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Synthesis and asymmetric resolution of a dopaminergic compound: 2-amino-5-methoxyindane

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ABSTRACT

The racemic synthesis and subsequent resolution of 2-amino-5-methoxyindane enantiomers were achieved starting from 5-bromoindan-2-ol in six steps with 38% total yield. The first step involved the substitution of the Br atom by using NaOMe in the presence of CuI to afford 5-methoxyindan-2-ol. The OH group of 5-methoxyindan-2-ol was converted into its mesylate ester, which was converted into the corresponding azide by reaction with sodium azide. The Pd–C-catalyzed hydrogenation of the azide functional group in the presence of $CHCl_3$, followed by neutralization of the amine hydrochloride salt with NaOH, furnished the *rac*-2-amino-5-methoxyindane. Next, *rac*-2-amino-5-methoxyindane was converted into its diastereomeric amide derivatives by reaction with (*R*)-mandeloyl chloride. The diastereomeric amide mixture was separated by recrystallization to give the (*R*,*S*)- and (*R*,*R*)-diastereomers. The absolute configuration of the (*R*,*S*)-isomer was determined by X-ray crystallography. The hydrolysis of these diastereomers gave (*R*)- and (*S*)-2-amino-5-methoxyindane with high enantiopurity.

1. Introduction

Dopamine **1** is a hormone-like neurotransmitter that plays an important role in central nervous system-related disorders such as schizophrenia and Parkinson's disease.[1] Many 2-aminotetralin and 2-aminoindane derivatives have been reported to have dopamine-like actions.[2] Dopamine-like compounds 2-amino-1,2,3,4-tetrahydronaphthalene-6,7-diol **2** (6,7-ADTN),[3,4] 2-amino-1,2,3,4-tetrahydronaphthalene-5,6-diol **3** (5,6-ADTN),[5,6] and 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT) **4**[7] are potential agonists at dopamine receptors. The drug rotigotine **5**, commercially known as Neupro®, is used in the treatment of Parkinson's disease as a transdermal patch (Fig. 1).[8] Some compounds derived from the aminoindane **6** moiety have been reported to show analgesic[9] and dopaminergic activities,[10,11] as well as activities in treating and preventing psychiatric diseases.[12] To the best of our knowledge, there is only one report in the literature on the preparation of (*S*)-**6** via the transformation of 5-methoxy-1-indanone into the corresponding racemic α-amino alcohol followed by asymmetric resolution with (*R*)-mandelic acid and then hydrogenolysis.[11]

In light of the limited approach to enantiopure amino-indane skeletons, efficient and adaptable synthetic routes to such compounds are desirable. A convenient synthesis for amino-indane enantiomers should facilitate structure–activity studies. Herein we report an alternative synthesis and a new methodology for the asymmetric resolution of the title compound starting from a readily available starting material.

2. Results and discussion

The starting material *rac*-**7** was prepared by the procedure described in the literature.[13] The introduction of an OMe group into the aromatic ring was accomplished by substitution of the bromine atom at the phenyl ring with NaOMe in the presence of CuI in DMF–MeOH.[13–17] Mesylation of (±)-**8** with $MeSO_2Cl$ followed by substitution with NaN_3 gave azide (±)-**9**. The structure of azide **9** was elucidated based on its physical behavior. Elemental analysis confirmed the theoretical molecular formula of the compound, while the azide functional group was established by the IR spectral absorptions at 2098 cm^{-1}. The Pd–C-catalyzed hydrogenation of (±)-**9** in $CHCl_3$–MeOH gave (±)-**10** as a hydrochloride salt, and (±)-**10** was converted into free amine (±)-**6** by treatment with NaOH solution and then used in the next step without further purification or characterization. It is well known that (*R*)- or (*S*)-mandelic acid is an efficient chiral derivatizing agent, which enables the resolution of racemates into enantiomers, e.g., the resolution of racemic dopaminergic aminotetralins.[18] When we applied this methodology to (±)-**6**, we were not able to separate stereoisomers with high enantiopurity. Berlingozzi et al.[19] reported resolving DL-amino acids by N-acylation with enantiomerically

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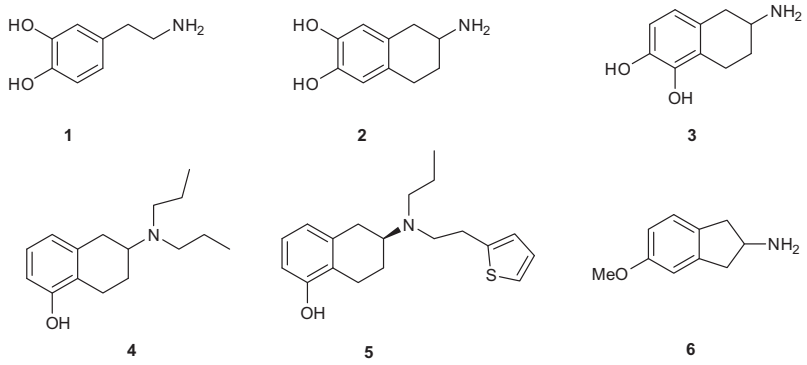


Figure 1. Some selected dopamine **1** and dopaminergic compounds **2**–**6**.

pure *O*-acetylmandeloyl chloride to give separable amides, which could be hydrolyzed by HCl to give enantiomerically pure amino acids. In a similar way, the asymmetric resolution of *myo*-inositol derivatives with *O*-acetylmandeloyl chloride via esterification was also reported by Sureshan et al.[20] Due to the important biological activities of 2-aminoindane and 2-aminotetralin derivatives, applying this methodology to the resolution of dopaminergic amine compounds would be useful for further synthetic and biological purposes. In this context, (*R*)-*O*-acetylmandeloyl chloride was first prepared according to the literature procedure.[19] The reaction of racemic (±)-**6** with (*R*)-*O*-acetylmandeloyl chloride in the presence of Et_3N afforded a diastereomeric amide mixture of **11a** and **11b**, which were easily separated by crystallization without racemization with high enantiopurity (diastereomeric ratios were 97.2:2.8% for **11a** and 96.2:3.8% for **11b** according to chiral HPLC). ^1H and ^{13}C NMR spectroscopic data of **11a** and **11b** clearly showed that those compounds were stereoisomers of each other. In particular, H-C(2), $H_2C(1)$, $H_2C(3)$, and CH-OAc gave very similar chemical shifts, coupling constants, and spin systems. Therefore, the assignment of the absolute configuration of one of these isomers, **11a**, was determined by X-ray crystallographic analysis. The results of this analysis confirmed that the absolute configuration of **11a** was (*R*,*S*), as shown in Figure 2. The comparison of ^1H and ^{13}C NMR spectroscopic data, chiral HPLC chromatograms, and specific rotations $\{[\alpha]_D^{25} = -38$ and $[\alpha]_D^{25} = -124\}$ of the two isomers **11a** and **11b** supported that the structure of stereoisomer **11b** had an (*R*,*R*)-configuration.

The most crucial step of our synthesis was the hydrolysis of amides (*R*,*S*)-**11a** and (*R*,*R*)-**11b** to give (*S*)-**6** and (*R*)-**6**. For the hydrolysis of the amides, HCl was the most suitable reagent among the hydrogen halide acids (HX; X = Cl, Br, I) because HBr and HI might lead to demethylation of ArOMe. For this reason, we used aqueous HCl to hydrolyze the amides under several conditions, but we failed to obtain pure amines. Furthermore, hydrolysis of the amides (*R*,*S*)-**11a** and (*R*,*R*)-**11b** in aqueous KOH in MeOH or EtOH, at ambient or reflux temperature also failed. Therefore, we decided to apply harsh reaction conditions such as heating in a sealed tube. In a sealed tube, heating the amides with KOH in a solution of EtOH–H_2O at 130 °C gave the corresponding amines (*S*)-**6** $\{[\alpha]_D^{25} = -7$ (*c* 1, $CHCl_3$)} and (*R*)-**6** $\{[\alpha]_D^{25} = +7$ (*c* 1, $CHCl_3$)}, without any racemization (Scheme 1).

3. Conclusion

In conclusion, the synthesis of (±)-2-amino-5-methoxyindane hydrochloride **10** has been achieved starting from 5-bromoindan-2-ol in four steps and with 58% overall yield. The asymmetric resolution of the racemic mixture of (±)-**6** with (*R*)-*O*-acetylmandeloyl chloride followed by basic hydrolysis afforded the corresponding amines (*S*)-**6** and (*R*)-**6** with high enantiopurity (>93%). Herein we have reported a convenient method for the asymmetric resolution of biologically active aminoindanes, which can be used for further synthetic purposes.

4. Experimental

4.1. General

All solvents (AR grade) and reagents were purchased from Sigma–Aldrich or Merck in the highest purity available. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed Merck Silica-Gel 60 F_{254} plates. Preparative TLC was performed using the Silica-Gel 60 $HF_{254+366}$ (Merck). IR spectra were recorded on a Mattson 1000 FT-IR spectrometer with KBr pellets. NMR spectra were recorded on either a Varian 400 (at 400 MHz for ^1H and 100 MHz for ^{13}C) or a Bruker 400 (at 400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer in $CDCl_3$ unless stated otherwise. All chemical shifts are reported in ppm and *J* values are given in Hz. Interchangeable hydrogens or carbons were assigned the same letter. Optical rotations were measured with a Bellingham + Stanley ADP220 spectropolarimeter (589 nm) at 25 °C. A polarimetric Chiralyser detector was used to assess the sign of the configuration of the diastereomer and enantiomer formed. Diastereomeric and enantiomeric excesses were determined by HPLC analysis on a Thermo Spectra Analysis HPLC System equipped with a UV detector using a chiral column (Chiralcel OD), *n*-hexane–*i*-PrOH (90:10) as the eluent, and a flow rate of 1 mL/min, with the detection performed at a wavelength of 220 nm. Diastereomeric and enantiomeric excess were determined directly from the areas under the curve. Compound **7** was synthesized according to the literature procedure.[13]

4.2. 5-Methoxyindan-2-ol 8

Sodium (2.30 g, 100.0 mmol) in small pieces was added to refluxing MeOH (80 mL) over 1 h under N_2. A solution of 5-bromoindan-2-ol **7** (5.00 g, 23.5 mmol) in freshly distilled DMF (30 mL) was added to this solution. While the reaction mixture was being heated at reflux, CuI (100 mg) was then added. The reaction mixture was heated for 20 h and then cooled to rt. After most of the solvent was removed under reduced pressure, H_2O (50 mL) and CH_2Cl_2 (100 mL) were added to the residue and the organic layer was separated. The organic layer was washed with H_2O (3 × 50 mL) and dried over Na_2SO_4. Evaporation of the solvent and chromatography of the residue on a short silica gel column (30 g) with hexane–EtOAc (9:1) gave 5-methoxyindan-2-ol **8** (3.10 g, 80%) as a white solid. Mp 75–77 °C. Lit.[21] mp 72–73 °C. ^1H NMR data of compound **8** are in agreement with data given in

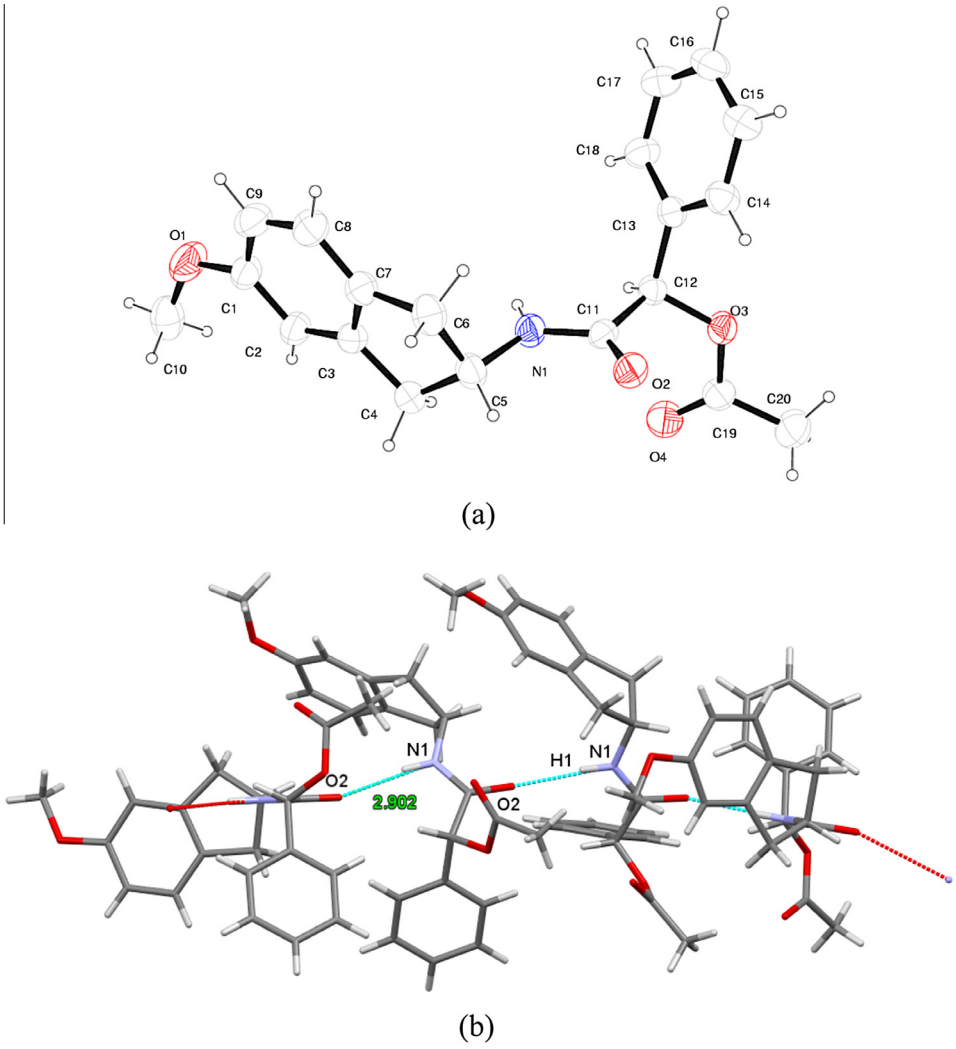


Figure 2. (a) ORTEP view of **11a** showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 40% probability level. The absolute configuration of the stereogenic centers in **11a** is (*R,S*). (b) 1D polymeric *H*-bonding pattern (dashed lines) along the *c*-axis in the unit cell. N1—H···O2^{a} = 2.902(7) Å, <(N1—H···O2^{a}) = 170° [Symmetry code (*a*) $y-1$, $-x+y$, $z-1/6$].

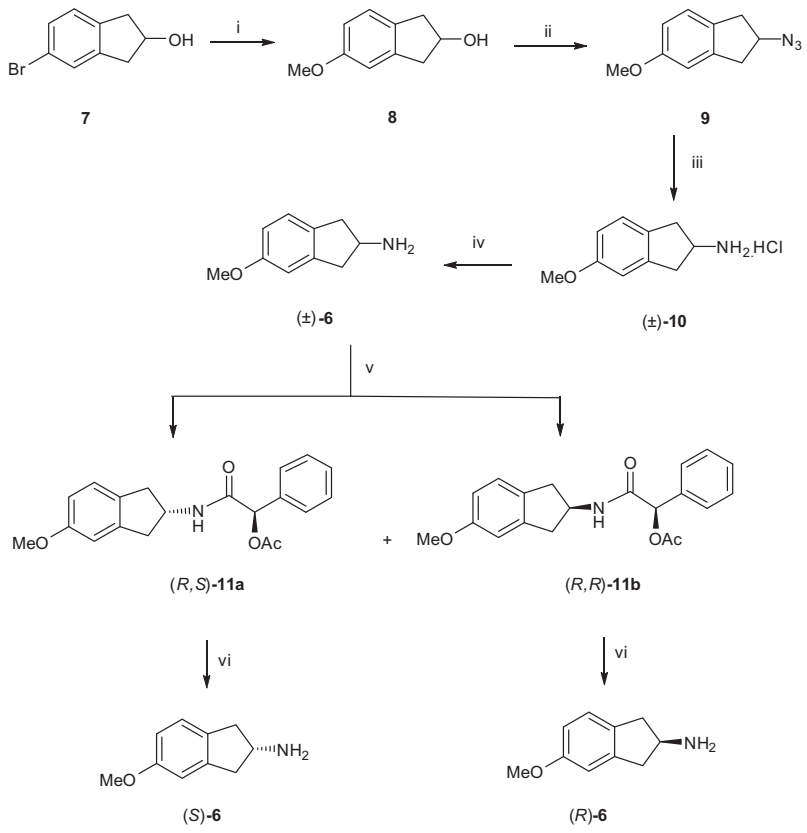
the literature.[22] ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2 (C), 142.6 (C), 133.0 (C), 125.7 (CH), 112.8 (CH), 110.7 (CH), 73.8 (C2), 55.6 (OMe), 43.0 (CH_2), 42.0 (CH_2).

4.3. 2-Azido-5-methoxyindane 9

To a stirred solution of 5-methoxyindan-2-ol **8** (1.00 g, 6.09 mmol) and NEt_3 (0.93 g, 9.20 mmol) in CH_2Cl_2 (30 mL) was added a solution of $MeSO_2Cl$ (1.76 g, 15.34 mmol) in CH_2Cl_2 dropwise at 0 °C over 15 min. The mixture was stirred at rt for 3.5 h. After filtration of the reaction mixture and removal of the solvent of the filtrate, freshly distilled DMF (20 mL) and NaN_3 (1.20 g, 18.4 mmol) were added to the mixture. The reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was cooled to rt after which H_2O (30 mL) and CH_2Cl_2 (100 mL) were added. The organic layer was separated and washed with H_2O (3 × 50 mL). The organic layer was dried over Na_2SO_4 and CH_2Cl_2 was evaporated. Chromatography of the crude product on a short silica gel column (20 g), eluting with hexane–EtOAc (9:1), gave 2-azido-5-methoxyindane (**9**) (0.93 g, 80%). Yellow oil. IR (CH_2Cl_2, cm^{-1}): 3001, 2942, 2835, 2098, 1611, 1587, 1492, 1465, 1434, 1321, 1305, 1259, 1195, 1144, 1097, 1032, 1004, 928. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, 1H, H-7, $J_{6,7}$ = 8.3 Hz), 6.80 (br s, 1H, H-4), 6.75 (dd, 1H, H-6, $J_{6,7}$ = 8.3, $J_{4,6}$ = 2.4 Hz), 4.34 (m, 1H, H-2), 3.79 (s, 3H, OMe), 3.21 (A part of AB, dd, 1H, ^2J = 12.1, ^3J = 6.6 Hz), 3.17 (A part of AB, dd, 1H, ^2J = 12.1, ^3J = 6.6 Hz), 2.98 (B part of AB, dd, 1H, ^2J = 12.1, ^3J = 4.4 Hz), 2.94 (B part of AB, dd, 1H, ^2J = 12.1, ^3J = 4.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2 (C), 141.8 (C), 132.3 (C), 125.4 (CH), 113.2 (CH), 110.4 (CH), 62.4 (CH), 55.6 (OMe), 39.5 (CH_2), 38.4 (CH_2). Anal. calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21; found: C, 63.48; H, 5.88; N, 22.22.

4.4. (±)-2-Amino-5-methoxyindane hydrochloride 10

Into a 100-mL flask were placed Pd–C (50 mg) and 2-azido-5-methoxyindane **9** (0.90 g, 4.80 mmol) in MeOH (35 mL) and $CHCl_3$ (2 mL). A balloon filled with H_2 gas (3 L) was fitted to the flask. The mixture was deoxygenated by flushing with H_2 and then hydrogenated at rt for 24 h. The catalyst was removed by filtration. Recrystallization of the residue from MeOH–Et_2O gave (±)-2-amino-5-methoxyindane hydrochloride **10** (0.90 g 95%). Light yellow crystal. Mp 234–236 °C. Lit.[9] mp 231–234 °C. ^{1}H NMR (400 MHz, D_2O): δ 7.13 (d, 1H, H-7, $J_{6,7}$ = 8.3 Hz), 6.83 (br s, 1H, H-4), 6.75 (d, 1H, H-6, $J_{6,7}$ = 8.3 Hz), 4.64 (br s, NH_3 + H_2O), 4.04 (m, 1H, H-2), 3.68 (s, 3H, OMe), 3.25 (A part of AB, dd, 1H,



Scheme 1. Synthesis and resolution of (±)-**6**. (i) NaOMe, CuI (cat.), MeOH–DMF, 100 °C, 20 h, 80%; (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0–25 °C, 3.5 h, then NaN_3, DMF, 90 °C, 80%; (iii) H_2, Pd–C (cat.), MeOH–$CHCl_3$, 24 h, 25 °C, 95%; (iv) 10% NaOH, MeOH, 0–25 °C; 3 h, 95%; (v) (*S*)-*O*-acetyl-mandeloyl chloride, Et_3N, CH_2Cl_2, 0–25 °C, 3 h, 82%; (vi) KOH (10 mol equiv), EtOH–H_2O (sealed tube), 130 °C, 80%.

^2J = 17.6, ^3J = 6.6 Hz), 3.21 (A part of AB, dd, 1H, ^2J = 17.6, ^3J = 7.0 Hz), 2.88 (B part of AB, dd, 1H, ^2J = 17.6, ^3J = 3.3 Hz), 2.84 (B part of AB, dd, 1H, ^2J = 17.6, ^3J = 3.3 Hz). ^{13}C NMR (100 MHz, D_2O): δ 158.8 (C), 141.2 (C), 132.0 (C), 126.0 (CH), 113.8 (CH), 110.7 (CH), 55.9 (OMe), 52.2 (CH), 37.6 (CH_2), 36.7 (CH_2). Anal. calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; N, 7.01; found: C, 60.16; H, 7.10; N, 7.04.

4.5. (±)-2-Amino-5-methoxyindane 6

Amine hydrochloride **10** (1.00 g. 5.0 mmol) was dissolved in MeOH (50 mL) and cooled to 0 °C. To this solution, a solution of 10% aqueous NaOH (10 mL) was added. The reaction mixture was stirred at rt for 3 h. After evaporation of MeOH, 50 mL of H_2O were added and the organic layer was extracted with EtOAc (3 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporation of the solvent gave (±)-2-amino-5-methoxyindane **6** (0.78 g, 95%). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, 1H, H-7, $J_{6,7}$ = 8.2 Hz), 6.75 (s, 1H, H-4), 6.69 (dd, 1H, H-6, $J_{6,7}$ = 8.2, $J_{4,6}$ = 2.6 Hz), 3.82–3.78 (m, H, CHN), 3.76 (s, 3H, OMe), 3.14 (A part of AB, dd, 1H, ^2J = 14.7, ^3J = 6.6 Hz), 3.11 (A part of AB, dd, 1H, ^2J = 14.7, ^3J = 6.6 Hz), 2.81 (br s, 2H, NH_2), 2.80 (m, 1H, H-2), 2.68 (B part of AB, dd, 1H, ^2J = 14.7, ^3J = 5.1 Hz), 2.64 (B part of AB, dd, 1H, ^2J = 14.7, ^3J = 4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1 (C), 143.1 (C), 133.6 (C), 125.5 (CH), 112.7 (CH), 110.6 (CH), 55.6 (OMe), 53.6 (CH), 43.0 (CH_2), 41.9 (CH_2).

4.6. The synthesis of diastereomeric amide mixture of (*R,S*)-11a and (*R,R*)-11b

To a stirred solution of 2-amino-5-methoxyindane **6** (1.00 g, 6.13 mmol) and Et_3N (0.62 g, 6.13 mmol) in CH_2Cl_2 (30 mL) was added a solution of *O*-acetylmandeloyl chloride (1.30 g, 6.13 mmol) in CH_2Cl_2 dropwise at 0 °C over 15 min. The mixture was stirred at rt for 3 h. After the filtration of the reaction mixture and evaporation of the solvent, the residue was filtered on a short silica gel column (30 g) eluting with hexane–EtOAc (7:3) to give (*R,S*)-**11a** and (*R,R*)-**11b** (1.70 g, 82%). The diastereomeric mixture of (*R,S*)-**11a** and (*R,R*)-**11b** was separated by crystallization with EtOAc–hexane (9:1).

4.6.1. (*R*)-2-(((*S*)-5-Methoxy-2,3-dihydro-1*H*-indan-2-yl)amino)-2-oxo-1-phenylethyl acetate (*R,S*)-11a

Colorless crystals. Mp 125–127 °C. $[\alpha]_D^{25} = -38$ (*c* 1, $CHCl_3$) de: 92.4%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.33 (m, 5H, Ph-H), 7.10 (d, 1H, H-7, $J_{6,7}$ = 8.1 Hz), 6.76 (s, 1H, H-4), 6.73 (d, 1H, H-6, $J_{6,7}$ = 8.1 Hz) 6.53 (br s, 1H, NH), 6.00 (s, 1H, CHOAc), 4.74–4.69 (m, 1H, H-2), 3.77 (s, 3H, OMe), 3.29 (m, 2H, H-1 and H-3), 2.78 (dd, 1H, H-1^1 or H-3^1, J = 5.1 Hz, ^2J = 16.4 Hz), 2.67 (dd, 1H, H-1^1 or H-3^1, J = 4.7 Hz, ^2J = 16.4 Hz), 2.14 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (acetate CO), 168.3 (CONH), 159.3 (C), 142.4 (C), 135.7 (C), 132.7 (C(Ph)), 129.2 (C7), 129.0 (2CH (Ph)), 127.6 (2CH (Ph)), 125.5 (CH (Ph)), 113.0 (CH), 110.4 (CH), 75.8 (CHOAc), 55.6 (OMe), 51.1 (CNH), 40.5 (CH_2), 39.3 (CH_2), 21.2 (CH_3). Anal. calcd for $C_{20}H_{21}NO_4$: C, 71.37; H, 6.56; N, 3.96; found: C, 71.39; H, 6.58; N, 3.94.

4.6.2. (*R*)-2-(((*R*)-5-Methoxy-2,3-dihydro-1*H*-indan-2-yl) amino)-2-oxo-1-phenylethyl acetate (*R,R*)-11b

Colorless crystals mp: 117–119 °C. $[\alpha]_D^{25} = -124$ (*c* 1, $CHCl_3$) de: 94.4%. IR (CH_2Cl_2, cm^{-1}): 3297, 3059, 2943, 2840, 1742, 1660, 1608, 1539, 1460, 1452, 1372, 1326, 1232, 1145, 1097, 1031. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.34 (m, 5H, Ph-H), 7.10 (d, 1H, H-7 $J_{6,7}$ = 8.1 Hz), 6.76 (s, 1H, H-4), 6.74 (d, 1H, H-6, $J_{6,7}$ = 8.1 Hz),

6.34 (d, 1H, NH, J = 7.7 Hz), 6.00 (s, 1H, CHOAc), 4.77–4.73 (m, 1H, H-2), 3.78 (s, 3H, OMe), 3.31–3.22 (m, 2H, H-1 and H-3), 2.75–2.70 (m, 2H, H-1[1] and H-3[1]), 2.12 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5 (acetate CO), 168.2 (CONH), 159.3 (C), 142.3 (C), 135.7 (C), 132.7 (C(Ph)), 129.2 (CH), 129.0 (2CH (Ph)), 127.6 (2CH (Ph)), 125.6 (CH (Ph)), 113.0 (CH), 110.4 (CH), 75.7 (CHOAc), 55.7 (OMe), 51.1 (CNH), 40.5 (CH_2), 39.4 (CH_2), 21.3 (CH_3). Anal. calcd for $C_{20}H_{21}NO_4$: C, 71.37; H, 6.56; N, 3.96; found: C, 71.38; H, 6.59; N, 3.95.

4.7. Hydrolysis of diastereomeric amides (*R*,*S*)-11a and (*R*,*R*)-11b

A solution of (*R*)-2-(((*S*)-5-methoxy-2,3-dihydro-1*H*-inden-2-yl)amino)-2-oxo-1-phenylethyl acetate (0.2 g, 0.6 mmol) (*R*,*S*)-**11** in EtOH (20 mL) was added to a solution of 30% KOH (aq) (10 mL) in a sealed tube The mixture was stirred at 130 °C for 5 days. After the evaporation of EtOH, 20 mL of H_2O were added to the residue and the organic layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried (Na_2SO_4) and evaporation of the solvent gave (*S*)-5-methoxy-2,3-dihydro-1*H*-inden-2-amine (*S*)-**6** (0.077 g, 80%). Yellow oil.

4.7.1. (*S*)-5-Methoxy-2,3-dihydro-1*H*-inden-2-amine (*S*)-6

Colorless oil. $[\alpha]_D^{25} = -7$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, 1H, H-7, $J_{6,7}$ = 8.1 Hz), 6.76 (s, 1H, H-4), 6.70 (dd, 1H, H-6, $J_{6,7}$ = 8.1, $J_{4,6}$ = 2.2 Hz), 3.83–3.77 (m, 1H, $CHNH_2$), 3.76 (s, 3H, OMe), 3.14 (A part of AB, dd, 1H, ^2J = 14.7, ^3J = 6.6 Hz), 3.10 (A part of AB, dd, 1H, ^2J = 14.7, ^3J = 6.6 Hz), 2.65 (B part of AB, dd, 1H, ^2J = 14.7, ^3J = 5.1 Hz), 2.61 (B part of AB, dd, 1H, ^2J = 14.7, ^3J = 4.8 Hz), 1.8 (br s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0 (C), 143.5 (C), 133.9 (C), 125.5 (CH), 112.5 (CH), 110.6 (CH), 55.6 (OMe), 53.8 (CH), 43.6 (CH_2), 42.5 (CH_2).

4.7.2. (*R*)-5-Methoxy-2,3-dihydro-1*H*-inden-2-amine (*R*)-6

Colorless oil. $[\alpha]_D^{25} = +7$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, 1H, H-7, $J_{6,7}$ = 8.1 Hz), 6.77 (s, 1H, H-4), 6.70 (dd, 1H, H-6, $J_{6,7}$ = 8.1, $J_{4,6}$ = 2.2 Hz), 3.84–3.79 (m, 1H, $CHNH_2$), 3.77 (s, 3H, OMe), 3.15 (A part of AB, dd, 1H, ^2J = 14.7, ^3J = 6.6 Hz), 3.10 (A part of AB, dd, 1H, ^2J = 14.7, ^3J = 6.6 Hz), 2.65 (B part of AB, dd, 1H, ^2J = 14.7, ^3J = 5.1 Hz), 2.61 (B part of AB, dd, 1H, ^2J = 14.7, ^3J = 4.8 Hz), 1.45 (br s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0 (C), 143.5 (C), 134.0 (C), 125.5 (CH), 112.5 (CH), 110.6 (CH), 55.6 (OMe), 53.8 (CH), 43.7 (CH_2), 42.6 (CH_2).

4.8. Crystallography

For the crystal structure determination, a single crystal of compound **11a** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and oscillation scan technique with $\Delta w = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects, and cell refinement were performed using CrystalClear (Rigaku/MSC Inc. 2005) software.[23] The structures were solved by direct methods using the program SHELXS-97[24] and refined by a full-matrix least-squares procedure using SHELXL-97.[24] H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for **11a**: $C_{20}H_{21}NO_4$, crystal system, space group: hexagonal, $P6_1$; (no: 169); unit cell dimensions: a = 10.4608(2), b = 10.4608(2), c = 28.6779(4) Å, α = 90, β = 90, γ = 120; volume: 2717.74(13) Å^3; Z = 6; calculated density: 1.244 g/cm^3; absorption coefficient: 0.087 mm^{-1}; F(000): 1080; θ-range for data collection 2.3–26.4°; refinement method: full-matrix least-square on F^2; data/parameters: 2696/227; goodness-of-fit on F^2: 0.971; final R-indices [$I > 2\sigma(I)$]: R_1 = 0.080, wR_2 = 0.189; largest diff. peak and hole: 0.353 and −0.281 e Å^{-3}. CCDC-1008037 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.04.005.

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