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A Convenient Enzymatic Route to Optically Active 1-Aminoindan-2-ol: Versatile Ligands for HIV-1 Protease Inhibitors and Asymmetric Syntheses

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Abstract

(1*S*,2*R*)- and (1*R*,2*S*)-1-aminoindan-2-ol were prepared in high enantiomeric excess (>96%) by an immobilized lipase-catalyzed selective acylation of racemic *trans*-1-azidoindan-2-ol.

The development of efficient syntheses of enantiomerically pure (1*S*,2*R*)-1-aminoindan-2-ol (**1**) is the subject of considerable attention because of its utility as an effective ligand in indinavir (**3**), a HIV protease inhibitor which has recently been approved by the United States Food and Drug Administration for the treatment of AIDS.¹ Either enantiomer of *cis*-1-aminoindan-2-ol is also of particular interest as an effective ligand in asymmetric catalysis² and asymmetric syntheses.³ Enantioselective synthesis of (1*S*,2*R*)-1-aminoindan-2-ol (**1**) utilizing Jacobson asymmetric epoxidation of indene as the key step⁴ as well as chemical resolution of the racemic m-1-aminoindan-2-ol⁵ have provided convenient access to either enantiomer. Similarly, baker's yeast reduction of β -oxo ester followed by Curtius rearrangement route by Didier et al.⁶ dioxygenase-catalyzed benzylic hydroxylation route by Boyd et al.,⁷ and lipase-catalyzed transesterification of racemic *trans*-2-bromoindan-1-ol route by Reglier et al.⁸ have shown great promise for large scale synthesis of both enantiomers. We recently reported⁹ an immobilized lipase-catalyzed enzymatic resolution of a racemic bis-tetrahydrofuran which is an important high affinity ligand for HIV-protease inhibitors.¹⁰ One of the intriguing features of this enzymatic resolution process is that the immobilized enzyme can be recovered and recycled without significant loss of activity. Herein we now report that the immobilized amino lipase can be further utilized to resolve racemic *trans*-1-azidoindan-2-ol in high optical purity. Optically active *trans*-1-azidoindan-2-ol has been efficiently converted to the corresponding enantiomer of *cis*-1-aminoindan-2-ol in optically pure form. Of particular note, the current route may provide an access to all four enantiomers of *cis*- and *trans*-1-amino-2-indanols as well as either enantiomer of the versatile chiral auxiliaries, (4*S*,5*R*)- and (4*R*,5*S*)-indano[1,2-*d*]oxazolidin-2-one¹¹ in high enantiomeric excess. It should be noted that Ogasawara and Takahashi have also reported recently¹² similar lipase-mediated resolution of *trans*-1-azidoindan-2-ol in high optical purity leading to a convenient route to enantiomerically pure *cis*-1-aminoindan-2-ol.

The racemic *trans*-1-azido-2-indanol (**5**) was conveniently prepared in multigram quantities starting from indene. Thus, epoxidation of indene with *m*-chloroperbenzoic acid (MCPBA) in a 1:1 mixture of dichloromethane and saturated aqueous sodium hydrogen carbonate solution at 0 to 23 °C for 12 hours afforded the epoxide **4**. The reaction of the resulting epoxide with 1.3 equivalents of sodium azide in the presence of ammonium chloride in a 4:1 mixture of ethanol and water at reflux for 24 hours furnished **5** in 55–78% yield (from **4**) after silica gel chromatography. The racemic azido alcohol **5** was then subjected to enzymatic acylation reaction under various reaction conditions. The optimum results were obtained when the azido alcohol **5** was exposed to immobilized amano lipase PS 30 (25 % by weight with respect to lipase PS30) on Celite in a 1; 1 mixture of dimethoxyethane and isopropenyl acetate at 23 °C for 24 hours to furnish the unacylated (1*S*,2*S*)-1-azido-2-indanol (**6**) (46 % yield) and acylated (1*R*,2*R*)-2-acetoxy-1-azido-indan (**7**) (44% yield) after separation by silica gel chromatography. The control experiment without the enzyme proved that the non-enzymatic reaction is extremely slow (only trace amount of acylated product after 48 h). The acetate **7** was readily hydrolyzed with potassium carbonate in methanol at 0°C for 1 hour to provide (1*R*,2*R*)-1-azido- indan-2-ol (**8**). Chiral HPLC analysis of the alcohols **6** and **8** (Daicel Chiracel OD column¹³) has established that the enzymatic process is very effective, providing high enantiomeric excess (>96% ee for **6** and **8**).¹⁴

The absolute configuration of the resolved azidoindanols **6** and **8** was assigned after their conversion to the corresponding *cis*-amino alcohols and comparison of their optical rotation with the literature values.⁵ Thus, the resolved *trans*-azido alcohols **6** and **8** were transformed into the corresponding enantiomeric di-amino alcohol as shown in the Scheme. Catalytic hydrogenation of **6** and **8** over 10 % Pd—C in ethyl acetate in the presence of diethyl pyrocarbonate (1.2 equivalents) afforded the ethyl carbamates **9** and **10** (68–76 % yield) respectively. As described by Didier and coworkers,⁶ treatment of **9** and **10** with excess of thionyl chloride at 23 °C for 12 hours provided (4*S*,5*R*)- and (4*R*,5*S*)-i ndano[1,2-*d*]oxa-zolidin-2-ones (**11** and **12**) after silica gel chromatography (86–96% yield). Basic hydrolysis of **11** and **12** with potassium hydroxide in a 1:1 mixture of ethanol and water at reflux for 16 hours furnished (1*S*,2*A*)-1-aminoindan-2- ol (**1**) and (1*R*,2*S*)-1-aminoindan-2-ol (**2**) in 85–87% yield after purification by silica gel chromatography.

In conclusion, the present enzymatic resolution route provides a convenient access to either enantiomer of the versatile ligand *cis*-1-aminoindan-2-ol in optically pure form. The overall process is concise and can be amenable to large scale synthesis.

Anhydrous solvents were obtained as follows: CH_2Cl_2 , distillation from P_4O_{10} ; THF, distillation from sodium/benzophenone; dimethoxyethane and pyridine, distillation from CaH_2 . Column chromatography was performed with Whatman 240–400 mesh silica gel under low pressure of 5–10 psi. TLC was carried out with E. Merck silica gel 60 F-254 plates. All melting points are uncorrected. ^1H NMR spectra were recorded on Bruker AC 200 and AM 400 MHz spectrometers. IR spectra were recorded on a ATI Mattson Genesis series FT-IR spectrometer. Mass spectra were recorded on a Finnigan Mat 90 mass spectrometer. Optical rotation was measured on a Perkin-Elmer 241 spectropolarimeter. Analytical HPLC analyses were performed on a Waters liquid chromatography system (m BondapakTM C-18 column, 4.6 mm x 25 cm, 50% EtOAc/hexanes as solvent, flow rate 2.0 mL/min, 1254 nm).

(+)-Epoxyindane (4):

To a stirred heterogeneous solution of freshly distilled indene (3.56 g, 30.6 mmol) in a mixture of CH_2Cl_2 (100 mL) and H_2O (100 mL) was added solid NaHCO_3 (10.3 g, 120.5 mmol) followed by MCPBA (10.6 g, 36.8 mmol, 60%, Aldrich). The resulting mixture was stirred at 23 °C for 12 h. After this period, 20% aq NaHSO_3 solution (100 mL) was added

and the mixture was stirred for 20 min and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×100 mL) and the combined organic extracts were washed successively with 5 % NaHCO_3 , H_2O and brine. The organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to provide a residue which was chromatographed over silica gel (5 % EtOAc/hexane) to provide the racemic epoxide (2.24 g, 55 %) as an oil.

^1H NMR (400 MHz, CDCl_3/TMS): δ = 7.5 (m, 1H), 7.25–7.4 (m, 3 H), 4.3 (d, 1 H, J = 2.7 Hz), 4.2 (t, J = 2.9 Hz, 1 H), 3.25 (d, 1H, J = 18 Hz), 3.0 (dd, 1 H, J = 2.9, 18 Hz).

(±)-*trans*-1-Azidoindan-2-ol (5):

To a stirred solution of racemic epoxide **4** (2.06 g, 15.6 mmol) in 80 % aq EtOH (50 mL) were added NaN_3 (1.32 g, 20.3 mmol) and NH_4Cl (1.08 g, 20.3 mmol) and the resulting mixture was stirred at reflux for 10 h. After this period, the mixture was poured into ice water (75 mL) and the resulting mixture was thoroughly extracted with (4×25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to provide a residue which was chromatographed over silica gel (5% EtOAc/ hexane) to provide the racemic **5** (2.14 g, 78%) as an oil.

^1H NMR (400 MHz, CDCl_3/TMS): δ = 7.2–7.4 (m, 4H), 4.7 (d, 1H, J = 5.0 Hz), 4.5 (m, 1 H), 3.3 (dd, 1H, J = 6.7, 16 Hz), 2.85 (dd, 1 H, J = 5.9, 16 Hz), 2.25 (br s, 1 H).

IR (neat): ν = 3350, 2102 cm^{-1} .

MS (CI): m/z = 176 (M^+ + H), 133.

Immobilized Amano Lipase PS 30:

Commercially available Celite 521 (4 g, Aldrich) was loaded on a Büchner funnel and washed successively with deionized H_2O (50 mL) and 0.05 N phosphate buffer (pH = 7.0, 50 mL; Fisher Scientific). The washed Celite was then added to a suspension of amano lipase 30 (1g) in 0.05 N phosphate buffer (20 mL). The resulting slurry was spread on a glass dish and allowed to dry in the air at 23 °C for 48 h (weight 5.4 g; water content about 2% by Fisher method).

Enzymatic Resolution of Racemic *trans*-1-Azidoindan-2-ol (5):

To a stirred solution of **5** (700 mg, 4 mmol) in isopropenyl acetate (5 mL) and DME (5 mL) was added immobilized amano lipase⁶ (880 mg, 25 % by weight of Lipase PS 30). The suspension was stirred at 23 °C for 24 h and the immobilized enzyme was filtered and the filter cake washed with EtOAc. Evaporation of the solvents under reduced pressure provided a residue which was chromatographed over silica gel (25 % EtOAc in hexane) to furnish 320 mg (46%) of **6** as an oil and 380 mg (44%) of **7** as an oil.

(1*S*,2*S*)-1-Azidoindan-2-ol (**6**): +64 (c = 18, CHCl_3). ^1H NMR (400MHz, CDCl_3/TMS): δ = 7.2–7.4 (m, 4H), 4.7 (d, 1 H, J = 5.0 Hz), 4.5 (m, 1 H), 3.3 (dd, 1 H, J = 6.7, 16 Hz), 2.85 (dd, 1 H, J = 5.9, 16 Hz), 2.25 (br s, 1 H).

IR (neat): $\nu = 3350, 2102 \text{ cm}^{-1}$.

MS (FAB): $m/z = 175 (\text{M}^+)$, $133 (\text{M}^+ - \text{N}_3)$.

HRMS: $m/z (\text{M}^+)$ calc, for $\text{C}_9\text{H}_9\text{N}_3\text{O}$, 175.07456, found 175.07619. (1*R*,2*R*)-2-Acetoxy-1-azidoindan (**7**): $\delta = 7.26\text{--}7.4$ (m, 4 H), 5.34 (m, 1H), 4.87 (d, 1 H, $J = 4.1 \text{ Hz}$), 3.49 (dd, 1 H, $J = 6.8, 16.6 \text{ Hz}$), 2.89 (dd, 1 H, $J = 4.7, 16.7 \text{ Hz}$), 2.1 (s, 3 H).

IR (neat): $\nu = 2100, 1745 \text{ cm}^{-1}$.

MS (FAB): $m/z = 175 (\text{M}^+ - \text{N}_3)$.

HRMS: $m/z (\text{M}^+ - \text{N}_3)$ calc, for $\text{C}_9\text{H}_9\text{O}_2$ 175.07590, found 175.07507.

(1*S*,2*S*)-1-Ethoxycarbonylaminoindan-2-ol (**9**):

To a stirred solution of **6** (310 mg, 1.97 mmol) and diethylpyrocar- bonate (354 mg, 2.18 mmol) in EtOAc (5 mL) was suspended 10 % Pd/C (30 mg) at 23 °C. The resulting mixture was hydrogenated under hydrogen-filled balloon for 12 h. The mixture was filtered through a pad of Celite and the Celite pad was washed with EtOAc (10 mL). Evaporation of the solvent provided a residue which was chromatographed over a short silica gel column (25 % EtOAc in hexane) to afford the title carbamate **9** (296 mg, 68 %) as white solid; mp 119–121 °C.

^1H NMR (400 MHz, CDCl_3/TMS): $\delta = 7.3\text{--}7.5$ (m, 4H), 5.2 (br,

1H), 4.9 (t, 1H, $J = 6.7 \text{ Hz}$), 4.44 (m, 1 H), 4.2 (q, 2 H, $J = 7.4 \text{ Hz}$),

3.4 (dd, 1 H, $J = 7.7, 15.8 \text{ Hz}$), 2.9 (dd, 1 H, $J = 8.2, 15.8 \text{ Hz}$), 1.30 (t, 3H, $J = 7.5 \text{ Hz}$).

IR (film): $\nu = 3600, 1704 \text{ cm}^{-1}$.

MS (CI): $m/z = 222 (\text{M}^+ + \text{H})$.

(1*R*,2*R*)-1-Ethoxycarbonylaminoindan-2-ol (**10**):

To a stirred solution of **7** (337 mg, 1.55 mmol) in MeOH (10 mL) at 23 °C was added solid K_2CO_3 (428 mg, 3.1 mmol). The resulting mixture was stirred for 1 h and the solvent was evaporated under reduced pressure and the residue was diluted with CHCl_3 (25 mL) and extracted thoroughly with CHCl_3 ($3 \times 10 \text{ mL}$). The combined organic extracts were dried Na_2SO_4 and evaporated under reduced pressure to provide **8** (255 mg, 94 %) which was used for the next reaction without further purification.

To a stirred solution of **8** (239 mg, 1.36 mmol) and diethyl pyro- carbonate (274 mg, 1.68 mmol) in EtOAc (5 mL) was suspended 10 % Pd/C (30 mg) at 23 °C. The resulting mixture was hydrogenated under hydrogen-filled balloon for 12 h. The mixture was then filtered through a pad of Celite and the Celite pad was washed with EtOAc (10 mL). Evaporation of the solvent provided a residue which was chromatographed over a short silica gel column

(25 % EtOAc in hexane) to afford the title urethane **10** (230 mg, 76 %) as a white solid, mp 118–120°C.

¹HNMR (400MHz, CDC1₃/TMS): δ = 7.3–7.5 (m, 4H), 5.2 (br, 1H), 4.9 (t, 1H, J = 6.7 Hz, 4.44 (m, 1 H), 4.2 (q, 2 H, J = 7.4 Hz),

3.4 (dd, 1 H, J = 7.7, 15.8 Hz), 2.9 (dd, 1 H, J = 8.2, 15.8 Hz), 1.30 (t, 3 H, J = 7.5 Hz).

IR (film): ν = 3600, 1704 cm⁻¹.

MS (CI): m/z = 222 (M⁺ +H).

(4*S*,5*R*)-Indano[1,2-*d*]oxazolidin-2-one (**11**):

Carbamate **9** (417 mg, 1.88 mmol) was dissolved in freshly distilled SOCl₂ (9 mL) and the resulting mixture was stirred at 23 °C for 12 h. After this period, the excess of SOCl₂ was removed by evaporation under reduced pressure and the residue was chromatographed over silica gel (50 % EtOAc in hexane) to furnish the title oxazolidinone **11** (283 mg, 86%) as a white solid; mp 205–207 °C; –78.8 (c = 1.5, CHCl₃).

¹HNMR (400MHz, CDC1₃/TMS): δ = 7.2–7.5 (m, 4H), 6.4 (br s, 1 H), 5.5 (m, 1 H), 5.2 (d, 1 H, J = 6.4 Hz), 3.35–3.5 (m, 2 H). IR (film): ν = 3090, 1695 cm⁻¹.

MS (CI): m/z = 176 (M⁺ +H).

Anal. (C₁₀H₉NO₂): Calc, for C, 68.56; H, 5.18; N, 8.00. Found: 68.23; H, 4.91; N, 8.36.

(4*R*,5*S*)-Indano(1,2-*d*]oxazolidin-2-one (**12**):

Following the procedure described above, carbamate **10** (231 mg, 1.04 mmol) was converted to oxazolidinone **12** (152 mg, 96%) as a white solid; mp 203–205 °C; +76.9 (c = 1.2, CHCl₃). IR, ¹HNMR, and mass spectra are same as **11**.

Anal. (C₁₀H₉NO₂): Calc, for C, 68.56; H, 5.18; N, 8.00. Found: 68.62; H, 4.97; N, 8.12.

(1*S*,2*R*)-I-Aminoindan-2-ol (**1**):

To a stirred solution of oxazolidinone **11** (244 mg, 1.39 mmol) in a mixture of EtOH and H₂O (10 mL) was added solid KOH (284 mg, 5 mmol). The resulting mixture was heated at reflux for 16 h. After this period, the solvents were evaporated under reduced pressure and the residue was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated under reduced pressure to provide a residue which was chromatographed over silica gel (5% MeOH in CHCl₃) to provide **1** (183 mg, 87%) as a light brown solid; mp 114–115°C (Lit.⁶ mp 115–116°C); [α]_D –64.7 (c = 2.1, CHCl₃) (Lit. –61.5, CHCl₃).

¹HNMR (CD₃OD): δ = 2.89 (dd, 1H, J = 2.9, 16.1 Hz), 3.06 (dd, 1H, J = 5.3, 16.1 Hz), 4.15 (d, 1 H, J = 4.87 Hz), 4.41 (m, 1 H), 7.20 (m, 3 H), 7.39 (m, 1H).

IR (film): $\nu = 3420, 1220 \text{ cm}^{-1}$.

MS (CI): $m/z = 150 (M^+ + H)$.

(1R,2S)-1-Aminoindan-2-ol (2):

Following the procedure described above, oxazolidinone **12** (294 mg, 1.68 mmol) was converted to the amino alcohol **2** (212.8 mg, 85%) as a white solid; mp 114–115°C (Lit.⁶ mp 115–116°C); +62 (c=1.8, CHCl₃) (Lit. +65.12, CHCl₃). IR, ¹HNMR, and mass spectra are same as **1**.

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