Enantioselective synthesis of 1,2,3,4-tetrahydroquinoline-4-ols and 2,3-dihydroquinolin-4(1*H*)-ones via a sequential asymmetric hydroxylation/diastereoselective oxidation process using *Rhodococcus equi* ZMU-LK19

Ke Li, Juxiang Wang, Kailin Wu, DaijunZheng, Xiaojian Zhou, Wenyong Han, Nanwei Wan, Baodong Cui and Yongzheng Chen*

Generic Drug Research Center of Guizhou Province, School of Pharmacy, Zunyi Medical University, Zunyi, 563000, China.

Email: yzchen@zmc.edu.cn

Supporting Information

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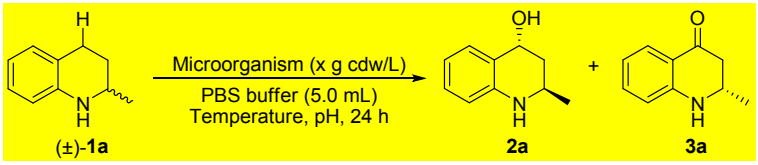
1. General experimental information

All reagents and solvents were obtained from commercial suppliers and used without further purification. 2-Methylquinoline, NADH and NADPH were purchased from J&K Chemicals, *rac*-2-methyl-1,2,3,4-tetrahydroquinoline were purchased from TCI. $^{18}O_2$ and $H_2{}^{18}O$ were bought from Xiya Chemicals. Water was distilled before use. All strains were isolated and preserved in our laboratory.

The reactions were monitored by TLC (silica gel 60 F_{254}). Column chromatography was performed on silica gel (200-400 mesh). ^{1}H NMR (400 MHz) chemical shifts were reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, br s= broad singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = double of triplet, td = triplet of doublets, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR (100 MHz) chemical shifts were reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Enantiomeric excess was determined by HPLC analysis, it was performed on SPD-M20A equipped with an Chiralcel OJ-H chiral column (4.6 mmΦ×250 mmL), Chiralcel OD-H chiral column (4.6 mmΦ×250 mmL), Chiralpak AD-H chiral column (4.6 mmΦ×250 mmL) and Chiralpak AS-H chiral column (4.6 mmΦ×250 mmL) purchased from Daicel Chemical Industries. MS HR-ESI was performed on a micrOTOF-Q II 10203 mass spectrometer. Optical rotation data were determined by Autopol II-Rudolph Polarimeter. Melting points (Mp) were measured on a G-4 micromelting point apparatus and are uncorrected values. Absolute configuration of product were determined by X-ray diffraction.

2. Table S1 Screening of whole-cell biocatalysts[a]



entry	whole cells	2a			3a	
		yield (%)[b]	dr[c]	ee (%)[d]	yield (%)[b]	ee (%)[c]
1	*Pseudomonas spicies* ZMU-T01	5	>99:1	95	14	98
2	*Pseudomonas monteilii* ZMU-T02	4	81:19	86	8	>99
3	*Pseudomonas monteilii* ZMU-T03	6	79:21	87	14	98
4	*Pseudomonas monteilii* ZMU-T04	6	92:8	93	18	98
5	*Pseudomonas monteilii* ZMU-T05	5	97:3	90	15	99
6	*Pseudomonas monteilii* ZMU-T06	8	99:1	91	20	98
7	*Pseudomonas monteilii* ZMU-T07	3	75:25	83	7	98
8	*Pseudomonas monteilii* ZMU-T08	4	>99:1	89	12	98
9	*Pseudomonas monteilii* ZMU-T09	3	89:11	76	6	>99
10	*Pseudomonas monteilii* ZMU-T12	5	83:17	93	12	97
11	*Pseudomonas monteilii* ZMU-T13	6	95:5	84	19	98

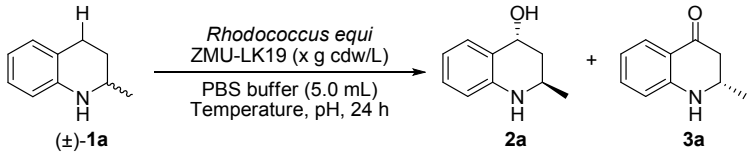
12	*Pseudomonas monteilii* ZMU-T14	4	74:26	83	8	99
13	*Pseudomonas monteilii* ZMU-T15	5	89:11	95	15	98
14	*Pseudomonas monteilii* ZMU-T16	0	-	-	0	-
15	*Pseudomonas monteilii* ZMU-T17	0	-	-	0	-
16	*Rhodococcus equi* ZMU-LK19	58	68:32	95	18	96

[a] All reactions (5.0 mL) were performed in pH 7.0 (50.0 mM Na_2HPO_4/KH_2PO_4) containing **(±)-1a** (3.0×10^{-2} mmol, 6.0 mM) and whole cell (30 g cdw/L) at 30 °C and 250 rpm for 24 h. [b] Determined by HPLC analysis of the crude reaction mixture by the external standard method. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis for major diastereoisomer.

3. Cultivation of *R. equi* ZMU-LK19

R. equi ZMU-LK19 obtained by screening the soil sample from Guizhou Province in P. R. China was grown in M9-agar plates under ethylbenzene vapor, subsequently inoculated to 10 mL LB liquid medium. The culture was incubated at 30 ºC and 250 rpm for 24 h and then transferred to 50 mL M9 liquid medium containing 50 μL trace elements (1 mol/L HCl, 4.87 g/L $FeSO_4 \cdot 7H_2O$, 4.12 g/L $CaCl_2 \cdot 2H_2O$, 1.50 g/L $MnCl_2 \cdot 4H_2O$, 1.05 g/L $ZnSO_4$, 0.3 g/L H_3BO_3, 0.25 g/L $Na_2MoO_4 \cdot 2H_2O$, 0.15 g/L $CuCl_2 \cdot 2H_2O$, 0.84 g/L $Na_2EDTA \cdot 2H_2O$), 100 μL Mg_2SO_4 (1 M) and 50 μL ethylbenzene. After the cell density reached 0.1 g cdw/L, a 15 mL tube containing 500 μL ethylbenzene was added into the flask and used as carbon source. Then the culture was incubated at 30 ºC and 250 rpm. After 24 h, the cells were harvested by centrifugation for immediate use.

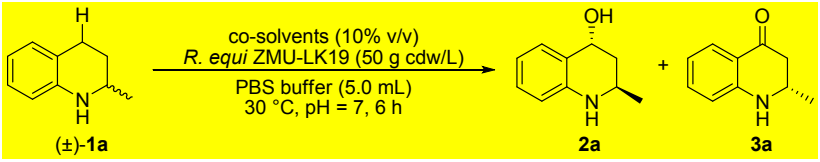
4. Table S2 Optimization of reaction conditions[a]



entry	cell density (g cdw/L)	subs. conc. (mm)	t (°c)	pH	2a			3a	
					yield (%)[b]	dr[c]	ee (%)[d]	yield (%)[b]	ee (%)[c]
1	30	6	30	7	58	68:32	95	18	96
2	50	6	30	7	56	78:22	98	25	96
3	70	6	30	7	50	78:22	96	26	97
4	50	4	30	7	55	76:24	97	25	97
5	50	8	30	7	50	79:21	97	14	95
6	50	6	20	7	44	53:47	95	15	98
7	50	6	37	7	55	76:24	86	13	86
8	50	6	30	6	54	55:45	75	6	97
9	50	6	30	8	60	53:47	90	9	98

[a] All reactions were performed in 5 mL PBS buffer (50 mM Na_2HPO_4/KH_2PO_4) and 250 rpm for 24 h. [b] determined by HPLC analysis of the crude reaction mixture by the external standard method. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis for major diastereoisomer.

5. Table S3 Investigation of cosolvents[a]



entry	co-solvent	2a			3a	
		yield (%)[b]	dr[c]	ee (%)[d]	yield (%)[b]	ee (%)[c]
1	None	83	59:41	96	9	99
2	Glycerol	70	57:43	98	8	>99
3	DMF	19	90:10	>99	0	-
4	DMSO	86	54:46	99	4	>99
5	MeOH	20	91:9	>99	1	>99
6	EtOH	1	-	>99	0	-
7	CH_3CN	2	-	>99	0	-
8	THF	1	-	>99	0	-
9	MTBE	4	90:10	>99	0	-

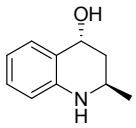
[a] All reactions (5.0 mL) were performed in pH 7.0 (50.0 mM Na_2HPO_4/KH_2PO_4) containing **1a** (3.0×10^{-2} mmol, 6.0 mM), *R. equi* ZMU-LK19 (50 g cdw/L) and the stated cosolvent (0.5 mL, 10% *v*/*v*) at 30 °C and 250 rpm for 6 h. [b] Determined by HPLC analysis of the crude reaction mixture by the external standard method. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis for major diastereoisomer.

6. Representative procedure for the synthesis of 2a and 3a (Table 1 entry 1)

The cells of *R. equi* ZMU-LK19 were suspended in 36 mL PBS buffer (50 mM Na_2HPO_4/KH_2PO_4, pH 7.0) to a cell density of 50 g cdw/L, and (±)-**1a** (35.3 mg, 0.24 mmol, 6 mM) was added with 4 mL DMSO. The mixture was shaken at 30 ºC and 250 rpm for 24 h. Then the mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo, generating brownish oil. The crude was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 15:1) to afford the corresponding compound **2a** as a yellowish solid (22.5 mg, 57% yield) and **3a** as a yellowish solid (9.7 mg, 25% yield).

7. Characterization data of compounds 2a-f, 3a-f

Table 1, entry 1

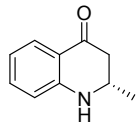


(2*R*,4*R*)-2a

(2*R*,4*R*)-2-methyl-1,2,3,4-tetrahydroquinoline-4-ol (2a): Yellowish solid, yield: 22.5 mg (57%). 96% *ee*, dr = 87:13 (>99% *ee* and 98:2 dr were obtained after recrystallization). Enantiomeric excess was determined by HPLC analysis using Chiralcel OJ-H column (90% hexane/2-propanol, flow 0.8 mL/min, λ 254 nm). t_R 28.3 min (minor); t_R 31.1 min (major). Mp: 101.9-102.7 °C. $[\alpha]_D^{25}$

= 70.3 (*c* 1.0, $CHCl_3$, the optical rotation was determined by using the recrystallized product). ^1H NMR (400 MHz, $CDCl_3$) *δ*/ppm = 7.20 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 6.8 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 4.71 (t, *J* = 2.8 Hz, 1H), 3.95 (br s, 1H), 3.58-3.51 (m, 1H), 2.00 (dt, *J* = 13.6 Hz, 2.4 Hz, 1H), 1.57-1.50 (m, 1H), 1.26 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*/ppm = 144.9, 130.4, 129.4, 122.4, 117.3, 114.7, 65.9, 41.8, 38.1, 22.1. IR (KBr) *ν* 3541, 3331, 3125, 2960, 2921, 1611, 1512, 1400, 1155, 1029, 755 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 164.1063 (calcd for $C_{10}H_{14}NO$ m/z = 164.1070).

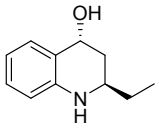
Table 1, entry 1



(*S*)-3a

(*S*)-2-methyl-1,2,3,4-tetrahydroquinoline-4-one (3a)[1]: Yellowish solid, yield: 9.7 mg (25%). 98% *ee* (>99% *ee* was obtained after recrystallization). Enantiomeric excess was determined by HPLC analysis using Chiralcel OJ-H column (90% hexane/2-propanol, flow 0.8 mL/min, λ 254 nm). t_R 21.7 min (minor); t_R 22.4 min (major). Mp: 94.7-95.9 °C. $[\alpha]_D^{25}$ = -217.0 (*c* 1.0, $CHCl_3$, the optical rotation was determined by using the recrystallized product). ^1H NMR (400 MHz, $CDCl_3$) *δ*/ppm = 7.83 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.73 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.25 (br s, 1H), 3.82-3.76 (m, 1H), 2.64 (dd, *J* = 16.4 Hz, 3.6 Hz, 1H), 2.51-2.44 (m, 1H), 1.34 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*/ppm = 194.2, 151.7, 135.3, 127.6, 119.0, 118.1, 115.8, 49.2, 45.9, 21.5. IR (KBr) *ν* 3414, 3325, 3128, 1656, 1615, 1400, 1152, 754 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 162.0913 (calcd for $C_{10}H_{12}NO$ m/z = 162.0913).

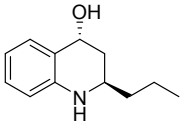
Table 1, entry 2



(2*R*,4*R*)-2b

(2*R*,4*R*)-2-ethyl-1,2,3,4-tetrahydroquinolin-4-ol (2b): Yellowish solid, yield 18.2 mg (43%). 94% *ee*, dr = 65:35 (98% *ee* and 79:21 dr were obtained after recrystallization). Enantiomeric excess was determined by HPLC analysis using Chiralcel OJ-H column (90% hexane/2-propanol, flow 0.8 mL/min, λ 254 nm). t_R 22.8 min (minor); t_R 25.3 min (major). Mp: 129.2-129.6 °C. $[\alpha]_D^{25}$ = 126.9 (*c* 1.0, $CHCl_3$, the optical rotation was determined by using the recrystallized product). ^1H NMR (400 MHz, $CDCl_3$) *δ*/ppm = 7.21 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.75 (s, 1H), 3.39-3.32 (m, 1H), 2.07-2.03 (m, 1H), 1.60 (t, *J* = 7.6 Hz, 2H), 1.55-1.51 (m, 1H), 1.03 (td, *J* = 7.2 Hz, 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*/ppm = 144.9, 130.3, 129.4, 122.7, 117.3, 114.7, 65.9, 47.5, 35.7, 29.1, 10.0. IR (KBr) *ν* 3291, 3135, 2925, 1609, 1486, 1400, 1260, 1034, 750 cm^{-1}. MS HR-ESI: m/z = $[M + Na]^+$ 200.1053 (calcd for $C_{11}H_{15}NO$ m/z = 200.1053).

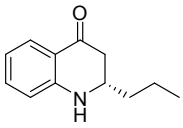
Table 1, entry 3



(2*R*,4*R*)-2c

(2*R*,4*R*)-2-propyl-1,2,3,4-tetrahydroquinolin-4-ol (2c): White solid, yield 17.0 mg (37%). >99% *ee*, dr = 99:1. Enantiomeric excess was determined by HPLC analysis using Chiralcel OJ-H column (90% hexane/2-propanol, flow 0.8 mL/min, λ 254 nm). t_R 17.6 min (minor); t_R 20.1 min (major). Mp: 113.9-114.5 °C. $[\alpha]_D^{25}$ = 128.2 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*/ppm = 7.20 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.09 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.67 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.74 (t, *J* = 2.8 Hz, 1H), 3.46-3.40 (m, 1H), 2.04 (dt, *J* = 13.6 Hz, 2.8 Hz, 1H), 1.56-1.52 (m, 3H), 1.50-1.44 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*/ppm = 144.9, 130.4, 129.4, 122.7, 117.3, 114.8, 65.9, 45.9, 38.5, 36.3, 18.9, 14.4. IR (KBr) *v* 3415, 3272, 3134, 2959, 2928, 1612, 1490, 1400, 1033, 752 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 192.1384 (calcd for $C_{12}H_{18}NO$ m/z = 192.1383).

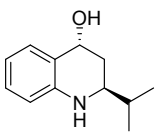
Table 1, entry 3



(*S*)-3c

(*S*)-2-propyl-2,3-dihydroquinolin-4(1*H*)-one (3c): Yellowish solid, yield 11.0 mg (24%). 71% *ee* (80% *ee* was obtained after recrystallization). Enantiomeric excess was determined by HPLC analysis using Chiralcel OJ-H column (90% hexane/2-propanol, flow 0.8 mL/min, λ 254 nm). t_R 14.1 min (minor); t_R 15.3 min (major). Mp: 105.0-105.5 °C. $[\alpha]_D^{25}$ = -175.1 (*c* 1.0, $CHCl_3$, the optical rotation was determined by using the recrystallized product). ^1H NMR (400 MHz, $CDCl_3$) *δ*/ppm = 7.81 (d, *J* = 8.0 Hz, 1H), 7.31-7.26 (m, 1H), 6.71 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.34 (br s, 1H), 3.67-3.60 (m, 1H), 2.67 (dd, *J* = 16.4 Hz, 3.6 Hz, 1H), 2.50-2.43 (m, 1H), 1.64-1.57 (m, 2H), 1.45-1.40 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*/ppm = 194.3, 151.6, 135.3, 127.6, 119.2, 118.0, 115.9, 53.2, 44.0, 37.4, 18.7, 14.1. IR (KBr) *v* 3349, 3130, 2961, 1656, 1612, 1401, 1150, 761 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 190.1219 (calcd for $C_{12}H_{16}NO$ m/z = 190.1226).

Table 1, entry 4

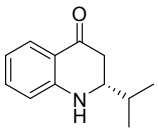


(2*S*,4*R*)-2d

(2*S*,4*R*)-2-isopropyl-1,2,3,4-tetrahydroquinolin-4-ol (2d): Yellow solid, yield 17.2 mg (37%).

97% *ee*, dr = 73:27 (>99% *ee* and 97:3 dr were obtained after recrystallization). Enantiomeric excess was determined by HPLC analysis using Chiralpak AD-H column (97% hexane/2-propanol, flow 0.5 mL/min, λ 254 nm). t_R 65.4 min (major); t_R 80.0 min (minor). Mp: 190.1-190.7 °C. $[\alpha]_D^{25}$ = 156.0 (*c* 1.0, $CHCl_3$, the optical rotation was determined by using the recrystallized product). ^1H NMR (400 MHz, DMSO-d_6) δ/ppm = 7.02 (d, *J* = 7.2 Hz, 1H), 6.93-6.89 (m, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.44 (t, *J* = 7.2 Hz, 1H), 5.54 (s, 1H), 4.89 (d, *J* = 4.0 Hz, 1H), 4.49 (s, 1H), 3.14 (d, *J* = 11.6 Hz, 1H), 1.78-1.70 (m, 2H), 1.38-1.32 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm = 145.1, 130.3, 129.4, 122.5, 117.2, 114.8, 66.0, 51.4, 32.4, 32.3, 18.4. IR (KBr) *v* 3413, 3307, 3133, 2977, 2916, 1612, 1488, 1399, 1033, 753 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 192.1374 (calcd for $C_{12}H_{18}NO$ m/z = 192.1383).

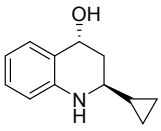
Table 1, entry 4



(*R*)-3d

(*R*)-2-isopropyl-2,3-dihydroquinolin-4(1*H*)-one (3d): Yellow solid, yield 7.1 mg (16%). 86% *ee*. Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H column (90% hexane/2-propanol, flow 1.0 mL/min, λ 254 nm). t_R 8.4 min (minor); t_R 13.4 min (major). Mp: 106.3-106.7 °C. $[\alpha]_D^{25}$ = -78.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CHCl_3$) δ/ppm = 7.80 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.31-7.27 (m, 1H), 6.74-6.69 (m, 1H), 6.67 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 4.29 (br s, 1H), 3.40-3.44 (m, 1H), 2.63-2.49 (m, 2H), 1.89-1.84 (m, 1H), 1.01 (dd, *J* = 6.8 Hz, 2.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm = 194.7, 151.7, 135.3, 127.5, 119.2, 118.1, 116.0, 58.9, 40.7, 31.8, 18.5, 18.1. IR (KBr) *v* 3353, 3125, 2963, 1657, 1613, 1399, 1152, 758 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 190.1221 (calcd for $C_{12}H_{16}NO$ m/z = 190.1226).

Table 1, entry 5

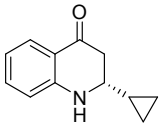


(2*S*,4*R*)-2e

(2*S*,4*R*)-2-cyclopropyl-1,2,3,4-tetrahydroquinolin-4-ol (2e): Yellow solid, yield 24.3 mg (54%). 95% *ee*, dr = 73:27 (94:6 dr were obtained after recrystallization). Enantiomeric excess was determined by HPLC analysis using Chiralpak AS-H column (90% hexane/2-propanol, flow 1.0 mL/min, λ 254 nm), t_R 9.9 min (minor); t_R 10.9 min (major). Mp: 190.0-190.7 °C. $[\alpha]_D^{25}$ = 208.1 (*c* 1.0, $CHCl_3$, the optical rotation was determined by using the recrystallized product). ^1H NMR (400 MHz, $CDCl_3$) δ/ppm = 7.19 (d, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.76 (s, 1H), 2.58-2.53 (m, 1H), 2.17 (d, *J* = 13.6 Hz, 1H), 1.77-1.70 (m, 1H), 0.96-0.88 (m, 1H), 0.56 (t, *J* = 8.8 Hz, 2H), 0.30 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm = 144.7, 130.3, 129.5, 122.4, 117.2, 114.5, 66.0, 52.2, 36.2, 16.7, 3.3, 2.1. IR

(KBr) *v* 3412, 3270, 3130, 3020, 2917, 1612, 1487, 1400, 1049, 751 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 190.1223 (calcd for $C_{12}H_{16}NO$ m/z = 190.1226).

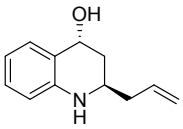
Table 1, entry 5



(*R*)-3e

(*R*)-2-cyclopropyl-2,3-dihydroquinolin-4(1*H*)-one (3e): Yellow solid, yield 9.5 mg (21%). >99% *ee*. Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H column (90% hexane/2-propanol, flow 1.0 mL/min, λ 254 nm), t_R 10.2 min (minor); t_R 13.8 min (major). Mp: 121.3-122.3 °C. $[\alpha]_D^{25}$ = -111.8 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*/ppm = 7.81 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.74-6.67 (m, 2H), 4.50 (br s, 1H), 2.79-2.66 (m, 3H), 1.07 (s, 1H), 0.60 (d, *J* = 8.0 Hz, 2H), 0.29-0.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*/ppm = 194.2, 151.6, 135.4, 127.6, 119.2, 118.1, 115.8, 59.5, 44.4, 16.1, 3.4, 2.3. IR (KBr) *v* 3338, 3130, 2994, 1651, 1611, 1399, 1156, 761 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 188.1062 (calcd for $C_{12}H_{14}NO$ m/z = 188.1070).

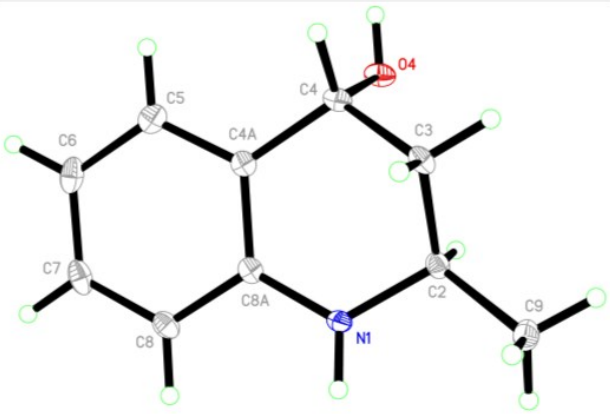
Table 1, entry 6

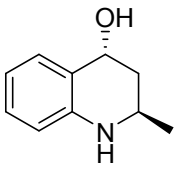


(2*R*,4*R*)-2f

(2*R*,4*R*)-2-allyl-1,2,3,4-tetrahydroquinolin-4-ol (2f): White solid, isolated yield 16.2 mg (36%). dr = 86:14 (determined by ^1H NMR of chiral compound **2f**). Mp: 97.7-98.1 °C. $[\alpha]_D^{25}$ = 131.6 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*/ppm = 7.20 (d, *J* = 7.6 Hz, 1H), 7.11-7.07 (m, 1H), 6.68 (t, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.91-5.80 (m, 1H), 5.24-5.18 (m, 2H), 4.75 (t, *J* = 2.8 Hz, 1H), 3.51-3.46 (m, 1H), 2.43-2.38 (m, 1H), 2.25-2.17 (m, 1H), 2.04 (dt, *J* = 13.6 Hz, 2.4 Hz, 1H), 1.58 (td, *J* = 12.4 Hz, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*/ppm = 144.6, 134.8, 130.3, 129.5, 122.6, 118.5, 117.4, 114.7, 65.9, 45.1, 40.8, 36.3. IR (KBr) *v* 3469, 3413, 3263, 3130, 2919, 1614, 1489, 1400, 1034, 752 cm^{-1}. MS HR-ESI: m/z = $[M + H]^+$ 190.1222. (calcd for $C_{12}H_{16}NO$ m/z = 190.1226.

8. X-ray crystal data for compound 2a





(2*R*,4*R*)-2a

Table S4 Crystal data and structure refinement for **2a**.

compound 2a	**data**
Empirical formula	$C_{10}H_{13}NO$
Formula weight	163.21
Temperature (K)	100(2)
Wavelength (Å)	1.54178
Crystal system	Orthorhombic
Space group	$P2_1$
a (Å)	5.98420(10)
b (Å)	9.1040(2)
c (Å)	16.0223(3)
α (º)	90.00
β (º)	90.00
γ (º)	90.00
Volume (Å^3)	872.90(3)
Z	4
Density (calcd. mg/m^3)	1.242
Absorption coeff. (mm^{-1})	0.634
F(000)	352
θ range data collection	5.59−69.57
Limiting indices	$-6\le h\le 7$, $-10\le k\le 7$, $-17\le l\le 19$
Reflections collected/unique	4936/1573
Completeness to θ= 69.57, %	97.2%
R(int)	0.0409
Data/restraints/parameters	1573/0/112
Goodness-of-fit on F^2	1.099
Final *R* indices [$I>2\sigma(I)$]	$R_1 = 0.0387$, $wR_2 = 0.1036$
R indices (all data)	$R_1 = 0.0387$, $wR_2 = 0.1036$
Largest diff. peak/hole [e/Å^3]	0.326/-0.372

Table S5 Atomic coordinates ($Å \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **2a**. U(eq) is defined as 1/3 of the trace of the orthogonalized Uij tensor.

atom	*x*	*y*	*z*	U(eq)
O(4)	7033(2)	6293(1)	8289(1)	22(1)
N(1)	9308(2)	2840(2)	7633(1)	19(1)
C(9)	10835(3)	2446(2)	9017(1)	26(1)
C(2)	9541(3)	3488(2)	8461(1)	18(1)
C(8A)	7811(3)	3406(2)	7070(1)	17(1)
C(4A)	6085(3)	4357(2)	7324(1)	17(1)
C(5)	4506(3)	4823(2)	6742(1)	22(1)
C(6)	4637(3)	4406(2)	5909(1)	26(1)
C(4)	5981(3)	4869(2)	8220(1)	18(1)
C(3)	7207(3)	3810(2)	8794(1)	19(1)
C(7)	6383(3)	3497(2)	5657(1)	25(1)
C(8)	7931(3)	2989(2)	6226(1)	22(1)

Table S6 Anisotropic displacement parameters ($Å^2 \times 10^4$) for **2a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11+...+2hka \times b \times U12]$.

atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(4)	24(1)	10(1)	31(1)	-3(1)	5(1)	-1(1)
N(1)	22(1)	20(1)	16(1)	-2(1)	1(1)	6(1)
C(9)	33(1)	22(1)	23(1)	-1(1)	-9(1)	3(1)
C(2)	23(1)	16(1)	16(1)	-1(1)	-2(1)	-1(1)
C(8A)	22(1)	14(1)	16(1)	2(1)	1(1)	-3(1)
C(4A)	21(1)	12(1)	19(1)	2(1)	1(1)	-3(1)
C(5)	24(1)	14(1)	30(1)	5(1)	-3(1)	-2(1)
C(6)	32(1)	22(1)	24(1)	10(1)	-11(1)	-8(1)
C(4)	18(1)	13(1)	22(1)	-1(1)	5(1)	-3(1)
C(3)	27(1)	14(1)	14(1)	0(1)	2(1)	-3(1)
C(7)	39(1)	22(1)	15(1)	3(1)	-3(1)	-10(1)
C(8)	27(1)	20(1)	17(1)	-1(1)	4(1)	-3(1)

Table S7 Bond lengths for **2a**.

atom	atom	length/Å	atom	atom	length/Å
O(4)	C(4)	1.4454(18)	C(4A)	C(5)	1.394(2)
O(4)	H(4)	0.8400	C(4A)	C(4)	1.510(2)
N(1)	C(8A)	1.3718(19)	C(5)	C(6)	1.391(2)
N(1)	C(2)	1.4585(18)	C(5)	H(5)	0.9500
N(1)	H(1)	0.8800	C(6)	C(7)	1.393(3)

C(9)	C(2)	1.515(2)	C(6)	H(6)	0.9500
C(9)	H(9A)	0.9800	C(4)	C(3)	1.521(2)
C(9)	H(9B)	0.9800	C(4)	H(4A)	1.0000
C(9)	H(9C)	0.9800	C(3)	H(3A)	0.9900
C(2)	C(3)	1.524(2)	C(3)	H(3B)	0.9900
C(2)	H(2)	1.0000	C(7)	C(8)	1.379(2)
C(8A)	C(8)	1.407(2)	C(7)	H(7)	0.9500
C(8A)	C(4A)	1.408(2)	C(8)	H(8)	0.9500

Table S8 Bond angles for **2a**.

atom	atom	atom	angles/°	atom	atom	atom	angles/°
C(4)	O(4)	H(4)	109.5	C(6)	C(5)	H(5)	119.3
C(8A)	N(1)	C(2)	120.53(13)	C(4A)	C(5)	H(5)	119.3
C(8A)	N(1)	H(1)	119.7	C(5)	C(6)	C(7)	118.88(15)
C(2)	N(1)	H(1)	119.7	C(5)	C(6)	H(6)	120.6
C(2)	C(9)	H(9A)	109.5	C(7)	C(6)	H(6)	120.6
C(2)	C(9)	H(9B)	109.5	O(4)	C(4)	C(4A)	109.36(12)
H(9A)	C(9)	H(9B)	109.5	O(4)	C(4)	C(3)	108.19(13)
C(2)	C(9)	H(9C)	109.5	C(4A)	C(4)	C(3)	111.05(12)
H(9A)	C(9)	H(9C)	109.5	O(4)	C(4)	H(4A)	109.4
H(9B)	C(9)	H(9C)	109.5	C(4A)	C(4)	H(4A)	109.4
N(1)	C(2)	C(9)	109.27(13)	C(3)	C(4)	H(4A)	109.4
N(1)	C(2)	C(3)	107.99(12)	C(4)	C(3)	C(2)	110.60(12)
C(9)	C(2)	C(3)	112.51(13)	C(4)	C(3)	H(3A)	109.5
N(1)	C(2)	H(2)	109.0	C(2)	C(3)	H(3A)	109.5
C(9)	C(2)	H(2)	109.0	C(4)	C(3)	H(3B)	109.5
C(3)	C(2)	H(2)	109.0	C(2)	C(3)	H(3B)	109.5
N(1)	C(8A)	C(8)	119.83(14)	H(3A)	C(3)	H(3B)	108.1
N(1)	C(8A)	C(4A)	121.32(13)	C(8)	C(7)	C(6)	120.78(15)
C(8)	C(8A)	C(4A)	118.79(14)	C(8)	C(7)	H(7)	119.6
C(5)	C(4A)	C(8A)	119.41(14)	C(6)	C(7)	H(7)	119.6
C(5)	C(4A)	C(4)	120.91(14)	C(7)	C(8)	C(8A)	120.70(15)
C(8A)	C(4A)	C(4)	119.67(13)	C(7)	C(8)	H(8)	119.6
C(6)	C(5)	C(4A)	121.39(16)	C(8A)	C(8)	H(8)	119.6

Table S9 Hydrogen atom coordinates ($Å^2×10^4$) and isotropic displacement parameters ($Å^2×10^3$) for **2a**.

atom	*x*	*y*	*z*	U(eq)
H(4)	6069	6925	8416	33
H(1)	10135	2079	7494	23
H(9A)	9995	1529	9082	39

H(9B)	11057	2898	9566	39
H(9C)	12291	2235	8764	39
H(2)	10386	4432	8412	22
H(5)	3315	5439	6919	27
H(6)	3554	4735	5518	31
H(4A)	4384	4945	8398	21
H(3A)	6352	2882	8837	22
H(3B)	7320	4242	9359	22
H(7)	6510	3224	5086	30
H(8)	9090	2350	6045	26

Table S10 Torsion angles for **2a**.

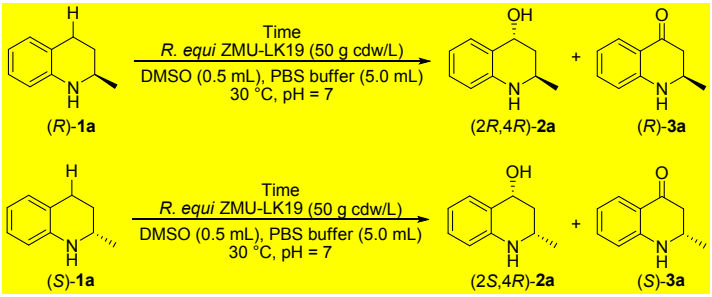
a	**b**	**c**	**d**	**angles/°**
C(8A)	N(1)	C(2)	C(9)	165.86(13)
C(8A)	N(1)	C(2)	C(3)	43.19(18)
C(2)	N(1)	C(8A)	C(8)	166.35(13)
C(2)	N(1)	C(8A)	C(4A)	-16.3(2)
N(1)	C(8A)	C(4A)	C(5)	-175.44(14)
C(8)	C(8A)	C(4A)	C(5)	1.9(2)
N(1)	C(8A)	C(4A)	C(4)	5.1(2)
C(8)	C(8A)	C(4A)	C(4)	-177.47(13)
C(8A)	C(4A)	C(5)	C(6)	-2.0(2)
C(4)	C(4A)	C(5)	C(6)	177.39(13)
C(4A)	C(5)	C(6)	C(7)	0.3(2)
C(5)	C(4A)	C(4)	O(4)	-83.11(17)
C(8A)	C(4A)	C(4)	O(4)	96.30(15)
C(5)	C(4A)	C(4)	C(3)	157.56(14)
C(8A)	C(4A)	C(4)	C(3)	-23.03(19)
O(4)	C(4)	C(3)	C(2)	-69.58(15)
C(4A)	C(4)	C(3)	C(2)	50.44(16)
N(1)	C(2)	C(3)	C(4)	-59.79(16)
C(9)	C(2)	C(3)	C(4)	179.54(13)
C(5)	C(6)	C(7)	C(8)	1.5(2)
C(6)	C(7)	C(8)	C(8A)	-1.5(2)
N(1)	C(8A)	C(8)	C(7)	177.23(14)
C(4A)	C(8A)	C(8)	C(7)	-0.2(2)

Crystal struction determination of 2a.

Crystal data: $C_{10}H_{13}NO$, M = 163.21, orthorhombic, a = 5.98420(10) Å, b = 9.1040(2) Å, c = 16.0223(3) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 872.90(3) Å^3, T = 100(2) K, space group $P212121$, Z = 4, μ(CuKα) = 0.634 mm^{-1},4963 reflections measured, 1573 independent reflections

(R_{int} = 0.0409). The final R_1 values were 0.0387 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1036 ($I > 2\sigma(I)$). The final R_1 values were 0.0388 (all data). The final $wR(F^2)$ values were 0.1036 (all data). The goodness of fit on F^2 was 1.099. Flack parameter = -0.1(3). The Hooft parameter is -0.01(9) for 615 Bijvoet pairs.

9. Table S11 The study on the process of asymmetric hydroxylation of (*R*)-1a and (*S*)-1a[a]



entry	time (h)	substrate[b]	2a			3a	
			yield (%)[c]	dr[d]	de (%)[e]	yield (%)[c]	ee (%)[d]
1	0.25	(*R*)-**1a**	14	>99:1	>99	0	-
2	0.5	(*R*)-**1a**	35	>99:1	>99	0	-
3	0.75	(*R*)-**1a**	61	>99:1	>99	0	-
4	1	(*R*)-**1a**	80	98:2	>99	0.1	14
5	3	(*R*)-**1a**	70	98:2	>99	0.2	8
6	5	(*R*)-**1a**	58	98:2	>99	0.8	26
7	9	(*R*)-**1a**	55	98:2	>99	0.8	27
8	0.25	(*S*)-**1a**	9	17:83	99	0	-
9	0.5	(*S*)-**1a**	28	14:86	>99	0.3	>99
10	0.75	(*S*)-**1a**	37	12:88	>99	0.6	>99
11	1	(*S*)-**1a**	50	12:88	>99	1	>99
12	3	(*S*)-**1a**	53	13:87	>99	10	>99
13	5	(*S*)-**1a**	69	15:85	>99	14	>99
14	9	(*S*)-**1a**	66	15:85	>99	15	>99

[a] All reactions (5.0 mL) were performed in pH 7.0 (50.0 mM Na_2HPO_4/KH_2PO_4) containing (*R*)-**1a** or (*S*)-**1a** (0.03 mmol, 6.0 mM) and *R. equi* ZMU-LK19 (50 g cdw/L) at 30 °C and 250 rpm. [b] Both (*R*)-**1a** and (*S*)-**1a** were synthesized with 98% *ee* according to the reported literatures.[2] [c] Determined by HPLC analysis of the crude reaction mixture by the external standard method. [d] Determined by chiral HPLC analysis. [e] Determined by chiral HPLC analysis for major diastereoisomer.

The cells of *R. equi* ZMU-LK19 were suspended in 5 mL PBS buffer (50 mM Na_2HPO4/KH_2PO_4, pH 7.0) to a cell density of 50 g cdw/L, and (*R*)-**1a** or (*S*)-**1a** (0.03 mmol, 6 mM) was added, the mixture was shaken at 30 ºC and 250 rpm. 7 Parallel reactions with (*R*)-**1a** or (*S*)-**1a** were stopped for monitoring at different time point, respectively. Every mixture was

extracted with EtOAc (5 mL) and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo, the crude reaction mixture was taken for the HPLC analysis to determine the yield, ee and dr.

10. ^{18}O labeling experiments

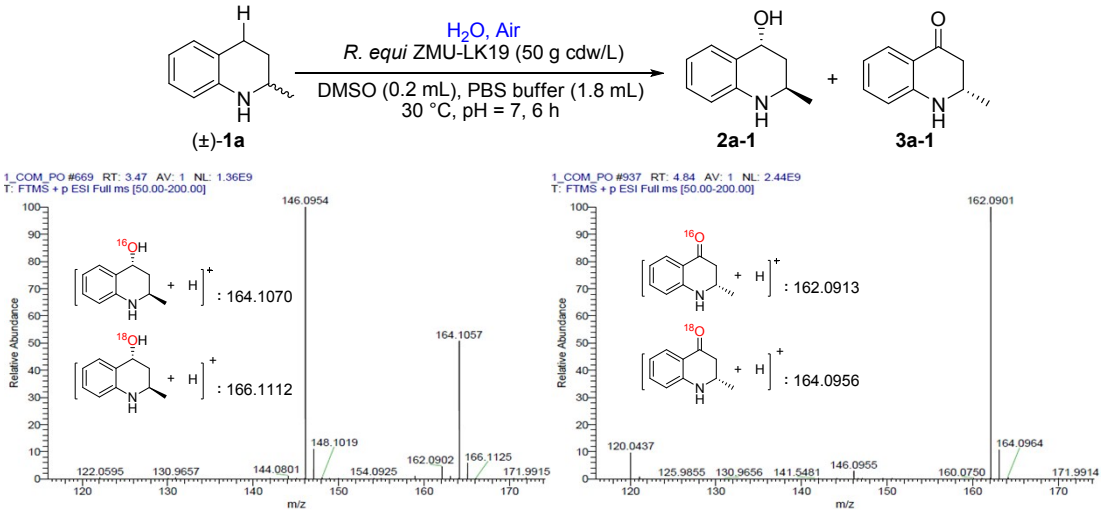


Figure S1. The LC-MS spectra of blank control group.

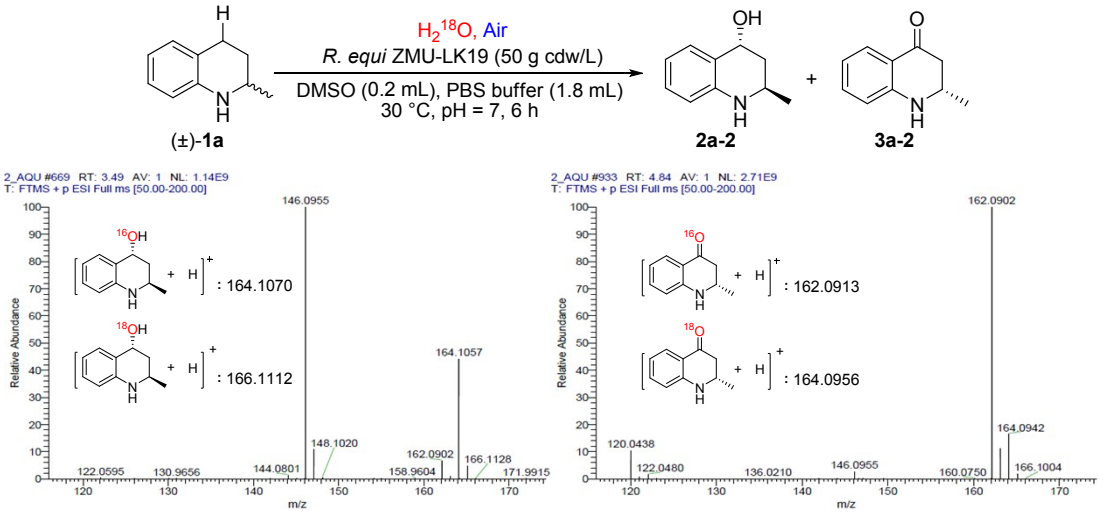
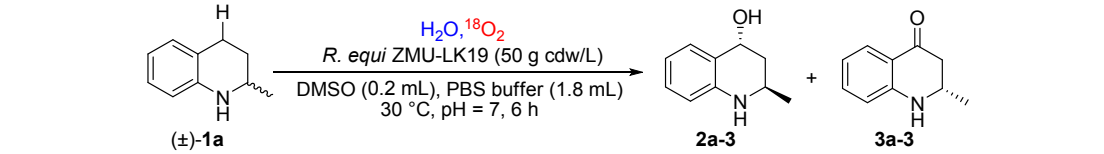


Figure S2. The LC-MS spectra using $H_2{}^{18}O$ as solvent.



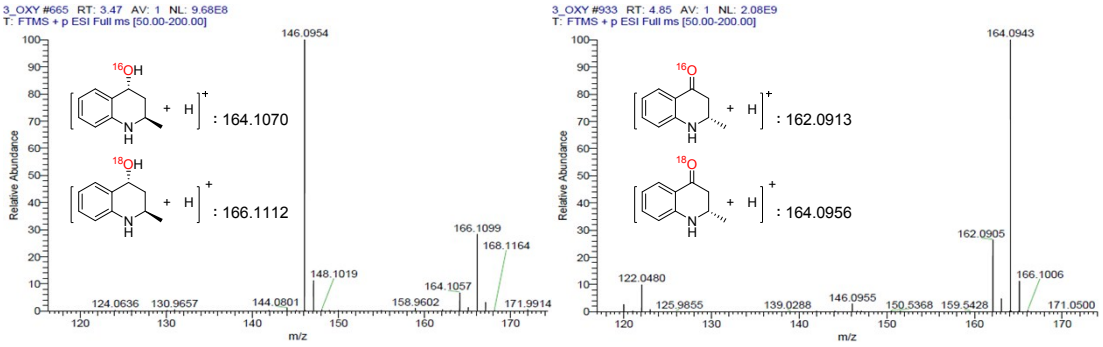
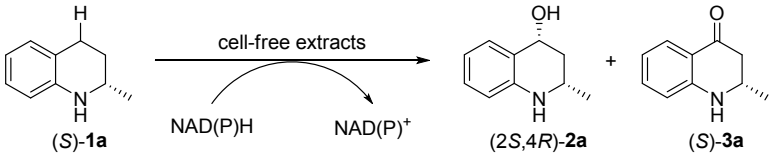


Figure S3. The LC-MS spectra under $^{18}O_2$ atmosphere.

11. Table S12 Biooxidation of (*S*)-1a with soluble cell-free extracts of *R. equi* ZMU-LK19[a]



entry	1	coenzyme	(2*S*,4*R*)-**2a**			(*S*)-**3a**	
			yield(%)[b]	dr[c]	ee (%)[d]	yield (%)[b]	ee (%)[c]
1	(*S*)-**1a**	-	24	11:89	>99	4	>99
2	(*S*)-**1a**	NADPH	27	11:89	>99	5	>99
3	(*S*)-**1a**	NADH	66	12:88	>99	11	>99

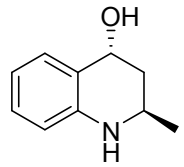
[a] Unless otherwise noted, all reactions (5.0 mL) were performed in buffer (50.0 mM Na_2HPO_4/KH_2PO_4, pH = 7.0) containing (*S*)-**1a** (5.0×10^{-3} mmol, 1.0 mM), cell density (50 g cdw/L), coenzyme (2.0 mM) at 30 °C and 250 rpm for 6 h. [b] Determined by HPLC analysis of the crude reaction mixture by the external standard method. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis for major diastereoisomer.

12. Refrences

1. (a) S. A. Bentley, S. G. Davies, J. A. Lee, P. M. Roberts and J. E. Thomson, *Org. Lett,.* 2011, **13**, 2544; (b) M. P. Paradisi and A. Romeo, *J. Chem. Soc., Perkin Trans. 1,* 1977, 596.
2. Both (*R*)-**1a** and (*S*)-**1a** were synthesized with 98% ee values according to the reported literatures, see: (a) C. Wang, C. Li, X. Wu, A. Pettman and J. Xiao, *Angew. Chem., Int. Ed.,* 2009, **48**, 6524; (b) W. Tang, Y. Sun, L. Xu, T. Wang, Q. Fan, K.-H. Lamc and A. S. C. Chan, *Org. Biomol. Chem.,* 2010, **8**, 3464.

13. ^{1}H, ^{13}C NMR and HPLC spectra of 2a-f, 3a-f

Table 1, entry 1



(2*R*,4*R*)-2a

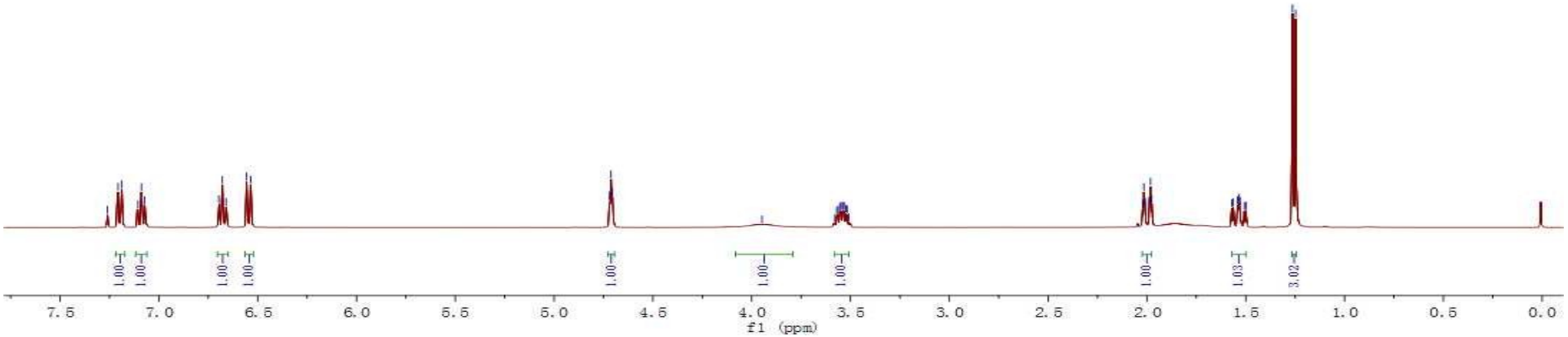
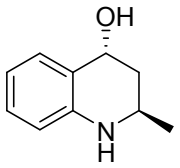
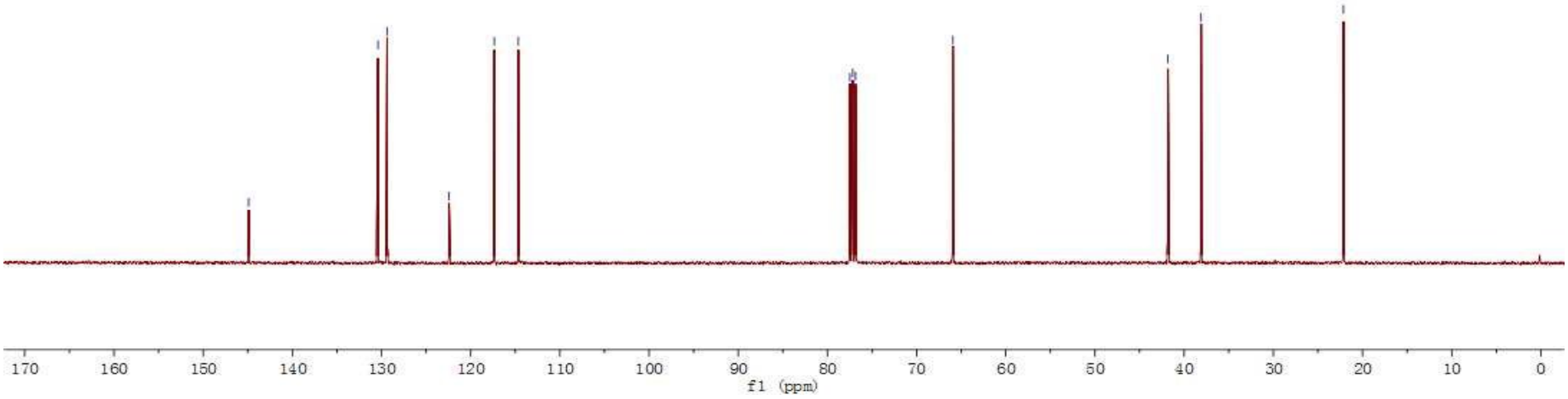
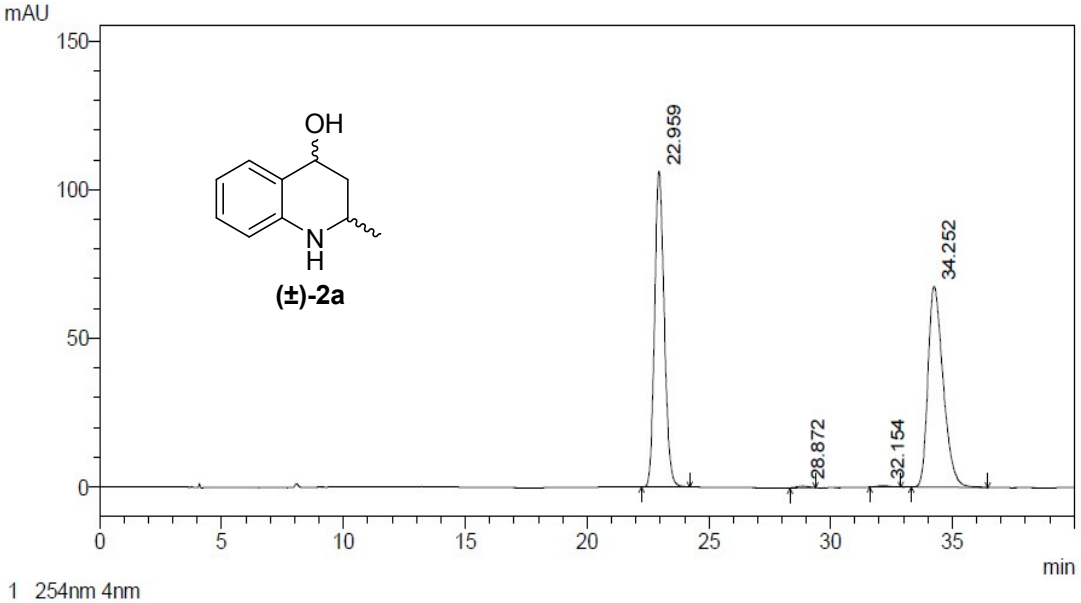


Table 1, entry 1



(2*R*,4*R*)-2a





1 254nm 4nm

PDA

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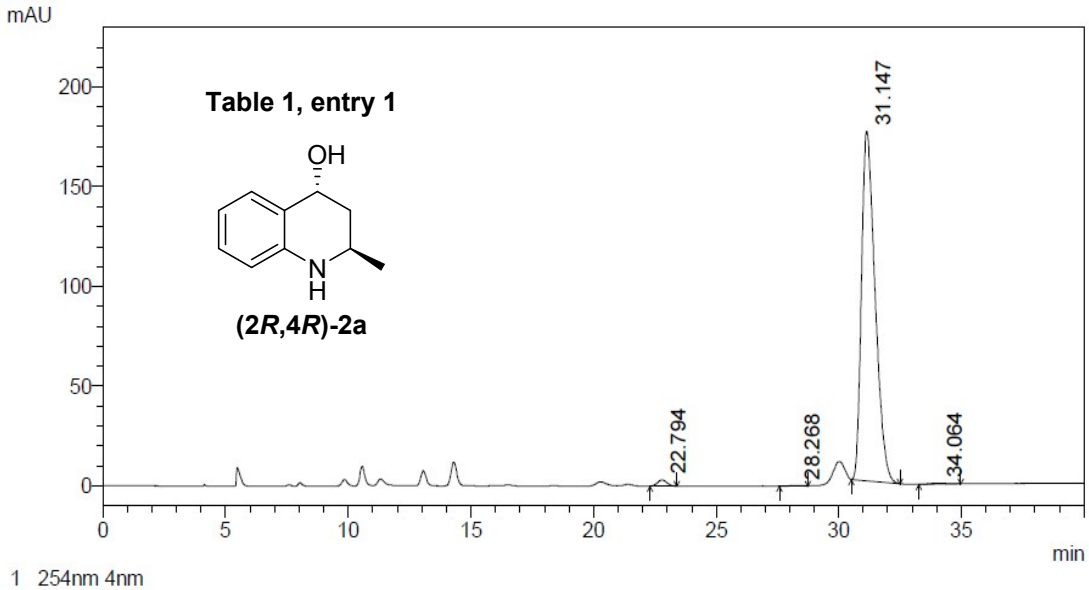
2	28.872	18520	623	0.315
3	32.154	19415	581	0.330
4	34.252	2928730	67510	49.754



1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	22.794	79698	3012	1.160
2	28.268	4265	133	0.062
3	31.147	6758017	175358	98.400
4	34.064	25925	662	0.377

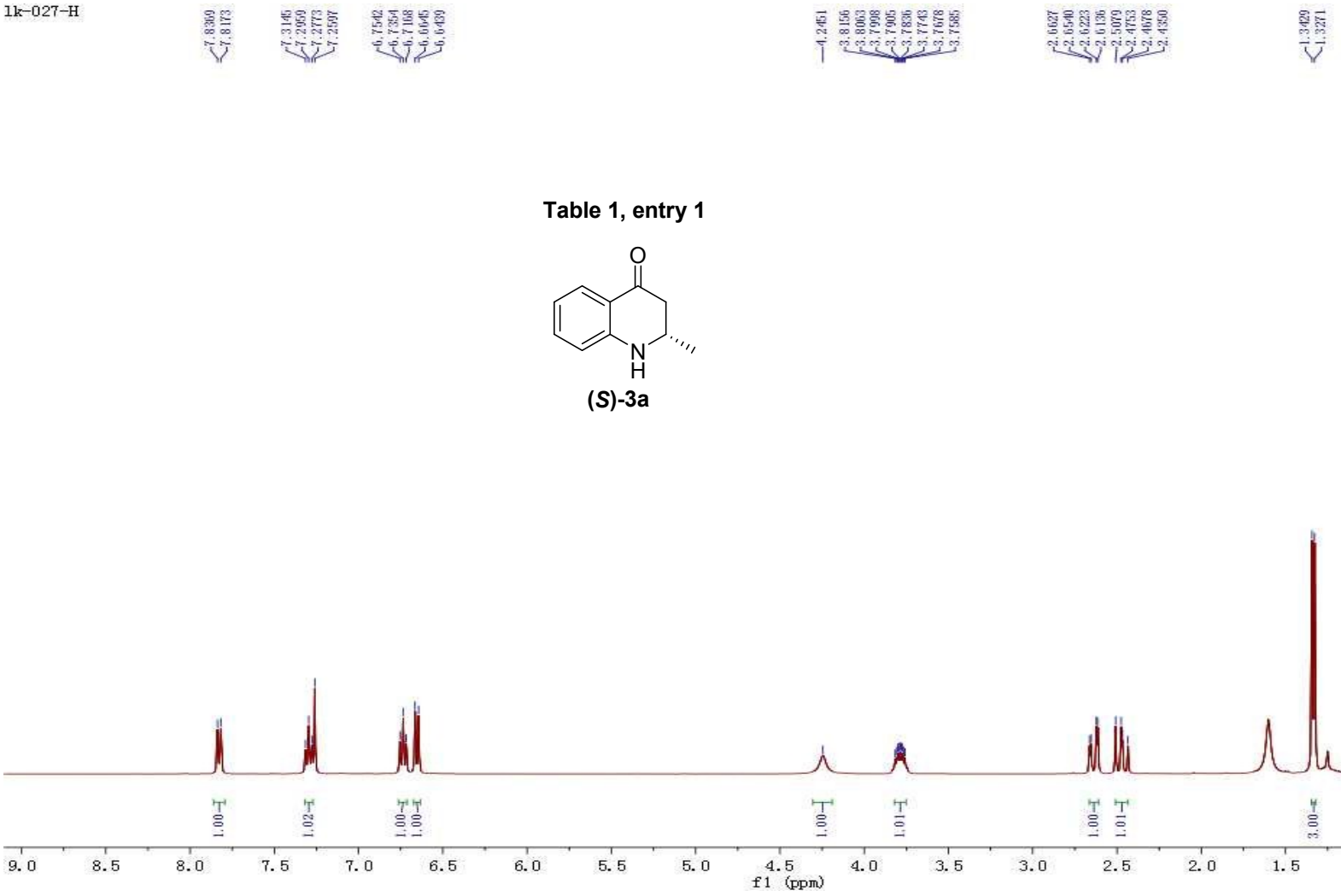


Table 1, entry 1

(*S*)-3a

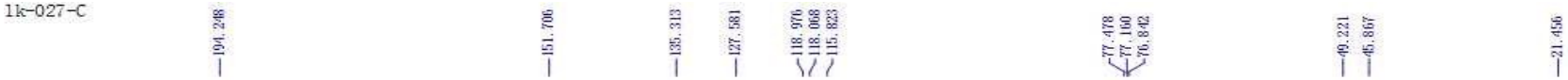
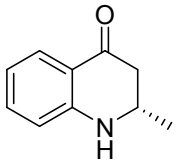
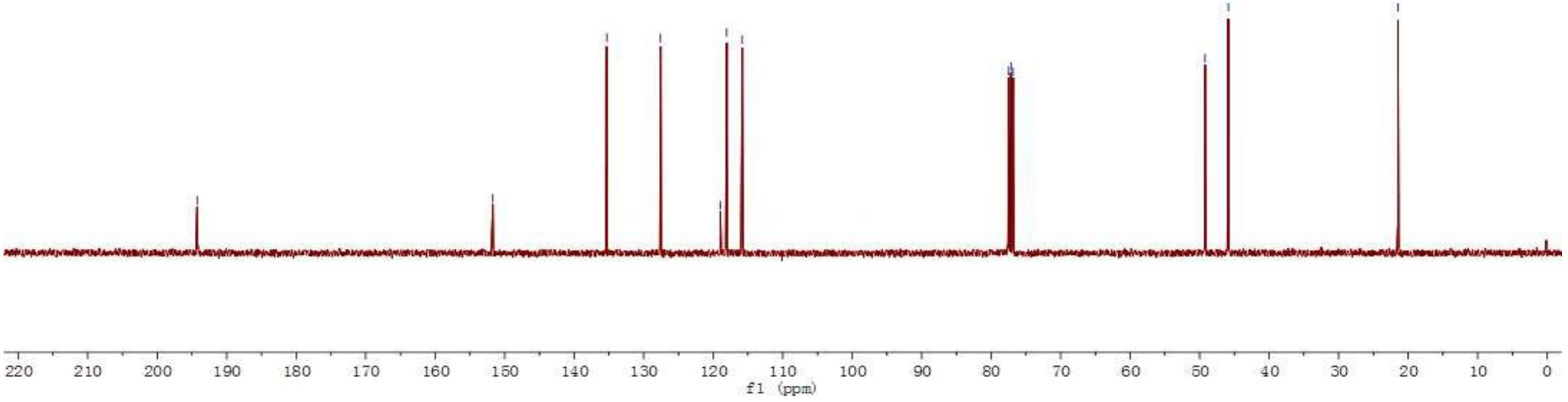
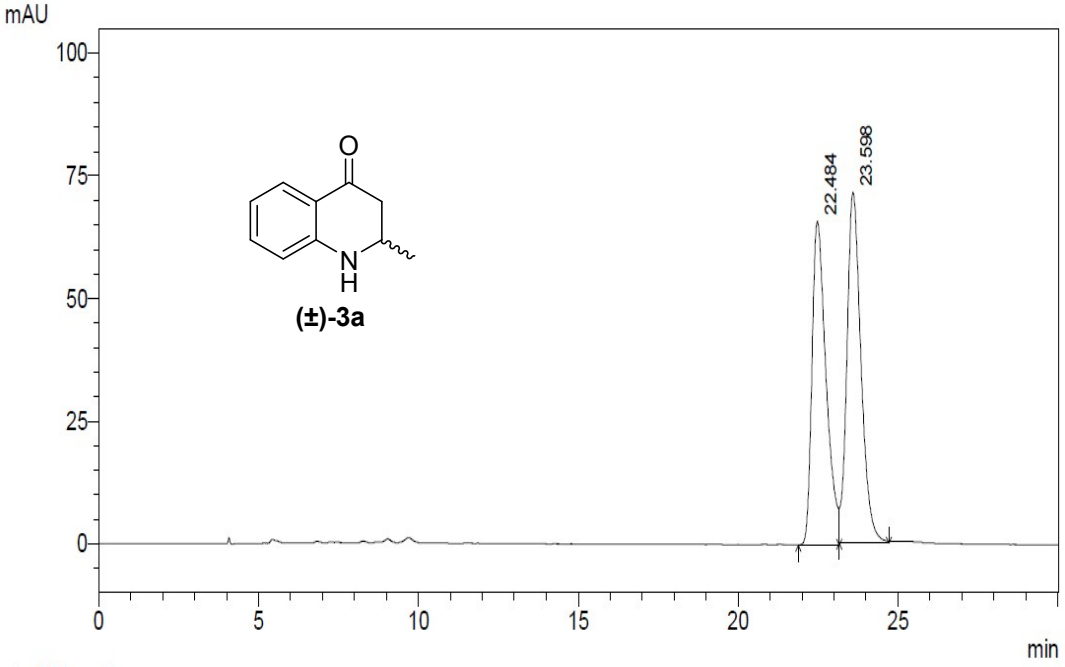


Table 1, entry 1



(*S*)-3a





1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
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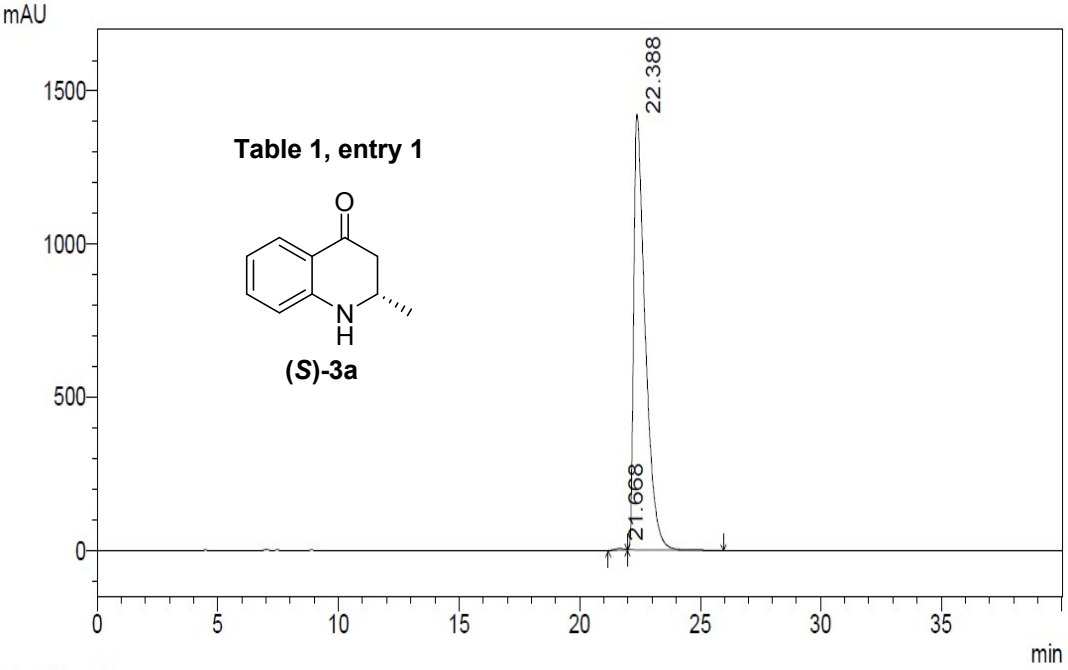
2	23.598	2181899	71501	51.889

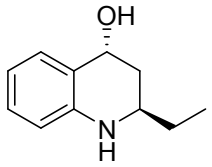


1 254nm 4nm

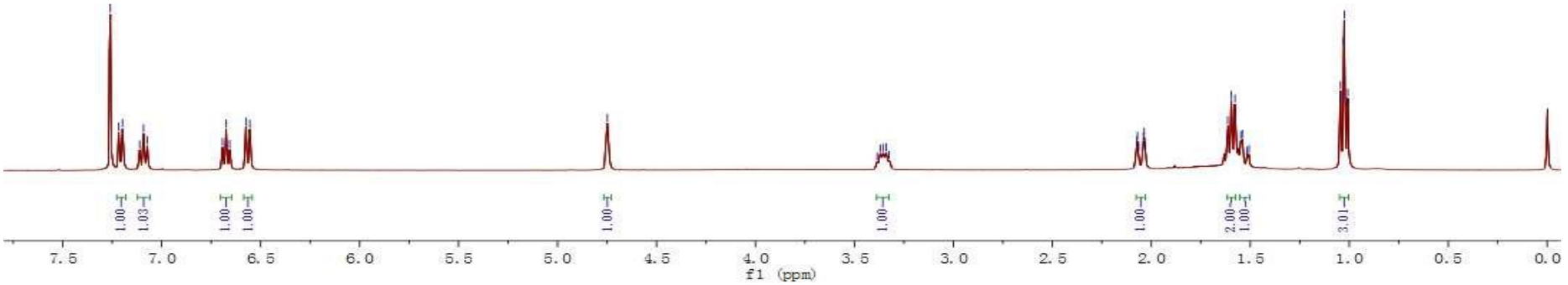
PDA

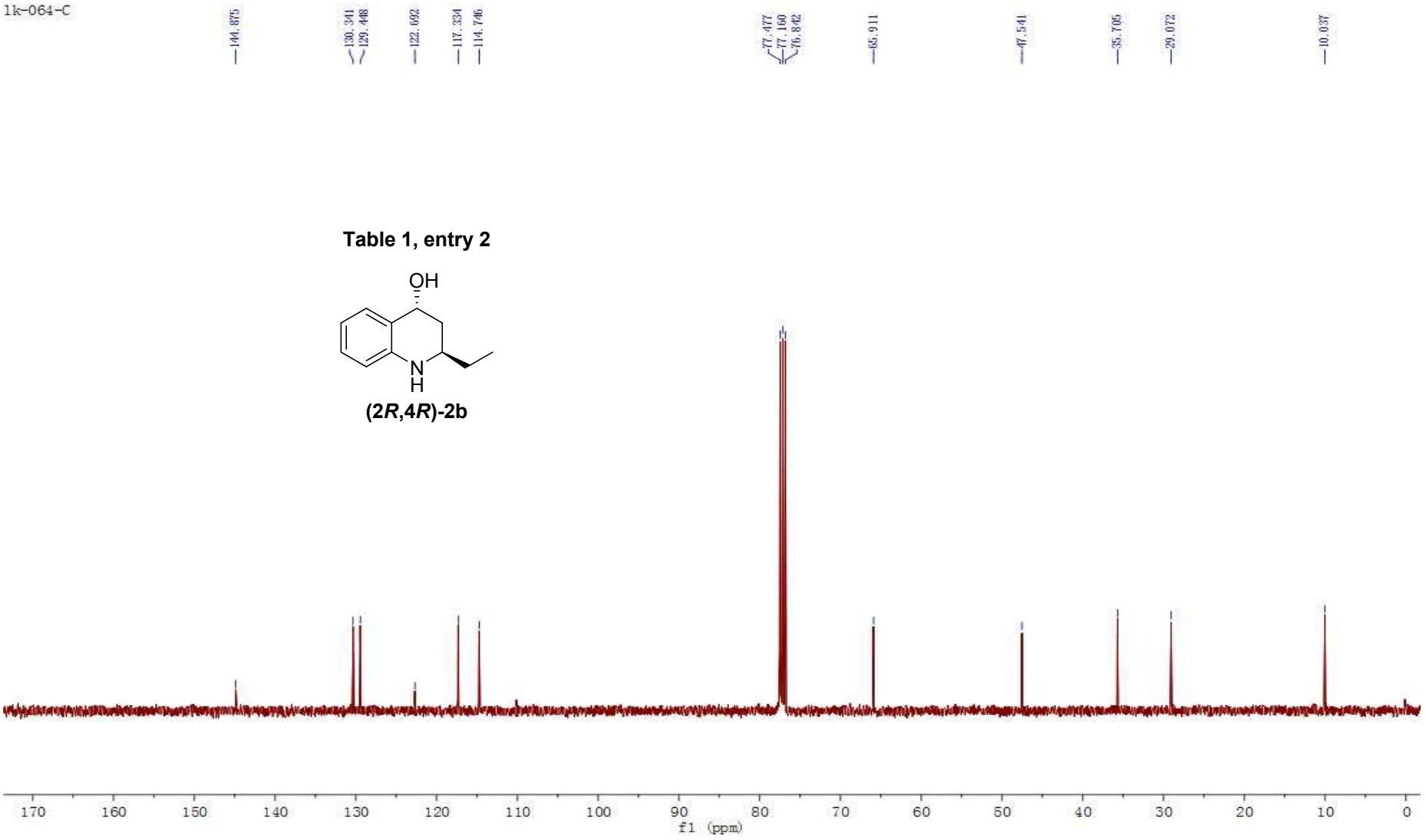
ID#	Reat. Time	Area	Height	Area %
1	21.668	102269	4808	0.217
2	22.388	46994763	1421716	99.783

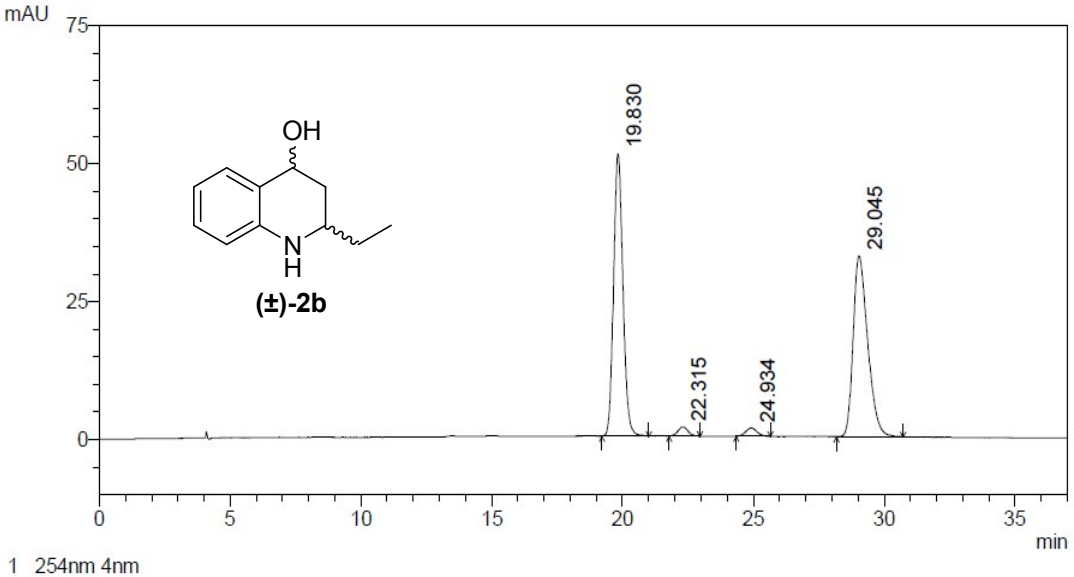
Table 1, entry 2



(2*R*,4*R*)-2b



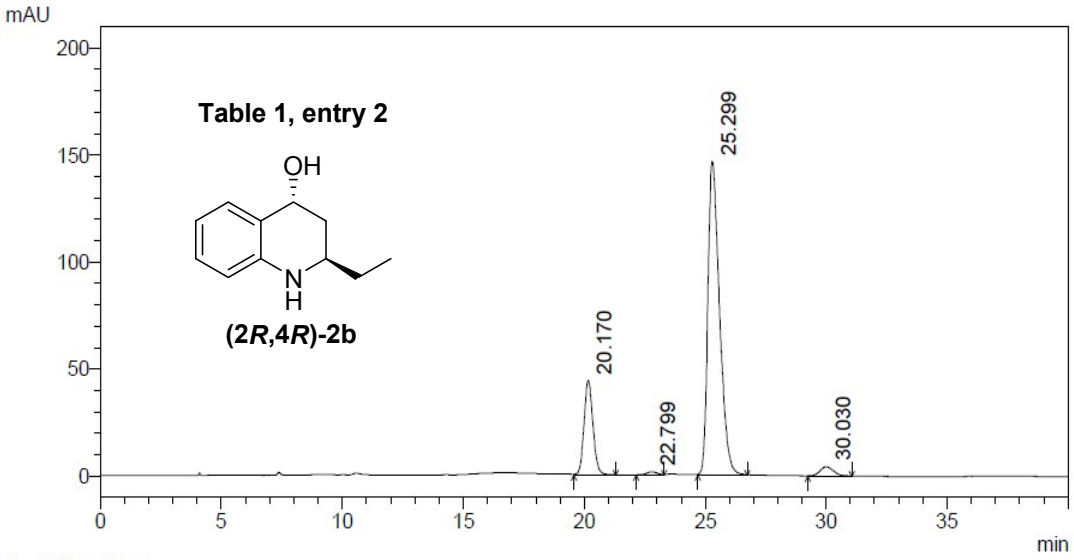

1k-064-C
144.875
130.341
129.448
122.692
117.334
114.746
77.477
77.160
76.842
65.911
47.541
35.705
29.072
10.037
Table 1, entry 2
OH
N
H
(2R,4R)-2b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



1 254nm 4nm

PDA

ID#	Ret. Time	Area	Height	Area %
1	19.830	1271506	51105	48.213
2	22.315	47383	1695	1.797
3	24.934	46478	1506	1.762
4	29.045	1271915	32729	48.228

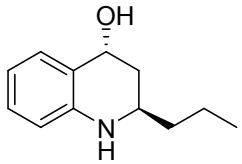


1 254nm 4nm

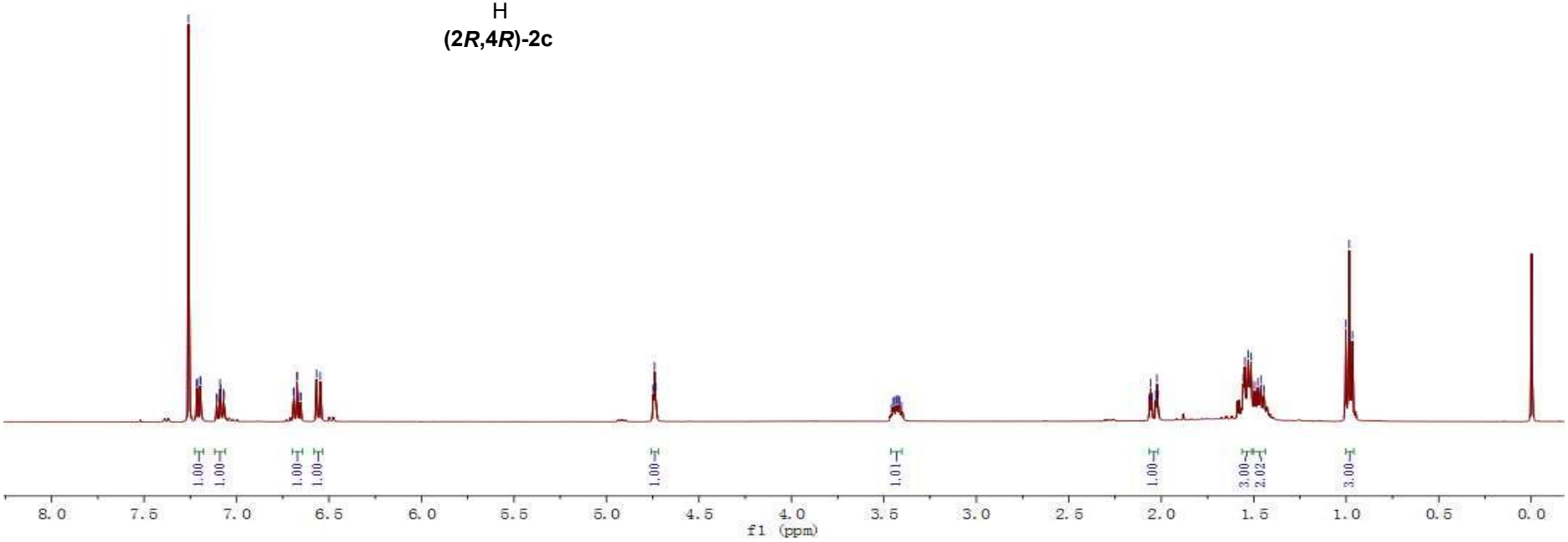
PDA

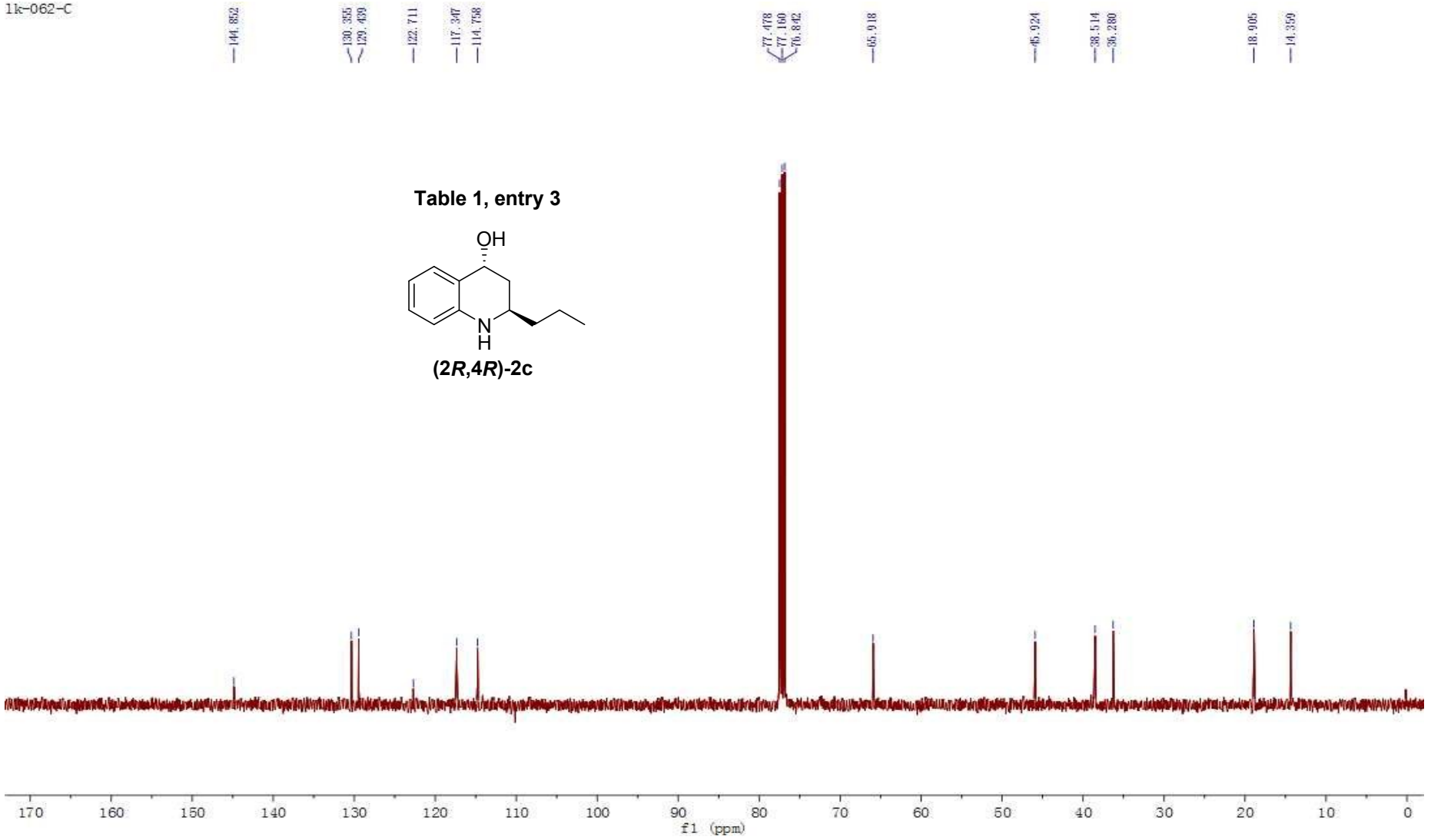
ID#	Reat. Time	Area	Height	Area %
1	20.170	1130354	44150	18.050
2	22.799	41751	1397	0.667
3	25.299	4914903	146558	78.482
4	30.030	175459	4382	2.802

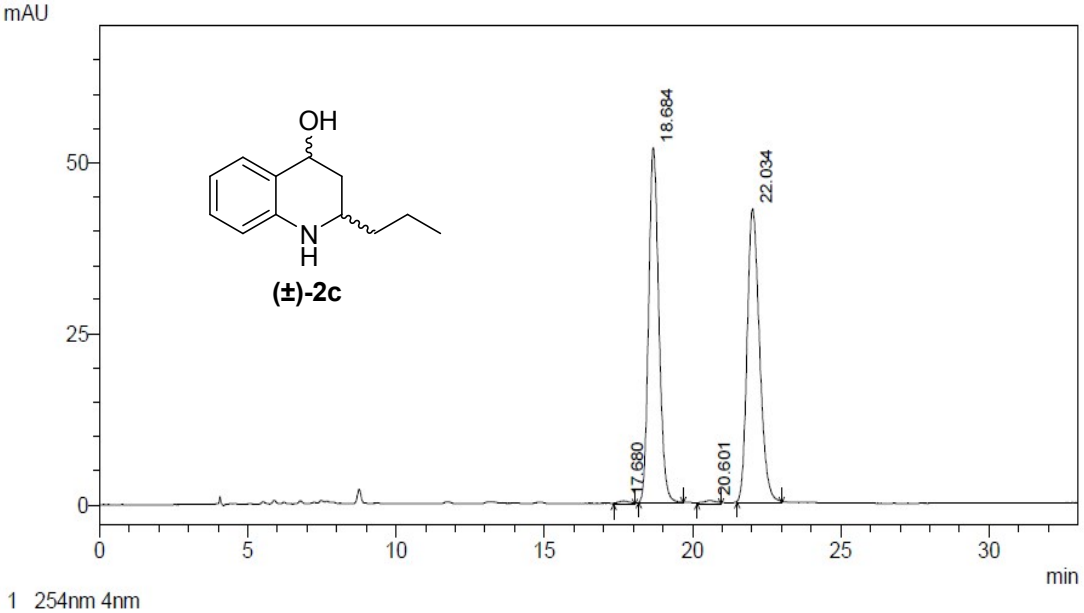
Table 1, entry 3



(2*R*,4*R*)-2c



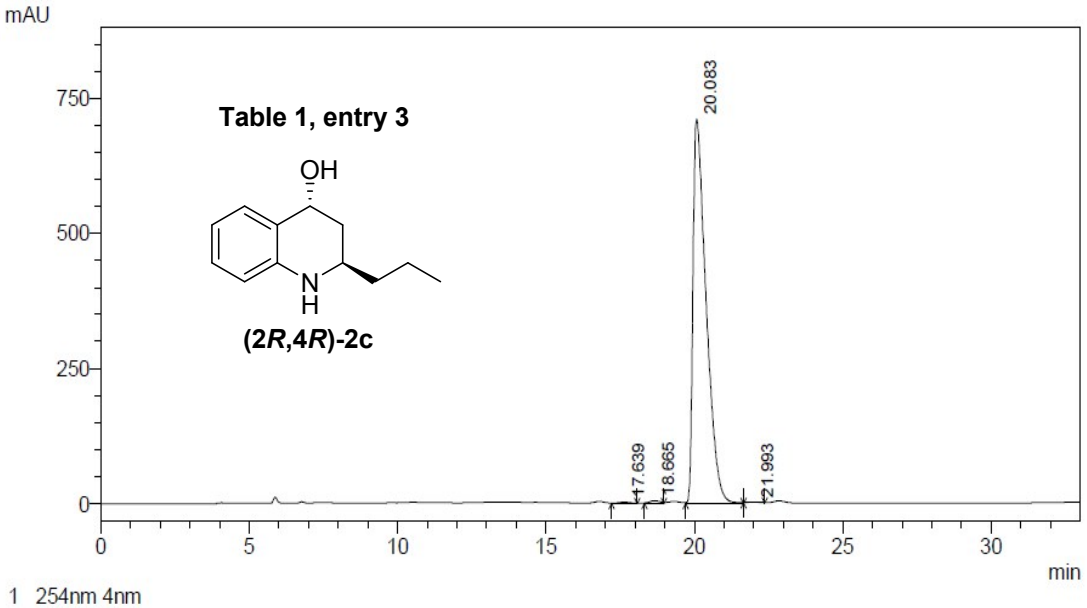

1k-062-C
144.852
130.355
129.439
122.711
117.347
114.758
77.478
77.160
76.842
65.918
45.924
38.514
36.280
18.905
14.359
Table 1, entry 3
OH
N
H
(2R,4R)-2c
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	17.680	13540	494	0.539
2	18.684	1243080	51906	49.504
3	20.601	13299	434	0.530
4	22.034	1241164	42895	49.427

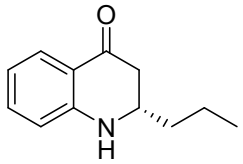


1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	17.639	60500	2440	0.275
2	18.665	109636	4795	0.497
3	20.083	21822534	710253	99.022
4	21.993	45463	1716	0.206

Table 1, entry 3



(*S*)-3c

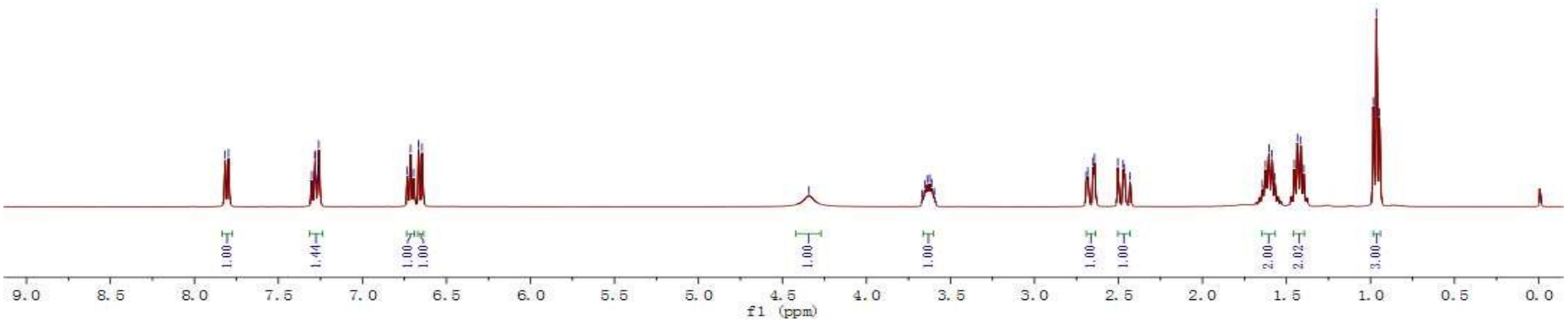
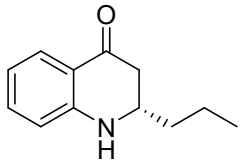
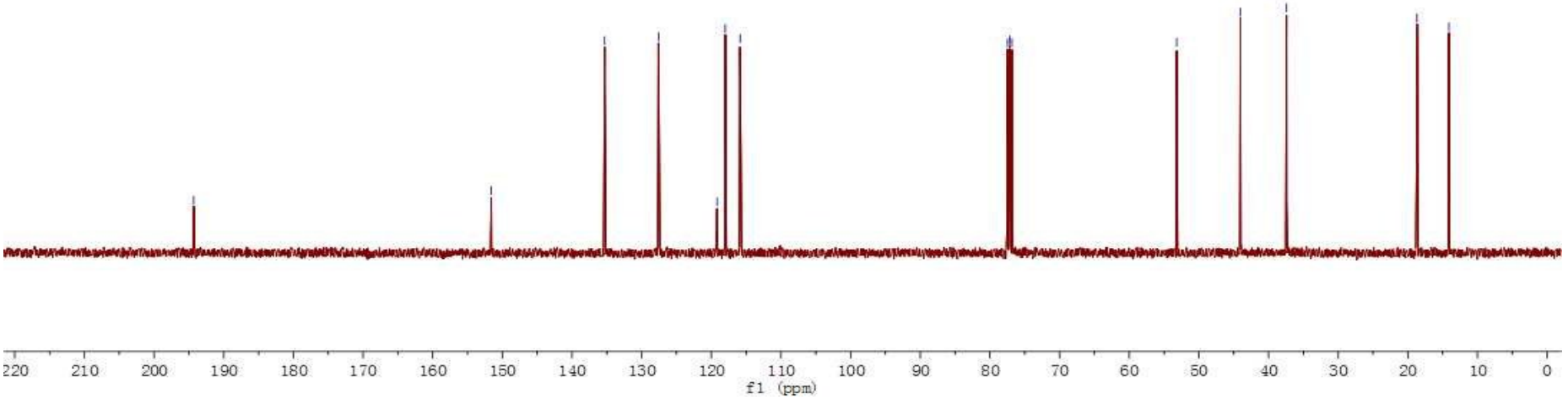
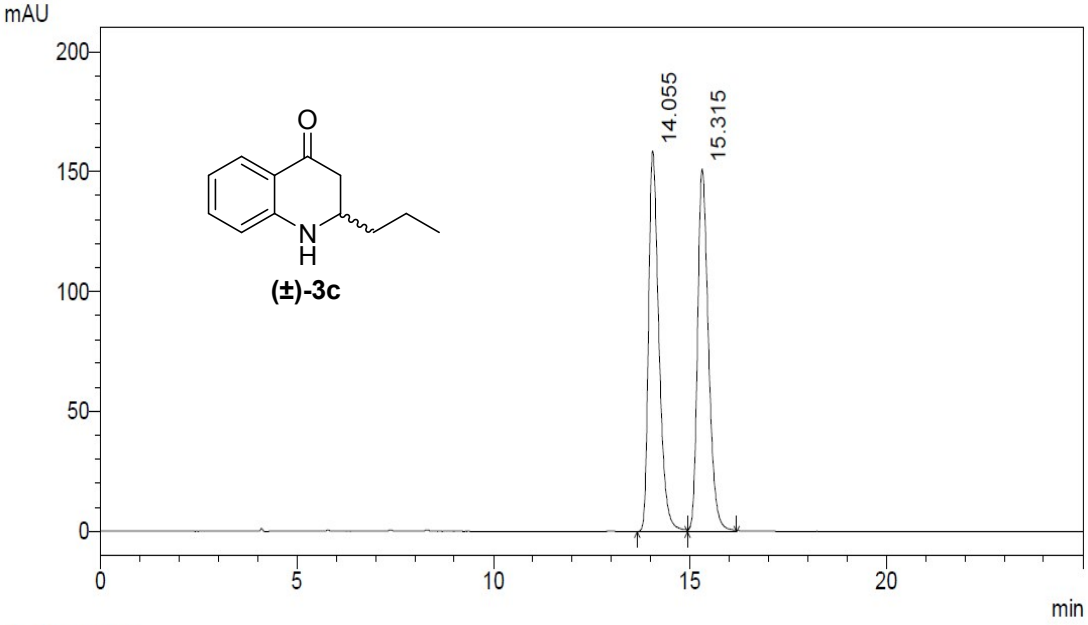


Table 1, entry 3



(*S*)-3c





1 254nm 4nm

PDA

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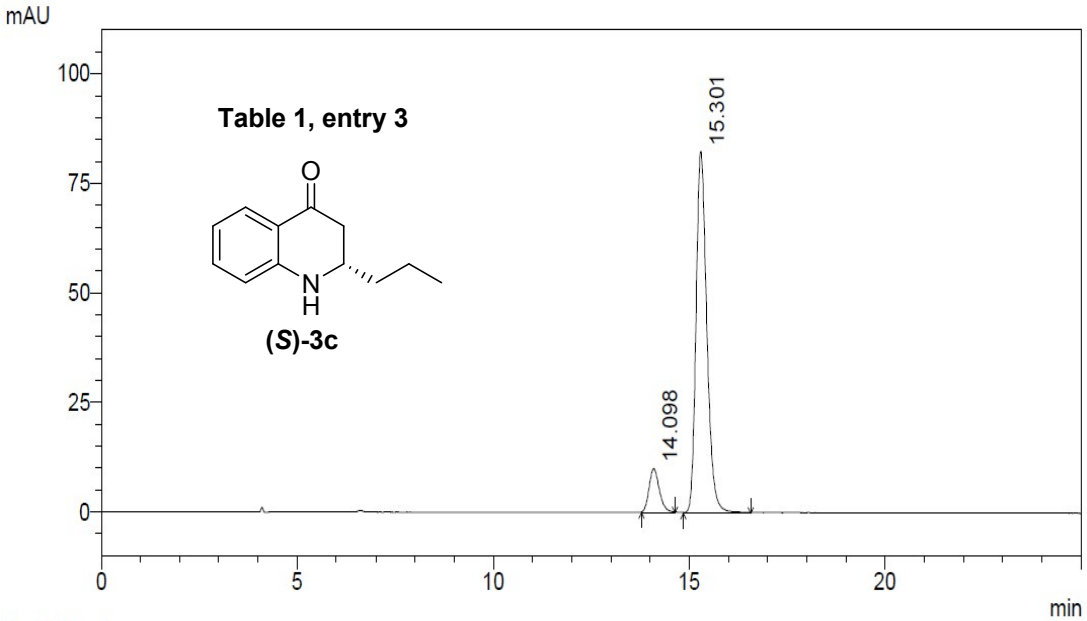
1	14.055	2905915	158778	49.905
2	15.315	2916938	151354	50.095



1 254nm 4nm

PDA

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1	14.098	179757	9934	10.240
2	15.301	1575746	82526	89.760

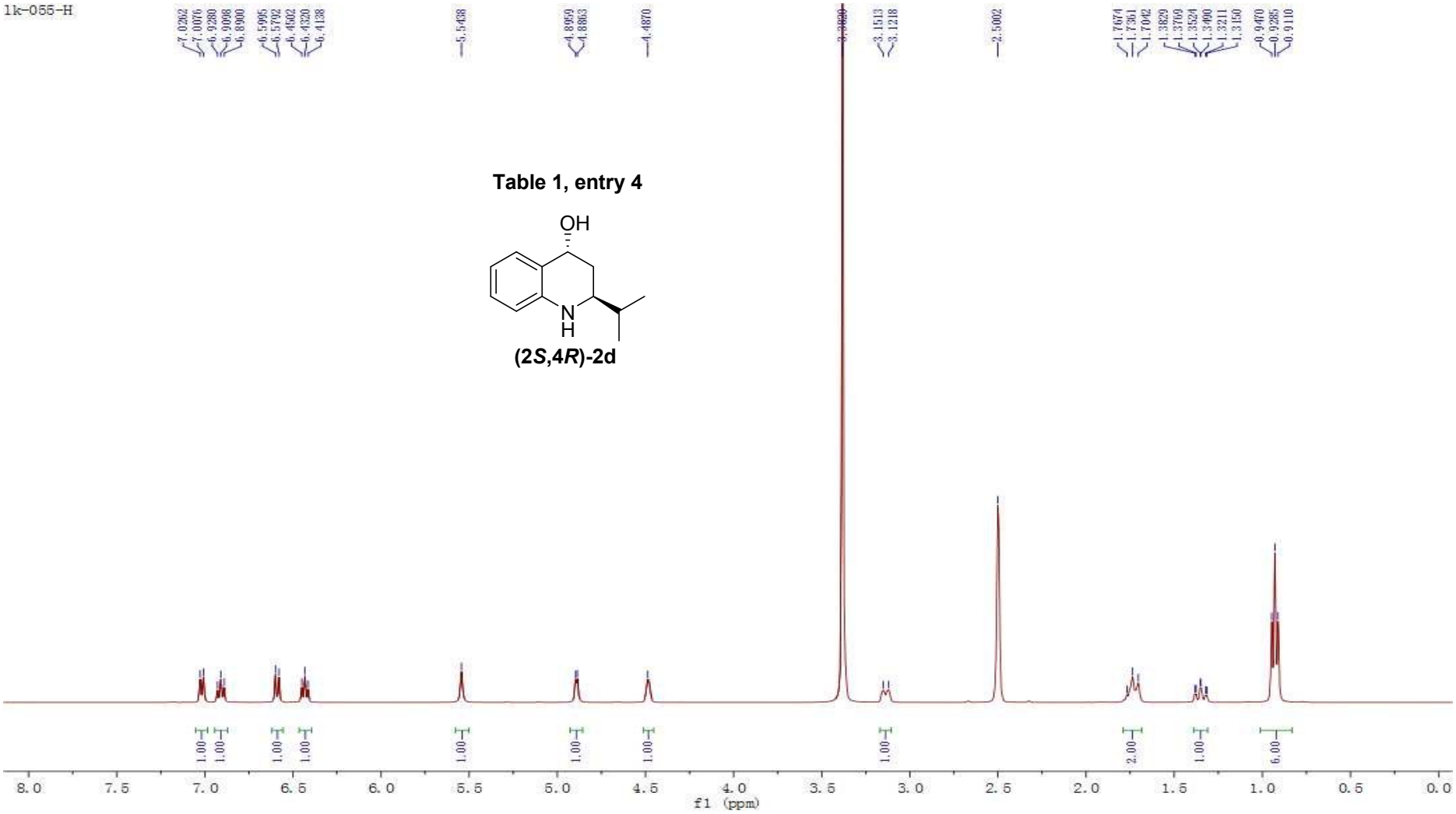
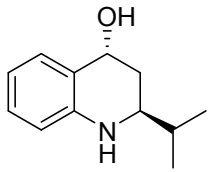


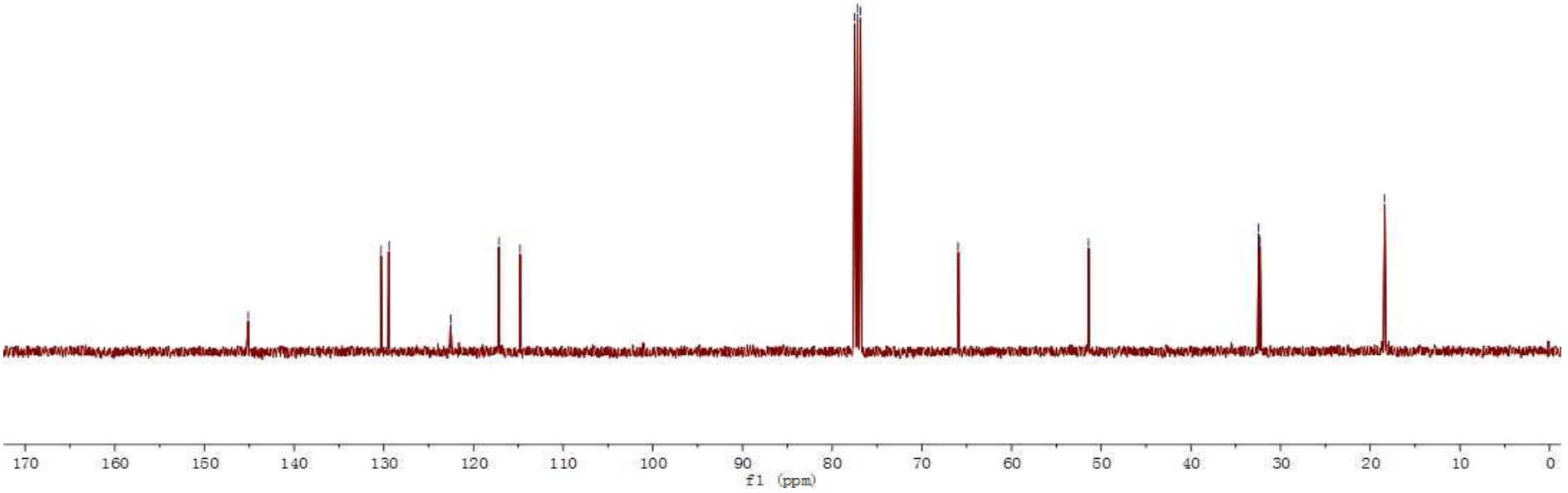
Table 1, entry 4

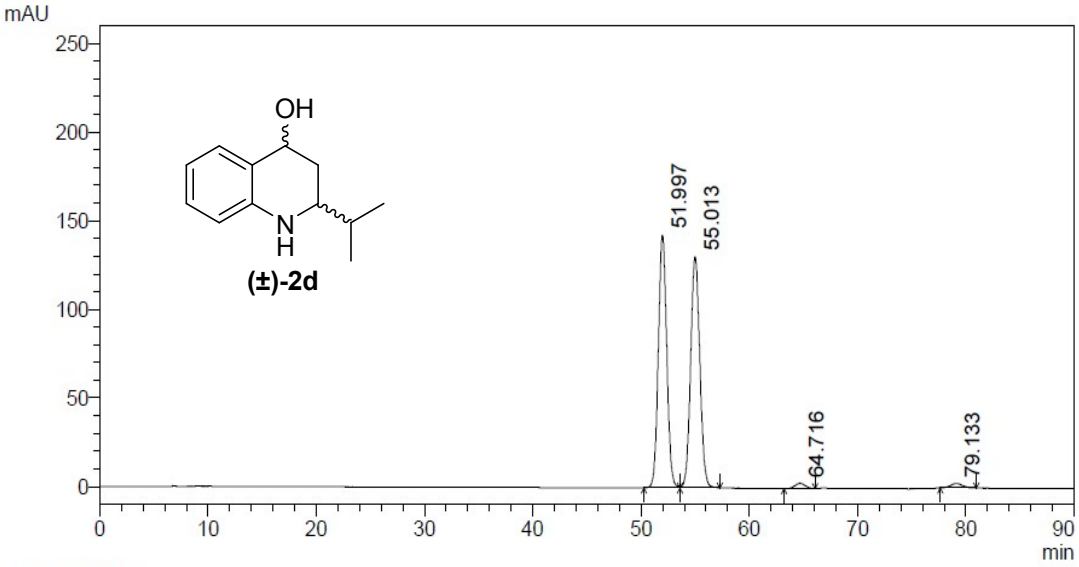
(2*S*,4*R*)-2d

Table 1, entry 4



(2*S*,4*R*)-2d

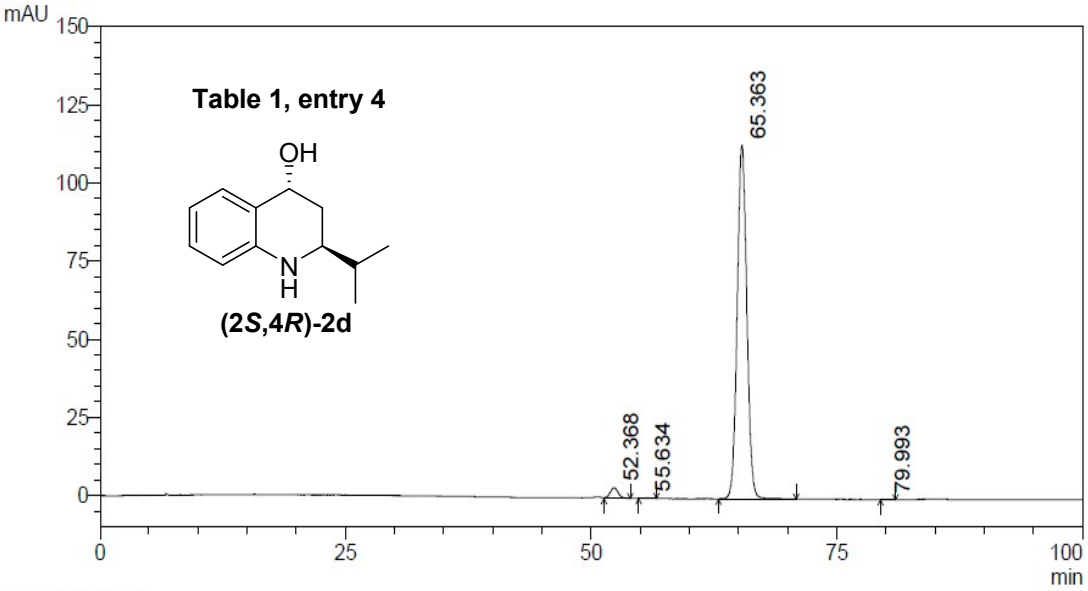




1 254nm 4nm

PDA

ID#	Ret. Time	Area	Height	Area %
1	51.997	7707267	142541	48.751
2	55.013	7705158	130385	48.738
3	64.716	196423	2971	1.242
4	79.133	200492	2540	1.268

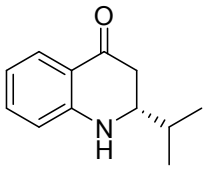


1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	52.368	192590	3420	2.437
2	55.634	10013	167	0.127
3	65.363	7695574	113077	97.395
4	79.993	3207	69	0.041

Table 1, entry 4



(*R*)-3d

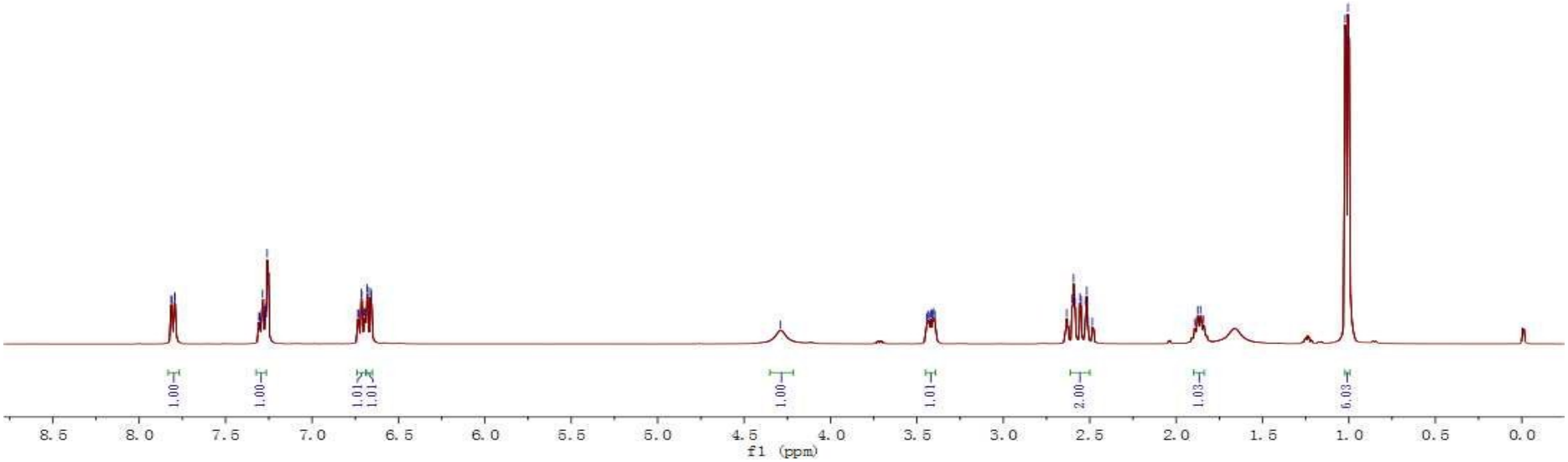
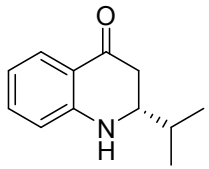
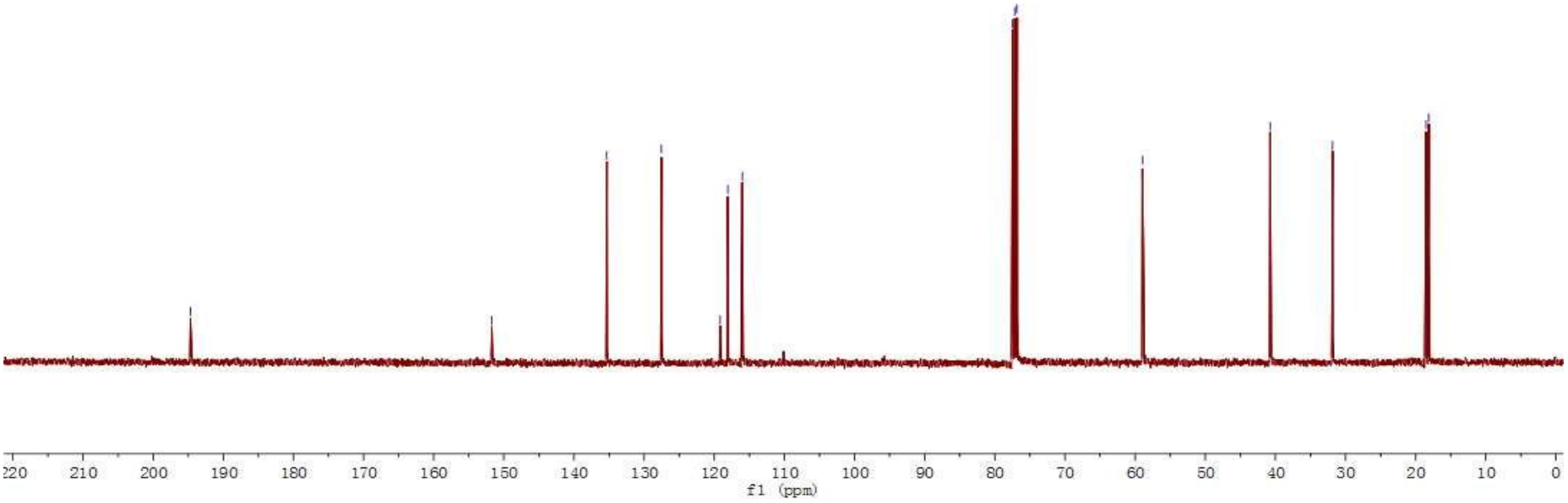
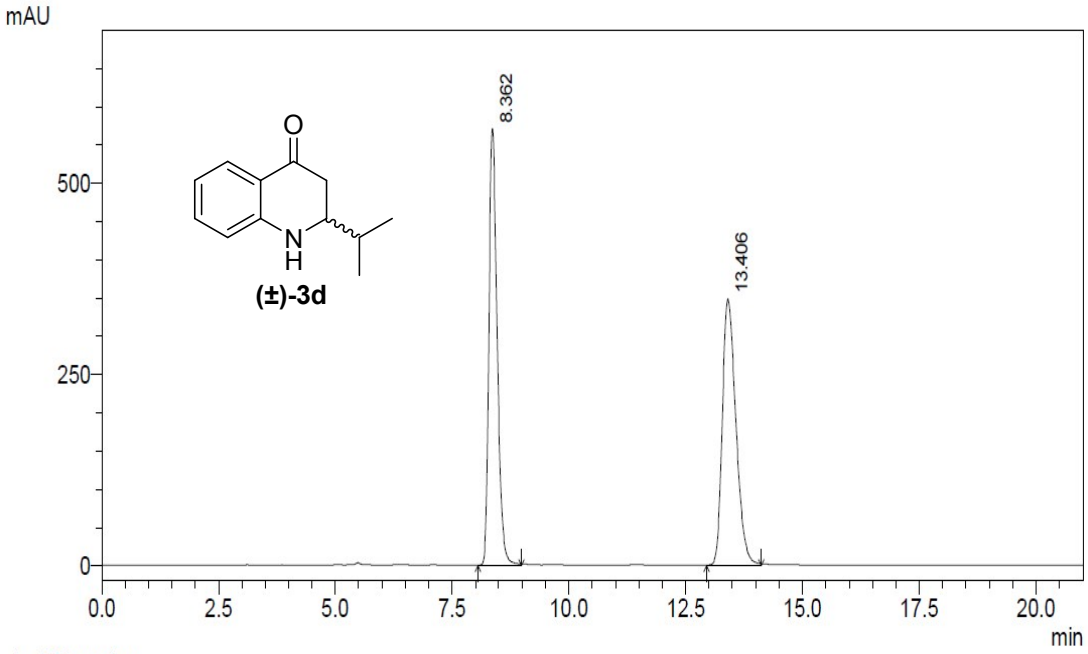


Table 1, entry 4



(*R*)-3d





1 254nm 4nm

PDA

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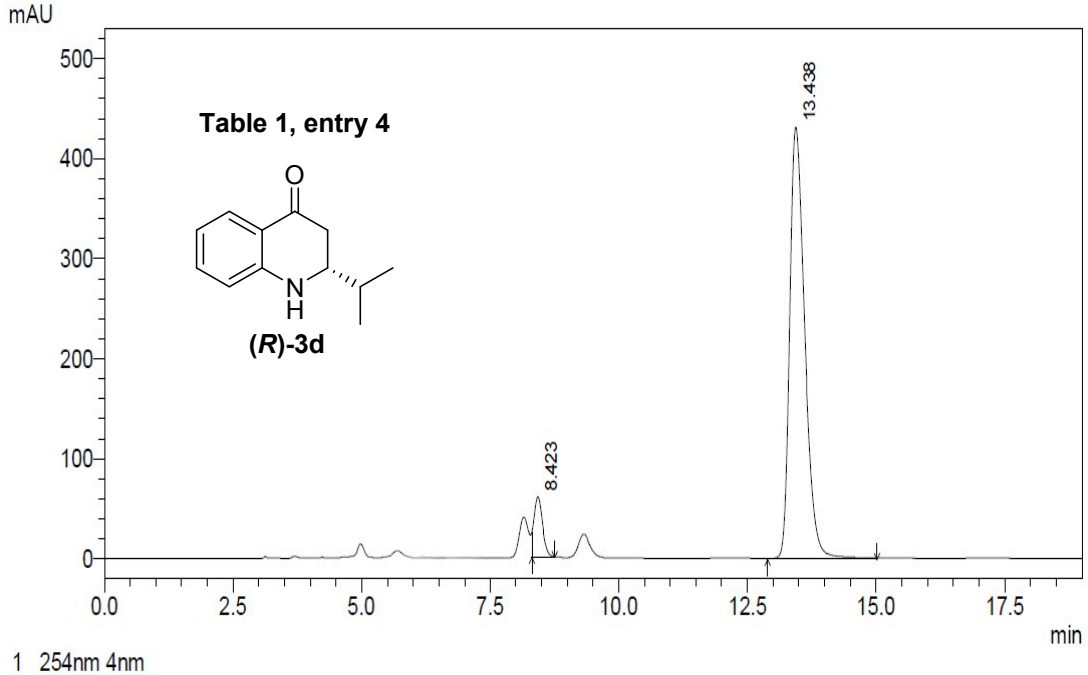
2	13.406	7063412	349004	50.160

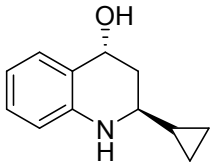


1 254nm 4nm

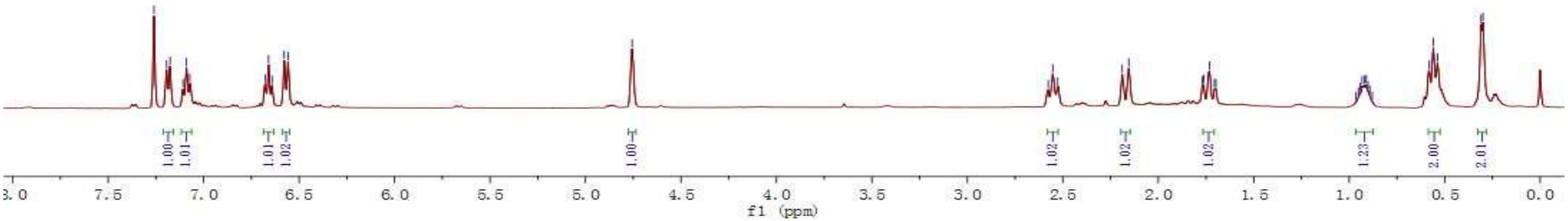
PDA

ID#	Reat. Time	Area	Height	Area %
1	8.423	711106	60340	7.468
2	13.438	8810702	431564	92.532

Table 1, entry 5



(2*S*,4*R*)-2e



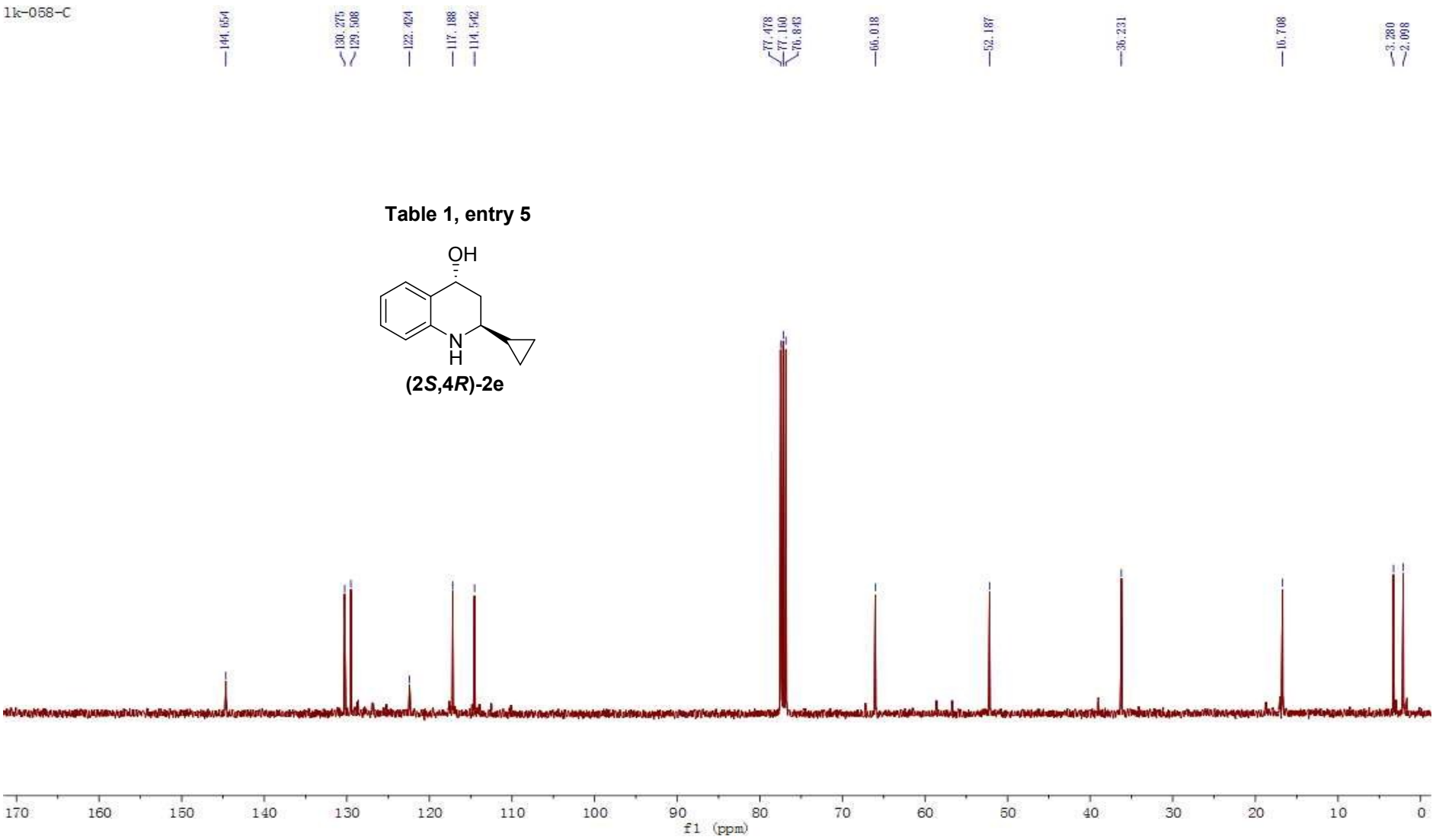
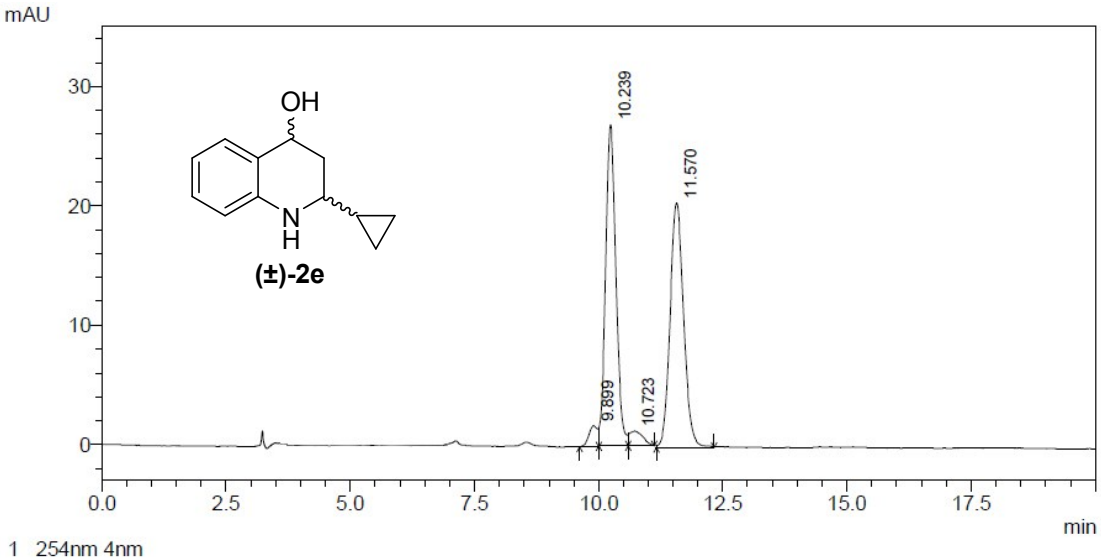


Table 1, entry 5

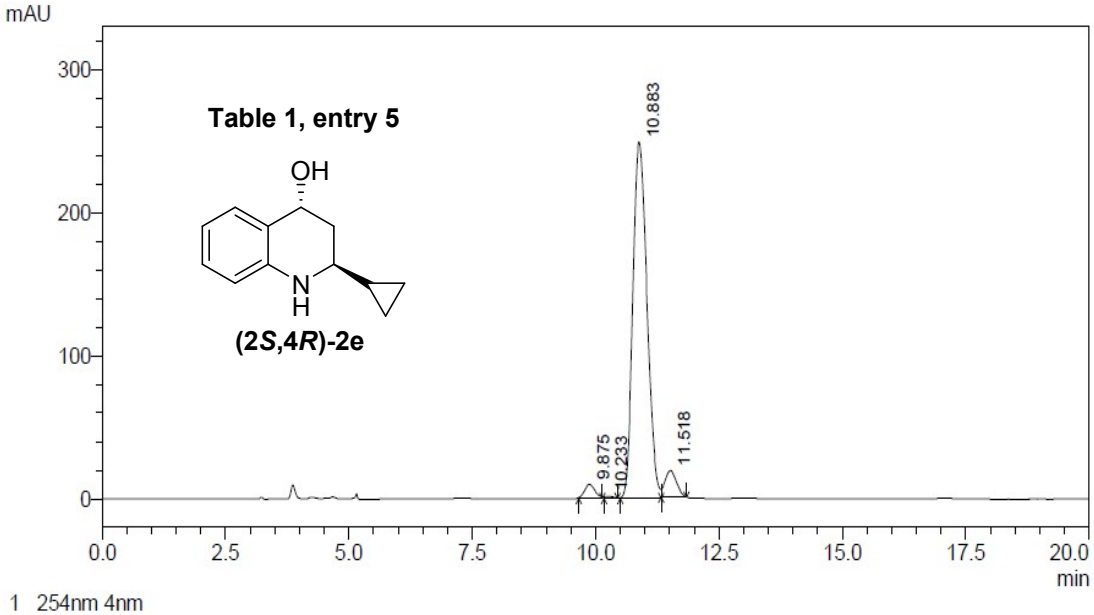
(2*S*,4*R*)-2e



1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	9.899	21886	1783	2.681
2	10.239	386121	26815	47.305
3	10.723	22115	1197	2.709
4	11.570	386115	20449	47.304

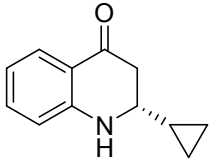


1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	9.875	136800	9518	2.526
2	10.233	14791	1382	0.273
3	10.883	4966597	249046	91.701
4	11.518	297903	18493	5.500

Table 1, entry 5



(*R*)-3e

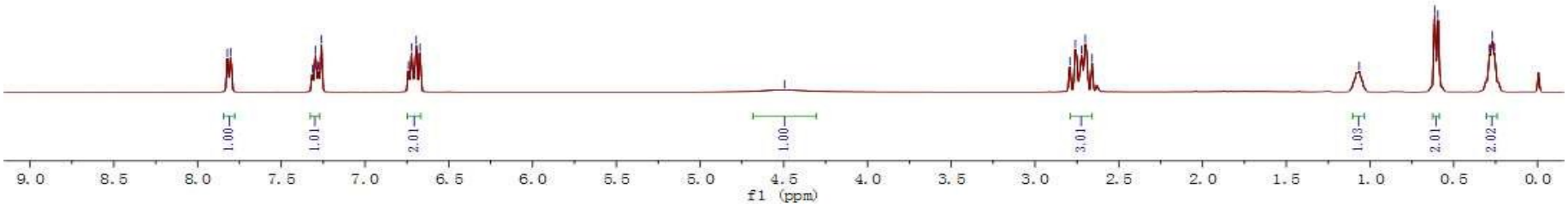
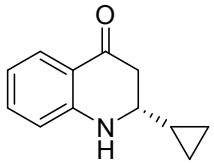
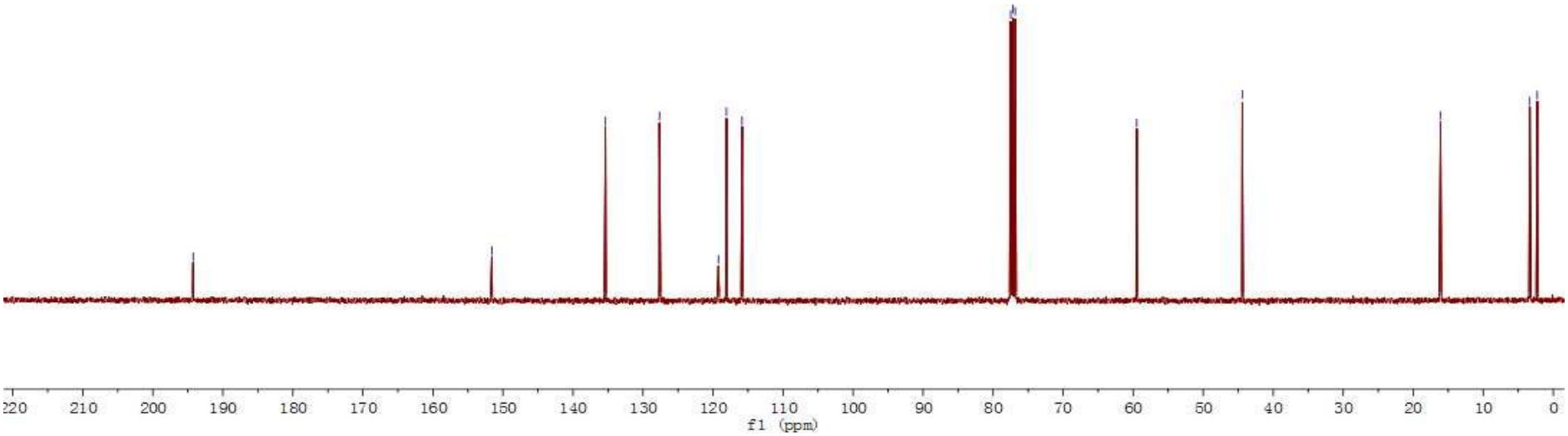
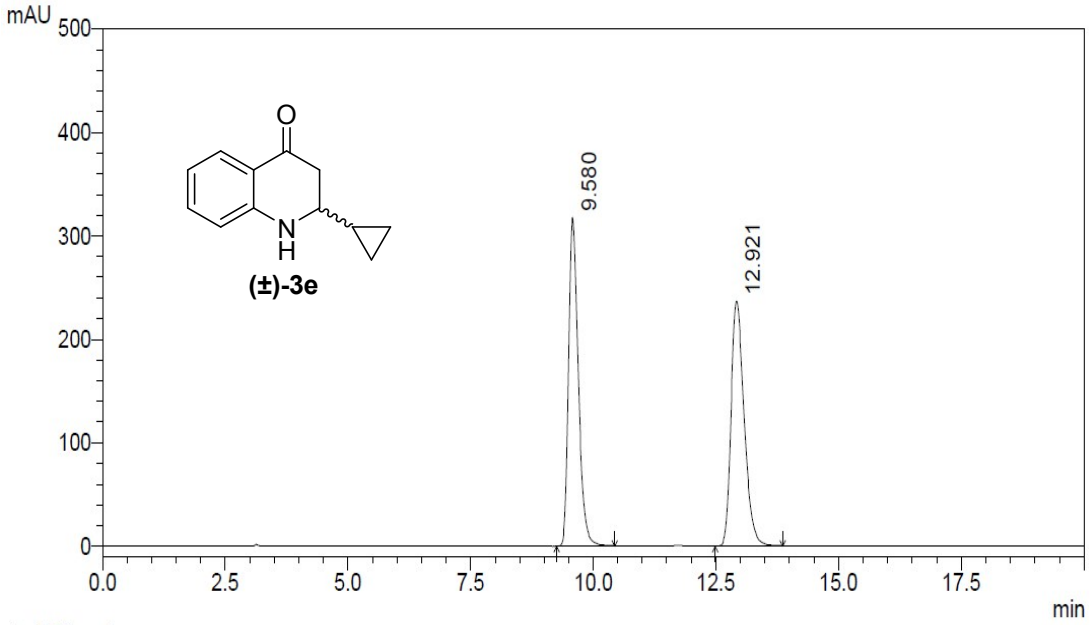


Table 1, entry 5



(*R*)-3e

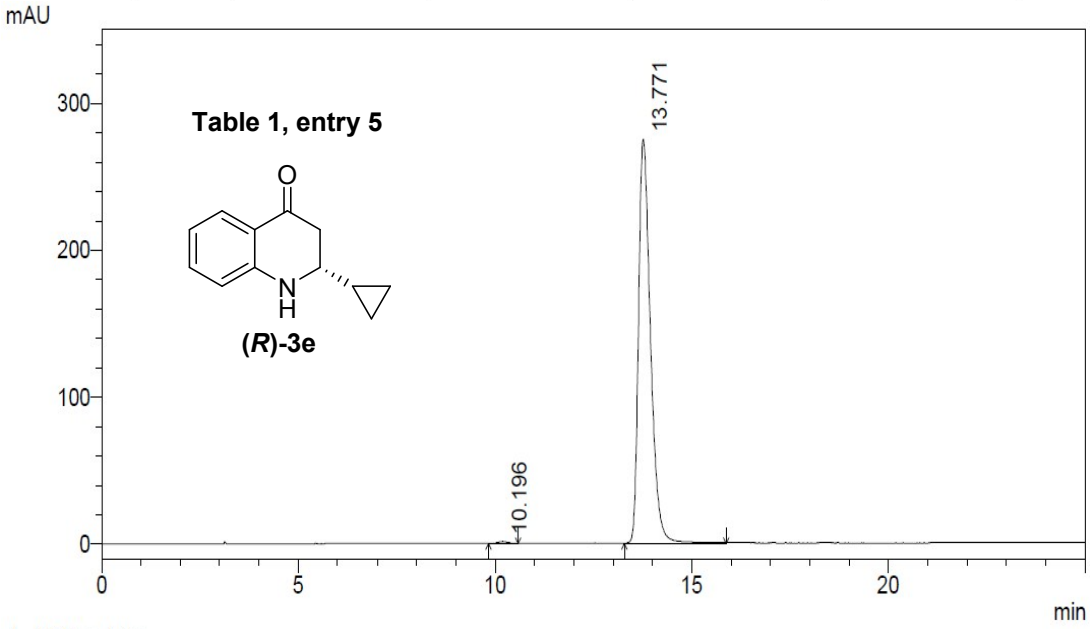




1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	9.580	4428288	317797	50.021
2	12.921	4424588	237003	49.979

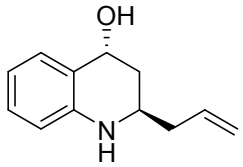


1 254nm 4nm

PDA

ID#	Reat. Time	Area	Height	Area %
1	10.196	18628	1182	0.321
2	13.771	5793464	274749	99.679

Table 1, entry 6



(2*R*,4*R*)-2f

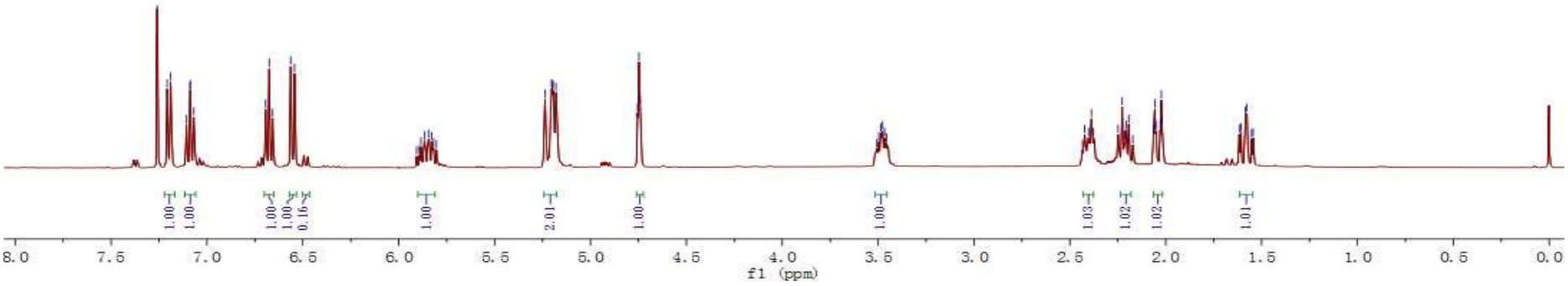
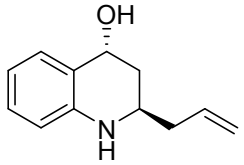


Table 1, entry 6



(2*R*,4*R*)-2f