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Chemo-enzymatic synthesis of all four diastereoisomers of 1-fluoro-2-amino-indane

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Abstract—The four diastereoisomers of 1-fluoro-2-amino-indane have been synthesized in high enantiomeric excess with lipase resolution of *cis*-2-azido-1-indanol as a key step.

1. Introduction

Dopamine β-monooxygenase (DBM; E.C. 1.14.17.1), a copper-containing monooxygenase present in a variety of mammalian tissues, catalyzes the benzylic hydroxylation of dopamine (DM) into norepinephrine (NE).[1] Given its key role in the biosynthetic production of noradrenalin, DBM presents an appealing target for the design of inhibitors as potential therapeutic agents for the modulation of adrenergic activity in vivo.[2] Very recently, Klinman et al. reported the use of β,β-difluorophenethylamine substrate analogue (F_2PheNH_2) as an experimental probe of the activated oxygen species in DBM.[3] They found that: (i) the F_2PheNH_2 analogue is a weak competitive inhibitor of substrate ($K_i = 26 \pm 3$ mM) for DBM and (ii) upon mixing pre-reduced copper sites of DBM with O_2 under rapid freeze-quench conditions, F_2PheNH_2 leads to an EPR-silent copper species, in contrast to a substrate with an active C–H bond. Klinman et al. concluded that either the reoxidation of the enzyme-bound copper sites in the presence of O_2 is tightly linked to C–H activation, or that a diamagnetic species $Cu_M(II)$–$O_2^{\cdot}$ is formed and blocked by F_2PheNH_2. A crucial question now arises: how does F_2PheNH_2 interact with the copper active site of DBM? In the absence of a three-dimensional structure of DBM, which could be useful in answering this question, we decided to use the conformationally restricted 2-aminoindane compounds, which thanks to its two benzylic stereogenic centers, have already demonstrated their efficiency in the three-dimensional aspects of the chemistry of DBM. Indeed in a previous paper,[4] we reported that the DBM-catalyzed hydroxylation of 2-aminoindane (**AI**) exclusively produces the *trans*-(1*S*)-aminoindanol **AIOH** (ee >99%). The kinetic deuterium isotope effects observed with the *trans*-deuterated derivatives ***d*-AI**[5] allowed us to propose that the reaction is the result of stereospecific *pro-S* hydrogen abstraction followed by the oxygen binding with overall retention of configuration. On the basis of these findings, we proposed a model for the interaction of the substrate with the DBM-active site as described in Scheme 1. In order to confirm this model and to gain more insight in the copper/oxygen species responsible for DBM-catalyzed hydroxylation we decided to study the 1-fluoro-2-amino indanes **5a** and **5b**. Before this we initiated the synthesis of all four diastereoisomers of 1-fluoro-2-amino indanes **5a** and **5b**. Our synthetic strategy was initially based on the enzymatic resolution of both *cis*- and *trans*-2-azido-1-indanol followed by S_N2 substitution of the OH group by a fluorine anion. However, over the course of our investigations, we found that *cis*-2-azido-1-indanol **2** could lead to both *trans*- and *cis*-1-fluoro-2-azido-indane **4a** and **4b** after reaction with DAST as fluorinating reagent. Thus, with this new strategy, the key step became the enzymatic resolution of *cis*-2-azido-1-indanol **2** followed by DAST fluorination, diastereoisomer separation, and finally reduction of the azido function.

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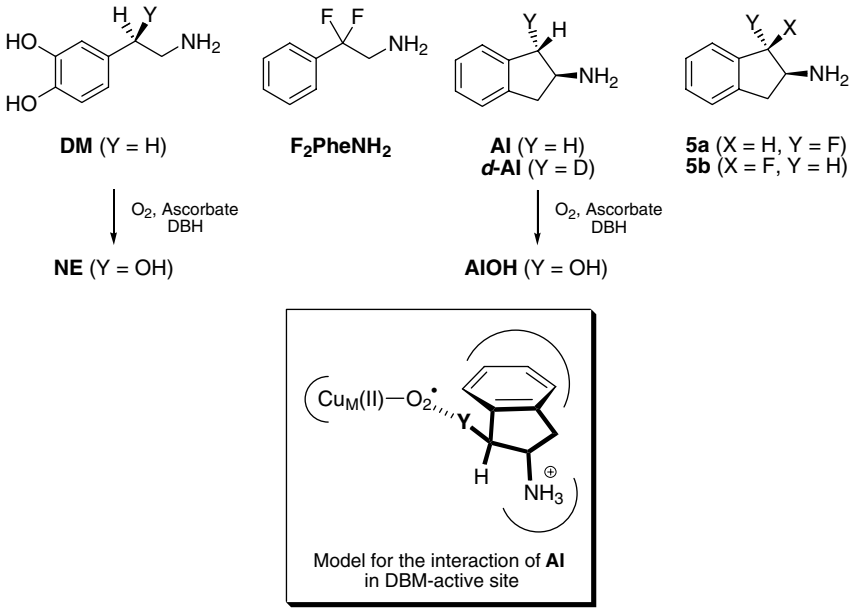


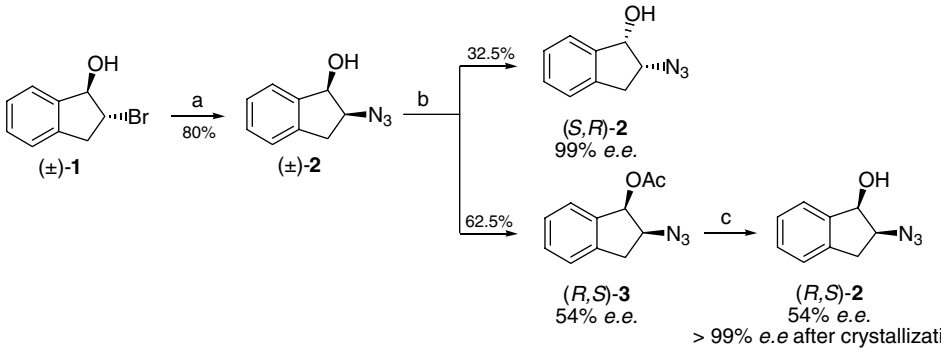
Scheme 1.

2. Results and discussion

2.1. Lipase-catalyzed asymmetric acetylation of *cis*-2-azido-1-indanol, (±)-2

The synthesis started by the transformation of commercially available *trans*-bromohydrin (±)-**1** into *cis*-2-azido-1-indanol (±)-**2** by the use of sodium azide in DMF, as previously described.[6] We have already described the bio-resolution of the racemic *cis*-2-azido-1-indanol (±)-**2** utilizing a series of lipases.[7] However, the observation of poor enantiomeric factors (E <9), led us to reconsider the lipase-catalyzed resolution of the racemic *cis*-2-azido-1-indanol (±)-**2** with commercially available enzymes, in order to find lipase-controlled preparations that were more efficient in this process. The reaction was conducted in the transesterification mode with vinyl acetate as an irreversible acyl donor. The progress of the reaction was followed by chiral HPLC (Chiralcel OD column), which allowed, in a single analysis, the determination of enantiomeric excesses of both starting alcohol **2** and acetate **3**, and the easy determination of the enantiomeric factor (E),[8] for each enzyme preparation (Scheme 2).

As reported in Table 1, the best enzyme is lipase Amano AK with an enantiomeric factor of 15, representing the largest E value reported to date for this biotransformation. We then conducted the resolution on a preparative scale starting from 1 g of (±)-**2** and using lipase AK as catalyst. The reaction was followed by chiral HPLC and quenched when the enantiomeric excess of the remaining substrate (−)-**2** reached 99% {$[\alpha]_D^{20} = -103$ (c 1, MeOH)}, an enantiomeric excess of 54% for acetate **3** was also achieved. The mixture of **2** and **3** was separated over silica (CH_2Cl_2) and we obtained **2** and **3** in 62.5% and 32.5% yield, respectively. The acetate **3** was then transformed into the corresponding alcohol (+)-**2** by methanolysis in 91% yield. In order to improve the enantiomeric purity of **3**, this product was recrystallized from carbon tetrachloride, finally affording enantiomerically pure (+)-**2** {$[\alpha]_D^{20} = +107$ (c 1 MeOH)}. According to the literature data, a (1*R*,2*S*)-absolute configuration was attributed to **3** and a (1*S*,2*R*)-configuration to alcohol (−)-**2**.[6]



Scheme 2. Synthesis and lipase-catalyzed asymmetric acetylation of the 2-azido-1-indanol (±)-**2**. Reagent and conditions: (a) NaN_3, DMF, 80 °C, 6 h; (b) lipase Amano AK, vinyl acetate, *i*-Pr_2O, 37 °C, 3 days; (c) NaOMe/MeOH, 0 °C, 1 h.

Table 1. Lipase-catalyzed asymmetric acetylation of the 2-azido-1-indanol (±)-**2**

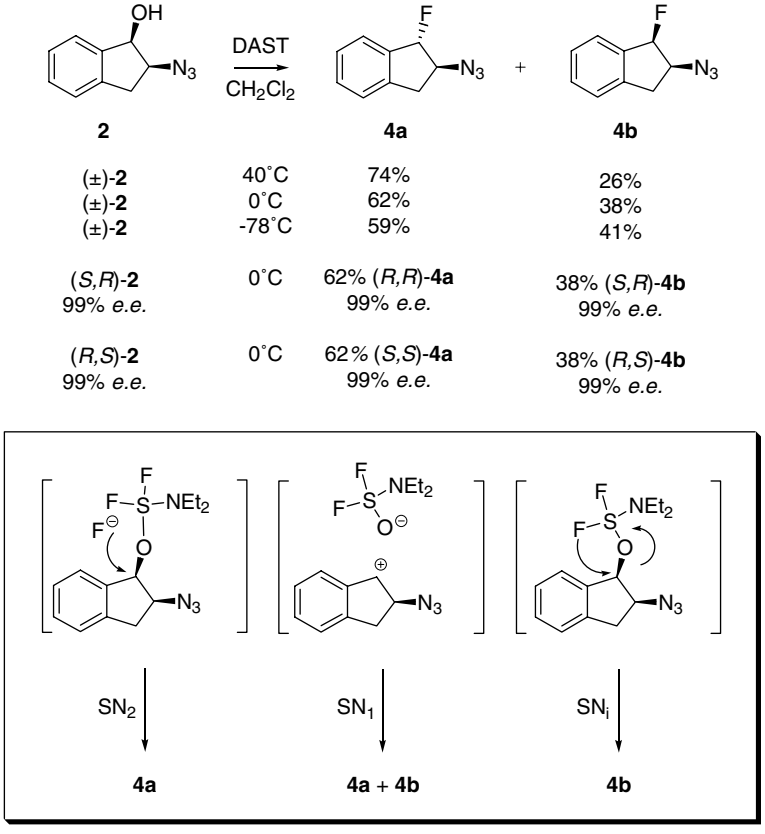
Lipase	Conversion	Time (days)	**2** ee	**3** ee	*E*
CAL-B	0.45	6	54% (*R*,*S*)	65% (*S*,*R*)	9
Lipozyme	0.31	8	23% (*S*,*R*)	52% (*R*,*S*)	3
PS	0.44	6	41% (*S*,*R*)	53% (*R*,*S*)	5
AK	**0.53**	**3**	**78% (*S*,*R*)**	**70% (*R*,*S*)**	**15**
Acylase 1	0.10	7	9% (*S*,*R*)	78% (*R*,*S*)	9
AY	0.23	7	17% (*S*,*R*)	58% (*R*,*S*)	11
PPL	No reaction	10	—	—	—

2.2. DAST fluorination of *cis*-1-hydroxy-2-azido-indane, (±)-2, (+)-2, and (−)-2

DAST fluorination[9] was first accomplished with (±)-**2** at room temperature. Two compounds were detected and were analyzed as *trans*-1-fluoro-2-azido-indane **4a** (major) and *cis*-1-fluoro-2-azido-indane **4b** (minor) after purification. This unexpected result prompted us to investigate the possible influence of temperature on the selectivity of the reaction.

As reported in Scheme 3, we confirmed that the selectivity of the reaction was temperature dependent. We found that the formation of *cis*-isomer **4b** increased at lower temperatures. This temperature effect could be rationalized by the mechanism of the fluorination mediated by DAST. It is generally accepted that the reaction of DAST with alcohol leads to the formation of an alkoxysulfur compound as the primary intermediate (Scheme 3).[10] At this stage, several processes can be envisaged: (i) substitution by a fluorine anion via an S_N2 process leading to the fluoro-compound with inversion of configuration (**4a**); (ii) substitution by a fluorine anion via an S_N1 process leading to a mixture of the fluoro compounds **4a** and **4b**, in which the *trans*-isomer should be the main product. S_N2 processes and the formation of rearranged compounds probably via the formation of carbenium ions (S_N1 process) have already been reported to occur in DAST-mediated fluorination.[11] However, neither of these two mechanisms would explain the low temperature effect on the formation of the *cis*-isomer **4b**. Since S_Ni processes (retention of configuration) are known to occur with alkyl halogenosulfite,[12] another possibility is to consider such a mechanism during the formation of the *cis*-isomer **4b**. Moreover, Shreeve et al. described the deoxofluor-mediated fluorination of enantiomerically pure amino alcohol with retention of configuration at low temperature (−78 °C).[13] In light of these results, in order to explain the temperature effect on the stereoselectivity, we proposed a competition between S_N2 and/or S_N1 processes with the S_Ni process. In this case, the low temperature conditions should favor the intramolecular S_Ni process and the increased formation of the *cis*-isomer **4b**.

For practical reasons and with the aim of obtaining all four diastereoisomers of **5**, we performed a DAST fluorination at 0 °C for the remainder of the synthesis. Subsequently, the reaction was applied to

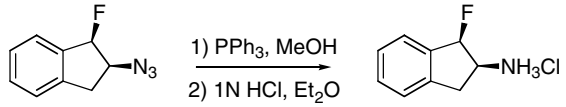


Scheme 3. DAST-mediated fluorination of 2-azido-1-indanol **2**.

both enantiomerically pure (+)-**2** and (−)-**2**. The ability of a Chiralcel-OD column to discriminate both enantiomers of *trans*- and *cis*-1-fluoro-2-azido-indanes **4a** and **4b** allowed the verification that DAST fluorination had no influence on the enantiomeric purity of the reaction products.

2.3. Azido group reduction

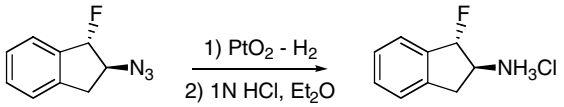
With the four enantiomerically pure diastereoisomers of **4** in hand, we continued the sequence with reduction of the azido group into the amino group. Initially we used Staudinger's conditions (triphenyl phosphine, MeOH).[14] Reduction under these conditions followed by reaction with HCl in diethyl ether of the *cis*-1-fluoro-2-azido-indanes (*R*,*S*)-**4b** and (*S*,*R*)-**4b** afforded the *cis*-1-fluoro-2-amino-indanes (*R*,*S*)-**5b**(HCl) and (*S*,*R*)-**5b**(HCl), respectively, in 93% overall yield. Under these conditions the reduction of *trans*-1-fluoro-2-azido-indanes (*R*,*R*)-**4a** and (*S*,*S*)-**4a** led to a complex mixture of compounds, which were difficult to analyze. One explanation could be the formation of the aziridino compounds via the adduct of triphenyl phosphine with azido group (Scheme 4).[15]



(±)-**4b** → 93% (±)-**5b**
(*S*,*R*)-**4b** (99% *e.e.*) → 93% (*S*,*R*)-**5b**(HCl)
(*R*,*S*)-**4b** (99% *e.e.*) → 93% (*R*,*S*)-**5b**(HCl)

Scheme 4. Staudinger reduction of *trans*- and *cis*-1-fluoro-2-azido-indanes **4a** and **4b**.

To avoid this problem, we used catalytic hydrogenation for the reduction of the azido group. After several trials, we found that platinum oxide was an efficient catalyst for performing this reaction. Under a hydrogen atmosphere and platinum oxide as a catalyst followed by reaction with HCl in diethyl ether, the *trans*-1-fluoro-2-azido-indanes (*R*,*R*)-**4a** and (*S*,*S*)-**4a** led to the hydrochloride salts of *trans*-1-fluoro-2-amino-indanes (*R*,*R*)-**5a**(HCl) and (*S*,*S*)-**5a**(HCl), respectively, in 93% yield. Specific rotations of all four diastereoisomers of **5**(HCl) were determined and are reported in Table 2 (Scheme 5).

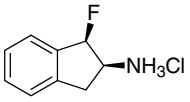
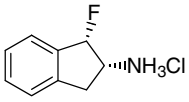
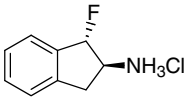
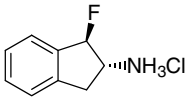


(±)-**4a** → 93% (±)-**5a**
(*R*,*R*)-**4a** (99% *e.e.*) → 93% (*R*,*R*)-**5a**(HCl)
(*S*,*S*)-**4a** (99% *e.e.*) → 93% (*S*,*S*)-**5a**(HCl)

Scheme 5. Catalytic reduction of *trans*-1-fluoro-2-azido-indane **4a**.

In order to check the structure of **5a** and **5b**, both compounds were synthesized in racemic form and crystallized. The X-ray structures of both compounds confirmed the previously attributed stereochemistry (Fig. 1).[16]

Table 2. Specific rotations of all four diastereoisomers of the 1-fluoro-2-amino-indane **5**(HCl)

Hydrochloride salts				
Configurations	(*R*,*S*)-**5b**	(*S*,*R*)-**5b**	(*S*,*S*)-**5a**	(*R*,*R*)-**5a**
$[\alpha]_D^{20}$ (MeOH)	−18.6 (*c* 0.47)	+18.3 (*c* 0.34)	−19.5 (*c* 0.84)	+19.3 (*c* 1)

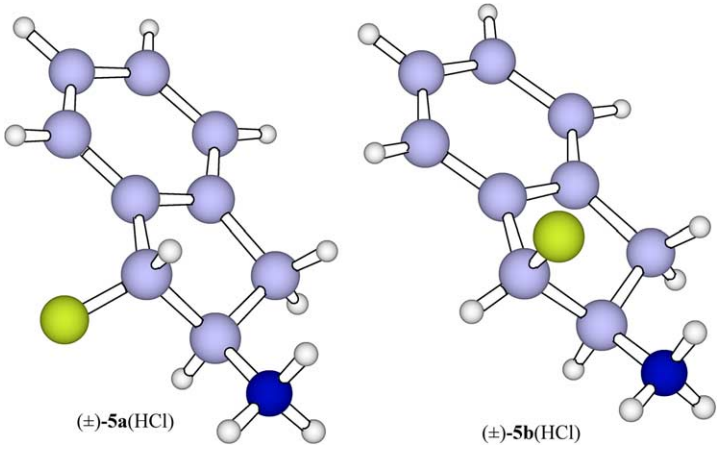


Figure 1. Perspective views of (±)-**5a**(HCl) and (±)-**5b**(HCl). Chlorine atoms and water molecules have been omitted for clarity.

3. Conclusion

Herein, we have reported for the first time the chemoenzymatic synthesis of all four diastereoisomers of 1-fluoro-2-amino-indane as their hydrochloride salts **5**(HCl). This synthesis relies on the lipase resolution of (±)-2-azido-1-indanol **2** and DAST fluorination of the two generated enantiomers, thus affording the four possible diastereoisomers of 1-fluoro-2-azido-indane **4** in high enantiomeric excess. Adequate reduction of the azido group finally generated the four-targeted 1-fluoro-2-amino-indane diastereoisomers as their hydrochloride salts **5**(HCl). Inhibitory studies on dopamine β-monooxygenase are currently under investigation and will be reported in due course.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC 300 spectrometer with TMS as the internal standard. Chemical shifts are given in parts per million downfield from an internal standard of TMS. ^{19}F NMR spectra are decoupled from ^{1}H. All melting points (mp) are uncorrected and were measured on an Electrothermal 9300 apparatus. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Chiral HPLC analysis were run with a Chiralcel OD column, using a 95/5 (hexane/2-propanol) mixture as eluent, delivered at 1 mL/min. UV detection occurred at 254 nm. Enzymatic reactions were carried out either in Schott GL 18 screw cap tubes for analytical experiments or in 100 mL Schott flasks for preparative experiments. The enzymatic reactions were conducted at 28 °C in an orbital shaker (Unitron, Infors) operating at 120 rpm. Lipase CAL-B (Novozyme 435) and lipase AK were from Aldrich, lipases PS, AY, and PPL were a kind gift from Amano, Lipozyme was from Fluka, and acylase I was from Sigma. All chemicals were from Aldrich-Fluka unless otherwise stated.

4.2. *cis*-2-Azido-1-indanol, (±)-2

To a stirred solution of (±)-**1** (5 g, 23.5 mmol) in anhydrous DMF (25 mL) was added NaN_3 (1.625 g, 25 mmol) at room temperature. The reaction was brought to 80 °C, stirred for 6 h and then diluted with 75 mL of water. The aqueous solution was extracted three times with 100 mL of diethyl ether. The organic phases were then combined, dried over sodium sulfate, filtrated, and finally evaporated. The residue was purified over silica (50/50, pentane/diethyl ether) affording (±)-**2** (3.29 g, 80%) as a white solid, mp = 129–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (1H, br d, $J = 8.3$ Hz), 3.13 (2H, d, $J = 4.7$ Hz), 4.31 (1H, dt, $J = 5.0$, 4.9 Hz), 5.13 (1H, dd, $J = 8.0$, 5.3 Hz), 7.2–7.5 (4H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 35.1 (CH_2), 65.7 (CH), 76.4 (CH), 124.7 (CH), 125.1 (CH), 127.5 (CH), 129.0 (CH), 139.0 (C), 141.8 (C).

4.3. *cis*-2-Azido-1-acetoxy indane, 3

To a stirred solution of (±)-**2** (175 mg, 1 mmol) in CH_2Cl_2 (25 mL) was added acetic anhydride (112 mg, 1.1 mmol) and DMAP in a catalytic amount at room temperature. The reaction was then brought to reflux and stirred for 1 h. The reaction mixture was then evaporated and the formed ester purified over silica (CH_2Cl_2) to afford the acetate of (±)-**2** (202 mg, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (3H, s), 3.18 (2H, d, $J = 6.4$ Hz), 4.24 (1H, dt, $J = 6.3$, 5.5 Hz), 6.16 (1H, d, $J = 5.4$ Hz), 7.2–7.4 (4H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.8 (CH_3), 35.4 (CH_2), 62.3 (CH), 77.1 (CH), 125.0 (CH), 125.7 (CH), 127.6 (CH), 129.7 (CH), 138.2 (C), 140.2 (C), 170.7 (C=O).

4.4. Analytical enzymatic resolution of *cis*-2-azido-1-indanol, (±)-2

In a screw cap tube Schott GL 18 were placed 50 mg of (±)-**2** (0.286 mmol), 9 mL of diisopropyl ether, 1 mL of vinyl acetate, and finally 50 mg of enzyme preparation. The tubes were placed on an orbital shaker working at 120 rpm and 28 °C. The reaction was monitored by chiral HPLC using a Chiralcel OD column operating at 1 mL/min with a 95/5 hexane/isopropanol eluent. The enantiomeric excesses of both remaining substrate [retention times of both enantiomers (1*R*,2*S*): 22.35 min and (1*S*,2*R*): 24.41 min] and product formed [retention times of both enantiomers (1*S*,2*R*): 11.12 min and (1*R*,2*S*): 12.04 min] were available in a single analysis allowing the direct determination of the enantiomeric factor *E* for each enzymatic preparation.

4.5. Preparative enzymatic resolution of *cis*-2-azido-1-indanol, (±)-2

In two 100 mL Schott flasks were placed 500 mg of (±)-**2** (2.86 mmol), 45 mL of diisopropyl ether, 5 mL of vinyl acetate, and finally 250 mg of lipase AK. The flasks were placed on an orbital shaker working at 120 rpm and 28 °C. The reaction was monitored by chiral HPLC using a Chiralcel OD column, operating at 1 mL/min with a 95/5 hexane/isopropanol eluent, and stopped when the ee of the remaining substrate reached 99% (3 days). The reaction suspensions were then filtrated to remove proteins, evaporated, and finally purified over silica (CH_2Cl_2) to afford 785 mg of the acetate (3.62 mmol, 63.5%, ee 54%) and 325 mg of remaining alcohol (−)-**2** (1.86 mmol, 32.5%, ee 99%) in 96% overall yield. The acetate was dissolved in 20 mL of MeOH and then reacted with sodium methanoate (0.3 mL of 30% MeONa in MeOH) at 0 °C for 30 min. The reaction was then diluted with 50 mL of water and extracted three times with 100 mL of diethyl ether. The organic phases were then combined, dried over sodium sulfate, filtrated, and finally evaporated. The residue was purified over silica (CH_2Cl_2) to afford 576 mg of (+)-**2** (3.30 mmol, 91%, ee 54%). The alcohol was then recrystallized from CCl_4 to afford 255 mg of enantiomerically pure (+)-**2** (1.70 mmol, 51%, ee >99%).

4.6. DAST fluorination of *cis*-2-azido-1-indanol, (±)-2, (+)-2, and (−)-2

To a stirred solution of (±)-**2** (350 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) containing MS 4 Å maintained at 0 °C (40, −78 °C) was added DAST (275 μL, 2.2 mmol). After 5 min the reaction was stopped with 275 μL of MeOH, left for 5 min under agitation and the reaction mixture filtrated over Celite and evaporated. The residue was then either diluted for HPLC analysis (*i*-Pr_2O) or purified over silica (pentane/diethyl ether, 95/5) affording 163 mg of *trans*-1-fluoro-2-azido-indane, (±)-**4a** (0.92 mmol, 46%), and 99 mg of *cis*-1-fluoro-2-azido-indane, (±)-**4b** (0.56 mmol, 28%) as colorless oils. Compound (±)-**4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (1H, ddd, $J = 16.2$, 5.7, 3.5 Hz), 3.41 (1H, dd, $J = 16.2$, 7.6 Hz), 4.37 (1H, m), 5.84 (1H, dd, $J = 56.3$, 4.2 Hz), 7.2–7.5 (4H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 35.5 (CH_2, d, $J = 2.4$ Hz), 66.7 (CH, d, $J = 23.9$ Hz), 99.3 (CH, d, $J = 183.2$ Hz), 125.0 (CH), 125.3 (CH), 127.7 (CH, d, $J = 2.5$ Hz), 130.3 (CH, d, $J = 3.2$ Hz), 137.5 (C, d, $J = 17.7$ Hz), 139.9 (C, d, $J = 4.9$ Hz). ^{19}F NMR (282.2 MHz, $CDCl_3$) δ −172.6. Compound (±)-**4b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (2H, m), 3.99 (1H, m), 5.80 (1H, dd, $J = 57.0$, 4.5 Hz), 7.2–7.5 (4H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 34.4 (CH_2), 62.0 (CH, d, $J = 18.8$ Hz), 95.0 (CH, d, $J = 184.2$ Hz), 125.3 (CH, d, $J = 2.5$ Hz), 126.2 (CH, d, $J = 2.2$ Hz), 127.7 (CH, d, $J = 3.6$ Hz), 130.9 (C, d, $J = 4.0$ Hz), 137.3 (C, d, $J = 16.5$ Hz), 141.4 (C, d, $J = 5.2$ Hz). ^{19}F NMR (282.2 MHz, $CDCl_3$) δ −180.5. The proportion of **4a** and **4b** formed during DAST fluorination on **2** was monitored by chiral phase HPLC using Chiralcel OD column operating at 1 mL/min using a 95/5 hexane/isopropanol eluent. The enantiomeric excesses of both **4a** (1*S*,2*S*: 5.16 min and 1*R*,2*R*: 6.10 min) and **4b** (1*S*,2*R*: 7.70 min and 1*R*,2*S*: 10.40 min) enantiomers are available in a single analysis.

4.7. Azido group reduction of *trans*-1-fluoro-2-azido-indane, 4a

To a stirred solution of **4a** (89 mg, 0.5 mmol) at room temperature in absolute ethanol (10 mL) in a Schlenck tube, was added 11 mg of PtO_2 (0.05 mmol). The reaction vessel was then placed and maintained under a hydrogen atmosphere. The progress of the reaction was followed by TLC (95/5, CH_2Cl_2/MeOH) with a *p*-anisaldehyde-sulfuric acid based detection (Merck). When the reduction was completed (6 h), the reaction was stopped by filtration, quickly evaporated, and the formed amine purified over a short pad of silica (95/5, CH_2Cl_2/MeOH). The fractions containing the amine were collected, evaporated, and 1 mL of 1 M HCl solution in diethyl ether (Acros) was added (1 mmol). A white precipitate formed immediately, which was dried, affording 101 mg of **5a**(HCl) (93%, 0.47 mmol). Compound (±)-**5a**(HCl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (1H, ddd, $J = 16.4$, 5.7, 5.7 Hz), 3.57 (1H, dd, $J = 16.5$, 8.2 Hz), 4.11 (1H, m), 4.89 (3H, br s), 6.16 (1H, dd, $J = 56.0$, 4.5 Hz), 7.3–7.5 (4H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 35.5 (CH_2, d, $J = 2.1$ Hz), 58.2 (CH, d, $J = 25.2$ Hz), 98.9 (CH, d, $J = 181.7$ Hz), 126.4 (CH), 126.4 (CH), 129.2 (CH, d, $J = 2.5$ Hz), 131.8 (CH, d, $J = 3.2$ Hz), 138.2 (C, d, $J = 19.3$ Hz), 140.6 (C, d, $J = 4.8$ Hz). ^{19}F NMR (282.2 MHz, $CDCl_3$) δ −173.0. Compound (+)-**5a**(HCl): $[\alpha]_D^{20} = +19.3$ (*c* 1, MeOH). Compound (−)-**5a**(HCl): $[\alpha]_D^{20} = -19.5$ (*c* 0.84, MeOH).

4.8. Azido group reduction of *cis*-1-fluoro-2-azido-indane, 4b

To a stirred solution of **4b** (89 mg, 0.5 mmol) at room temperature in methanol (10 mL) was added 144 mg of triphenyl phosphine (0.55 mmol) and the reaction mixture brought to 40 °C. The progress of the reaction was followed by TLC (95/5, CH_2Cl_2/MeOH) with a *p*-anisaldehyde-sulfuric acid based detection (Merck). When the reduction was completed (2 h), the reaction mixture quickly evaporated and the amine formed purified over a short pad of silica (95/5, CH_2Cl_2/MeOH). The fractions containing the amine were collected, evaporated, and 1 mL of 1 M HCl solution in diethyl ether (Acros) was added (1 mmol). A white precipitate formed immediately, which was dried, to afford 101 mg of chlorydrate **5b**(HCl) (93%, 0.47 mmol). Compound (±)-**5b**(HCl): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (1H, ddd, $J = 15.9$, 7.7, 3.5 Hz), 3.41 (1H, ddd, $J = 16.0$, 7.7, 1.9 Hz), 4.02 (1H, m), 4.88 (3H, br s), 5.99 (1H, dd, $J = 57.4$, 5.1 Hz), 7.3–7.6 (4H, m). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 35.4 (CH_2), 53.5 (CH, d, $J = 19.1$ Hz), 94.7 (CH, d, $J = 180.7$ Hz), 126.4 (CH, d, $J = 3.4$ Hz), 127.7 (CH, d, $J = 2.3$ Hz), 129.1 (CH, d, $J = 3.6$ Hz), 132.6 (C, d, $J = 4.4$ Hz), 137.9 (C, d, $J = 16.1$ Hz), 142.6 (C, d, $J = 5.5$ Hz). ^{19}F NMR (282.2 MHz, $CDCl_3$) δ −181.3. Compound (+)-**5b**(HCl): $[\alpha]_D^{20} = +18.3$ (*c* 0.34, MeOH). Compound (−)-**5b**(HCl): $[\alpha]_D^{20} = -18.6$ (*c* 0.47, MeOH).

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16. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre under the access number CCDC 276398 for **5a**(HCl) and number CCDC 276397 for **5b**(HCl).