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Supporting Information

Organocatalytic Approach to Benzofused Nitrogen-Containing Heterocycles: Enantioselective Total Synthesis of (+)-Angustureine

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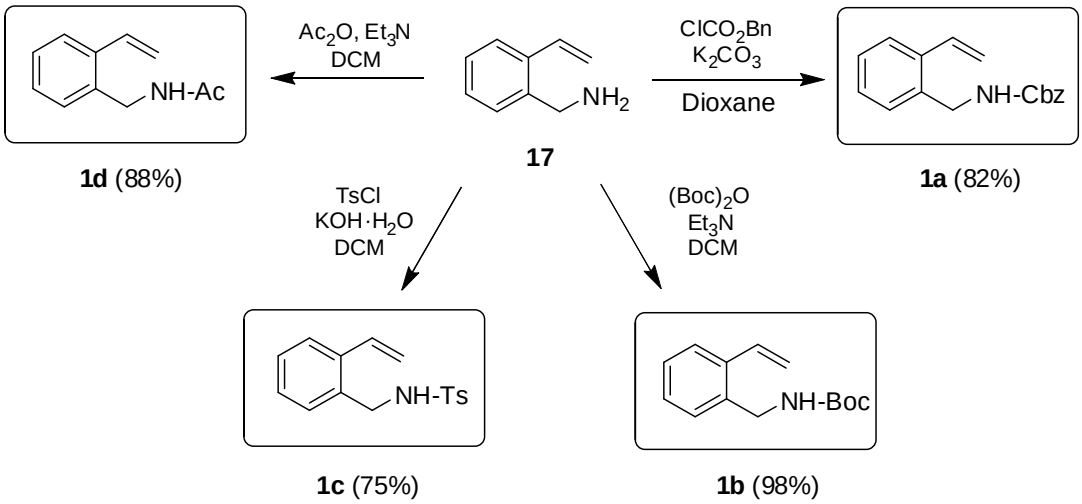
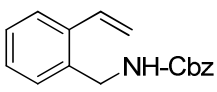
Contents

General Methods. NMR spectra were obtained on a Bruker 300 spectrometer, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. All reactions were carried out in anhydrous solvents and under argon atmosphere. THF and Et_2O were distilled from sodium-benzophenone under argon, and CH_2Cl_2 was distilled from P_2O_5. Flash column chromatography was performed using silica gel Merck-60 (230-400 mesh). The enantiomeric ratios were determined with the aid of HPLC analysis with Chiracel IC column (25 cm x 0.46 cm) with mixtures of hexanes:*i*propanol as eluents.

Materials. Commercially available starting materials and solvents were used without further purification. Amines **17**,[1] **18**,[2] **19**,[1] **6**[3] and nitroderivative **20**[4] had previously been described.

Synthesis of *N*-protected *o*-vinylbenzylamines 1



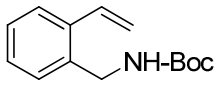


1a

Synthesis of *N*-Benzyloxycarbonyl-2-vinylbenzylamine (1a).

[1] M. L. Bennasar, T. Roca, M. Monerris, D. García-Díaz, *J. Org. Chem.* **2006**, *71*, 7028.
[2] M. G. Organ, J. Xu, B. N´Zemba, *Tetrahedron Lett.* **2002**, *43*, 8177.
[3] X. Han, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2006**, *45*, 1747.
[4] R. A. Bunce, D. M. Herron, M. L. Ackerman, *J. Org. Chem.* **2000**, *65*, 2847.

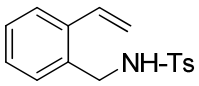
To a solution of *o*-vinylbenzyl amine **17** (224 mg, 1.68 mmol) in dioxane (8 mL) was added K_2CO_3 (348 mg, 2.53 mmol). To this suspension $ClCO_2Bn$ (0.48 mL, 3.37 mmol) was added dropwise and the mixture was vigorously stirred for 1 h. Then, solvent was then removed under reduced pressure and the residue was diluted with 1M HCl (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After solvent was removed, the crude mixture was purified by flash chromatography with hexanes:ethyl acetate 10:1 to afford **1a** (367 mg, 82%) as a yellow solid. M.p. 58-60ºC. ^{1}H-NMR (300 MHz): 4.44 (d, J = 5.6 Hz, 2H), 4.93 (br s, 1H), 5.12 (s, 2H), 5.33 (d, J = 10.9 Hz, 1H), 5.66 (dd, J_1 = 17.3, J_2 = 1.1 Hz, 1H), 6.95 (dd, J_1 = 17.3, J_2 =10.9 Hz, 1H), 7.25-7.37 (m, 8H), 7.50 (d, J = 6.8 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 43.5 (CH_2), 67.3 (CH_2), 117.3 (CH_2), 126.6 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.4 (CH), 134.0 (CH), 135.3 (C), 136.9 (C), 137.2 (C), 156.5 (C) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{17}H_{17}NO_2$ (M^+): 267.1259. Found: 267.1252.



1b

Synthesis of *N*-*tert*-butoxycarbonyl-2-vinylbenzylamine (1b).

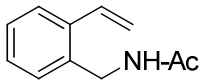
Et_3N (0.35 mL, 2.51 mmol) and a catalytic amount of DMAP (5 mg) were added to a solution of *o*-vinylbenzyl amine **17** (111 mg, 0.84 mmol) in CH_2Cl_2 (1.5 mL). After 5 min, $(Boc)_2O$ (201 mg, 0.92 mmol) was added to the resulting solution and the mixture stirred at rt for 4 h. The solvent was then removed, the residue diluted with water (8 mL), acidified with 1M HCl until pH = 5, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After the solvent was removed, the crude mixture was purified by flash chromatography with hexanes:ethyl acetate 10:1 to afford **1b** (192 mg, 98%) as a yellow oil. ^{1}H-NMR (300 MHz): 1.45 (s, 9H), 4.38 (d, J = 5.6 Hz, 2H), 4.68 (br s, 1H), 5.34 (dd, J_1 = 10.9, J_2= 1.3 Hz, 1H), 5.67 (dd, J_1 = 17.3, J_2 = 1.3 Hz, 1H), 6.96 (dd, J_1 = 17.3, J_2 = 10.9 Hz, 1H) 7.24-7.31 (m, 3H), 7.50-7.53 (m, 1H) ppm. ^{13}C-NMR (75 MHz): 27.9 ($3CH_3$), 42.1 (CH_2), 79.0 (C), 116.1 (CH_2), 125.6 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH), 133.3 (CH), 135.0 (C), 136.3 (C), 155.1 (C) ppm. HRMS (FAB+) (*m/z)*: calcd. for $C_{14}H_{20}NO_2$ ($M+H^+$): 234.1494. Found: 234.1498.



1c

Synthesis of *N*-Tosyl-2-vinylbenzylamine (1c).

KOH (6.63 g, 0.12 mmol) was added to a solution of *o*-vinylbenzyl amine **17** (450 mg, 3.38 mmol) in H_2O:CH_2Cl_2 (15 + 15 mL). After 5 min, TsCl (1.61 g, 8.46 mmol) was added to the resulting suspension and the mixture vigorously stirred at rt. After 1 h, the reaction mixture was hydrolyzed with water (10 mL), extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After solvent evaporation, the crude mixture was subjected to flash chromatography with hexanes:ethyl acetate 5:1 to afford **1c** (726 mg, 75%) as a white solid. M.p. 124-126ºC. ^{1}H-NMR (300 MHz): 2.45 (s, 3H), 4.16(d, J = 5.8 Hz, 2H), 4.43 (br s, 1H), 5.28 (dd, J_1 = 10.9, J_2 = 1.3 Hz, 1H), 5.62 (dd, J_1 = 17.3, J_2 = 1.3 Hz, 1H), 6.76 (dd, J_1 = 17.3, J_2 = 10.9 Hz, 1H), 7.11-7.24 (m, 3H), 7.31 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.2 Hz, 2H) ppm. ^{13}C-NMR (75 MHz): 21.5 (CH_3), 45.2 (CH_2), 117.3 (CH_2), 126.2 (CH), 127.2 (CH), 128.0 (CH), 128.6 (CH), 129.5 (CH), 129.7 (CH), 132.7 (C), 133.3 (CH), 136.5 (C), 137.0 (C), 143.6 (C) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{16}H_{17}NO_2S$ (M^+): 287.0980. Found: 287.0982.

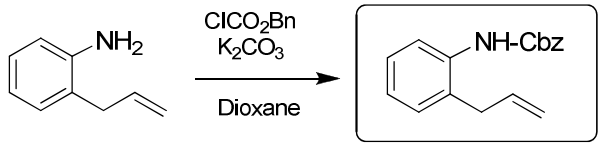


1d

Synthesis of *N*-*tert*-Butoxycarbonyl-2-vinylbenzylamine (1d).

Acetic anhydride (2.67 mL, 2.98 mmol) and Et_3N (0.30 mL, 2.98 mmol) were added to a solution of *o*-vinylbenzyl amine **17** (397 mg, 2.98 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 12 h, then hydrolyzed with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were succesively washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. After the solvent was removed, the crude mixture was purified by flash chromatography with hexanes:ethyl acetate 3:1 to afford **1d** (464 mg, 88%) as a light brown solid. M.p. 83-85ºC. ^{1}H-NMR (300 MHz): 1.98 (s, 3H), 4.48 (d, J = 5.3 Hz, 2H), 5.35 (dd, J_1 = 10.9, J_2 = 1.1 Hz, 1H), 5.68 (dd, J_1 = 17.3, J_2 = 1.1 Hz, 1H), 6.94 (dd, J_1 = 17.3, J_2 = 10.9 Hz, 1H) 7.25-7.33 (m, 3H), 7.53 (d, J = 7.0 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 23.1 (CH_3), 41.7 (CH_2), 116.7 (CH_2), 126.1 (CH), 128.0 (CH), 128.2 (CH), 129.4 (CH), 133.7 (CH), 134.8 (C), 136.9 (C), 169.6 (C) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{11}H_{13}NO$ (M^+): 175.0997. Found: 175.1000.

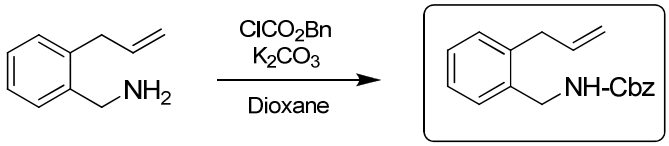
Synthesis of *N*-Benzyloxycarbonyl-2-allylaniline 2



18 **2** (97%)

Following the previously described procedure for the preparation of **1a,** starting from *o*-allylaniline **18** (240 mg, 1.80 mmol) **2** was obtained as a yellow oil (240 mg) in 97% yield. ^{1}H-NMR (300 MHz): 3.36 (d, J = 6.0 Hz, 2H), 5.04 (dd, J_1 = 17.3, J_2 = 1.7 Hz, 1H), 5.14 (dd, J_1 = 9.9, J_2 = 1.7 Hz, 1H), 5.21 (s, 2H), 5.88-6.02 (m, 1H), 6.65 (br s, 1H), 7.06-7.43 (m, 8H), 7.81 (br s, 1H) ppm. ^{13}C-NMR (75 MHz): 36.5 (CH_2), 67.0 (CH_2), 116.7 (CH_2), 124.5 (CH), 127.5 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 129.0 (C), 130.1 (C), 135.7 (CH), 136.0 (C), 136.2 (CH), 153.8 (C) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{17}H_{17}NO_2$ (M^+): 267.1259. Found: 267.1253.

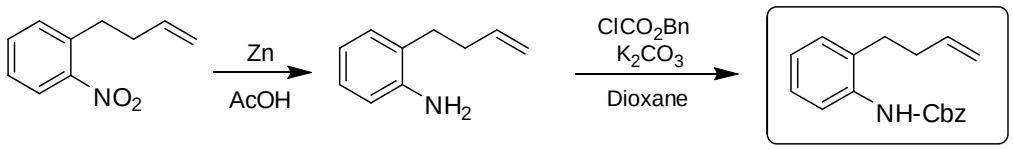
Synthesis of *N*-Benzyloxycarbonyl-2-allylbenzyl amine 3



19 **3** (86%)

Following the previously described procedure for the preparation of **1a,** starting from *o*-allylbenzyl amine **19** (400 mg, 2.72 mmol) **3** was obtained as a yellow oil (654 mg) in 86% yield. ^{1}H-NMR (300 MHz): 3.43 (d, J = 6.0 Hz, 2H), 4.40 (d, J = 5.6 Hz, 2H), 4.94-5.09 (m, 3H), 5.13 (s, 2H), 5.90-6.03 (m, 1H), 7.17-7.36 (m, 9H) ppm. ^{13}C-NMR (75 MHz): 36.9 (CH_2), 42.7 (CH_2), 66.8 (CH_2), 116.0 (CH_2), 126.8 (CH), 127.9 (CH), 128.1 (CH), 128.5 (CH), 128.7 (CH), 130.1 (CH), 136.0 (C), 136.5 (C), 136.9 (CH), 137.8 (C), 156.1 (C) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{18}H_{19}NO_2$ (M^+): 281.1415. Found: 281.1418.

Synthesis of *N*-Benzyloxycarbonyl-2-homoallylaniline 4



20 **21** **4** (81%)

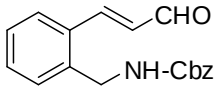
Zinc dust (2.3 g, 33.9 mmol) was added to a solution of **20** (1.0 g, 5.7 mmol) in acetic acid (50 mL). After the suspension was stirred at rt for 5h, the reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2. The solution was diluted with saturated Na_2CO_3 (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvents under reduced pressure, the resulting oil (**21**) was used without further purification in the next step.

From oil **21**, following the previously described procedure for the preparation of **1a, 4** was obtained as a white solid (1.01 g) in 69% yield (2 steps). M.p. 45-47ºC. ^{1}H-NMR (300 MHz): 2.39-2.47 (m, 2H), 2.72-2.77 (m, 2H), 5.10-5.19 (m, 2H), 5.31 (s, 2H) 5.88-6.01 (m, 1H), 6.80 (br s, 1H), 7.17-7.22 (m,

3H), 7.31-7.52 (m, 5H) 7.85 (br s, 1H) ppm. ^{13}C-NMR (75 MHz): 30.5 (CH_2), 33.5 (CH_2), 66.8 (CH_2), 115.4 (CH_2), 124.6 (CH), 126.7 (CH), 128.1 (2CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 130.2 (C), 135.0 (C), 136.0 (C), 137.3 (CH), 153.9 (C) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{18}H_{19}NO_2$ (M^+): 281.1416. Found: 281.1419.

General procedure for the CM reaction

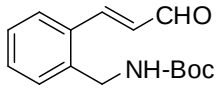
To a solution of the corresponding *N*-protected amine **1**-**4** (1 equiv) in CH_2Cl_2 (0.1 M) under nitrogen, acrolein (5 equiv) and Hoveyda-Grubbs catalyst **9** (5 mol %) were added. The resulting solution was stirred at rt for 12 h and then, the solvents removed and the crude mixture purified by flash chromatography with hexanes:ethyl acetate.



5a

Synthesis of (*E*)-2-Benzyloxycarbonylaminomethyl cinnamaldehyde 5a.

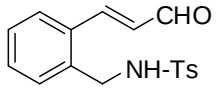
By means of the general procedure described above, **5a** (92 mg) was obtained from **1a** (143 mg) as a white solid in 60% yield after flash chromatography with hexanes:ethyl acetate 3:1. M.p. 65-67 ºC. ^{1}H-NMR (300 MHz): 4.55 (d, J = 5.8 Hz, 2H), 5.05 (br s, 1H), 5.13 (s, 2H), 6.64 (dd, J_1 = 15.8, J_2 = 7.7 Hz, 1H), 7.28-7.41 (m, 8H), 7.62-7.64 (m, 1H), 7.85 (d, J = 15.8 Hz, 1H), 9.66 (d, J = 7.7 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 42.9 (CH_2), 67.1 (CH_2), 127.2 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 129.7 (CH), 130.6 (CH), 131.1 (CH), 132.9 (C), 136.2 (C), 137.4 (C), 149.1 (CH), 155.9 (C), 193.8 (CH) ppm. HRMS (FAB+) (*m/z)*: calcd. for $C_{18}H_{18}NO_3$ ($M+H^+$): 296.1287. Found: 296.1296.



5b

Synthesis of (*E*)-2-*tert*-Butoxycarbonylaminomethyl cinnamaldehyde 5b.

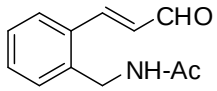
By means of the general procedure described above, **5b** (73 mg) was obtained from **1b** (93 mg) as a white solid in 70% yield after flash chromatography with hexanes:ethyl acetate 3:1. M.p. 109-111 ºC. ^{1}H-NMR (300 MHz): 1.44 (s, 9H), 4.49 (d, J = 5.8 Hz, 2H), 4.78 (br s, 1H), 6.66 (dd, J_1 = 15.8, J_2 = 7.7 Hz, 1H), 7.32-7.43 (m, 3H), 7.64 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 15.8 Hz, 1H), 9.72 (d, J = 7.7 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 28.3 ($3CH_3$), 42.6 (CH_2), 79.9 (C), 127.2 (CH), 128.4 (CH), 129.7 (CH), 130.4 (CH), 131.1 (CH), 133.0 (C), 138.0 (C), 149.5 (CH), 155.3 (C), 193.9 (CH) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{15}H_{19}NO_3$ (M^+): 261.1365. Found: 261.1367.



5c

Synthesis of (*E*)-Tosylaminomethyl cinnamaldehyde 5c.

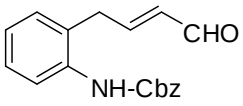
By means of the general procedure described above, **5c** (177 mg) was obtained from **1c** (231 mg) as a white solid in 65% yield after flash chromatography with hexanes:ethyl acetate 4:1. M.p. 140-142 ºC. ^{1}H-NMR (300 MHz): 2.46 (s, 3H), 4.24 (d, J = 6.0 Hz, 2H), 4.67 (br s, 1H), 6.60 (dd, J_1 = 15.8, J_2 = 7.7 Hz, 1H), 7.23-7.37 (m, 5H), 7.58-7.62 (m, 1H), 7.69-7.78 (m, 3H), 9.55 (d, J = 7.7 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 21.6 (CH_3), 45.2 (CH_2), 127.2 (CH), 127.3 (CH), 129.1 (CH), 129.9 (CH), 130.4 (CH), 130.7 (CH), 131.1 (CH), 133.3 (C), 134.7 (C), 136.3 (C), 144.0 (C), 148.5 (CH), 193.8 (C) ppm. HRMS (EI+) (*m/z*): calcd. for $C_{17}H_{17}NO_3S$ (M^+): 315.0929. Found: 315.0919.



5d

Synthesis of (*E*)-Acetamidomethyl cinnamaldehyde 5d.

By means of the general procedure described above, **5d** (170 mg) was obtained from **1d** (464 mg) as a brown solid in 35% yield after flash chromatography with hexanes:ethyl acetate 1:3. M.p. 110-112 ºC. ^{1}H-NMR (300 MHz): 2.00 (s, 3H), 4.60 (d, J = 5.6 Hz, 2H), 5.78 (br s, 1H), 6.64 (dd, J_1 = 15.8, J_2 = 7.7 Hz, 1H), 7.33-7.44 (m, 3H), 7.64 (d, J = 6.8 Hz, 1H), 7.86 (d, J = 15.8 Hz, 1H), 9.71 (d, J = 7.7 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 22.7 (CH_3), 40.9 (CH_2), 126.8 (CH), 128.2 (CH), 129.7 (CH), 130.1 (CH), 130.7 (CH), 132.6 (C), 137.0 (C), 148.8 (CH), 169.1 (C), 193.5 (C) ppm. HRMS (EI+) (*m/z*): calcd. for $C_{12}H_{13}NO_2$ (M^+): 203.0941. Found: 203.0946.

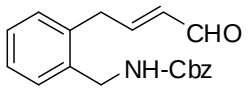


6

Synthesis of (*E*)-4-(2-benzyloxycarbonylamino)phenyl-2-butenal 6.

By means of the general procedure described above, **6** (109 mg) was obtained from **2** (212 mg) as a yellow oil in 50% yield after flash chromatography with hexanes:ethyl acetate 5:1. ^{1}H-NMR (300 MHz): 3.62 (dd, J_1 = 6.2, J_2 = 1.7 Hz, 2H), 5.19 (s, 2H), 6.03 (dd, J_1 = 15.6, J_2 = 7.9 Hz, 1H), 6.33 (br s, 1H), 6.93 (dt, J_1 = 15.6, J_2 = 6.2 Hz, 1H), 7.15-7.17 (m, 2H), 7.26-7.38 (m, 6H), 7.65 (br s, 1H), 9.52 (d, J = 7.9 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 35.3 (CH_2), 67.8 (CH_2), 124.6 (CH) 126.2 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 130.6 (CH), 130.7 (C), 134.2 (CH), 135.7 (C), 136.3 (C),

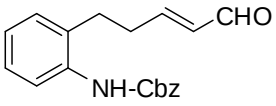
154.4 (C), 155.0 (CH), 193.8 (CH) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{18}H_{17}NO_3$ (M^+): 295.1208. Found: 295.1205.



7

Synthesis of (*E*)-4-(2-benzyloxycarbonylaminomethyl)phenyl-2-butenal 7.

By means of the general procedure described above, **7** (132 mg) was obtained from **3** (210 mg) as a white solid in 60% yield after flash chromatography with hexanes:ethyl acetate 3:1. M.p. 75-77 ºC. ^{1}H-NMR (300 MHz): 3.69 (d, *J* = 5.8 Hz, 2H), 4.35 (d, J = 5.7 Hz, 2H) 4.96 (br s, 1H), 5.10 (s, 2H), 5.95 (dd, J_1 = 15.6, J_2 = 7.7 Hz, 1H), 6.89-6.98 (m, 1H), 7.15 (m, 1H), 7.27-7.34 (m, 8H), 9.46 (d, *J* = 7.7 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 35.7 (CH_2), 42.8 (CH_2), 66.9 (CH_2), 127.6 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.2 (CH), 130.4 (CH), 133.5 (CH), 135.4 (C), 136.1 (C), 136.3 (C), 156.0 (C), 156.1 (CH), 193.5 (CH) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{19}H_{19}NO_3$ (M^+): 309.1365. Found: 309.1363.



8

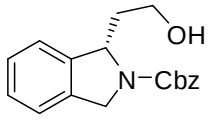
Synthesis of (*E*)-5-(2-benzyloxycarbonylamino)phenyl-2-pentenal 8.

By means of the general procedure described above, **8** (249 mg) was obtained from **4** (369 mg) as a yellow oil in 73% yield after flash chromatography with hexanes:ethyl acetate 3:1. ^{1}H-NMR (300 MHz): 2.66-2.73 (m, 2H), 2.84-2.89 (m, 2H), 5.30 (s, 2H), 6.20 (dd, J_1 = 15.6, J_2 = 7.9 Hz, 1H), 6.78 (br s, 1H), 6.88 (dt, J_1 = 15.6, J_2 = 6.8 Hz, 1H), 7.21-7.27 (m, 2H), 7.32-7.36 (m, 1H), 7.45-7.49 (m, 5H), 7.74 (br s, 1H), 9.55 (d, *J* = 7.9 Hz, 1H) ppm. ^{13}C-NMR (75 MHz): 29.3 (CH_2), 32.4 (CH_2), 67.1 (CH_2), 123.9 (CH), 125.4 (CH), 127.3 (CH), 128.3 (2CH), 128.5 (CH), 129.2 (CH), 132.0 (C), 133.3 (CH), 135.0 (C), 135.9 (C), 154.2 (CH), 156.8 (C), 193.8 (CH) ppm. HRMS (EI+) (*m/z)*: calcd. for $C_{19}H_{19}NO_3$ ($M+H^+$): 309.1365. Found: 309.1375.

<u>General procedure for the intramolecular aza-Michael reaction</u>

In a flame-dried, 10 mL round bottomed flask, unsaturated aldehydes **5-8** (1 equiv) were dissolved in dry chloroform (0.1 M) and the solution was cooled to −30 ºC. To this solution, a mixture of catalyst **I** or **II** (20 mol %) and benzoic acid (0.2 equiv) in chloroform was added and the resulting solution was stirred at this temperature for 12 h (except for substrate **8**, which was maintained for 24 h). The mixture was then diluted with methanol and $NaBH_4$ (3 equiv) was added in portions. The mixture was allowed

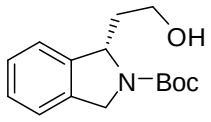
to reach 0ºC and, after 30 minutes at this temperature, the reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. After flash chromatography over silica gel using mixtures of hexane:ethyl acetate as eluents, the corresponding alcohols **10**-**13** were obtained as colorless oils. The enantiomeric ratios were determined with the aid of HPLC analysis with Chiracel IC column (25 cm x 0.46 cm).



(+)-**10a**

Synthesis of (1*S*)-*N*-Benzyloxycarbonyl-1-(2-hydroxyethyl)isoindoline 10a.

By means of the general procedure described above, **10a** (16 mg) was obtained from **5a** (22 mg) as a colorless oil in 72% yield and 98% *ee* with catalyst **I** (68% yield and 99% *ee* with catalyst **II**) after flash chromatography with hexanes:ethyl acetate 3:1. The *ee* was determined by HPLC analysis using a Chiralpack IC column (hexane:isopropanol 87:13); flow rate = 1.1 mL/min, t_{major}=36.9 min, t_{minor}=39.2 min. ^{1}H-NMR (300 MHz): 1.60-1.69 (m, 2H), 2.16-2.27 (m, 1H), 3.70 (br s, 1H), 3.96 (br s, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.91 (d, *J* = 14.9 Hz, 1H), 5.22 (s, 2H), 5.38 (d, *J* = 10.0 Hz, 1H), 7.21-7.40 (m, 9H) ppm. ^{13}C-NMR (75 MHz): 40.4 (CH_2), 51.8 (CH_2), 59.0 (CH_2), 60.6 (CH), 67.5 (CH_2), 122.3 (CH), 122.4 (CH), 127.6 (2CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 135.8 (C), 136.3 (C), 141.3 (C), 156.6 (C) ppm. $[\alpha]_D^{25}$: +21.0 (*c* 1.0, $CHCl_3$). HRMS (EI+) (*m/z*): calcd. for $C_{18}H_{19}NO_3$ (M^+): 297.1365. Found: 297.1360.

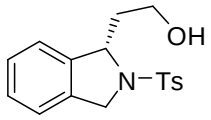


(+)-**10b**

Synthesis of (1*S*)-*N*-*tert*-Butoxycarbonyl-1-(2-hydroxyethyl)isoindoline 10b.

By means of the general procedure described above, **10b** (9.1 mg) was obtained from **5b** (14.5 mg) as a colorless oil in 72% yield and 94% *ee* with catalyst **I** (68% yield and 91% *ee* with catalyst **II**) after flash chromatography with hexanes:ethyl acetate 2:1. The *ee* was determined by HPLC analysis using a Chiralpack IC column (hexane:isopropanol 87:13); flow rate = 1.1 mL/min, t_{major}=12.3 min, t_{minor}=13.5 min. ^{1}H-NMR (300 MHz): 1.51 (s, 9H), 1.55-1.65 (m, 2H), 2.11-2.22 (m, 1H), 3.70 (br s, 1H), 4.29 (m, 1H), 4.53 (dd, J_1 = 15.0, J_2 = 2.1 Hz, 1H), 4.80 (d, *J* = 15.0 Hz, 1H), 5.31 (d, *J* = 10.1, Hz, 1H), 7.21-7.29 (m, 4H) ppm. ^{13}C-NMR (75 MHz): 28.1 ($3CH_3$), 40.3 (CH_2), 51.5 (CH_2), 58.7 (CH_2), 59.4 (CH),

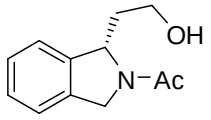
80.1 (C), 122.0 (CH), 127.0 (CH), 135.9 (C), 141.4 (C), 155.9 (C) ppm. $[\alpha]_D^{25}$: +18.6 (*c* 0.8, $CHCl_3$). HRMS (EI+) (*m/z)*: calcd. for $C_{15}H_{21}NO_3$ (M^+): 263.1521. Found: 263.1525.



(+)-**10c**

Synthesis of (1*S*)-*N*-Tosyl-1-(2-hydroxyethyl)indoline 10c.

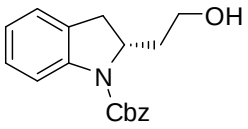
By means of the general procedure described above, **10c** (21.7 mg) was obtained from **5c** (33.8 mg) as a pale brown oil in 61% yield and 94% *ee* with catalyst **I** (63% yield and 91% *ee* with catalyst **II**) after flash chromatography with hexanes:ethyl acetate 3:1. The *ee* was determined by HPLC analysis using a Chiralpack IC column (hexane:isopropanol 40:60); flow rate = 1.0 mL/min, t_{major}=18.6 min, t_{minor}=20.3 min. ^{1}H-NMR (300 MHz): 1.77-1.87 (m, 1H), 2.15-2.26 (m ,1H), 2.33 (s, 3H), 2.62 (br s, 1H), 3.70-3.74 (m, 1H), 4.01-4.08 (m, 1H), 4.65 (s, 2H), 5.19 (dd, J_1 = 8.7, J_2 = 3.8 Hz, 1H), 7.08-7.20 (m, 6H), 7.66 (d, *J* = 8.3 Hz, 2H) ppm. ^{13}C-NMR (75 MHz): 21.4 (CH_3), 40.0 (CH_2), 53.5 (CH_2), 58.8 (CH_2), 63.3 (CH), 122.3 (2CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 129.7 (CH), 134.0 (C), 135.5 (C), 140.5 (C), 143.8 (C) ppm. $[\alpha]_D^{25}$: +30.0 (*c* 1.0, $CHCl_3$). HRMS (EI+) (*m/z)*: calcd. for $C_{17}H_{19}NO_3S$ (M^+): 317.1085. Found: 317.1084.



(+)-**10d**

Synthesis of (1*S*)-*N*-Acetyl-1-(2-hydroxyethyl)isoindoline 10d.

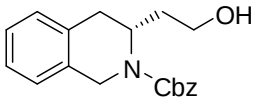
By means of the general procedure described above, **10d** (7 mg) was obtained from **5d** (19 mg) as a pale brown oil in 36% yield and 64% *ee* with catalyst **I** (28% yield and 58% *ee* with catalyst **II**) after flash chromatography with hexanes:ethyl acetate 1:20. The *ee* was determined by HPLC analysis using a Chiralpack IC column (hexane:isopropanol 90:10); flow rate = 1.1 mL/min, t_{major}=21.3 min, t_{minor}=17.3 min. ^{1}H-NMR (300 MHz): 1.53-1.63 (m, 1H), 2.11-2.24 (m, 1H), 2.20 (s, 3H), 3.56-3.66 (m, 2H), 4.45 (br s, 1H), 4.77 (d, *J* = 14.3 Hz, 1H), 4.82 (d, J = 14.3 Hz, 1H), 5.53 (dd, J_1 = 10.1, J_2 = 2.6 Hz, 1H), 7.24-7.31 (m, 4H) ppm. ^{13}C-NMR (75 MHz): 22.2 (CH_3), 40.0 (CH_2), 52.5 (CH_2), 58.6 (CH_2), 59.2 (CH), 122.0 (CH), 122.2 (CH), 127.2 (CH), 127.6 (CH), 134.6 (C), 141.3 (C), 154.3 (C) ppm. $[\alpha]_D^{25}$: +4.1 (*c* 1.0, $CHCl_3$). HRMS (EI+) (*m/z)*: calcd. for $C_{12}H_{15}NO_2$ (M^+): 205.1103. Found: 205.1104.



(+)-**11**

Synthesis of (2*R*)-*N*-Benzyloxycarbonyl-2-(2-hydroxyethyl)indoline 11.

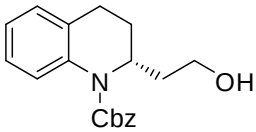
By means of the general procedure described above, **11** (19 mg) was obtained from **6** (27 mg) as a colorless oil in 70% yield and 93% *ee* with catalyst **I** (67% yield and 92% *ee* with catalyst **II**) after flash chromatography with hexanes:ethyl acetate 3:1. The *ee* was determined by HPLC analysis using a Chiralpack IC column (hexane:isopropanol 87:13); flow rate = 1.1 mL/min, t_{major}=16.4 min, t_{minor}=19.7 min. ^{1}H-NMR (300 MHz): 1.80 (br s, 2H), 2.60-2.80 (m, 1H), 3.40 (dd, J_1 = 15.6, J_2 = 9.2 Hz, 1H), 3.58-3.66 (m, 3H), 4.77 (br s, 1H), 5.26-5.33 (m, 2H), 6.97-7.02 (m, 1H), 7.17-7.19 (m, 2H), 7.35-7.46 (m, 6H) ppm. ^{13}C-NMR (75 MHz): 34.5 (CH_2), 38.2 (CH_2), 56.5 (CH), 58.6 (CH_2), 67.9 (CH_2), 116.6 (CH), 123.3 (CH), 125.2 (CH), 127.4 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 135.8 (C), 137.4 (C), 138.1 (C), 154.9 (C) ppm. $[\alpha]_D^{25}$: +4.0 (*c* 0.6, $CHCl_3$). HRMS (EI+) (*m/z)*: calcd. for $C_{18}H_{19}NO_3$ (M^+): 297.1365. Found: 297.1364.



(+)-**12**

Synthesis of (3*R*)-*N*-Benzyloxycarbonyl-3-(2-hydroxyethyl)tetrahydro isoquinoline 12.

By means of the general procedure described above, **12** (14 mg) was obtained from **7** (21 mg) as a colorless oil in 67% yield and 99% *ee* with catalyst **I** (63% yield and 99% *ee* with catalyst **II**) after flash chromatography with hexanes:ethyl acetate 2:1. The *ee* was determined by HPLC analysis using a Chiralpack IC column (hexane:isopropanol 87:13); flow rate = 1.1 mL/min, t_{major}=14.3 min, t_{minor}=11.6 min. ^{1}H-NMR (300 MHz): 1.40-1.48 (m, 1H), 1.61-1.69 (m, 1H), 2.67 (d, *J* = 15.8 Hz, 1H), 3.16-3.23 (m, 1H), 3.40-3.57 (m, 3H), 4.29 (d, J = 16.8 Hz, 1H), 4.70-4.84 (m, 2H), 5.18 (d, J = 12.1 Hz, 1H), 5.26 (d, J = 12.1 Hz, 1H), 7.06-7.22 (m, 4H), 7.33-7.43 (m, 5H) ppm. ^{13}C-NMR (75 MHz): 34.0 (CH_2), 35.3 (CH_2), 43.3 (CH_2), 46.3 (CH), 58.7 (CH_2), 67.7 (CH_2), 126.0 (CH), 126.4 (CH), 126.9 (CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 129.1 (CH), 131.6 (C), 132.8 (C), 136.4 (C), 157.2 (C) ppm. $[\alpha]_D^{25}$: +26.2 (*c* 1.0, $CHCl_3$). HRMS (EI+) (*m/z)*: calcd. for $C_{19}H_{21}NO_3$ (M^+): 311.1521. Found: 311.1521.

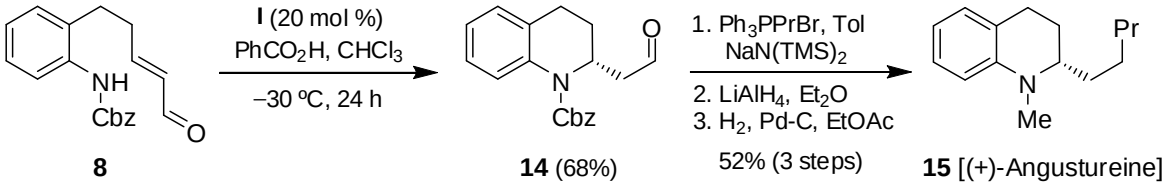


(+)-**13**

Synthesis of (2*R*)-*N*-Benzyloxycarbonyl-2-(2-hydroxyethyl)tetrahydroquinoline 13.

By means of the general procedure described above, **13** (14. mg) was obtained from **7** (22 mg) as a colorless oil in 70% yield and 92% *ee* with catalyst **I** (60% yield and 91% *ee* with catalyst **II**) after flash chromatography with hexanes:ethyl acetate 2:1. The *ee* was determined by HPLC analysis using a Chiralpack IC column (hexane:isopropanol 87:13); flow rate = 1.1 mL/min, t_{major}=17.4 min, t_{minor}=20.6 min. ^{1}H-NMR (300 MHz): 1.45-1.75 (m, 3H), 2.28-2.40 (m, 1H), 2.69 (t, *J* = 6.6 Hz, 2H), 3.20 (br s, 1H), 3.54-3.65 (m, 2H), 4.74-4.83 (m, 1H), 5.15 (d, J = 12.4 Hz, 1H), 5.33 (d, *J* = 12.4 Hz, 1H), 7.04-7.17 (m, 3H), 7.29-7.39 (m, 6H) ppm. ^{13}C-NMR (75 MHz): 24.8 (CH_2), 29.7 (CH_2), 36.1 (CH_2), 49.7 (CH), 58.8 (CH_2), 67.8 (CH_2), 124.7 (CH), 125.5 (CH), 126.1 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.5 (CH), 131.9 (C), 135.8 (C), 136.0 (C), 155.9 (C) ppm. $[\alpha]_D^{25}$: +7.8 (*c* 0.8, $CHCl_3$). HRMS (EI+) (*m/z)*: calcd. for $C_{19}H_{21}NO_3$ (M^+): 311.1521. Found: 311.1524.

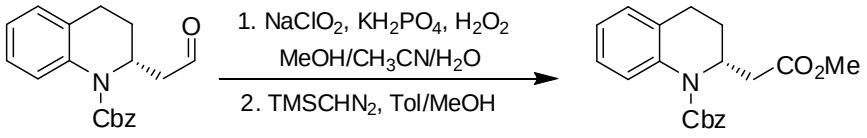
Total synthesis of (+)-Angustureine 15



Following the previously described General procedure for the intramolecular aza-Michael reaction without addition of $NaBH_4$, compound **14** (62 mg, 68%) was synthesized and purified by flash chromatography with hexanes:ethyl acetate 5:1. Propyl triphenylphosphonium bromide (385 mg, 1 mmol) was suspended in toluene (5 mL) and then $NaN(TMS)_2$ (1.0 mL, 1.0 mmol, 1.0 M solution in THF) was added dropwise at 0 ºC. After stirring for 30 min at rt, the reaction mixture containing the ylide was cooled with an ice bath and a solution of aldehyde **14** (62 mg, 0.2 mmol) in toluene (5 mL) was added dropwise and the mixture allowed to reach room temperature and stirred for 3 h. The reaction was hydrolyzed with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. After flash chromatography over silica gel using hexane:ethyl acetate (10:1) as eluent, the Wittig adduct was isolated as a colorless oil (45 mg, 67%) and redissolved in ethyl ether (10 mL) and then, $LiAlH_4$ (6 mg, 0.15 mmol) was added at 0 ºC. The suspension was stirred for 3 h at rt and then, $Na_2SO_4.10H_2O$ (200 mg) was added and the mixture vigorously stirred for 1 h. The reaction mixture was filtered over a pad of celite, washed with ether, and the solvents removed. The residue was redissolved in ethyl acetate (10 mL) and after the addition of Pd-C (40 mg), the suspension was stirred under atmosphere of hydrogen (1 atm) at rt for 12 h. The mixture was

filtered over a pad of Celite, and the residue subjected to flash chromatography using hexanes:CH_2Cl_2 (5:1) to afford 23 mg of (+)-**15** (78%, two steps). $[\alpha]_D^{25}$: +5.6 (*c* 1.0, $CHCl_3$). ^{1}H-NMR data are in accordance with the previously described in the literature.[5]

Synthesis of β-Amino ester (+)-16.

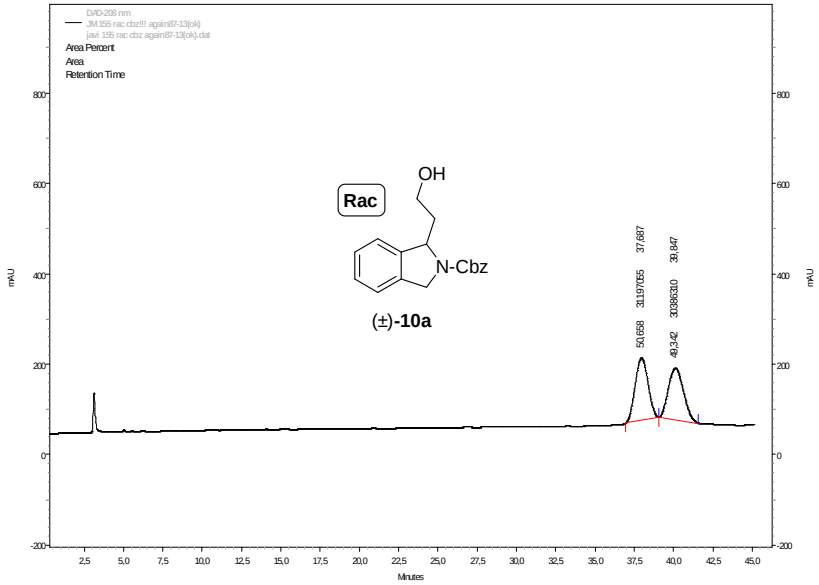


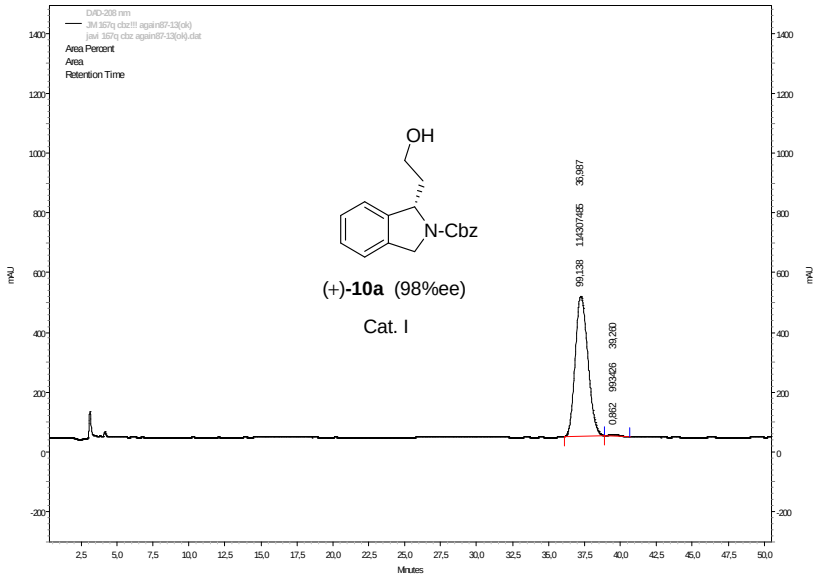
14 (+)-**16** (50%)

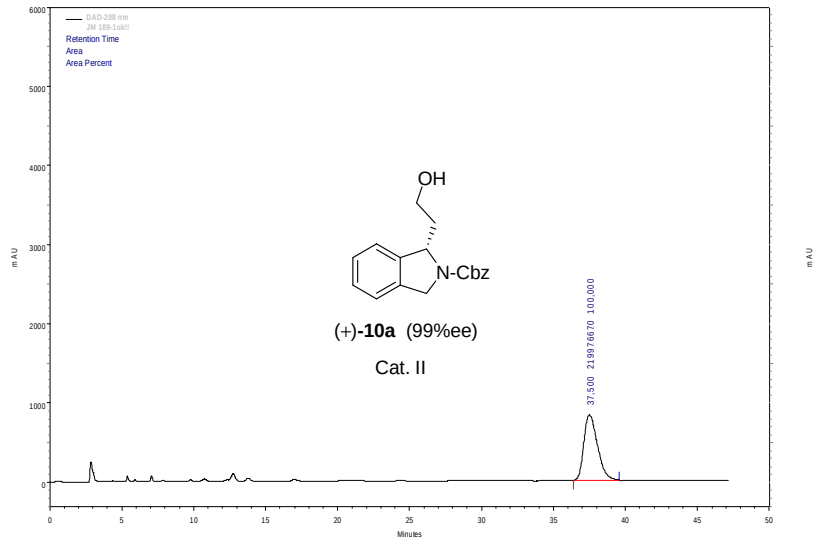
Aldehyde **14** (60 mg, 0.2 mmol) was dissolved in a mixture of MeOH (1 mL), CH_3CN (1 mL) and water (1 mL). The solution was cooled down to 0 ºC and and KH_2PO_4 (76 mg, 0.55 mmol) and $NaClO_2$ (38 mg, 0.42 mmol) were added. After the injection of H_2O_2 (30% solution, 0.6 mL), the mixture was warmed up to rt and stirred for 2 h. The pH was adjusted to 3 with 1M HCl and saturated Na_2SO_3 solution (20 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were washed with water (10 mL), and dried over anhydrous Na_2SO_4. The organic layer was concentrated under vacuum and the residue was dissolved in toluene (1 mL) and methanol (3 mL). Trimethylsilyl diazomethane (0.1 mL, 0.2 mmol, 2.0 M in *n*-hexane) was added dropwise. The solution was stirred for additional 10 min and quenched with four drops of neat AcOH. The solvents were evaporated under vacuum and the crude residue subjected to flash chromatography with hexanes:ethyl acetate (7:1) to afford ester (+)-**16** (34 mg) in 50% yield (two steps) as a pale yellow oil. ^{1}H-NMR (300 MHz): 1.56-1.66 (m, 1H), 2.22-2.37 (m, 2H), 2.54-2.63 (m, 3H), 3.52 (s, 3H), 4.86-4.95 (m, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 5.22 (d, *J* = 12.6 Hz, 1H), 6.97-7.09 (m, 3H), 7.23-7.30 (m, 6H) ppm. ^{13}C-NMR (75 MHz): 24.7 (CH_2), 28.9 (CH_2), 38.3 (CH_2), 50.5 (CH), 51.6 (CH_3), 67.5 (CH_2), 124.5 (CH), 125.6 (CH), 126.2 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.5 (CH), 131.4 (C), 136.1 (C), 136.3 (C), 154.4 (c), 171.4 (c) ppm. $[\alpha]_D^{25}$: +63.4 (*c* 1.0, $CHCl_3$). HRMS (*m/z)*: calcd. for $C_{20}H_{21}NO_4$ (M^+): 339.1521. Found: 339.1524.

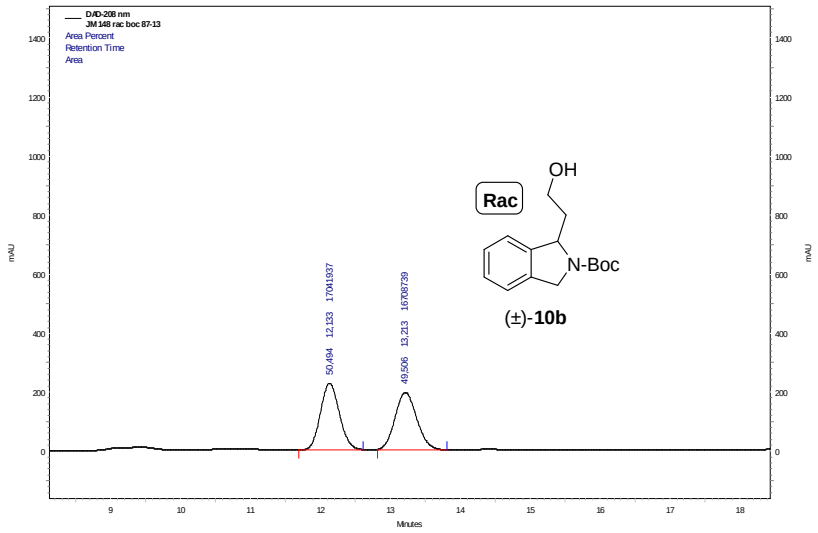
[5] C. Theeraladonon, M. Arisawa, M. Nakagawa, A. Nishida, *Tetrahedron: Asymm.* **2005**, *16*, 827.

Determination of the *ee* of 10-13 by chiral phase HPLC analysis





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Retention Time
Area
mAU
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Rac
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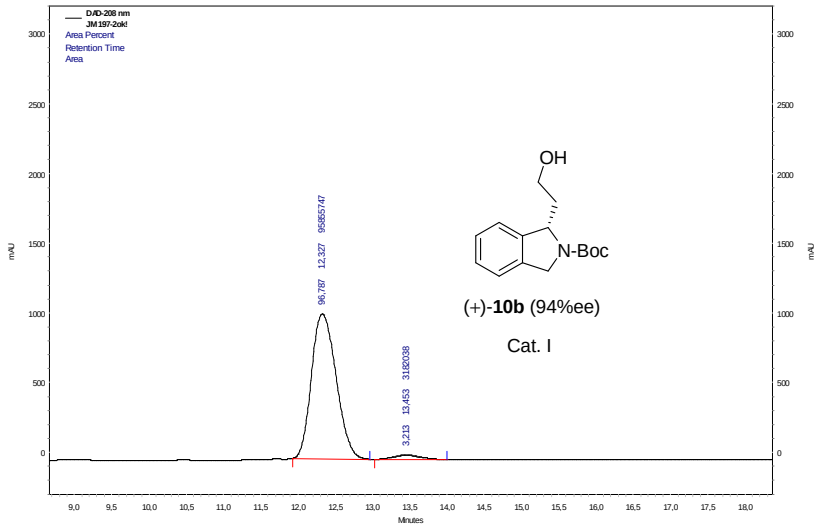
(±)-10b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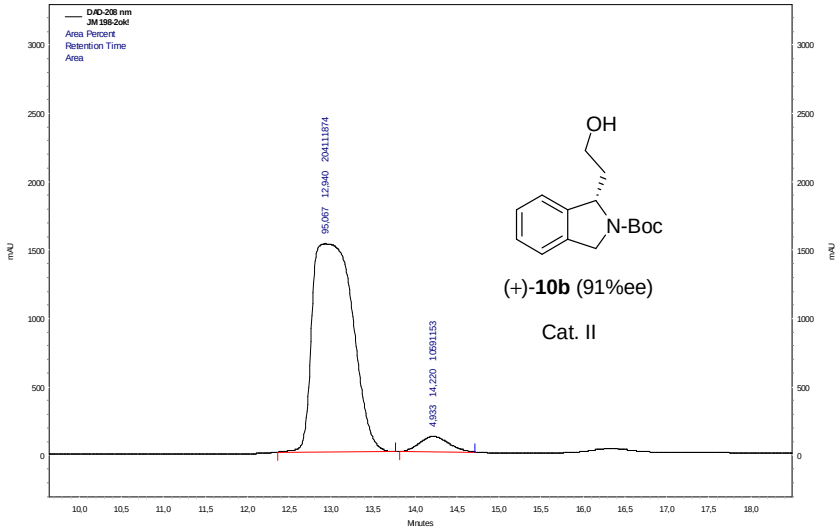
(+)-10b (94%ee)
Cat. I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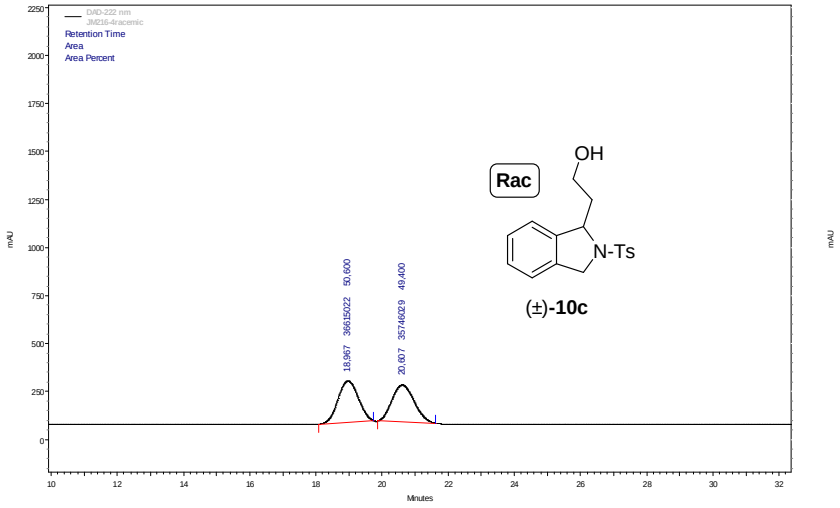
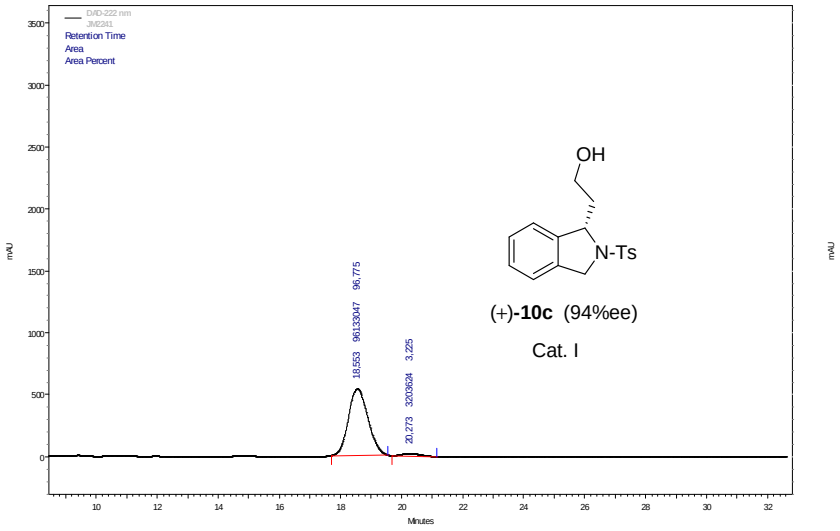
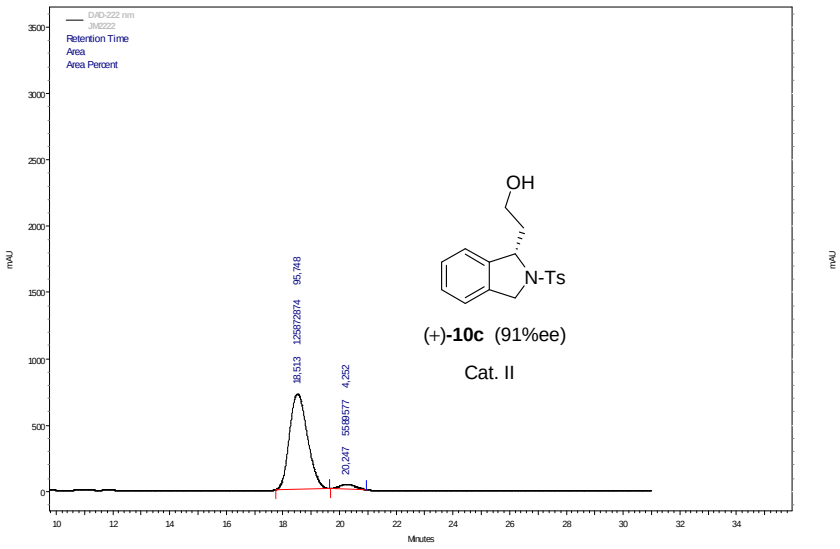
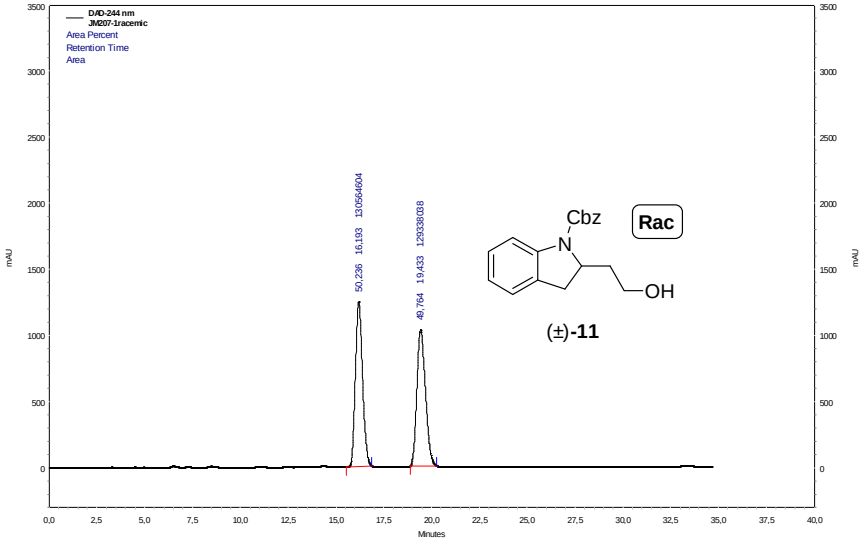
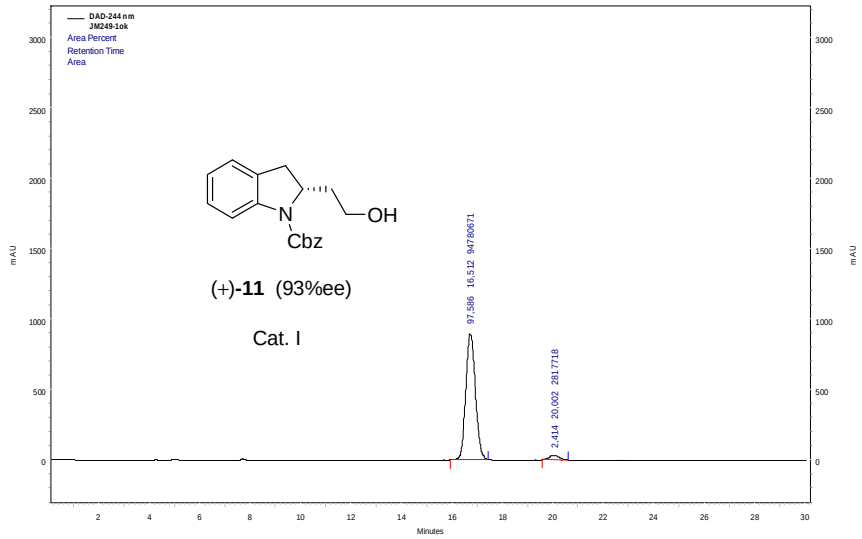
mAU
Minutes
204111674
12,940
95,067
16691153
14,220
4,933
OH
N-Boc
(+)-10b (91%ee)
Cat. II

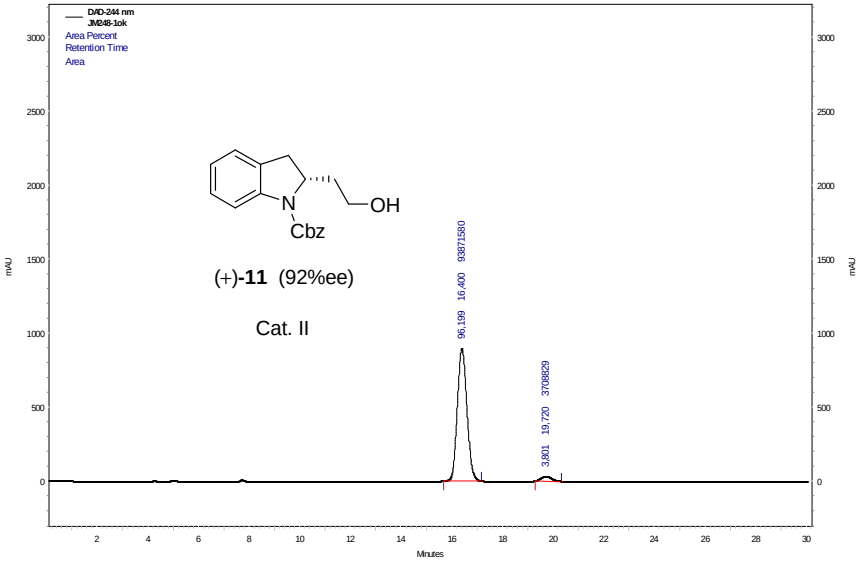

DAD-222 nm
JM216-4racemic
Retention Time
Area
Area Percent
mAU
Minutes
Rac
OH
N-Ts
(±)-10c
18,967
36615022
50,600
20,607
35746029
49,400

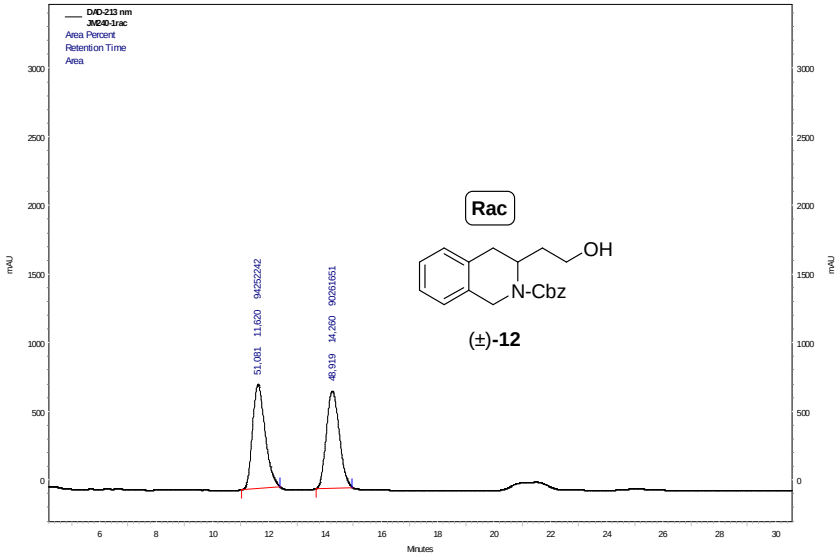

DAD-222 nm
JM241
Retention Time
Area
Area Percent
mAU
Minutes
OH
N-Ts
(+)-10c (94%ee)
Cat. I
18,553
96133047
96,775
20,273
3203624
3,225

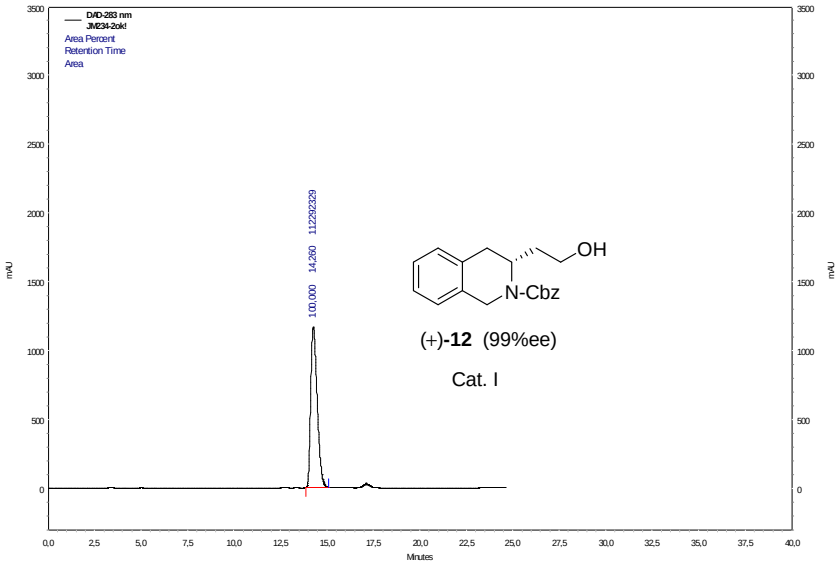

DAD-222 nm
JM222
Retention Time
Area
Area Percent
mAU
Minutes
OH
N-Ts
(+)-10c (91%ee)
Cat. II
18,513
125872874
95,748
20,247
5589577
4,252

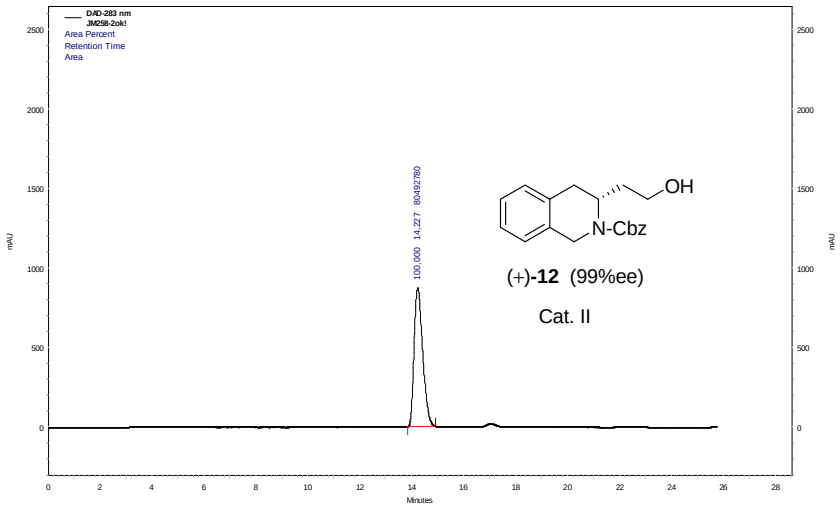

DAD-244 nm
JM207-1racemic
Area Percent
Retention Time
Area
mAU
Minutes
Cbz
N
OH
Rac
(±)-11
50,236 16,193 130564604
40,764 19,433 129338038

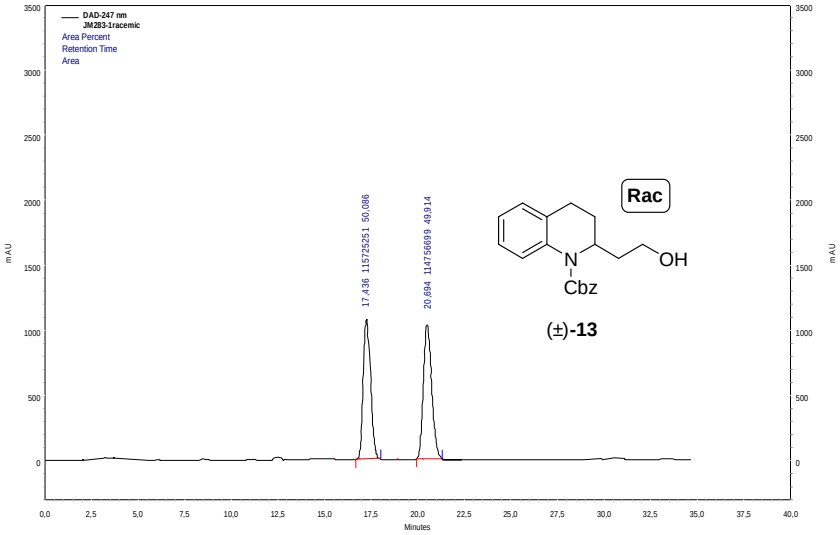

DAD-244 nm
JM249-1ok
Area Percent
Retention Time
Area
mAU
Minutes
N
OH
Cbz
(+)-11 (93%ee)
Cat. I
97,586 16,512 94780671
2,414 20,002 2817718

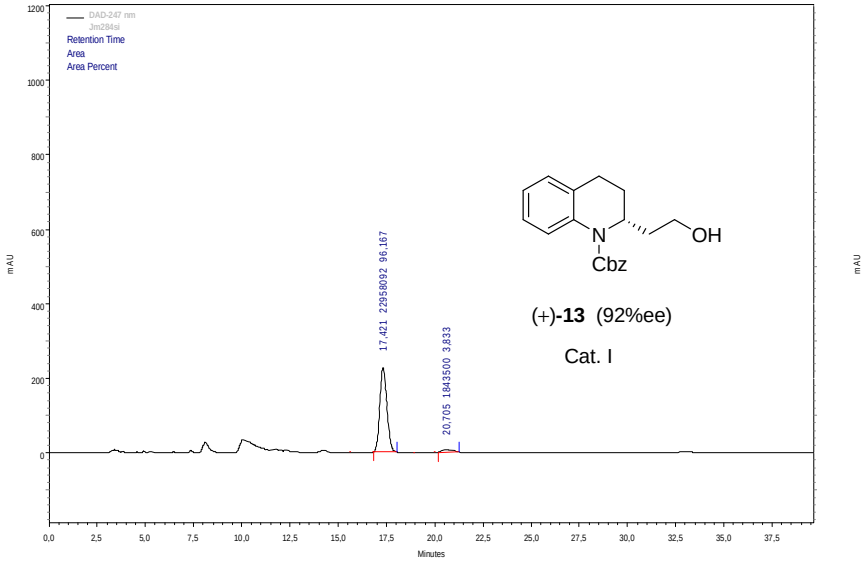

DAD-244 nm
JM248-1ok
Area Percent
Retention Time
Area
mAU
Minutes
N
OH
Cbz
(+)-11 (92%ee)
Cat. II
96,199 16,400 93871580
3,801 19,720 3708829

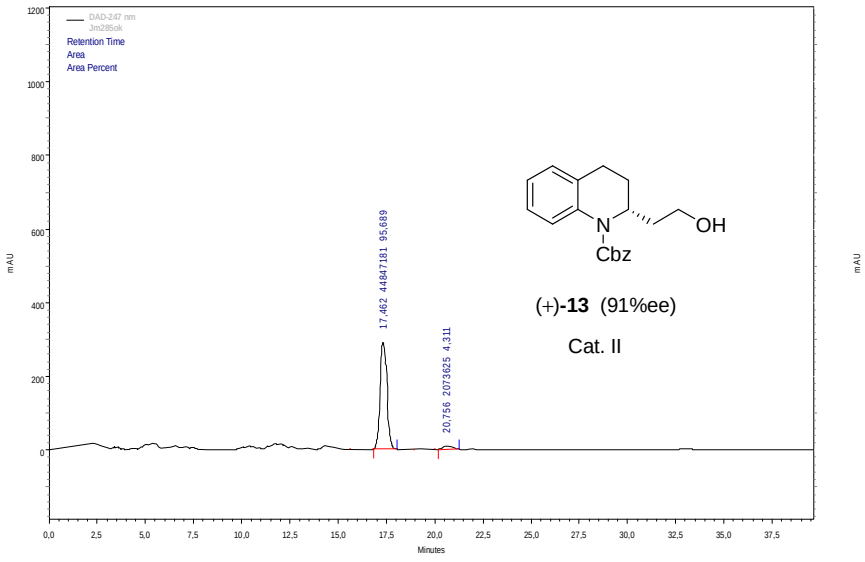

D/AD-213 nm
JM240-1rac
Area Percent
Retention Time
Area
mAU
Minutes
Rac
OH
N-Cbz
(±)-12
94252242
11,620
51,061
90261651
14,260
48,919


D/AD-283 nm
JM234-2ok!
Area Percent
Retention Time
Area
mAU
Minutes
112292329
14,260
100,000
OH
N-Cbz
(+)-12 (99%ee)
Cat. I


D/AD-283 nm
JM258-2ok!
Area Percent
Retention Time
Area
mAU
Minutes
80492780
14,227
100,000
OH
N-Cbz
(+)-12 (99%ee)
Cat. II


DAD-247 nm
JM283-1racemic
Area Percent
Retention Time
Area
17,436 115726251 50,086
20,694 114756699 49,914
Rac
OH
N
Cbz
(±)-13
mAU
Minutes


DAD-247 nm
Jm284si
Retention Time
Area
Area Percent
17,421 2958092 96,167
20,705 118435500 3,833
OH
N
Cbz
(+)-13 (92%ee)
Cat. I
mAU
Minutes


DAD-247 nm
Jm285ok
Retention Time
Area
Area Percent
17,462 44847181 95,689
20,756 2073625 4,311
OH
N
Cbz
(+)-13 (91%ee)
Cat. II
mAU
Minutes