Tetrahedron: *Asymmetry* 20 (2009) 220–224

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereoselective synthesis of (+)-isoindolo-β-carboline

Prasad B. Wakchaure [a], Vedavati G. Puranik [b], Narshinha P. Argade [a,*]

[a] *Division of Organic Chemistry, National Chemical Laboratory, Pune 411 008, India*
[b] *Centre for Material Characterization, National Chemical Laboratory, Pune 411 008, India*

ARTICLE INFO

Article history:
Received 25 November 2008
Accepted 9 January 2009
Available online 31 January 2009

ABSTRACT

Starting from homophthalic anhydride and (*S*)-tryptophan, the stereoselective synthesis of (+)-isoindolo-β-carboline has been described via the corresponding homophthalimide, its chemoselective oxidative ring contraction, and the intramolecular dehydrative ring closure followed by a geometry-specific demethoxycarbonylation.

1. Introduction

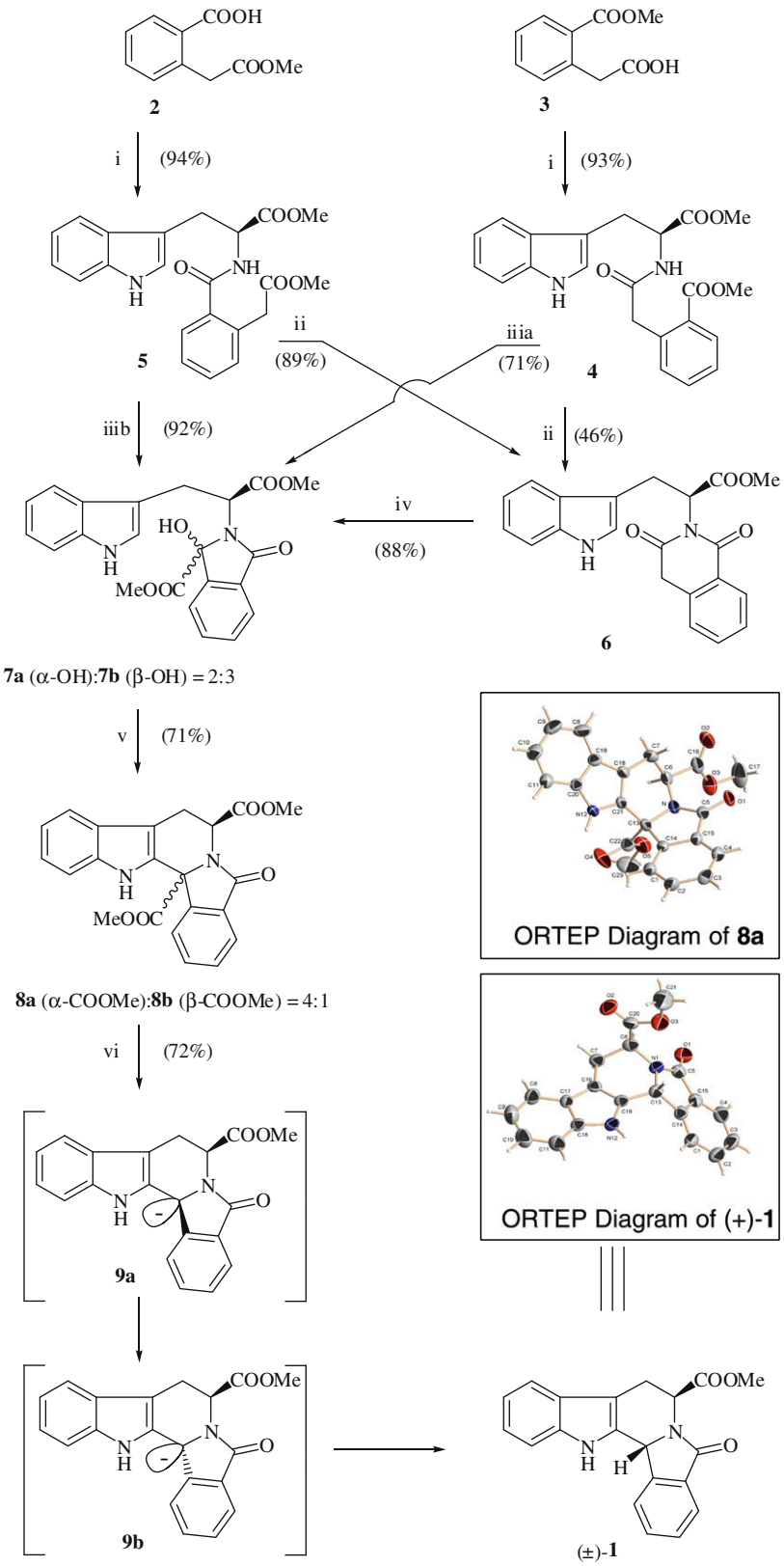
The β-carboline nucleus is present in very important bioactive natural products, such as reserpine, yohimbine, rutacarpine, and ajmalicine.[1] Both natural and unnatural β-carboline compounds, as well as their analogues and congeners, are of high synthetic interest as important hypotensive agents.[1,2] An important target is the isoindolo-β-carboline system, for which several racemic syntheses, starting from 3-hydroxyphthalide or phthalimide derivatives, and one stereoselective approach affording a 20% diastereomeric excess, are known in the literature.[3,4] Recently, a stereoselective approach to isoindolo-β-carbolines has been reported, which takes advantage of a palladium-catalyzed carbonylation process, but with an observed partial racemization.[5] The above-mentioned studies revealed that starting from the (*S*)-tryptophan and pre-reduced 3-hydroxyphthalide, the stereoselectivity obtained during the course of intramolecular cyclization was weak.[4] On the other hand, in the case of requisite phthalimide as a starting material, the chemoselective reduction of an imide carbonyl group in the presence of a methoxycarbonyl unit without any racemization at the sensitive stereogenic center would be a difficult task. During our extensive studies on cyclic anhydrides and their use in the construction of structurally interesting and biologically important natural/unnatural products,[6] we have recently witnessed a facile air-oxidation of the active methylene group in homophthalimide to the corresponding carbonyl group; this strategy was successfully used for the synthesis of the natural product nuevamine.[7] Hence, we envisaged homophthalic anhydride and (*S*)-tryptophan as suitable building blocks for the synthesis of enantiomerically and diastereomerically pure isoindolo-β-carbolines. Herein, we report another application of such a propensity of homophthalimides to undergo air-oxidation to complete the stereoselective synthesis of isoindolo-β-carboline (Scheme 1).

2. Results and discussion

We started the synthesis of (+)-1 from the isomeric acids **2**/**3** and (*S*)-tryptophan via the requisite precursor, imide **6**. Homophthalic anhydride upon treatment with methanol in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) underwent a highly regioselective methanolysis at the more reactive unconjugated carbonyl group and furnished the mono-ester **2** in quantitative yield.[8a] On the other hand, the reaction of homophthalic acid with one equivalent of diazomethane in diethyl ether furnished the opposite mono-ester **3**[8b] in 95% yield via the reaction of the more acidic aromatic carboxylic group. The *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI) induced dehydrative coupling reactions of isomeric acids **2** and **3** with (*S*)-tryptophan furnished the corresponding homophthalamic esters **5** and **4**, respectively, in high yields. Both **5** and **4** upon treatment with triethylamine furnished the corresponding imide **6**. As anticipated, the intramolecular cyclization of **5**, involving the non-conjugated ester unit, to form **6** was faster and more efficient (89% yield) than the cyclization of **4** to **6** involving an aromatic ester unit (46% yield). Treatment of any of the three precursors **4**/**5**/**6** with triethylamine in methanol furnished directly a mixture of diastereomeric lactamols **7a**/**b**, not separable by silica-gel column chromatography, in a 2:3 ratio (by ^{1}H NMR) with 71%/92%/88% yields, respectively. In the case of **4**/**5**, the entire transformation occurs in one-pot. The sequence consists of an initial conversion of **4**/**5** to the imide **6**, followed by a facile in situ chemoselective air-oxidation of the methylene group in homophthalimide **6** to the corresponding reactive trione intermediate. This subsequently undergoes regioselective methanolysis at the unconjugated imide carbonyl group and then an intramolecular ring closure to yield the oxidative ring-contracted product. Herein, the possibility of attack of methanol on the more reactive newly generated benzylic carbonyl group followed by an in situ facile intramolecular 1,2-shift of the methoxy group to form the corresponding un-isolable keto-ester intermediate leading to the intramolecular cyclization

* Corresponding author. Tel.: +91 20 25902333; fax: +91 20 25902629.
E-mail address: np.argade@ncl.res.in (N.P. Argade).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.01.001



Scheme 1. Reagents, conditions, and yields: (i) **2**/**3**, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), (*S*)-tryptophan methyl ester hydrochloride, DMAP, DCM, NEt_3, rt, 6 h (94/93%); (ii) **4**/**5**, NEt_3, MeOH, rt, 24/4 h (46/89%); (iii) (a) NEt_3, MeOH, rt, 48 h, (71%), (b) NEt_3, MeOH, oxygen atmosphere, rt, 18 h, (92%); (iv) NEt_3, MeOH, rt, 12 h, (88%); (v) AcOH, cat. H^+/H_2SO_4, rt, 6 h (**8a**: 57%, ~100% ee, **8b**: 14%); (vi) **8a**, NaCl, DMSO, H_2O, AcOH, 210 °C, 2 h (72%, 98% ee).

with the net formation of lactamols **7a**/**b** also exists. We could also enhance the rates of these air-oxidation reactions by carrying them out under an oxygen atmosphere. The ^1H NMR spectrum of the mixture of **7a**/**b** (2:3) revealed that in **7b**, the signal for the methyl ester of the tryptophan subunit was shielded due to the intramolecular influence of the free β-hydroxyl group, present on the same

face, on an ester moiety. Initially, we were unhappy with the 20% diastereomeric excess obtained in the formation of **7a**/**b**; however, in the next transformation of **7a**/**b** to **8a**/**b**, it was possible to gain some diastereoselectivity. The above mixture of **7a/b** on treatment with trifluoroacetic acid at room temperature furnished **8a** exclusively, but with only 21% yield. When a catalytic amount of sulfuric acid in acetic acid was used to carry out the same reaction, a separable mixture of intramolecular dehydrative cyclization products **8a**/**b** was obtained in a 4:1 ratio (by ^{1}H NMR), but with an improved yield of 71%. We presume that the present acid-catalyzed cyclization takes place via an S_N1 mechanism, and in the conversion of **7a**/**b** (20% de) to **8a**/**b** (60% de), the cyclization of a transient *N*-acyliminium ion[9] takes place with the predominant formation of the *trans*-isomer **8a**. In the event of an S_N2 mechanism being in operation, we feel that a dynamic kinetic resolution of the substrate **7a** could be occurring via the partial racemization of **7b** through the ring-chain tautomerism. Unfortunately, all our attempts to further improve the diastereomeric excess met with failure, as the rate of cyclization was plausibly faster than the rate of formation of *N*-acyliminium ion/racemization of **7b**. We separated the diastereomeric mixture of **8a** and **8b** by silica-gel column chromatography and further confirmed the structure as well as the enantiomeric purity of the major isomer **8a** from X-ray crystallographic data and chiral HPLC (~100% ee), respectively. In the ^{1}H NMR spectrum of **8a**, we noticed a considerable geometry-dependent shielding of the α-methine proton. In **8a**/**b**, the angular carbomethoxy group is attached to the carbon, which is both allylic and benzylic with an adjacent tertiary amide nitrogen atom. Hence, we systematically studied the demethoxycarbonylation of both **8a** and **8b** under the Krapcho and Lovey conditions, suitable for geminal diesters, β-ketoesters, and α-cyano esters.[10] The reaction of the major isomer **8a** with sodium chloride in moist dimethyl sulfoxide at 210 °C furnished ~100% diastereomerically pure **1** in 72% yield. Plausibly, this proceeds via the regioselective decarbomethoxylation of the angular α-ester moiety, followed by inversion of the formed α-carbanion **9a** to the β-carbanion **9b** and subsequent abstraction of a proton from the same β-face. At this stage, we felt that the possible escaping of methyl chloroformate/hydrochloric acid formed during the course of the reaction at 210 °C can result in in situ formation of sodium hydroxide, causing the excessive racemization of the asymmetric center present in the tryptophan subunit. The synthesis of (±)-**1** and the comparison of chiral HPLC data of the racemic mixture with (+)-**1** revealed that our concern about the racemization of (+)-**1** was indeed correct and it was obtained with only 66% ee. We reasoned that, it should be possible to stop such a racemization of (+)-**1** by carrying out the decarbomethoxylation in the presence of acetic acid, which would then generate only the weak base sodium acetate in situ. Thus, we repeated the decarbomethoxylation of (−)-**8a** in the presence of acetic acid and obtained (+)-**1** with a similar yield of 72%, but this time with 98% ee (by chiral HPLC). Thus, starting from homophthalic anhydride, enantiomerically pure (+)-isoindolo-β-carboline **1** was obtained in five steps with 35% overall yield. The analytical and spectroscopic data obtained for (+)-**1** were in complete agreement with the reported data;[5] the structure of (+)-**1** was also confirmed from the X-ray crystallographic data. Pure **8b** or **8b** in the mixture of **8a**/**b** (4:1) on treatment with sodium chloride in moist dimethyl sulfoxide at 210 °C remained completely unreacted, and we were unable to force the decarbomethoxylation of the angular ester moiety in **8b**. On the basis of a manually prepared flexible molecular model, we feel that in the case of compound **8b**, the negatively charged chloride ion is unable to access the carbonyl group of the angular ester moiety because of the internal steric crowding and also repulsive π-cloud interactions reasons. Further, decarbomethoxylation of the second carbomethoxy group on compounds of the type (+)-**1**, without any racemization at the asymmetric angular position, is already known in the literature.[11]

3. Conclusion

In summary, we have demonstrated the first stereoselective approach to enantiomerically pure (+)-isoindolo-β-carboline by taking advantage of a facile chemoselective air-oxidation of homophthalimide and gain in the diastereoselectivity during the intramolecular dehydrative cyclization process. We feel that the highly stereoselective geometry-dependent demethoxycarbonylation in the present approach is also noteworthy.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-*d* using TMS as an internal standard on 200 and 400 MHz spectrometers. ^{13}C NMR spectra were recorded on 200, 400, and 500 NMR spectrometers (50, 100, and 125 MHz, respectively). IR spectra were recorded on a FT-IR spectrometer. Column chromatographic separations were done on silica gel (60–120, 230–300 mesh). Commercially available homophthalic anhydride, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), and (*S*)-tryptophan were used.

4.2. (*S*)-Methyl 2-(2-(3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-ylamino)-2-oxoethyl)benzoate 4

To a stirred slurry of acid **3** (300 mg, 1.54 mmol) in DCM (20 mL) were added *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI, 590 mg, 3.09 mmol), (*S*)-tryptophan methyl ester hydrochloride (391 mg, 1.54 mmol), and cat. DMAP under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C, and NEt_3 (0.20 mL, 1.54 mmol) was added slowly, and the reaction mixture was stirred at room temperature for further 6 h. DCM was removed in vacuo, and to the reaction mixture was added water (30 mL), and then it was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with 1 M HCl, brine, and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica-gel column chromatographic purification of the residue obtained using petroleum ether–ethyl acetate (2:3) as an eluent gave compound **4** as a thick oil (566 mg, 93%). $[\alpha]_D^{20} = +29.6$ (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3477, 3422, 1740, 1717, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.24 (d, J = 4 Hz, 2H), 3.62 (s, 3H), 3.74 (s, 3H), 3.82 (d, J = 16 Hz, 1H), 3.92 (d, J = 16 Hz, 1H), 4.83–4.91 (m, 1H), 6.77 (d, J = 4 Hz, 1H), 6.84 (br d, J = 8 Hz, 1H), 7.05 (t, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 7.28–7.38 (m, 3H), 7.42–7.48 (m, 2H), 7.91 (d, J = 8 Hz, 1H), 8.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3, 41.8, 51.9, 52.0, 52.9, 109.1, 111.2, 118.1, 119.1, 121.5, 122.9, 127.1, 127.2, 129.0, 130.8, 131.9, 132.4, 136.0, 136.2, 167.7, 170.7, 172.2. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.09; H, 5.53; N, 7.22.

4.3. (*S*)-Methyl 3-(1*H*-indol-3-yl)-2-(2-(2-methoxy-2-oxoethyl)benzamido)propanoate 5

To a stirred slurry of acid **2** (1.50 g, 7.73 mmol) in DCM (50 mL) were added *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI, 2.95 g, 15.46 mmol), (*S*)-tryptophan methyl ester hydrochloride (1.96 g, 7.73 mmol), and cat. DMAP under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C, and NEt_3 (1.10 mL, 7.78 mmol) was added slowly, and the reaction

mixture was stirred at room temperature for further 6 h. DCM was removed in vacuo, and to the reaction mixture was added water (50 mL), and then it was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with 1 M HCl, brine, and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica-gel column chromatographic purification of the residue obtained using petroleum ether–ethyl acetate (2:3) as an eluent provided compound **5** as a thick oil (2.86 g, 94%). $[\alpha]_D^{20} = +41.1$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3477, 3422, 1736, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.33–3.45 (m, 2H), 3.59 (s, 3H), 3.72 (s, 3H), 3.81 (d, *J* = 16 Hz, 1H), 3.88 (d, *J* = 16 Hz, 1H), 5.07–5.14 (m, 1H), 7.02 (br d, *J* = 8 Hz, 1H), 7.07 (br s, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.17 (t, *J* = 8 Hz, 1H), 7.20–7.28 (m, 2H), 7.31–7.42 (m, 3H), 7.56 (d, *J* = 8 Hz, 1H), 8.19 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 38.6, 52.0, 52.3, 53.2, 109.5, 111.3, 118.3, 119.3, 121.9, 123.1, 127.3, 127.4, 127.8, 130.4, 131.2, 132.4, 135.7, 136.1, 168.9, 172.4, 172.7. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.11; H, 5.54; N, 7.17.

4.4. (*S*)-Methyl 2-(1,3-dioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-3-(1*H*-indol-3-yl)propanoate 6

Method A: To a stirred solution of compound **5** (300 mg, 0.76 mmol) in methanol (20 mL) at room temperature was added NEt_3 (two drops), and the reaction mixture was stirred for further 4 h under argon atmosphere. The reaction mixture was concentrated in vacuo, and the obtained residue was purified by silica-gel column chromatography using petroleum ether–ethyl acetate (3:2) as an eluent to obtain compound **6** as a thick oil (245 mg, 89%). $[\alpha]_D^{20} = -131.0$ (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3477, 1744, 1720, 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.53–3.79 (m, 3H), 3.74 (s, 3H), 3.85 (d, *J* = 24 Hz, 1H), 5.87 (dd, *J* = 8 and 8 Hz, 1H), 6.99 (t, *J* = 8 Hz, 1H), 7.03 (s, 1H), 7.09 (t, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 7.25 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.54 (t, *J* = 8 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.97 (bs, 1H), 8.12 (d, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 36.0, 52.3, 53.7, 111.0, 111.1, 118.3, 119.1, 121.6, 123.0, 124.7, 126.9, 127.3, 127.5, 128.9, 133.6, 133.9, 135.9, 164.4, 169.5, 170.3. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.47; H, 4.94; N, 7.74.

Method B: To a stirred solution of compound **4** (400 mg, 1.01 mmol) in methanol (15 mL) at room temperature was added NEt_3 (two drops), and the reaction mixture was stirred for a further 24 h under an argon atmosphere. The reaction mixture was concentrated in vacuo, and the residue obtained was purified by silica-gel column chromatography using petroleum ether–ethyl acetate (3:2) as an eluent to obtain compound **6** as a thick oil (170 mg, 46%).

4.5. (*R*)-Methyl 2-((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)-1-hydroxy-3-oxoisoindoline-1-carboxylate (7a) and (*S*)-methyl 2-((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)-1-hydroxy-3-oxoisoindoline-1-carboxylate 7b

Method A: To a stirred solution of amide **5** (2.00 g, 5.07 mmol) in methanol (50 mL) at room temperature was added NEt_3 (1 mL), and the reaction mixture was stirred for a further 6 h at room temperature. The reaction mixture was oxygenated by bubbling excess of oxygen gas for 6 h and stirred for further 6 h. The reaction mixture was concentrated in vacuo, and the obtained residue was purified by silica-gel column chromatography using petroleum ether–ethyl acetate (1:1) as an eluent to obtain the mixture of compounds **7a**/**b** inseparable by column chromatography (2:3, 1.90 g, 92%). Mp 72–74 °C; $[\alpha]_D^{20} = -98.0$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3476, 3398, 1744, 1736, 1709, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.78 (s, 1.80H), 3.38 (s, 1.20H), 3.44–3.75 (m, 1.40H), 3.69 (s, 1.20H), 3.75 (s, 1.80H), 3.96 (dd, *J* = 14 and 10 Hz, 0.60H), 4.09 (br s, 0.40H), 4.49 (br s, 0.60H), 4.71 (dd, *J* = 10 and 6 Hz, 0.60H), 4.93 (dd, *J* = 10 and 6 Hz, 0.40H), 7.04–7.21 (m, 3H), 7.27–7.43 (m, 2H), 7.50–7.58 (m, 2H), 7.59–7.70 (m, 1H), 7.77–7.90 (m, 1H), 8.08 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.70, 25.63, 52.47, 52.69, 52.97, 53.47, 54.13, 56.40, 87.53, 88.69, 110.70, 110.92, 111.16, 111.23, 118.31, 118.35, 119.30, 119.32, 121.67, 121.82, 121.93, 122.21, 123.09, 123.55 (2-carbons), 124.00, 126.95, 127.04, 130.26 (2-carbons), 130.76, 130.81, 132.76 (2-carbons), 135.96, 136.09, 143.74, 143.93, 167.88, 168.65, 169.18, 170.26, 171.17, 171.86. Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.57; H, 5.06; N, 6.99.

Method B: To a stirred solution of amide **4** (100 mg, 0.253 mmol) in methanol (10 mL) at room temperature was added NEt_3 (two drops), and the reaction mixture was stirred for 48 h under atmospheric conditions. The reaction mixture was concentrated in vacuo, and the obtained residue was purified by silica-gel column chromatography using petroleum ether–ethyl acetate (1:1) as an eluent to obtain a mixture of compounds **7a**/**b** (2:3, 73 mg, 71%).

Method C: To a stirred solution of imide **6** (200 mg, 0.55 mmol) in methanol (15 mL) at room temperature was added NEt_3 (two drops), and the reaction mixture was stirred for 12 h under atmospheric conditions. The reaction mixture was concentrated in vacuo, and the obtained residue was purified by silica-gel column chromatography using petroleum ether–ethyl acetate (1:1) as an eluent to obtain a mixture of compounds **7a**/**b** (2:3, 198 mg, 88%).

4.6. (*S*)-Methyl 5,7,8,13b-tetrahydro-5-oxo-13*H*-13b-methoxycarbonyl-(*S*)-indolo[2,3-*c*]isoindolo[2,1-*a*] pyridine-7-carboxylate 8a and (*R*)-methyl 5,7,8,13b-tetrahydro-5-oxo-13*H*-13b-methoxycarbonyl-(*S*)-indolo[2,3-*c*]isoindolo[2,1-*a*] pyridine-7-carboxylate 8b

To a stirred solution of mixture of **7a**/**b** (1.70 g, 4.16 mmol) in AcOH (15 mL) at 10 °C was added concd H_2SO_4 (two drops), and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate (30 mL), and the organic layer was washed with 5% aqueous $NaHCO_3$ solution, brine, and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the residue obtained using petroleum ether–ethyl acetate (7:3) as an eluent furnished compound **8a** (920 mg, 57%) and **8b** (230 mg, 14%) as crystalline solids with a total yield of 71%.

Compound **8a**: Mp 189–191 °C; $[\alpha]_D^{20} = -43.6$ (*c* 1.0, $CHCl_3$); ~100% ee by chiral HPLC; IR ($CHCl_3$) ν_{max} 3248, 1755, 1749, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.16 (dd, *J* = 16 and 4 Hz, 1H), 3.36 (dd, *J* = 16 and 8 Hz, 1H), 3.89 (s, 3H), 3.97 (s, 3H), 4.54 (dd, *J* = 12 and 4 Hz, 1H), 7.11 (dt, *J* = 8 and 2 Hz, 1H), 7.22 (dt, *J* = 8 and 2 Hz, 1H), 7.38 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.52 (dt, *J* = 8 and 2 Hz, 1H), 7.66 (dt, *J* = 8 and 2 Hz, 1H), 7.82 (dd, *J* = 8 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.3, 52.2, 53.3, 53.9, 68.8, 108.5, 111.9, 118.9, 119.5, 122.7, 123.8, 124.2, 125.5, 129.5, 130.1, 130.3, 133.3, 137.1, 143.1, 167.7, 168.3, 169.6. Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.65; H, 4.80; N, 7.12. HPLC details: Column: chiralcel ODH (250 × 4.6 mm), mobile phase: Ethanol/*n*-hexane (15:85), wavelength: 240 nm, flow rate: 0.5 mL/min, retention time: 25.4 min (−)-isomer, 27.5 min (+)-isomer.

Compound **8b**: Mp 120–122 °C; $[\alpha]_D^{20} = +63.5$ (*c* 2.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3454, 1742, 1740, 1701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.17 (dd, *J* = 16 and 6 Hz, 1H), 3.31 (dd, *J* = 16 and 2 Hz, 1H), 3.67 (s, 3H), 3.73 (s, 3H), 5.86 (dd, *J* = 8 and 2 Hz, 1H), 7.04–7.24 (m, 2H), 7.36–7.66 (m, 4H), 7.80–7.95 (m, 2H), 9.06 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.9, 51.0, 52.4, 53.3, 66.9, 107.7, 111.5, 118.7, 119.9, 121.9, 123.0, 124.8, 126.1, 128.2, 129.7, 130.2, 133.0,

137.3, 144.7, 170.1, 170.8, 171.0. Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.72; H, 4.56; N, 7.07.

4.7. (*S*)-7-Oxo-6,7,11b,12-tetrahydro-5*H*-6a,12-diaza-(*R*)-indeno [1,2-*a*]fluorene-6-carboxylic acid Methyl ester 1

To a stirred solution of compound **8a** (700 mg, 1.79 mmol) in a mixture of DMSO (20 mL), water (1 mL), and acetic acid (1 mL) was added NaCl (100 mg, 1.79 mmol). The reaction mixture was deoxygenated by bubbling an excess of nitrogen gas for 12 h. Then, it was heated at 210 °C for 2 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (25 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (100–200 mesh) column chromatographic purification of the residue obtained using petroleum ether–ethyl acetate (4:1) as an eluent gave compound **1** as a white crystalline solid (429 mg, 72%). Mp 238–240 °C (ethyl acetate) (lit.[5] 166–168 °C); $[\alpha]_D^{20} = +101.6$ (*c* 1.0, $CHCl_3$), 98% ee by chiral HPLC; IR ($CHCl_3$) ν_{max} 3470, 1742, 1739, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.20 (ddd, *J* = 16, 8 and 2 Hz, 1H), 3.47 (td, *J* = 16 and 2 Hz, 1H), 3.72 (s, 3H), 5.78 (d, *J* = 6 Hz, 1H), 6.24 (s, 1H), 7.06–7.23 (m, 2H), 7.36 (dd, *J* = 8 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.51 (t, *J* = 8 and 2 Hz, 1H), 7.64 (dt, *J* = 8 and 2 Hz, 1H), 7.85 (d, *J* = 8 Hz, 1H), 7.92 (d, *J* = 8 Hz, 1H), 8.53 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.5, 50.3, 52.6, 55.5, 106.2, 111.2, 118.4, 119.8, 122.5, 122.7, 124.3, 126.4, 128.8, 129.3, 131.2, 132.4, 136.7, 143.6, 168.7, 171.6;. Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.09; H, 4.68; N, 8.43. HPLC details: Column: chiralcel ODH (250 × 4.6 mm), mobile phase: isopropyl alcohol/Pet Ether (30:70), wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 11.2 min (+)-isomer, 12.7 min (−)-isomer.

4.8. Crystallographic data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 710301 and 710302. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

P.B.W. thanks CSIR, New Delhi for the award of research fellowship. We thank Mrs. S. S. Kunte from NCL, Pune for the chiral HPLC data.

References

1. (a) Hudlicky, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, 2007; (b) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.
2. Hoefgen, B.; Decker, M.; Mohr, P.; Schramm, A. M.; Rostom, S. A. F.; Subbagh, H. E.; Schweikert, P. M.; Rudolf, D. R.; Kassack, M. U.; Lehmann, J. *J. Med. Chem.* **2006**, *49*, 760. and references cited therein.
3. (a) Gihani, M. T. E.; Heaney, H.; Shuhaibar, K. F. *Synlett* **1996**, 871; (b) Heaney, H.; Shuhaibar, K. F. *Synlett* **1995**, 47; (c) Hitchings, G. J.; Helliwel, M.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 83; (d) Laguerre, M.; Atfani, C. B. M. *Tetrahedron* **1988**, *44*, 7109; (e) Rahman, A. U.; Ghazala, M.; Sultana, N.; Bashir, M. *Tetrahedron Lett.* **1980**, *21*, 1773; (f) Rahman, A. U.; Waheed, N. *Tetrahedron Lett.* **1979**, *19*, 1715; (g) Rahman, A. U.; Waheed, N. *Tetrahedron Lett.* **1977**, *47*, 4101; (h) Wawzonek, S.; Nelson, G. E. *J. Org. Chem.* **1962**, *27*, 1377. and references cited therein **3a**–**h**.
4. Bailey, P. D.; Cochrane, P. J.; Forster, A. H.; Morgan, K. M.; Pearson, D. P. J. *Tetrahedron Lett.* **1999**, *40*, 4597.
5. Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Sridharan, V.; Suganthan, S.; Thornton-Pett, M.; Jhang, J. *Tetrahedron* **2000**, *56*, 6585.
6. Haval, K. P.; Argade, N. P. *J. Org. Chem.* **2008**, *73*, 6936.
7. (a) Wakchaure, P. B.; Easwar, S.; Puranik, V. G.; Argade, N. P. *Tetrahedron* **2008**, *64*, 1786; (b) Heaney, H.; Taha, M. O.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3051; (c) Wakchaure, P. B.; Argade, N. P. *Synthesis* **2008**, 2321; (d) Liu, H.; Siegel, D. R.; Danishefsky, S. J. *Org. Lett.* **2006**, *8*, 423.
8. (a) Sabitha, G.; Srividya, R.; Yadav, J. S. *Tetrahedron* **1999**, *55*, 4015; (b) Yadav, J. S.; Reddy, B. V. S.; Rao, K. S.; Harikishan, K. *Synlett* **2002**, 826.
9. Padwa, A.; Waterson, A. G. *Tetrahedron* **2000**, *56*, 10159.
10. Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *14*, 957.
11. (a) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79; (b) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914; (c) Kametani, T.; Takagi, N.; Kanaya, N.; Honda, T. *J. Heterocycl. Chem.* **1982**, *19*, 1217.