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Synthesis of Enantiomerically Pure *cis* and *trans*-2-Amino-1-indanol.

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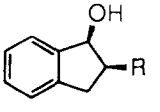
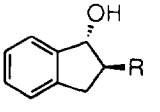
Abstract: Enantiomerically pure *cis* and *trans*-2-amino-1-indanols **1** and **2** were synthesized *via* a highly enantioselective lipase catalyzed transesterification of racemic *cis*-2-azido-1-indanol **3**.

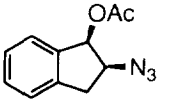
Enantiomerically pure aminoindanols constitute widely studied structures of interest for pharmacophore producing dopamimetic activity,[1] as metabolites of aminoindane in urine of rabbits and rats,[2] as components of the inhibitor of a key enzyme in the human immunodeficiency virus (HIV),[3] and as highly efficient chiral ligands in titanium catalyzed asymmetric Diels Alder reactions [4] or borane reductions of aromatic ketones.[5] Moreover, we have observed that 2-amino-1-indanol is a metabolite[6] of dopamine β-hydroxylase (DBH),[7] a copper-containing monooxygenase which catalyses the transformation of dopamine into noradrenaline. In the course of these studies, the need for preparing useful quantities of the four enantiomerically pure aminoindanols **1** and **2** became apparent.



1 (R = NH_2)
3 (R = N_3)



2 (R = NH_2)
4 (R = N_3)
5 (R = Br)



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Enantiomerically pure 2-amino-1-indanols **1** and **2** have been prepared by reduction of 2-hydroxyimino-1-indanone followed by resolution with tartaric acid [8] or by Friedel-Crafts cyclisation of (-) and (+) phenylalanine.[9]

Recently, we have described the preparation of (1*S*, 2*R*)-2-amino-1-indanol **1a** by reduction of (1*S*, 2*R*)-2-azido-1-indanol **3a** obtained *via* enantioselective lipase catalyzed transesterification of racemic *trans*-2-bromo-1-indanol **5**.[10] By this way it was not possible to obtain enantiomer (1*R*, 2*R*)-**5** in higher enantiomeric excess than 70%. A preparative kinetic resolution of racemic *cis*-2-azido-1-indanol **3** with lipases has been considered instead. Results obtained with seven lipases in organic solvent and vinyl acetate as acyl donor are shown in table 1.[11] After 4 days, LP 237.87 lipase gave 75% of acetate (1*R*, 2*S*)-**6a** with low enantiomeric

excess (e. e. = 21%) but the 25% of remaining azidoalcool (1*S*, 2*R*)-**3a** were obtained in high enantiomeric purity (e. e. 95%; 99% after recrystallization from carbon tetrachloride). On the other hand, the lipase of *Mucor Javanicus* produced acetate (1*R*, 2*S*)-**6a**. with 95% e. e. and 20% yields. The results with the lipase of *Candida Antartica* A which gave the opposite diastereoisomer (1*R*, 2*S*)-2-azido-1-indanol **3b** in 93% e. e. (99% after recrystallization from carbon tetrachloride) after 10 days and 66% conversion were more interesting.

Table 1. Lipase catalyzed transesterification of racemic *cis*-2-azido-1-indanol **3**.

Lipases	Reaction Times in days	*cis*-1-acetoxy-2-azidoindane 6			*cis*-2-azido-1-indanol 3		
		Yields	Config.	e. e. [i]	Yields	Config. [ii]	e. e. [i]
LP 237.87 [iii]	4	75%	(1*R*, 2*S*)	21%	25%	(1*S*, 2*R*)	95%(99%)
Mucor Miehi	20	15%	(1*R*, 2*S*)	2%	85%	(1*S*, 2*R*)	4%
Mucor Javanicus	20	20%	(1*R*, 2*S*)	95%	80%	(1*S*, 2*R*)	6%
Mucor Genevenis	20	6%	(1*R*, 2*S*)	20%	94%	(1*S*, 2*R*)	5%
LCC	3	3%	(1*S*, 2*R*)	2%	2%	(1*R*, 2*S*)	2%
C. Antartica A [iv]	10	66%	(1*S*, 2*R*)	35%	34%	(1*R*, 2*S*)	93% (99%)
C. Antartica B [iv]	5	6%	(1*S*, 2*R*)	12%	94%	(1*R*, 2*S*)	5%

[i] In parentheses, e. e. after recrystallization from carbon tetrachloride. e. e determined by HPLC using Chiralcel column OD-H (Daicel) with hexane/isopropyl alcohol (98:2) as eluant. [ii] From the $[\alpha]_D^{25} = +53$ (*c* 1, $CHCl_3$) for (1*R*, 2*S*) enantiomer (Ref. 4). [iii] Gist Brocades. [iv] Novo.

The transformations outlined in scheme 1 were performed with enantiomerically pure *cis*-2-azido-1-indanol **3a** and **3b**[12] resulting from, respectively, the reaction of lipases LP 237.87 and *Candida Antartica A*. Hydrogenation of *cis*-2-azido-1-indanol **3a** and **3b** in ethanol catalyzed by palladium on charcoal gave, respectively, enantiomerically pure *cis*-2-amino-1-indanol **1a** and **1b**[13] in quantitative yields (99%). The reaction of cis-2-azido-1-indanol **3a** and **3b** with *para*-nitrobenzoic acid under Mitsunobu conditions,[14] afforded respectively *trans*-benzoic esters **7a** and **7b**[15] in good yields. By treatment with MeONa in $MeOH/CH_2Cl_2$, *trans*-benzoic ester **7a** and **7b** were transformed into enantiomerically pure *trans*-2-azido-1-indanol **4a** and **4b**[16] in quantitative yields and 99% e. e. (determined by HPLC on Daicel Chiralcel column OD-H with hexane/isopropyl alcohol (98:2) as eluant). Hydrogenation in ethanol catalyzed by palladium on charcoal gave *trans*-2-amino-1-indanol **2a** and **2b**[17] quantitatively and enantiomerically pure form.

In summary, enantioselective lipase catalyzed transesterification of racemic *cis*-2-azido-1-indanol **3** followed by simple chemical transformations (Mitsunobu inversion, hydrogenation) provides all four stereoisomers of 2-amino-1-indanol in good yields and high enantiomeric excess.

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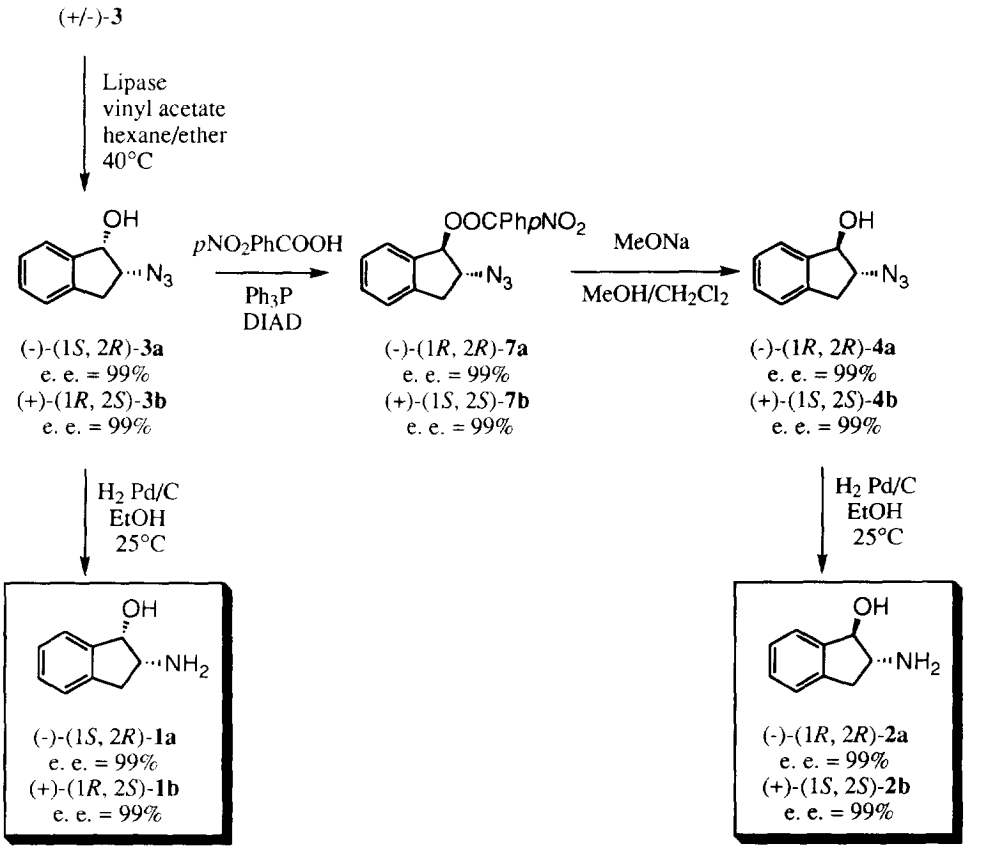
Scheme 1. Synthesis of enantiomerically pure *cis* and *trans*-2-amino-1-indanols **1a,b** and **2a,b**.



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12 *cis*-2-azido-1-indanol **3**. ^{1}H N.M.R. (200 MHz, $CDCl_3$, δ in ppm/TMS): 2.42 (d; *J* 8,3 Hz; 1H); 3.14 (d; *J* 4.6 Hz; 2); 4.32 (dt; *J* 4.6, 4.0 Hz; 1H); 5.13 (d; *J* 4 Hz; 1); 7.20-7.50 (m; 4H). ^{13}C N.M.R. (50 MHz, $CDCl_3$, δ in ppm/TMS): 35.2 (CH_2), 65.7 (CH), 76.4 (C_1), 124.7 (CH), 125.1 (CH), 127.6 (CH), 129.0 (CH), 139.0 (C), 141.6 (C). (-)-(1*S*, 2*R*)-**3a** $[\alpha]_D^{25}$ - 112.0 (*c* 11 $CHCl_3$). (+)-(1*R*, 1*S*)-**3b** $[\alpha]_D^{25}$ +109.8 (*c* 11, $CHCl_3$).

13 *cis*-2-amino-1-indanol **1**. ^{1}H N.M.R. (200 MHz, $CDCl_3$, δ in ppm/TMS): 2.15 (bs; 1H), 2.75 (dd; *J* 15.8, 5.1 Hz; 1H), 3.15 (dd; *J* 15.8, 6.6 Hz; 1H), 3.75 (dt; *J* 6.6, 5.5, 5.1 Hz; 1H), 4.82 (d; *J* 5.5 Hz; 1H), 7.15-7.6 (m; 4H). ^{13}C N.M.R. (50 MHz, $CDCl_3$, δ in ppm/TMS): 41.1 (CH_2), 56.8 (CH); 77.2 (CH), 126.7 (CH), 126.8 (CH), 129.0 (CH), 130.5 (CH), 143.0 (C), 145.4 (C). (-)-(1*S*, 2*R*)-**1a** $[\alpha]_D^{25}$ - 60.6 (*c* 5, $CHCl_3$). (+)-(1*R*, 2*S*)-**1b** $[\alpha]_D^{25}$ + 63.0 (*c* 5, $CHCl_3$).

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15 *para*-nitrobenzoic-*trans*-2-azido-1-indanyl ester **7**. ^{1}H N.M.R. (200 MHz, $CDCl_3$, δ in ppm/TMS): 3.0 (dd; *J* 16, 5.6 Hz; 1H), 3.5 (dd; *J* 16, 7.7 Hz; 1H), 4.35 (dt; *J* 7.7, 5.6, 4.3 Hz; 1H), 6.43 (d; *J* 4.3 Hz; 1H), 7.3-7.4 (m; 4H), 8.2-8.3 (m; 4H). ^{13}C N.M.R. (50 MHz, $CDCl_3$, δ in ppm/TMS): 30.4 (CH_2), 60.6 (CH), 70.7 (CH), 117.9 (2 CH), 125.2 (2 CH), 119.4 (CH), 119.9 (CH), 122.1 (CH), 124.3 (CH), 129.3 (CH), 131.9 (CH), 134.6 (C), 144.9 (C), 158.7 (C). (-)-(1*R*, 2*R*)-**7a**: $[\alpha]_D^{25}$ - 106.7 (*c* 9, $CHCl_3$). (+)-(1*S*, 2*S*)-**7b**: $[\alpha]_D^{25}$ + 112.0 (*c* 11, $CHCl_3$)

16 *trans*-2-azido-1-indanol **4**. ^{1}H N.M.R. (200 MHz, $CDCl_3$, δ in ppm/TMS): 2.30 (s; 1H); 2.75 (dd; *J* 16.0, 8.0 Hz; 1H); 3.2 (dd; *J* 16.0, 8.0 Hz; 1H); 4.0 (dt; *J* 8.0, 6.0 Hz; 1H); 5.0 (d; *J* 6.0 Hz; 1H); 7.1-7.3 (m; 4H). ^{13}C N.M.R. (50 MHz, $CDCl_3$, δ in ppm/TMS): 35.1 (CH_2), 69.2 (CH), 80.3 (CH), 123.9 (CH), 124.9 (CH), 127.6 (CH), 128.9 (CH), 138.4 (C), 141.5 (C). (-)-(1*R*, 2*R*)-**4a** $[\alpha]_D^{25}$ -34 (*c* 11, $CHCl_3$). (+)-(1*S*, 2*S*)-**4b** $[\alpha]_D^{25}$ + 32 (*c* 11, $CHCl_3$).

17 *trans*-2-amino-1-indanol **2**. ^{1}H N.M.R. (200 MHz, $CDCl_3$, δ in ppm/TMS): 2.0 (bs; 3H), 2.65 (dd; *J* 15.3, 8.0 Hz; 1H), 3.25 (dd; *J* 15.3, 8.0 Hz; 1H), 3.45 (dt; *J* 8.0, 6.5 Hz; 1H), 4.82 (d; *J* 6.5 Hz; 1H), 7.15-7.60 (m; 4H). ^{13}C N.M.R. (50 MHz, $CDCl_3$ δ in ppm/TMS), 38.8 (CH_2), 62.9 (CH), 82.4 (CH), 123.7 (CH), 124.7 (CH), 126.9 (CH), 128.1 (CH), 139.5 (C), 143.3 (C). (-)-(1*R*, 2*R*)-**2a** $[\alpha]_D^{25}$ - 15.0 (*c* 5 $CHCl_3$). (+)-(1*S*, 2*S*)-**2b** $[\alpha]_D^{25}$ + 13.4 (*c* 5 $CHCl_3$).

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