SUPPORTING INFORMATION FOR:

Stereoselective C9 Arylation and Vinylation of *Cinchona* Alkaloids

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General

Melting points were determined using a Boëtius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DRX (^{1}H, 300 MHz) or a Bruker Avance (^{1}H, 600 MHz) spectrometer using TMS as an internal standard. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. High resolution Mass Spectra were recorded on Mariner Spectrometer operating on the ESI (MeOH) or EI (70

eV) mode. Microanalysis was performed on VarioEL (Elementary Analysensysteme GmbH) apparatus.

Separations of products by chromatography were performed on silica gel 60 (230-400 mesh) purchased from Merck. The solvents (ether and THF) were prepared by refluxing for 4h with $LiAlH_4$ and distilling, followed by refluxing with benzophenone over sodium until deep-blue ketyl was visible and distilling. Other solvents were distilled once before use.

Grignard reagents

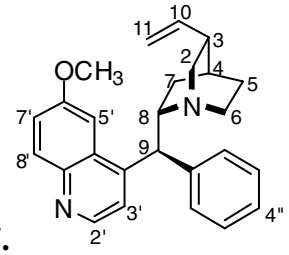
Fresh magnesium turnings (1.5 mmol) were suspended in a dry solvent (diethylether or THF) (4 mL) under argon atmosphere. Aryl halide (1.4 mmol) and 1,2-dibromoethane (0.01 mL) were added and the mixture was heated under reflux until all magnesium dissolved (30-75 minutes). The solution was used immediately. Vinylmagnesium bromide 1M solution in THF was purchased from Aldrich.

General procedure for preparation of 9-aryl-cinchonans

To a stirred solution of arylmagnesium halide (1.4-1.6 mmol) in dry diethyl ether or THF under argon was added a solution of chloro-alkaloid (1.0 mmol) in toluene (4 mL). The mixtutre was heated at reflux temperature for 4 hours. The mixture was allowed to attain room temperature and ammonia buffer was added (10 mL, 3.0 M). The mixture was diluted with $CHCl_3$ (12 mL) and extracted with $CHCl_3$ (3 x 25 mL). The combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The resulting yellow or brown oils were purified on 30 g silicagel column with $CHCl_3$:CH_3OH (25:1 v/v) as an eluent.

Compounds **7**, **13** and **14** could be alternatively purified *via* crystallization of their thiocyanate salts: Crude products were dissolved in methanol (5 mL) together with ammonium thiocyanate (140 mg) and heated under reflux for 10 minutes. The colorless crystals were collected by filtration, suspended in 5% aqueous sodium hydroxide and

extracted with dichloromethane (3 x 25 mL). The combined extracts were dried over K_2CO_3 and concentrated *in vacuo*.



(8*S*,9*S*)-6'-methoxy-9-phenyl-cinchonan, 9*S*-PhQN, **7.**

The general procedure was followed for 9*S*-chloroquinine and 1.4 eq of phenylmagnesium bromide in dry diethyl ether obtained from magnesium turnings and bromobenzene. Yield 65%, white solid. (When 2.0 eq of PhMgBr in THF were used and the mixture refluxed for 6h 88% yield was obtained) mp = 145-152 °C, (lit.[1] mp = 139.5 °C) $[\alpha]^{20}_D$ −73.7 (c 0.97, $CHCl_3$) (lit.[1] $[\alpha]^{20}_D$ −74).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (1H, d, J = 4.8 Hz, H-2'), 7.96 (1H, d, J = 9.1 Hz, H-8'), 7.47 (1H, br.s, H-5'), 7.29-7.37 (4H, m) and 7.16-7.22 (2H, m) (H-3', H-7', H-2", H-3", H-5", H-6"), 7.10 (1H, m, H-4"), 5.91 (1H, m, H-10), 5.00-5.07 (2H, m, H-11), 4.72 (1H, d, J = 10.9 Hz, H-9), 3.92 (3H, s, OCH_3), 3.69 (1H, m, H-8), 3.25 (1H, m, H-6a), 3.19 (1H, dd, J = 13.8, 10.1 Hz, H-2a), 2.63-2.77 (2H, m, H-2b, H-6b), 2.26 (1H, m, H-3), 1.85 (1H, m) and 1,45-1.67 (3H, m) (H-4, H-5a, H-5b, H-7a), 0.81 (1H, m, H-7b).

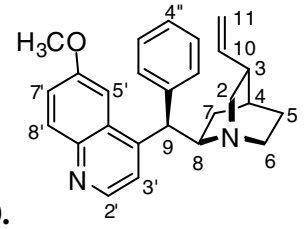
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 147.6, 146.8, 144.8, 142.2, 142.0, 131.9, 128.8, 128.5, 127.9, 126.7, 120.9, 119.7, 114.3, 102.1, 59.5, 56.6, 55.5, 49.5, 40.9, 39.6, 28.8, (28.1, 28.1 overlapped).

IR (KBr) ν_{max} 3073, 2940, 2866, 1620, 1595, 1506, 1476, 1446, 1421, 1360, 1321, 1225, 1023, 912, , 821, 736 cm^{-1}.

(1) Ochiai, E.; Kobayashi, Y. *J. Pharm. Soc. Japan* **1949**, *69*, 161. *Chem. Abstr.* **1950**, *44*, 3508.

Thiocyanate salt of **7**: mp = 249-250 °C (dec.) (methanol). (lit.[1] mp = 249 °C (dec.))

IR (KBr) ν_{max} 2959, 2830, 2061, 1617, 1589, 1505, 1474, 1430, 1398, 1360, 1228, 1087, 1026, 921, 845, 742, 709 cm^{-1}.



(8*R*,9*R*)-6'-methoxy-9-phenyl-cinchonan, 9*R*-Ph-QD, 10.

The general procedure was followed for 9*R*-chloroquinidine and 1.4 eq of phenylmagnesium bromide in dry diethyl ether obtained from magnesium turnings and bromobenzene. Yield 60%, oil, $[\alpha]^{20}_D$ +160.7 (c 1.3, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, J = 4.8 Hz, H-2'), 7.92 (1H, d, J = 9.2 Hz, H-8'), 7.43 (1H, br.s, H-5'), 7.24-7.32 (4H, m, H-3', H-7', H-2", H-6"), 7.14-7.20 (2H, m, H-3", H-5"), 7.06 (1H, m, H-4"), 5.82 (1H, ddd, J = 17.3, 10.5, 7.0 Hz, H-10), 4.99 (1H, dt, J = 17.3, 1.6 Hz, H-11a), 4.97 (1H, dt, J = 10.5, 1.6 Hz, H-11b), 4.76 (1H, d, J = 10.9 Hz, H-9), 3.88 (3H, s, OCH_3), 3.62 (1H, m, H-8), 2.79-3.00 (4H, m, H-2a, H-2b, H-6a, H-6b), 2.19 (1H, m, H-3), 1.48-1.64 (3H, m) and 1.45 (1H, m) (H-4, H-5a, H-5b, H-7a), 1.14 (1H, m, H-7b).

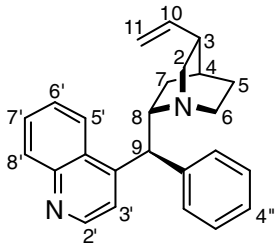
^{1}H NMR (600 MHz, C_6D_6) δ 8.89 (1H, d, J = 4.5 Hz, H-2'), 8.36 (1H, d, J = 9.3 Hz, H-8'), 7.68 (1H, br.s, H-5'), 7.45 (2H, d, J = 7.3 Hz, H-2", H-6"), 7.30 (1H, m, H-7'), 7.24 (2H, t, J = 7.4 Hz, H-3", H-5"), 7.16 (1H, d, J = 4.4 Hz, H-3'), 7.10 (1H, t, J = 7.4 Hz, H-4"), 5.87 (1H, ddd, J = 17.8, 10.7, 7.0 Hz, H-10), 5.03-5.08 (2H, m, H-11), 4.96 (1H, d, J = 7.1 Hz, H-9), 3.55 (3H, s, OCH_3), 3.53 (1H, m, H-8), 3.09 (1H, m H-2b), 2.90 (1H, d, J = 14.1, 9.8 Hz, H-2a), 2.88 (1H, m, H-6a), 2.72 (1H, m, H-6b), 2.06 (1H, m, H-3), 1.51 (1H, m, H-4), 1.42 (1H, m, H-5a), 1.31 (1H, m, H-5b), 1.20-1.26 (2H, m, H-7a, H-7b).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 147.5, 147.2, 144.8, 142.3, 140.9, 131.9, 128.8, 128.5, 128.0, 126.6, 121.3, 120.0, 114.4, 101.7, 59.1, 55.4, 49.6, 48.1, 47.6, 39.8, 28.0, 27.7, 26.7.

^{13}C NMR (150 MHz, C_6D_6) δ 158.1 (C-6'), 147.8 (C-2'), 146.6 (C^{IV}), 145.7 (C^{IV}), 143.0 (C^{IV}), 141.1 (C-10), 132.8 (C-8'), 129.1 (C^{IV}), 128.5 (C-3", C-5"), 128.1 (C-2", C-6"), 126.3 (C-4"), 121.0 (C-7'), 120.6 (br. C-3'), 114.1 (C-11), 102.1 (C-5'), 59.1 (br. C-8), 54.7 (OCH_3), 49.6 (C-6), 48.5 (br. C-9), 47.8 (C-2), 40.1 (C-3), 28.4 (C-4), 27.8 (C-7), 26.8 (C-5).

IR (neat) ν_{max} 3062 2934, 2868, 1621, 1586, 1507, 1471, 1452, 1431, 1361, 1246, 1227, 1032, 910, 850, 832, 712, 698 cm^{-1}.

Microanalysis: Calcd for $C_{30}H_{28}N_2O \cdot H_2O$: C, 77.58; H, 7.51; N 6.96. Found: C, 77.55; H, 7.26; N, 6.94%.



(8*S*,9*S*) 9-phenyl-cinchonan, 9*S*-Ph-CD, 11.

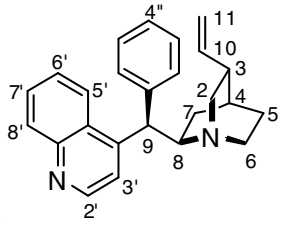
The general procedure was followed for 9*S*-chlorocinchonidine and 1.4 eq of phenylmagnesium bromide in dry diethyl ether obtained from magnesium turnings and bromobenzene. Yield 23%, white, crystaline, mp = 131-134 °C, $[\alpha]^{20}_D$ −16.3 (c 0.4, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (1H, d, J = 4.6 Hz, H-2'), 8.26 (1H, d, J = 8.1 Hz, H-5'), 8.04 (1H, d, J = 8.2 Hz, H-8'), 7.62 (1H, m, H-7'), 7.52 (1H, m, H-6'), 7.37 (1H, d, J = 4.7 Hz, H-3'), 7.31 (2H, d, J = 7.7 Hz, H-2", H-6"), 7.13-7.21 (2H, m, H-3", H-5"), 7.06 (1H, t, J = 7.6 Hz, H-4"), 5.82 (1H, ddd, J = 17.3, 9.8, 7.4 Hz, H-10), 4.95-5.03 (2H, m, H-11), 4.87 (1H, d, J = 11.3 Hz, H-9), 3.67 (1H, m, H-8), 3.22 (1H, m, H-6a), 3.17 (1H, dd, J = 14.0, 10.1 Hz, H-2a), 2.61-2.75 (2H, m, H-2b, H-6b), 2.21 (1H, m, H-3), 1.61 (1H, m, H-4), 1.76 (1H, m) and 1.41-1.58 (2H, m) (H-5a, H-5b, H-7a), 0.74 (1H, dd, J = 13.5, 7.1 Hz, H-7b).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 148.7, 148.5, 142.1, 142.0, 130.6, 129.0, 128.5, 127.8, (126.8, 126.8 overlapped), 123.2, 119.5, 114.3, 100.0, 59.4, 56.6, 48.8, 40.9, 39.6, 28.6, (28.0, 28.0 overlapped).

IR (KBr) ν_{max} 3077, 2954, 2927, 2862, 1637, 1585, 1567, 1507, 1463, 1450, 1389, 1308, 1019, 1003, 913, 757, 731, 702 cm^{-1}.

Microanalysis: Calcd for $C_{25}H_{26}N_2 \cdot H_2O$: C, 80.61; H, 7.57; N, 7.52. Found C, 80.24; H, 7.25; N, 7.71%.



(8*R*,9*R*)-9-phenyl-cinchonan, 9*R*-Ph-CN, 12.

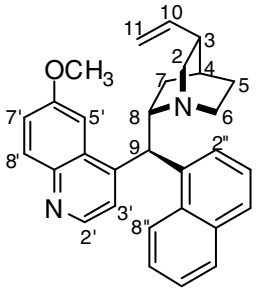
The general procedure was followed for 9*S*-chlorocinchonine and 1.4 eq of phenylmagnesium bromide in dry diethyl ether. Yield 39%, oil, $[\alpha]^{20}_D$ +100.5 (c 1.2, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (1H, d, J = 4.5 Hz, H-2'), 8.25 (1H, d, J = 7.4 Hz, H-5'), 8.03 (1H, d, J = 8.4 Hz, H-8'), 7.61 (1H, m) and 7.51 (1H, m) (H-6', H-7'), 7.35 (1H, d, J = 4.5 Hz, H-3'), 7.25-7.30 (2H, m) and 7.12-7.19 (2H, m) (H-2", H-3", H-5", H-6"), 7.05 (1H, m, H-4"), 5.79 (1H, ddd, J = 17.3, 10.6, 7.0 Hz, H-10), 4.98 (1H, dt, J = 17.3, 1.5 Hz, H-11a), 4.97 (1H, dt, J = 10.6, 1.5 Hz, H-11b), 4.91 (1H, d, J = 11.1 Hz, H-9), 3.62 (1H, m, H-8), 2.78-3.00 (4H, m, H-2a, H-2b, H-6a, H-6b), 2.17 (1H, q, J = 8.0 Hz, H-3), 1.42-1.61 (3H, m) and 1.30 (1H, m) (H-4, H-5a, H-5b, H-7a), 1.10 (1H, m, H-7b).

^{13}C NMR (75 MHz, $CDCl_3$, 305K) δ 150.0, 148.8, 148.8, 142.3, 140.8, 130.6, 128.9, 128.4, 128.0, 126.6, 126.6, 126.5, 123.23, 120.0, 114.42, 59.0, 49.6, 47.8, 47.6, 39.9, 28.1, 27.6, 26.7.

IR (neat) ν_{max} 3431 (H_2O), 3060, 3026, 2933, 2865, 1635, 1586, 1567, 1507, 1494, 1450, 1308, 1071, 1052, 1029, 910, 819, 755, 726, 697, 608 cm^{-1}.

HRMS (ESI): Found $[M+H]^+$, 355.2142. $C_{25}H_{26}N_2$ requires $[M+H]^+$ m/z 355.2174,.



(8*S*,9*S*)-6'-methoxy-9-naphtalen-1-yl-cinchonan, 14.

The general procedure was followed for 9*S*-chloroquinine and 1.6 eq of 1-naphtylmagnesium bromide in dry diethyl ether. Yield 60%, off-white, amorphous, $[\alpha]^{20}_D$ −25.7 (c 0.8, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, J = 4.7 Hz, H-2'), 8.28 (1H, m, H-8"), 7.98 (1H, d, J = 9.2 Hz, H-8'), 7.78 (1H, m) and 7.66-7.70 (3H, m) (H-5' H-2", H-4", H-5"), 7.46 (1H, t, J = 7.7 Hz, H-3"), 7.29-7.40 (4H, m, H-3', H-7', H-6", H-7"), 5.94 (1H, ddd, J = 17.5, 10.7, 7.3 Hz, H-10), 5.56 (1H, d, J = 10.8 Hz, H-9), 5.01-5.09 (2H, m, H-11), 3.83 (3H, s, OCH_3), 3.82 (1H, m, H-8), 3.28 (1H, m, H-6a), 3.14 (1H, dd, J = 13.8, 9.9 Hz, H-2a), 2.81 (1H, m, H-2b), 2.65 (1H, m, H-6b), 2.25 (1H, m, H-3), 1.62-1.83 (3H, m, H-7a, H-4, H-5a), 1.52 (1H, m, H-5b), 1.18 (1H, m, H-7b).

^{1}H NMR (600 MHz, C_6D_6) δ 8.80 (1H, d, J = 4.5 Hz, H-2'), 8.57 (1H, d, J = 8.7 Hz, H-8"), 8.36 (1H, d, J = 9.1 Hz, H-8'), 7.89 (1H, d, J = 2.5 Hz, H-5'), 7.79 (1H, d, J = 7.2 Hz, H-2"), 7.71 (1H, d, J = 8.0 Hz, H-5"), 7.61 (1H, d, J = 8.0 Hz, H-4"), 7.43 (1H, t, J = 7.9 Hz, H-3"), 7.33 (1H, d, J = 4.5 Hz, H-3'), 7.24-7.28 (3H, m, H-7', H-6", H-7"), 5.93 (1H, ddd, J = 17.2, 10.3, 7.6 Hz, H-10), 5.72 (1H, d, J = 10.6 Hz, H-9), 5.13 (1H, d, J = 10.3 Hz, H-11a), 5.09 (1H, d, J = 17.2 Hz, H-11b), 3.82 (1H, m, H-8), 3.47 (3H, s, OCH_3), 3.25 (1H, m, H-6a), 2.99 (1H, dd, J = 13.7, 10.2 Hz, H-2a), 2.81 (1H, m, H-2b), 2.45 (1H, m, H-6b), 2.06 (1H, m, H-3),

1.82 (1H, m, H-7a), 1.58 (1H, m, H-4), 1.51 (1H, m, H-5a), 1.24 (1H, m, H-5b), 1.20 (1H, dd, J = 13.7, 7.7 Hz, H-7b).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.6, 147.5, 144.7, 142.1, 138.4, 134.1, 132.2, 132.1, 129.4, 128.9, 127.3, 125.9, 125.6, 125.6, 125.1, 122.9, 121.3, 120.9, 114.3, 101.9, 60.5, 56.4, 55.6, 43.4, 41.6, 39.7, 28.3, 28.0, 27.9.

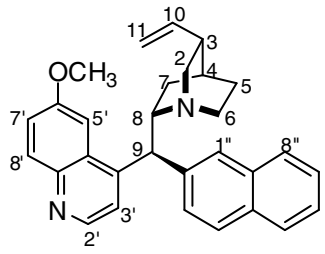
^{13}C NMR (150 MHz, C_6D_6) δ 158.2 (C-6'), 147.9 (C-2'), 147.0 (C^{IV}), 145.6 (C^{IV}), 142.4 (C-10), 139.1 (C^{IV}), 134.4 (C^{IV}), 133.0 (C-8'), 132.7 (C^{IV}), 129.6 (C-5"), 129.2 (C^{IV}), 127.2 (C-4"), 126.3 (C-2"), 125.9 (C-7"), 125.6 (C-3"), 125.0 (C-6"), 123.2 (C-8"), 121.0 (C-3', C-7'), 113.9 (C-11), 102.4 (C-5'), 61.0 (br. C-8), 56.6 (C-2), 55.0 (OCH_3), 43.8 (br. C-9), 41.6 (C-6), 40.0 (C-3), 28.31, 28.26 (C-4, C-5), 28.0 (C-7).

IR (KBr) ν_{max} 3049, 2937, 2862, 1620, 1585, 1507, 1467, 1426, 1317, 1241, 1229, 1086, 1030, 911, 848, 828, 781 cm^{-1}.

Microanalysis: Calcd for $C_{30}H_{28}N_2O \cdot 0.65H_2O$: C, 81.11; H, 6.65; N, 6.31. Found C, 81.10; H, 6.94; N, 6.34%.

Thiocyanate salt of **14**: mp = 245-247 °C (dec.)

IR (KBr) ν_{max} 3430, 3049, 2941, 2824, 2049, 1619, 1586, 1507, 1467, 1428, 1395, 1360, 1319, 1247,1212, 1090, 1028, 921, 854, 836, 786 cm^{-1}.



(8*S*,9*S*)-6'-methoxy-9-naphtalen-2-yl-cinchonan, 13.

The general procedure was followed for 1.6 eq of 9*S*-chloroquinine and 2-naphtylmagnesium bromide in dry diethyl ether. Yield 59%, off-white, amorphous, $[\alpha]^{20}_{D}$ −136.5 (c 0.9, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (1H, d, J = 4.7 Hz, H-2'), 7.98 (1H, d, J = 9.3 Hz, H-8'), 7.78 (1H, s, H-1"), 7.57 (1H, br.s, H-5'), 7.63-7.72 (3H, m) and 7.47 (1H, dd, J = 9.0, 1.9 Hz) and 7.25-7.37 (3H, m) (H-7', H-3", H-4", H-5", H-6", H-7", H-8"), 7.45 (1H, d, J = 4.7 Hz, H-3'), 5.92 (1H, ddd, J = 17.4, 9.9, 7.3 Hz, H-10), 5.00-5.08 (2H, m, H-11), 4.90 (1H, d, J = 11.2 Hz, H-9), 3.90 (3H, s, OCH_3), 3.81 (1H, m, H-8), 3.36 (1H, m, H-6a), 3.17 (1H, dd, J = 13.9, 9.9 Hz, H-2a), 2.61-2.80 (2H, m, H-2b, H-6b), 2.24 (1H, m, H-3), 1.91 (1H, m) and 1.43-1.64 (2H, m) (H-5a, H-5b, H-7a), 1.67 (1H, m, H-4), 0.87 (1H, dd, J = 13.8, 7.1 Hz, H-7b).

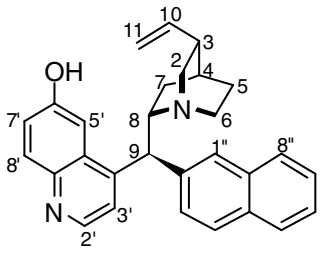
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 147.7, 146.6, 144.9, 142.1, 139.8, 133.4, 132.4, 132.0, 128.9, 128.2, 127.7, 127.6, 126.7, 126.2, 126.0, 125.5, 120.9, 119.9, 114.3, 102.2, 59.5, 56.7, 55.5, 49.9, 41.1, 39.6, 28.9, (28.1, 28.1 overlapped).

IR (KBr) ν_{max} 3053, 2937, 2861, 1620, 1587, 1507, 1466, 1363, 1314, 1229, 1171, 1031, 908, 851, 819, 746 cm^{-1}.

Microanalysis: Calcd for $C_{30}H_{28}N_2O{\cdot}½H_2O$: C, 81.60; H, 6.62; N, 6.34. Found C, 82.01; H, 7.02; N, 6.41%.

Thiocyanate salt of **13:** mp = 215-217°C (methanol).

IR (KBr) ν_{max} 3424, 2946, 2052, 1620, 1589, 1510, 1477, 1365, 1252, 1229, 1026, 920, 850, 825, 744, 480 cm^{-1}.



(8*S*,9*S*)-6'-hydroxy-9-naphtalen-2-yl-cinchonan, 15.

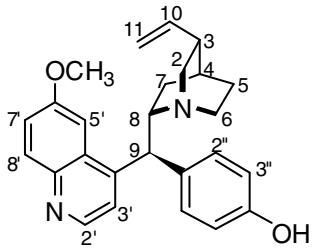
2-Naphtyl quinine (**17**) (117 mg, 0.27 mmol) was dissolved in dry DMF (4 mL) and sodium ethyltiolate (110 mg) was added and the mixture was heated in a sealed vial at 105°C for 24h. The mixture was then allowed to attain room temperature and saturated aqueous NH_4Cl was added (10 mL) and the mixture extracted with ethyl acetate (4 x 15 mL), the combined organic phases were extracted with 2M HCl (4 x 15 mL). The extracts were alkalized with aqueous ammonia and the mixture extracted with ethyl acetate (4 x 20 mL), the combined extracts were dried over Na_2SO_4 concentrated *in vacuo* and purified on 10 g of silicagel using $CHCl_3$:MeOH 15:1 as eluent. The product was obtained in 75% yield as white solid, mp = 201-202 °C, $[\alpha]^{20}_D$ −259.1 (c 1.04, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, d, J = 4.7 Hz, H-2'), 8.4 (1H, br., OH), 7.91 (1H, d, J = 9.1 Hz, H-8'), 7.64 (1H, s, H-1"), 7.53 (1H, s, H-5'), 7.36-7.42 (3H, m) and 7.33 (1H, d, J = 7.9 Hz) and 7.22 (1H, d, J = 8.7 Hz) and 7.02-7.15 (3H, m) (H-3', H-7', H-3", H-4", H-5", H-6", H-7", H-8"), 5.76 (1H, ddd, J = 17.2, 10.5, 7.3 Hz, H-10), 4.89-4.99 (2H, m, H-11), 4.66 (1H, d, J = 11.3 Hz, H-9), 3.69 (1H, m, H-8), 2.90 (1H, dd, J = 13.5, 10.7 Hz, H-2a), 2.73 (1H, m, H-6a), 2.58 (1H, m, H-2b), 2.14 (1H, m, H-6b), 1.94 (1H, m, H-3), 1.43 (1H, m, H-4), 1.72 (1H, m) and 0.96-1.21 (2H, m) (H-5a, H-5b, H-7a), 0.69 (1H, m, H-7b).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 147.7, 145.7, 142.6, 141.5, 139.0, 133.3, 132.3, 130.3, 129.6, 128.3, 127.5, 127.3, 126.5, 125.8, 125.7, 125.4, 122.7, 119.6, 114.5, 105.1, 59.5, 56.2, 48.9, 40.5, 39.0, 28.2, 27.7, 27.4.

IR (KBr) ν_{max} 3427, 3055, 2924, 2859, 1615, 1586, 1509, 1471, 1243, 1229, 907, 847, 741 cm^{-1}.

Microanalysis: Calcd for $C_{29}H_{28}N_2O \cdot ½H_2O$: C, 81.08; H, 6.80; N, 6.52. Found C, 80.63; H, 6.66; N, 6.36%.



(8*S*,9*S*)-9-(4-hydroxyphenyl)-6'-methoxy-cinchonan, 16.

The general procedure was followed for 9*S*-chloroquinine and the Grignard reagent (1.6eq) obtained from 4-methoxymethoxy-iodobenzene[2] and magnesium in dry THF. The intermediate product, **(8*S*,9*S*)-6'-methoxy-9-(4-methoxymethoxyphenyl)-cinchonan, 16a** was isolated in 45% yield as white crystals, mp = 166-168 °C, $[\alpha]^{20}_D$ –93.2 (c 0.4, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (1H, d, J = 4.8 Hz, H-2'), 7.93 (1H, d, J = 9.2 Hz, H-8'), 7.43 (1H, br.s, H-5'), 7.31 (1H, d, J = 4.8 Hz, H-3'), 7.28 (1H, dd, J = 9.2, 2.4 Hz, H-7'), 7.20 (2H, d, J = 8.7 Hz, H-2"), 6.85 (2H, d, J = 8.7 Hz, H-3"), 5.87 (1H, ddd, J = 17.4, 9.9, 7.1 Hz, H-10), 5.01 (2H, s, OCH_2O), 4.97-5.03 (2H, m, H-11), 4.65 (1H, d, J = 11.1 Hz, H-9), 3.89 (3H, s, 6'-OCH_3), 3.62 (1H, m, H-8), 3.34 (3H, s, MOM-CH_3), 3.24 (1H, m, H-6a), 3.19 (1H, dd, J = 13.9, 10.1 Hz, H-2a), 2.63-2.75 (2H, m, H-2b, H-6b), 2.24 (1H, m, H-3), 1.83 (1H, m) and 1.44-1.61 (2H, m) (H-5a, H-5b, H-7a), 1.64 (1H, m, H-4), 0.77 (1H, m, H-7b).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 155.8, 147.7, 147.0, 144.7, 142.0, 135.4, 131.9, 128.7, 127.8, 120.9, 119.6, 116.2, 114.3, 102.1, 94.3, 59.5, 56.6, 55.9, 55.4, 48.6, 40.9, 39.6, 28.8, (28.1, 28.1 overlapped).

IR (KBr) ν_{max} 3432 (H_2O), 2945, 2873, 1620, 1610, 1586, 1509, 1471, 1429, 1245, 1227, 1202, 1152, 1083, 1023, 991, 835 cm^{-1}.

(2) Takatori, K.; Nisihara, M.; Nishiyama, Y.; Kajiwara, M. *Tetrahedron* **1998**, *54*, 15861

The MOM-ether **16a** (222 mg, 0.4 mmol) was dissolved in trifluoroacetic acid: water mixture (4 mL, 15:1 v/v) mixture. The solution was stirred for 2 hours at room temperature, then concentrated *in vacuo*, suspended in aqueous ammonia (7.5 mL, 10%) and extracted with chloroform (4 x 20 mL). The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo*. The cleavage of the MOM group was quantitative and the product required no further purification. (8*S*,9*S*)-9-(4-Hydroxyphenyl)-6'-methoxy-cinchonan, **16** was obtained as slowly crystallizing oil, $[\alpha]^{20}_D$ –92.0 (c 0.5, ethanol:CH_2Cl_2, 4:1 v/v).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (1H, d, J = 4.7 Hz, H-2'), 7.89 (1H, d, J = 9.2 Hz, H-8'), 7.34 (1H, d, J = 2.6 Hz, H-5'), 7.28 (1H, d, J = 4.7 Hz, H-3'), 7.23 (1H, dd, J = 9.2, 2.6 Hz, H-7'), 6.96 (2H, d, J = 8.4 Hz, H-2", H-6"), 6.18 (2H, d, J = 8.4 Hz, H-3", H-5"), 5.84 (1H, ddd, J = 17.3, 10.6, 7.1 Hz, H-10), 4.96-5.05 (2H, m, H-11), 4.54 (1H, d, J = 11.2 Hz, H-9), 3.84 (3H, s, OCH_3), 3.63 (1H, m, H-8), 3.38 (1H, m, H-6a), 3.13 (1H, dd, J = 13.8, 10.1 Hz, H-2a), 2.62-2.79 (2H, m, H-2b, H-6b), 2.28 (1H, m, H-3), 1.68 (1H, m, H-4), 1.97 (1H, m) and 1.52-1.64 (2H, m) (H-5a, H-5b, H-7a), 0.79 (1H, m, H-7b).

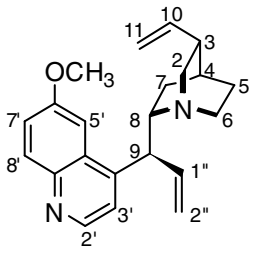
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 155.8, 147.3, 146.5, 144.6, 140.9, 131.7, 131.2, 128.6, 128.4, 121.0, 118.9, 116.5, 114.9, 102.1, 60.3, 56.0, 55.5, 49.4, 40.5, 38.7, 29.2, 27.8, 27.3.

IR (KBr) ν_{max} 3391, 2996, 2938, 2865, 1675, 1620, 1588, 1509, 1471, 1455, 1363, 1223, 1172, 1031, 828, 758 cm^{-1}.

Microanalysis: Calcd for $C_{26}H_{28}N_2O_2 \cdot ½CH_2Cl_2 \cdot ½H_2O$: C, 69.28; H, 6.57; N, 6.10. Found C, 69.22; H, 6.55; N, 6.26%.

EI MS m/z (70 eV) 400 ($M^{+\bullet}$, 1%), 399 (1), 359 (1), 277 (2), 265 (15), 233 (3), 136 (100).

HRMS (EI) Found: $M^{+\bullet}$ 400.21664. $C_{26}H_{28}N_2O_2$ requires $M^{+\bullet}$, 400.21508.



(8*S*,9*S*)-6'-methoxy-9-vinyl-cinchonan, 18.

To a stirred solution of 9*S*-chloroquinine (686 mg, 2.0 mmol) in THF (4 mL) a solution of vinylmagnesium bromide (2.8 mL, 1.0 M in THF) was added at room temperature and the mixture was stirred for 5h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was diluted with $CHCl_3$ (12 mL), and extracted with $CHCl_3$ (3 x 25 mL). The combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified on 20 g silicagel column with $CHCl_3$:CH_3OH 25:1 as an eluent affording the product as a pale oil in 65% yield, $[\alpha]^{20}_D$ +77.9 (c 0.82, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (1H, d, J = 4.6 Hz, H-2'), 7.97 (1H, d, J = 8.8 Hz, H-8'), 7.30-7.36 (2H, m, H-5', H-7'), 7.17-7.18 (1H, m, H-3'), 6.08 (1H, ddd, J = 17.7, 10.0, 8.5 Hz, H-1"), 5.78 (1H, ddd, J = 17.6, 10.5, 7.6 Hz, H-10), 4.91-5.05 (4H, m, H-11, H-2"), 4.09 (1H, m, H-9), 3.91 (3H, s, OCH_3), 3.27 (1H, dd, J = 13.7, 10.1 Hz, H-2a), 3.14-3.29 (2H, m, H-6a, H-8), 2.67-2.79 (2H, m, H-2b, H-6b), 2.24 (1H, m, H-3), 1.47-1.60 (4H, m, H-4, H-5a, H-5b, H-7a), 0.64 (1H, m, H-7b).

^{1}H NMR (600 MHz, C_6D_6) δ 8.88 (1H, d, J = 4.5 Hz, H-2'), 8.43 (1H, d, J = 9.0 Hz, H-8'), 7.60 (1H, d, J = 2.7 Hz, H-5'), 7.35 (1H, dd, J = 9.1, 2.7 Hz, H-7'), 7.00 (1H, d, J = 4.6 Hz, H-3'), 6.53 (1H, m, H-1"), 5.82 (1H, ddd, J = 17.7, 9.8, 7.6 Hz, H-10), 5.15 (1H, d, J = 10.5, H-2"a), 5.04-5.08 (2H, m, H-11), 5.02 (1H, d, J = 17.4 Hz, H-2"b), 4.25 (1H, br., H-9), 3.52 (3H, s, OCH_3), 3.33 (1H, m, H-8), 3.24 (1H, dd, J = 13.9, 10.0 Hz, H-2a), 3.21 (1H, m, H-6a), 2.86 (1H, ddd, J = 13.9, 5.2, 2.3 Hz, H-2b), 2.66 (1H, ddd, J = 15.3, 10.5, 5.7 Hz, H-6b), 2.13 (1H, m, H-3), 1.55 (1H, m, H-7a), 1.47 (m, 1H, H-4), 1.27-1.38 (2H, m, H-5a, H-5b), 0.63 (1H, dd, J = 13.6, 6.7 Hz, H-7b).

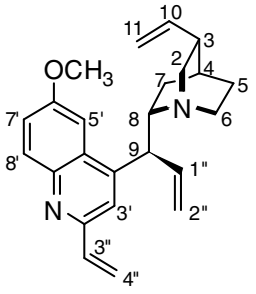
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 147.7, 146.0, 144.8, 141.7, 139.7, 132.0, 128.6, 120.9, 120.2, 115.9, 114.3, 102.0, 59.7, 56.7, 55.5, 48.3, 40.6, 39.6, 28.0, (27.9, 27.9 overlapped)

^{13}C NMR (150 MHz, C_6D_6) δ 158.0 (C-6'), 148.0 (C-2'), 145.7 (C^{IV}), 145.5 (C^{IV}), 142.1 (C-10), 140.3 (C-1"), 132.9 (C-8'), 129.2, (CIV), 121.0 (br. C-3'), 120.7 (C-7'), 115.1 (C-2"), 113.9 (C-11), 102.5 (C-5'), 59.7 (br. C-8), 56.9 (C-2), 54.7 (OCH_3), 48.0 (br. C-9), 40.7 (C-6), 40.1 (C-3), 28.22, 28.21 (C-4, C-5), 28.0 (C-7).

IR (neat) ν_{max} 3075, 2938, 2861, 1635, 1621, 1586, 1508, 1473, 1455, 1431, 1361, 1249, 1228, 1033, 991, 912, 850, 826, 717 cm^{-1}.

EI MS m/z (70 eV) 334 ($M^{+\bullet}$, 2%), 319 (4), 210 (4), 198 (4), 184 (4), 167 (4), 154 (3), 136 (100).

HRMS Found: $M^{+\bullet}$ 334.20314. $C_{22}H_{26}N_2O$ requires $M^{+\bullet}$, 334.20451.



(8*S*,9*S*)-6'-methoxy-2',9-divinyl-cinchonan, 19.

Isolated in the reaction of 9*S*-Cl-QN (**5**) with vinylmagnesium bromide as a byproduct (apart from **18**) in 15-28%[3] yield as a pale oil, $[\alpha]^{20}_D$ +50.5 (c 1.20, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (1H, d, J = 9.9 Hz, H-8'), 7.26-7.34 (3H, m, H-3', H-5', H-7'), 6.91 (1H, dd, J = 17.8, 11.0 Hz, H-3"), 6.16 (1H, dd, J = 17.8, 0.7 Hz, H-4a"), 6.11 (1H, m, H-1"), 5.76 (1H, ddd, J = 17.5, 10.5, 7.6 Hz, H-10), 5.52 (1H, dd, J = 11.0, 0.7 Hz, H-4b"), 4.88-5.04 (4H, m, H-10, H-2"), 4.06 (1H, m, H-9), 3.89 (3H, s, OCH_3), 3.26 (1H, dd, J = 13.9, 10.3 Hz, H-2a), 3.11-3.32 (2H, m, H-6a, H-8), 2.66-2.77 (2H, m, H-2b, H-6b), 2.22 (1H, m, H-3), 1.46-1.59 (4H, m, H-4, H-5a, H-5b, H-7a), 0.66 (1H, m, H-7b).

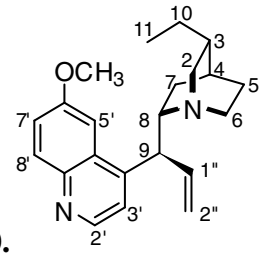
(3) 15% refers to 1.4 and 28% to 1.7 equivalents of vinylmagnesium bromide used.

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 153.3, 146.2, 144.5, 141.6, 139.7, 137.9, 131.9, 127.8, 120.9, 118.6, 117.7, 115.9, 114.3, 102.2, 59.8, 56.6, 55.5, 48.4, 40.6, 39.6, 28.0, 27.9, 27.8.

IR (neat) ν_{max} 3075, 2997, 2936, 2861, 1633, 1619, 1593, 1522, 1504, 1475, 1455, 1423, 1361, 1261, 1250, 1228, 1037, 991, 913, 830, 735 cm^{-1}.

EI MS m/z (70 eV) 360 ($M^{+\bullet}$, 1%), 345 (2), 224 (3), 210 (4), 198 (3), 136 (100)

HRMS Found: $M^{+\bullet}$ 360.21940. $C_{24}H_{28}N_2O$ requires $M^{+\bullet}$, 360.22016.



(8*S*,9*S*)-10,11-dihydro-6'-methoxy-9-vinyl-cinchonan, 20.

To a stirred solution of 9*S*-chloro-10,11-dihydro-quinine (344mg, 1.0mmol) in THF (3 mL) a solution of vinylmagnesium bromide (1.7 mL, 1M in THF) was added. The mixture was heated under reflux for 2h and then at room temperature for 24h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was diluted with $CHCl_3$ (12mL), and extracted with $CHCl_3$ (3 x 25 mL). The combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified as above affording product as s pale oil with 60% yield, $[\alpha]^{20}_D$ +46.6 (c 1, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (1H, d, J = 4.7 Hz, H-2'), 7.95 (1H, d, J = 9.1 Hz, H-8'), 7.27-7.34 (2H, m, H-5', H-7'), 7.17 (1H, d, J = 4.6 Hz, H-3'), 6.06 (1H, ddd, J = 17.6, 9.9, 8.1Hz, H-1"), 4.99 (1H, d, J = 9.9 Hz, H-2a"), 4.94 (1H, d, J = 17.6 Hz, H-2b"), 4.07 (1H, m, H-8), 3.88 (3H, s, OCH_3), 3.22 (1H, dd, J = 13.7, 9.6 Hz, H-2a), 3.09-3.24 (2H, m, H-6a, H-8), 2.68 (1H, m, H-6b), 2.41 (1H, m, H-2b), 1.14-1.54 (7H, m, H-3, H-4, H-5a, H-5b, H-7a, H-10a, H-10b), 0.74 (3H, t, J = 7.2 Hz, H-11), 0.59 (1H, m, H-7b).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 147.6, 146.2, 144.7, 139.8, 131.9, 128.7, 120.9, 120.1, 115.8, 102.0, 59.6, 58.3, 55.5, 48.3, 40.7, 37.2, 28.6, 27.7, 27.4, 25.7, 12.0.

IR (neat) ν_{max} 3075, 2933, 2860, 1622, 1586, 1508, 1472, 1431, 1362, 1250, 1235, 1082, 1033, 917, 950, 927, 732, 717 cm^{-1}.

EI MS m/z (70 eV) 336 ($M^{+\bullet}$, 28%), 335 (28), 321 (100), 307 (49), 279 (25), 210 (32), 198 (27), 184 (24), 138 (52).

HRMS Found: $M^{+\bullet}$ 336.21943. $C_{22}H_{28}N_2O$ requires $M^{+\bullet}$, 336.22016.

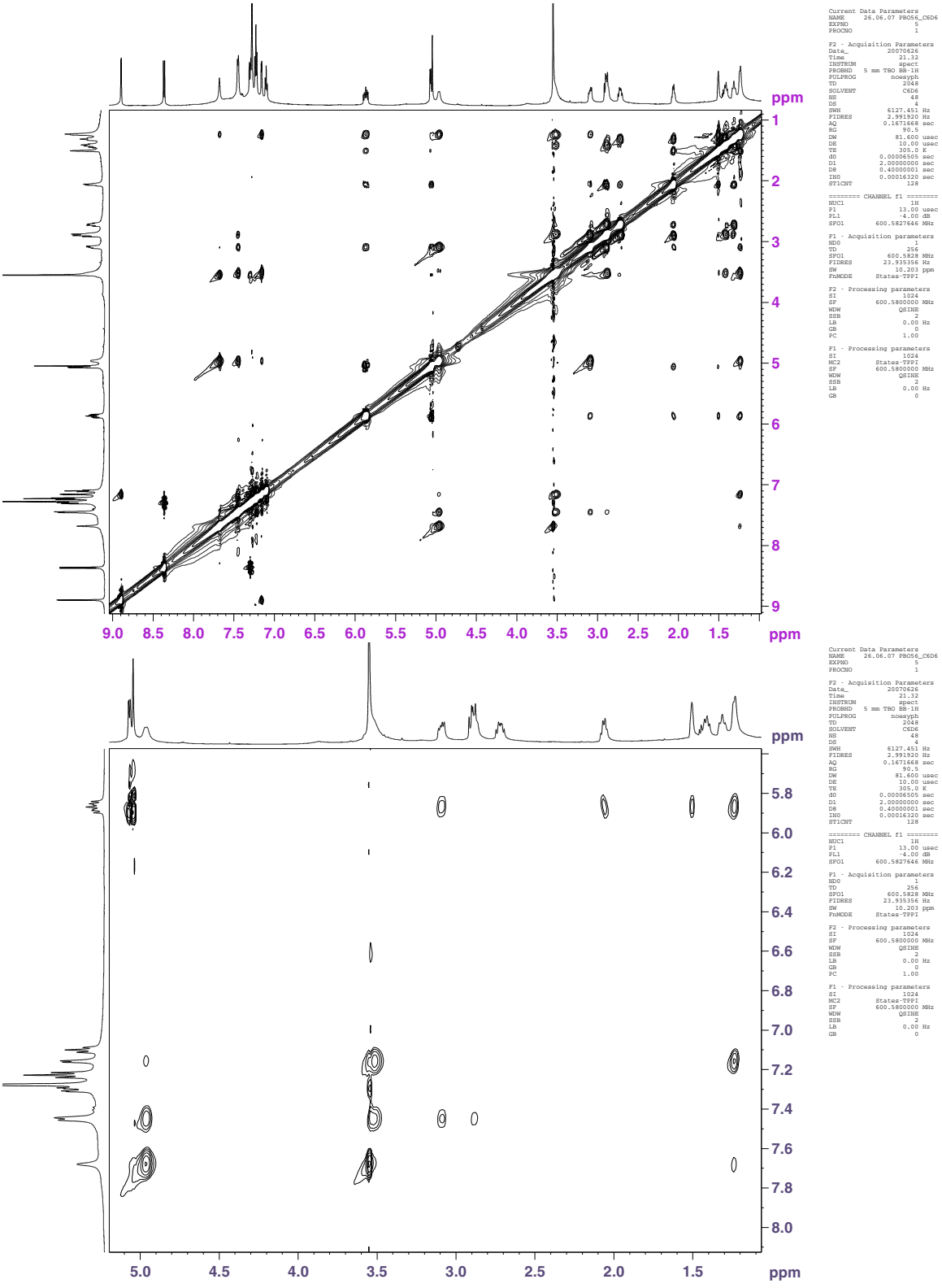
Crystallographic study on compound 7.

A monocrystal of **7** thiocyanate was obtained by slow evaporation of MeOH solution.

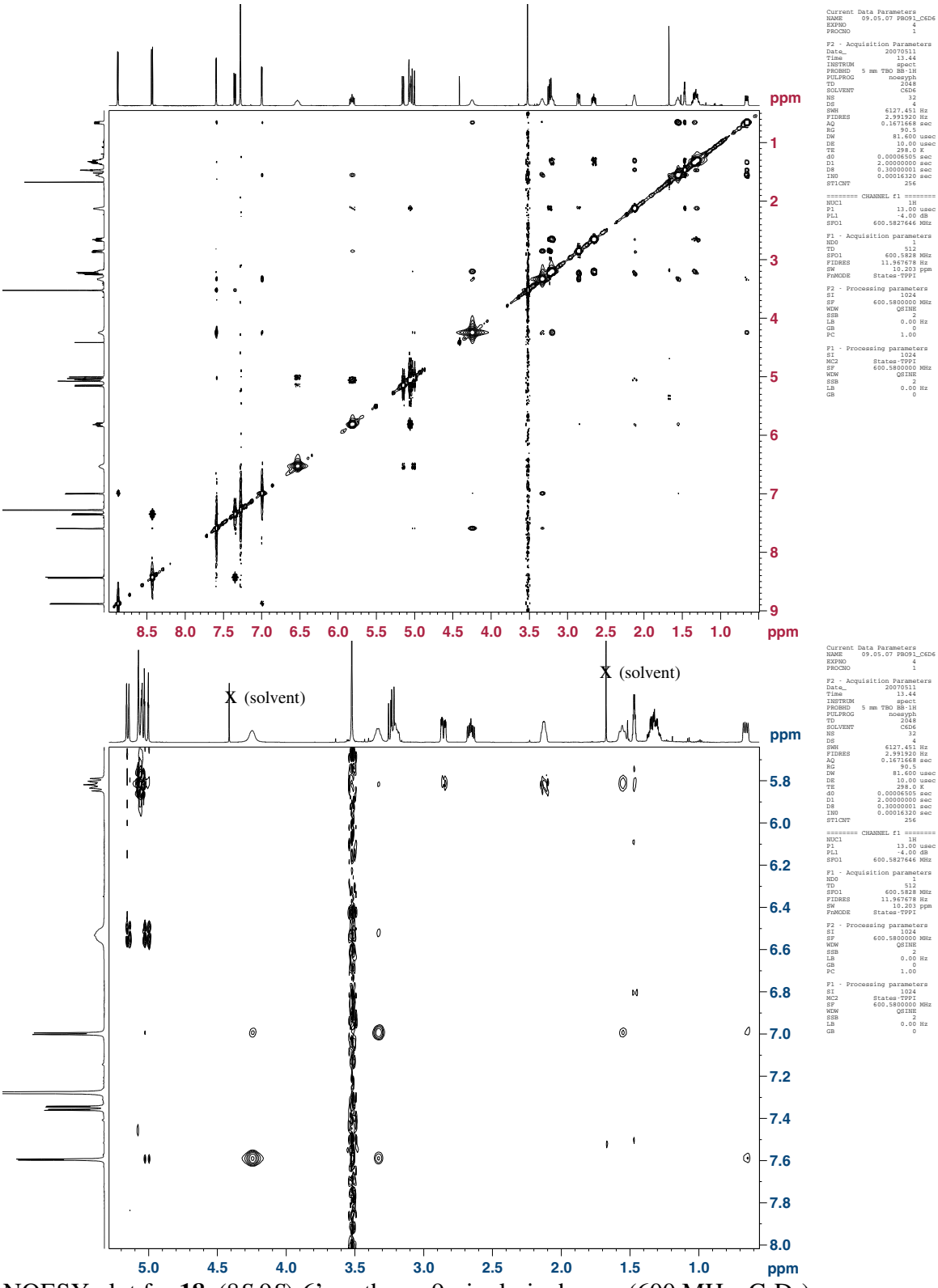
Table 1. Crystallographic experimental details for **7** thiocyanate salt.

Crystal data	
Chemical formula	$C_{27}H_{29}N_3OS$
M_r	443.59
Cell setting, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	299 (2)
a, b, c (Å)	9.4513 (7), 10.0331 (8), 24.638 (2)
V (Å ^{3})	2336.3 (3)
Z	4
D_x (Mg m^{-3})	1.261
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.16
Crystal form, colour	Block, colourless
Crystal size (mm)	0.50 × 0.40 × 0.25
Data collection	
Diffractometer	Kuma KM4CCD
No. of measured, independent and observed reflections	12653, 4125, 3299
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.030
θ_{max} (°)	25.0
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.050, 0.153, 1.05
H-atom treatment	Constrained to parent site
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.24, –0.39
Flack parameter	0.01 (13)

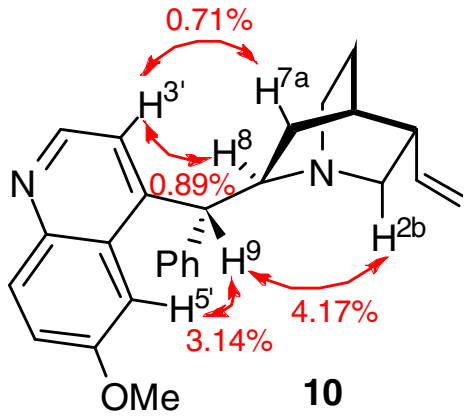
Computer programs: *CRYSALIS* (Oxford Diffraction, 2003); *SHELXS-97*; *SHELXL-97* (Sheldrick, 1997); *ORTEP3* (Farrugia, 1997).

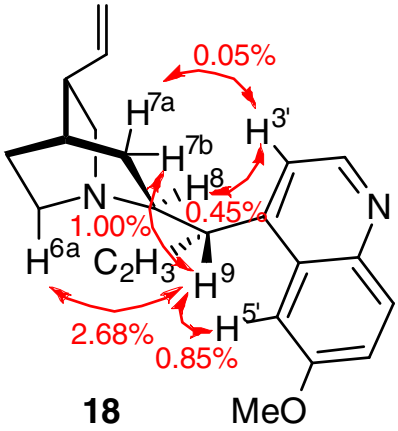


NOESY plot for **10,** 9*R*-Ph-QD, (8*R*,9*R*)-6'-methoxy-9-phenyl-cinchonan (600 MHz, C_6D_6)



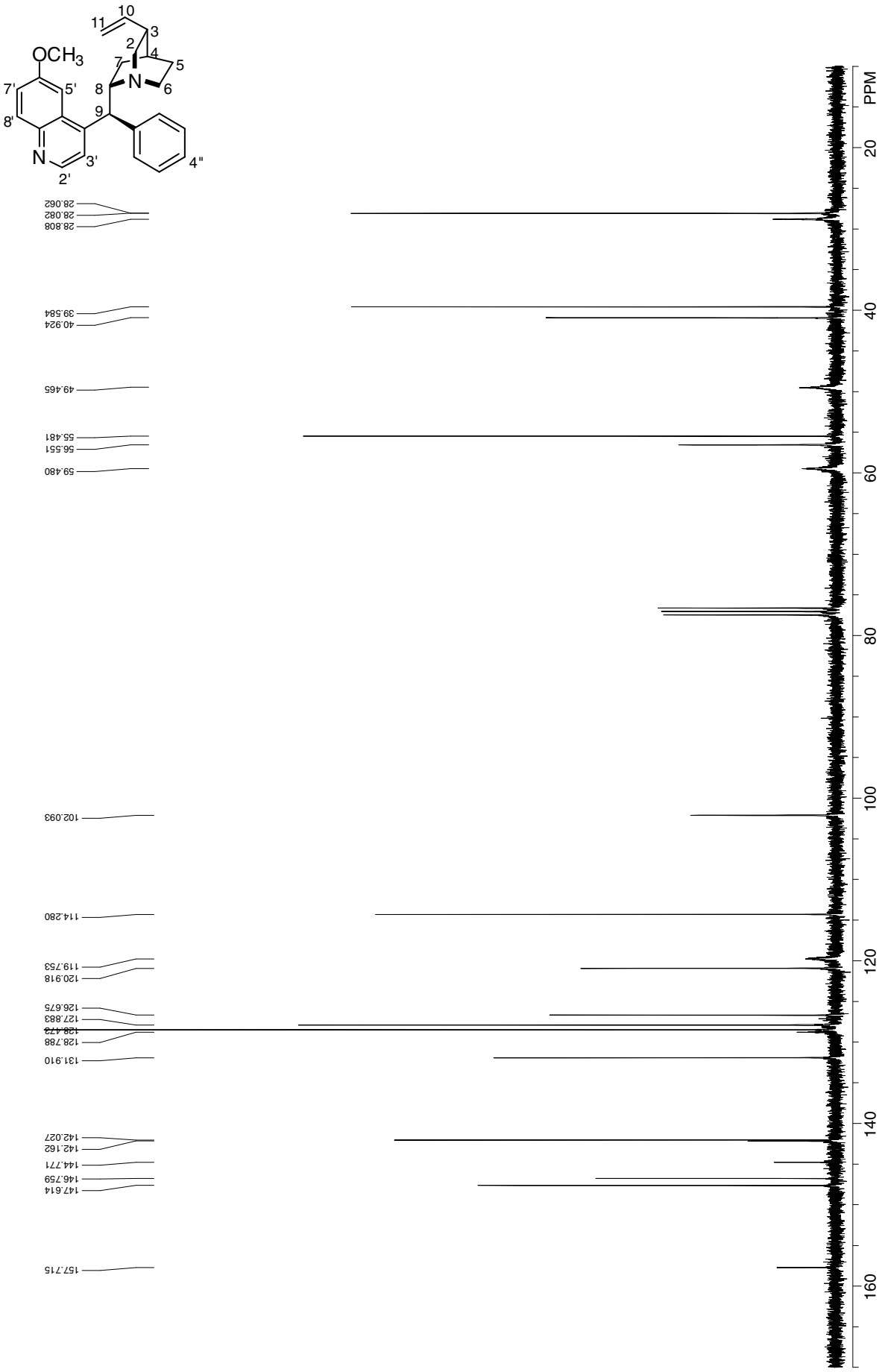
NOESY plot for **18,** (8*S*,9*S*)-6'-methoxy-9-vinyl-cinchonan (600 MHz, C_6D_6)



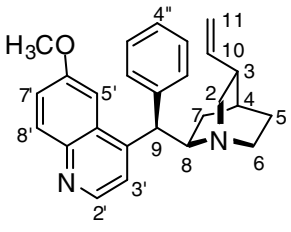


NOE correlations extracted from 2D-NOESY experiments

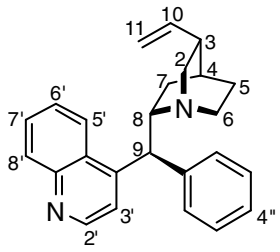
^{13}C NMR (75 MHz, $CDCl_3$): **7**, (8*S*,9*S*)-6'-methoxy-9-phenyl-cinchonan

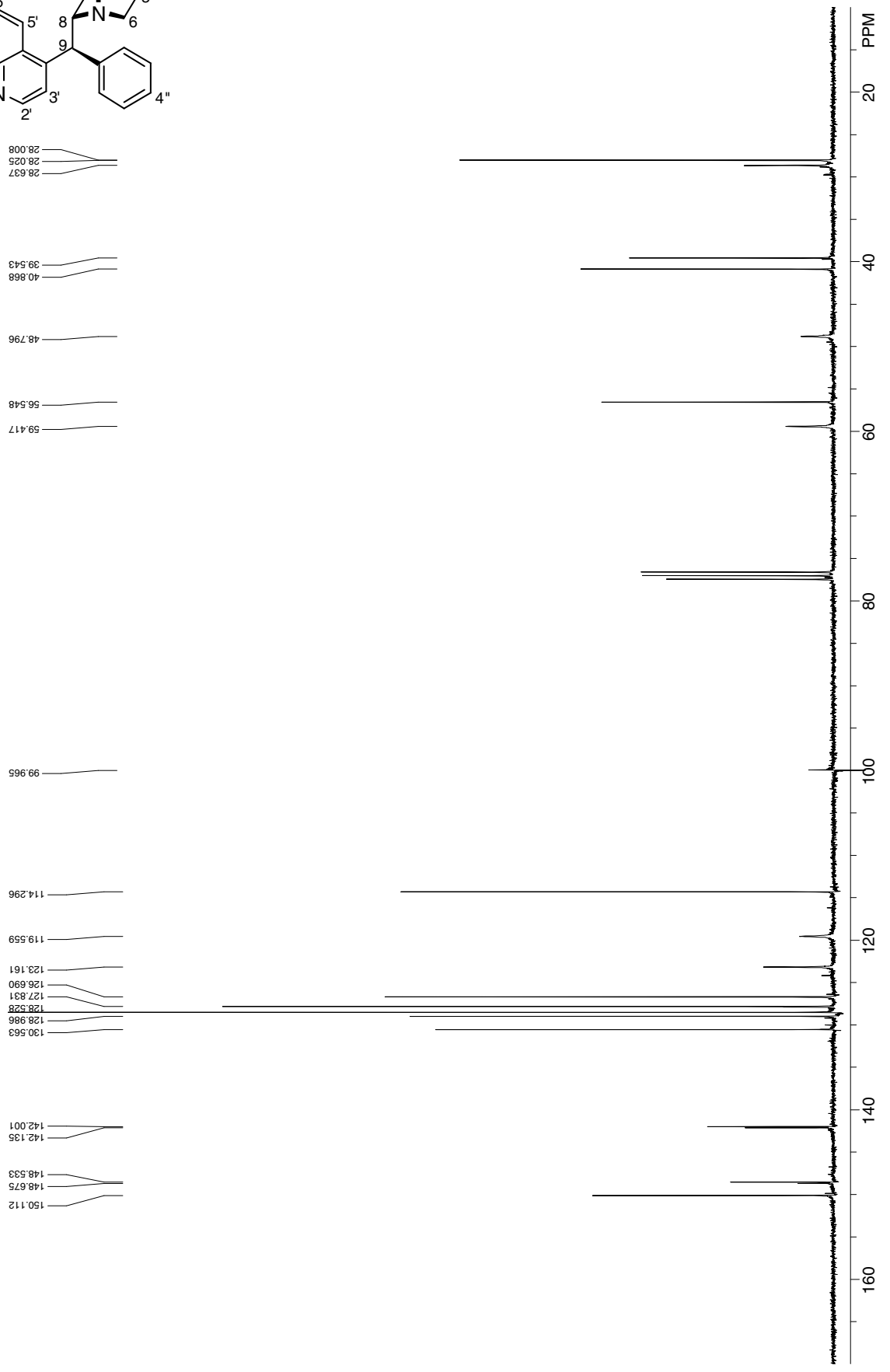


^{13}C NMR (75 MHz, $CDCl_3$): **10**, (8*R*,9*R*)-6'-methoxy-9-phenyl-cinchonan

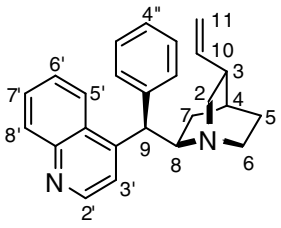


^{13}C NMR (75 MHz, $CDCl_3$): **11**, (8*S*,9*S*)-9-phenyl-cinchonan

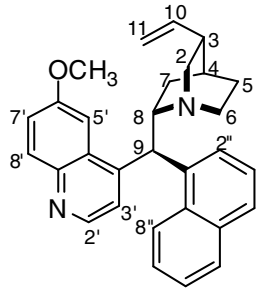


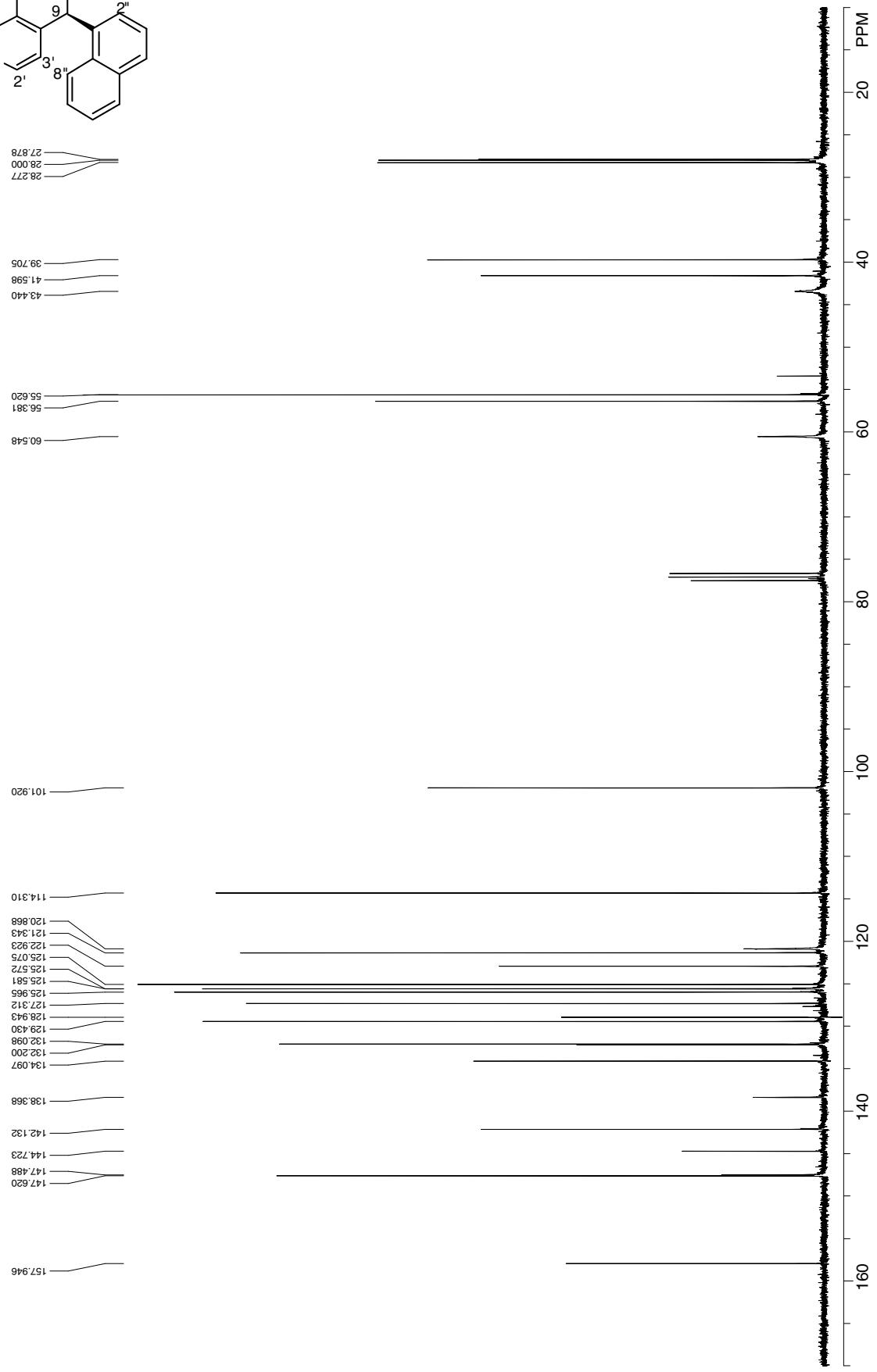


^{13}C NMR (75 MHz, $CDCl_3$): **12**, (8*R*,9*R*)-9-phenyl-cinchonan

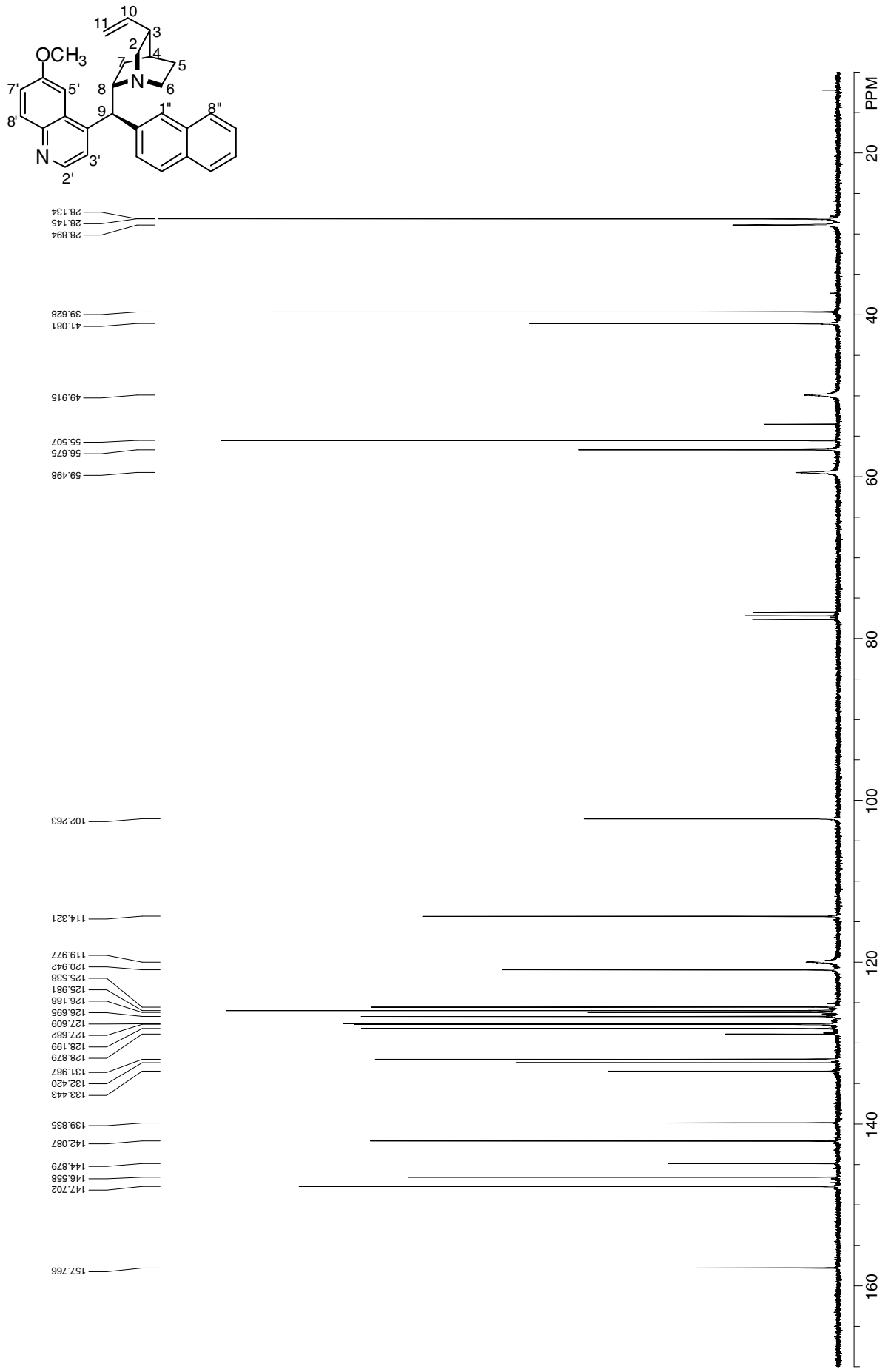


^{13}C NMR (75 MHz, $CDCl_3$): **14**, (8*S*,9*S*)-6'-methoxy-9-naphtalen-1-yl-cinchonan

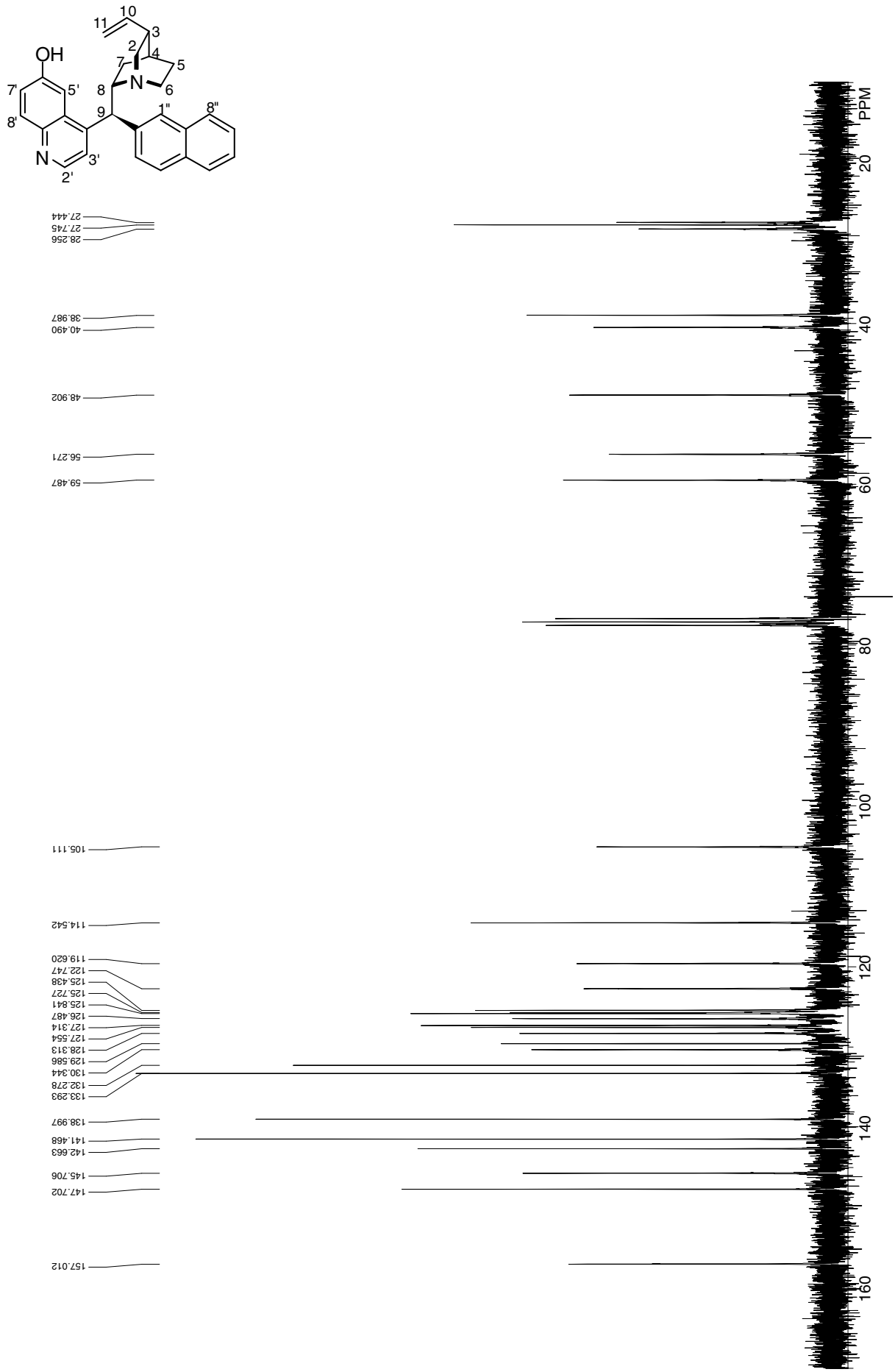




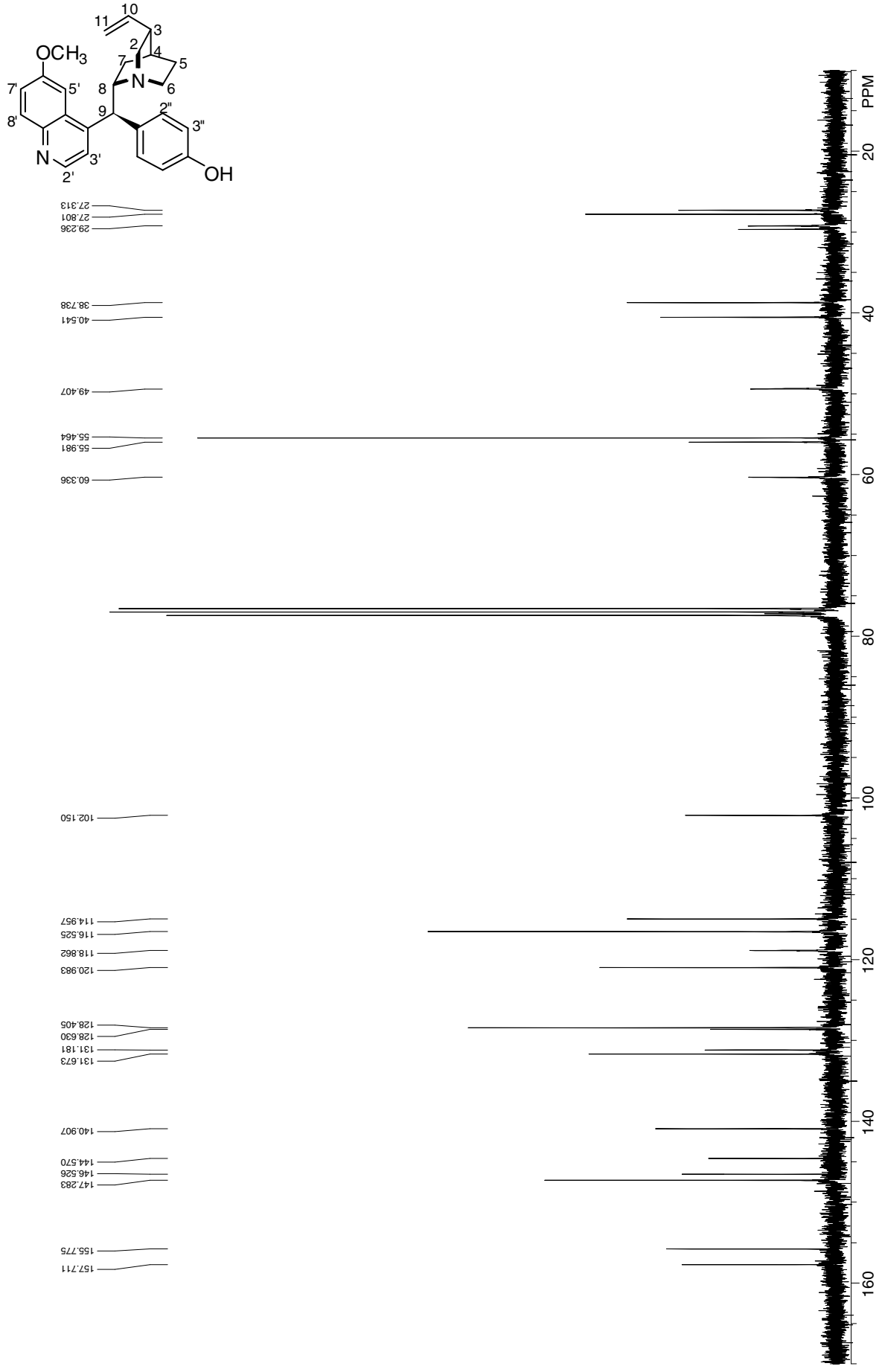
^{13}C NMR (75 MHz, $CDCl_3$): **13**, (8*S*,9*S*)-6'-methoxy-9-naphtalen-2-yl-cinchonan



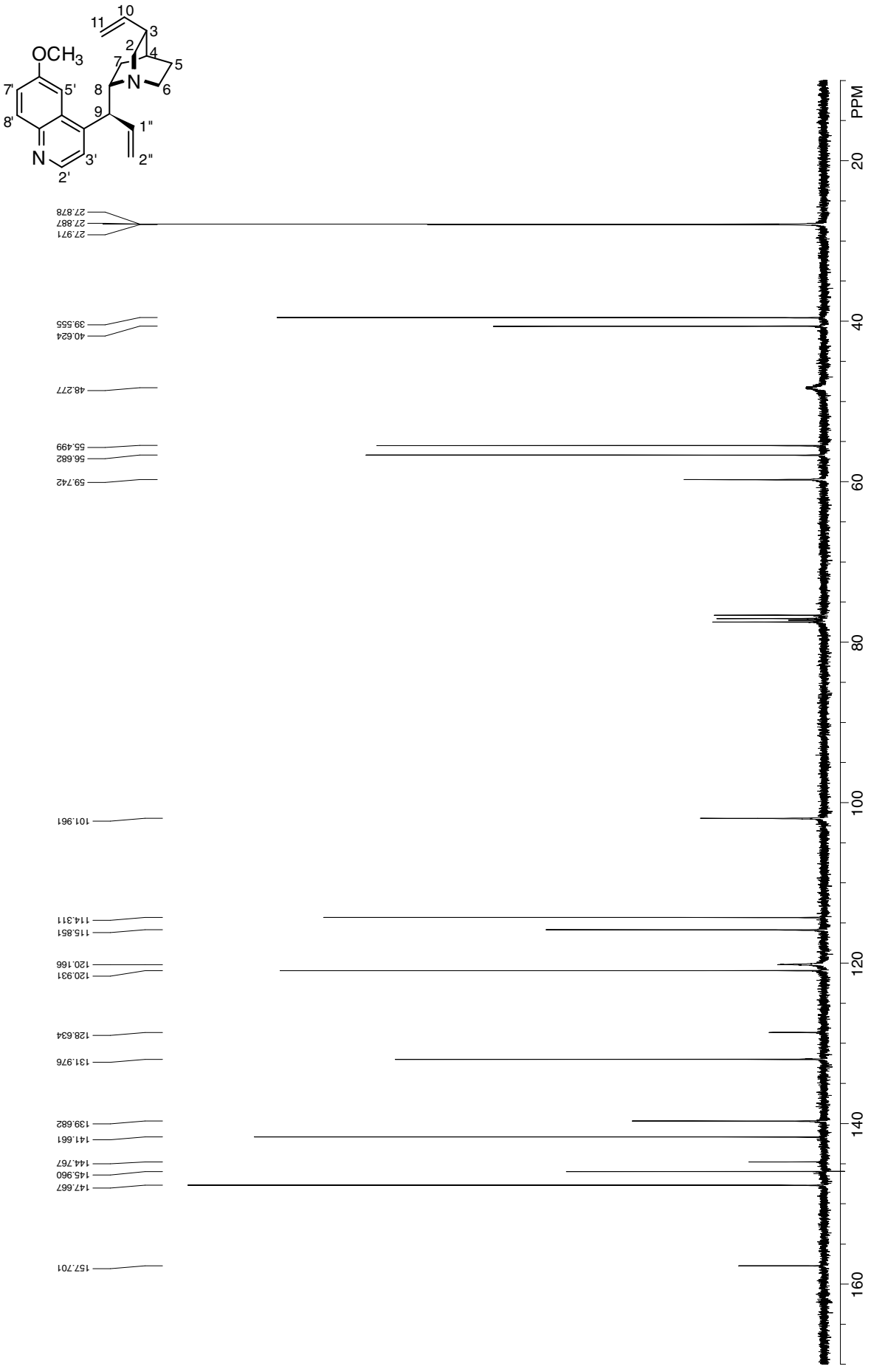
^{13}C NMR (75 MHz, $CDCl_3$): **15**, (8*S*,9*S*)-6'-hydroxy-9-naphtalen-2-yl-cinchonan



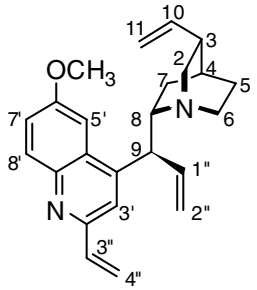
^{13}C NMR (75 MHz, $CDCl_3$): **16**, (8*S*,9*S*)-9-(4-hydroxyphenyl)-6'-methoxy-cinchonan

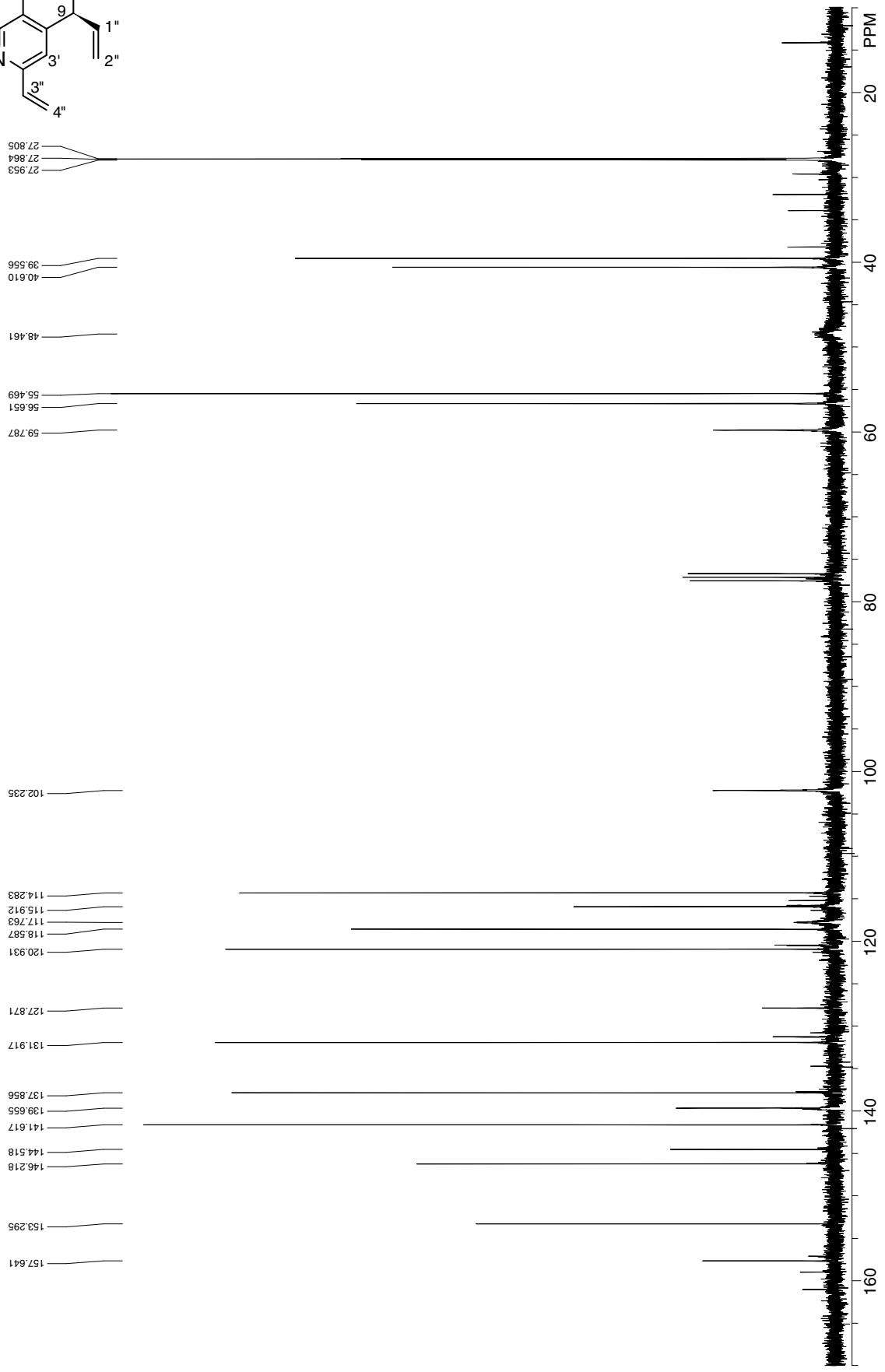


^{13}C NMR (75 MHz, $CDCl_3$): **18**, (8*S*,9*S*)-6'-methoxy-9-vinyl-cinchonan

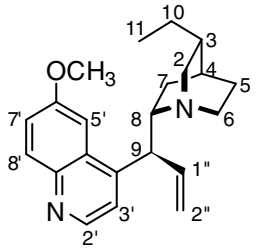


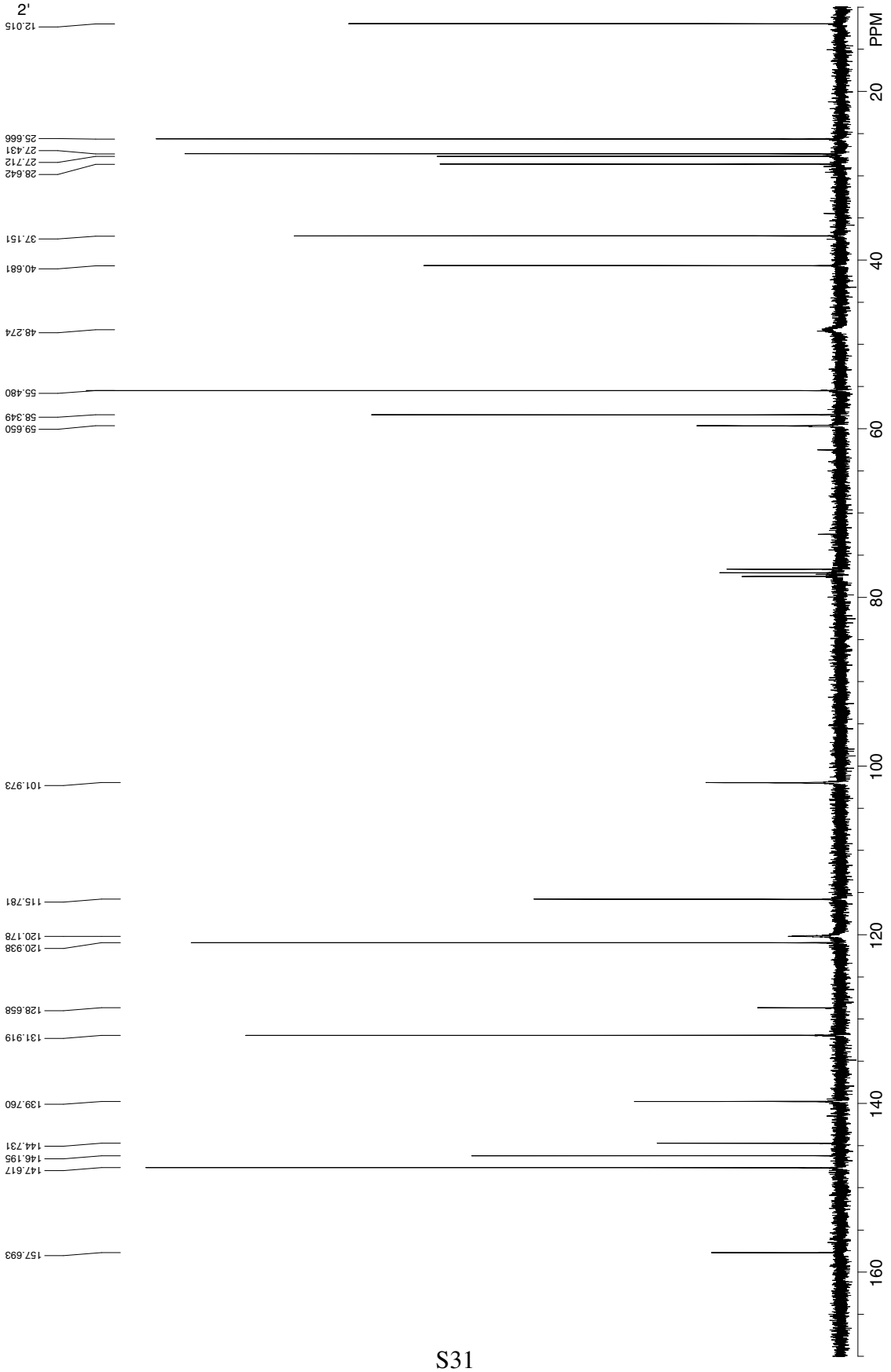
^{13}C NMR (75 MHz, $CDCl_3$): **19**, (8*S*,9*S*)-6'-methoxy-2',9-diviyl-cinchonan



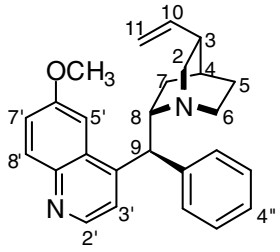


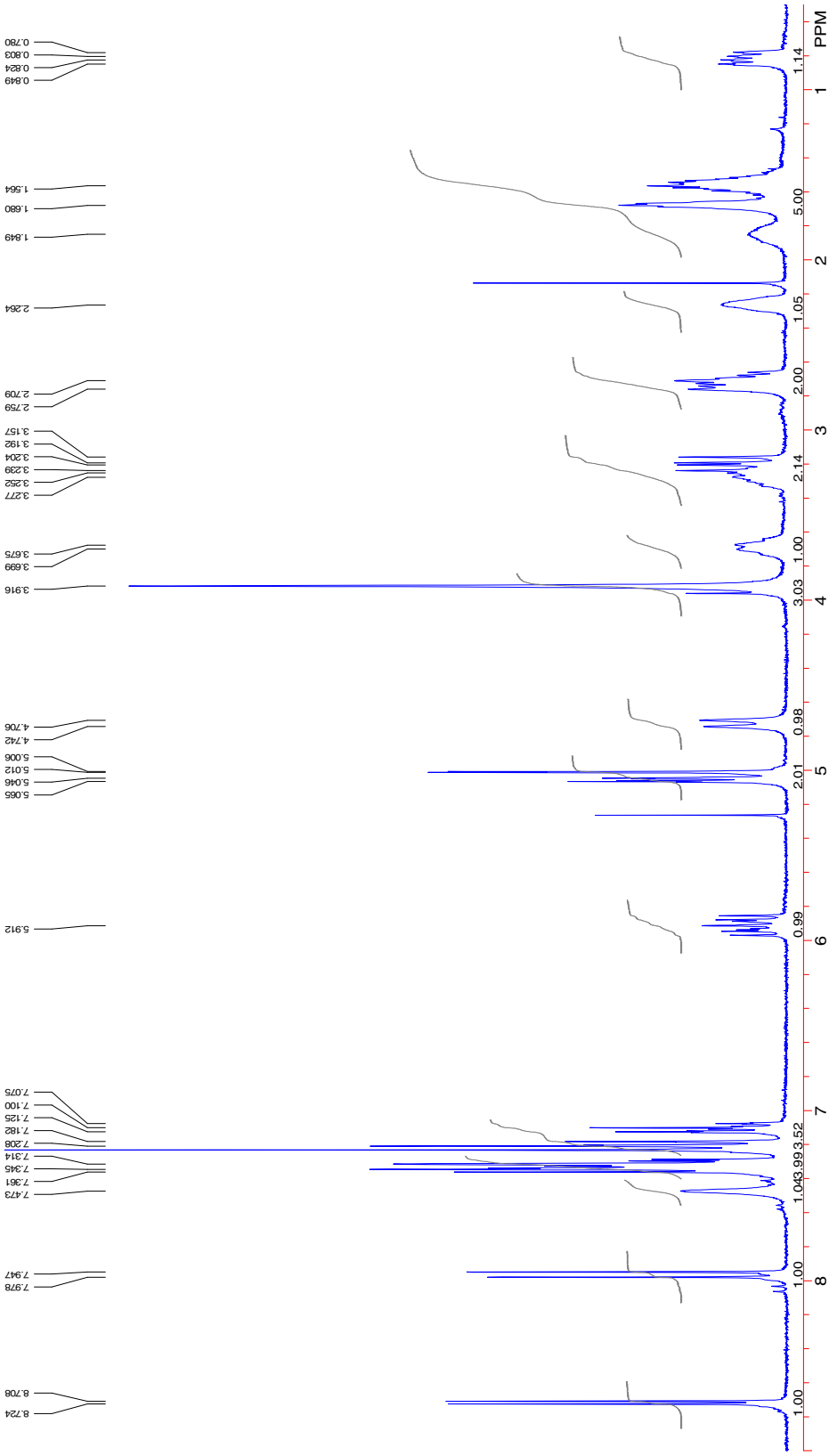
^{13}C NMR (75 MHz, $CDCl_3$): **20**, (8*S*,9*S*)-10,11-dihydro-6'-methoxy-9-vinyl-cinchonan



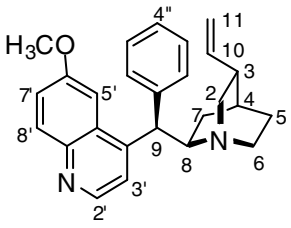


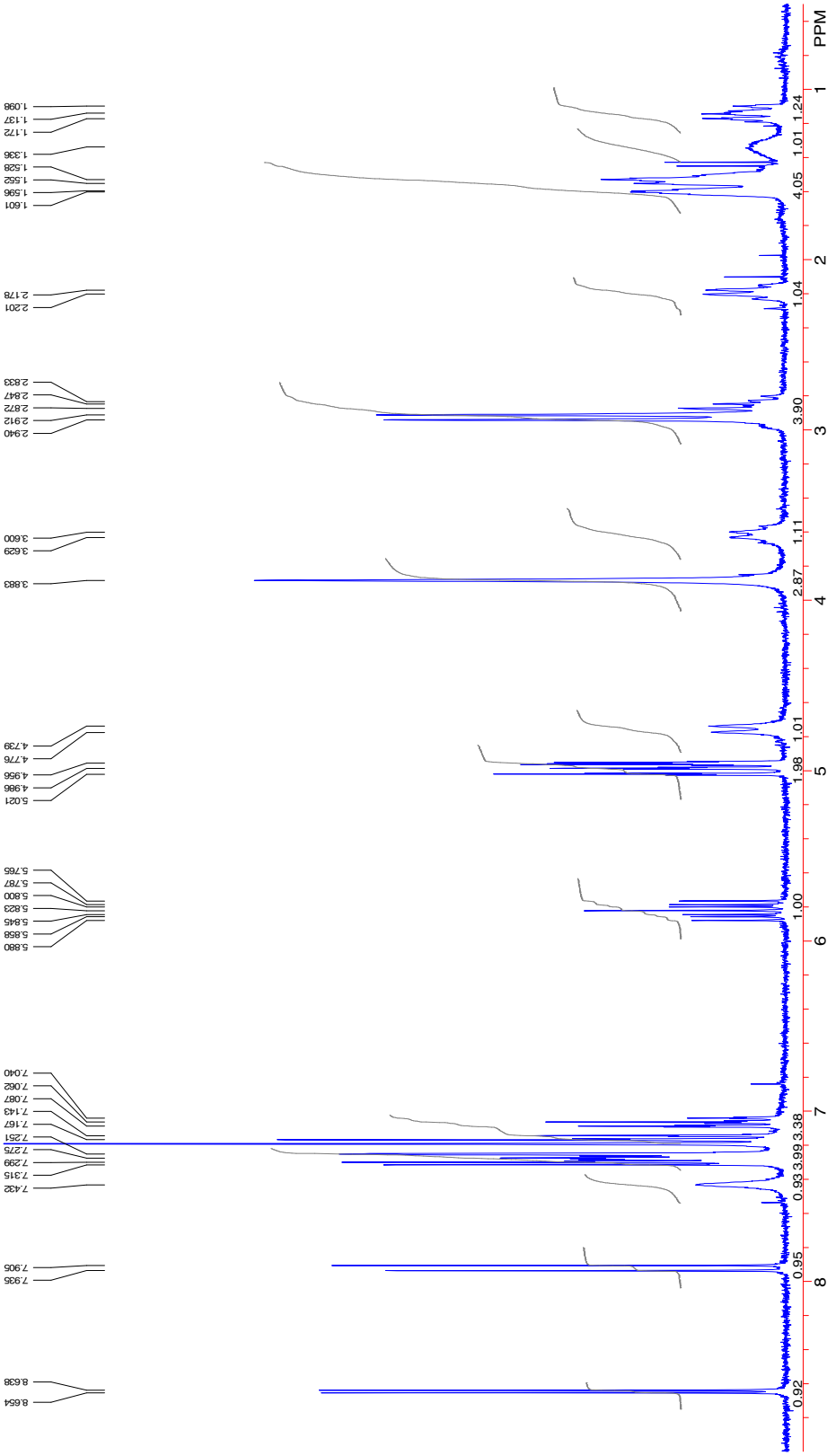
^{13}C NMR (75 MHz, $CDCl_3$): **7**, (8*S*,9*S*)-6'-methoxy-9-phenyl-cinchonan



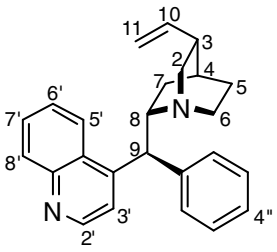


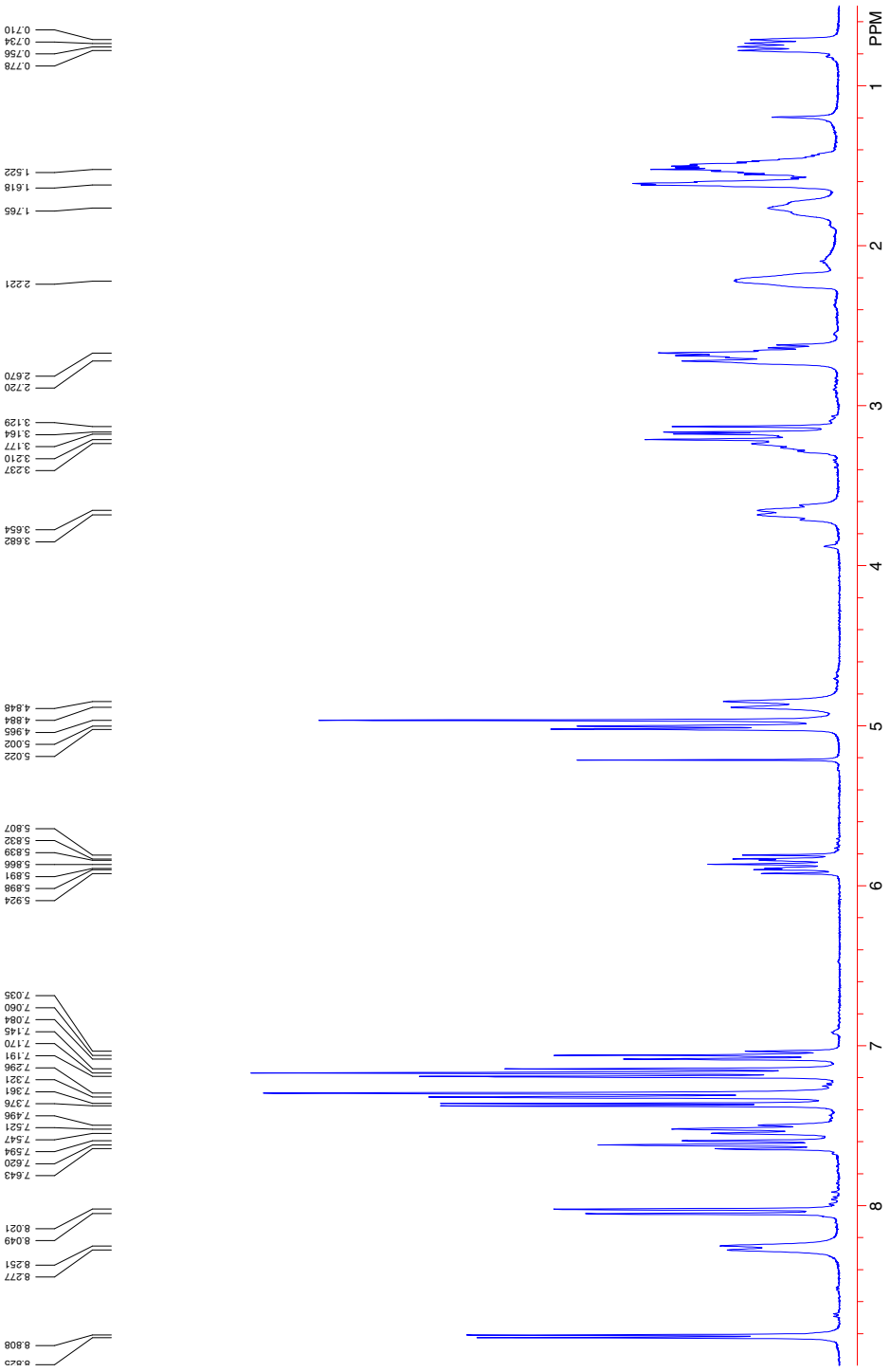
^{1}H NMR (300 MHz, $CDCl_3$): **10**, (8*R*,9*R*)-6’-methoxy-9-phenyl-cinchonan



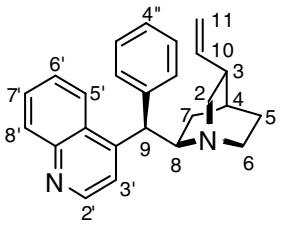


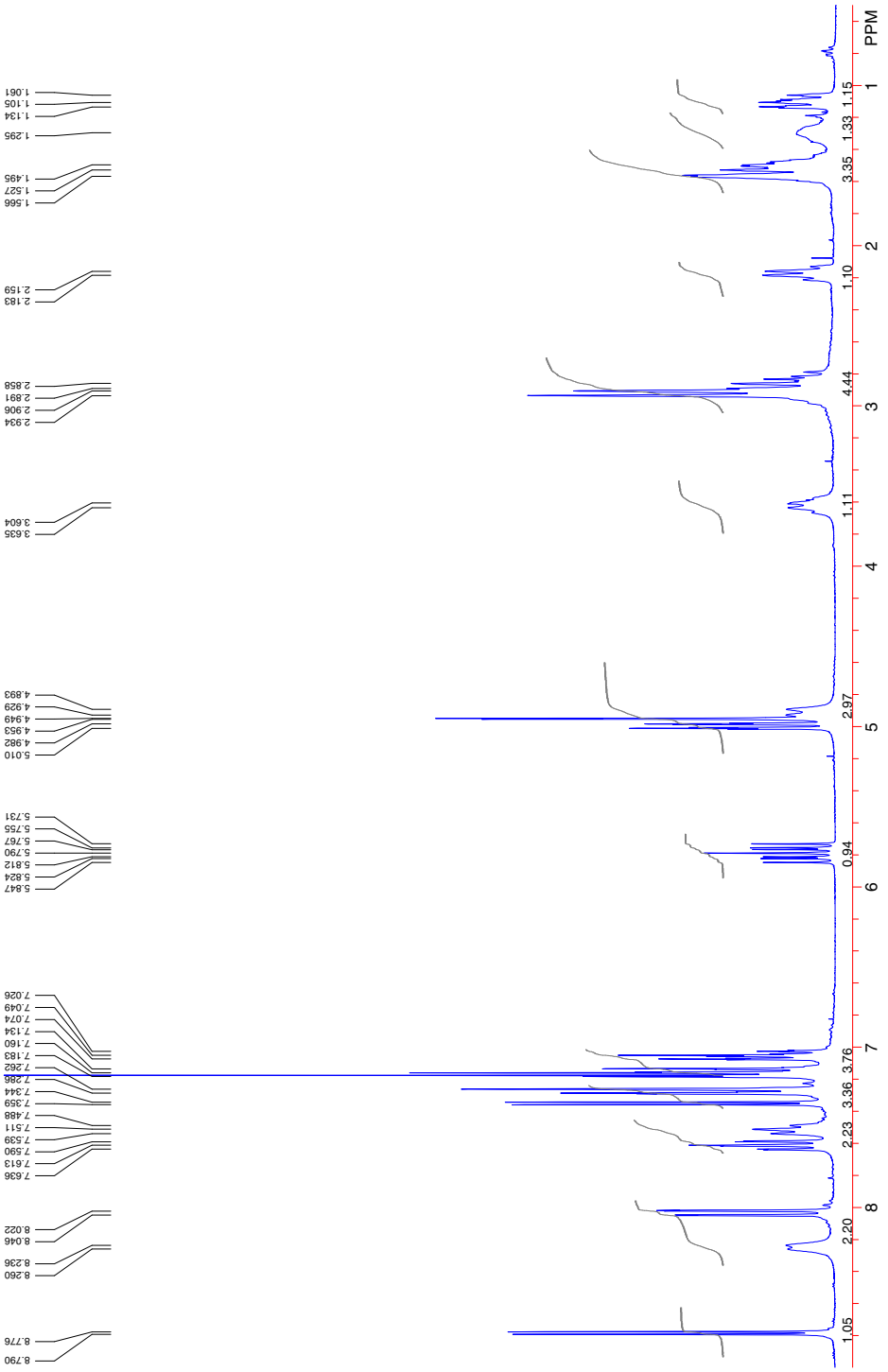
^{1}H NMR (300 MHz, $CDCl_3$): **11**, (8*S*,9*S*)-9-phenyl-cinchonan



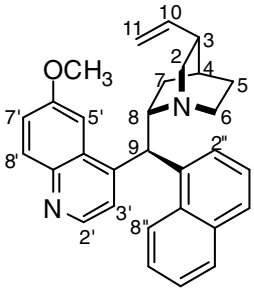


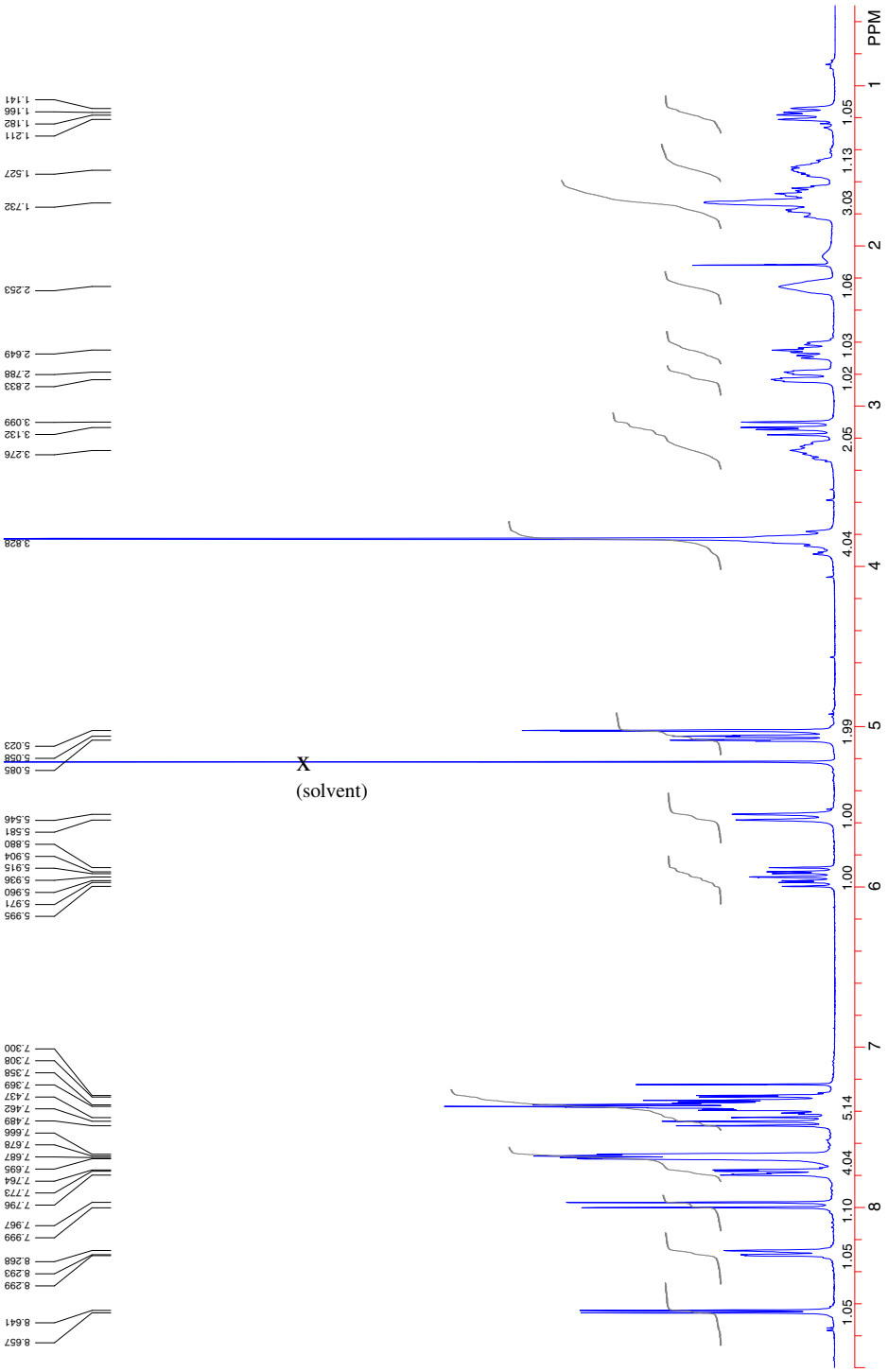
^{1}H NMR (300 MHz, $CDCl_3$): **12**, (8*R*,9*R*)-9-phenyl-cinchonan



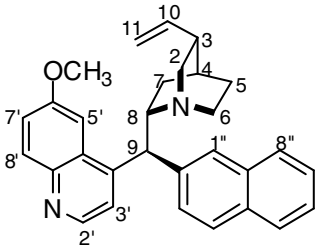


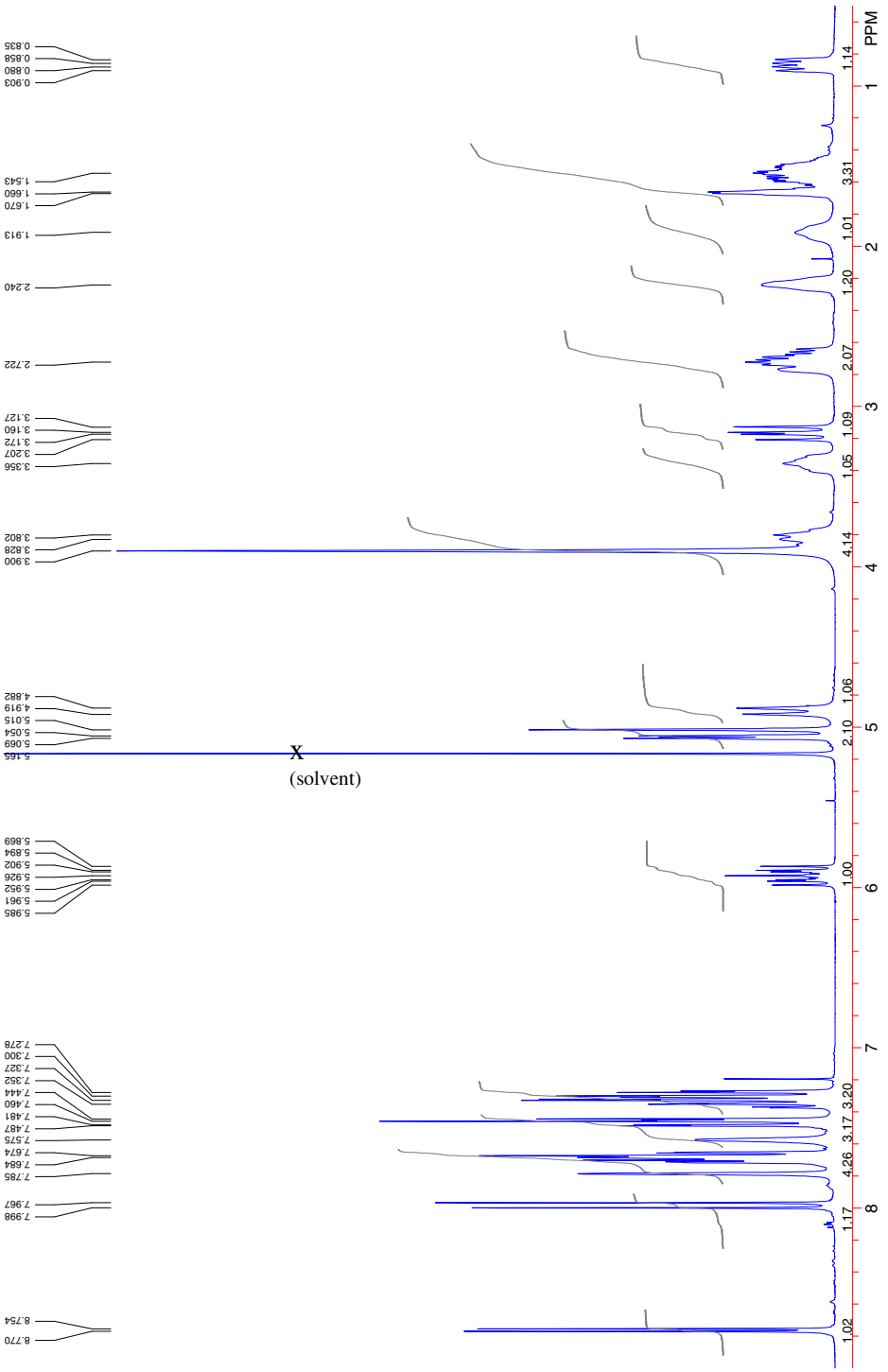
^{1}H NMR (300 MHz, $CDCl_3$): **14**, (8*S*,9*S*)-6'-methoxy-9-naphtalen-1-yl-cinchonan



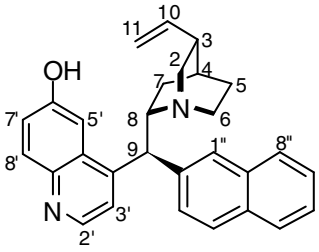


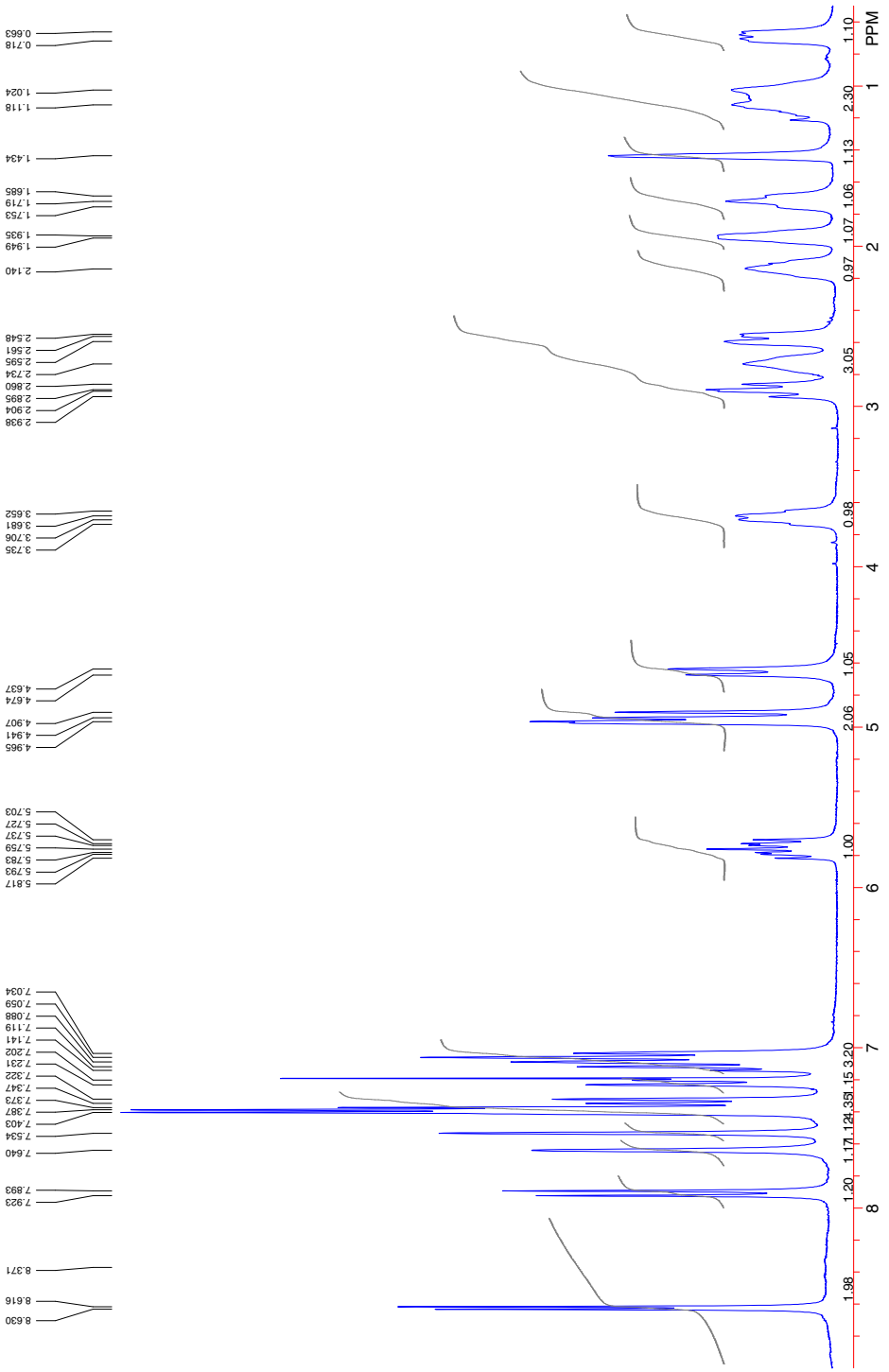
^{1}H NMR (300 MHz, $CDCl_3$): **13**, (8*S*,9*S*)-6'-methoxy-9-naphtalen-2-yl-cinchonan



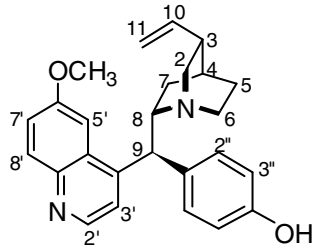


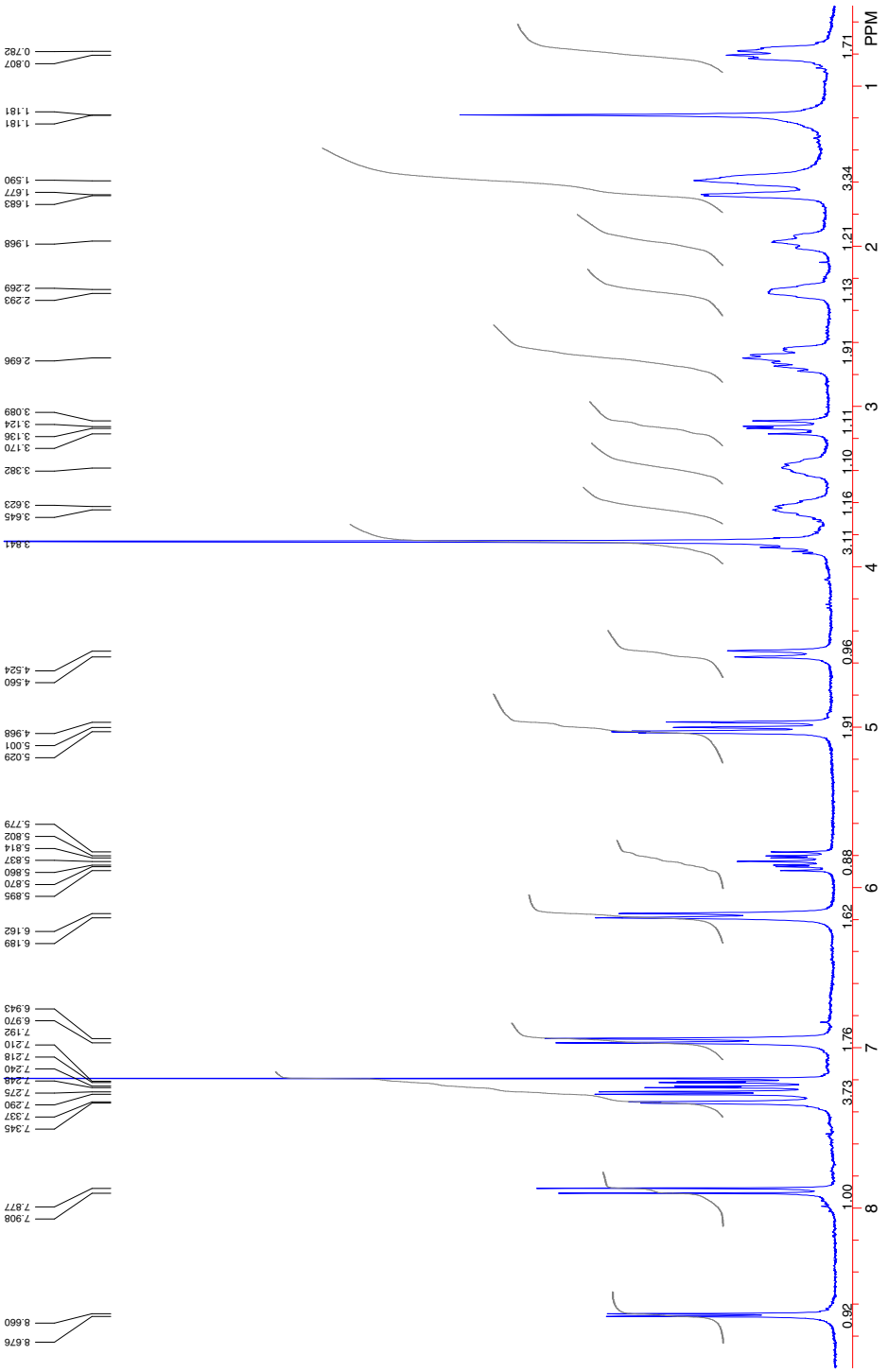
^{1}H NMR (300 MHz, $CDCl_3$): **15**, (8*S*,9*S*)-6'-hydroxy-9-naphtalen-2-yl-cinchonan



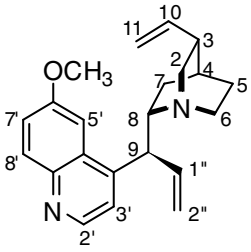


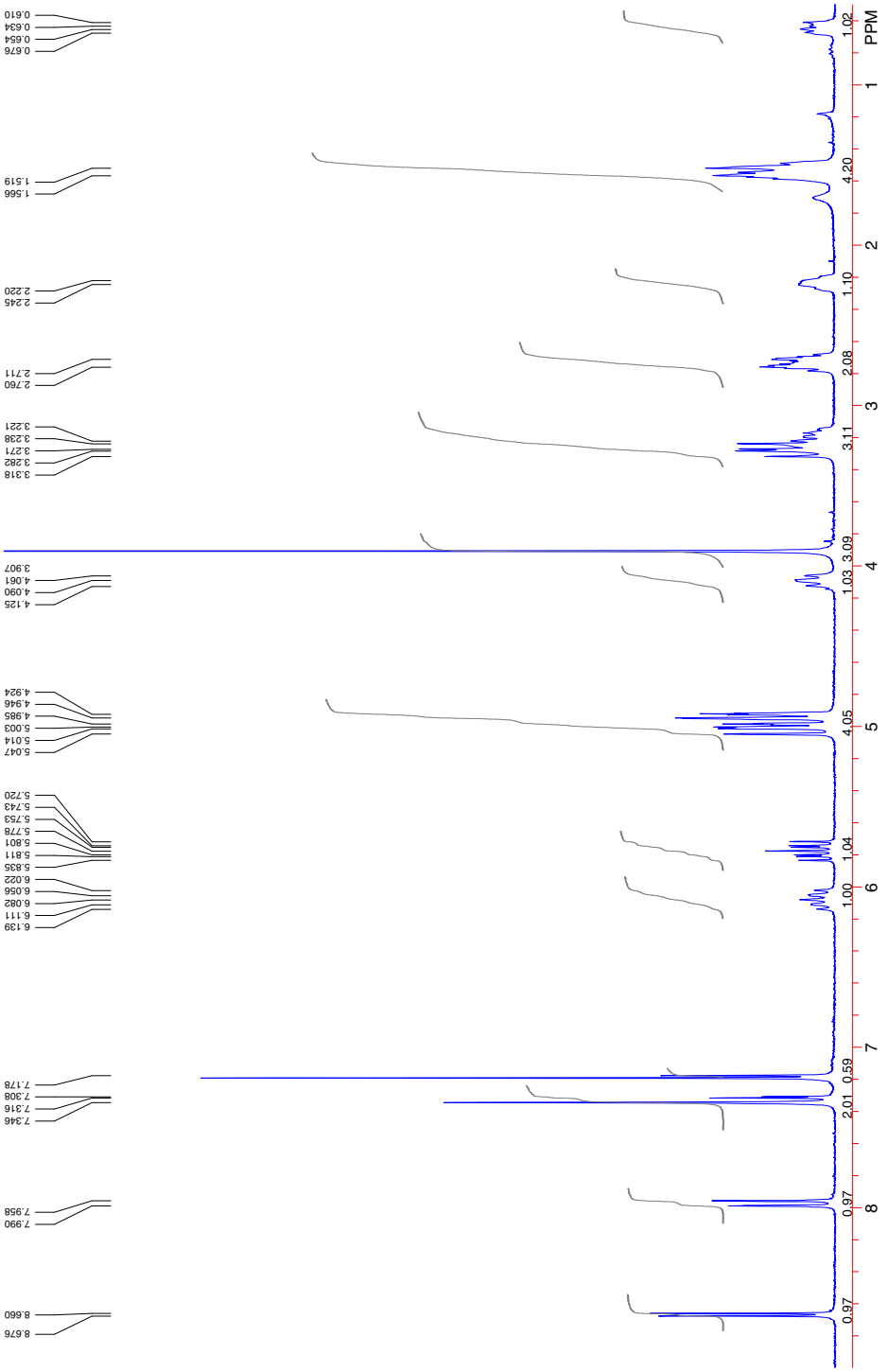
^{1}H NMR (300 MHz, $CDCl_3$): **16**, (8*S*,9*S*)-9-(4-hydroxyphenyl)-6'-methoxy-cinchonan



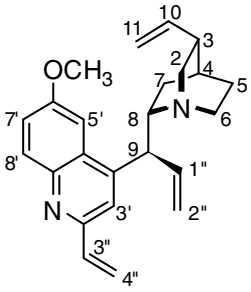


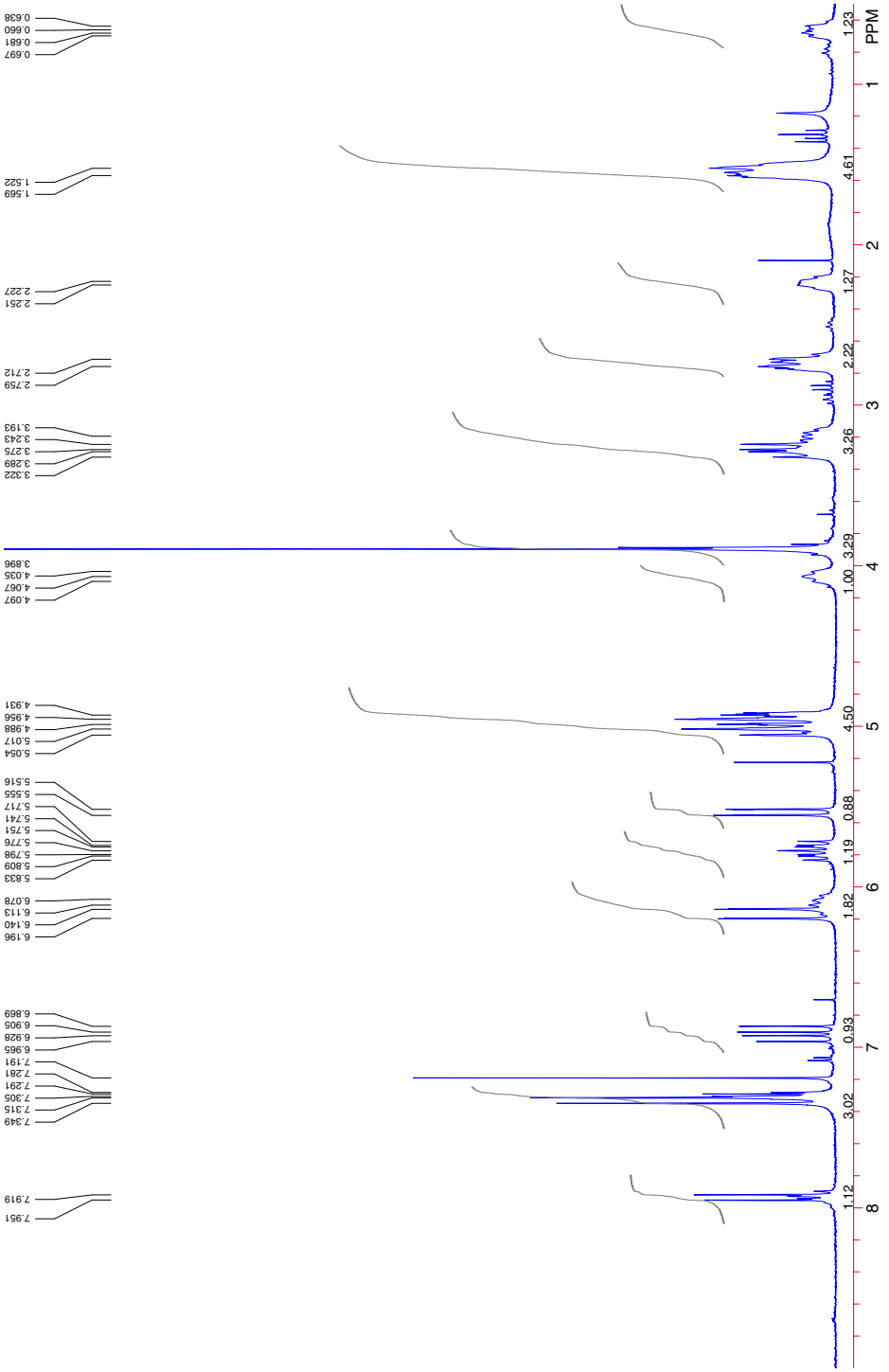
^{1}H NMR (300 MHz, $CDCl_3$): **18**, (8*S*,9*S*)-6'-methoxy-9-vinyl-cinchonan





^{1}H NMR (300 MHz, $CDCl_3$): **19**, (8*S*,9*S*)-6'-methoxy-2',9-diviyl-cinchonan





^{1}H NMR (300 MHz, $CDCl_3$): **20**, (8*S*,9*S*)-10,11-dihydro-6'-methoxy-9-vinyl-cinchonan