Catalytic Asymmetric Pictet-Spengler Reaction

Jayasree Seayad, Abdul Majeed Seayad, and Benjamin List*

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim an der Ruhr, Germany

Supporting Information

General: Reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel coated glass plates (60F-254) using UV light to visualize the course of reaction. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.040–0.063 mm). Chemical yields refer to pure isolated substances. HPLC was conducted by using Shimadzu LC-2010C coupled with LCMS-2010A. ^1H and ^{13}C NMR spectra were obtained using either a Bruker DPX-300 or AV-400 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, b = broad. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet).

Preparation of Catalysts: Phosphoric acids **5** were prepared according or in analogy to the reported procedures^{1,2}

5f: ^1H NMR (400 MHz, DMSO- D_6) δ 0.86 (d, J = 6.8 Hz, 6H), 1.08 (d, J = 6.9 Hz, 6H), 1.14 – 1.18 (m, 12H), 1.27 (d, J = 6.9 Hz, 12H), 2.58 (q, J

- (1) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583-2585; also see: (c) T. Akiyama, PCT Int. Appl. WO 200409675, 2004. (d) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal.* **2005**, *347*, 1523-1526.
(2) (a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357. (b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804-11805. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360-9361; also see: (d) Terada, M.; Uraguchi, D.; Sorimachi, K.; Shimizu, H. PCT Int. Appl. WO 2005070875, 2005.

= 6.8 Hz, 2H), 2.86 – 3.01 (m, 4H), 7.01 (d, $J = 1.5$ Hz, 2H), 7.04 (d, $J = 8.5$ Hz, 2H), 7.11 (d, $J = 1.5$ Hz, 2H), 7.27 (t, $J = 8.2$ Hz, 2H), 7.39 (t, $J = 7.9$ Hz, 2H), 7.77 (s, 2H), 7.98 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- D_6) δ 149.5, 149.4, 147.9, 147.3, 146.6, 134.0, 133.5, 132.5, 131.1, 129.8, 128.5, 125.9, 125.9, 124.4, 122.5, 120.9, 119.7, 34.1, 30.9, 30.3, 26.6, 24.9, 24.5, 24.4, 23.7, 23.5; ^{31}P NMR (161 MHz, DMSO- D_6) δ 4.57; HRMS, calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5 \cdot \text{H}^+$ (MH^+) 751.392175, found 751.391649. The optical purity is determined to be >99% by HPLC analysis (Chiral OD-H column, 90% MeOH/0.1% TFA, 0.5 mL/min, 220 nm, t_{R} (S-isomer 20.64 min), t_{R} (R-isomer 24.76 min).

Preparation of substituted tryptamines

Tryptamines **3a-d** were prepared by the procedure of Hagen et al.³

3b ^1H NMR (400 MHz, CDCl_3) δ 1.16 (t, $J = 6.9$ Hz, 6H), 2.98 (s, 2H), 3.45 (s, 2H), 3.76 (s, 3H), 4.12 (t, $J = 5.8$ Hz, 4H), 6.74 (d, $J = 8.6$ Hz, 1H), 6.98 (s, 2H), 7.12 (d, $J = 8.7$ Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.408, 153.8, 130.8, 128.0, 124.5, 112.1, 111.6, 107.6, 100.3, 66.3, 61.8, 55.6, 30.3, 13.6; HRMS (ESI), calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5 \cdot \text{H}^+$ (MH^+) 335.160147, found 335.159872.

3c ^1H NMR (300 MHz CDCl_3) δ 1.19 (t, $J = 7.1$ Hz, 6H), 2.02 (bs, 2H), 3.42 (s, 2H), 3.76 (s, 3H), 4.06 – 4.21 (m, 4H), 6.70 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.75 (d, $J = 2.0$ Hz, 1H), 6.90 (d, $J = 2.3$ Hz, 1H), 7.40 (d, $J = 8.7$ Hz, 1H), 7.99 (s, 1H); ^{13}C NMR (75 MHz CDCl_3) δ 171.5, 156.9, 137.1, 122.8, 122.8, 120.0, 110.1, 109.2, 94.9, 66.8, 62.3, 56.1, 31.1, 14.4, HRMS (ESI), calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5 \cdot \text{Na}^+$ (MNa^+) 357.142088, found 357.142431.

(3) Hagen, T. G.; Narayanan, K.; Names, J.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 2170-2178.

¹H NMR (300 MHz CDCl₃) δ 1.18 (t, *J* = 7.1 Hz, 6H), 2.02 (s, 2H), 3.43 (s, 2H), 4.05 – 4.20 (m, 4H), 5.02 (s, 2H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.99 (d, *J* = 2.4 Hz 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 7.24 – 7.34 (m, 3H), 7.41 (dd, *J* = 7.7, 1.1 Hz, 2H), 8.01 (s, 1H); ¹³C NMR (75 MHz CDCl₃) δ 171.5, 153.8, 137.9, 131.7, 128.9, 128.8, 128.1, 128.0, 124.9, 113.6, 112.2, 109.1, 102.8, 71.3, 67.1, 62.4, 31.2, 14.4; HRMS (ESI), calcd for C₂₃H₂₆N₂O₅·Na⁺ (MNa⁺) 433.173393 found, 433.173706.

Screening of additional catalysts

^aDetermined by GC. ^bDetermined by HPLC (Chiralcel OD-RH). Absolute configuration determined by hydrolytic decarboxylation to the monoester.
^copposite isomer.

Optimization experiments

T[°C]	Catalyst [mol%]	Solvent	Yield [%] ^a (time,h)	ee, % ^b
r.t	20	Toluene	90 (2)	66
-10	20	Toluene	88(72)	75
-30	20	Toluene	86(120)	88
-45	20	Toluene	57(120)	86
-45	20	Pentane:Toluene(1:1)	52(120)	83
-30	20	CH_2Cl_2	60(72)	55
-30	20	Et_2O	53(96)	81
r.t	10	Toluene	44(2)	64
r.t	5	Toluene	38(2)	65
r.t	1	Toluene	20(2)	63
r.t	20	Toluene	90(2)	65 ^c
-30	20	Toluene	50(57)	79 ^c

^aDetermined by GC. ^bDetermined by HPLC (Chiralcel OD-RH). Absolute configuration determined by hydrolytic decarboxylation to the monoester. ^creaction without Na_2SO_4 .

Representative experimental procedure for the catalytic asymmetric Pictet-Spengler reaction.

Method A (Pictet-Spengler reactions of aliphatic aldehydes): To a solution of the tryptamine **3** (0.15 mmol) and the chiral phosphoric acid catalyst **5f** (20 mol%) in dry toluene (1 mL) was added Na_2SO_4 (500 mg) and the mixture was cooled to -30°C or -45°C and then the pre cooled-aldehyde (1.5 eq) solution in toluene (0.5 ml) at the reaction temperature was transferred by a syringe. The reaction mixture was then stirred for 3-5 days at the same temperature after which the reaction was quenched with aqueous Na_2CO_3 and allowed to warm to r.t. The organic phase was then separated, the aqueous phase washed three times with CH_2Cl_2 and the combined organic layers dried with MgSO_4 and evaporated to give a residue

that was chromatographed on silicagel (10% EtOAc-CH₂Cl₂ or 25% EtOAc-CH₂Cl₂) to give the pure products **4** as yellow oil which were then triturated in hexane to form white or pale yellow solid.

Method B (Pictet-Spengler reactions of aromatic aldehydes):

To a solution of the tryptamine **3** (0.15 mmol), the aldehyde (1.5eq) and the chiral phosphoric acid catalyst **5f** (20 mol%) in dry dichloromethane (1.5 mL) was added Na₂SO₄ (500 mg) and the mixture was cooled to -10°C and stirred for 6 days after which the reaction was quenched with aqueous Na₂CO₃ and warmed to r.t. The organic phase was then separated, the aqueous phase washed three times with CH₂Cl₂ and the combined organic layers dried with MgSO₄ and evaporated to give a residue that was chromatographed on silicagel (20% EtOAc-CH₂Cl₂) to give the pure products **4** as yellow oil which were then triturated in hexane to form white or pale yellow solid.

The synthesis of the racemic compounds were performed according to the above mentioned procedure at room temperature using TFA(1 eq) as the catalyst.

¹H NMR (300 MHz CDCl₃) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 1H), 1.66 (h, *J* = 7.2 Hz, 1H), 1.77 – 1.90 (m, 1H), 3.05 (dd, *J* = 15.3, 2.4 Hz, 1H), 3.28 (s, 1H), 3.59 (dd, *J* = 15.3, 1.5 Hz, 1H), 3.91 – 4.11 (m, 2H), 4.17 – 4.30 (m, 3H), 6.98 – 7.07 (m, 2H), 7.18 (dd, *J* = 6.5, 1.9 Hz, 1H), 7.43 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.83 (s, 1H); ¹³C NMR (75 MHz CDCl₃) δ 169.2, 168.6, 135.3, 132.97, 126.1, 120.6, 118.3, 117.1, 109.7, 105.6, 66.0, 61.2, 60.8, 49.9, 27.283, 26.172, 13.0, 12.9, 8.4; HRMS (ESI), calcd for C₁₉H₂₄N₂O₄.Na⁺ (MNa⁺) 367.16283, found, 367.162975. The enantiomeric excess was determined to be 88 % by chiral HPLC (Chiral OD-RH column, 45% CH₃CN/H₂O, 0.5 mL/min, 220 nm, *t*_R (Major 19.32 min), *t*_R (minor 21.28 min).

^1H NMR (400 MHz CDCl_3) δ 0.97 (t, $J = 7.4$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.67 (h, $J = 7.3$ Hz, 1H), 1.80 – 1.90 (m, 1H), 3.02 (dd, $J = 15.1, 2.2$ Hz, 1H), 3.55 (dd, $J = 15.1, 1.6$ Hz, 1H), 3.79 (s, 3H), 3.95 – 4.11 (m, 2H), 4.19 – 4.27 (m, 3H), 6.72 (dd, $J = 8.7, 2.5$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 7.10 (d, $J = 8.7$ Hz, 1H), 7.53 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 153.7, 130.9, 127.2, 111.1, 111.0, 106.3, 100.0, 66.7, 61.9, 61.4, 55.5, 50.5, 28.0, 26.9, 13.7, 13.6, 9.1; HRMS (ESI), calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_5\cdot\text{Na}^+$ (MNa^+) 397.17339, found, 397.173588. The enantiomeric excess was determined to be 90 % by chiral HPLC (Chiral AD-RH column, 40% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_{R} (Major 16.58 min), t_{R} (minor 13.72 min).

^1H NMR (400 MHz CDCl_3) δ 0.96 (t, $J = 7.4$ Hz, 3H), 1.05 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.64 (h, $J = 7.2$ Hz, 1H), 1.78 – 1.88 (m, 1H), 3.00 (dd, $J = 15.2, 2.5$ Hz, 1H), 3.54 (dd, $J = 15.2, 1.4$ Hz, 1H), 3.73 (s, 3H), 3.94 – 4.10 (m, 1H), 4.16 – 4.27 (m, 3H), 6.69 (dd, $J = 8.5, 2.2$ Hz, 1H), 6.73 (d, $J = 2.1$ Hz, 1H), 7.30 (d, $J = 8.5$ Hz, 1H), 7.63 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 170.0, 169.5, 155.8, 136.7, 132.5, 121.3, 118.286, 108.4, 106.2, 94.6, 61.8, 61.4, 55.4, 50.4, 28.1, 26.9, 13.7, 13.6, 9.1; HRMS (ESI), calcd for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_5\cdot\text{Na}^+$ (MNa^+) 397.173395, found, 397.173357. The enantiomeric excess was determined to be 86 % by chiral HPLC (Chiral AD-RH column, 45% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_{R} (Major 11.64 min), t_{R} (minor 10.25 min).

^1H NMR (400 MHz CDCl_3) δ 0.96 (t, $J = 7.4$ Hz, 3H), 1.05 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.66 (h, $J = 7.2$ Hz, 1H), 1.79 – 1.89 (m, 1H), 3.00 (dd, $J = 15.1, 2.3$ Hz, 1H), 3.53 (dd, $J = 15.1, 1.5$ Hz, 1H), 3.95 – 4.10 (m, 2H), 4.17 – 4.28 (m, 3H), 5.03 (s, 2H), 6.80 (dd, $J = 8.7, 2.4$ Hz, 1H), 7.00 (d,

$J = 2.3$ Hz, 1H), 7.10 (d, $J = 8.7$ Hz, 1H), 7.22 – 7.27 (m, 1H), 7.32 (t, $J = 7.31$ Hz, 2H), 7.41 (d, $J = 7.0$ Hz, 2H), 7.57 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 169.9, 169.4, 152.9, 137.3, 134.6, 131.1, 128.1, 127.3, 127.2, 111.7, 110.9, 106.3, 101.6, 70.5, 66.6, 61.8, 61.4, 50.5, 28.1, 26.9, 13.7, 13.6, 9.1, HRMS (ESI), calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_5\cdot\text{H}^+$ (MH^+) 451.222749, found, 451.222810. The enantiomeric excess was determined to be 90 % by chiral HPLC (Chiral AD-RH column, 45% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_{R} (Major 33.52 min), t_{R} (minor 25.93 min).

^1H NMR (400 MHz CDCl_3) δ 0.92 (t, $J = 7.3$ Hz, 3H), 1.07 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.39 – 1.53 (m, 1H), 1.59 – 1.69 (m, 1H), 1.71 – 1.80 (m, 1H), 3.01 (dd, $J = 15.1, 2.2$ Hz, 1H), 3.55 (dd, $J = 15.1, 1.5$ Hz, 1H), 3.79 (s, 3H), 3.95 – 4.11 (m, 2H), 4.17 – 4.29 (m, 3H), 6.72 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.90 (d, $J = 2.3$ Hz, 1H), 7.10 (d, $J = 8.7$ Hz, 1H), 7.53 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 169.8, 169.4, 153.7, 134.7, 130.8, 127.2, 111.1, 110.9, 106.1, 100.1, 66.6, 61.8, 61.4, 55.5, 49.1, 37.3, 26.8, 18.1, 13.7, 13.6; HRMS (ESI), calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_5\cdot\text{Na}^+$ (MNa^+) 411.189039, found, 411.188993. The enantiomeric excess was determined to be 88 % by chiral HPLC (Chiral AD-RH column, 40% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_{R} (Major 23.32 min), t_{R} (minor 20.15 min).

^1H NMR (400 MHz CDCl_3) δ 0.87 (t, $J = 7.1$ Hz, 3H), 1.07 (t, $J = 7.1$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.29 – 1.35 (m, 2H), 1.35 – 1.45 (m, 2H), 1.59 – 1.68 (m, 1H), 1.74 – 1.83 (m, 1H), 3.01 (dd, $J = 15.1, 1.6$ Hz, 1H), 3.55 (dd, $J = 15.1, 1.4$ Hz, 1H), 3.79 (s, 3H), 3.95 – 4.11 (m, 1H), 4.17 – 4.29 (m, 3H), 6.72 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.91 (d, $J = 2.3$ Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 1H), 7.53 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 153.7, 130.8, 127.2, 111.1, 110.9, 106.1, 100.1, 95.2, 66.6, 61.9, 61.4, 55.5, 49.4, 34.9, 27.0, 26.8, 22.4, 13.7, 13.6; HRMS (ESI), calcd for

$C_{22}H_{30}N_2O_5 \cdot Na^+$ (MNa^+) 425.204692, found, 425.204867. The enantiomeric excess was determined to be 88 % by chiral HPLC (Chiral AD-RH column, 35% CH_3CN/H_2O , 0.5 mL/min, 220 nm, t_R (Major 73.27 min), t_R (minor 65.89 min).

1H NMR (400 MHz $CDCl_3$) δ (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.30 – 1.36 (m, 2H), 1.37 – 1.47 (m, 2H), 1.61 – 1.70 (m, 1H), 1.76 – 1.85 (m, 1H), 3.04 (dd, $J = 15.2, 2.3$ Hz, 1H), 3.59 (dd, $J = 15.2, 1.6$ Hz, 1H), 3.94 – 4.11 (m, 2H), 4.17 – 4.29 (m, 3H), 7.00 – 7.08 (m, 2H), 7.22 (d, $J = 8.0$ Hz, 1H), 7.44 (d, $J = 7.3$ Hz, 1H), 7.68 (s, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 169.8, 169.4, 135.8, 133.8, 126.8, 121.2, 119.1, 117.8, 110.3, 106.1, 66.6, 61.8, 61.4, 49.352, 35.0, 27.0, 26.8, 22.4, 13.7, 13.6, 13.6, HRMS (ESI), calcd for $C_{21}H_{28}N_2O_4 \cdot Na^+$ (MNa^+) 395.194125, found, 395.194255. The enantiomeric excess was determined to be 88 % by chiral HPLC (Chiral AD-RH column, 50% CH_3CN/H_2O , 0.5 mL/min, 220 nm, t_R (Major 13.24 min), t_R (minor 15.29 min).

1H NMR (400 MHz $CDCl_3$) δ 0.94 (d, $J = 6.6$ Hz, 3H), 0.99 (d, $J = 6.6$ Hz, 3H), 1.09 (t, $J = 7.1$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 1H), 1.49 – 1.56 (m, 1H), 1.60 – 1.67 (m, 1H), 1.86 – 1.96 (m, 1H), 2.64 (bs, 1H), 3.04 (d, $J = 15.0$ Hz, 1H), 3.58 (dd, $J = 15.2, 1.4$ Hz, 1H), 3.79 (s, 3H), 3.96 – 4.13 (m, 2H), 4.19 – 4.29 (m, 3H), 6.72 (dd, $J = 8.7, 2.4$ Hz, 1H), 6.90 (d, $J = 2.3$ Hz, 1H), 7.10 (d, $J = 8.7$ Hz, 1H), 7.52 (s, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 153.7, 130.8, 127.2, 114.0, 111.1, 110.9, 105.8, 100.0, 66.6, 62.0, 61.5, 55.5, 47.2, 44.0, 26.7, 23.9, 23.4, 20.8, 13.7, 13.6; HRMS (ESI), calcd for $C_{22}H_{30}N_2O_5 \cdot Na^+$ (MNa^+) 425.204690, found 425.204591. The enantiomeric excess was determined to be 80 % by chiral HPLC (Chiral AD-RH column, 40% CH_3CN/H_2O , 0.5 mL/min, 220 nm, t_R (Major 28.17 min), t_R (minor 23.71 min).

^1H NMR (300 MHz CDCl_3) δ 1.03 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.53 (bs, 1H), 2.95 – 3.08 (m, 3H), 3.55 (dd, $J = 15.2$, 1.3 Hz, 1H), 3.78 (s, 3H), 3.90 – 4.12 (m, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 4.59 (t, $J = 6.9$ Hz, 1H), 6.69 (dd, $J = 8.7$, 2.4 Hz, 1H), 6.89 (d, $J = 2.3$ Hz, 1H), 6.98 (d, $J = 8.7$ Hz, 1H), 7.12 (s, 1H), 7.20 – 7.34 (m, 5H); ^{13}C NMR (75 MHz CDCl_3) δ 154.4, 138.0, 131.3, 129.7, 129.3, 127.5, 112.0, 111.7, 106.8, 100.7, 67.4, 62.6, 62.2, 56.2, 51.8, 42.8, 27.6, 14.4, 14.3, HRMS (ESI), calcd for $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_5\cdot\text{Na}^+$ (MNa^+) 459.189042, found 459.188844. The enantiomeric excess was determined to be 80 % by chiral HPLC (Chiral AD-RH column, 40% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_R (Major 45.05 min), t_R (minor 34.90 min).

^1H NMR (400 MHz CDCl_3) δ 1.02 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.51 (s, 1H), 2.98 – 3.12 (m, 3H), 3.60 (dd, $J = 15.3$, 1.5 Hz, 1H), 3.90 – 3.98 (q, 1H), 4.02 – 4.10 (m, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 4.63 (t, $J = 7.0$ Hz, 1H), 6.99 – 7.10 (m, 3H), 7.21 (s, 1H), 7.26 – 7.35 (m, 5H), 7.44 (d, $J = 6.9$ Hz, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 135.5, 129.0, 128.5, 126.7, 126.3, 121.4, 119.0, 117.8, 114.0, 110.3, 106.3, 95.2, 66.6, 61.9, 61.4, 51.0, 26.8, 13.6, 13.6; MS (EI), 406. The enantiomeric excess was determined to be 79 % by chiral HPLC (Chiral OD-RH column, 50% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_R (Major 32.70 min), t_R (minor 37.39 min).

^1H NMR (400 MHz CDCl_3) δ 0.75 (t, $J = 7.5$ Hz, 3H), 0.98 (t, $J = 7.2$ Hz, 3H), 1.05 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.29 – 1.56 (m, 6H), 2.97 (dd, $J = 15.0$, 2.4 Hz, 1H), 3.55 (dd, $J = 15.0$, 1.5 Hz, 1H), 3.79 (s, 3H), 3.95 – 4.09 (m, 2H), 4.23 (dq, $J = 7.1$, 0.8 Hz, 2H), 4.44 (d, $J = 1.5$ Hz, 1H), 6.72 (dd, $J = 8.7$, 2.5 Hz, 1H), 6.91 (d, $J =$

2.4 Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 170.1, 153.7, 134.4, 130.8, 127.3, 110.9, 107.3, 99.9, 95.3, 66.8, 61.8, 61.3, 55.5, 51.0, 46.2, 26.8, 22.6, 22.1, 13.7, 12.4, 11.9; HRMS (ESI), calcd for $\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_5 \cdot \text{Na}^+$ (MNa^+) 439.220338, found 439.220323. The enantiomeric excess was determined to be 81 % by chiral HPLC (Chiral AD-RH column, 33% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_R (Major 122.40 min), t_R (minor 133.64 min).

^1H NMR (400 MHz CDCl_3) δ 0.80 (d, $J = 6.8$ Hz, 3H), 1.00 – 1.03 (m, 6H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.49 (s, 1H), 1.98 – 2.05 (m, 1H), 2.98 (dd, $J = 15.0, 2.3$ Hz, 1H), 3.53 (dd, $J = 15.0, 1.4$ Hz, 1H), 3.79 (s, 3H), 3.91 – 4.07 (m, 2H), 4.19 – 4.26 (m, 2H), 4.28 (s, 1H), 6.72 (dd, $J = 8.7, 2.5$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 7.10 (d, $J = 8.7$ Hz, 1H), 7.48 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 170.3, 169.3, 153.6, 134.2, 130.9, 127.1, 110.9, 110.9, 107.1, 99.9, 95.2, 66.7, 61.7, 61.2, 55.5, 54.7, 32.5, 26.8, 18.3, 16.1, 13.7, 13.6, HRMS (ESI), calcd for $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_5 \cdot \text{Na}^+$ (MNa^+) 411.189041, found 411.188919. The enantiomeric excess was determined to be 81 % by chiral HPLC (Chiral AD-RH column, 35% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_R (Major 38.92 min), t_R (minor 44.98 min).

^1H NMR (400 MHz CDCl_3) δ 1.01 (t, $J = 7.1$ Hz, 3H), 1.06 – 1.13 (m, 2H), 1.17 – 1.23 (m, 2H), 1.16 – 1.33 (t, $J = 7.1$ Hz, 6H), 1.50 (s, 1H), 1.55 – 1.67 (m, 2H), 1.69 – 1.78 (m, 2H), 2.96 (dd, $J = 14.9, 2.3$ Hz, 1H), 3.51 (dd, $J = 14.9, 1.4$ Hz, 1H), 3.79 (s, 3H), 3.90 – 4.06 (m, 2H), 4.19 – 4.27 (m, 3H), 6.72 (dd, $J = 8.7, 2.5$ Hz, 1H), 6.90 (d, $J = 2.4$ Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 1H), 7.49 (s, 1H); ^{13}C NMR (100 MHz CDCl_3) δ 170.2, 169.3, 153.6, 130.9, 127.2, 110.9, 110.8, 107.1, 99.9, 95.2, 66.8, 61.7, 61.2, 55.5, 54.5, 43.2, 28.9, 26.8, 26.5, 26.4, 26.1, 26.0, 13.7, 13.6, HRMS (ESI), calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5 \cdot \text{Na}^+$ (MNa^+) 451.220342, found, 451.220792.

The enantiomeric excess was determined to be 94 % by chiral HPLC (Chiral AD-RH column, 35% CH₃CN/H₂O, 0.5 mL/min, 220 nm, *t_R* (Major 126.53 min), *t_R* (minor 170.28 min).

¹H NMR (400 MHz CDCl₃) δ 1.11 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.50 (s, 1H), 3.25 (dd, *J* = 15.4, 2.3 Hz, 1H), 3.65 (dd, *J* = 15.4, 1.4 Hz, 1H), 3.80 (s, 3H), 4.00 – 4.08 (m, 1H), 4.10 – 4.17 (m, 1H), 4.17 – 4.27 (m, 2H), 5.54 (s, 1H), 6.73 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.96 (d, *J* =

2.3 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 7.14 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (100 MHz CDCl₃) δ 169.9, 168.5, 153.9, 148.6, 132.3, 131.2, 129.1, 126.8, 123.7, 111.9, 111.2, 106.8, 100.2, 95.2, 66.7, 62.1, 61.7, 55.5, 54.6, 26.7, 13.6, HRMS (ESI), calcd for C₂₄H₂₅N₃O₇.Na⁺ (MNa⁺) 490.158471, found, 490.158387. The enantiomeric excess was determined to be 96 % by chiral HPLC (Chiral AD-RH column, 40% CH₃CN/H₂O, 0.5 mL/min, 220 nm, *t_R* (Major 54.37 min), *t_R* (minor 65.88 min).

¹H NMR (400 MHz CDCl₃) δ 1.10 (t, *J* = 7.1 Hz 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.52 (bs, 1H), 3.29 (dd, *J* = 15.5, 2.5 Hz, 1H), 3.69 (dd, *J* = 15.5, 1.6 Hz, 1H), 3.99 – 4.07 (m, 1H), 4.09 – 4.17 (m, 1H), 4.17 – 4.27 (m, 2H), 5.58 (s, 1H), 7.04 – 7.14 (m, 3H), 7.25 (s, 1H), 7.51 (dd, *J* = 6.4, 2.4 Hz,

1H), 7.55 (d, *J* = 8.7 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (100 MHz CDCl₃) δ 174.9, 129.2, 123.7, 122.1, 119.5, 110.5, 100.0, 95.2, 86.7, 86.7, 68.5, 66.7, 62.1, 61.7, 55.3, 54.6, 26.6, 13.6; MS (EI), 437. The enantiomeric excess was determined to be 88 % by chiral HPLC (Chiral AD-RH column, 50% CH₃CN/H₂O, 0.5 mL/min, 220 nm, *t_R* (Major 18.59 min), *t_R* (minor 24.30 min).

^1H NMR (400 MHz CDCl_3) δ 1.10 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 1H), 3.23 (dd, $J = 15.4, 2.4$ Hz, 1H), 3.63 (dd, $J = 15.4, 1.6$ Hz, 1H), 3.79 (s, 3H), 3.99 – 4.07 (m, 1H), 4.09 – 4.16 (m, 1H), 4.16 – 4.26 (m, 1H), 5.46 (s, 1H), 6.72 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.95 (d, $J = 2.4$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 7.21 (s, 1H), 7.46 (d, $J = 8.2$ Hz, 2H), 7.56 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (100 MHz CDCl_3) δ 169.9, 168.6, 153.8, 146.7, 132.4, 132.2, 131.2, 129.0, 126.8, 118.1, 111.8, 111.2, 106.7, 100.2, 95.2, 66.7, 62.0, 61.7, 55.5, 54.9, 26.6, 13.8, 13.6; HRMS (ESI), calcd for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_5\cdot\text{Na}^+$ (MNa^+) 470.168639, found, 470.168807. The enantiomeric excess was determined to be 80 % by chiral HPLC (Chiral AD-RH column, 35% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_R (Major 67.03 min), t_R (minor 80.11 min)).

^1H NMR (400 MHz CDCl_3) δ 1.09 (t, $J = 7.1$ Hz, 3H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.54 (bs, 1H), 3.27 (dd, $J = 15.5, 2.5$ Hz, 1H), 3.68 (dd, $J = 15.5, 1.6$ Hz, 1H), 3.98 – 4.06 (m, 1H), 4.09 – 4.15 (m, 1H), 4.16 – 4.26 (m, 2H), 5.50 (s, 1H), 7.03 – 7.08 (m, 1H), 7.09 – 7.14 (m, 1H), 7.27 (s, 1H), 7.48 (d, $J = 8.3$ Hz, 3H), 7.46 – 7.51 (m, 1H), 7.58 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz CDCl_3) δ 169.9, 168.5, 146.6, 136.2, 132.3, 131.6, 129.1, 126.4, 122.0, 119.4, 118.2, 118.1, 111.9, 110.5, 107.0, 95.2, 66.7, 62.1, 61.7, 54.8, 26.6, 13.6; MS (EI), 417. The enantiomeric excess was determined to be 89 % by chiral HPLC (Chiral AD-RH column, 40% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.5 mL/min, 220 nm, t_R (Major 50.01 min), t_R (minor 37.61 min)).

Determination of the absolute configuration of **4a**

The absolute configuration of **4a** was determined by hydrolytic decarboxylation⁴ to the monoester (eq 1, Scheme 1), and comparing with (*1R*, *3S*) - and (*1S*, *3S*) - ethyl 1-ethyl-

(4) Krapcho, A. P. *Synthesis*, **1982**, 805-822.

2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylates, prepared from the Pictet-Spengler reaction of (*S*)-tryptophan ethyl ester and propionaldehyde (eq 2, Scheme 1),⁵ using chiral HPLC (Chiral AD-RH column, 40% CH₃CN/H₂O, 0.5 mL/min, 220 nm, *t_R* ((*1R*, 3*S*)-major enantiomer 22.88 min), *t_R* ((*1S*, 3*S*)-minor enantiomer 17.55 min), *t_R* ((*1S*, 3*R*)-minor enantiomer 18.94 min), *t_R* ((*1R*, 3*R*)-major enantiomer 21.07 min).

Scheme 1. Determination of the absolute stereochemistry of (*1R*, 3*S*)-ethyl 1-ethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate from **4a**.

¹H NMR (400 MHz CDCl₃) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.55 (bs, 1H), 1.71 (m, 1H), 1.64 – 1.75 (m, 1H), 1.90 – 2.00 (m, 1H), 2.73 (ddd, *J* = 15.1, 4.2, 1.9 Hz, 1H), 3.06 (ddd, *J* = 15.1, 4.2, 1.9 Hz, 1H), 3.71 (dd, *J* = 11.2, 4.2 Hz, 1H), 4.80 – 4.12 (m, 1H), 4.22 (dq, *J* = 7.1, 1.6 Hz, 2H), 7.03 (dt, *J* = 7.1, 1.1 Hz, 1H), 7.09 (dt, *J* = 7.1, 1.2 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.70 (s, 1H); ¹³C NMR (100 MHz CDCl₃) δ 172.9, 135.1, 126.9, 121.3, 119.2, 117.7, 110.4, 108.1, 95.3, 60.7, 56.1, 53.3, 27.1, 25.6, 13.9, 9.3. HRMS (ESI), calcd for C₁₆H₂₀N₂O₂.Na⁺ (MNa⁺) 295.141693, found 295.141861.

(5) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 6976-6984

^1H NMR (400 MHz CDCl_3) δ 1.02 (t, $J = 7.4$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.63 – 1.93 (m, 3H), 2.91 (ddd, $J = 15.3, 7.5, 1.4$ Hz, 1H), 3.05 (ddd, $J = 15.3, 5.2, 0.9$ Hz, 1H), 3.90 (dd, $J = 7.4, 5.2$ Hz, 1H), 4.07 – 4.21 (m, 2H), 7.06 (dtd, $J = 22.0, 7.3, 1.1$ Hz, 2H), 7.24 (d, $J = 7.9$ Hz, 1H), 7.42 (d, $J = 7.7$ Hz, 1H), 7.69 (s, 1H). ^{13}C NMR (100 MHz CDCl_3) δ 173.377, 135.538, 126.794, 121.345, 119.114, 117.728, 110.359, 106.825, 95.314, 60.689, 52.309, 51.397, 28.151, 24.688, 13.880, 10.347; HRMS (ESI), calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\cdot\text{Na}^+$ (MNa^+) 295.141698, found 295.141881.

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	19.324	93.917
2	21.283	6.083
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	20.397	49.186
2	22.307	50.814
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	13.720	5.185
2	16.580	94.815
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	13.689	49.600
2	16.490	50.400
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	10.258	6.869
2	11.644	93.131
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	10.239	48.771
2	11.663	51.229
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	25.936	5.227
2	33.521	94.773
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	25.934	49.960
2	33.469	50.040
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	20.157	5.831
2	23.326	94.169
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	20.076	49.151
2	23.203	50.849
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	65.897	6.171
2	73.278	93.829
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	65.793	49.429
2	73.044	50.571
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	13.243	93.765
2	15.295	6.235
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	13.009	49.492
2	14.839	50.508
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	23.716	10.218
2	28.172	89.782
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	23.581	49.883
2	28.486	50.117
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	34.900	14.151
2	45.053	85.849
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	35.994	49.855
2	46.739	50.145
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	32.701	89.726
2	37.393	10.274
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	32.664	50.179
2	37.362	49.821
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	122.405	90.501
2	133.648	9.499
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	120.501	48.956
2	131.346	51.044
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	38.920	90.373
2	44.984	9.627
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	40.170	49.673
2	45.456	50.327
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	126.530	96.776
2	170.287	3.224
Total		100.000

Detector A Ch1 220nm		
Peak #	Ret. Time	Area %
1	125.460	50.072
2	168.354	49.928
Total		100.000

Peak #	Ret. Time	Area %
1	54.377	98.156
2	65.886	1.844
Total		100.000

Peak #	Ret. Time	Area %
1	55.160	49.111
2	66.581	50.889
Total		100.000

Peak #	Ret. Time	Area %
1	18.595	93.955
2	24.304	6.045
Total		100.000

Peak #	Ret. Time	Area %
1	18.817	50.068
2	24.478	49.932
Total		100.000

Peak #	Ret. Time	Area %
1	67.036	90.083
2	80.110	9.917
Total		100.000

Peak #	Ret. Time	Area %
1	69.919	49.814
2	82.848	50.186
Total		100.000

Peak #	Ret. Time	Area %
1	37.608	5.641
2	50.011	94.359
Total		100.000

Peak #	Ret. Time	Area %
1	37.986	49.326
2	52.721	50.674
Total		100.000

Product after hydrolytic decarboxylation of **4a**