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Synthesis of optically pure pyrroloquinolones via Pictet–Spengler and Winterfeldt reactions

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Abstract—Diastereomers of substituted 2,3,4,9-tetrahydro-1*H*-β-carbolines were synthesized via asymmetric Pictet–Spengler reaction of the chiral tryptamine derived from *R*-1-naphthalen-1-yl-ethylamine with 67% of d.e. The *S*,*R*-β-carboline can be converted to the *R*,*R* form by treating with TFA. Optically pure pyrroloquinolones were obtained from Winterfeldt oxidation of the β-carbolines without epimerization.

Recently, we have reported several series of novel PDE5 inhibitors for the treatment of erectile dysfunction.[1] During our search for PDE5 inhibitors, we discovered pyrroloquinolones[1d] as extremely potent and selective PDE5 inhibitors. Systematic SAR studies of the pyrroloquinolones revealed that the *R*-enantiomers are more potent inhibitors of PDE5 and are more selective versus other isozymes of PDEs than their antipodes. These compounds are also efficacious and orally bioavailable in animal models for erectile dysfunction. An efficient way of synthesizing enantiomerically pure pyrroloquinolone **1**[1d] became a necessity for further development in this field. We wish to report one of our approaches to structure **1**: via asymmetric Pictet–Spengler reaction (Fig. 1).

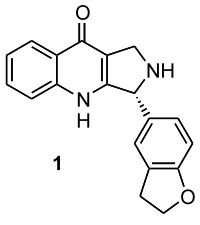

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Figure 1. Target compound.

Asymmetric syntheses of 2,3,4,9-tetrahydro-β-carbolines are well documented in the literature. These include: (a) asymmetric reduction of an imine precursor using chiral sodium acyloxyborohydride,[2d] chiral oxaborolidines,[2f] or a chiral ruthenium catalyst;[2e] (b) asymmetric Pictet–Spengler reaction using chiral tryptamine derived from chiral 1-phenyl-ethylamine[2b,j,r] or 1-naphthalen-1-yl-ethylamine,[2a] or using phthalimide as chiral auxiliary;[2c] and (c) asymmetry introduced by chiral tryptaphan methyl ester.[2g,h,i] We decided to access the *R*-enantiomers of the pyrroloquinolones via asymmetric Pictet–Spengler reaction with chiral auxiliaries and Winterfeldt reaction[3] sequence based on the chemistry we developed in the synthesis of the racemic analogs. In addition, the expense and scarcity of chiral Ru catalysts and chiral boron reagents make the chiral reduction route less desirable for the large scale synthesis of compound **1**. Furthermore, we chose the inexpensive commercially available chiral 1-phenyl-ethylamine and 1-naphthalen-1-yl-ethylamine as chiral auxiliaries over phthalimide due to the ease of chemistry.

Chiral naphthyl amine was used in an asymmetric Pictet–Spengler reaction of tryptamine in protic conditions.[2a] The yields varied when electronic factors changed in the aldehyde. When PhCHO, *p*-NO_2PhCHO or MeCHO were used, the yield of Pictet–Spengler reaction was 90, 58 and 30%, respectively. When 4-MeO-C_6H_4CHO was used, the yield was only 9%. When 2,3-dihydrobenzo[*b*]furan-5-carboxaldehyde **3** was used, we found no product under the following conditions: (a) TFA/DCM/25°C; (b) TFA/benzene,

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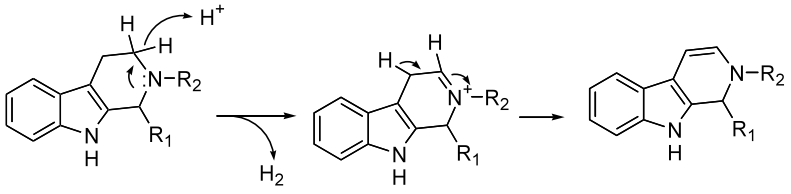
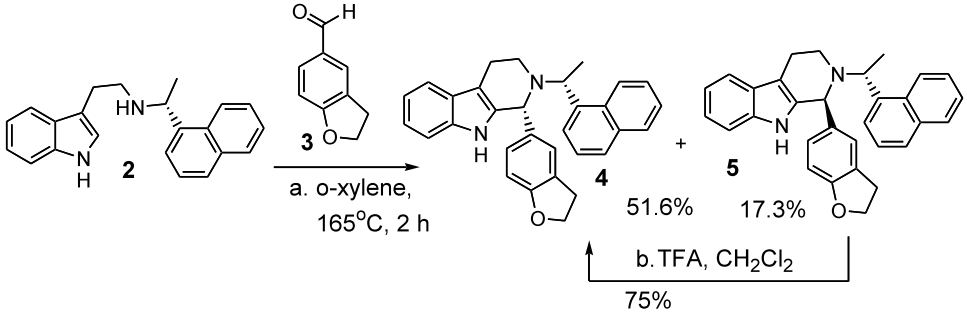
80°C; (c) TsOH/benzene 80°C, or (d) TsOH/toluene, 110°C. This might be due to the high steric hindrance in the amine introduced by a bulky naphthyl group in Pictet–Spengler reaction. Moreover, the aldehyde bearing an electron-donating group probably decreases the reactivity of the iminium ion intermediate in the Pictet–Spengler reaction and hence prevents the formation of β-carboline. However, products were formed when heated in neat xylene at 165°C in the absence of acid.[4] In the presence of acid, we were unable to isolate the desired Pictet–Spengler product. Instead, we only observed dehydrogenated β-carboline with molecular ion (M-2) detected by LC-MS. Similar observation under basic condition was reported.[2l] We proposed the following mechanism for the formation of dehydrogenated product (Scheme 1).

High temperature (165°C) seems to be necessary to overcome the high enthalpy due to the unfavorable steric and electronic factors, and the unfavorable entropy of converting two molecules into one in the reaction. The β-carbolines were obtained as a result of kinetic control under such conditions in good overall yields with 66% diastereomeric excess. Interestingly, we discovered that the *S*,*R* diastereomer **5** can be converted to the *R*,*R* diastereomer **4** under catalysis with TFA in CH_2Cl_2, resulting in the thermodynamically controlled equilibrated ratio of **5**:**4** = 7:93. After recrystalization from acetone, pure compound **4** was obtained from **5** with a yield of 75% (Scheme 2).[5]

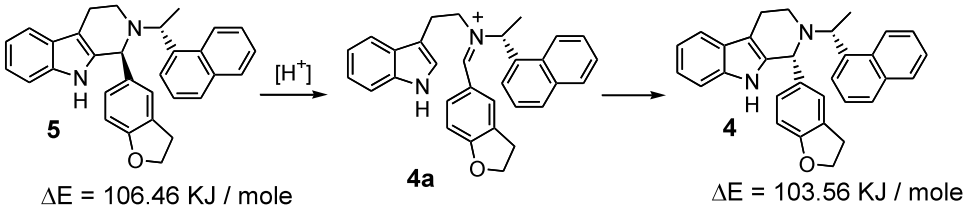
The mechanism of conversion of the diastereomers under acidic condition happened by microscopic reverse of Pictet–Spengler reaction via the iminium intermediate **4a**[2k] (Scheme 3). A molecular modeling study by Monte Carlo simulations using Macromodel software was used to compare the comformational energy of **4** and **5**. The effect of organic solvent was treated by GB/SA method. The identified lowest-energy comformation was further optimized in MM2 force field. The global minimum conformation of compound **5** and compound **4** are shown as follows. The conformational energy is 106.46 KJ/mol for **5** and 103.56 KJ/mol for **4** in MM2 force field, respectively. Compound **4** is slightly more stable in $CHCl_3$. It may be due to its better packing of two ring systems. This is consistent with the experimental observations and supports the hypothesis of thermodynamic process (Scheme 3).



Scheme 1.



Scheme 2.



Scheme 3.

The stereochemical outcome can be explained by assuming a model in which S-*trans* conformation of iminium ion was preferred due to π–π stacking between 2,3-dihydro-benzofuran-5-yl group and indole group (Scheme 4). This model can also be used to explain the observations of the stereochemical outcome of similar substrates reported in the literature.[2a] Furthermore, this is complimentary to other models used to explain structurally different substrates in asymmetric Pictet–Spengler reactions.[2c,m–q]

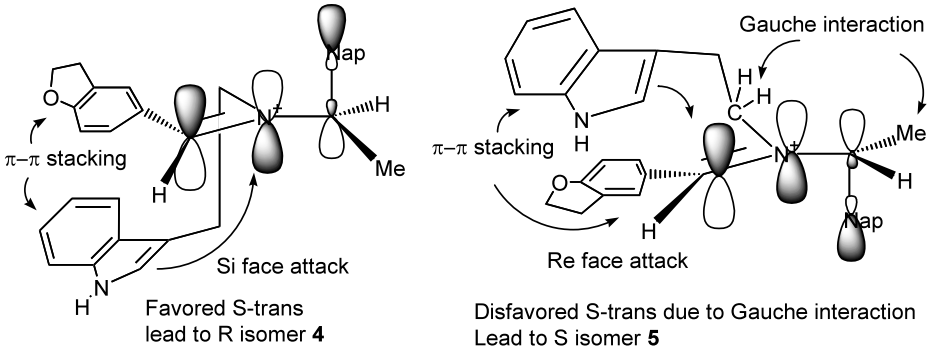
In our earlier studies, we attempted the Winterfeldt oxidation[3] for various β-carbolines where the substituent on the piperidine nitrogen is acyl, benzoyl, Boc or benzyl group. We observed that the acyl, benzoyl or Boc groups are poorly tolerated in the Winterfeldt oxidation conditions. However, arylalkyls such as benzyl are well tolerated (Scheme 5).

These studies laid the foundation for our naphthylmethyl chiral auxillary approach. Thus, under the Winterfeldt reaction conditions, pyrroloquinolone **6** was obtained from β-carboline **4** as a single diastereomer upon treatment of $KOtBu/O_2$[3d] with retention of chirality. Compound **5** can also be converted to pyrroloquinolone **7** under the same conditions. The diastereomers **6** and **7** can be easily separated on TLC. In both cases, only one diastereomer was formed (Scheme 6). This indicates under $KOtBu/O_2$ conditions, there is no epimerization occured at 3-position. Furthermore, when we subjected a mixture of **4** and **5** to the same conditions, a mixture of **6** and **7** can be obtained in the same diastereomeric ratio as the starting material in similar yield. This pair of diastereomers is separable by silica gel chromatography to give **6** and **7** with >98% of de (Scheme 6).[6]

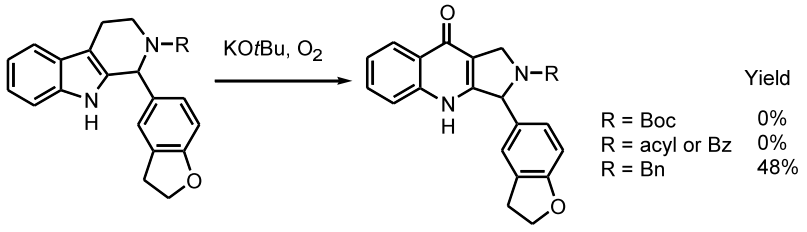
Since it is γ to a conjugated ketone, the chiral center (position 3 in compound **7** in Scheme 6) might be epimerized under basic conditions. We also attempted to convert the undesired compound **7** to desired compound **6**. We treated compound **7** with the following conditions: (1) DMAP (1 equiv.) in THF (0.001 M) at 80°C for 16 h; (2) DIEA (1 equiv.) in THF (0.001 M) at 80°C for 16 h; (3) K_2CO_3 (4 equiv.) in 1,4-dioxane and H_2O (4:1) (0.0015 M) at 100°C for 16 h. For the first two conditions, starting material **7** was observed and no converted product **6** obtained. For the last case, all starting material **7** decomposed and no product **6** formed.

The chiral auxiliary can be removed under hydrogenolysis conditions.[2a,r] The over-reduced product **9** can only be observed under very high catalyst loading or prolonged reaction time. However, by carefully monitoring of the reaction, side product **9** can be reduced to less than 5% and desired product **1** can be isolated in 72% yield. Pyrroloquinolone **1** was obtained in ≥94% e.e. before purification as determined by chiral HPLC (Scheme 7).[7]

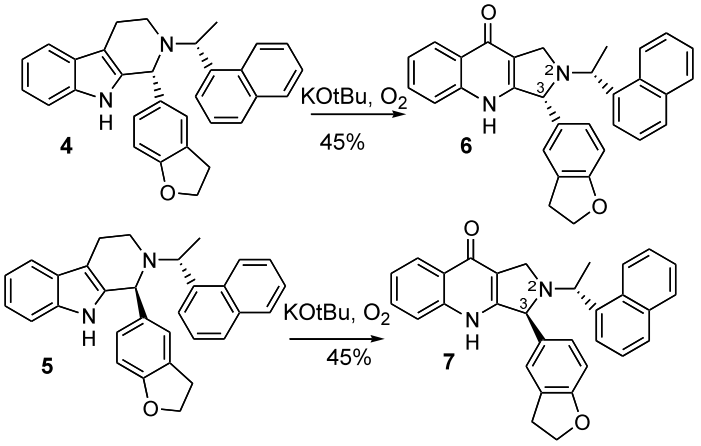
In summary, pyrroloquinolone **1** was obtained with high enantiomeric purity through an asymmetric Pictet–Spengler reaction by using chiral 1-naphthalen-1-ylethylamine as chiral auxiliary, followed by Winterfeldt oxidation.



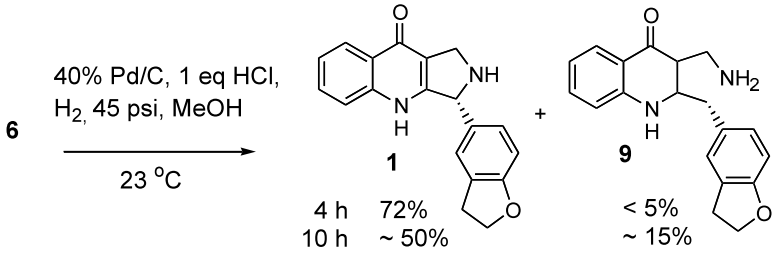
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

Acknowledgements

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References

1. (a) Sui, Z.; Macielag, M. J.; Guan, J.; Jiang, W.; Lanter, J. C. *PCT Int. Appl.* 2001 WO 0187882; (b) Sui, Z.; Macielag, M. J. *PCT Appl.* WO 0187038, 2001; (c) Sui, Z.; Guan, J.; Jiang, W.; Macielag, M. J.; Walsh, S. P.; Lanter, J. C.; Fiordeliso, J. J.; Alford, V. C., Jr.; Qiu, Y.; Patricia, K.; Bhattacharjee, S.; Lombardi, E.; Haynes-Johnson, D.; John, T. M.; Clancy, J. Abtracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18–22, 2002, MEDI-278; (d) Sui, Z.; Guan, J.; Macielag, M. J.; Jiang, W.; Zhang, S.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; John, T. M.; Haynes-Johnson, D.; Clancy, J. *J. Med. Chem.* **2002**, *45*, 4094–4096; (e) Jiang, W.; Sui, Z.; Macielag, M. J.; Walsh, S. P.; Fiordeliso, J. C.; Lanter, J.; Guan, J.; Qiu, Y.; Kraft, P.; Bhattacharjee, S.; Craig, E.; Haynes-Johnson, D.; John, T. M.; Clancy, J. *J. Med. Chem.*, submitted; (f) Lanter, J. C.; Sui, Z.; Macielag, M. J.; Fiordeliso, J. J.; Jiang, W.; Qiu, Y.; Bhattacharjee, S.; Kraft, P.; John, T. M.; Haynes-Johnson, D.; Craig, E.; Clancy, J. *J. Med. Chem.*, submitted.
2. (a) Kawate, T.; Yamanaka, M.; Nakagawa, M. *Heterocycles* **1999**, *50*, 1033–1039; (b) Legseir, B.; Aichaoui, H.; Ladjama, D. *J. Soc. Alger. Chim.* **1996**, *6*, 17–27; (c) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402–2403; (d) Hajipour, A. R.; Hantehzadeh, M. *J. Org. Chem.* **1999**, *64*, 8475–8478; (e) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917; (f) Nakagawa, M.; Kawate, T.; Kakikawa, T.; Yamada, H.; Matsui, T.; Hino, T. *Tetrahedron* **1993**, *49*, 1739; (g) Czerwinski, K. M.; Cook, J. M. *Adv. Heterocycl. Nat. Prod. Synth.* **1996**, *3*, 217–277; (h) Cox, E. D.; Cook, J. M. *Chem. Rev.* (*Washington, D. C.*) **1995**, *95*, 1797–1842; (i) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998–7010; (j) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347–358; (k) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089–1119; (l) Harrison, D. M.; Sharma, B. *Tetrahedron* **1993**, *49*, 3165–3184; (m) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164–168; (n) Waldmann, H.; Schmidt, G. *Tetrahedron* **1994**, *50*, 11865–11884; (o) Melnyk, P.; Ducrot, P.; Thal, C. *Tetrahedron* **1993**, *49*, 8589–8596; (p) Comins, D.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327–16340; (q) Kawate, T.; Yamada, H.; Matsumizu, M.; Nishida, A.; Nakasawa, M. *Synlett* **1997**, 761–762; (r) Reddy, M. S.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 5413–5416.
3. (a) Winterfeldt, E. *Liebigs Ann. Chem.* **1971**, *745*, 23–30; (b) Warneke, J.; Winterfeldt, E. *Chem. Ber.* **1972**, *105*, 2120–2125; (c) Boch, M.; Korth, T.; Nelke, J. M.; Pike, D.; Radunz, H.; Winterfeldt, E. *Chem. Ber.* **1972**, *105*, 2126–2142; (d) Carniaux, J.-F.; Kan-Fan, C.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1997**, 2997–3000.

4. Sandrin, J.; Soerens, D.; Mokry, P.; Cook, J. *Heterocycles* **1977**, *6*, 1133–1139.

5. **Synthesis of compound 4 and 5**: [2-(1*H*-Indol-3-yl)-ethyl]-(1-naphthalen-1-yl-ethyl)-amine (**2**) (1.0 g, 3.18 mmol) and 2,3-dihydro-benzofuran-5-carbaldehyde (**3**) (2.356 g, 15.92 mmol) were stirred in *p*-xylene (20 mL) at 165°C for 7 h. To the reaction mixture was added silica gel (10 g) and hexane (200 mL). The reaction mixture was filtered and the colorless filtrate was discarded. The silica gel was washed with ethyl acetate (100 mL). The ethyl acetate solution was evaporated, the concentrated crude material was dissolved in a small amount of CH_2Cl_2 and packed on a silica gel column. The column was eluted with 5% ethyl acetate/hexane to yield two diastereomers. 1-(2,3-dihydro-benzofuran-5-yl)-2-(1*R*-1-naphthalen-1-yl-ethyl)-2,3,4,9-tetrahydro-1*S*-1*H*-β-carboline (**5**) (R_f=0.59 in 30% EtOAc/Hex) was obtained as yellow solid (0.21 g, 17%). ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.60 (d, 3H, J=6.5 Hz), 2.61 (m, 1H), 2.91 (m, 1H), 3.05∼3.20 (m, 4H), 4.51 (t, 2H, J=8.8 Hz), 4.72 (m, 1H), 4.81 (s, 1H), 6.68 (m, 1H), 6.92 (m, 4H), 7.05∼7.65 (m, 5H), 7.70∼7.95 (m, 4H); MS (m/z) MH^+ (445), MH^- (443). 1-(2,3-Dihydro-benzofuran-5-yl)-2-(1*R*-1-naphthalen-1-yl-ethyl)-2,3,4,9-tetrahydro-1*R*-1*H*-β-carboline (**4**) (R_f=0.51 in 30% EtOAc/Hex) was obtained as a yellow solid (0.65 g, 51%). ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.58 (d, 3H, J=6.5 Hz), 2.65 (m, 1H), 2.91 (m, 2H), 3.05 (t, 2H, J=8.8 Hz), 3.15 (m, 1H), 4.51 (t, 2H, J=8.8 Hz), 4.65 (m, 1H), 5.10 (s, 1H), 6.68 (m, 1H), 6.85 (s, 2H), 7.11 (m, 2H), 7.20∼7.50 (m, 5H), 7.68 (m, 2H), 7.81 (m, 1H), 8.21 (m, 1H); MS (m/z) MH^+ (445), MH^- (443). Anal. calcd for $C_{31}H_{28}N_2O$ (**4**) is C, 83.75; H, 6.35; N, 6.30; found: C, 83.66; H, 6.37; N, 6.26. **Conversion of 5 to 4**: 1-(2,3-Dihydro-benzofuran-5-yl)-2-(1*R*-1-naphthalen-1-yl-ethyl)-2,3,4,9-tetrahydro-1*S*-1*H*-β-carboline (**5**) (190 g, 0.428 mol) was stirred in 1000 mL CH_2Cl_2 with TFA (52 mL, 0.701 mol) at room temperature overnight. The reaction was quenched with NaOH (35 g, 0.875 mol) in 100 mL water. After mixing well and staying still for 0.5 h, precipitate came out. This was filtered. Solid was washed with more water. After drying under high vacuum, product (157 g, 83%) was obtained. ^{1}H NMR showed 6% starting material by integration. Recrystalization from acetone (18 g product in 500 mL acetone) provide pure product as white solid (12 g, 67%). ^{1}H NMR showed pure compound **4**.

6. **Synthesis of compound 6**: 1-(2,3-Dihydro-benzofuran-5-yl)-2-(1*R*-1-naphthalen-1-yl-ethyl)-2,3,4,9-tetrahydro-1*R*-1*H*-β-carboline (**4**) (0.6469 g, 1.46 mmol) and potassium-*t*-butoxide (0.279 g, 2.48 mmol) were stirred in DMF (14 mL) at room temperature. O_2 gas was bubbled into the reaction mixture overnight. The reaction was quenched with HCl (2.48 mL, 1.0N aqueous). Ethyl acetate (50 mL) and H_2O (50 mL) were then added. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (50 mL) and CH_2Cl_2 (50 mL). The organic layers were washed with brine (3×50 mL) and dried over $MgSO_4$. The resulting product was concentrated and purified via silica gel (2% methanol/CH_2Cl_2) to yield the product as a yellow solid (0.288 g, 43%). ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.65 (d, 3H, J=6.5 Hz), 3.05 (t, 2H, J=8.8 Hz), 4.01 (m, 2H), 4.51 (t, 2H, J=8.8 Hz), 4.68 (m, 1H), 5.31 (s, 1H), 6.62 (s, 1H), 6.88∼7.89 (m, 12H), 8.25 (d, 1H); MS (m/z) MH^+ (459), MH^- (457); HRMS calcd MH^+ for $C_{31}H_{26}N_2O_2$ 459.2072; found 459.2060.

7. **Synthesis of compound 1**: 3-(2,3-Dihydro-benzofuran-5-yl)-2-(1*R*-1-naphthalen-1-yl-ethyl)-1,2,3,4-tetrahydro-1*R*-9*H*-pyrrolo[3,4-*b*]quinolinone (**6**) (3.60 g, 9.13 mmol) was dissolved in EtOH (200 mL) with HCl (9.13 mL, 1.0 M in ether) and Pd (1.943 g, 10% on carbon). This was stirred with H_2 (35∼45 psi) at 25°C until starting material disappeared checked by LCMS, taking ∼5 h. The solid was filtered away on a plug of Celite. The concentrated residue was purified on silica gel column to provide final product as greenish yellow solid (3.27 g, ∼quantitative). This material was pure judged by ^{1}H NMR, MS and chiral HPLC. However, if purified by silica gel (10% MeOH/DCM) final product was obtained as nice yellow solid (2.64 g, 85%). ^{1}H NMR ($CDOD_3$) δ 3.26 (t, 2H, J=8 Hz), 3.61 (t, 2H, J=8 Hz), 4.78 (m, 2H), 6.34 (s, 2H), 6.89 (d, 1H, J=15 Hz), 7.29 (m, 2H), 7.62∼7.86 (m, 3H), 8.41 (d, 1H); MS (m/z) 305 (MH^+), 303 (MH^-); HRMS calcd MH^+ for $C_{19}H_{16}N_2O_2$ 305.1290; found 305.1279. Chiralpak AD (0.46×25 cm) was used to analyze the e.e. (1.0 mL/min, mobile phase: 90/10/0.1 CH_3CN/IPA/DEA) on the crude product, Tr_1=7.08 min, Tr_2=12.34 min. Ratio of the two peak=1.01:95.01. The racemic material was used to confirm the retention time for two enantiomers. $[\alpha]_D$=−37.9° (*c* 1.00, MeOH).