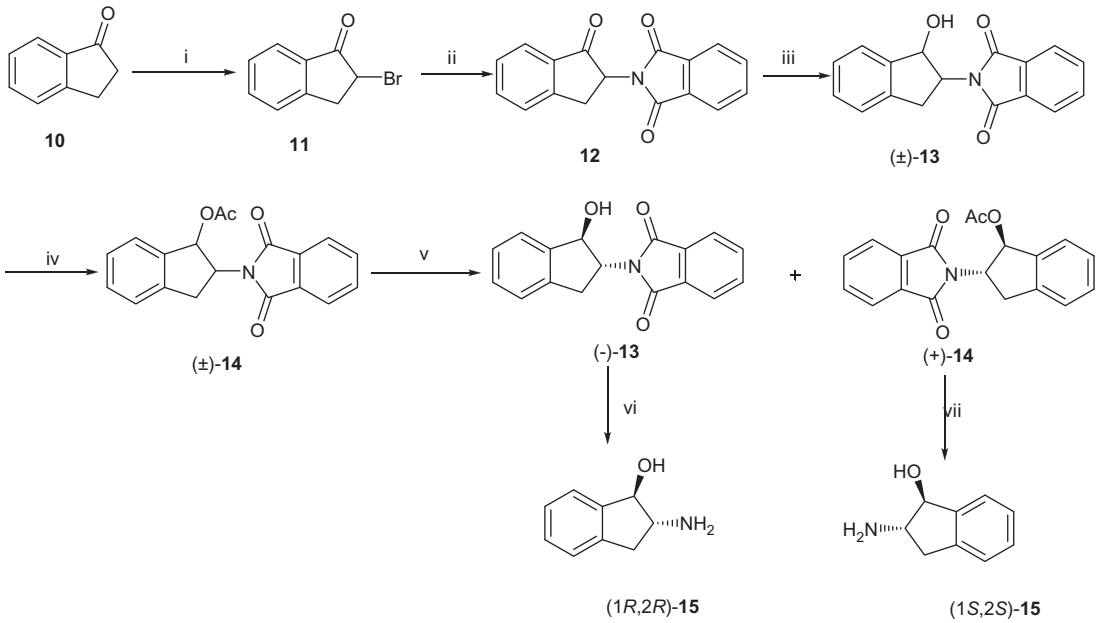


Figure 4. Literature routes for the preparation of enantiomerically enriched amino-indanols.



Scheme 2. Reagents and conditions: (i) NBS, THF/H_2O (4:1); (ii) concentrated NH_4OH; (iii) phthalic anhydride, Et_3N, toluene, reflux; (iv) Ac_2O, DMAP, CH_2Cl_2; (v) *Arthrobacter* sp. lipase, 10% toluene in phosphate buffer, pH 7.0; (vi, vii) hydrazine hydrate, H_2O, 60 °C, 3 h.

For the kinetic resolution studies, racemic *trans*-1-phthalimido-2-indanol **8** could not be synthesized via ring opening of the corresponding epoxide. However, it was prepared from bromohydrin derivative **6** in two steps (Scheme 2). On the other hand, the



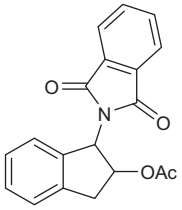
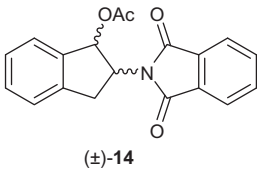
Scheme 3. Reagents and conditions: (i) Br_2, dioxane; (ii) potassium phthalimide, [bmim]BF_4, rt, 10–15 min, >95%; ionic liquid; (iii) $NaCNBH_3$ in acetic acid; (iv) Ac_2O, DMAP, CH_2Cl_2; (v) PLAP, 10% toluene in phosphate buffer, pH 7.0; (vi, vii) hydrazine hydrate, H_2O, 60 °C.

trans-2-phthalimido-1-indanol **13** was synthesized from bromo indanone **11**[23] (Scheme 3).

Commercially available as well as indigenous lipases were screened for the enantioselective hydrolysis of racemic substrates **9** and **14**, and it was observed that *Arthrobacter* sp. lipase could enantioselectively hydrolyze **9**, while PLAP was the only esterase which successfully hydrolyzed **14** (Table 3). In an aqueous phosphate buffer (0.1 M, pH 7.0) in the absence of a co-solvent, no hydrolysis was observed.

Therefore, nonpolar as well as polar solvents in ratios ranging from 5% to 30% (v/v) in a buffer were screened. Again toluene (10% v/v) was found to be the preferred co-solvent (Table 3). In

Table 3
Screening of different enzymes for the hydrolysis of phthalimido-indan-acetates **9** and **14** in toluene co-solvent at 20 g/L

Entry	Substrate	Enzyme	Concn (%)	Time (h)	ee_p (%)	ee_s (%)	*E*
1	 (±)-**9**	PSL	15	168	99	18	71
2		ABL	39	168	99	60	384
3	**9**[a]	**ABL**	**50**	**92**	**>99**	**>99**	**>1000**
4	**14**	ABL	ND	168	—	—	—
5	**14**	PSL	ND	168	—	—	—
6	**9**,**14**	PLF	ND	168	—	—	—
7	**9**,**14**	CALB	ND	168	—	—	—
8	**9**,**14**	NOVAZYME	ND	168	—	—	—
9	**9**,**14**	AA	ND	168	—	—	—
10	**9**,**14**	MM	ND	168	—	—	—
11	**9**,**14**	CRL	ND	168	—	—	—
12	**9**,**14**	CCL	ND	168	—	—	—
13	**9**	PLAP	ND	168	—	—	—
14	 (±)-**14**	PLAP	38	168	98	60	183
15	**14**[a]	**PLAP**	**48**	**120**	**98**	**90**	**311**

[a] Substrate immobilized on Celite. All reactions were carried out in a shaker at 250 rpm. Substrate/Enzyme 1:2 ratio (w/w), 10% (v/v) co-solvent used with respect to buffer, conversion and ee were calculated from chiral HPLC, *E* was determined by using $E = [\ln(1-\text{convn}(1+\text{eep})]/[\ln(1-\text{convn}(1-\text{eep})]$, NR = No reaction, ABL = *Arthrobacter* sp. lipase, PSL = *Pseudomonas* sp. lipase, AA = *Amono acylase*, CAL-B = *Candida antarctica* lipase-B, MM = *Mucor miehei*, CRL = *Candida rugosa* lipase.

both resolution reactions, due to the slow reaction rates the hydrolysis took longer time (6–7 days). Therefore, we envisaged immobilizing the substrate on an inert support to improve the rate of reaction, a methodology highly useful in the kinetic resolution of spiro-β-lactams as reported in our recent work.[24] The immobilization of the substrate on Celite support (5% w/w) reduced the reaction time from 168 to 92 h for **9** and 120 h for **14** at the same substrate concentrations (20 g/L). The immobilization also resulted in a substantial improvement in the enantioselectivity factor *E* from 384 to >1000 and 183 to 311 respectively (Table 3, entries 3 and 15).

The enantiomerically pure masked 1,2-amino alcohols thus obtained were quantitatively converted into 1,2-amino alcohols by an improved Ing–Manske reaction.[25] The improved methodology[23] involved stirring phthalimide protected amines in water at 60 °C in the presence of 2 equiv of hydrazine hydrate. The amino alcohol products were isolated in high purity simply by ethyl acetate extraction without any chromatographic purification. The absolute configurations of all of the optically active compounds were determined by comparing the sign of specific rotations with those reported in the literature.[15k,26]

3. Conclusions

In conclusion an efficient and facile method for the preparation of enantiomerically pure *trans*-2-aminocycloalkanols (ee, >99%) and *trans*-1/2-amino-indanols (ee, 98–99%) by the whole cells of *Arthrobacter* sp. lipase and the PLAP catalyzed kinetic resolution of their phthalimido analogues has been demonstrated. In the case of indanols, immobilization of the substrates on a celite support improved the hydrolysis rates and significantly reduced the reaction time.

4. Experimental

4.1. General

^{1}H NMR spectra in $CDCl_3$ were recorded on Bruker 200, 400 and 500 MHz spectrometers with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ ppm). Reagents and solvents used were mostly of LR grade. Silica gel coated aluminum plates coated on alumina from M/s Merck were used for TLC. MS were recorded on Jeol MSD-300 and Bruker Esquire 3000 LC-Mass spectrometer. Optical rotations were measured on Perkin-Elmer 241 polarimeter at 25 °C using sodium D light. Melting points were determined on Buchi B-542 apparatus by an open capillary method and are uncorrected. Enantiomeric excess (ee%) was determined by chiral HPLC on OJH and ADH chiral columns. Chemicals were purchased from M/s Aldrich Chemicals, Mumbai.

4.2. Synthesis of (±)-*trans*-2-phthalimidocyclopentanol 3a

A catalytic amount of triethylamine was added to a solution of phthalic anhydride (1 mmol) and (±)-2-aminocyclopentanol **2** (1 mmol) in toluene (30 mL), and the solution was refluxed for 3 h. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with water and ethyl acetate. The organic layer was concentrated under reduced pressure to obtain crude 2-phthalimidocyclopentanol **3a**, which was purified by column chromatography (yield 95%); ($C_{13}H_{13}NO_3$); mp 106–108 °C; ^{1}H NMR: δ 1.56–1.98 (m, 4H), 2.04–2.13 (m, 2H), 4.31 (dt, *J* = 7.1 Hz, 9.2 Hz, 1H), 4.60–4.66 (m, 1H), 7.59–7.65 (m, 2H), 7.71–7.76 (m, 2H). ^{13}C NMR: δ 21.1, 27.2, 33.3, 59.3, 75.1, 123.2, 132.0, 134.0, 168.7. ESI-MS (*m*/*z*): 231. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found C, 67.59; H, 5.65; N, 6.03.

4.3. Synthesis of (±)-*trans*-2-phthalimidocyclohexanol 3b

Compound **3b** was prepared from 2-aminocyclohexanol (1 mmol) following the procedure described for **3a** (yield 95%); ($C_{14}H_{15}NO_3$); mp 90–92 °C; ^{1}H NMR: δ 1.21–1.42 (m, 4H), 1.68–1.83 (m, 2H), 2.13–2.24 (m, 2H), 3.97 (ddd, *J* = 3.7, 10.1 and 12.4 Hz), 4.26–4.37 (m, 1H), 7.67–7.74 (m, 2H), 7.78–7.85 (m, 2H). ^{13}C NMR: δ 24.2, 25.1, 28.6, 34.6, 57.1, 68.6, 122.7, 131.7, 133.8, 169.5. ESI-MS (*m*/*z*): 245. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found C, 68.59; H, 6.15; N, 5.73.

4.4. Synthesis of (±)-*trans*-1-phthalimidoindan-2-ol 8

Compound **8** was prepared from 1-amino indan-2-ol (1 mmol) following the procedure described for **3a** (yield 95%); ($C_{17}H_{13}NO_3$); mp 124.2 °C. ^{1}H NMR, δ 1.51 (s, OH), 2.94–2.99 (dd, *J* = 6.7 Hz,15.8 Hz, 1H), 3.56–3.61 (dd, *J* = 7.5 Hz, 15.8 Hz, 1H), 5.11–5.15 (q, *J* = 6.1 Hz, 12.88 Hz, 1H), 5.67 (d, *J* = 6.3 Hz, 1H), 7.02 (d, *J* = 7.1 Hz, 2H), 7.2 (d, *J* = 4.3 Hz, 2H), 7.26 (m, 2H), 7.74 (q, 3.1 Hz, 5.3 Hz, 2H), 7.85 (q, 3.0 Hz, 5.4 Hz, 2H). ^{13}C NMR: δ 31.59, 62.81, 123.11, 123.43, 125.13, 127.08, 128.42, 131.90, 134.17, 137.78, 139.91, 168.16. ESI-MS (*m*/*z*): 279. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found C, 73.54; H, 4.15; N, 6.45.

4.5. Synthesis of (±)-2-phthalimidoindan-1-one 12

A mixture of potassium phthalimide (1.1 mmol) and bromo ketone **11** (1 mmol) in a 10 mL conical flask was added to 1 mL of ionic liquid [1-butyl-3-methylimidazolium tetrafluoroborate] and the resulting reaction mixture was stirred at room temperature for 10–15 min. The reaction mixture was extracted from the ionic liquid phase with diethylether (2 × 5 mL). The organic layer was concentrated and evaporated under reduced pressure. The residue was purified by column chromatography to obtain product **12** in a 96% yield. The ionic liquid left in the flask was further washed with diethylether, dried under vacuum and reused in four to five subsequent reactions without loss in activity. Mp 191 °C; ^{1}H NMR, δ 3.41 (dd, *J* = 5.9 Hz and 16.5 Hz, 1H), 3.61 (dd, *J* = 8.4 Hz, 16.6 Hz, 1H), 5.09 (dd, *J* = 6.0 Hz, 8.4 Hz, 1H), 7.41–7.52 (m, 2H), 7.64–788 (m, 6H). ^{13}C NMR, δ 32.0, 53.8, 123.7, 124.7, 126.8, 128.2, 132.3, 134.4, 135.8. 151.1, 167.7, 200.2. ESI-MS (*m*/*z*): 277. Anal. Calcd for $C_{11}H_9NO_3$: C, 73.64; H, 4.00; N, 5.05. Found C, 73.63; H, 4.03; N, 5.02.

4.6. Synthesis of (±)-*trans*-2-phthalimidoindan-1-ol 13

$NaCNBH_3$ (2 mmol) was added at room temperature to a solution of α-phthalimido ketone **12** in acetic acid (1 mmol in 15 mL). After completion of the reaction (48 h) as indicated by thin layer chromatography, the reaction was quenched by a saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain product **13** in an 85% yield. The product was purified on a silica gel column (yield 85%); mp 217–219 °C; ^{1}H NMR, δ 1.56 (s, OH), 3.15–3.21 (dd, *J* = 8.4 Hz, 16.0, 1H), 3.98–4.04 (dd, *J* = 8.4 Hz and 16.0 Hz, 1H), 5.11–5.18 (m, 2H), 7.29–7.37 (m, 3H), 7.50–7.52 (m, 1H), 7.73–7.76 (m, 2H), 7.84–7.87 (m, 2H). ^{13}C NMR, δ 32.7, 52.9, 76.2, 123.4, 124.9, 125.6, 127.5, 129.4, 131.9, 134.2, 140.2, 142.5, 169.6. ESI-MS (*m*/*z*): 279. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found C, 73.13; H, 4.65; N, 5.03.

4.7. General method for the acylation of phthalimido amino alcohols

Acetic anhydride (1.2 mmol) and a catalytic amount of DMAP were added to a solution of racemic protected amino alcohols

(1 mmol) in dry dichloromethane and the reaction mixture kept overnight at room temperature. The contents of the reaction mixture were poured into ice-cold water and extracted with dichloromethane. The organic layer was washed, dried, and evaporated to provide protected amino acetoxy derivatives in a quantitative yield.

4.8. (±)-*trans*-1-Acetoxy-2-phthalimidocyclopentane 4a

($C_{15}H_{15}NO_4$); mp 94–96 °C; ^{1}H NMR: δ 1.74–1.78 (m, 2H), 1.99 (s, 3H), 1.95–2.13 (m, 3H), 2.26–2.38 (m, 1H), 4.49–4.61 (m, 1H), 5.49–5.58 (m, 1H), 7.67–7.72 (m, 2H), 7.78–7.85 (m, 2H). ^{13}C NMR: δ 21.1, 22.7, 28.7, 31.5, 56.7, 77.8, 123.3, 132.1, 133.9, 168.2, 170.9. ESI-MS (*m*/*z*): 273. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found C, 65.99; H, 5.55; N, 5.13.

4.9. (±)-*trans*-1-Acetoxy-2-phthalimidocyclohexane 4b

($C_{16}H_{17}NO_4$); mp 90–92 °C; ^{1}H NMR: δ 1.30–1.47 (m, 4H), 1.78–1.85 (m, 2H), 1.84 (s, 3H), 2.16–2.22 (m, 1H), 2.27–2.40 (m, 1H), 4.11–4.25 (m, 1H), 5.46 (dt, *J* = 4.7 Hz, 10.5 Hz, 1H), 7.68–7.74 (m, 2H), 7.79–785 (m, 2H). ^{13}C NMR: δ 19.9, 22.8, 24.0, 27.6, 30.6, 52.7, 70.8, 122.2, 130.8, 132.9, 169.3, 171.2. ESI-MS (*m*/*z*): 287. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 66.89; H, 5.96; N, 5.96. Found C, 66.88; H, 5.95; N, 5.93.

4.10. (±)-*trans*-1-Phthalimido-2-acetoxyoindane 9

($C_{19}H_{15}NO_4$); mp134.9 °C; ^{1}H NMR: δ 2.06 (s, 3H) 3.01–3.12 (dd, *J* = 5.2 Hz, 16.6 Hz, 1H), 3.72–3.84 (dd, *J* = 7.9 Hz, 16.6 Hz, 1H), 5.80 (d, *J* = 4.8 Hz, 1H), 5.90 (m, 1H), 7.12- 7.29 (m, 4H), 7.70–7.74 (q, *J* = 3.1 Hz, 5.6 Hz, 2H), 7.82–7.87 (q, *J* = 2.9 Hz, 5.5 Hz, 2H). ^{13}C NMR: δ 20.90, 37.49, 60.44, 77.86, 123.28, 123.36, 124.87, 127.26, 128.66, 131.88, 134.07, 137.61, 140.09, 167.62, 173.73. ESI-MS (*m*/*z*): 321. Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found C, 71.32; H, 4.99; N, 5.23.

4.11. (±)-*trans*-2-Phthalimido-1-acetoxyoindan 14

($C_{19}H_{15}NO_4$); mp 117–119 °C; ^{1}H NMR: δ 1.85 (s, 3H) 3.14–3.19 (dd, *J* = 8.5 Hz, 15.8 Hz, 1H), 4.36–4.41 (dd, *J* = 8.7 Hz, 15.8 Hz, 1H), 5.11–5.16 (m, 1H), 6.27 (d, *J* = 6.2 Hz, 1H), 7.26–7.36 (m, 4H), 7.73–7.75 (q, *J* = 3.0 Hz, 5.4 Hz, 2H), 7.85–7.87 (dd, *J* = 3.0 Hz, 5.4 Hz, 2H). ^{13}C NMR: δ 20.81, 31.97, 52.41, 75.93, 123.32, 124.74, 126.36, 127.21, 129.76, 131.75, 134.13, 138.33, 142.18, 168.35, 170.57. ESI-MS (*m*/*z*): 321. Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found C, 71.62; H, 4.63; N, 4.87.

4.12. General procedure for the hydrolysis of acetyl derivatives of 2-phthalimidocycloalkanols and phthalimidoindanols

The racemic acetates (50 mg), aqueous phosphate buffer (2.5 mL, 0.1 M, pH. 7.0), toluene (250 μl), and wet whole cells of *Arthrobacter* sp. lipase/PLAP(150 mg) were shaken (320 rpm) continuously at 25 ± 1 °C. After a certain degree of conversion (~50%) as indicated by high performance liquid chromatography (HPLC), the reaction was terminated by adding ethyl acetate and centrifuging the mixture at 10,000–15,000*g* to remove the enzyme and the suspended particles. The clear solution was decanted and the centrifuged mass was extracted separately with ethyl acetate (3 × 25 mL). The organic layer was combined and washed with water. The combined organic layer was then dried and evaporated under reduced pressure to furnish a mixture of hydrolyzed alcohol and unhydrolyzed ester, which was separated by column chromatography.

4.13. (1*R*,2*R*)-(−)-2-Phthalimidocyclopentan-1-ol 3a

HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25} = -32.5$ (*c* 1, $CHCl_3$); HPLC condition (OJH chiral column, eluent 2-propanol–hexane–acetic acid (4:96:0.1), flow rate: 0.5 mL/min, t_1 = 38.0, 42.0 min).

4.14. (1*R*,2*R*)-(−)-2-Phthalimidocyclohexan-1-ol 3b

HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25} = -34.0$ (*c* 1, $CHCl_3$); HPLC condition (OJH chiral column, eluent 2-propanol–hexane–acetic acid (1:99:0.1), flow rate: 1 mL/min, t_1 = 31.5, 35.6 min).

4.15. (1*R*,2*R*)-(−)-1-Phthalimidoindan-2-ol 8

HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25} = -84.8$ (*c* 0.25, $CHCl_3$); HPLC condition (ADH chiral column, eluent 2-propanol–hexane (20:80), flow rate: 0.8 mL/min, t_1 = 15.3, 21.2 min).

4.16. (1*R*,2*R*)-(−)-2-Phthalimidoindan-1-ol 13

HPLC purity >98%; HPLC ee >98%; $[\alpha]_D^{25} = -23.0$ (*c* 1, $CHCl_3$); HPLC condition (ADH chiral column, eluent 2-propanol–hexane–acetic acid (5:95:0.1), flow rate: 0.8 mL/min, t_1 = 20.3, 22.3 min).

4.17. (1*S*,2*S*)-(+)-2-Phthalimido-1-acetoxy-cyclopentane 4a

HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25} = +10.0$ (*c* 0.5, $CHCl_3$); HPLC condition (OJH chiral column, eluent 2-propanol–hexane–acetic acid (4:96:0.1), flow rate: 0.5 mL/min, t_1 = 16.1, 31.5 min).

4.18. (1*S*,2*S*)-(+)-2-phthalimido-1-acetoxy-cyclohexane (4b)

HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25} = +7.5$ (*c* 1, $CHCl_3$); HPLC condition (OJH chiral column, eluent 2-propanol–hexane–acetic acid (1:99:0.1), flow rate: 1 mL/min, t_1 = 13.1, 13.1 min).

4.19. (1*S*,2*S*)-(+)-1-Phthalimido-2-acetoxyindan 9

HPLC purity >99%; HPLC ee >99%; $[\alpha]_D^{25} = +96.0$ (*c* 1, $CHCl_3$); HPLC condition (ADH chiral column, eluent 2-propanol–hexane (20:80), flow rate: 0.8 mL/min, t_1 = 9.9, 12.9 min).

4.20. (1*S*,2*S*)-(+)-2-Phthalimido-1-acetoxyindan 14

HPLC purity >90%; HPLC ee >90%; $[\alpha]_D^{25} = +20.0$ (*c* 1, $CHCl_3$); HPLC condition (ADH chiral column, eluent 2-propanol–hexane–acetic acid (5:95:0.1), flow rate: 0.8 mL/min, t_1 = 25.7, 48.2 min).

4.21. (1*R*,2*R*)-*trans*-2-Amino-1-cyclopentanol 2a

($C_5H_{11}NO$) $[\alpha]_D^{25} = -31.3$ (*c* 1.0, methanol); >99% ee; mp: 80 °C; {lit:[15b] $[\alpha]_D^{25} = -30.6$ (*c* 0.78 methanol) >99% ee; mp: 82–83 °C}; ^{1}H NMR, δ: 1.23–1.48 (m, 2H), 1.50–1.83 (m, 2H), 1.84–2.02 (m, 5H), 2.80–3.22 (m, 1H), 3.80–3.06 (m, 1H), ^{13}C NMR, δ: ^{13}C NMR, δ: 21.1, 31.1, 33.1, 60.6, 79.2, ESI-MS (*m*/*z*):101. Anal. Calcd for $C_5H_{11}NO$: C, 59.36; H, 10.97; N, 13.85. Found C, 59.24; H, 10.99; N, 13.80

4.22. (1*S*,2*S*)-*trans*-2-Amino-1-cyclopentanol 2a

($C_5H_{11}NO$) $[\alpha]_D^{25} = +30.6$ (*c* 1.0, methanol); >99% ee; mp: 80–82 °C; {lit:[15b] $[\alpha]_D^{25} = +30.65$ (*c* 0.71 methanol) >99% ee, mp: 82–83 °C}; ^{1}H NMR, δ: 1.23–1.48 (m, 2H), 1.50–1.83 (m, 2H), 1.84–2.02 (m, 5H), 2.80–3.22 (m, 1H), 3.80–3.06 (m, 1H),^{13}C NMR, δ: 21.1, 31.1, 33.1, 60.6, 79.2, ESI-MS (*m*/*z*): 101. Anal. Calcd for

$C_5H_{11}NO$: C, 59.36; H, 10.97; N, 13.85. Found C, 59.34; H, 10.92; N, 13.82.

4.23. (1*R*,2*R*)-*trans*-2-Amino-1-cyclohexanol 2b

($C_6H_{13}NO$) $[\alpha]_D^{25} = -39.1$ (*c* 0.50, methanol); >99% ee; mp: 86 °C; {lit:[15b] $[\alpha]_D^{25} = -40.1$ (*c* .41 MeOH) 100% ee, mp: 87 °C}; ^{1}H NMR,, δ: 0.90–1.40 (m, 2H), 1.51–1.83 (m, 2H), 1.84–2.12 (m, 2H), 2.21–2.50 (m, 2H), 3.10–4.23 (m, 1H), ^{13}C NMR, δ: 23.4, 24.6, 31.5, 34.4, 55.8, 75.0; ESI-MS (*m*/*z*): 115. $C_6H_{13}NO$: C 62.55; H, 11.38; N, 12.17. Found C, 62.35; H, 11.30; N, 12.19.

4.24. (1*S*,2*S*)-*trans*-2-Amino-1-cyclohexanol 2b

($C_6H_{13}NO$) $[\alpha]_D^{25} = +40.1$ (*c* 0.50, methanol); >99% ee; mp: 86 °C; {lit:[15b] $[\alpha]_D^{25} = +40.4$ (*c* .41 MeOH) 100% ee, mp: 87 °C}; ^{1}H NMR, δ: 0.90–1.40 (m, 2H), 1.51–1.83 (m, 2H), 1.84–2.12 (m, 2H), 2.21–2.50 (m, 2H), 3.10–4.23 (m, 1H), ^{13}C NMR, δ: 23.4, 24.6, 31.5, 34.4, 55.8, 75.0; ESI-MS (*m*/*z*): 115. Anal. Calcd for $C_6H_{13}NO$: C 62.55; H, 11.38; N, 12.17. Found C, 62.32; H, 11.33; N, 12.12.

4.25. (1*R*,2*R*)-*trans*-1-Amino-2-indanol 7

($C_9H_{11}NO$) $[\alpha]_D^{25} = -22.0$ (*c* 0.54, $CHCl_3$); >99% ee; mp: 143.0 °C; {lit:[26d] $[\alpha]_D^{25} = -21.5$ (*c* 0.58, MeOH); >99% ee; mp: 144.0–145.0 °C}; ^{1}H NMR, δ: 2.04 (br s, 3H), 2.80–2.843 (dd, *J* = 15.4 Hz, 8.1 Hz, 1H), 3.19–3.23 (dd, 1H, *J* = 15.5 Hz, 7.1 Hz), 4.08–4.34 (m, 2H), 7.14–7.28 (m, 4H).^{13}C NMR ($CDCl_3$): 38.2, 64.0, 82.1, 123.1, 124.8, 127.1, 127.8, 138.9, 143.8. ESI-MS (*m*/*z*): 149. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found C, 72.37; H, 7.58; N, 9.47.

4.26. (1*S*,2*S*)-*trans*-1-Amino-2-indanol 7

($C_9H_{11}NO$) $[\alpha]_D^{25} = +22.4$ deg (*c* 0.98, methanol); >99% ee; mp: 141.0–143.0 °C; {lit:[26d] $[\alpha]_D^{25} = +22.8$ (*c* 1.12, MeOH); >99% ee; mp: 144.0–145.0 °C}; ^{1}H NMR δH 2.04 (br s, 3H), 2.80–2.843 (dd, *J* = 15.4 Hz, 8.1 H*E*z, 1H), 3.19–3.23 (dd, 1H, *J* = 15.5 Hz, 7.1 Hz), 4.08–4.34 (m, 2H), 7.14–7.28 (m, 4H).^{13}C NMR ($CDCl_3$): 38.2, 64.0, 82.1, 123.1, 124.8, 127.1, 127.8, 138.9, 143.8. ESI-MS (*m*/*z*): 149. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found C, 72.34; H, 7.54; N, 9.52.

4.27. (1*R*,2*R*)-*trans*-2-Amino-1-indanol 15

($C_9H_{11}NO$) $[\alpha]_D^{25} = -14.3$ (*c* 5, $CHCl_3$); 98% ee; mp: 157 °C; {lit:[26d] $[\alpha]_D^{25} = -15.0$ (*c* 5, $CHCl_3$); >99% ee; mp:160.0–161.0 °C}; ^{1}H NMR, δ: 2.60 (dd, *J* = 15.3 Hz, 8.0 Hz, 1H), 3.22 (dd, *J* = 15.3 Hz, 8.0 Hz, 1H), 3.47 (dt, *J* = 8.0 Hz, 6.5 Hz, 1H) 4.79 (d, 6.5 Hz, 1H), 7.15–7.60 (m, 4H), ^{13}C NMR, δ: 38.8, 62.9, 82.2, 123.6,124.7, 126.9, 128.1, 139.5, 143.3. ESI-MS (*m*/*z*): 149. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found C, 72.44; H, 7.52; N, 9.47.

4.28. (1*S*,2*S*)-*trans*-2-Amino-1-indanol 15

($C_9H_{11}NO$) $[\alpha]_D^{25} = +10.3$ (*c* 5, $CHCl_3$); 90% ee; mp: 154–156 °C; {lit:[26d] $[\alpha]_D^{25} = +13.4$ (*c* 5, $CHCl_3$); >99% ee; mp:160.0–161.0 °C}; ^{1}H NMR, δ: 2.60 (dd, *J* = 15.3 Hz, 8.0 Hz, 1H), 3.22 (dd, *J* = 15.3 Hz, 8.0 Hz, 1H), 3.47 (dt, *J* = 8.0 Hz, 6.5 Hz, 1H) 4.79 (d, 6.5 Hz, 1H), 7.15–7.60 (m, 4H), ^{13}C NMR, δ: 38.8, 62.9, 82.2, 123.6,124.7, 126.9, 128.1, 139.5, 143.3. ESI-MS (m/z): 149. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found C, 72.40; H, 7.55; N, 9.43.

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