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Supplementary Information

Enantioselective Synthesis of both (–)-(*R*)- and (+)-(*S*)-Angustureine Controlled by Enzymatic Resolution

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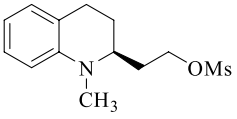
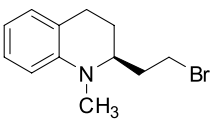
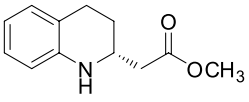


(*S*)-Methanesulfonic acid 2-(1-methyl-1,2,3,4,-tetrahydro-quinolin-2-yl)-ethyl ester (**9**): *N*-methylation and reduction of **5** (530 mg, 2.45 mmol) was performed as described in the synthesis of **4**. Et_3N (376 µL, 2.7 mmol) and methanesulfonyl chloride (246 µL, 3.2 mmol) were added, successively, to the resulting crude alcohol (470 mg, 2.45 mmol) in CH_2Cl_2 (16.8 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 1 h, quenched with a saturated solution of $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to give 541 mg (82%, 3 steps) of (*S*)-mesylate (**9**) as a clear oil; $[a]_D$ –9.4 (*c* 1.0 $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 3021, 2938, 1061, 1498, 1336, 1170, 952, 905, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (td, 1H, *J* 7.7, 1.4 Hz, H6), 7.01 (d, 1H, *J* 7.2 Hz, H8), 6.68 (td, 1H, *J* 7.3, 1.0 Hz, H7), 6.59 (d, 1H, *J* 8.2 Hz, H5), 4.35-4.28 (m, 2H, H12), 3.55-3.50, (m, 1H, H2), 3.04 (s, 3H, NC$\underline{H}_3$), 2.98 (s, 3H, S(=O)$_2$C$\underline{H}_3$), 2.86-2.70 (m, 2H, H4), 2.11-1.95 (m, 2H, H11), 1.92-1.84 (m, 2H, H3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (C_0), 128.8 (CH), 127.1 (CH), 121.2 (C_0), 115.9 (CH), 111.3 (CH), 67.3 (CH_2), 55.0 (CH), 38.6 (N$\underline{C}$H$_3$), 37.3 (S(=O)$_2$$\underline{C}H_3$), 31.2 ($CH_2$), 24.4 ($CH_2$), 23.1 ($CH_2$); HRMS (ESI$^+$) calcd. for $C_{13}H_{19}NO_3S$ (M + H)$^+$ 270.1161, found 270.1163.



(*S*)-2-(2-Bromo-ethyl)-1-methyl-1,2,3,4-tetrahydro-quinoline (**10**): (*S*)-mesylate (**9**) (120 mg, 0.44 mmol) dissolved in THF (tetrahydrofuran, 3 mL) was treated with LiBr (115 mg, 1.32 mmol) at room temperature. The resulting mixture was refluxed for 24 h, quenched with brine and extracted with Et_2O. The organic layer was then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% EtOAc/hexanes) to give 67.1 mg (60%) of (*S*)-bromide (**10**) as a clear oil; $[a]_D$+115.9 (*c* 1.0 $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 3019, 2934, 1061, 1497, 1257, 1213, 743, 719; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, 1H, *J* 7.7 Hz, H6), 7.02 (d, 1H, *J* 7.3 Hz, H8), 6.66 (t, 1H, *J* 7.3 Hz, H7), 6.60 (d, 1H, *J* 8.1 Hz, H5), 3.58-3.43 (m, 3H, H2/H12), 3.05 (s, 3H, NC$\underline{H}_3$), 2.86-2.73 (m, 2H, H4), 2.24-2.16 (sext, 1H, *J* 6.7 Hz, H3), 2.03-1.90 (m, 3H, H3/H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8 (C_0), 127.2 (CH), 121.2 (C_0), 115.8 (CH), 111.0 (CH), 56.8 (CH), 38.5 (N$\underline{C}$H$_3$), 34.6 (CH_2), 30.8 (CH_2), 24.1 (CH_2), 23.3 (CH_2); HRMS (ESI$^+$) calcd. for $C_{12}H_{16}BrN$ (M + H)$^+$ 254.05444, found 254.05388.



Synthesis of (*R*)-methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate (**8**): The aqueous layer containing (*R*)-sodium carboxylate (**7**) from the enzymatic resolution reaction was dried for a long time under heating in vacuum, generating a light yellow powder. The crude carboxylate (**7**) (100 mg, 0.47 mmol) was dissolved in dry methanol (1.5 mL), and thionyl chloride (100 µL, 1.41 mmol) was added at 0 °C. The mixture was refluxed for 5 h and concentrated in vacuum, saturated sodium bicarbonate (5 mL) was slowly added and extracted with EtOAc. The combined extracts were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica using 10% EtOAc/hexanes as

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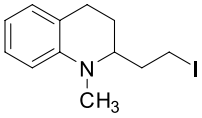
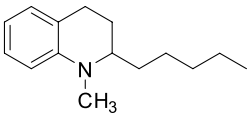
eluent to give 29 mg (30% yield, 96.4% ee) of (*R*)-β-amino ester (**8**) as a pale yellow oil; $[a]_D$ −100.6 (*c* 1.0 $CHCl_3$)]; IR (neat) ν_{max}/cm^{-1} 3392, 3016, 2949, 2846, 1727, 1606, 1586, 1484, 1435, 1198, 1008, 746; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.00-7.01 (m, 1H, H6), 6.99-6.95 (m, 1H, H8) 6.64 (td, 1H, *J* 7.4, 1.1 Hz, H7), 6.52 (dd, 1H, *J* 7.9, 0.8 Hz, H5), 4.48 (bs, 1H, NH), 3.79-3.68 (m, 1H, H2), 3.73 (s, 3H, OCH_3), 2.86 (dq, 1H, *J* 16.2, 5.6 Hz, H4), 2.74 (dt, 1H, *J* 16.5, 5.3 Hz, H4), 2.55 (s, 1H, H11), 2.53 (d, 1H, *J* 1.2 Hz, H11), 2.05-1.94 (m, 1H, H3), 1.78-1.68 (m, 1H, H3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C_0), 143.9 (C_0),, 129.1 (CH), 126.8 (CH), 120.8 (C_0), 117.3 (CH), 114.5 (CH), 51.7 (OCH_3), 47.7 (CH), 40.6 (CH_2), 27.9 (CH_2), 25.5 (CH_2); HRMS (CI^+) calcd. for $C_{12}H_{16}NO_2$ $(M + H)^+$ 206.1181, found 206.1182.



(±)-2-(2-Iodo-ethyl)-1-methyl-1,2,3,4-tetrahydro-quinoline (**14**): To a suspension of $LiAlH_4$ (172 mg, 4.53 mmol) in THF (3.7 mL), the *rac*-β-amino ester (**6**) (310 mg, 1.51 mmol) in THF (6.4 mL) was added dropwise at room temperature. The mixture was refluxed for 4 h, and then excess reagent was decomposed by addition of water (3.7 mL) at 0 °C. To this mixture, 1 mol L^{-1} aqueous NaOH (3.7 mL), H_2O (3.7 mL) and diethyl ether (80 mL), in succession, were added. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude alcohol was dissolved in a mixed solvent of 5:1 toluene/acetonitrile (5 mL) treated with imidazole (247 mg, 3.62 mmol) and triphenylphosphine (475 mg, 1.81 mmol) and cooled at 0 °C. The mixture was treated with iodine (385 mg, 1.52 mmol) and stirred for 2 h at 0 °C. Aqueous sodium thiosulfate solution (10 mL) was added and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was triturated with diethyl ether and the insoluble materials were removed by filtration. The filtrate was concentrated, the residual oil was dissolved in THF (7 mL) and treated with K_2CO_3 (423 mg, 2.5 mmol) in THF (3 mL) and MeI (0.82 mL, 15.1 mmol) under an argon atmosphere. The mixture was stirred for 48 h at 50 °C and quenched by addition of water. Organic compounds were extracted with Et_2O, washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (20% CH_2Cl_2/hexanes) to give 403 mg (89%, 3 steps) of *rac*-iodeto (**14**) as a pale yellow oil; IR (neat) ν_{max}/cm^{-1} 3018, 2929, 2795, 1601, 1574, 1497, 1214, 741, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (td, 1H, *J* 7.7, 1.5 Hz, H6), 7.01 (d, 1H, *J* 7.1 Hz, H8), 6.65 (td, 1H, *J* 7.3, 1.0 Hz, H7), 6.58 (d, 1H, *J* 8.2 Hz, H5), 3.49-3.44 (m, 1H, H2), 3.30 (dq, 1H, *J* 10.0, 7.5 Hz, H12), 3.17 (dt, 1H, *J* 10.0, 7.6 Hz, H12), 3.01 (s, 3H, NCH_3), 2.85-2.71 (m, 2H, H4), 2.22-2.13 (m, 1H, H3), 2.00-1.85 (m, 3H, H3/H11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (C_0), 128.8 (CH), 127.2 (CH), 121.3 (C_0), 115.8 (CH), 110.9 (CH), 58.9 (CH), 38.4 (NCH_3), 35.2 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 3.1 (CH_2); HRMS (CI^+) calcd. for $C_{12}H_{17}IN$ $(M + H)^+$ 302.0406, found 302.0402.



Synthesis of (±)-angustureine (**13**): the synthesis of **13** was performed as described in the synthesis of **1** from *rac*-iodide (**14**) (100 mg, 0.33 mmol) to give 64.6 mg (90%, 2 steps) of **(±)-**angustureine (**13**) as a pale yellow oil; IR (neat) ν_{max}/cm^{-1} 2927, 2857, 1602, 1498, 1214, 741, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (t, 1H, *J* 7.4 Hz, H6), 7.01 (d, 1H, *J* 7.2 Hz, H8), 6.62 (t, 1H, *J* 7.2 Hz, H7), 6.56 (d, 1H, *J* 8.1 Hz, H5), 3.27 (sext, 1H, *J* 4.3 Hz, H2), 2.96 (s, 3H, NCH_3), 2.89-2.80 (m, 1H, H4), 2.69 (dt, 1H, *J* 16.2, 4.0 Hz, H4), 1.95-1.89 (m, 2H, H3), 1.66-1.60 (m, 1H, H11), 1.46-1.30 (m, 7H, H11/H12/H13/H14), 0.93 (t, 3H, *J* 7.0 Hz, H15); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3 (C10), 128.6 (C8), 127.0 (C6), 121.8 (C9), 115.1 (C7), 110.3 (C5), 58.9 (C2), 37.9 (NCH_3), 32.0 (C13), 31.1 (C11), 25.7 (C3), 24.3 (C12), 23.5 (C4), 22.6 (C14), 14.0 (C15); HRMS (ESI^+) calcd. for $C_{15}H_{24}N$ $(M + 1)^+$ 218.19087 found 218.19229.

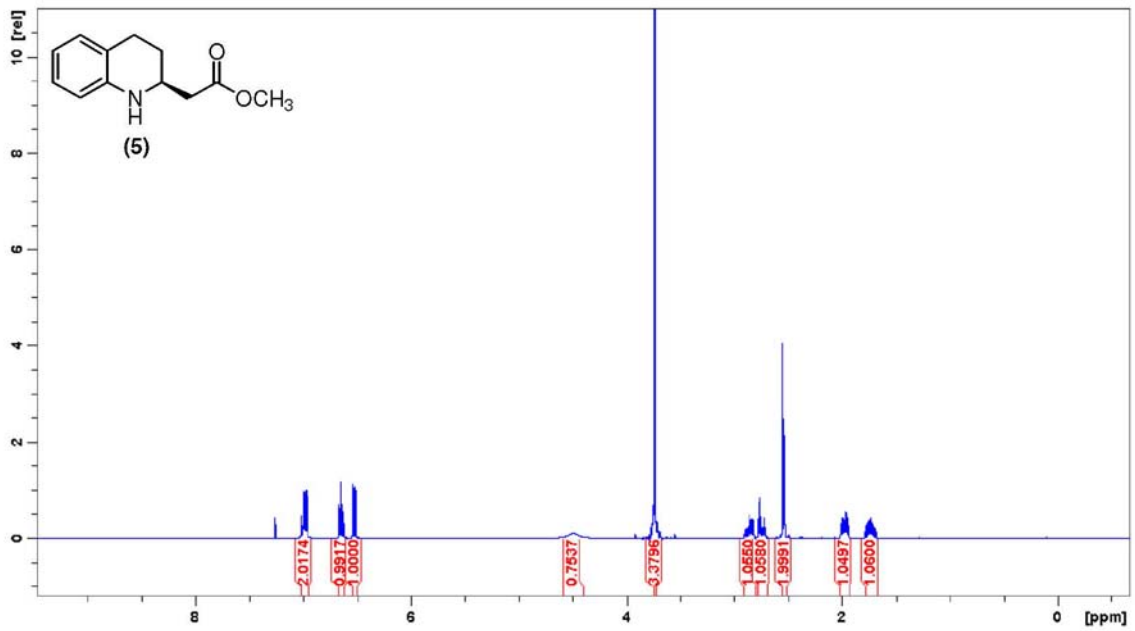


Figure S1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (*S*)-β-amino ester **5**.

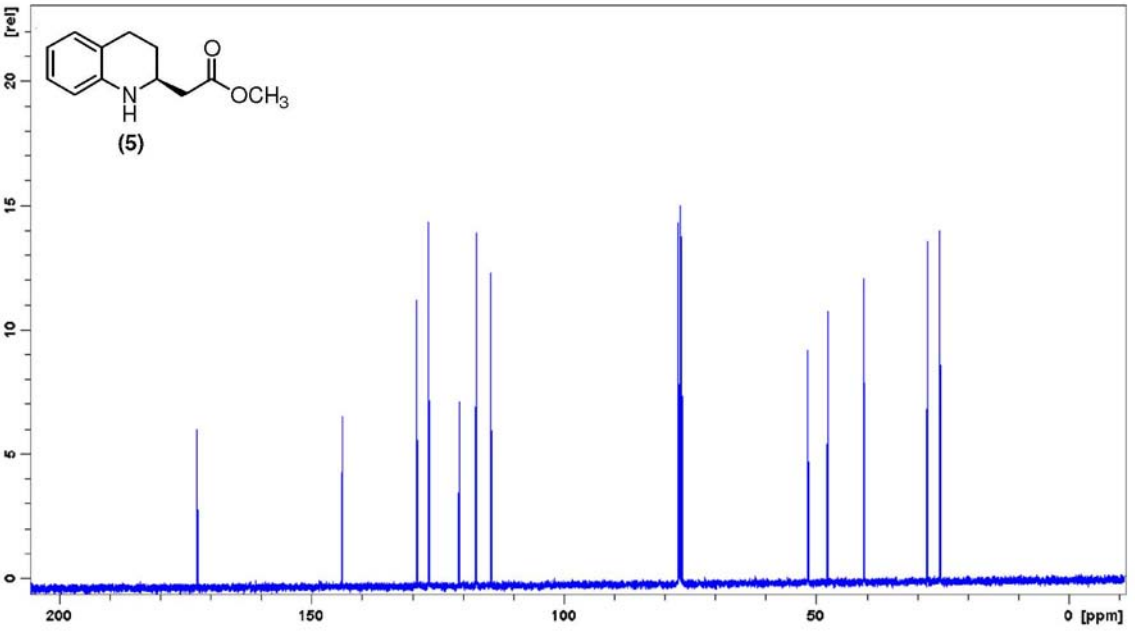


Figure S2. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (*S*)-β-amino ester **5**.

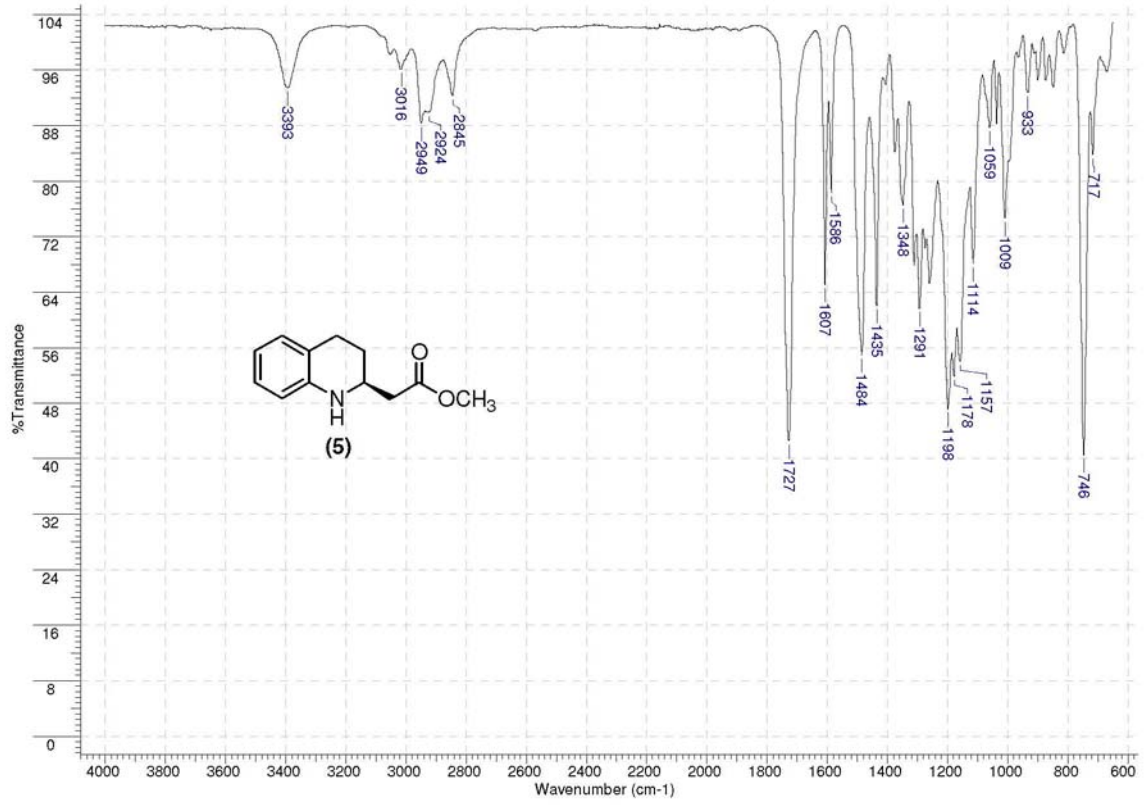


Figure S3. IR (film) spectrum of (*S*)-β-amino ester **5**.

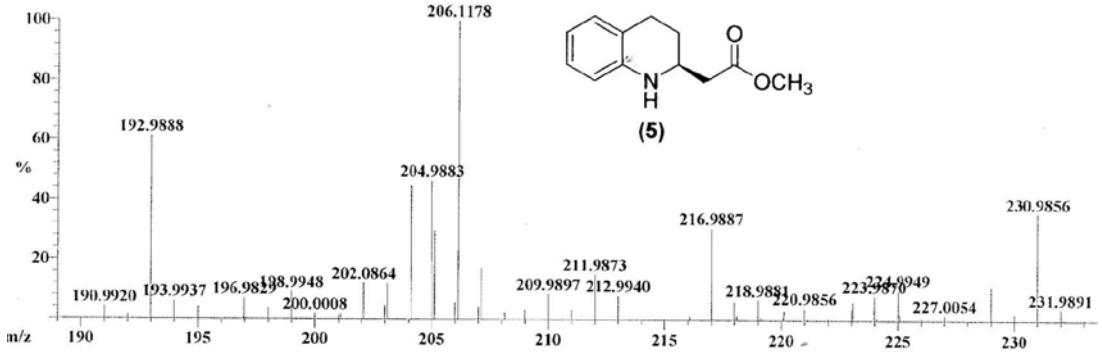


Figure S4. HRMS (CI$^+$) *m/z* (M + H)$^+$ for $C_{12}H_{16}NO_2$ of **5**.

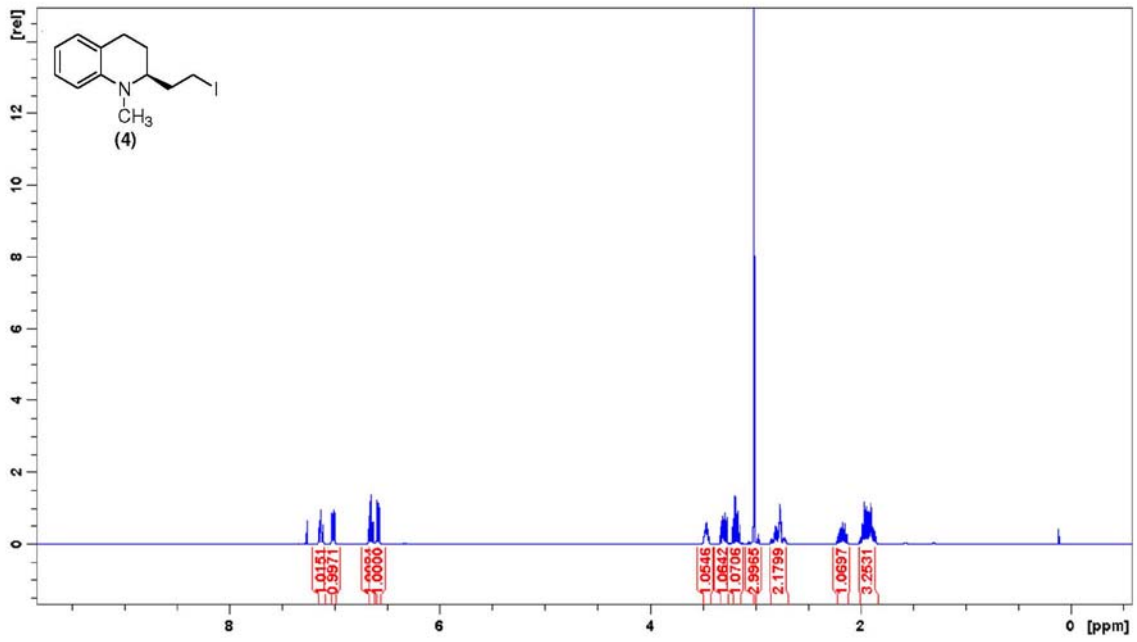


Figure S5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (*S*)-iodide **4**.

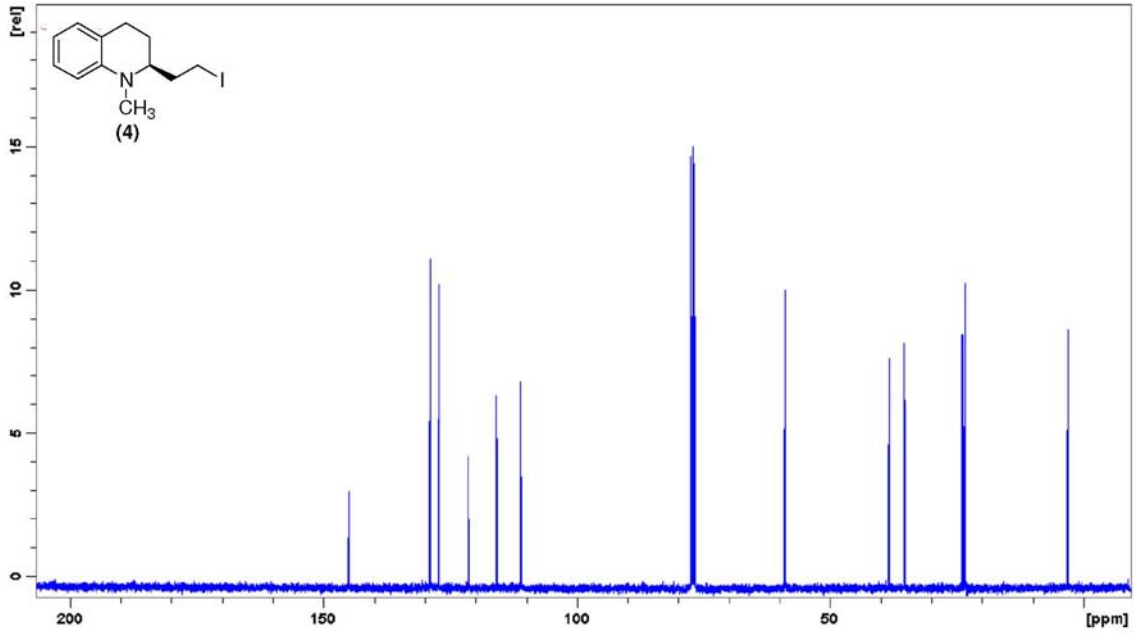


Figure S6. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (*S*)-iodide **4**.

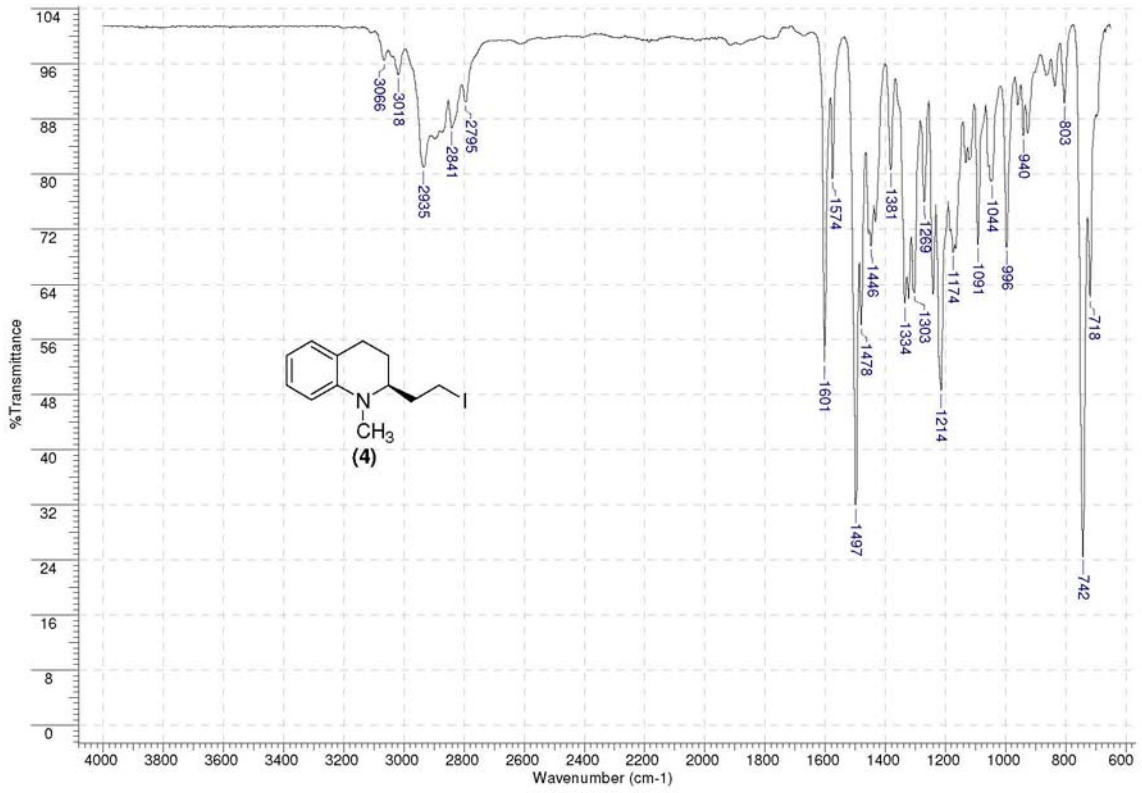


Figure S7. IR (film) spectrum of (*S*)-iodide **4**.

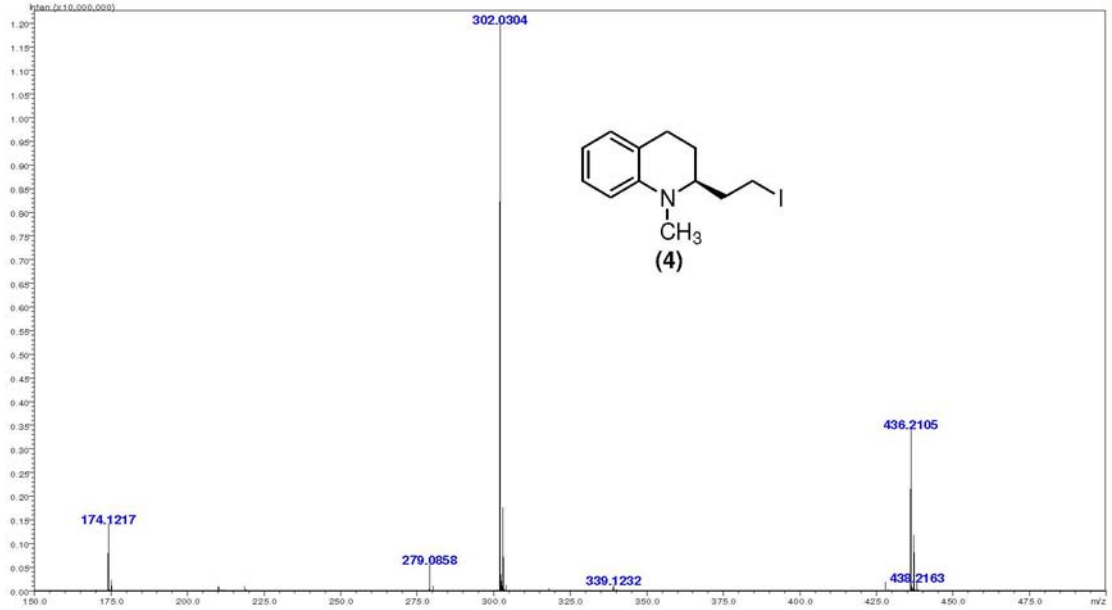


Figure S8. HRMS (ESI$^+$) *m/z* (M + H)$^+$ for $C_{12}H_{17}IN$ of **4**.

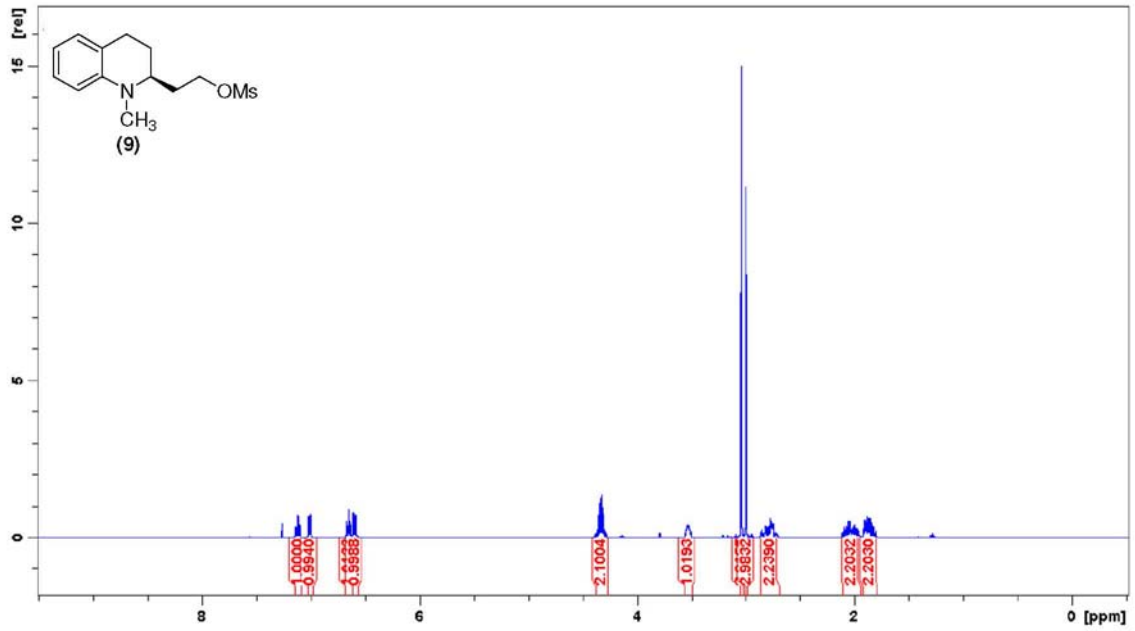


Figure S9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of mesylate **9**.

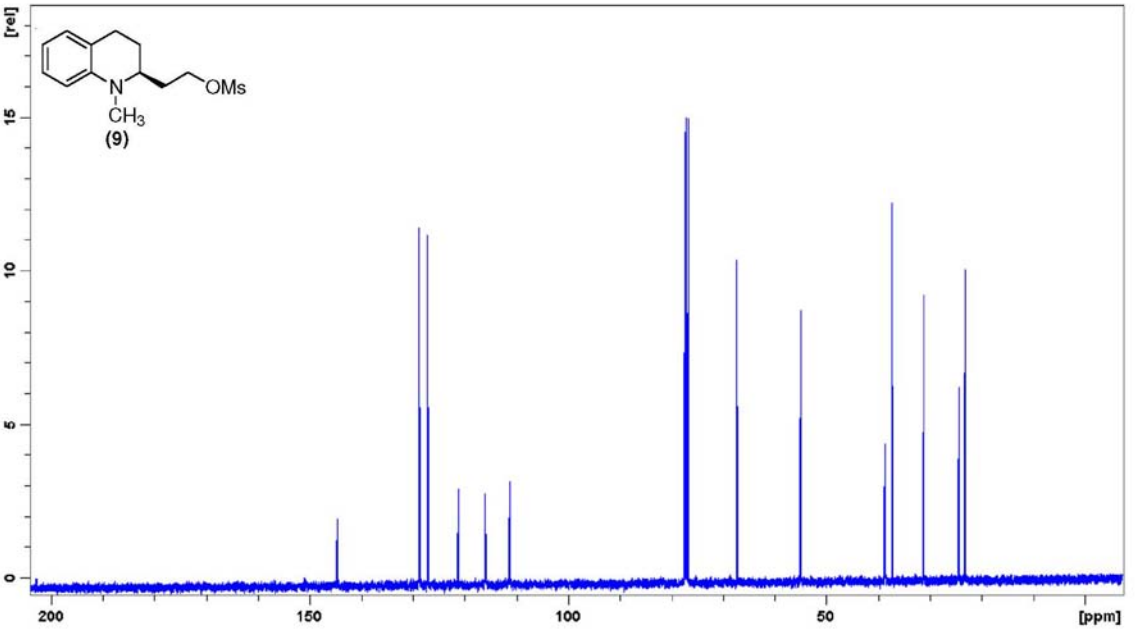


Figure S10. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of mesylate **9**.

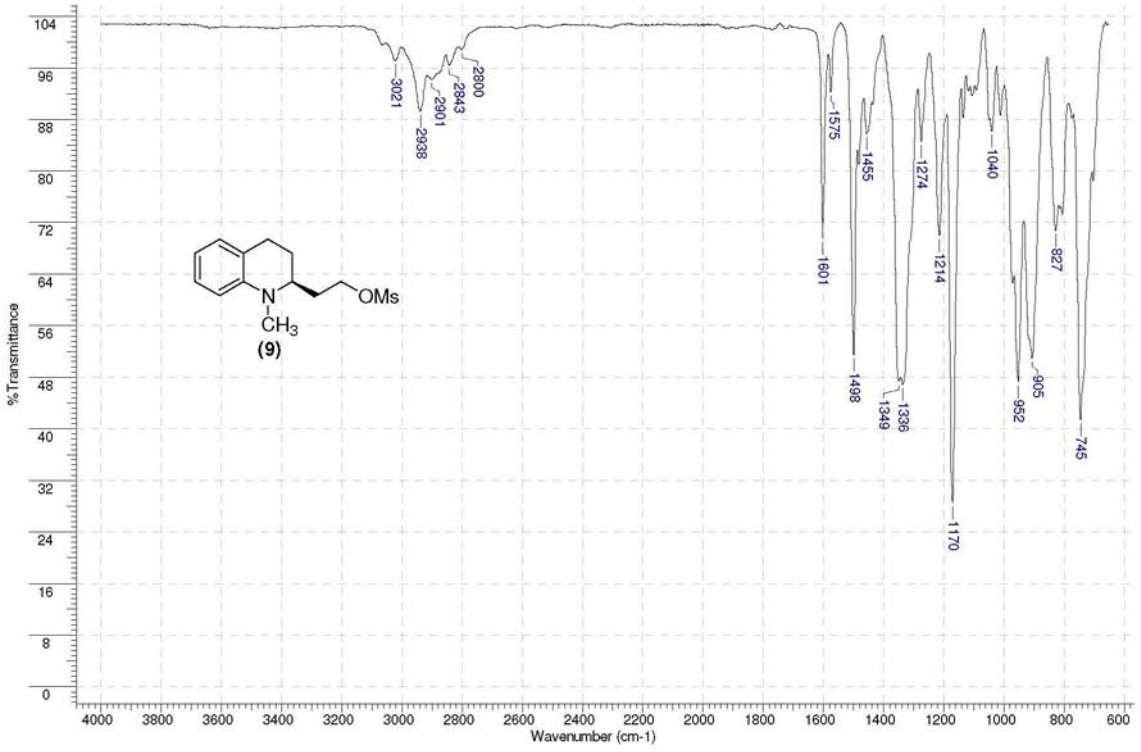


Figure S11. IV (film) spectrum of mesylate **9**.

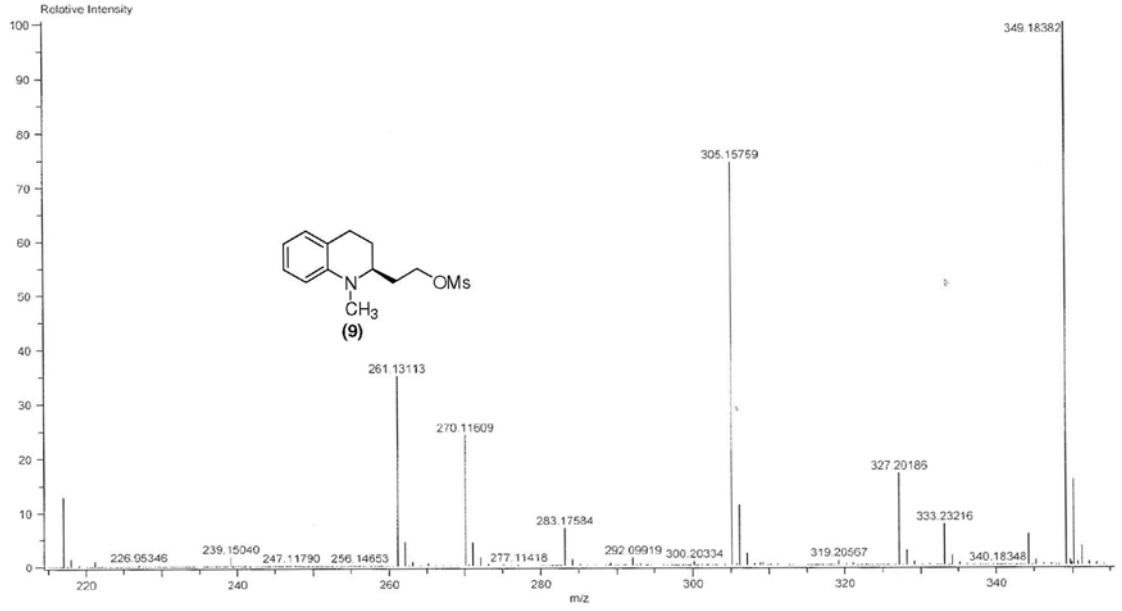


Figure S12. HRMS (ESI$^+$) *m/z* $(M + H)^+$ for $C_{13}H_{19}NO_3S$ of **9**.

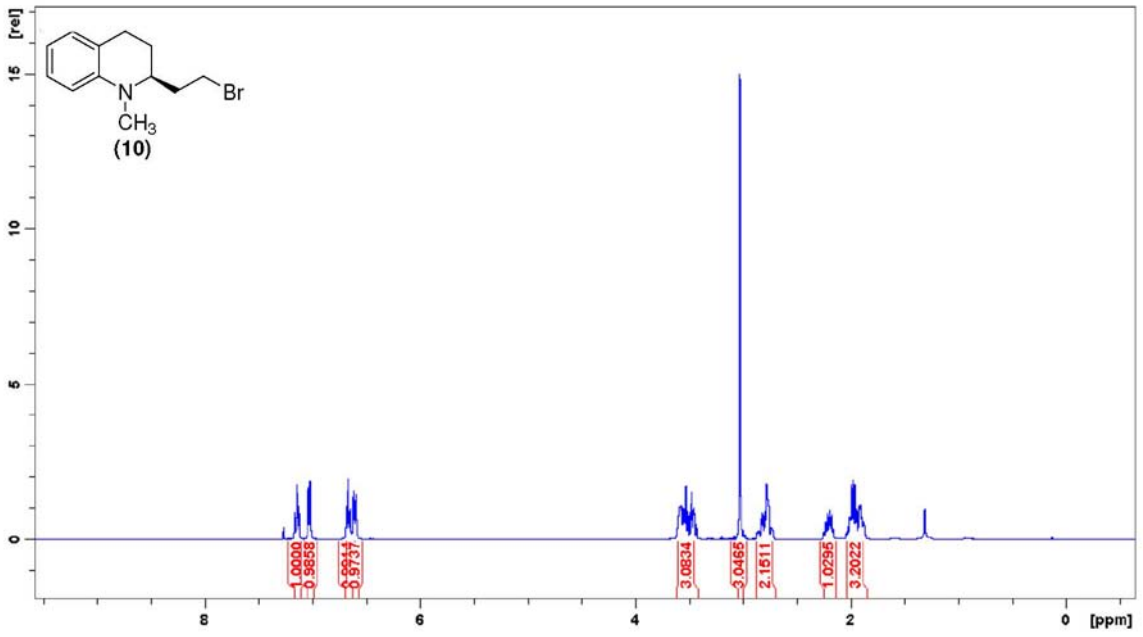


Figure S13. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of bromide **10**.

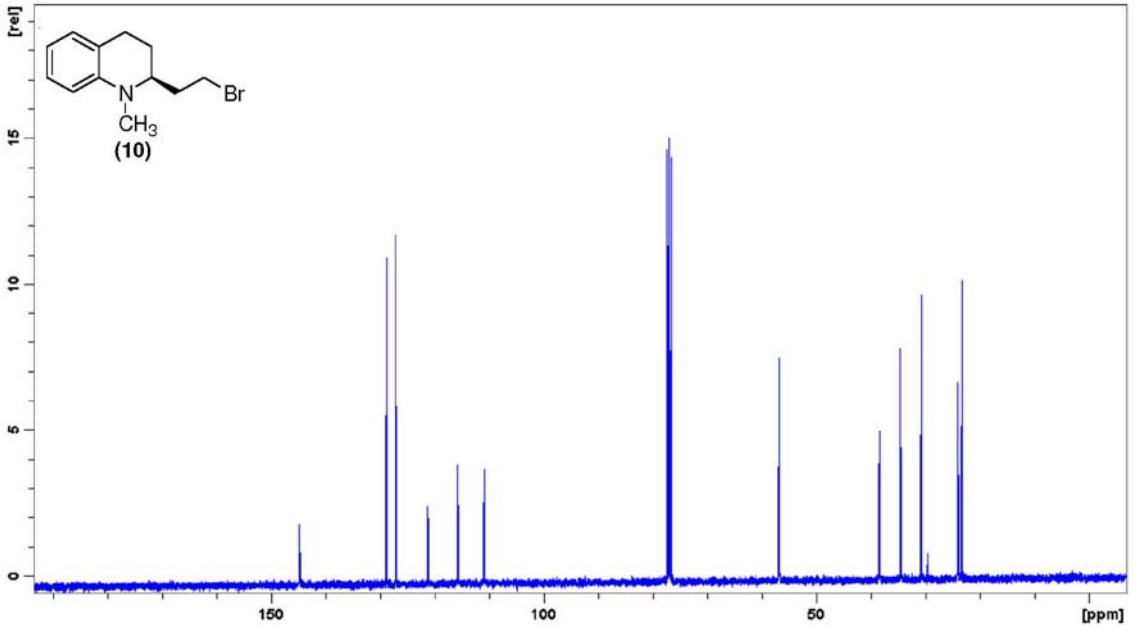


Figure S14. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of bromide **10**.

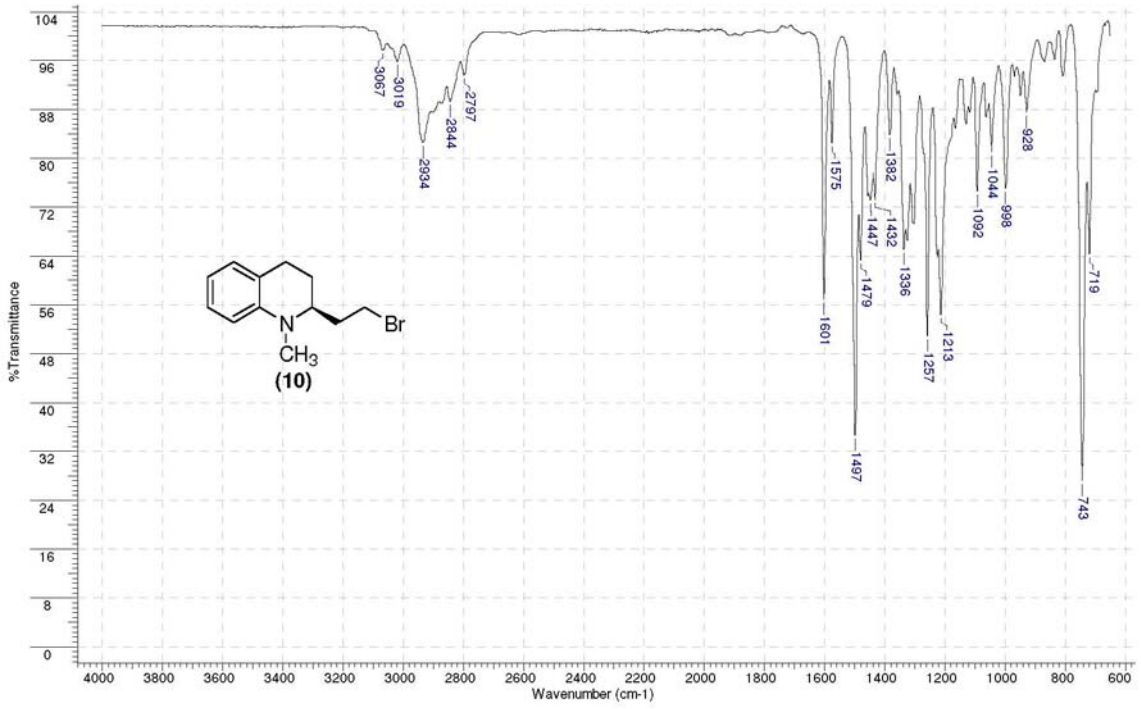


Figure S15. IV (film) spectrum of bromide **10**.

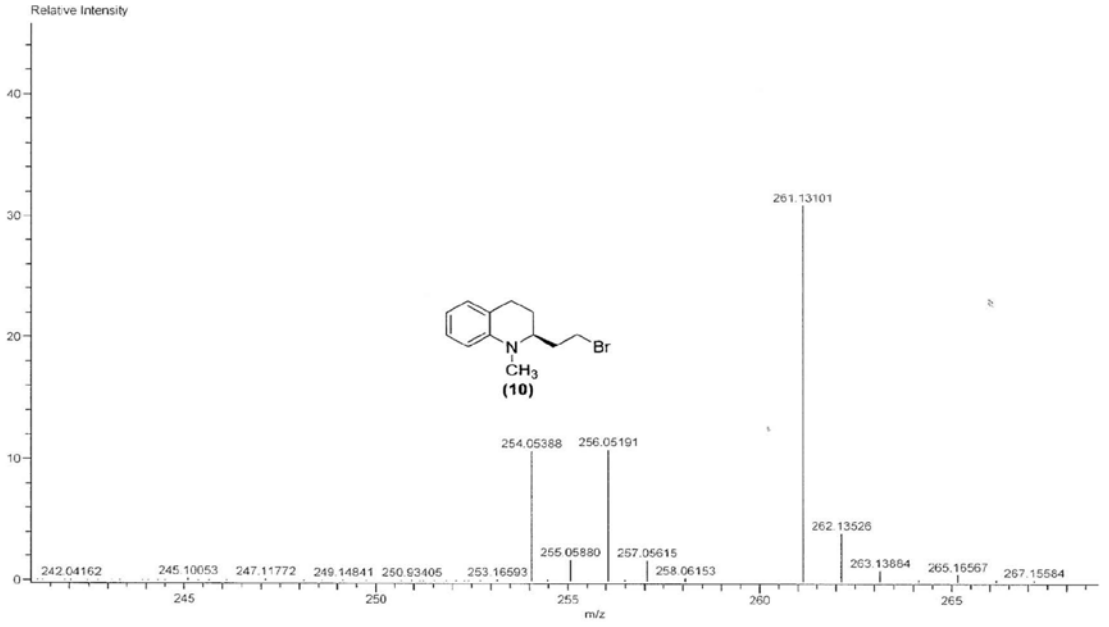


Figure S16. HRMS (ESI$^+$) *m/z* $(M + H)^+$ for $C_{12}H_{16}BrN$ of **10**.

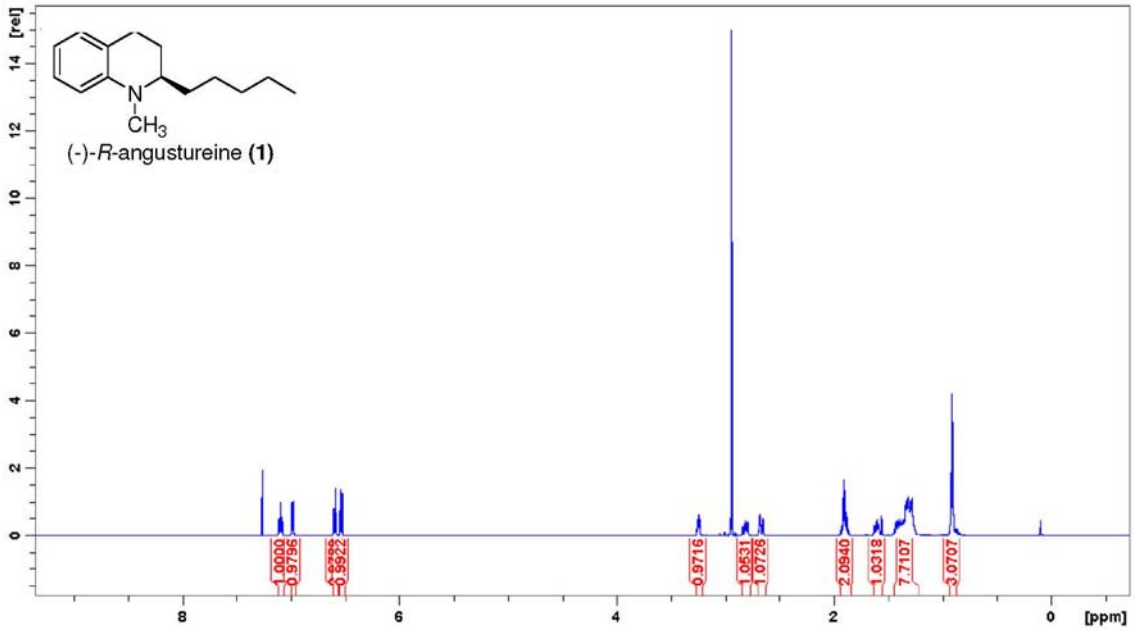


Figure S17. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of (*R*)-angustureine **1**.

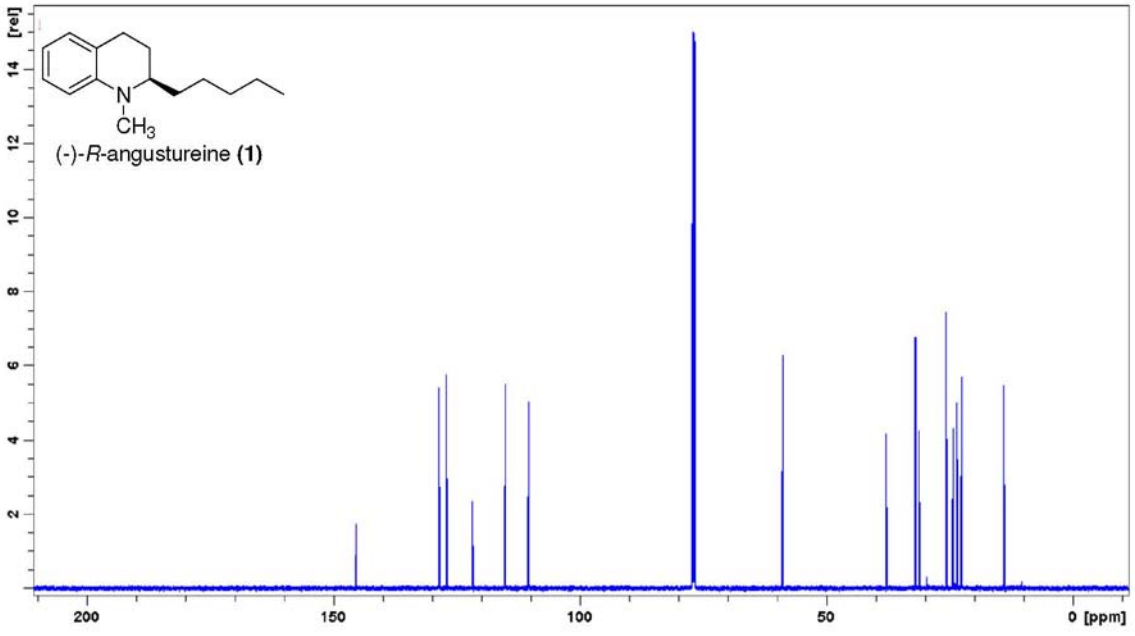


Figure S18. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of (*R*)-angustureine **1**.

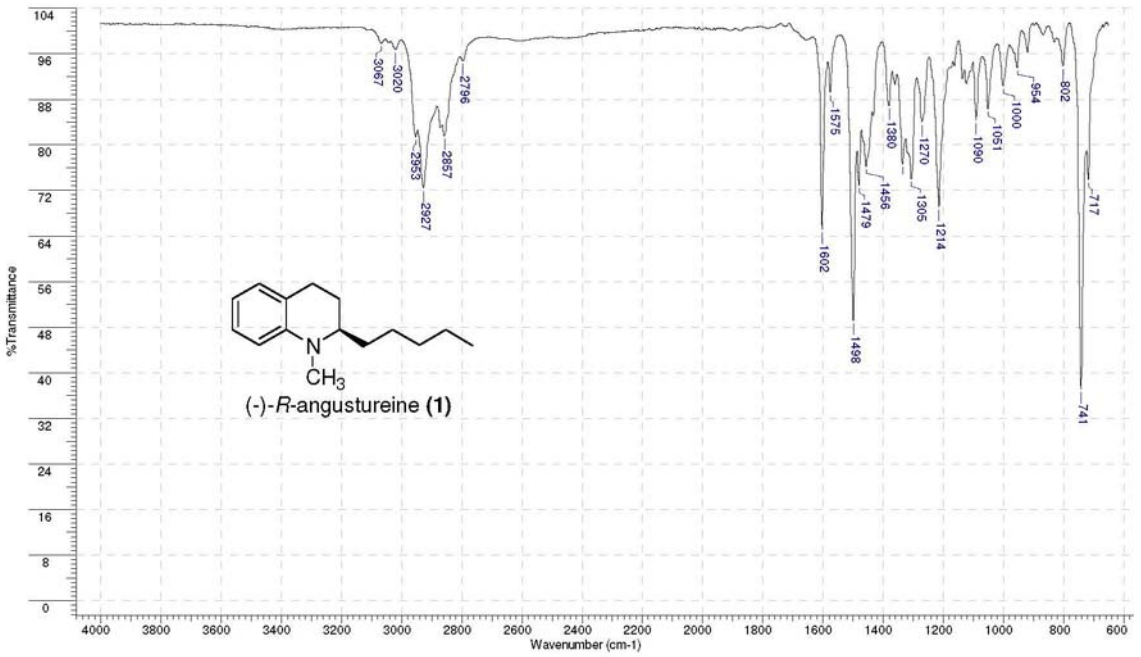


Figure S19. IV (film) spectrum of (*R*)-angustureine **1**.

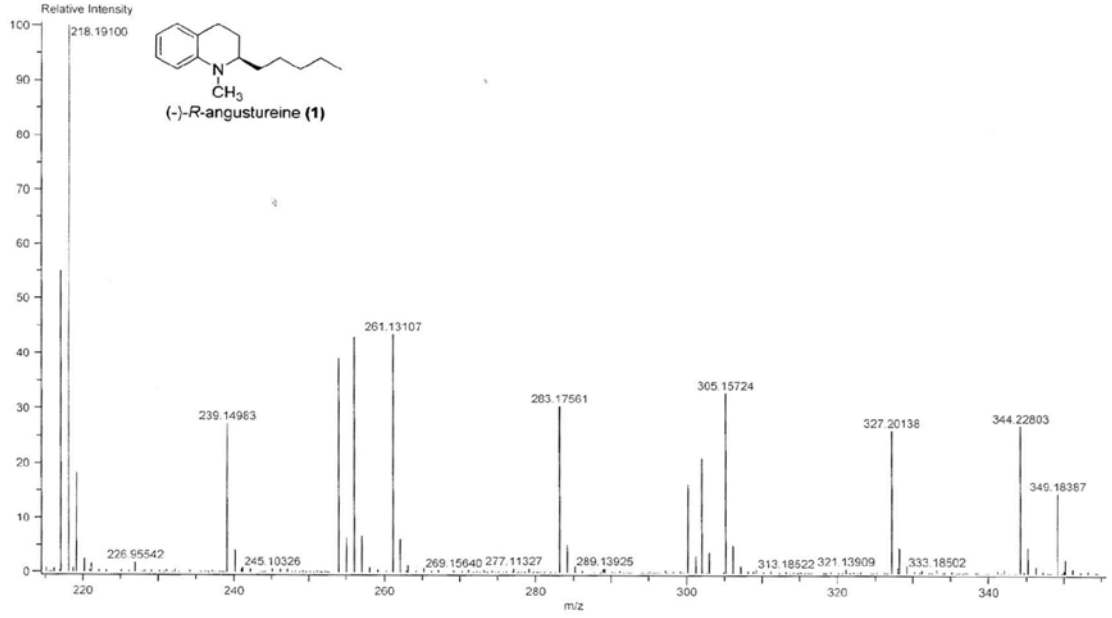


Figure S20. HRMS (ESI$^+$) *m/z* $(M + H)^+$ for $C_{15}H_{24}N$ of **1**.

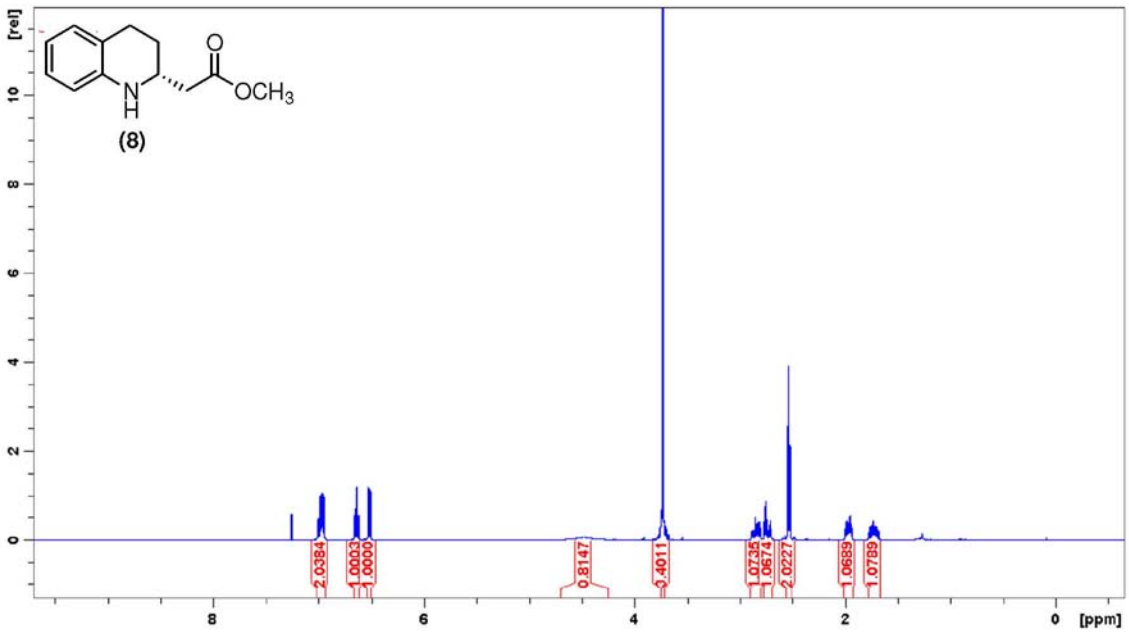


Figure S21. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (*R*)-β-amino ester **8**.

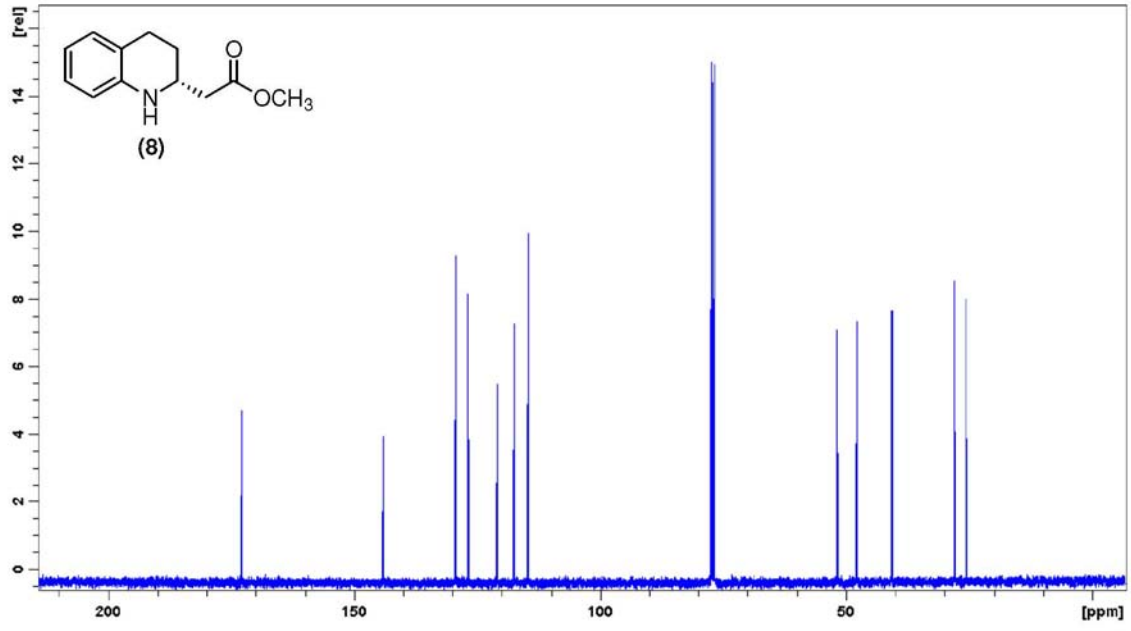


Figure S22. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (*R*)-β-amino ester **8**.

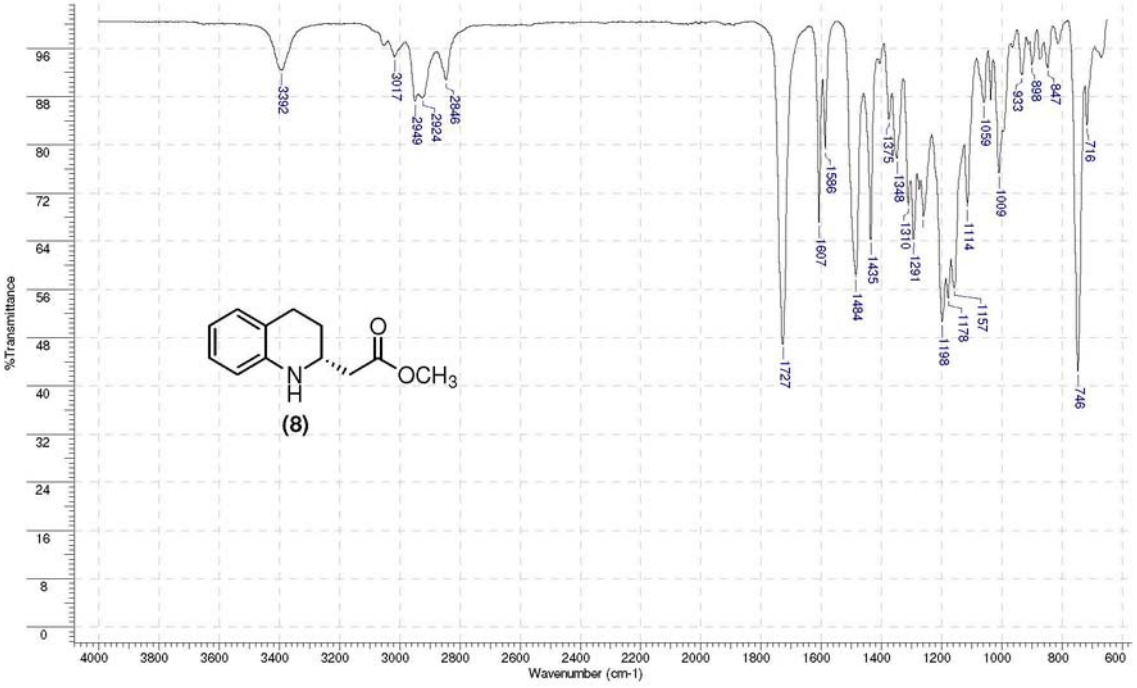


Figure S23. IV (film) spectrum of (*R*)-β-amino ester **8**.

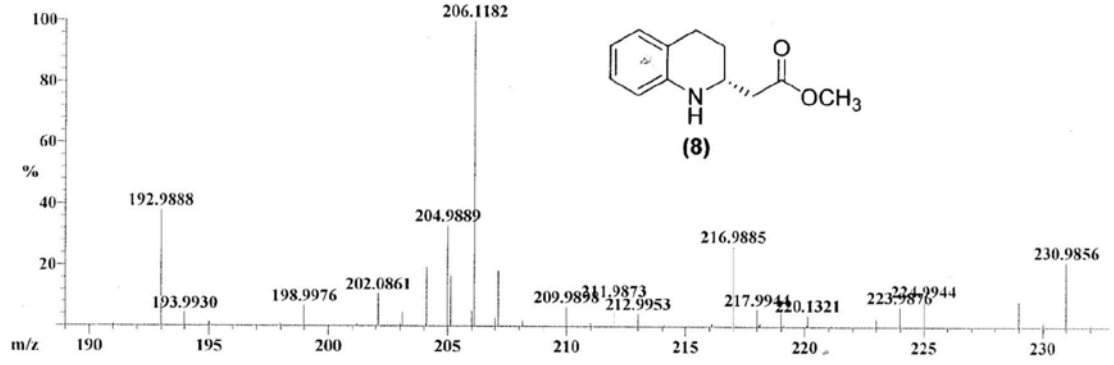


Figure S24. HRMS (CI⁺) *m/z* $(M + H)^+$ for $C_{12}H_{16}NO_2$ of **8**.

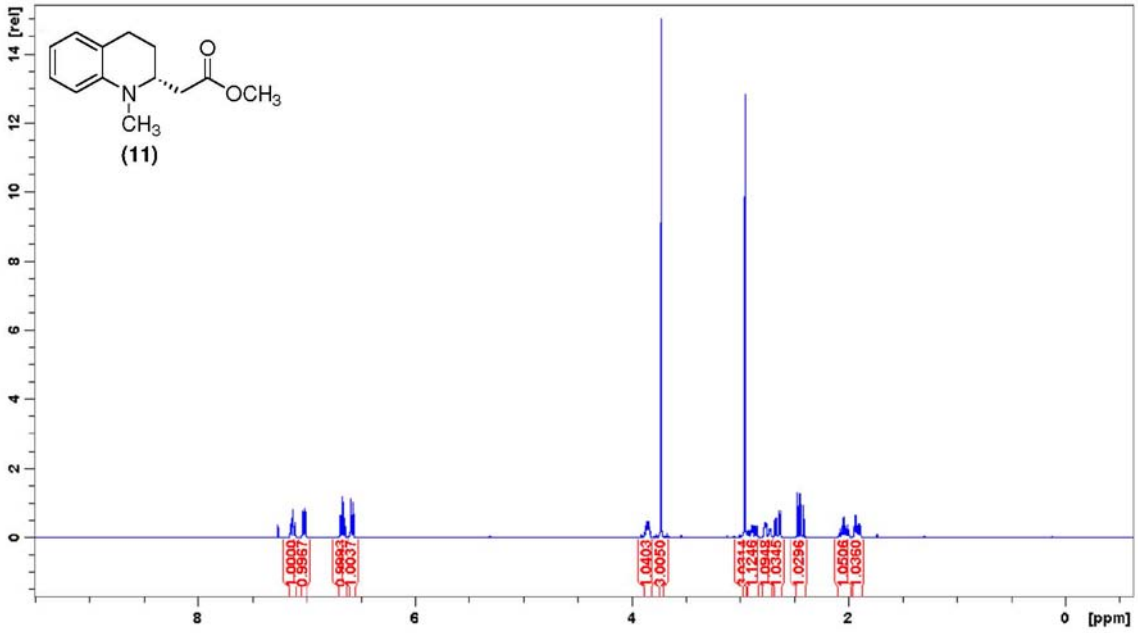


Figure S25. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (*R*)-*N*-methyl-β-amino ester **11**.

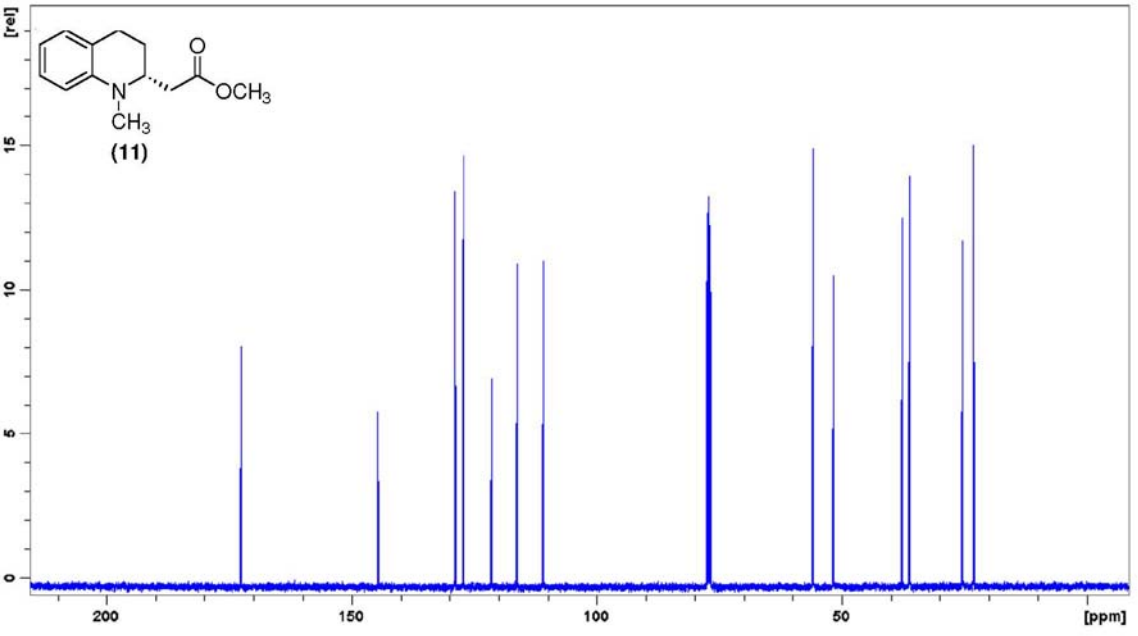


Figure S26. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (*R*)-*N*-methyl-β-amino ester **11**.

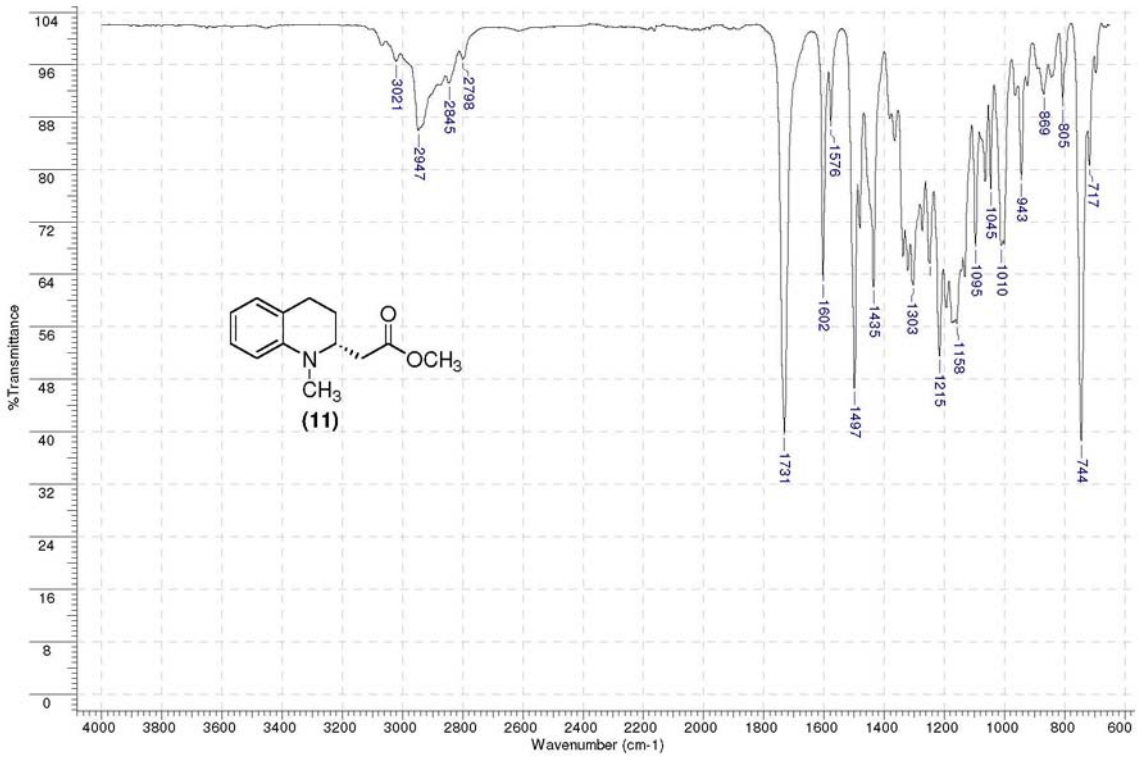


Figure S27. IV (film) spectrum of (*R*)-*N*-methyl-β-amino ester **11**.

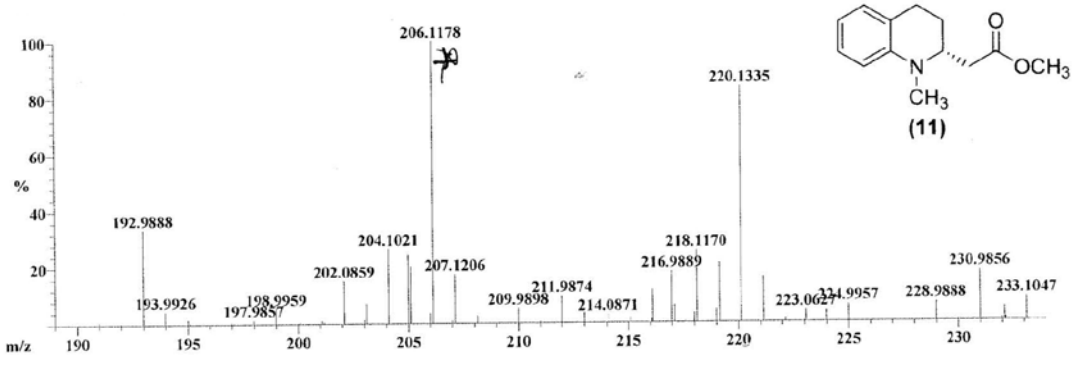


Figure S28. HRMS (CI$^+$) *m/z* $(M + H)^+$ for $C_{13}H_{18}NO_2$ of **11**.

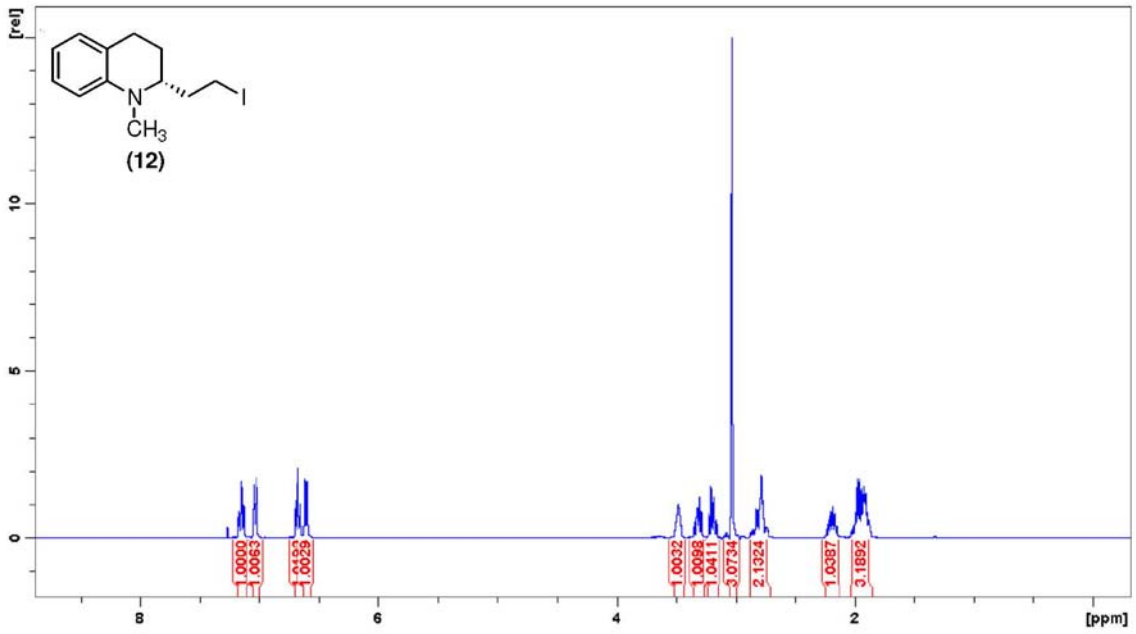


Figure S29. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (*R*)-iodide **12**.

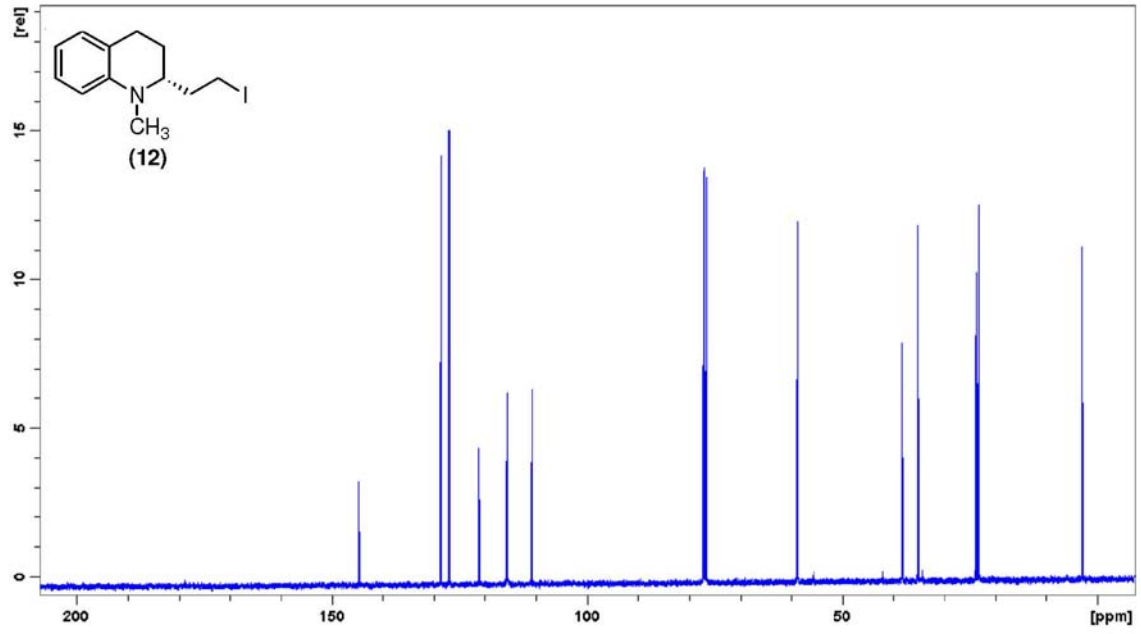


Figure S30. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of (*R*)-iodide **12**.

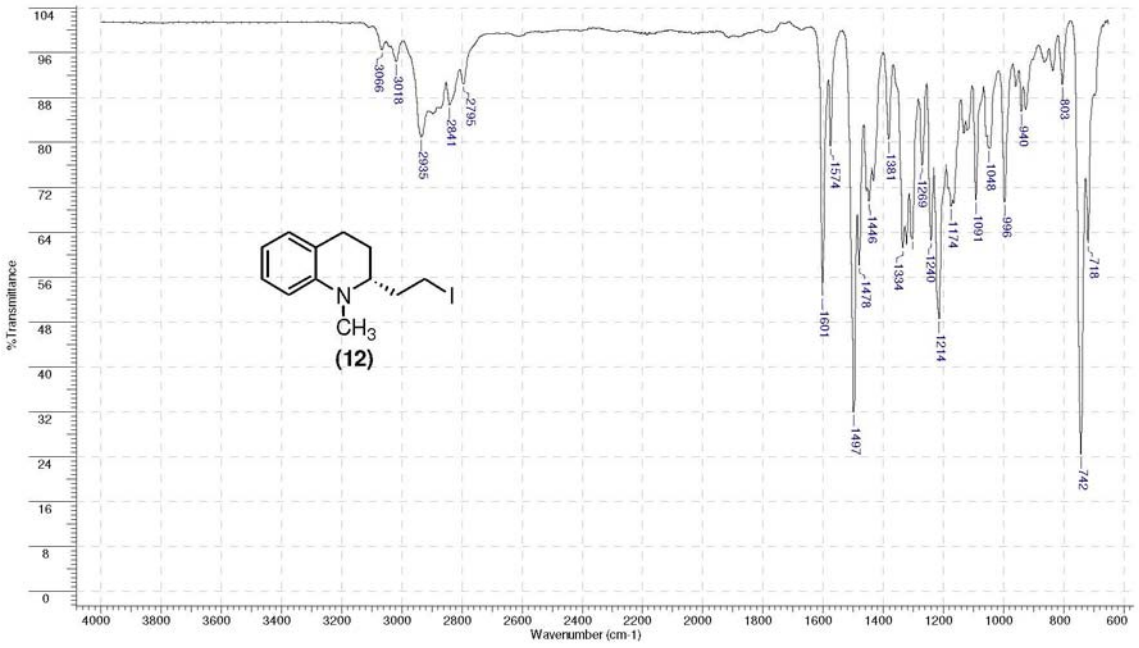


Figure S31. IV (film) spectrum of (*R*)-iodide **12**.

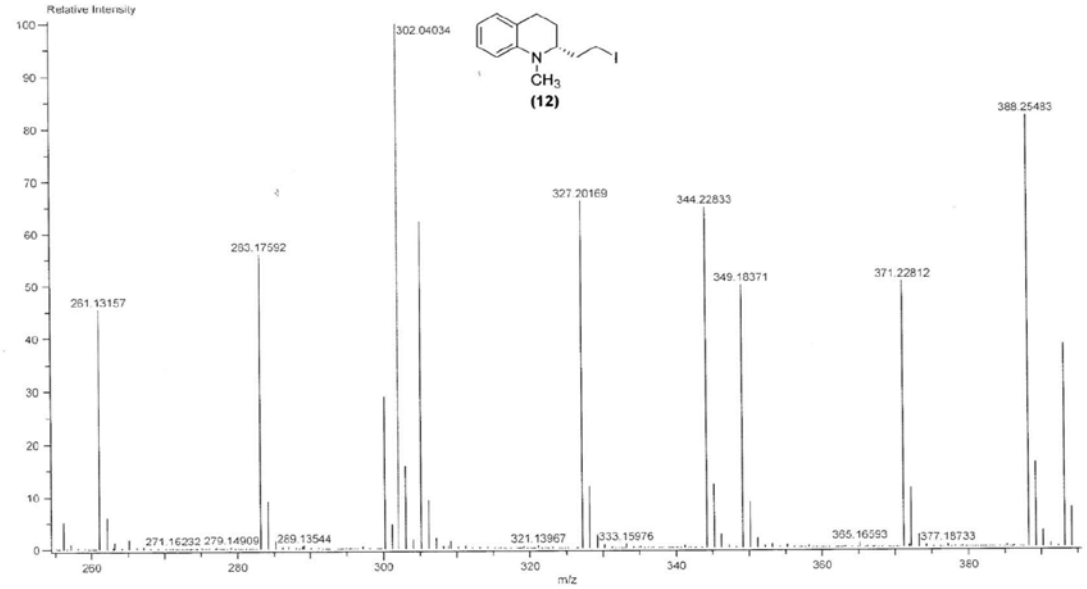


Figure S32. HRMS (ESI$^+$) *m/z* (M + H)$^+$ for $C_{12}H_{17}IN$ of **12**.

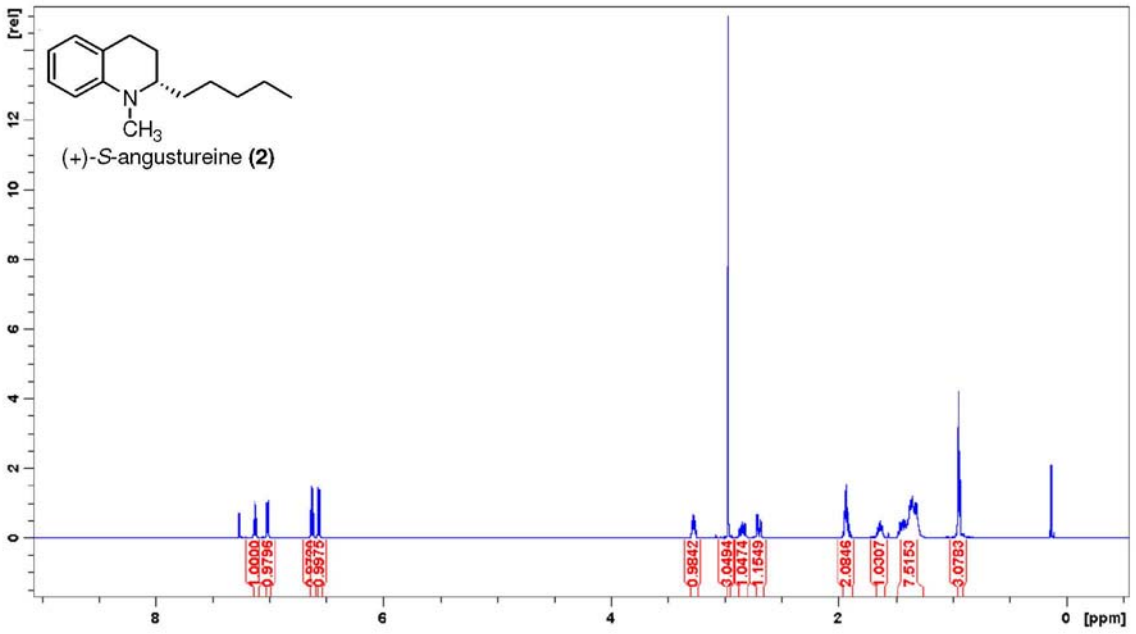


Figure S33. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of (*S*)-angustureine **2**.

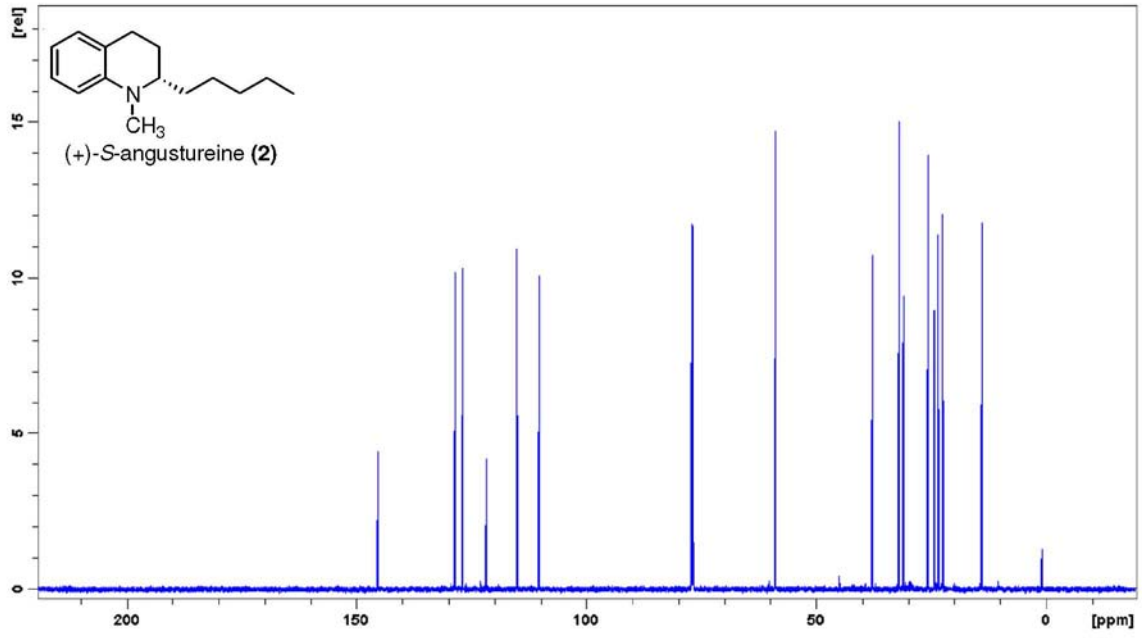


Figure S34. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of (*S*)-angustureine **2**.

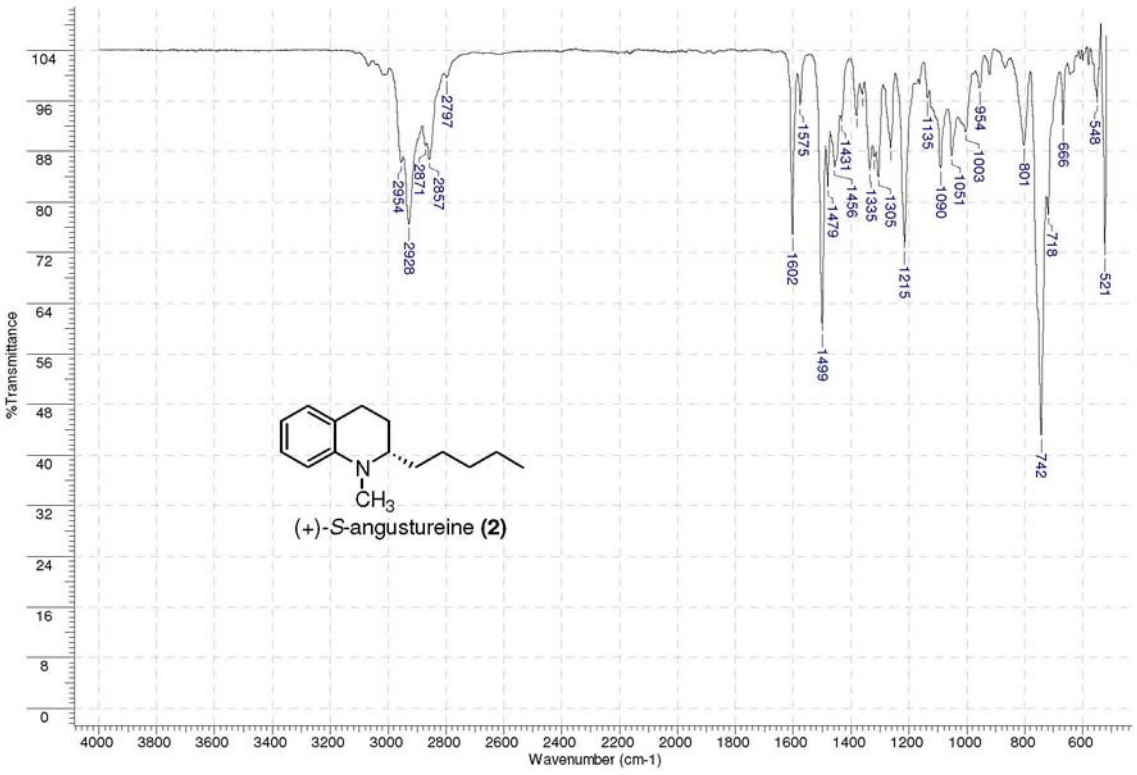


Figure S35. IV (film) spectrum of (*S*)-angustureine **2**.

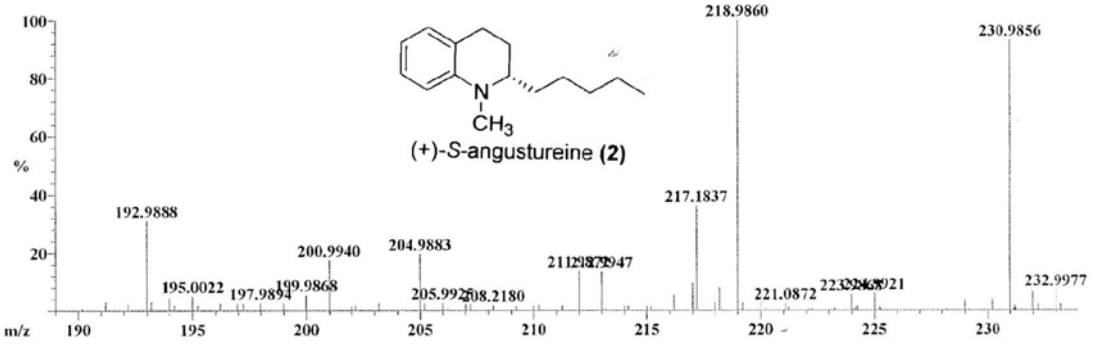


Figure S36. HRMS (EI⁺) *m/z* (M^+) for $C_{15}H_{23}N$ of **2**.

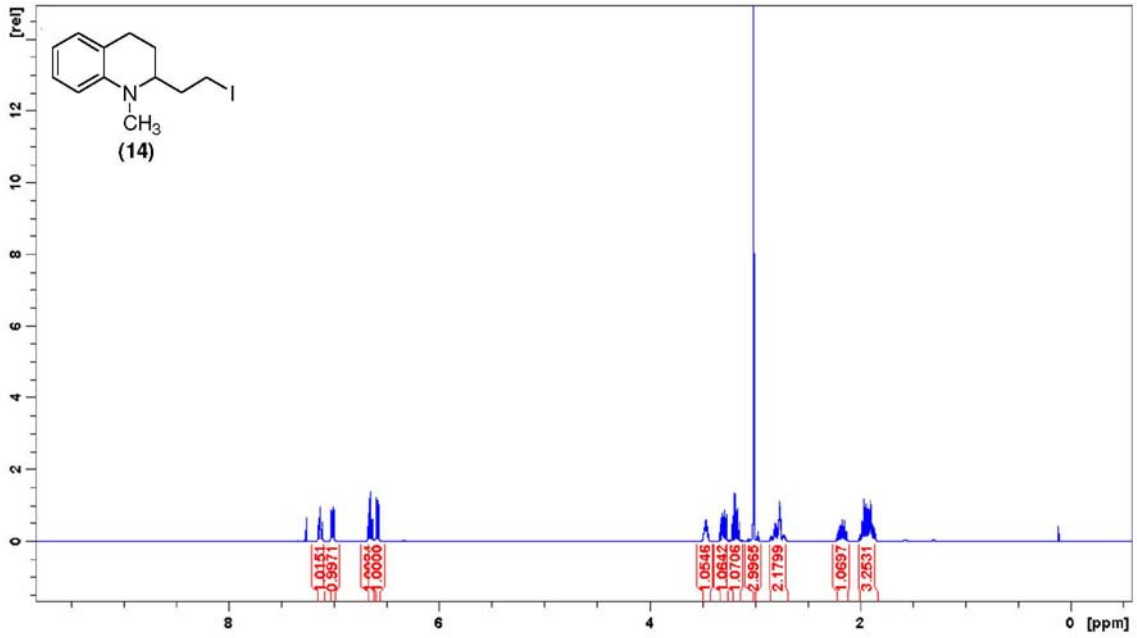


Figure S37. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of *rac*-iodide **14**.

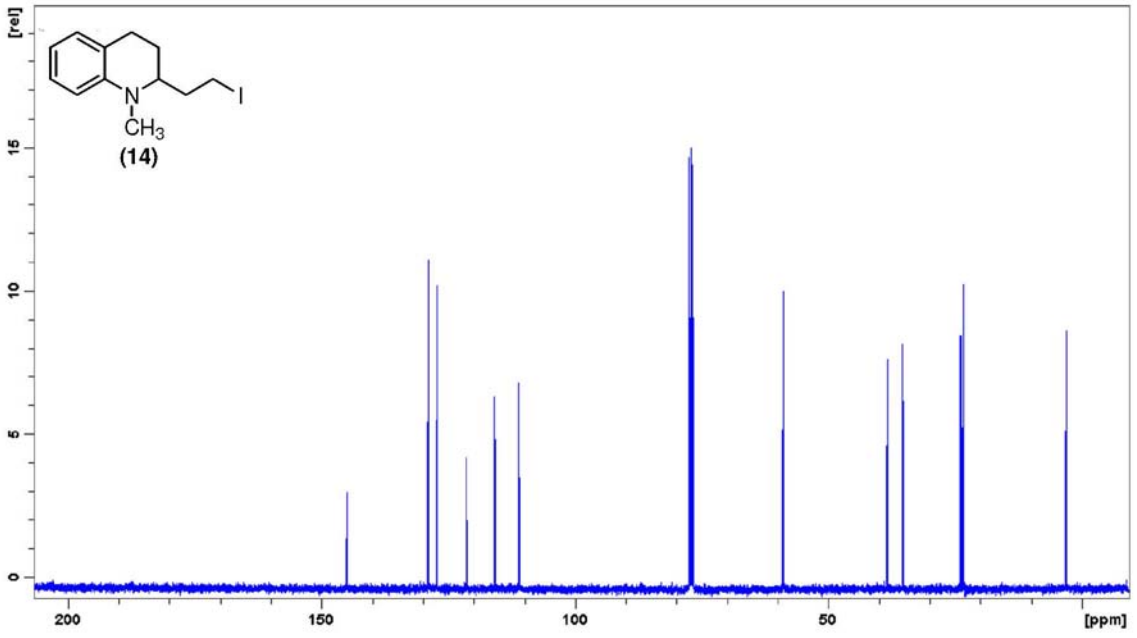


Figure S38. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of *rac*-iodide **14**.

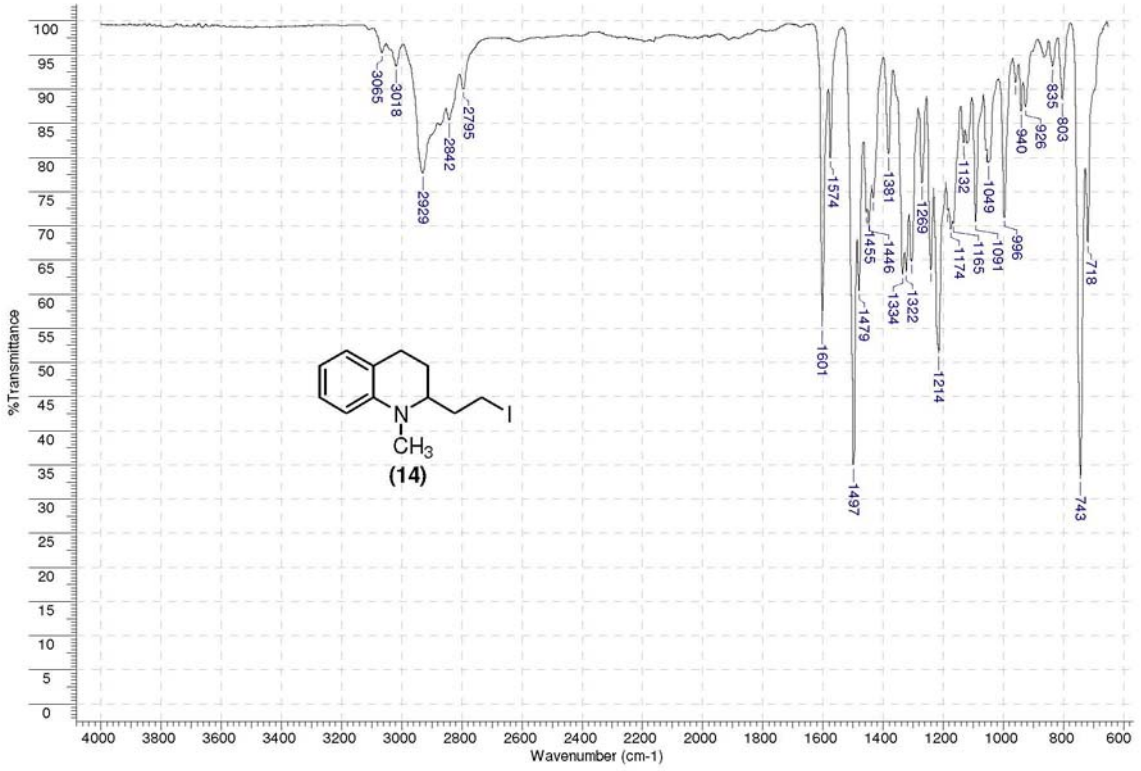


Figure S39. IV (film) spectrum of *rac*-iodide **14**.

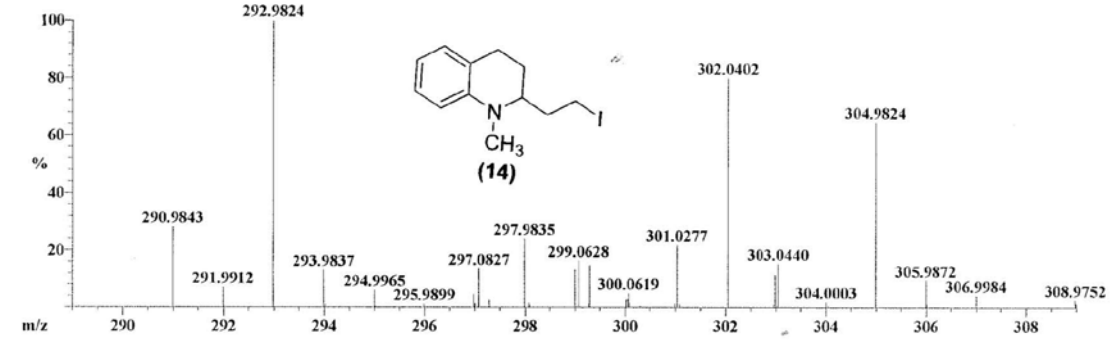


Figure S40. HRMS (CI$^+$) *m/z* $(M + H)^+$ for $C_{12}H_{17}IN$ of **14**.

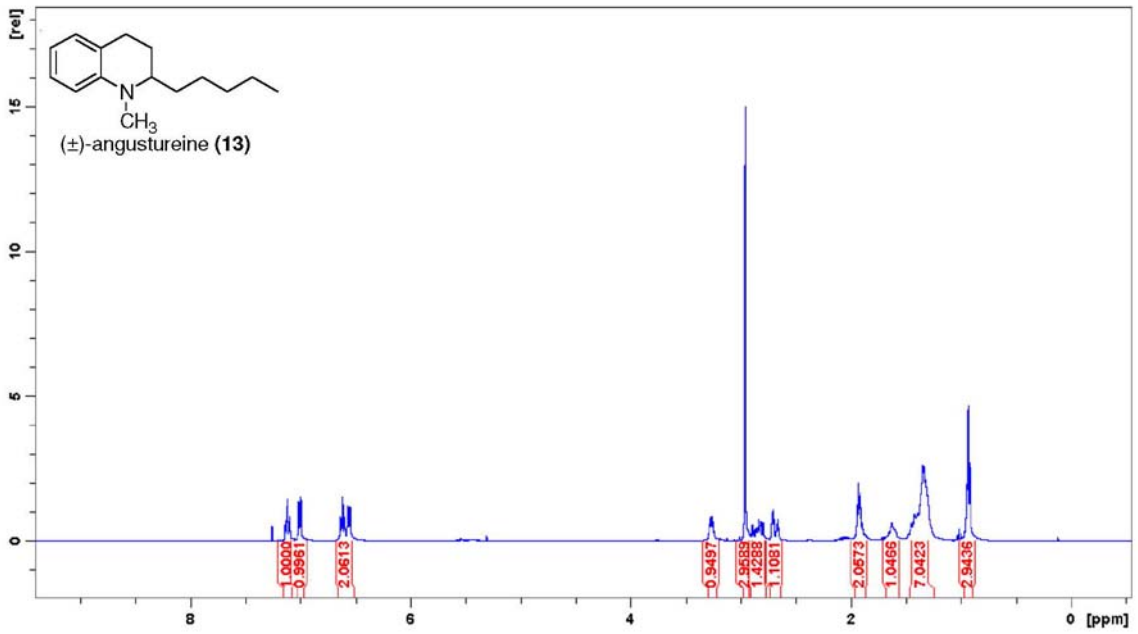


Figure S41. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of *rac*-angustureine **13**.

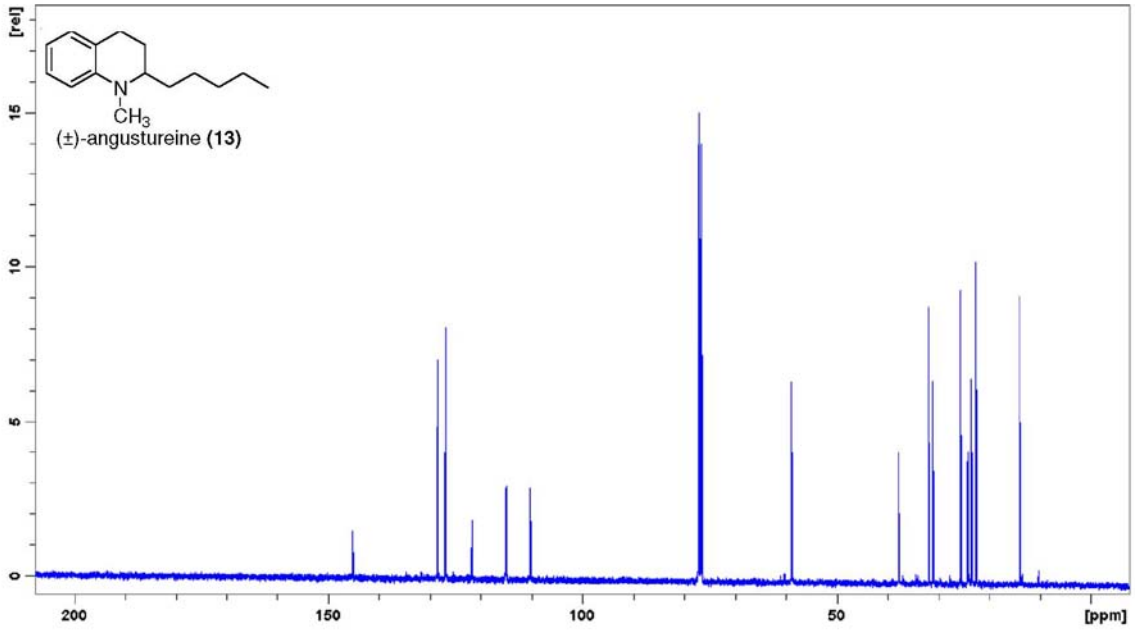


Figure S42. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of *rac*-angustureine **13**.

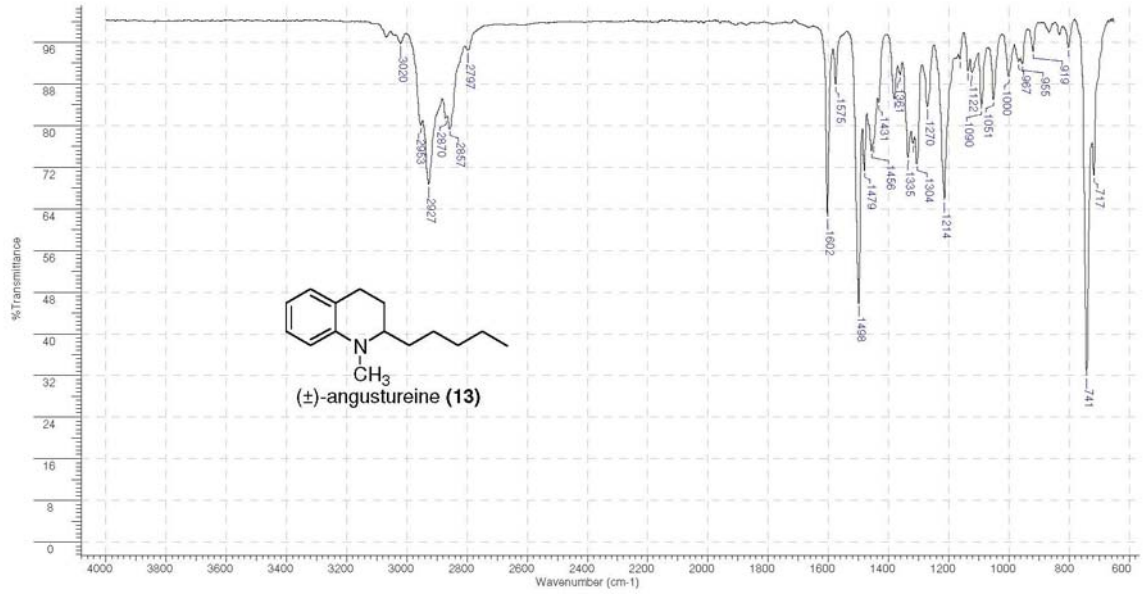


Figure S43. IV (film) spectrum of *rac*-angustureine **13**.

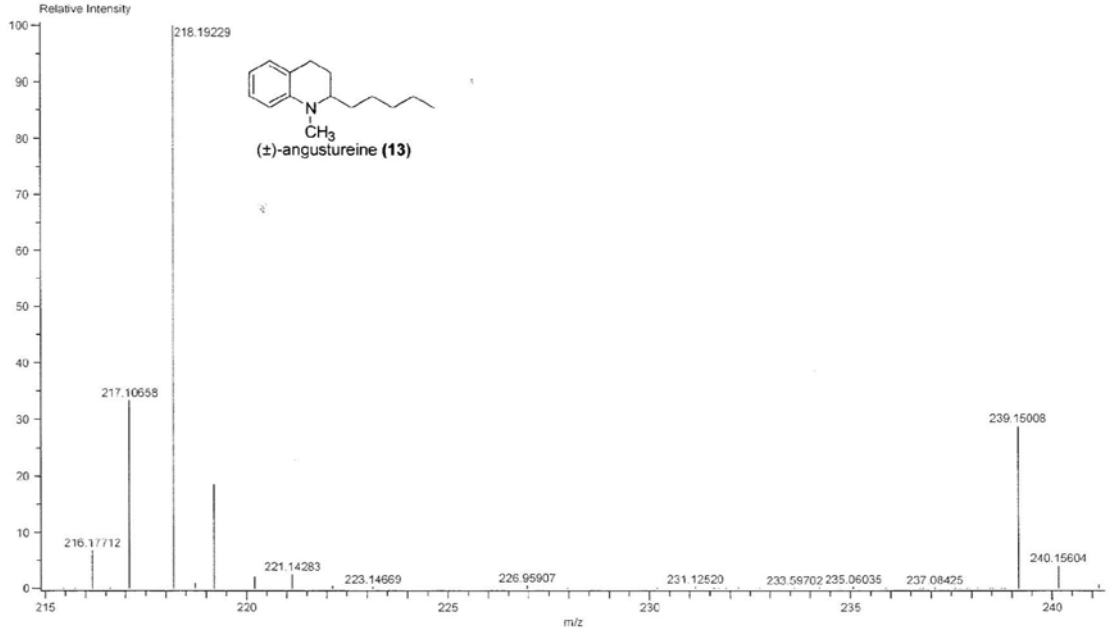
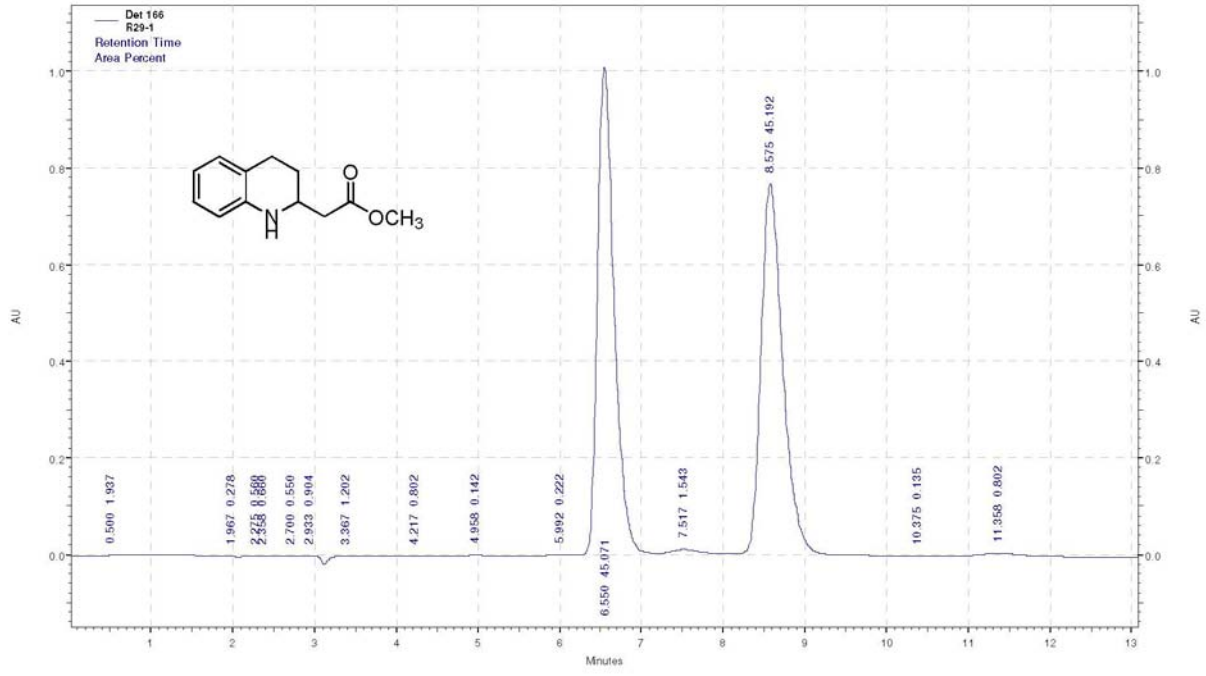


Figure S44. HRMS (ESI$^+$) *m/z* $(M + 1)^+$ for $C_{15}H_{24}N$ of **13**.

(±)-Methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate (**6**)

R-isomer rt = 6.55 min *S*-isomer rt = 8.57 min



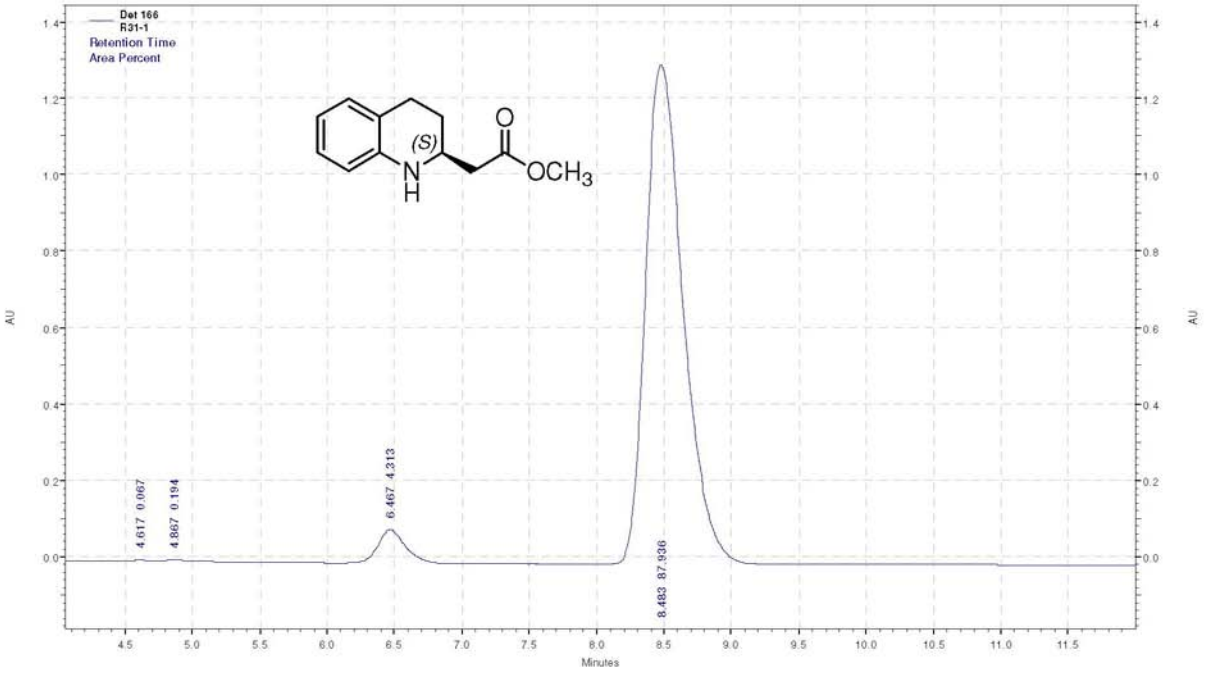
Det 166 Result

time	Area	Area / %	Height	Height / %
0.500	620589	1.94	4326	0.23
1.967	89110	0.28	11333	0.60
2.275	179491	0.56	12770	0.67
2.358	211402	0.66	13285	0.70
2.700	176123	0.55	14984	0.79
2.933	289617	0.90	16510	0.87
3.367	385301	1.20	14308	0.75
4.217	256943	0.80	3356	0.18
4.958	45401	0.14	2211	0.12
5.992	71136	0.22	2433	0.13
6.550	14442236	45.07	1012872	53.26
7.517	494476	1.54	14311	0.75
8.575	14481109	45.19	770642	40.53
10.375	43216	0.13	1575	0.08
11.358	257062	0.80	6702	0.35
Total	32043212	100.00	19016118	100.00

Figure 45. Chromatogram of *rac*-β-amino ester **6.**

(*S*)-methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate (5)

R-isomer rt = 6.46 min *S*-isomer rt = 8.48 min



Det 166 Result

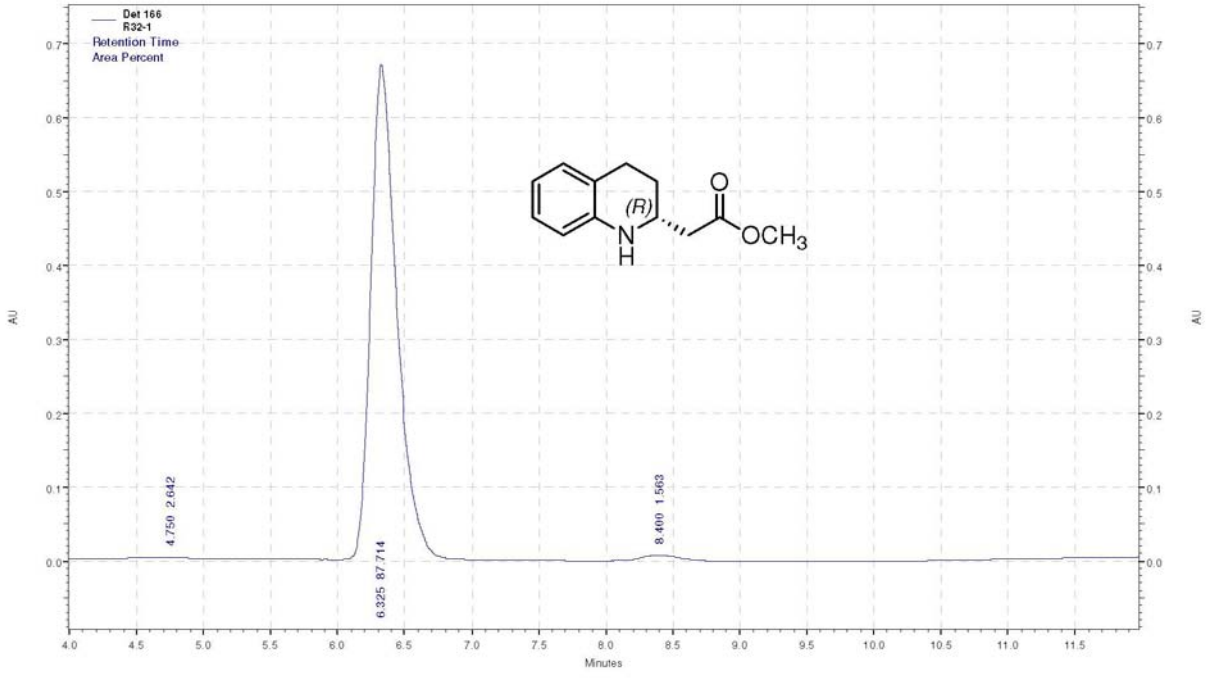
time	Area	Area / %	Height	Height / %
0.483	233773	0.81	16740	1.13
1.042	374902	1.30	6183	0.42
1.800	228992	0.79	10706	0.72
2.058	89262	0.31	13004	0.87
2.283	439557	1.53	13672	0.92
2.725	445280	1.55	14937	1.00
3.367	346526	1.20	12960	0.87
4.617	19407	0.07	2141	0.14
4.867	55875	0.19	3381	0.23
6.467	1242737	4.31	88718	5.97
8.483	25340054	87.94	1304244	87.73
Total	28816365	100.00	1486686	100.00

er (%) = [25340054/(25340054 + 1242737)] 100 = 95.3
1st peak:2nd peak = 4.7:95.3
ee (%) = 95.3-4.7 = 91

Figure 46. Chromatogram of (*S*)-β-amino ester **5**.

(*R*)-methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate (**8**)

R-isomer rt = 6.33 min *S*-isomer rt = 8.4 min



Det 166 Result

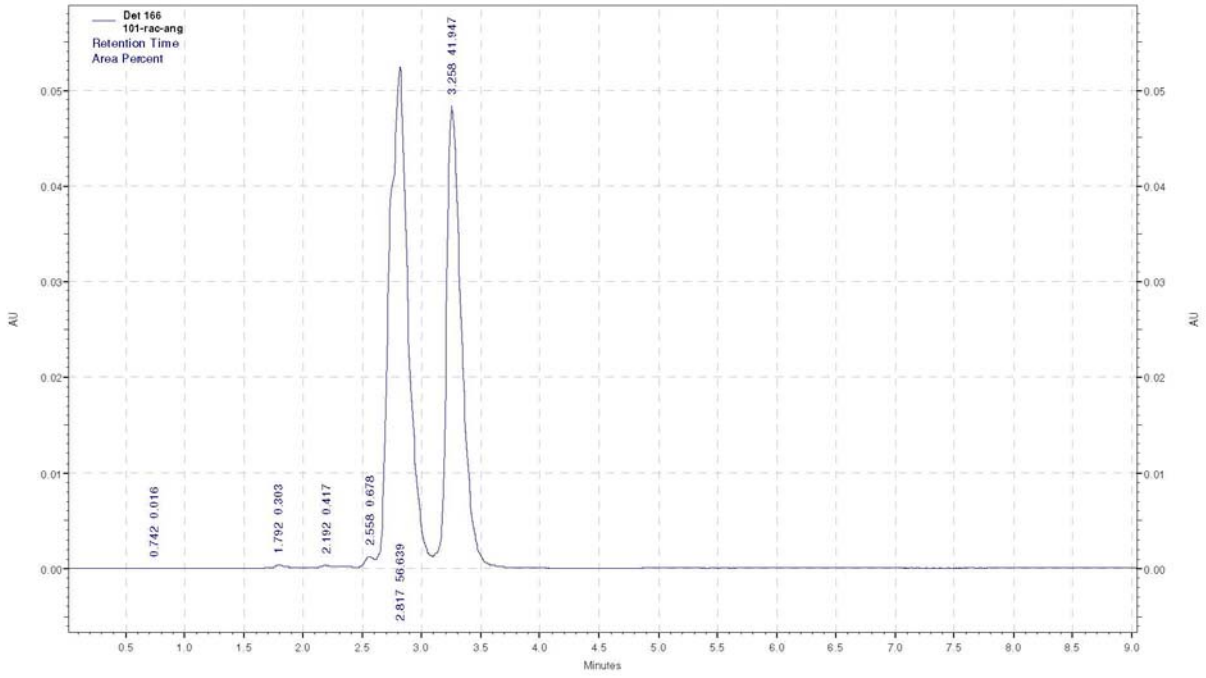
time	Area	Area / %	Height	Height /%
0.442	58198	0.56	1228	0.17
1.325	68020	0.66	2714	0.37
1.833	92964	0.90	4207	0.58
1.950	34516	0.33	4736	0.65
2.325	156783	1.51	5754	0.79
2.683	67735	0.65	6735	0.92
2.967	137505	1.33	8032	1.10
3.308	138851	1.34	7686	1.05
3.425	83584	0.81	7029	0.96
4.750	273974	2.64	2277	0.31
6.325	9097319	87.71	670156	91.96
8.400	162088	1.56	8216	1.13
Total	10371537	100.00	728770	100.00

er (%) = [9097319/(9097319 + 162088)] 100 = 98.3
1st peak:2nd peak = 1.7:98.2
ee (%) = 98.2-1.7 = 96

Figure 47. Chromatogram of (*S*)-β-amino ester **8**.

(±)-*N*-Methyl-2-*n*-pentyl-1,2,3,4-tetrahydroquinoline (**13**)

R-isomer rt = 3.26 min *S*-isomer rt = 2.82 min



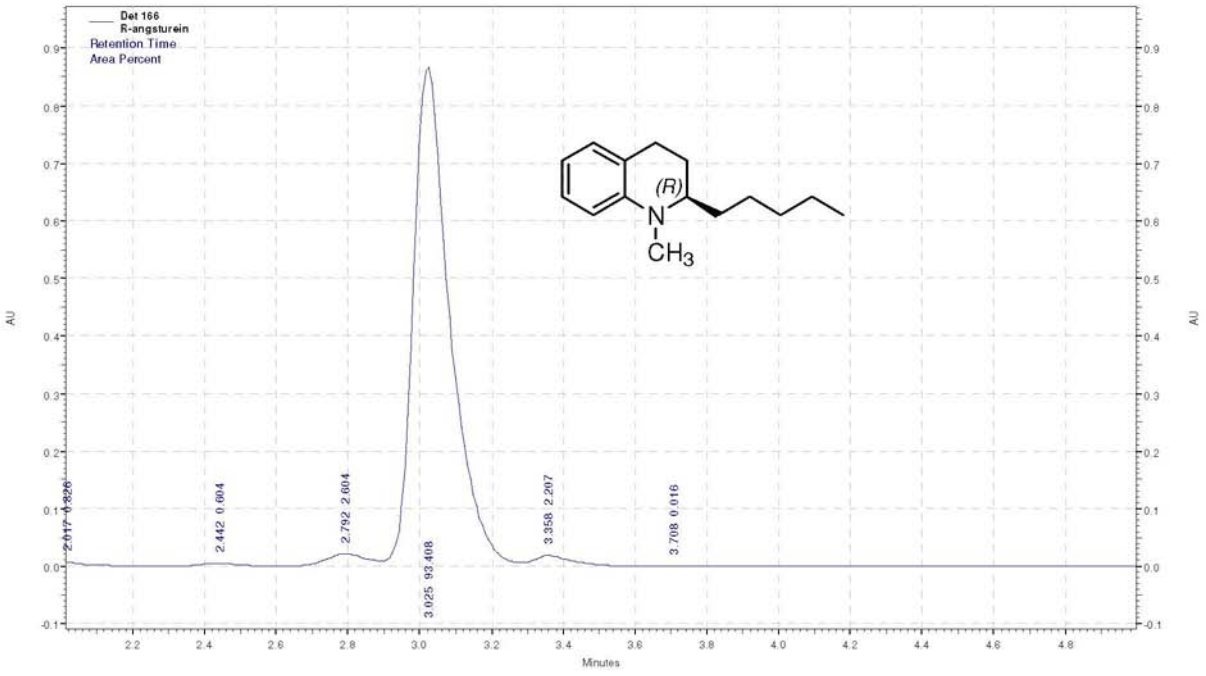
Det 166 Result

time	Area	Area / %	Height	Height / %
0.742	163	0.02	27	0.03
1.792	3077	0.30	353	0.34
2.192	4238	0.42	279	0.27
2.558	6891	0.68	1167	1.14
2.817	575763	56.64	52334	51.12
3.258	426414	41.95	48221	47.10
Total	1016546	100.00	102381	100.00

Figure 48. Chromatogram of *rac*-angustureine **13**.

(*R*)-(–)-*N*-Methyl-2-*n*-pentyl-1,2,3,4-tetrahydroquinoline (1)

R-isomer rt = 3.03 min *S*-isomer rt = 2.79 min



Det 166 Result

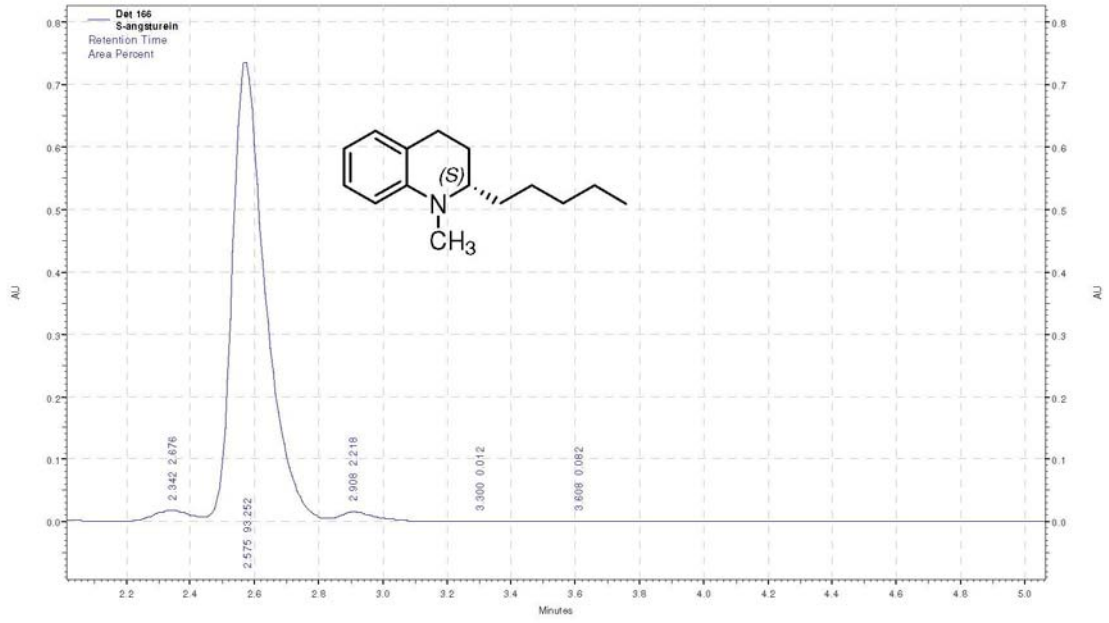
Time	Area	Area / %	Height	Height / %
0.258	144	0.00	34	0.00
0.408	297	0.00	50	0.01
0.983	117	0.00	29	0.00
2.017	54641	0.83	7005	0.76
2.442	39994	0.60	4900	0.53
2.792	172335	2.60	21493	2.34
3.025	6182508	93.41	866069	94.19
3.358	146110	2.21	18690	2.03
3.708	1061	0.02	149	0.02
9.350	21620	0.33	1075	0.12
Total	6618827	100.00	919494	100.00

er (%) = [6182508/(6182508 + 172335)] 100 = 97.3
1st peak:2nd peak = 2.7:97.3
ee (%) = 97.3-2.7 = 95

Figure 49. Chromatogram of (*R*)-angustureine **1**.

(*S*)-(+)-*N*-Methyl-2-*n*-pentyl-1,2,3,4-tetrahydroquinoline (**2**)

R-isomer rt = 2.91 min *S*-isomer rt = 2.58 min



Det 166 result

time	Area	Area / %	Height	Height / %
0.167	124	0.00	31	0.00
0.408	377	0.01	38	0.00
0.700	245	0.00	35	0.00
0.850	134	0.00	40	0.01
1.550	46382	0.82	5818	0.75
1.975	34122	0.60	4172	0.53
2.342	151045	2.68	18240	2.34
2.575	5262979	93.25	735319	94.18
2.908	125164	2.22	15601	2.00
3.300	669	0.01	127	0.02
3.608	4633	0.08	455	0.06
8.950	17935	0.32	868	0.11
9.750	0	0.00	0	0.00
Total	5643809	100.00	780744	100.00

er (%) = [5262979/(5262979 + 125164)] 100 = 98
1st peak:2nd peak = 2:98
ee (%) = 98-2 = 96

Figure 50. Chromatogram of (*S*)-angustureine **2**.