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Synthesis of enantiomerically pure *cis*- and *trans*-1,2-diaminoindanes

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Abstract

The four isomers of *cis*- and *trans*-1,2-diaminoindanes **5** and **11** were prepared in three steps and high enantiomeric excess by a key lipase-catalyzed selective transesterification of racemic *cis*-2-azido-1-indanol and *trans*-1-azido-2-indanol, respectively.

1. Introduction

Recently, we reported on indano-[1,2-*b*]aziridine derivatives as mechanism-based inhibitors[1] and 2-aminoindanes as substrates[2] of dopamine β-hydroxylase (DBH; EC 1.14.17.1),[3] a copper-containing monooxygenase which catalyses the transformation of dopamine into noradrenaline. In the course of this study designed to investigate the topology of the DBH active site, the need for preparing useful quantities of enantiomerically pure *cis*- and *trans*- 1,2-diaminoindanes **5** and **11** became apparent. Despite the importance of this functionality, the synthesis of *cis*-1,2-diaminoindane **11** is only described in the literature.[4] A simple retrosynthetic analysis suggested that the target molecules **5** and **11** might be easily accessible from azidoindanols **1** and **7**, respectively, by an S_N2 type substitution of the OH group by an azido anion followed by reduction (Scheme 1).

2. Results and discussion

Using this strategy, the transformation of (±)-*cis*-2-azido-1-indanol **1** into (±)-*trans*-1,2-diaminoindane **5** was realized in three steps as depicted in Scheme 2. Reaction of (±)-**1** with NaH in THF gave quantitatively the corresponding alcoholate which reacted in situ with tosylchloride

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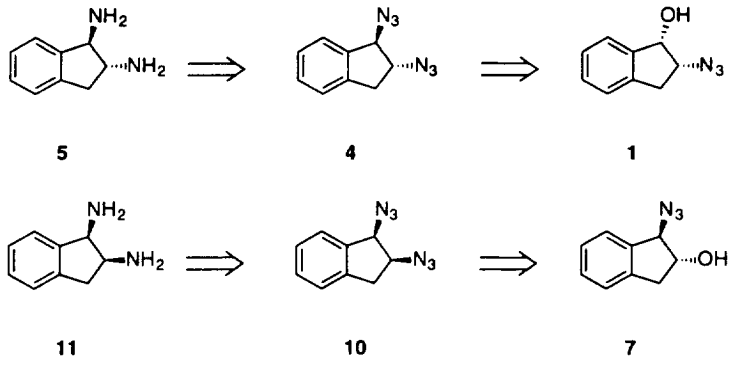
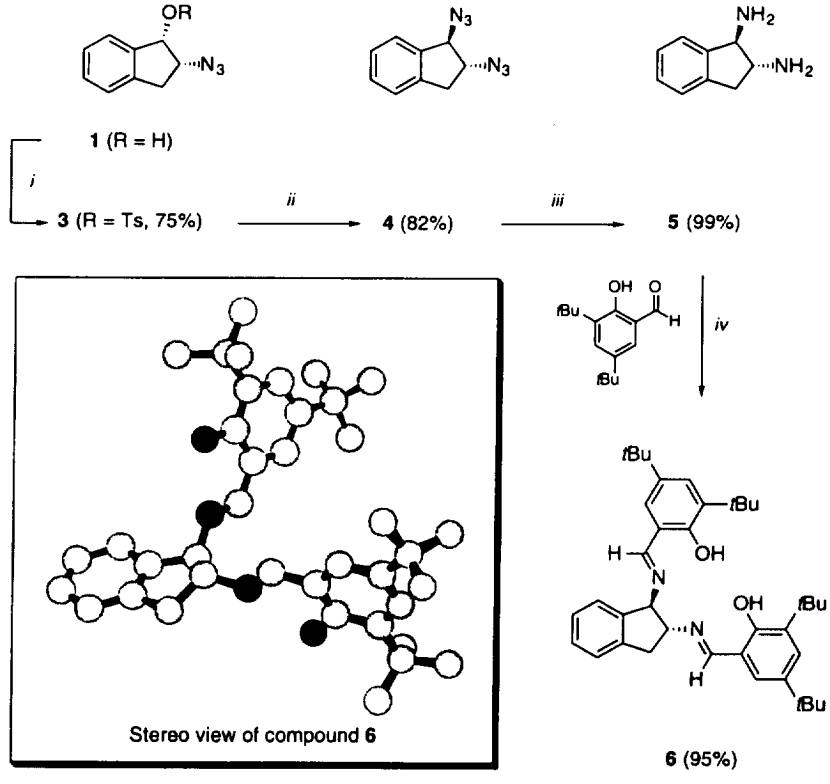


Scheme 1. Retrosynthetic analysis for the synthesis of 1,2-diaminoindane compounds **5** and **11**

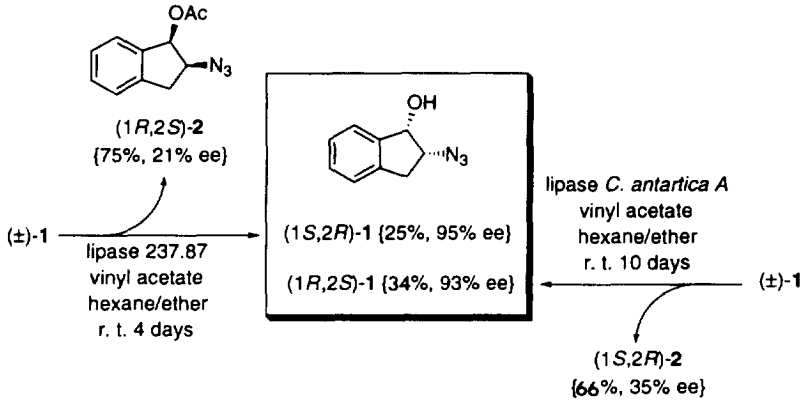
to give tosylate derivative (±)-**3**. S_N2 type substitution of the tosyl group with NaN_3 in DMF afforded (±)-*trans*-1,2-diazidoindane **4**. Catalytic reduction with H_2 in the presence of palladium on charcoal in absolute ethanol gave (±)-*trans*-1,2-diaminoindane **5**, quantitatively.



Scheme 2. Preparation of *trans*-1,2-diaminoindane **5** and its bis-imine derivative **6**: (i) NaH in THF at rt, then TsCl; (ii) NaN_3 in DMF at 60°C; (iii) H_2, Pd/C in EtOH at rt; (iv) in EtOH at 70°C

Encouraged by the simplicity and the efficiency (61% in three steps) of this preparation, we decided to apply this sequence to the synthesis of chiral *trans*-1,2-diaminoindanes **5**. Recently, we described the preparation of *cis*-2-azido-1-indanol **1** in both enantiomerically pure forms by enantioselective lipase

catalyzed transesterification.[5,6] We found that lipase 237.87† was able to transform 75% of (±)-**1** to (1*R*,2*S*)-*cis*-1-acetoxy-2-azidoindane **2** with low enantiomeric excess (21% *ee*) after 4 days at room temperature. On the contrary, the 25% of remaining (1*S*,2*R*)-*cis*-2-azido-1-indanol **1** showed an excellent enantiomeric excess (95% *ee*, 99% after recrystallization in CCl_4). Since it was not possible to obtain (1*R*,2*S*)-*cis*-1-acetoxy-2-azidoindane **2** in higher enantiomeric excess than 20% with lipase 237.87, we looked for more efficient lipases. We found that lipase *Candida antarctica A* catalyzed the transformation of 66% of (±)-**1** to (1*S*,2*R*)-**2** with 35% *ee*, and the 34% of remaining (1*R*,2*S*)-**1** was obtained with 93% *ee* (99% after recrystallization in CCl_4) (Scheme 3).



Scheme 3. Lipase catalyzed enzymatic resolution of (±)-*cis*-2-azido-1-indanol **1**

By the same method used for racemic **1**, optically active aminoindanols (1*R*,2*S*)-**1** (93% *ee*) and (1*S*,2*R*)-**1** (95% *ee*) were converted into the *trans*-diazido compounds (1*S*,2*S*)-**4** (90% *ee*), $[\alpha]_D^{25}$=+30.5 (*c* 0.1, $CHCl_3$) and (1*R*,2*R*)-**4** (90% *ee*), $[\alpha]_D^{25}$=−28 (*c* 0.3, $CHCl_3$), respectively, without significant loss of enantiomeric purity as determined by HPLC. Finally, hydrogenation led to the *trans*-diamino compounds (1*S*,2*S*)-**5**, $[\alpha]_D^{25}$=+12.3 (*c* 3, $CHCl_3$) and (1*R*,2*R*)-**5**, $[\alpha]_D^{25}$=−20.4 (*c* 0.7, $CHCl_3$) in quantitative yields. Determination of the enantiomeric excesses of diamines **5** is more problematic because the two enantiomers were not resolved by HPLC. In order to determine their enantiomeric excesses, we chose to derivatize compounds **5** into bis-imine compounds **6** by reaction with 2 equiv. of 3,5-di-*tert*-butyl-2-hydroxy-benzaldehyde. After this operation, the two enantiomers (1*S*,2*S*)-**6** (99% *ee*), $[\alpha]_D^{25}$=+262.5 (*c* 0.7, $CHCl_3$) and (1*R*,2*R*)-**6** (99% *ee*), $[\alpha]_D^{25}$=−292.5 (*c* 0.5, $CHCl_3$) can be resolved by HPLC (Chiralcel column OD-H, Daicel; hexane:*i*PrOH=99.75:0.25), and the enantiomeric excesses measured indicate that both diamino compounds (1*S*,2*S*)-**5** and (1*R*,2*R*)-**5** were obtained in high enantiomeric purity. Another advantage of the derivatization into bis-imine derivatives is that compounds **6** are crystalline. Thus crystallization of (±)-**6** in CH_2Cl_2/MeOH gave crystals suitable for an X-ray analysis (Table 1).

As an alternative to the methodology above described, it was envisaged that the *cis*-1-amino-2-indanol **13** which is commercially available in both enantiomeric forms could serve as precursors for *trans*-1,2-diaminoindane **5** via a three-step sequence involving the S_N2 type substitution of the hydroxyl group by the azido anion and a reduction step. In order to avoid the formation of the undesired *N*-Tos derivative during the tosylation reaction, introduction of the *t*Boc amino protective group on (1*S*,2*R*)-**13** was realized by the classical method.[7] With the protected substrate, *O*-tosylation using NaH and TsCl in THF at room temperature afforded 13% of the expected tosylate (1*S*,2*R*)-**15**, in addition to 58% of the oxazolidinone

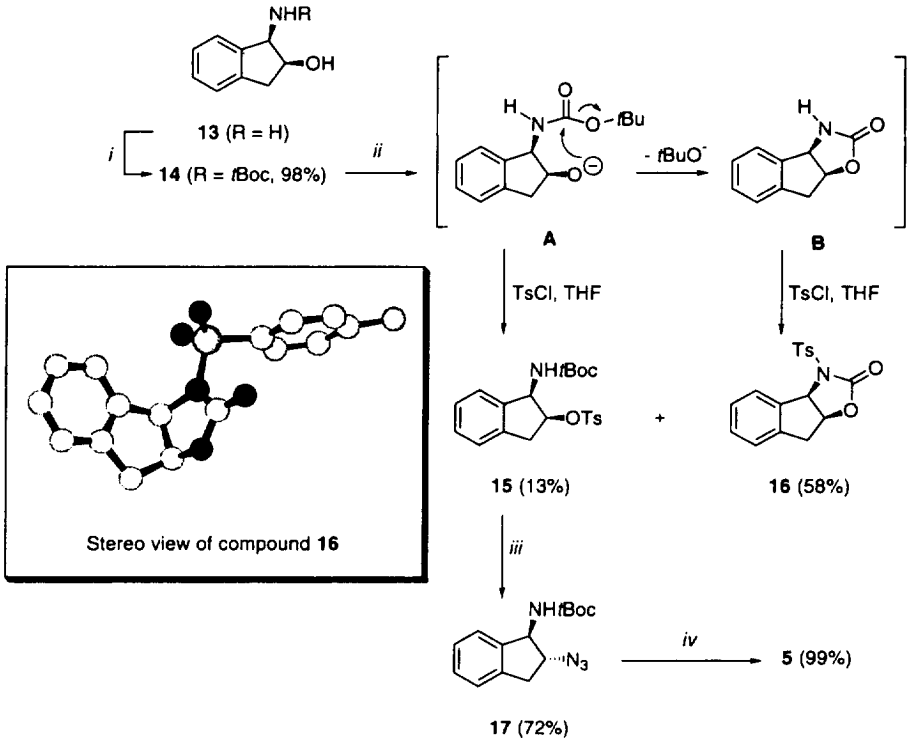
† We thank Rohm GmbH company for the gift of this lipase.

Table 1
Crystallographic data for compounds **6**, **12** and **16**

Compounds	**6**	**12**	**16**
Crystal data			
Formula	$C_{39}H_{52}N_2O_2$	$C_{39}H_{52}N_2O_2$	$C_{17}H_{15}NO_4S$
M_r	580.86	580.86	329.37
Crystal system	monoclinic	triclinic	triclinic
Space group	P21/C	P-1	P1
a [Å]	13.312(4)	10.00(2)	5.451(1)
b [Å]	9.335(7)	12.874(9)	8.900(1)
c [Å]	29.71(1)	18.092(6)	9.337(1)
α [°]	90.00(4)	78.75(5)	116.609(1)
β [°]	93.80(4)	76.9(1)	93.297(1)
γ [°]	90.00(4)	71.4(1)	105.698(1)
V [Å^3]	3684(5)	2130(3)	381.4(2)
D_{calc} [g cm^{-3}]	1.05	0.9	1.43
Z	4	2	1
F(000) [e]	1264	632	172
μ (Mo-K$_\alpha$) [cm^{-1}]	0.059	0.051	0.925
DataCollection			
diff. type	CAD4 Enraf-Nonius		Kappa CCD
scan mode	Ω - 2Θ		Phi scan
measured refl.	7038	6920	1389
unique refl.	6464	6436	1389
refl. used for refinement	3149	4239	1335
absorption correction type		none	
extinction correction	0	0	∅
extinction coefficient	0	0	∅
Structure refinement			
refined parameters	389	433	205
H atoms		included not refined	
R	0.073	0.076	0.031
R_w	0.072	0.085	0.034
w	1	1	1
(shift/esd)$_{max}$	0.623	0.32	0.2848
goodness of fit	1.826	1.379	0.219
$\Delta\rho_{fin}$(max/min) [e Å^{-3}]	0.3284/-0.2980	0.3532/-0.2595	0.10/-0.13

(1*S*,2*R*)-**16**. The structure of (1*S*,2*R*)-**16** was established by ^{1}H NMR and ^{13}C NMR spectroscopy and confirmed by X-ray analysis (Table 1). The formation of compound (1*S*,2*R*)-**16** can be easily explained by an intramolecular attack of alcoholate anion **A** to the *t*Boc group followed by the displacement of *t*BuO$^-$ anion and tosylation of the N–H group of **B**. Finally, when performing the reaction at 0°C, tosylate (1*S*,2*R*)-**15** was obtained in 60% yield as the unique product. Substitution of tosyl group with NaN_3 in

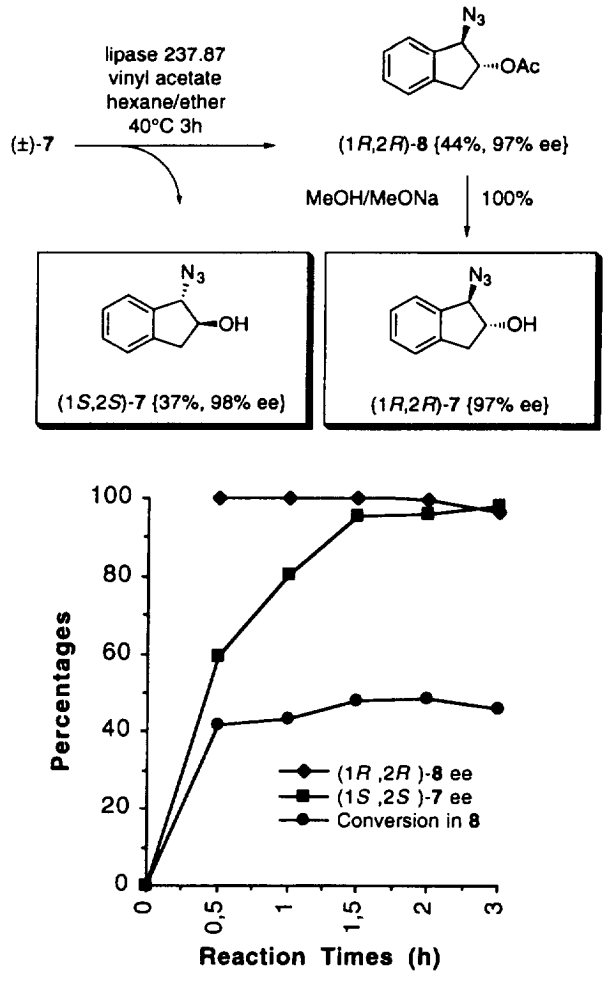
DMF followed by catalytic hydrogenation afforded (1*S*,2*S*)-**5** which was transformed into the bis-imine derivative (1*S*,2*S*)-**6** 99% *ee*. In the same way, optically active aminoindanol (1*R*,2*S*)-**13** was converted into (1*R*,2*R*)-**5** and (1*R*,2*R*)-**6** 99% *ee* (Scheme 4).



Scheme 4. Alternative preparation of *trans*-1,2-diaminoindane **5**: (i) $(Boc)_2O$ in MeOH at rt; (ii) NaH in THF; (iii) NaN_3 in DMF at 60°C; (iv) H_2, Pd/C in EtOH at rt

cis-1,2-Diazidoindane **10** can be considered as a precursor of *cis*-1,2-diaminoindane **11**. *cis*-1,2-Diazidoindane **10** can be obtained from epoxyindane via the *trans*-1-azido-2-indanol **7** (NaN_3).[8] Thus, when realizing the preparative kinetic resolution of (±)-*trans*-1-azido-2-indanol **7**,[8,9] we found that lipase 237.87 converts racemic *trans*-1-azido-2-indanol **7** to 44% of (1*R*,2*R*)-*trans*-2-acetoxy-1-azidoindane **8**, $[\alpha]_D^{25}=-81.6$ (*c* 46, $CHCl_3$), lit.[8] $[\alpha]_D^{25}=-85.5$ (*c* 1.5, $CHCl_3$) with 97% *ee*. The remaining (1*S*,2*S*)-**7**, $[\alpha]_D^{25}=+74.2$ (*c* 41, $CHCl_3$), lit.[8] $[\alpha]_D^{25}=+64$ (*c* 18, $CHCl_3$) was obtained in 37% yield and 98% *ee*. The corresponding *trans* alcohol (1*R*,2*R*)-**7** (97% *ee*), $[\alpha]_D^{25}=-60$ (*c* 11, $CHCl_3$) was obtained in high yields by transesterification of the acetoxy group in (1*R*,2*R*)-**8** with MeONa in MeOH (Scheme 5).

Transformations of 1-azido-2-indanols **7** to *cis*-1,2-diaminoindanes **11** were realized once more by the three classical steps already used for the synthesis of compounds **5** (Scheme 6). Crystallization of compound **12** in CH_2Cl_2 gave crystals suitable for an X-ray analysis (Table 1). Optically active *cis*-azidoindanols (1*S*,2*S*)-**7** (98% *ee*) and (1*R*,2*R*)-**7** (97% *ee*) were converted into *cis*-diamino compounds (1*S*,2*R*)-**11**, $[\alpha]_D^{25}=-42.5$ (*c* 0.8, $CHCl_3$) and (1*R*,2*S*)-**11**, $[\alpha]_D^{25}=+38.6$ (*c* 1.2, $CHCl_3$), respectively, and their bis-imine derivatives (1*S*,2*R*)-**12** (99% *ee*), $[\alpha]_D^{25}=+45.9$ (*c* 0.6, $CHCl_3$) and (1*R*,2*S*)-**12** (99% *ee*), $[\alpha]_D^{25}=-45.1$ (*c* 0.5, $CHCl_3$) were separated by HPLC (Chiralcel column OD-H, Daicel; hexane:*i*PrOH=95:5.



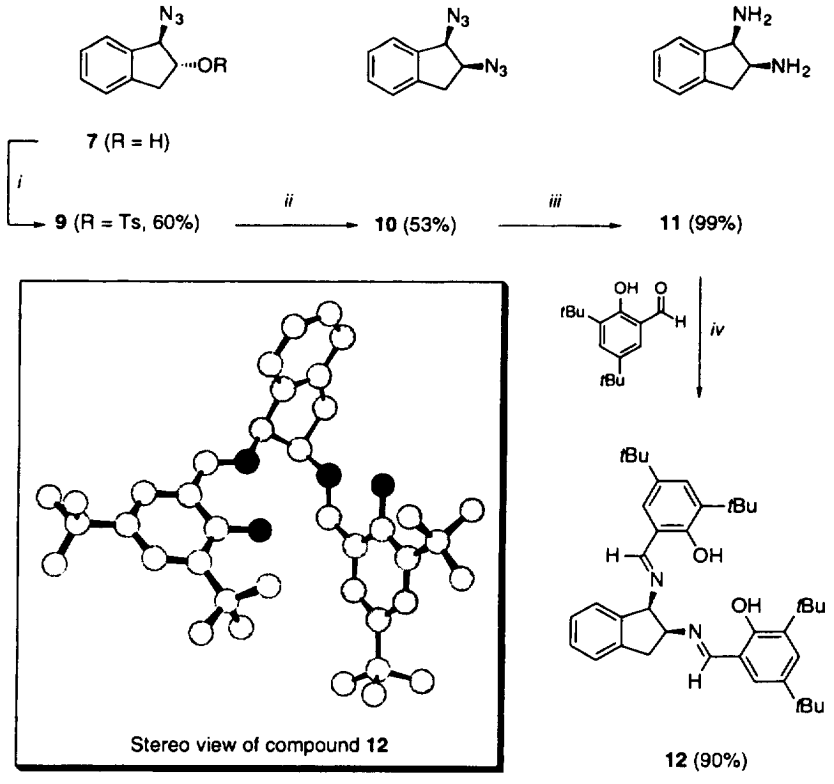
Scheme 5. Lipase catalyzed enzymatic resolution of (±)-*trans*-1-azido-2-indanol **7**

3. Conclusion

In summary, enantioselective lipase catalyzed transesterification of (±)-*cis*-2-azido-1-indanol **1** and (±)-*trans*-1-azido-2-indanol **7** followed by simple chemical transformations (*O*-tosylation, stereospecific azidation and hydrogenation) provides a simple and rapid access to the four isomers of *cis*- and *trans*-1,2-diaminoindane **5** and **11** in good yields and very high enantiomeric excess.

4. Experimental

All the reagents were purchased from Sigma–Aldrich and used without purification. Lipase 237.87 was obtained from Rohm GmbH. Solvents were freshly distilled under Ar: MeOH/Mg, THF/sodium benzophenone ketyl, DMF/CaH_2 and CCl_4/P_2O_5. Elemental analyses: CHN Technicon microanalyser. NMR: Bruker AC-200 (200 MHz and 50.32 MHz, for ^1H and ^{13}C, respectively), $CDCl_3$ as solvent and TMS as internal standard. HPLC: Chiralcel OD-H column (250×4.6 mm), 20°C, UV detection at 214



Scheme 6. Preparation of *cis*-1,2-diaminoindane **7** and its bis-imine derivative **12**: (i) NaH in THF at rt, then TsCl; (ii) NaN_3 in DMF at 60°C; (iii) H_2, Pd/C in EtOH at rt; (iv) in EtOH at 70°C

nm. Each enantiomer was identified by spiking with an authentic sample. Specific rotation: Perkin–Elmer 341, concentrations c are given in g 100 mL^{-1}.

4.1. cis-*2-Azido-1-tosyloxyindane* **3**

A solution of **1** (2 g, 11.4 mmol) in anhydrous THF (10 mL) was slowly added to NaH/THF suspension (300 mg, 12.5 mmol in 30 mL) placed under Ar and maintained at rt. The mixture was stirred for 30 min and TsCl (500 mg, 2.5 mmol) in anhydrous THF (10 mL) was slowly added. The mixture was stirred at rt for 3 h, washed with brine and water and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and flash chromatography (SiO_2, CH_2Cl_2) gave **3** (2.8 g, 75%). ^1H NMR, δ: 7.90 (d, J 8.2 Hz; 2H), 7.50–7.10 (m; 6H), 5.85 (d, J 5.2 Hz; 1H), 4.10 (dt, J 6.7 and 5.2 Hz; 1H), 3.15 (m; 2H), 2.50 (s; 3H). ^{13}C NMR, δ: 145.1 (C), 140.1 (C), 136.1 (C), 133.7 (C), 130.0 (CH), 129.8 (CH), 127.7 (CH), 127.6 (CH), 125.8 (CH), 125.0 (CH), 83.1 (CH), 62.2 (CH), 34.8 (CH_2), 21.6 (CH_3).

4.2. trans-*1,2-Diazidoindane* **4**

A solution of **3** (460 mg, 1.4 mmol) in DMF (20 mL) was treated with NaN_3 (100 mg, 1.5 mmol) at 60°C for 3 h. The mixture was then cooled to room temperature, diluted with water (40 mL) and extracted with CH_2Cl_2 (4×20 mL). The combined extracts were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography (SiO_2, pentane:Et_2O=1:1) gave **4** (230 mg, 82%). $C_9H_8N_6$ (200.08): calcd C 53.98, H 4.03, N 41.99; found: C 54.36, H 4.12, N 41.35.

^{1}H NMR, δ: 7.50–7.10 (m; 4H), 4.80 (d, *J* 5.5 Hz; 1H), 4.15 (ddd, *J* 7.6, 6.6 and 5.5 Hz; 1H), 3.35 (dd, *J* 16.3 and 7.6 Hz; 1H), 2.95 (dd, *J* 16.3 and 6.6 Hz; 1H). ^{13}C NMR, δ: 140.0 (C), 139 (C), 129.4 (CH), 127.6 (CH), 125.0 (CH), 124.4 (CH), 70.1 (CH), 67.5 (CH), 36 (CH_2). HPLC: hexane:isopropanol (99.75:0.25), 1 mL/min; retention time: 7 min for (1*S*,2*S*)-**4** and 16 min for (1*R*,2*R*)-**4**.

4.3. trans-*1,2-Diaminoindane* ***5***

A solution of **4** (500 mg, 2.5 mmol) in absolute EtOH (40 mL) was hydrogenated with H_2 in the presence of 10% Pd/C (50 mg) at rt for 12 h. The mixture was centrifuged and concentrated under reduced pressure to give **5** (370 mg, 99%) as the crude product. ^{1}H NMR, δ: 7.40–7.20 (m; 4H), 3.75 (d, *J* 7.2 Hz; 1H), 3.20 (m; 2H), 2.60 (dd, *J* 13 and 6.5 Hz; 1H), 1.80 (br. s; 4H). ^{13}C NMR, δ: 144.6 (C), 139.5 (C), 127.2 (CH), 126.5 (CH), 124.2 (CH), 122.8 (CH), 64.3 (CH), 63.4 (CH), 38.8 (CH_2).

4.4. trans-*[N,N′-Di(3,5-di-*tert*-butyl-2-hydroxy-benzylideneamino)-indane]* ***6***

3,5-di-*tert*-Butyl-2-hydroxy-benzaldehyde (0.47 g, 2 mmol) was added as a solid to a solution of **5** (0.2 g, 1 mmol) in absolute EtOH (10 mL). The mixture was heated to reflux for 1 h and then water was added (3 mL). The resulting yellow solid was collected by filtration to give **6** (0.55 g, 95%). $C_{39}H_{52}N_2O_2$ (580.4): calcd C 80.63, H 9.03, N 4.83; found C 79.39, H 8.50, N 4.18. ^{1}H NMR, δ: 13.55 (s; 1H), 13.50 (s; 1H), 8.50 (s; 1H), 8.45 (s; 1H), 7.40–7.00 (m; 8H), 4.90 (d, *J* 7.3 Hz; 1H), 4.30 (dt, *J* 8.6 and 7.3 Hz; 1H), 3.35 (d, *J* 8.6 Hz; 2H), 1.45 (s; 9H), 1.25 (s; 9H). ^{13}C NMR, δ 168.0 (CH), 167.2 (CH), 158.1 (C), 142.2 (C), 140.4 (C), 140.3 (C), 136.7 (C), 128.3 (CH), 127.9 (CH), 127.3 (CH), 127.2 (CH), 126.6 (CH), 126.5 (CH), 124.8 (CH), 124.2 (CH), 117.8 (C), 79.7 (CH), 78.0 (CH), 39.1 (CH_2), 35.1 (C), 34.2 (C), 31.5 (CH_3), 29.5 (CH_3). HPLC: hexane:isopropanol (99.75:0.25), 1 mL/min; retention time: 2.9 min for (1*S*,2*S*)-**6** and 3.7 min for (1*R*,2*R*)-**6**.

4.5. Lipase catalyzed transesterification of (±)-trans-*1-azido-2-indanol* ***7***

A suspension of (±)-**7** (4.28 g, 24 mmol), vinyl acetate (11 g, 123 mmol) and lipase 237.87 (1.73 g) in hexane:ether (120:80 mL) was stirred at 40°C for 3 h. The suspension was filtered and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography (SiO_2, CH_2Cl_2) gave (1*R*,2*R*)-**8** (2.33 g, 44%, 97% *ee*) and (1*S*,2*S*)-**7** (1.59 g, 37%, 98% *ee*).

(+)-(1*S*,2*S*)-*trans*-1-Azido-2-indanol (1*S*,2*S*)-**7**: Clear yellow oil. $[\alpha]_D^{25}$=+74.2 (*c* 41, $CHCl_3$). $C_9H_9N_3O$ (175.07): calcd C 61.69, H 5.18, N 23.0; found C 60.58, H 5.12, N 23.96. ^{1}H NMR, δ: 7.40–7.10 (m; 4H), 4.65 (d, *J* 5.1 Hz; 1H), 4.45 (ddd, *J* 6.6, 5.8 and 5.1 Hz; 1H), 3.25 (dd, *J* 16.2 and 6.6 Hz; 1H), 2.86 (dd, *J* 16.2 and 5.8 Hz; 1H), 2.08 (br. s; 1H). ^{13}C NMR, δ: 139.8 (C), 137.9 (C), 129.2 (CH), 127.5 (CH), 125.4 (CH), 124.7 (CH), 78.7 (CH), 71.9 (CH), 39.0 (CH_2). HPLC: hexane:isopropanol (98:2), 1 mL/min; retention time: 19 min for (1*S*,2*S*)-**7** and 24 min for (1*R*,2*R*)-**7**.

(−)-(1*R*,2*R*)-*trans*-1-Azido-2-acetoxyindane (1*R*,2*R*)-**8**: Clear yellow oil. $[\alpha]_D^{25}$=−81.6 (*c* 46, $CHCl_3$). $C_{11}H_{11}N_3O_2$ (217.08): calcd C 60.81, H 5.11, N 19.35; found C 60.69, H 5.06, N 20.12. ^{1}H NMR, δ: 7.40–7.10 (m; 4H), 5.32 (ddd, *J* 6.9, 4.6 and 4.1 Hz; 1H), 4.85 (d, *J* 4.1 Hz; 1H), 3.50 (dd, *J* 16.8 and 6.9 Hz; 1H), 2.85 (dd, *J* 16.8 and 4.8 Hz; 1H), 2.05 (s; 3H). ^{13}C NMR, δ: 170.7 (C), 139.8 (C), 137.4 (C), 129.4 (CH), 127.5 (CH), 125.2 (CH), 124.7 (CH), 79.4 (CH), 69.4 (CH), 36.8 (CH_2), 21.0 (CH_3). HPLC: hexane:isopropanol (98:2), 1 mL/min; retention times: 5 min for (1*S*,2*S*)-**8** and 7 min for (1*R*,2*R*)-**8**.

4.6. (−)-(1R,2R)-trans-1-Azido-2-indanol (1R,2R)-7

A mixture of (1*R*,2*R*)-**8** (0.3 g, 1.4 mmol) and MeONa (0.11 g, 1.7 mmol) in MeOH (10 mL) was stirred for 30 min. The solution was filtered and washed with brine. The product was then dried with Na_2SO_4 and the solvent was removed *in vacuo*. (1*R*,2*R*)-**7** (0.245 g, 100%, 99% *ee*) was isolated as a yellow oil.

4.7. trans-1-Azido-2-tosyloxyindane 9

Under the same conditions used for the preparation **3**, treatment of compound **7** (175 mg, 1 mmol) with NaH (30 mg, 1.2 mmol) and TsCl (210 mg, 1.1 mmol) in THF (10 mL) gave compound **9** (193 mg, 60%) which was used without further purification. $C_{16}H_{15}O_3N_3S$ (329.08): calcd C 58.34, H 4.59, N 12.77; found C 57.17, H 4.73, N 13.04. ^{1}H NMR, δ: 7.85 (d, *J* 8.2 Hz; 2H), 7.40 (d, *J* 8.6 Hz; 2H), 7.30–7.10 (m; 4H), 4.90 (m; 2H), 3.35 (dd, *J* 15.9 and 6.5 Hz; 1H), 3.05 (dd, *J* 15.9 and 5.1 Hz; 1H), 2.50 (s; 3H). ^{13}C NMR, δ: 145.4 (C), 138.6 (C), 136.6 (C), 133.2 (C), 130.1 (CH), 128.0 (CH), 129.7 (CH), 127.8 (CH), 125.3 (CH), 124.6 (CH), 85.3 (CH), 69.4 (CH), 36.9 (CH_2), 21.6 (CH_3).

4.8. cis-1,2-Diazidoindane 10

Under the same conditions used for the preparation of **4**, treatment of **9** (330 mg, 1 mmol) in DMF (15 mL) with NaN_3 (70 mg, 1.1 mmol) at 60°C for 3 h gave **10** (106 mg, 53%). $C_9H_8N_6$ (200.08): calcd C 53.98, H 4.03, N 41.99; found C 53.93, H 3.78, N 42.31. ^{1}H NMR, δ: 7.40–7.10 (m; 4H), 4.80 (t, *J* 5.5 Hz; 1H), 4.25 (dt, *J* 6.5 and 5.5 Hz; 1H), 3.15 (d, *J* 6.5 Hz; 2H). ^{13}C NMR, δ: 139.5 (C), 137.3 (C), 129.5 (CH), 127.5 (CH), 125.2 (CH), 124.7 (CH), 66.8 (CH), 63.9 (CH), 35.4 (CH_2). HPLC: hexane:isopropanol (99.75:0.25), 1 mL/min; retention time: 14 min for (1*S*,2*R*)-**10** and 31 min for (1*R*,2*S*)-**10**.

4.9. cis-1,2-Diaminoindane 11

Under the same conditions used for the preparation of **5**, hydrogenation of **10** (0.5 g, 2.5 mmol) in MeOH (40 mL) gave **11** (370 mg, 99%). ^{1}H NMR, δ: 7.60–7.10 (m; 4H), 4.23 (d, *J* 5.5 Hz; 1H), 3.73 (ddd, *J* 16.2, 5.5 and 4.1 Hz; 1H), 3.11 (dd *J* 15.8 and 6.2 Hz; 1H), 2.75 (dd *J* 15.8 and 4.1 Hz; 1H), 1.80 (br. s; 4H). ^{13}C NMR, δ: 144.6 (C), 140.4 (C), 127.2 (CH), 126.5 (CH), 124.2 (CH), 122.8 (CH), 64.3 (CH), 63.4 (CH), 38.8 (CH_2).

4.10. cis-[N,N′-Di(3,5-di-tert-butyl-2-hydroxy-benzylideneamino)-indane] 12

Under the same conditions used for the preparation of **6**, diamine **11** (0.2 g, 1.3 mmol) was transformed into **12** (0.5 g, 90%). $C_{39}H_{52}N_2O_2$ (580.40): calcd C 80.63, H 9.03, N 4.83; found C 80.06, H 9.20, N 4.84. ^{1}H NMR, δ: 13.45 (s; 1H), 13.3 (s; 1H), 8.45 (s; 1H), 8.4 (s; 1H), 7.0–7.5 (m; 8H), 4.95 (d, *J* 5.9 Hz; 1H), 4.4 (ddd, *J* 5.9, 6.8 and 6.6 Hz; 1H), 3.4 (dd, *J* 15.6 and 6.6 Hz; 1H), 3.25 (dd, *J* 15.6 and 6.8 Hz; 1H), 1.35 (s; 9H), 1.25 (s; 9H). ^{13}C NMR, δ: 166.1 (CH), 165.9 (CH), 158.2 (C), 141.8 (C), 141.4 (C), 139.6 (C), 136.7 (C), 128.5 (CH), 127.0 (CH), 126.0 (CH), 125.8 (CH), 125.2 (CH), 124.9 (CH), (CH) 117.7 (C), 76.2 (CH), 73.3 (CH), 38.6 (CH_2), 34.9 (C), 34.0 (C), 31.5 (CH_3), 29.3 (CH_3). HPLC: hexane:isopropanol (95:5), 1 mL/min; retention time: 3.4 min for (1*S*,2*R*)-**12** and 4.3 min for (1*R*,2*S*)-**12**.

4.11. cis-1-(tert-*Butoxycarbonylamino)-2-indanol* **14**

A mixture of **13** (0.15 g, 1 mmol) and $(Boc)_2O$ (0.3 g, 1.4 mmol) in MeOH (30 mL) was stirred for 1 h at reflux and 1 h at rt. Concentration under reduced pressure followed by flash chromatography (SiO_2, CH_2Cl_2:MeOH=90:10) gave **14** (200 mg, 98%) as a white solid. ^1H NMR, δ: 7.20–7.00 (m; 4H), 5.20 (d, *J* 5.2 Hz; 1H), 4.90 (dd, *J* 5.1 and 5.2 Hz; 1H), 4.45 (tdd, *J* 5.1, 4.8 and 2 Hz; 1H), 3.00 (dd, *J* 16.5 and 4.8 Hz; 1H), 2.80 (dd, *J* 2 and 16.5 Hz; 1H), 2.65 (d, *J* 5.1 Hz; NH), 1.40 (s; 9H).

4.12. cis-1-(tert-*Butoxycarbonylamino)-2-tosyloxy-indane* **15**

Under the same conditions used for the preparation of **3**, treatment of **14** (300 mg, 1.2 mmol) with NaH (30 mg, 1.3 mmol) and TsCl (340 mg, 1.8 mmol) in THF (20 mL) gave a mixture of compounds **15** (60 mg, 13%) and **16** (230 mg, 58%) which were separated by flash chromatography (SiO_2, CH_2Cl_2:MeOH=90:10).

cis-1-(*tert*-Butoxycarbonylamino)-2-tosyloxy-indane **15**. ^1H NMR, δ: 7.80 (d, *J* 8.2 Hz; 2H), 7.10–7.40 (m; 6H), 5.20–5.30 (m; 2H), 5.00 (d, *J* 9.3 Hz; NH), 3.08 (bs; 2H), 2.40 (s; 3H), 1.4 (s; 9H). ^{13}C NMR, δ: 155.7 (C=O), 145 (C), 139 (C), 138.1 (C), 133.7 (C), 130.0 (CH), 128.5 (CH), 127.9 (CH), 127.4 (CH), 125.1 (CH), 123.6 (CH), 83.7 (CH), 57.6 (CH), 37.5 (CH_2), 29.7 (C), 29.4 (3 CH_3), 21.7 (CH_3).

N-Tosyl-indano[1,2-*d*]oxazolidin-2-one **16**. ^1H NMR, δ: 7.90 (d, *J* 8.2 Hz; 2H), 7.40–7.20 (m; 6H), 5.90 (d, *J* 7.2 Hz; 1H), 5.28 (ddd, *J* 7.2, 4.9 and 2.7 Hz; 1H), 3.30 (m; 2H), 2.41 (s; 3H). ^{13}C NMR, δ: 151.7 (C=O), 145.5 (C), 139.6 (C), 137.6 (C), 135 (C), 130.26 (CH), 129.7 (CH), 128.5 (CH), 128.2 (CH), 127.1 (CH), 125.4 (CH), 78.9 (CH), 65.2 (CH), 38 (CH), 21.7 (CH_3).

4.13. trans-2-*Azido-1-(tert-butoxycarbonylamino)-indane* **17**

Under the same conditions used for the preparation of **4**, treatment of **15** (100 mg, 0.25 mmol) in DMF (5 mL) with NaN_3 (20 mg, 0.28 mmol) at 60°C for 3 h gave **17** (50 mg, 72%). ^1H NMR, δ: 7.40–7.10 (m; 4H), 5.10 (t, *J* 7.2 Hz; 1H), 4.75 (d, *J* 7.2 Hz; NH), 4.00 (dt, *J* 7.5 and 7.2 Hz; 1H), 3.25 (dd, *J* 15.9 and 7.5 Hz; 1H), 2.85 (dd, *J* 15.9 and 7.2 Hz; 1H), 1.40 (s; 9H). ^{13}C NMR, δ: 162.5 (C=O), 141.5 (C), 137.6 (C), 129.6 (CH), 127 (CH), 126.8 (CH), 125.1 (CH), 78.8 (CH), 65.1 (CH), 38 (CH_2), 31.1 (C), 28.3 ($3CH_3$).

4.14. *X-Ray structure analysis*

Crystals of suitable quality and size were obtained by slow evaporation of CH_2Cl_2/MeOH **6** and **12** and CH_2Cl_2/Et_2O **16** solutions, mounted on a glass fibre and used for measurements. For compounds **6** and **12**, the data were measured at room temperature on an Enraf–Nonius CAD4 diffractometer [Mo-K_α radiation, λ(Mo-K_α)=0.71073 Å]. During data collection, three standard reflections were measured periodically as a general check of crystal and instrument stability. The data reduction was performed with Begin in SDP-Plus.[10] The structures were solved by direct methods with MULTAN80[11] and were refined with LSFM-Plus. The scattering factors were taken from the *International Tables for X-Ray Crystallography*.[12] For compound **16**, the data were measured at room temperature on an Enraf–Nonius Kappa CCD diffractometer [Mo-K_α radiation, λ(Mo-K_α)=0.71073 Å] and a 180° φ scan was performed with 2° steps. The structure was solved by direct methods using SIR.[13] All non-hydrogen atoms were

refined anisotropically with Maxus[14] through cycles of full-matrix least squares. Hydrogen atoms were introduced at idealized positions, included in the calculations but not refined.

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