Electronic Supplementary Material (ESI) for ChemComm.

Gram-scale Route to Phlegmarine Alkaloids: Rapid Total Synthesis of (-)-Cermizine B

Ben Bradshaw, Carlos Luque Corredera, and Josep Bonjoch

Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB,
Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

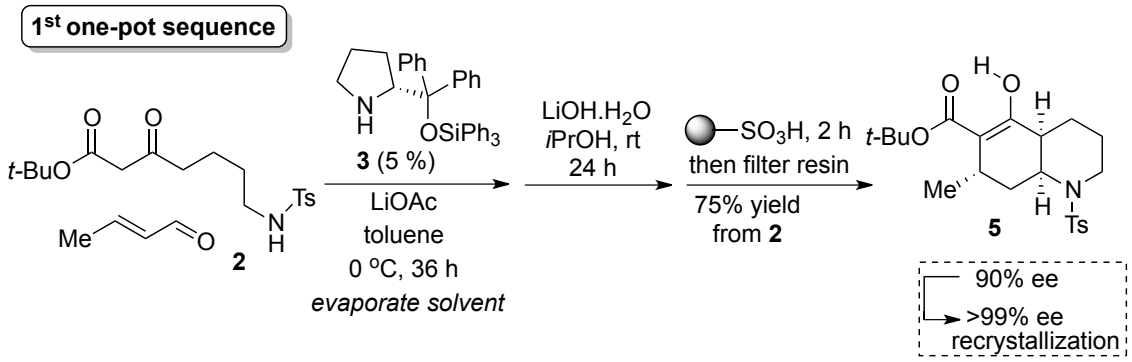
josep.bonjoch@ub.edu
benbradshaw@ub.edu

Contents

Experimental Section

General: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical thin-layer chromatography was performed on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located with 1% aqueous $KMnO_4$ or 2% ethanolic anysaldehyde. Chromatography refers to flash chromatography and was carried out on SiO_2 (SDS silica gel 60 ACC, 35-75 μm, 230-240 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous $MgSO_4$. Evaporation of solvent was accomplished with a rotatory evaporator. NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 300 or Varian VNMRS 400. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. HPLC analyses for the determination of enantiomeric excess were carried out using a DAICEL CHIRALPAK IC column (250×4.6 mm I.D., 5 μm; Chiral Technologies Europe) on a Waters model 2487 Dual Absorbance Detector and set at the wavelength of 254 nm. The chromatog. resoln. of compound **5** was achieved using hexane/*i*PrOH 80: 20 as the mobile phase in an isocratic run.

(4a*S*,7*S*,8a*S*)-*tert*-Butyl 7-Methyl-5-oxo-1-tosyldecahydroquinoline-6-carboxylate (5)



To a solution of keto ester **2** (500 mg, 1.35 mmol) in toluene (12.5 mL) at 0 ºC was added crotonaldehyde (104 mg, 1.49 mmol), triphenylsilyl ether **3**[1] (35 mg, 0.07 mmol), LiOAc (45 mg, 0.7 mmol) and the resulting mixture was stirred for 36 h at 0 ºC. Excess crotonaldehyde was removed on a rotary evaporator before addition[2] of *i*PrOH (12.5 mL), LiOH·H_2O (57 mg, 1.35 mmol) and H_2O (0.24 mL, 13.5 mmol), and the resulting solution stirred for 24 h. To this flask was added the polymer support (*PS*) of *p*-toluenesulfonic acid (2.1 g) and the mixture was stirred for 2 h. The solid support was filtered, and the filtrate was concentrated *in vacuo*, and the crude was purified by chromatography (0→5→10→25% EtOAc/hexane) to give the enantioenriched keto ester **5**[3] (427 mg, 75%, 90% ee by HPLC) as a white solid upon standing.

Recovery of the organocatalyst: The solid support was stirred for 2 h with a mixture of 10% triethylamine in methanol (20 mL), filtered and the solvent removed *in vacuo*. Purification by column chromatography (0→1→2.5→5% MeOH/CH_2Cl_2) gave the recovered catalyst (33 mg, 93%).

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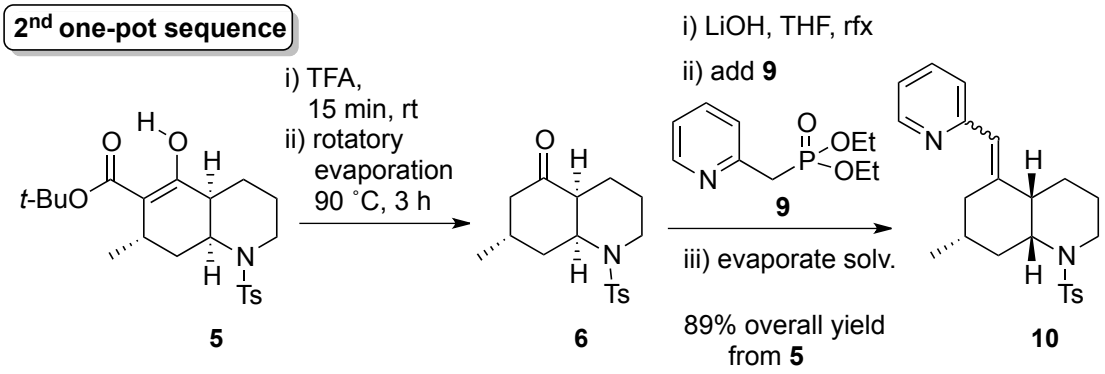
[1] Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci* **2011**, *2*, 353-357. If the catalyst was used without recrystallization the enantiomeric excess of **5** decreased to 85% ee.

[2] At this time compound **4** can be checked by ^{1}H NMR and shows to be an epimeric mixture at the β-keto ester methine carbon: ^{1}H NMR (300 MHz) 0.96 and 1.01 (2d, J = 6.6 Hz, CH_3), 1.44 and 1.45 (2s, $C(CH_3)_3$), 2.36 and 2.43 (2s, ArMe), 2.81 (br quint, J = 6.6 Hz, CHMe), 2.92 (q, J = 6.6 Hz, CH_2N), 3.35 (dd, J = 6.4, 2.8 Hz, CH), 4.51 and 4.53 (2t, J = 6.4 Hz,NHTs), 9.70 and 9.73 (2t, J = 1.5 Hz, CHO).

[3] For NMR of **5** as well as obtention of an enantiopure sample, see: Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett* , **2013**, 15, 326-329.

(4a*S*,7*R*,8a*R*)-7-Methyl-1-(4-methylsulfonyl)-5-(pyridin-2-ylmethylene) decahydroquinoline (10)



Keto ester **5** (582 mg, 1.4 mmol) was dissolved in TFA (1.4 mL) and stirred under nitrogen for 15 min at room temperature. The solvent was evaporated under reduced pressure, and the last traces of TFA were removed by azeotroping with toluene (3 × 15 mL). The reaction flask was maintained on the rotatory evaporator under vacuum at 80 ºC for 3 h to give the crude decahydroquinoline **6** as a brown oil. The crude decahydroquinoline **6** was dissolved in THF (4.8 mL) and LiOH (67 mg, 2.8 mmol) was added and the resulting mixture was refluxed for 24 h.[4] After cooling to room temperature, phosphonate **9** (963 mg, 4.2 mmol) was added in one portion followed by further portions of LiOH (168 mg, 7.0 mmol), and the solvent was evaporated. The mixture was stirred without solvent at room temperature for 3 days. The crude was dissolved in Et_2O (5 mL) and was acidified to pH = 1 with 2 N HCl (15 mL). The layers were separated and the acidic phase was carefully basified with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL), dried and concentrated *in vacuo*. The crude material was purified by chromatography (0→2.5→5→10% EtOAc/hexane) to give the pure coupled product **10** (485 mg, 89%) as a white solid and as a 5:1 mixture of *E*/*Z* isomers.[5]

***E* isomer:** $[\alpha]_D$ -61.9 (c 1, $CHCl_3$); R_f 0.49 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.94 (d, *J* = 6.0 Hz, CH_3), 1.42 (qt, 12.8, 4.4 Hz, H-3ax), 1.48-1.58 (m, H-4, H-7, 2H-8), 1.60-1.70 (masked, H-3), 1.65 (td, *J* = 13, 1.6 Hz, H-6ax), 1.81 (qd, *J* = 13.2, 4.0 Hz, H-4ax), 2.35 (dt, *J* = 12.8, 4.6 Hz, H-4a), 2.44 (s, $ArCH_3$), 3.01 (td, *J* =

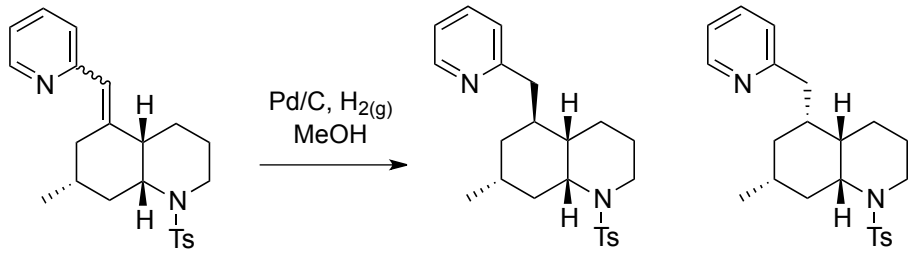
[4] At this time decahydroquinoline **8** can be isolated. For its NMR data, see: Bradshaw, B.; Luque-Corredera, C.; Saborit, G.; Cativiela, C.; Dorel, R.; Bo, C.; Bonjoch, J. *Chem. Eur. J.* **2013**, *19*, 13881-13892.

[5] Pure samples of (*E*)-**10** and (*Z*)-**10** were obtained if the crude material was purified by chromatography (0→2.5→5→10% EtOAc/hexane). Firstly eluted was the minor *Z* isomer, followed by the major *E* isomer.

13.2, 2.8 Hz, H-2ax), 3.22 (dd, *J* = 13.2, 2.0 Hz, H-6eq), 3.76 (dm, *J* = 13.2 Hz, H-2eq), 4.14 (dt, *J* = 12.0, 4.8 Hz, H-8a), 6.30 (d, *J* = 1.6 Hz, =CH), 7.09 (dd, *J* = 8.0, 4.4 Hz, H-5 Py), 7.13 (d, *J* = 8 Hz, H-3 Py), 7.30 and 7.74 (2d, *J* = 8 Hz, 2 H each, Ts), 7.61 (td, *J* = 8.0, 2 Hz, H-4 Py), 8.57 (d, *J* = 4.4 Hz, H-6 Py); ^{13}C NMR (100 MHz, HSQC) 21.5 (CH_3Ar), 22.1 (CH_3), 24.8 (C-4) , 25.4 (C-3), 31.9 (C-8), 32.7 (C-6), 32.7 (C-7), 40.1 (C-2), 46.2(C-4a), 54.9 (C-8a), 121.0 (C-5 Py), 124.2 (C-3 Py), 124.2 (=CH), 126.9 (*o*-Ts), 129.6 (*m*-Ts), 136.0 (C-4 Py), 138.7 (*p*-Ts), 142.9 (*ipso*-Ts), 147.7 (C-5), 149.1 (C-6 Py), 156.6 (C-2 Py). HRMS calcd for $C_{23}H_{29}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.1945.

***Z* isomer:** $[\alpha]_D$ -12.2 (*c* 1, $CHCl_3$); R_f 0.56 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.97 (d, *J* = 5.6 Hz, Me), 1.32 (qt, *J* = 12.8, 4.4 Hz, H-3ax), 1.55-1.65 (m, 5H, H-3eq, H-4eq, H-7ax, 2H-8), 1.72 (qd, *J* = 13.2, 4.0 Hz, H-4ax), 1.96 (td, *J* = 12, 1.6 Hz, H-6ax), 2.08 (dm, *J* = 12 Hz, H-6eq), 2.39 (s, 3H, $ArCH_3$), 3.02 (td, *J* = 13.6, 2.8 Hz, H-2ax), 3.44 (dt, *J* = 12.8, 4.6 Hz, H-4a), 3.77 (dm, *J* = 13.6 Hz, H-2eq), 4.02 (ddd, *J* = 10.8, 5.6, 4.4 Hz, H-8a), 6.26 (d, *J* = 1.6 Hz, =CH), 7.00 (d, *J* = 8 Hz, H-3 Py), 7.09 (ddd, *J* = 8.0, 4.4, 0.8 Hz, H-5 Py), 7.13 and 7.63 (2d, *J* = 8 Hz, 2 H each, ArH), 7.56 (td, *J* = 8.0, 2 Hz, H-4 Py), 8.47 (d, *J* = 4.4 Hz, H-6 Py); ^{13}C NMR (100 MHz, HSQC) 21.5 (CH_3Ar), 22.1 (7-CH_3), 23.9 (C-4), 24.3 (C-3), 32.2 (C-8), 33.0 (C-7), 36.9 (C-4a), 40.3 (C-2), 41.1 (C-6), 54.6 (C-8a), 120.7 (C-5 Py), 123.6 (C-3 Py), 124.3 (=CH), 126.7 (*o*-Ts), 129.5 (*m*-Ts), 135.9 (C-4 Py), 138.8 (*p*-Ts), 142.5 (*ipso*-Ts), 147.4 (C-5), 149.2 (C-6 Py), 156.4 (C-2 Py). HRMS calcd for $C_{23}H_{29}N_2O_2S$ $(M+H)^+$ 397.1944, found 397.1946.

(4a*S*,5*S*,7*R*,8a*R*)-7-Methyl-1-(4-methylsulfonyl)-5-(pyridin-2-ylmethyl)decahydroquinoline (11)



10 (E/Z mixture) **11** (75%) *epi*-**11** (15%)

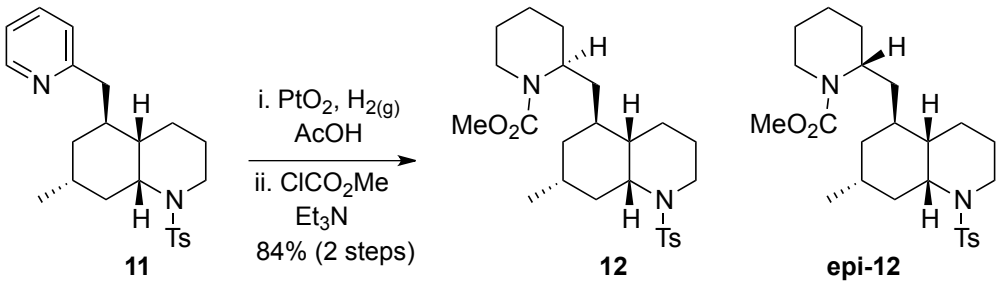
To a stirred solution of **10** (909 mg, 2.3 mmol) in MeOH (18 mL) was added Pd/C (20% w/w, 182 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 overnight. The mixture was diluted with CH_2Cl_2 (≈ 20 mL) before it was filtered through a pad of celite, washed through with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Purification by chromatography (0→2.5→5→10→25% EtOAc/hexane) gave **11** (627 mg, 67%) as a colorless oil, followed by a mixture of **11** and *epi*-**11** (126 mg, 16%), and finally *epi*-**11** (75 mg, 8%) was obtained as a white solid. Overall yield 90% (5:1 ratio for **11**/*epi*-**11**).

Data for 11: $[\alpha]_D$ -15.1 (*c* 1, $CHCl_3$); R_f 0.65 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.86 (d, *J* = 6.8 Hz, CH_3), 1.16 (td, 13.6, 4.8 Hz, H-6ax), 1.20-1.31 (m, 3H, H-3, H-4, H-6eq), 1.40-1.60 (m, 4 H, H-4a, H-3eq, 2H-8) 1.65 (qd, *J* = 12.8, 4.0 Hz, 1H, H-4ax), 1.83 (m, H-7ax), 2.12 (m, H-5eq), 2.41 (s, 3H, $ArCH_3$), 2.82 (dd, *J* = 13.6, 7.6 Hz, CH_2Py), 2.89 (dd, *J* = 13.6, 8.0 Hz, CH_2Py), 2.97 (td, *J* = 13.6, 3.2 Hz, H-2ax), 3.71 (dm, *J* = 13.6, H-2eq) 2.0 Hz, H-6eq), 4.27 (dt, *J* = 12, 4.8 Hz, H-8a), 7.05 (dt, *J* = 8.0, 1.0 Hz, H-3 Py), 7.12 (ddd, *J* = 8.0, 4.8, 1.2 Hz, H-5 Py), 7.24 and 7.70 (2d, *J* = 8 Hz, 2H each, Ts), 7.59 (td, *J* = 8.0, 2 Hz, H-4 Py), 8.53 (d, *J* = 4.8 Hz, H-6 Py). ^{13}C NMR (100 MHz, HSQC) 21.5 (CH_3Ar), 22.4 (7-CH_3), 24.8 (C-4), 25.1 (C-3), 26.8 (C-7), 32.5 (C-6), 32.9 (C-8), 37.8 (C-4a), 40.3 (C-5), 40.5 (C-2), 41.4 (CH_2Py), 51.7 (C-8a), 121.1 (C-5 Py), 123.6 (C-3 Py), 126.9 (*o*-Ts), 129.5 (*m*-Ts), 136.2 (C-4 Py), 138.8 (*p*-Ts), 142.7 (*ipso*-Ts), 149.5 (C-6 Py), 160.7 (C-2 Py). HRMS calcd for $C_{23}H_{31}N_2O_2S$ $(M + H)^+$ 399.2101, found 399.2104.

Data for *epi*-11: $[\alpha]_D$ -39.1 (*c* 1, $CHCl_3$); R_f 0.59 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.83 (d, *J* = 5.6 Hz, CH_3), 0.84 (q, *J* = 12.4 Hz, 1H, H-6ax), 1.18-1.30

(m, 2H, H-3, H-6eq), 1.38-1.48 (m, 4H, H-4, H-8, H-7ax), 1.50-1.62 (m, 3H, H-4, H-3, H-4a) 2.02 (m, 1H, H-5ax), 2.39 (s, 3H, $ArCH_3$), 2.59 (dd, *J* = 13.2, 8.4 Hz, 1H, CH_2Py), 2.66 (dd, *J* = 13.2, 7.2 Hz, 1H, CH_2Py), 2.95 (td, *J* = 13.6, 2.4 Hz, 1H, H-2ax), 3.64 (ddd, *J* = 13.2, 4.4, 3.2 Hz, H-2eq), 3.96 (ddd, *J* = 10.4, 5.2, 5.2 Hz, 1H, H-8a), 7.05 (dd, *J* = 8.4, 1.2 Hz, H-3 Py), 7.12 (ddd, *J* = 8.4, 4.8, 1.2 Hz, 1H, H-5 Py), 7.20 and 7.64 (2d, *J* = 8.4 Hz, 2 H each, *m*- and *o*-Ts), 7.56 (td, *J* = 7.6, 2 Hz, H-4 Py), 8.50 (dm, *J* = 4.8 Hz, H-6 Py); ^{13}C NMR (100 MHz, HSQC) 18.0 (C-4), 21.4 ($ArCH_3$), 22.1 (CH_3), 24.9 (C-3), 31.4 (C-8), 32.3 (C-7), 34.5 (C-6), 38.0 (C-4a), 40.5 (C-2), 40.9 (C-5), 41.8 (CH_2Py), 55.5 (C-8a), 121.0 (C-5 Py), 123.3 (C-3 Py), 126.8 (*o*-Ts), 129.5 (*m*-Ts), 136.2 (C-4 Py), 138.6 (*p*-Ts), 142.6 (*ipso*-Ts), 149.3 (C-6 Py), 160.6 (C-2 Py). HRMS calcd for $C_{23}H_{31}N_2O_2S$ $(M+H)^+$ 399.2101, found 399.2116.

(4a*S*,5*S*,7*R*,8a*R*)-5-[(*S*)-(1-Methoxycarbonyl)-2-piperidylmethyl)]-7-methyl-1-(4-methylsulfonyl)decahydroquinoline (12)



To a stirred solution of **11** (500 mg, 1.25 mmol) in AcOH (9.4 mL) was added PtO_2 (20% w/w, 100 mg) at rt. The resulting mixture was evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 for 16 h. The mixture was diluted with CH_2Cl_2 (≈ 15 mL) before it was filtered through a pad of celite and washed through with CH_2Cl_2. The filtered solution was washed with 1 N NaOH, dried and concentrated *in vacuo* to give the epimeric mixture of piperidines (not shown) as a colorless oil which was used in the next step wihout further purification.

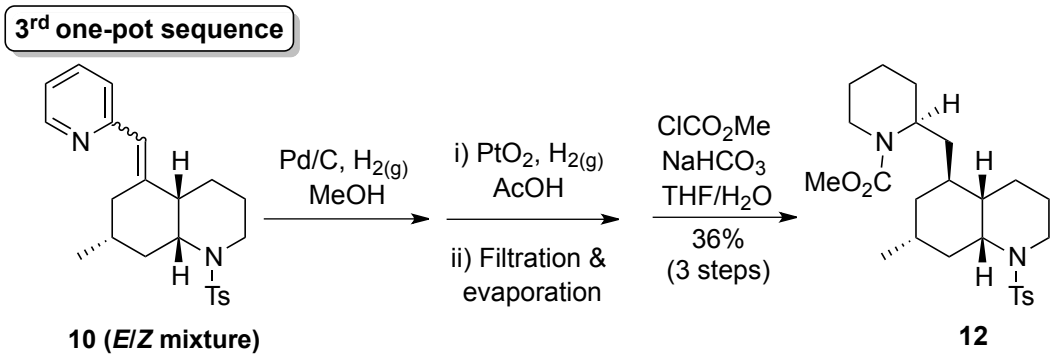
To a stirred solution of the above mixture (1.25 mmol) in CH_2Cl_2 (6.2 mL) was added triethylamine (0.87 mL, 6.25 mmol) followed by methyl chloroformate (0.29 mL, 3.75 mmol). After 24 h the reaction was quenched by the addition of 3 N HCl (2 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification by chromatography (0→5 →10→25%

EtOAc/hexane) gave *epi*-**12** (206 mg, 35%) as a colorless oil, followed by a mixture of **12** and *epi*-**12** (61 mg, 11%), and finally the product **12** (204 mg, 35%) eluted.

Data for 12: white solid, mp 115 ºC; $[\alpha]_D$ -18.8 (*c* 1, $CHCl_3$); R_f 0.48 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.83 (d, *J* = 6 Hz, CH_3), 1.15 (m, 2 H), 1.30-1.60 (m, 16 H), 1.69 (m, 1 H, 5-CH_2), 2.41 (s, ArCH_3), 2.73 (br, H-6′ax), 2.90 (td, *J* = 13.2, 2.8 Hz, H-2ax), 3.57 (br s, OMe), 3.72 (br d, *J* =12.0 Hz, H-2eq), 3.98 (br, H-6′eq), 4.05 (dt, *J* = 12.0, 4.8 Hz, H-8a), 4.12 (br, H-2′), 7.26 (d, *J* = 8.4 Hz, *m*-Ts), 7.70 (d, *J* = 8.4 Hz, 2 H, *o*-Ts). ^{13}C NMR (100 MHz, HSQC) 19.1 (C-4′), 21.6 (CH_3Ar), 22.6 (CH_3), 25.2 (C-4), 25.4 (C-3), 25.7 (C-5′), 27.4 (C-7), 29.2 (br, C-3′), 33.0 (C-8), 33.1 (5-CH_2), 34.8 (br, C-6), 36.4 (br, C-4a) 39.0 (br, C-6′), 40.5 (br, C-5), 40.6 (C-2), 48.8 (br, C-2′), 51.9 (C-8a), 52.4 (br, OMe), 127.1 (*o*-Ts), 129.7 (*m*-Ts), 138.9 (*p*-Ts), 143.0 (*ipso*-Ts), 156.2 (CO_2Me); HRMS calcd for $C_{25}H_{39}N_2O_4S$ $(M+H)^+$ 463.2625, found 463.262.

Data for *epi*-12: $[\alpha]_D$ -0.9 (*c* 1, $CHCl_3$); R_f 0.52 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, COSY) δ 0.85 (d, *J* = 6.4 Hz, CH_3), 1.07 (td, *J* = 12.4, 4.8 Hz, 1H, H-8ax), 1.25-1.44 (m, 7H, H-5, H-4a, 2H-3′, H-3, H-4, H-8eq), 1.45-1.80 (m, 9H, 5-CH_2, 2H-5′,H-3, H-4, 2H-4′, H-7), 2.41 (s, 3H, ArCH_3), 2.72 (t, *J* = 13.2 Hz, 1H, H-6′ax), 2.91 (td, *J* = 13.2, 2.8 Hz, 1H, H-2ax), 3.63 (dm, *J* = 13.2 Hz, H-2eq), 3.68 (s, 3H, OMe), 3.96 (br, 1H, H-6′eq), 4.14 (dt, *J* = 12.0, 4.2 Hz, 1H, H-8a), 4.28 (br, 1H, H-2′eq), 7.27 (d, *J* = 8.0 Hz, 2H, *m*-Ts), 7.71 (d, *J* = 8.0 Hz, 2H, *o*-Ts); ^{13}C NMR (100 MHz, HSQC) 19.0 (C-4′), 21.5 (ArCH_3), 22.4 (CH_3), 24.9 (C-4), 25.3 (C-3), 25.6 (br, C-5′), 26.7 (C-7), 29.1 (C-3′), 32.2 (C-8), 32.7 (C-6), 33.0 (br, 5-CH_2), 36.6 (C-4a), 39.0 (C-6′), 40.0 (br, C-5), 40.4 (C-2), 48.9 (C-2′), 52.0 (C-8a), 52.4 (OMe), 127.0 (*o*-Ts), 129.5 (*m*-Ts), 138.8 (*p*-Ts), 142.8 (*ipso*-Ts), 156.3 (CO_2Me); HRMS calcd for $C_{25}H_{39}N_2O_4S$ $(M+H)^+$ 463.2625, found 463.2622.

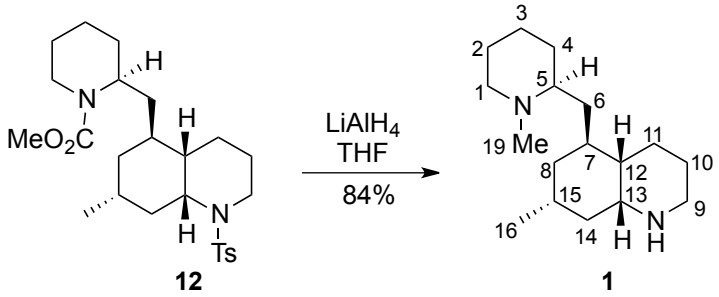
(4a*S*,5*S*,7*R*,8a*R*)-5-[(*S*)-(1-Methoxycarbonyl)-2-piperidylmethyl)]-7-methyl-1-(4-methylsulfonyl)decahydroquinoline (12)



To a stirred solution of **10** (519 mg, 1.31 mmol) in MeOH (10 mL) was added Pd/C (20% w/w, 104 mg) at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 overnight. To the same flask was added $PtO_2 \cdot H_2O$ (20% w/w, 104 mg) and AcOH (10 mL), then the hydrogen purging operation was repeated, and the resulting mixture stirred overnight. The mixture was diluted with CH_2Cl_2 (≈ 20 mL) before it was filtered through a pad of celite and washed through with CH_2Cl_2. The filtered solution was concentrated *in vacuo*. The resulting product was dissolved in a 1:1 mixture of THF/H_2O (42 mL in total), $NaHCO_3$(s) (2.2 g, 26.2 mmol) was added and the mixture cooled at 0 ºC. Methyl chloroformate (0.51 mL, 6.6 mmol) was added and the reaction was allowed to warm to rt. After 24 h the THF was evaporated and the mixture was diluted with CH_2Cl_2 (≈ 20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried and concentrated in vacuo. Purification by chromatography (0→5 →10→25% EtOAc/hexane) gave *epi*-**12** (237 mg, 39%) as a colorless oil, followed by a diastereomeric mixture (77 mg)[6], and finally **12** (218 mg, 36%) eluted as a white solid. For compounds **12** and *epi*-**12** the combined overall yield from **10** was 85%.

[6] This sample was contaminated with minor quantities of epimers at C-5 coming from the initial hydrogenation of the double bond.

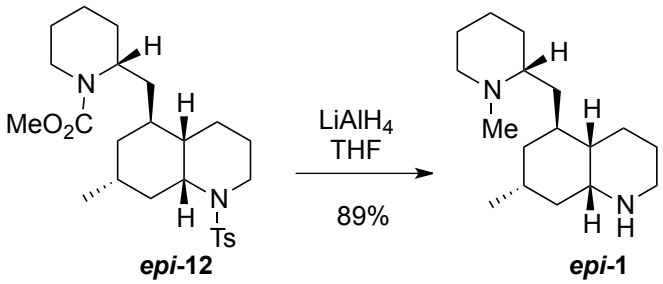
(4aS,5S,7R,8aR)-7-Methyl-5-[(*S*)-(1-methylpiperidin-2-yl)methyl]decahydro-quinoline (1) [Cermizine B]



To a stirred solution of the carbamate **12** (50 mg, 0.108 mmol) in THF (10 mL) was added $LiAlH_4$ (471 mg, 1.08 mmol) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by the careful addition of water (0.05 mL), 15% aq. NaOH (0.05 mL) and a second portion of water (0.15 mL). The mixture was then diluted with CH_2Cl_2 before it was filtered through a pad of celite, and washed through with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the product was purified by column chromatography (2.5 →5% MeOH/CH_2Cl_2 followed by 1:2:0.1 MeOH/CH_2Cl_2/concd NH_4OH) to give cermizine B **1** (24 mg, 84%) as a colourless oil with spectral data identical to those previously reported for the isolated natural product. R_f 0.2 (MeOH/CH_2Cl_2/concd NH_4OH=1:2:0.1); $[\alpha]_D$ -3.1 (*c* 0.7, MeOH); lit[7] : $[\alpha]_D$ -2 (*c* 0.6, MeOH); ^{1}H NMR (400 MHz, COSY) δ 0.94 (d, *J* = 6.4 Hz, CH_3), 1.15 (m, 1H, H-8), 1.18 (m, 1H, H-6), 1.22 (m, 1H, H-4), 1.30 (m, 1H, H-3), 1.32 (m, 1H, H-8), 1.38 (m, 1H, H-11), 1.40 (m, 2H, H-14, H-2), 1.55 (m, 1H, H-10), 1.56 (m, 1H, H- 7), 1.60 (m, 2H, H-2, H-14), 1.64 (m, 1H, H-12), 1.65 (m, 1H, H-15), 1.70 (m, 2H, H-3, H-10), 1.75 (m, 1H, H-11) 1.78 (m, 1H, H-4), 1.90 (m, 1H, H-5), 1.95 (m, 1H, H-6), 2.17 (td, *J* = 11.6, 3.2 Hz, 1H, H-1ax), 2.25 (s, 3H, H-19), 2.72 (br d, *J* = 12.4 Hz, 1H, H-9), 2.82 (td, *J* = 12.4, 2.8 Hz, 1H, H-9), 2.85 (br d, *J* = 11.6 Hz, 1H, H-1eq), 3.19 (dt, *J* = 12.0, 4.4 Hz, 1H, H-13). ^{13}C NMR (100 MHz, HSQC) 22.9 (C-16), 25.0 (C-3), 26.2 (C-11), 26.2 (C-2), 27.0 (C-10), 28.0 (C-15), 31.9 (C-4), 33.7 (C-8), 34.2 (C-14), 36.9 (C-6), 38.4 (C-7), 40.4 (C-9), 41.6 (C-12), 43.0 (C-19), 52.0 (C-13), 57.9 (C-1), 63.9 (C-5). HRMS calcd for $C_{17}H_{33}N_2$ $(M+H)^+$ 265.2638, found 265.2635.

[7] Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015.

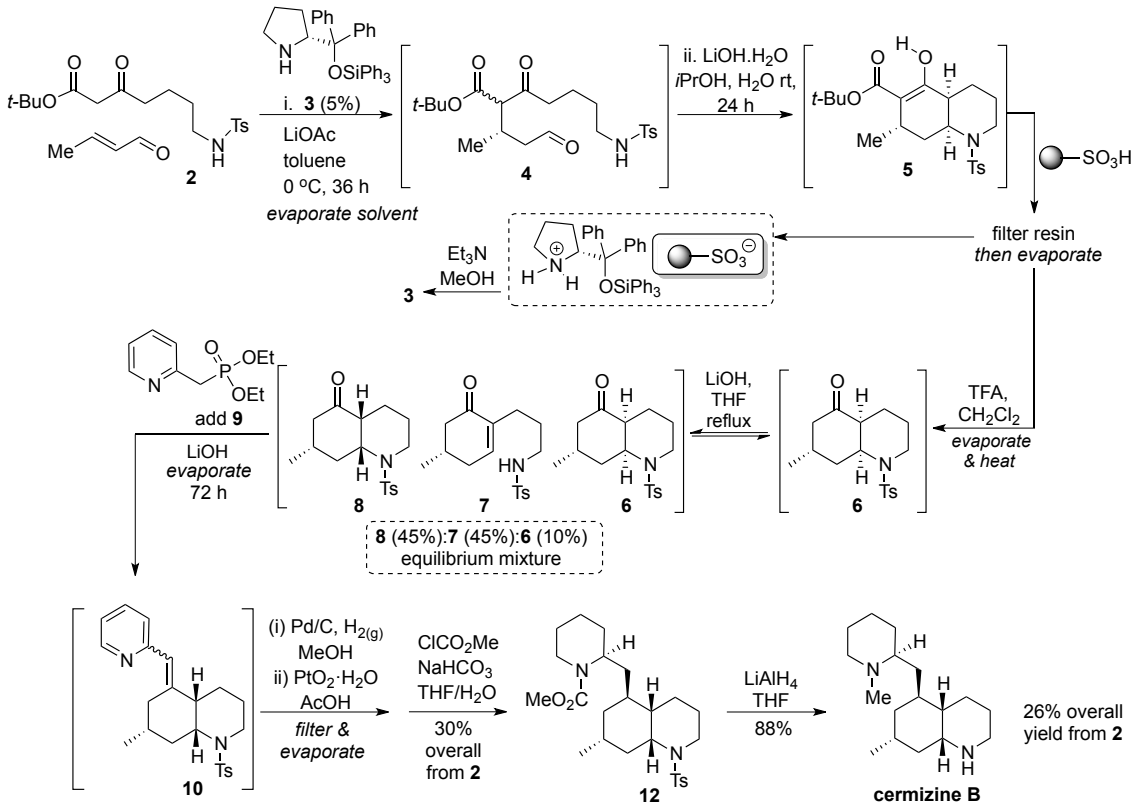
(4aS,5S,7R,8aR)-7-Methyl-5-[(*R*)-(1-methylpiperidin-2-yl)methyl]decahydro-quinoline (1) [*epi*-Cermizine B]



***epi*-12** ***epi*-1**

To a stirred solution of the carbamate **12** (69 mg, 0.149 mmol) in THF (13 mL) was added $LiAlH_4$ (57 mg, 1.49 mmol) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by the careful addition of water (0.07 mL), 15% aq. NaOH (0.07 mL) and a second portion of water (0.21 mL). The mixture was then diluted with CH_2Cl_2 before it was filtered through a pad of celite, and washed through with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the product was purified by column chromatography (2.5 →5% MeOH/CH_2Cl_2 followed by 1:2:0.1 MeOH/CH_2Cl_2/concd NH_4OH) to give ***epi*-1** (35 mg, 89%) as a colourless oil with spectral data identical to those previously reported for the isolation of the natural product. R_f 0.2 (MeOH/CH_2Cl_2/concd NH_4OH=1:2:0.1); $[\alpha]_D$ +50.0 (*c* 0.95, MeOH); ^{1}H NMR (400 MHz, COSY) δ 0.91 (d, *J* = 6 Hz, CH_3), 1.05 (ddd, *J* = 14.2, 9.2, 4.4 Hz, 1H, H-6), 1.20 (m, 2H, H-4, H-8), 1.30 (m, 1H, H-8), 1.35 (m, 1H, H-14), 1.25-1.40 (m, 3H, H-3, H-2, H-11), 1.45 (m, 1H, H-15), 1.50 (m, 1H, H-7), 1.60 (m, 1H, H-14), 1.50-1.65 (m, 10H, H-2, 2H-10, H-11, 1.60-1.80 (m, 4H, H-3, H-4, H-12, H-14), 1.95 (m, 1H, H-5), 2.00 (m, 1H, H-6), 2.17 (td, *J* = 12.0, 4.0 Hz, 1H, H-1), 2.27 (s, 3H, H-19), 2.64 (brd, *J* = 12.4 Hz, 1H, H-9), 2.76 (ddd, *J* = 13.2, 12.4, 3.2 Hz, 1H, H-9), 2.84 (brd, *J* = 12.2 Hz, 1H, H-1), 3.03 (dt, *J* = 12.2, 4.4 Hz, 1H, H-13). ^{13}C NMR (100 MHz, HSQC) 23.1 (C-16), 25.0 (C-3), 26.3 (C-11), 26.9 (C-2), 27.9 (C-10), 28.4 (C-15), 32.0 (C-4), 34.8 (C-14), 36.7 (C-8), 36.9 (C-6), 38.6 (C-7), 39.3 (C-12), 40.5 (C-9), 43.1 (C-19), 51.4 (C-13), 57.9 (C-1), 64.1 (C-5); HRMS calcd for $C_{17}H_{33}N_2$ $(M+H)^+$ 265.2638, found 265.2634.

Cermizine B (1) via an 'uninterrupted' sequence



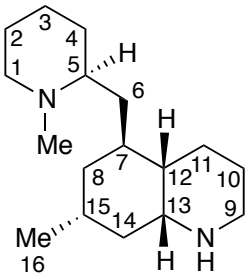
To a solution of keto ester **2** (5 g, 13.5 mmol) in toluene (126 mL) at 0 ºC was added crotonaldehyde (1.23 mL, 14.9 mmol), triphenylsilyl ether **3** (346 mg, 0.68 mmol), and LiOAc (445 mg, 6.75 mmol), and the resulting mixture was stirred for 36 h at 0 ºC. Excess crotonaldehyde and toluene were removed on a rotary evaporator before addition of *i*PrOH (125 mL) and LiOH·H_2O (567 mg, 13.5 mmol) was added, and the resulting solution was stirred for 24 h. To this flask was added the polymer-bound of *p*-toluenesulfonic acid (21.0 g, 30-60 mesh, Aldrich) and the mixture was stirred for 2 h. The solid support was filtered[8] and the filtrate was concentrated in vacuo to give the enantioenriched keto ester **5** (90% ee by HPLC). The crude material was dissolved in TFA (13.5 mL) and stirred under nitrogen for 15 min at room temperature. The solvent was evaporated under reduced pressure, the last traces of TFA were removed by azeotroping with toluene (3 × 50 mL) and the reaction flask was maintained on the rotatory evaporator under vacuum at 80 ºC for 3 h to give decahydroquinoline **6** as a brown oil. The crude reaction product was dissolved in THF (46 mL), LiOH (647 mg,

[8] Recovery of the catalyst according to the method outlined before gave 321 mg, (92%) of **3**.

27 mmol) was added, and the resulting mixture was refluxed for 24 h before addition of the phosphonate **9** (9.4 g, 40.5 mmol) at room temperature, followed by further portions of LiOH (1.62 g, 67.5 mmol). The solvent was removed *in vacuo* and the resulting mixture was stirred at room temperature for 3 days before being dissolved in CH_2Cl_2 (250 mL). The precipitate of LiOH was removed by simple filtration[9], washed through with CH_2Cl_2 (1 L), concentrated *in vacuo* into the filtrate the original flask. The crude mixture was dissolved in MeOH (100 mL) and Pd/C (5% w/w, 270 mg) was added at room temperature. The resulting mixture was rapidly evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H_2 for 16 h. The reaction was purged with argon before AcOH (100 mL) was added to the mixture, followed by $PtO_2 \cdot H_2O$ (5% w/w, 270 mg), at room temperature. The flask was purged with hydrogen as described above and the reaction was stirred for 24 h at rt. After purging the mixture with argon, it was diluted with CH_2Cl_2 (≈ 20 mL) and the heterogenous catalysts (Pd and $PtO_2 \cdot H_2O$) were removed by filtration through a pad of celite and the cake was washed through with CH_2Cl_2. The solvents were concentrated *in vacuo* to give a brown oil. This crude material was dissolved in a 1:1 mixture of THF/H_2O (430 mL), $NaHCO_3$ (22.7 g, 270 mmol) was added and the mixture cooled to 0 ºC. Methyl chloroformate (5.21 mL, 67.5 mmol) was added dropwise and the mixture allowed to warm rt. After 24 h the THF was evaporated and the mixture was diluted with CH_2Cl_2 (≈ 100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification by chromatography (0→5 →10→25% EtOAc/hexane) gave *epi*-**12** as colorless oil, followed by **12** (1.90 g, 30% from **2**).[10] To a stirred solution of carbamate **12** (1.90 g, 4.1 mmol) in THF (350 mL) was added $LiAlH_4$ (1.6 g, 41 mmol) at 0 ºC. The resulting mixture was stirred at room temperature overnight. The reaction was quenched by the careful addition of water (1.6 mL), 15% aq. NaOH (1.6 mL) and a second portion of water (4.8 mL). The mixture was then diluted with CH_2Cl_2 before it was filtered through a pad of celite, and washed through with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the product was purified by column chromatography (2.5 →5% MeOH/CH_2Cl_2 followed by 1:2:0.1 MeOH/CH_2Cl_2/concd NH_4OH) to give **1** (960 mg, 88%) as a colorless oil.

[9] The mixture was filtered through a short pad (0.5 cm) of silica. This served to not only remove the precipitated LiOH but also retain the unreacted excess phosphonate).
[10] The specific rotation value of this sample: $[\alpha]_D$ -19.0 (*c* 1, $CHCl_3$) agrees with the sample of **12** synthesized from enantiopure **5** (see page S7).

Table S1. Comparison of ^{1}H NMR data for (-) cermizine B, **1** and *epi*-**1** in CD_3OD

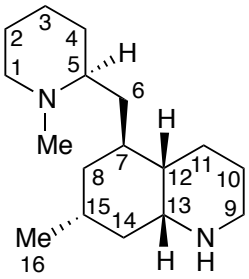


cermizine B

	Cermizine B[1]	Synthetic **1**[2]	Synthetic *epi*-**1**[2]
1	2.84 (br d, 11.1)	2.85 (br d, 11.6)	2.84 (br d, 12.2)
	2.17 (td, 11.1, 3.6)	2.17 (td, 11.6, 3.2)	2.17 (td, 12.0, 4.0)
2	1.60 (m)	1.60 (m)	1.50-1.70 (m)
	1.41 (m)	1.40 (m)	1.25-1.40 (m)
3	1.73 (m)	1.70 (m)	1.60-1.80 (m)
	1.32 (m)	1.30 (m)	1.25-1.40 (m)
4	1.78 (m)	1.78 (m)	1.75 (m)
	1.24 (m)	1.22 (m)	1.15-1.25 (m)
5	1.92 (m)	1.90 (m)	1.95 (m)
6	1.97 (m)	1.95 (m)	2.00 (m)
	1.19 (m)	1.18 (m)	1.05 (ddd, 14.2, 9.2, 4.4)
7	1.56 (m)	1.56 (m)	1.50 (m)
8	1.32 (m)	1.32 (m)	1.30 (m)
	1.18 (m)	1.15 (m)	1.20 (m)
9	2.78 (td, 12.6, 2.9)	2.82 (td, 12.4, 2.8)	2.76 (ddd, 13.2, 12.4, 3.2)
	2.67 (br d, 12.6)	2.72 (br d, 12.4)	2.64 (br d, 12.4)
10	1.66 (m)	1.70 (m)	1.50-1.65 (m)
	1.52 (m)	1.55 (m)	1.50-1.65 (m)
11	1.76 (m)	1.70-1.80 (m)	1.50-1.65 (m)
	1.38 (m)	1.38 (m)	1.25-1.40 (m)
12	1.61 (m)	1.64 (m)	1.70 (m)
13	3.09 (dt, 12.1, 4.5)	3.19 (dt, 12.0, 4.4)	3.03 (dt, 12.2, 4.4)
14	1.61 (m)	1.60 (m)	1.60 (m)
	1.41 (m)	1.40 (m)	1.35 (m)
15	1.63 (m)	1.65 (m)	1.45 (m)
16	0.94 (d, 6.2)	0.94 (d, 6.4)	0.91 (d, 6.0)
19	2.26 (s)	2.25 (s)	2.27 (s)

[1] Recorded at 500 MHz (*Tetrahedron* 2004, **60**, 7015-7023). [2] Recorded at 400 MHz. Assignments were aided by gCOSY and gHSQCAD spectra.

Table S2. Comparison of ^{13}C NMR data for (-) cermizine B, **1** and *epi*-**1** in CD_3OD

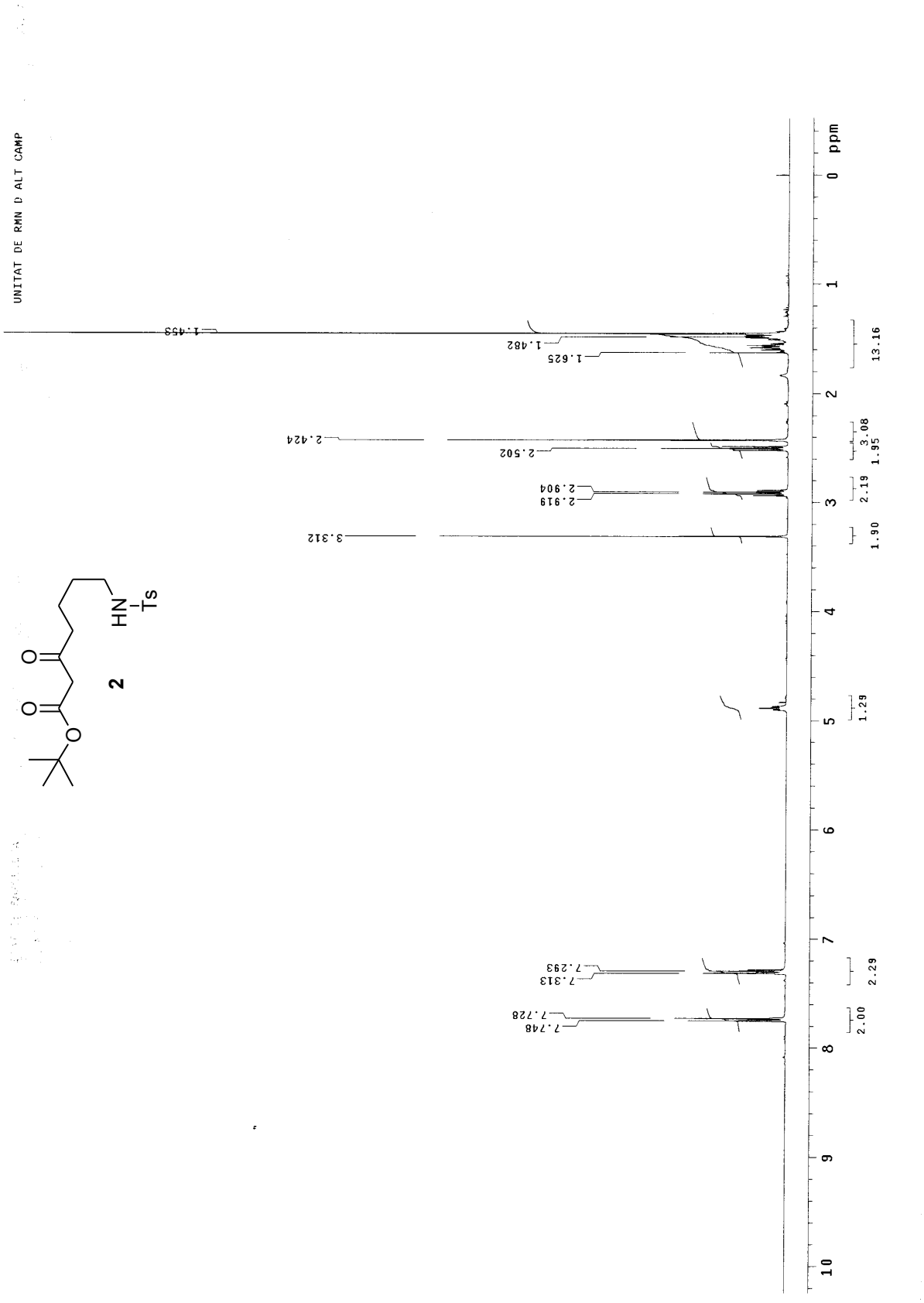


cermizine B

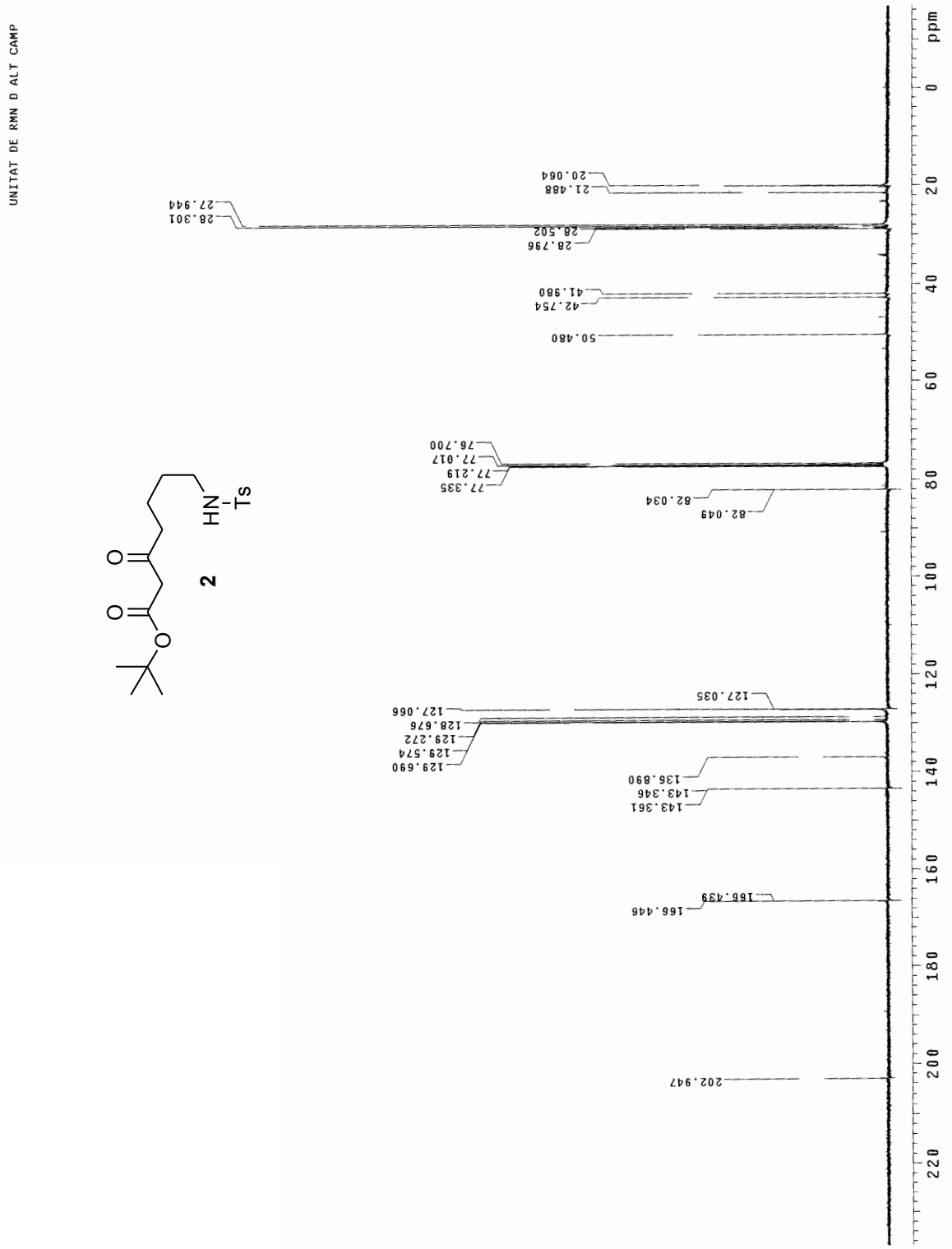
carbon	Cermizine B[1]	Synthetic **1**[2]	Synthetic *epi*-**1**[2]
1	57.9	57.9	57.9
2	26.7	26.2	26.8
3	25.0	25.0	25.0
4	32.0	31.9	32.0
5	64.0	63.9	64.1
6	37.0	36.9	36.9
7	38.6	38.4	38.6
8	33.9	33.7	36.7
9	40.5	40.4	40.5
10	27.7	27.0	27.9
11	26.3	26.2	26.3
12	42.1	41.6	39.3
13	51.7	52.0	51.4
14	34.8	34.2	34.8
15	28.1	28.0	28.4
16	23.0	22.9	23.1
19	43.1	43.0	43.1

[1] Recorded at 125 MHz (*Tetrahedron* 2004, **60**, 7015-7023). [2] Recorded at 100 MHz. Assignments were aided by gHSQCAD spectra.

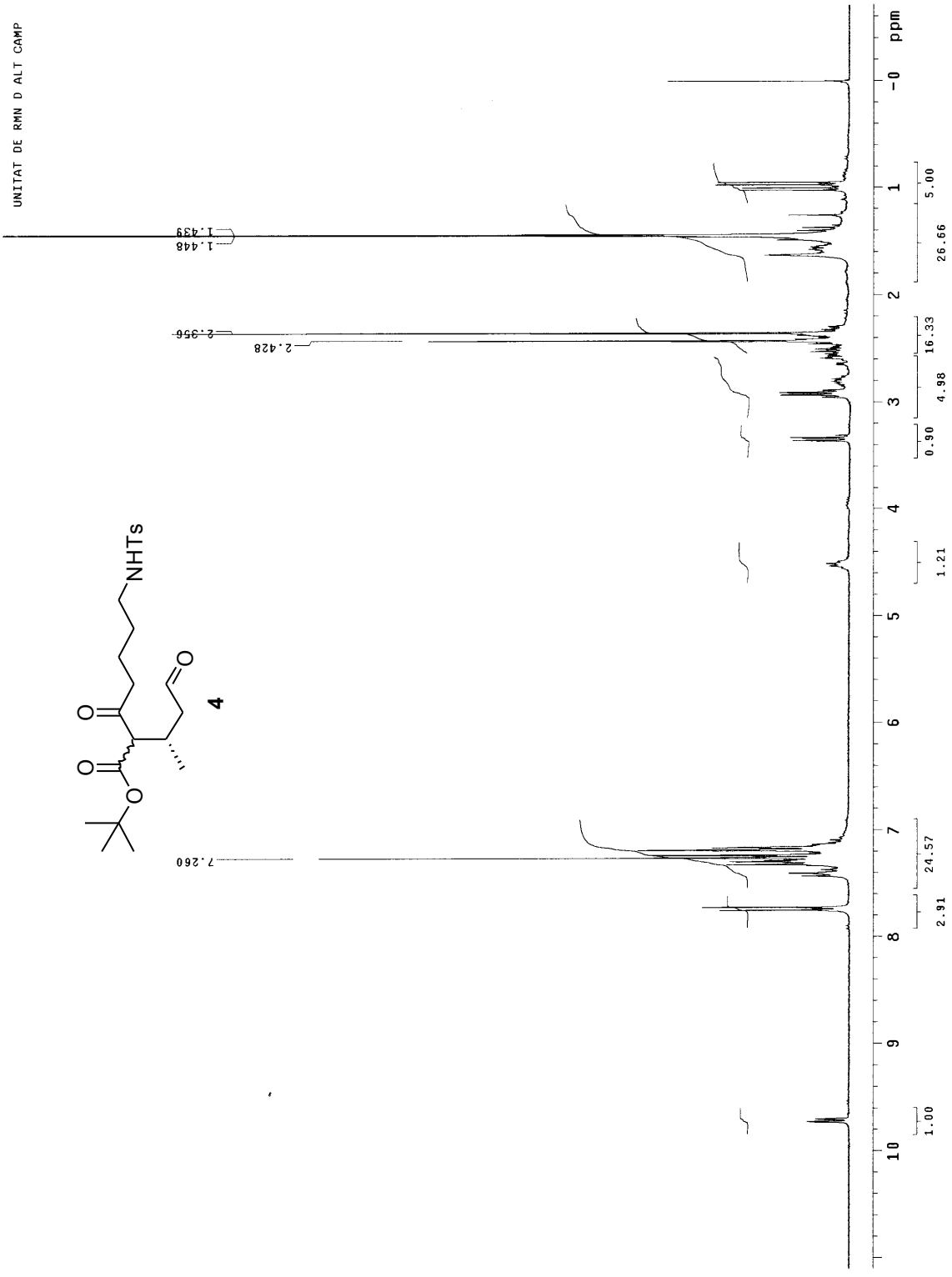
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **2**



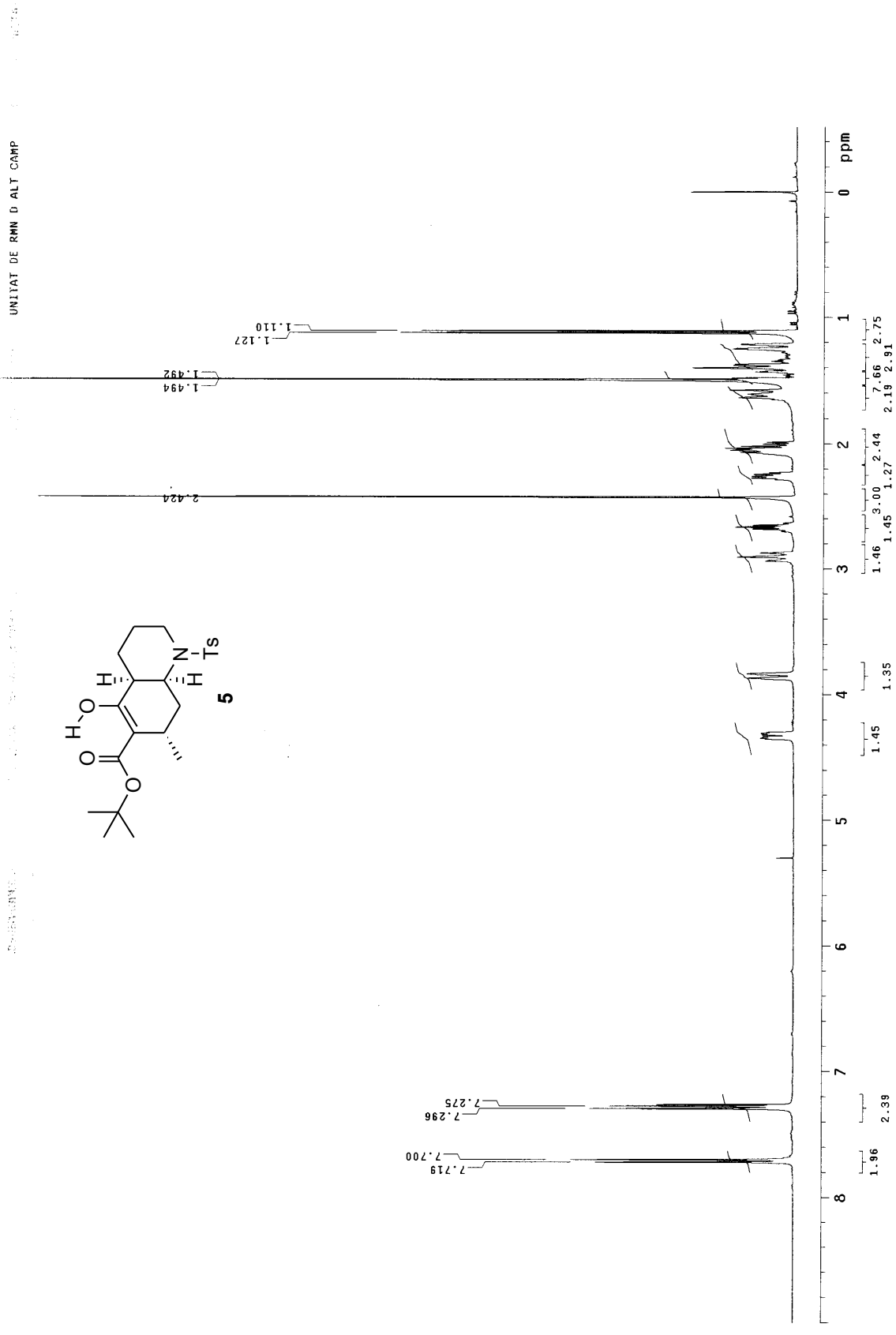
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **2**



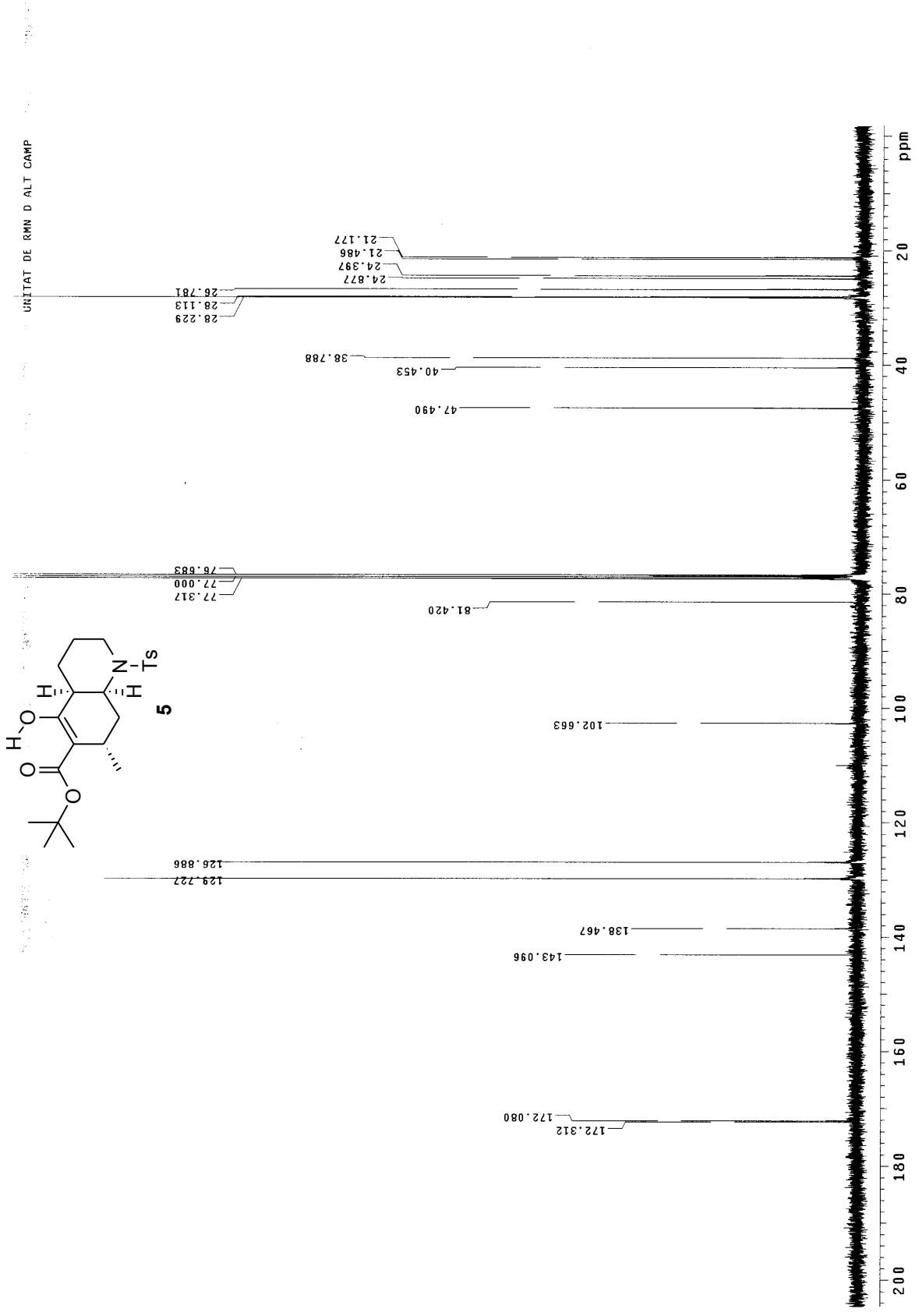
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4**



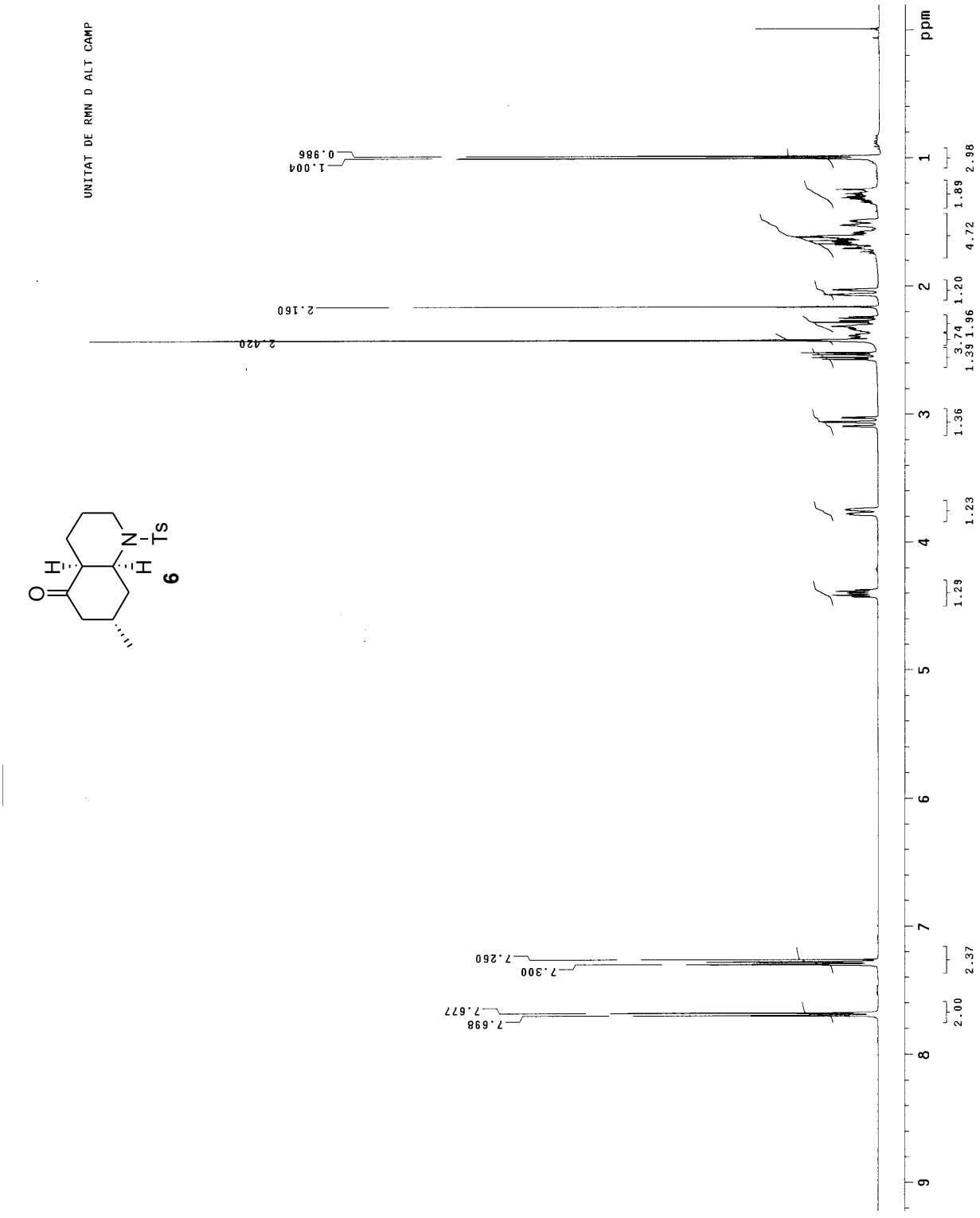
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5**



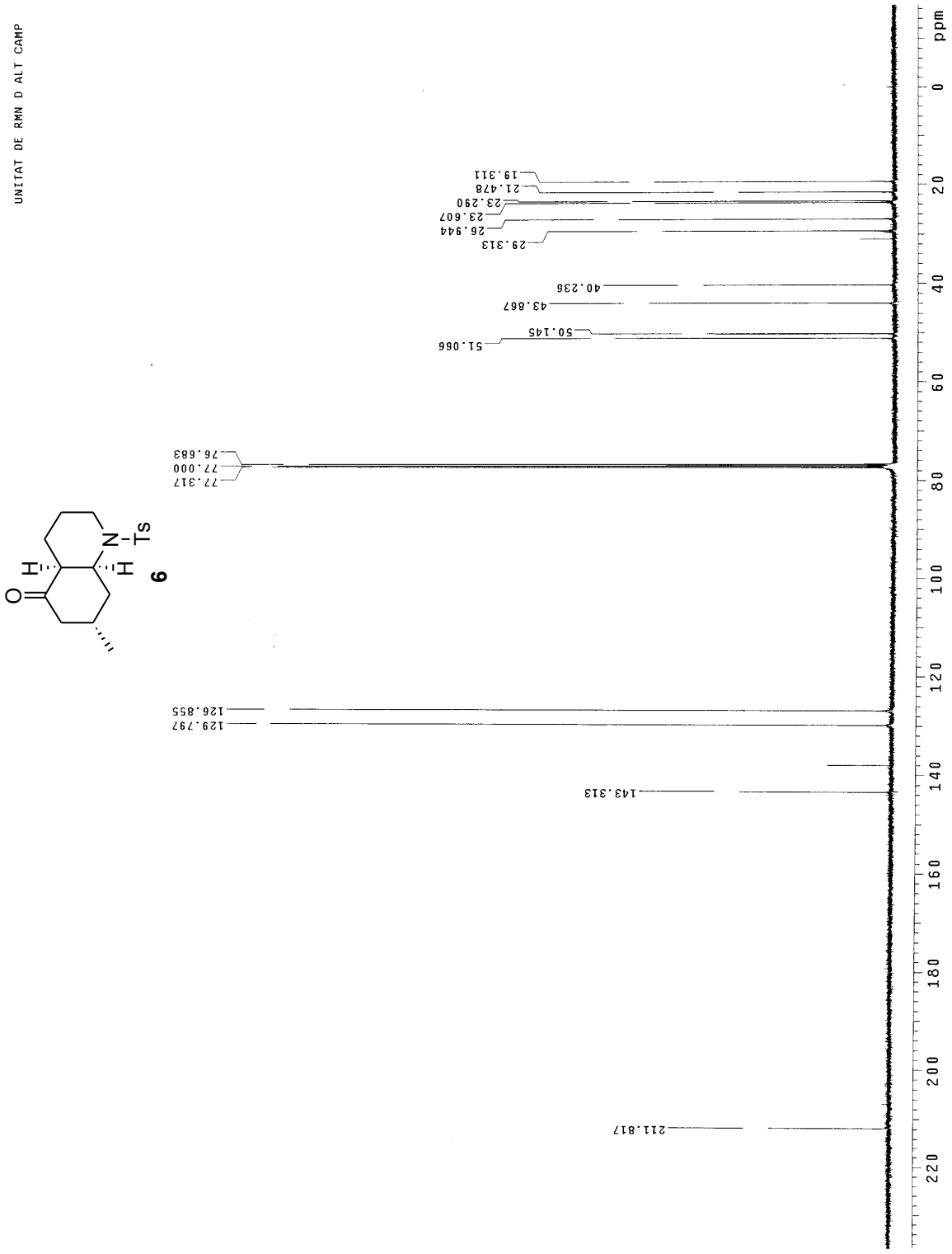
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5**



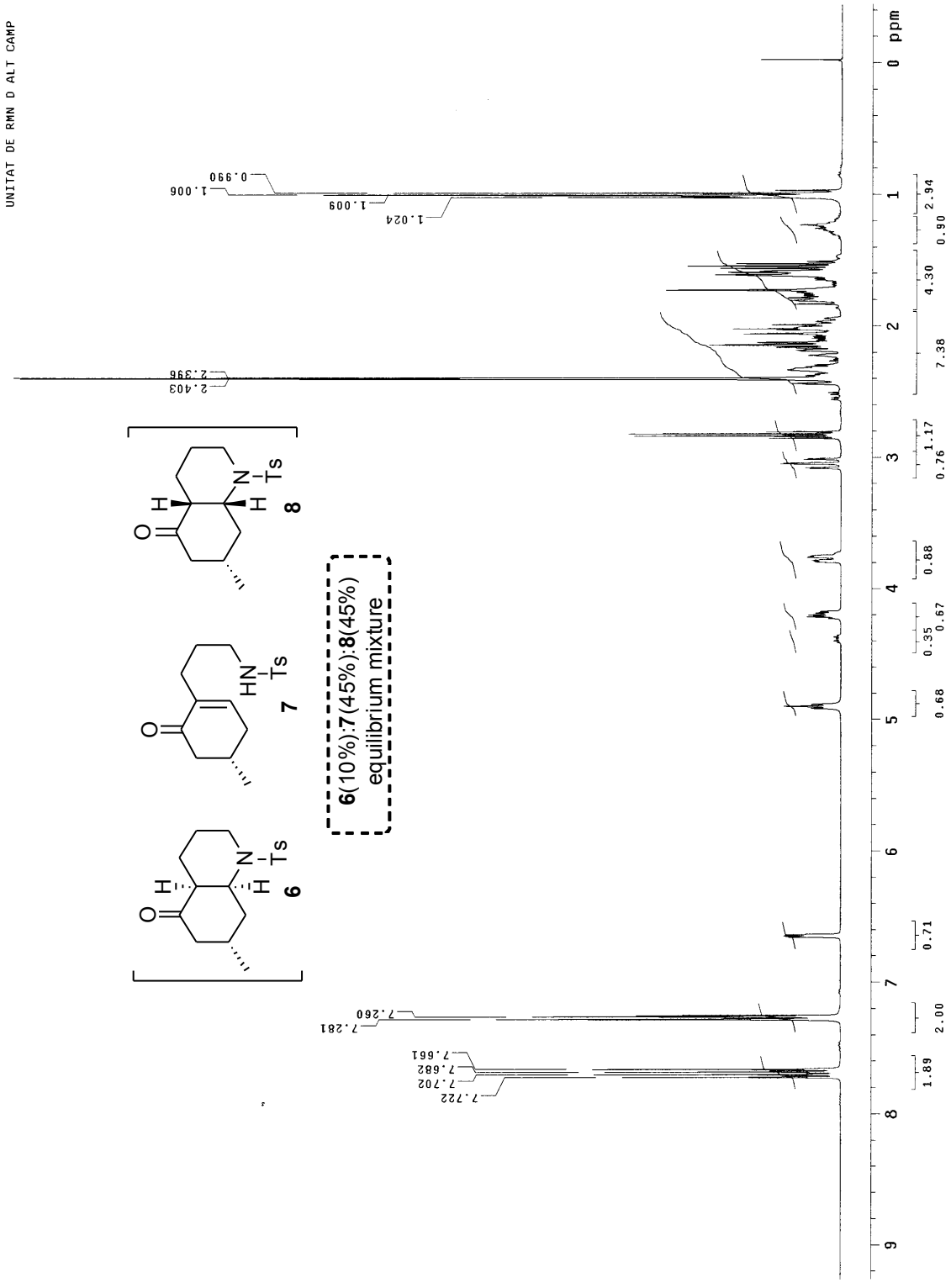
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **6**



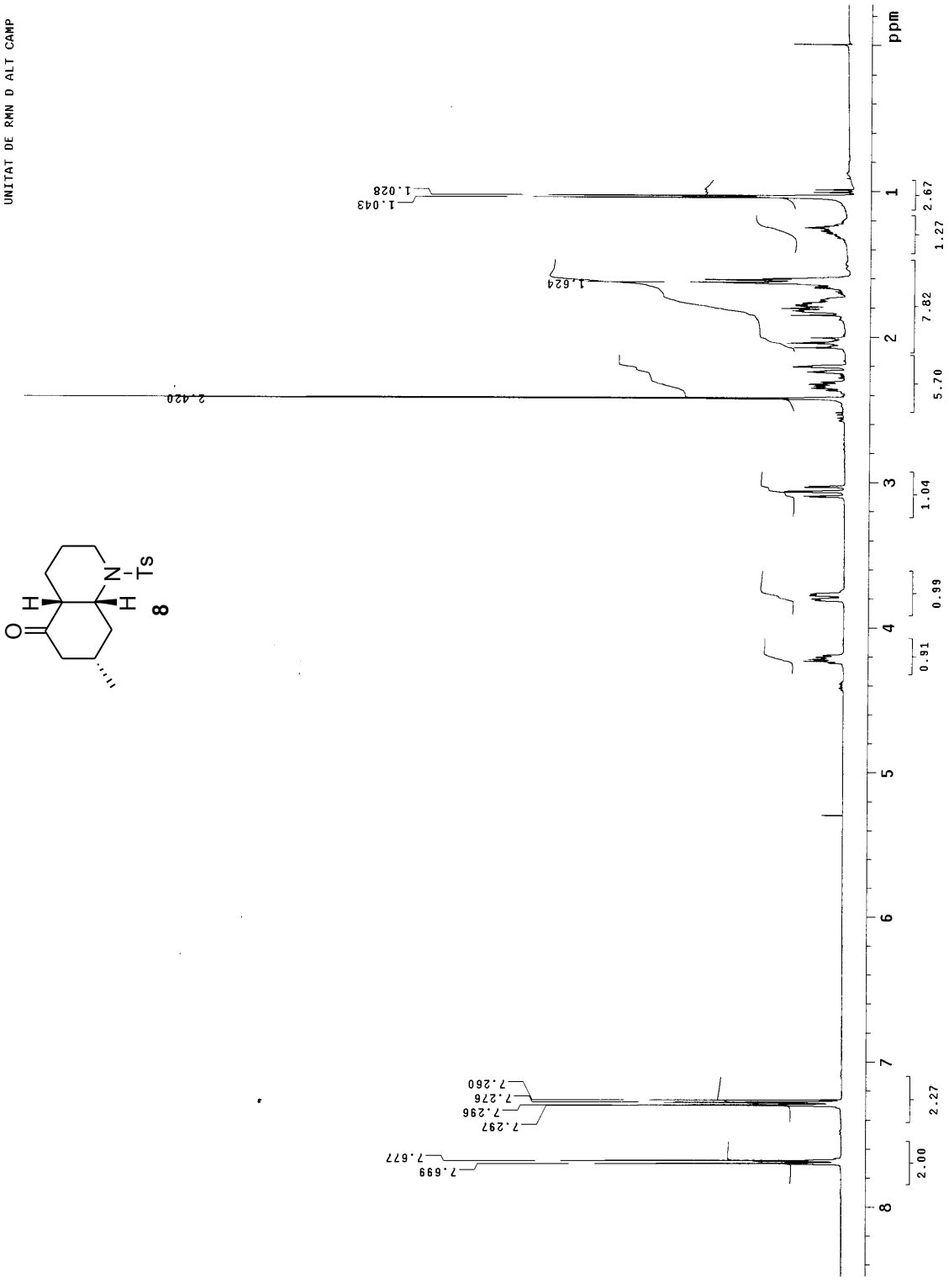
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **6**



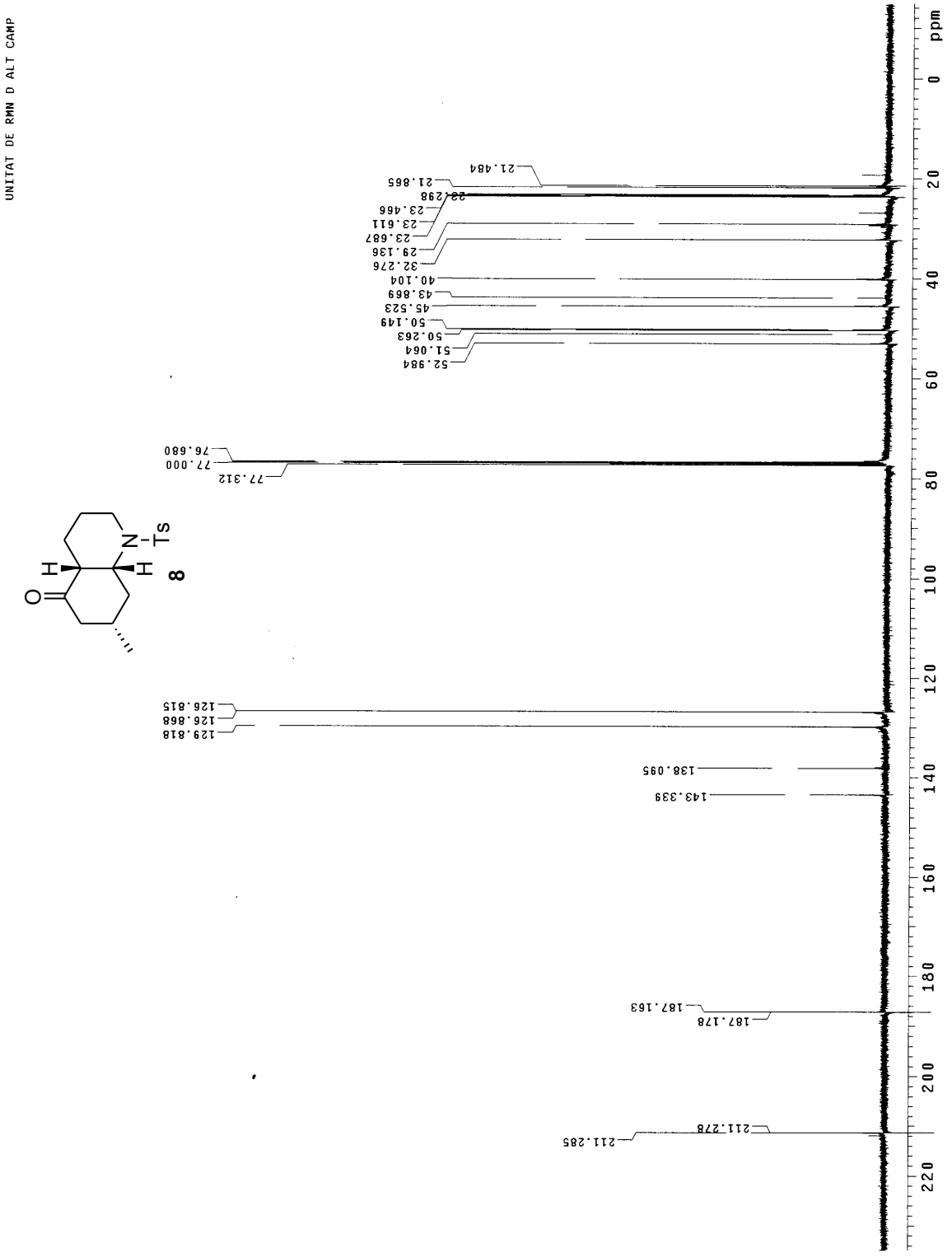
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for equilibrium mixture **6** + **7** + **8**



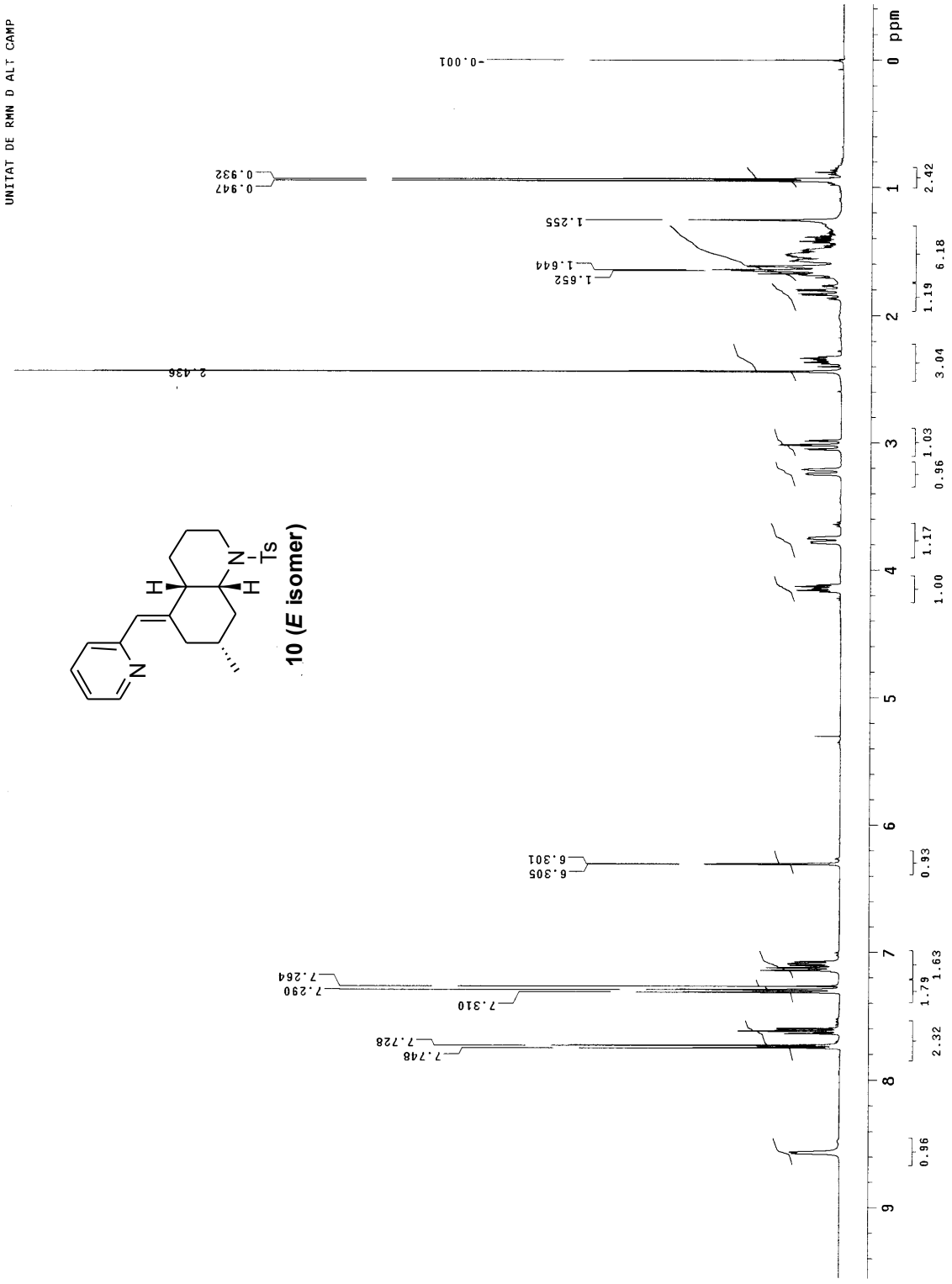
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **8**



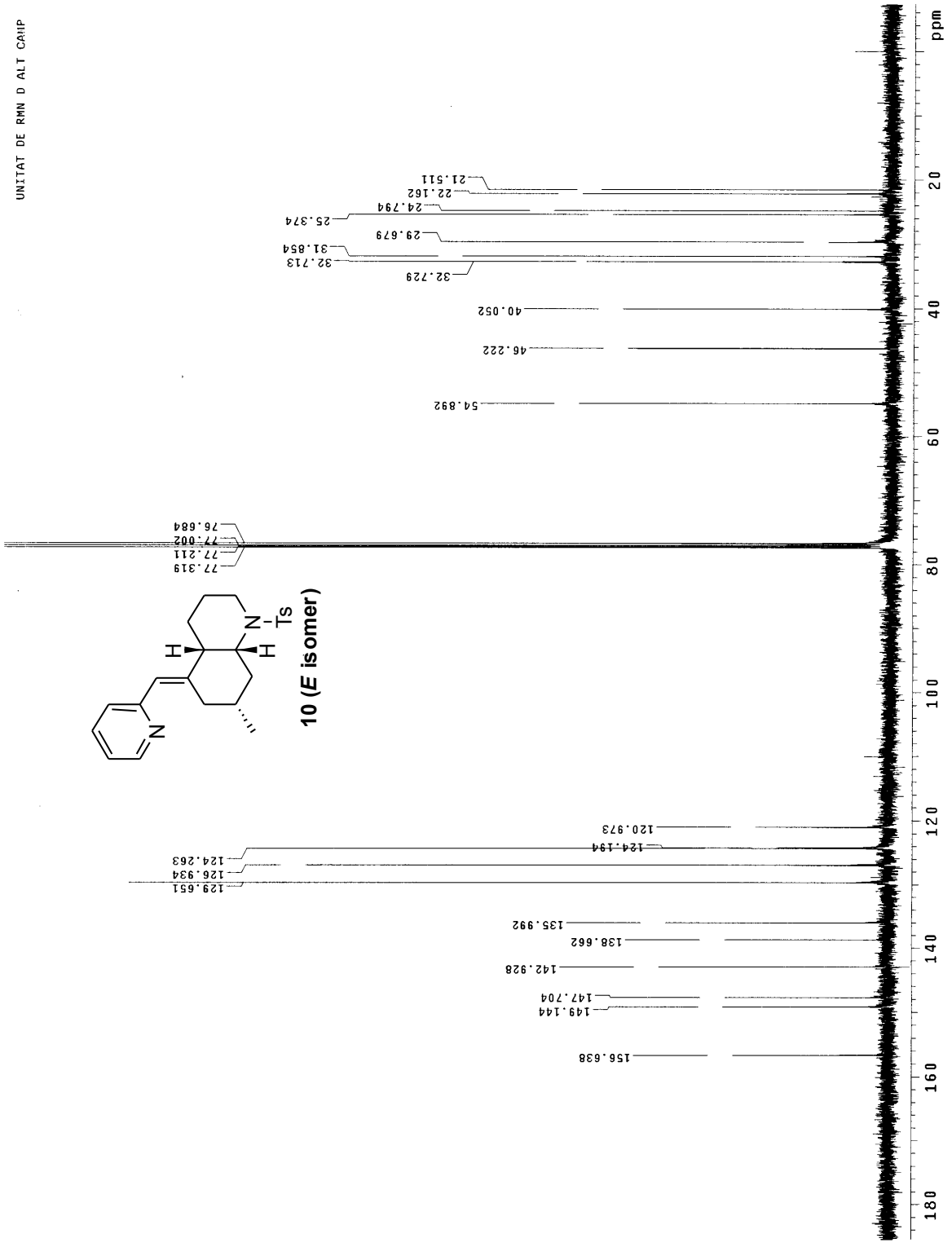
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **8**



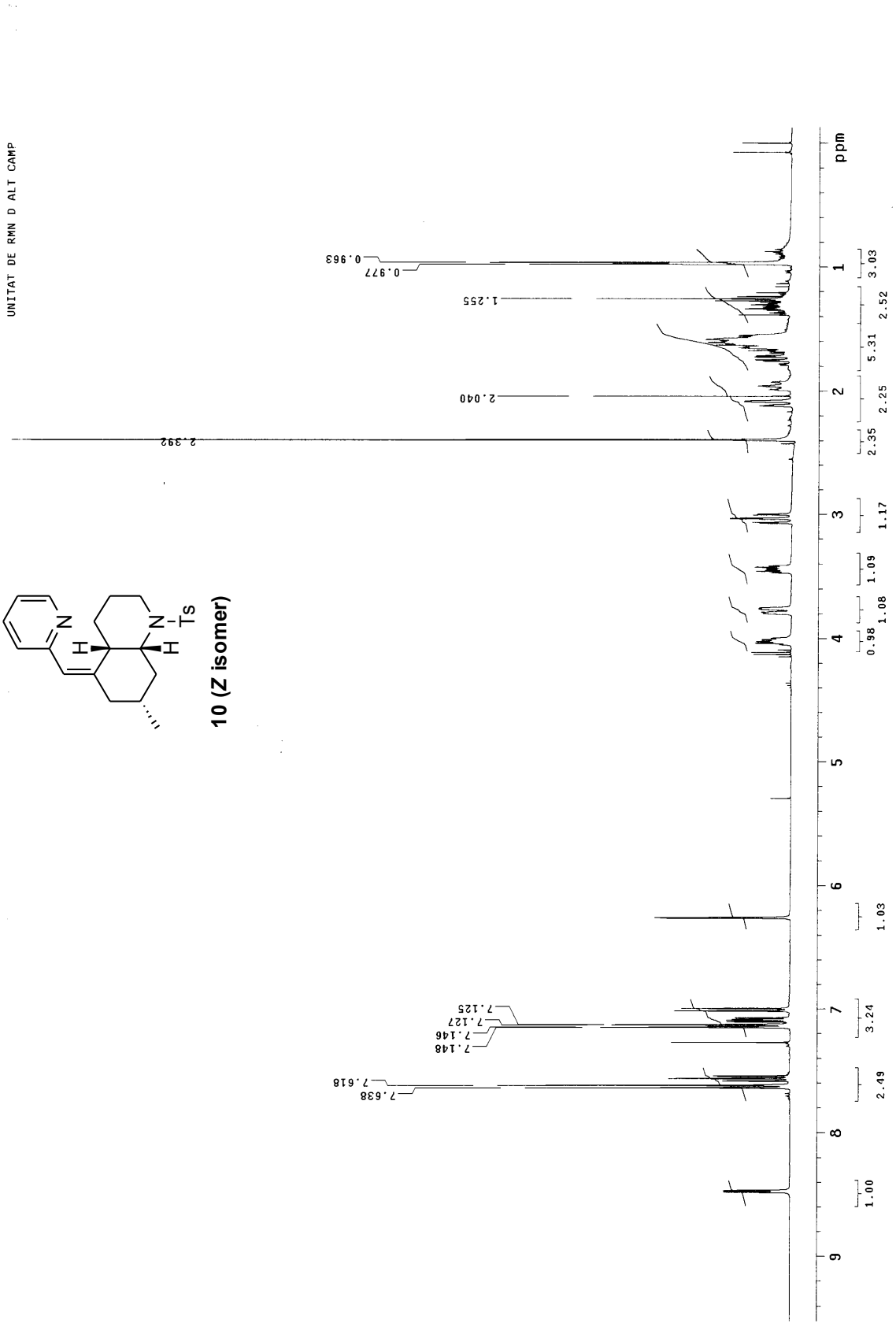
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **10 (*E* isomer)**



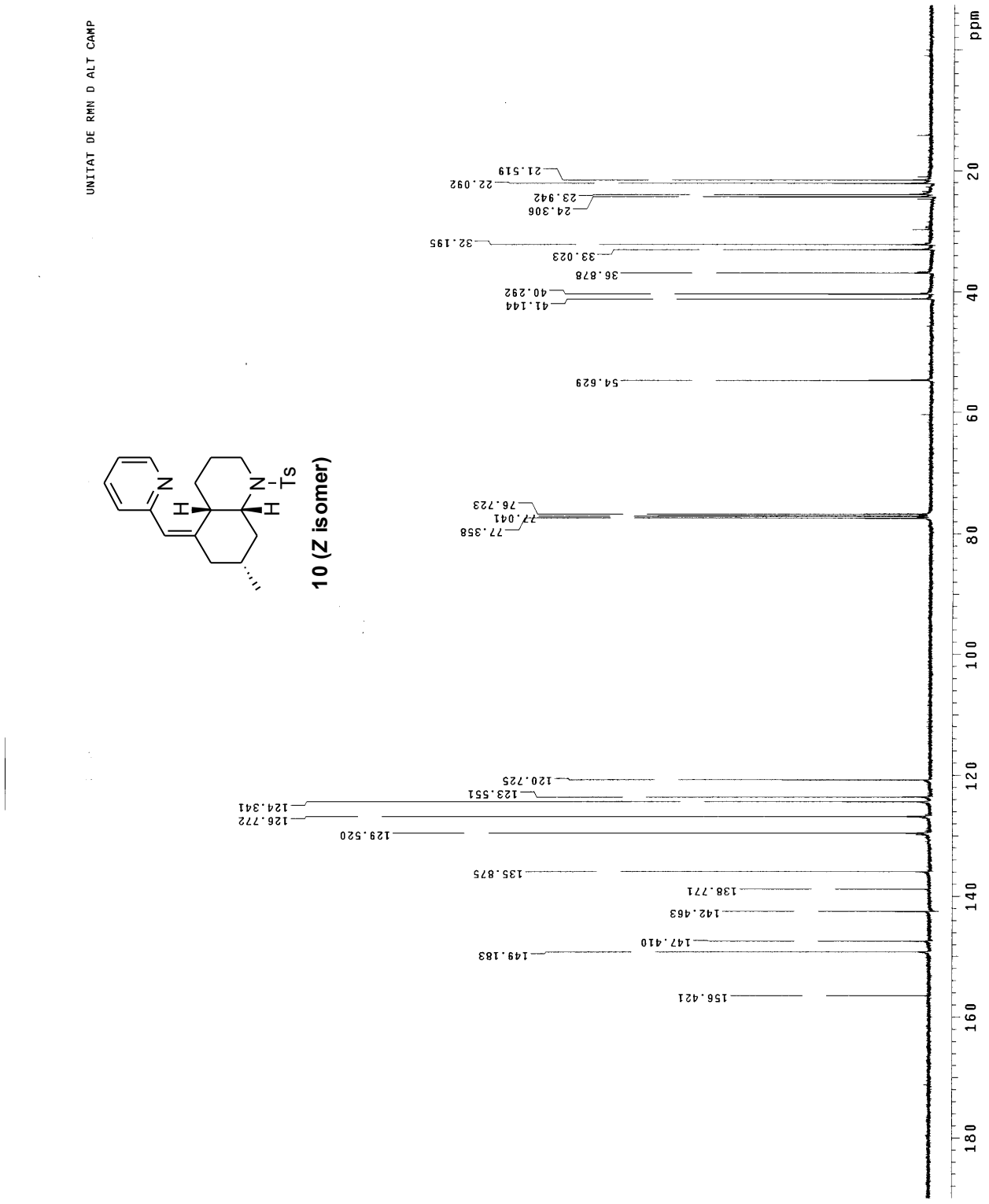
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **10 (*E* isomer)**



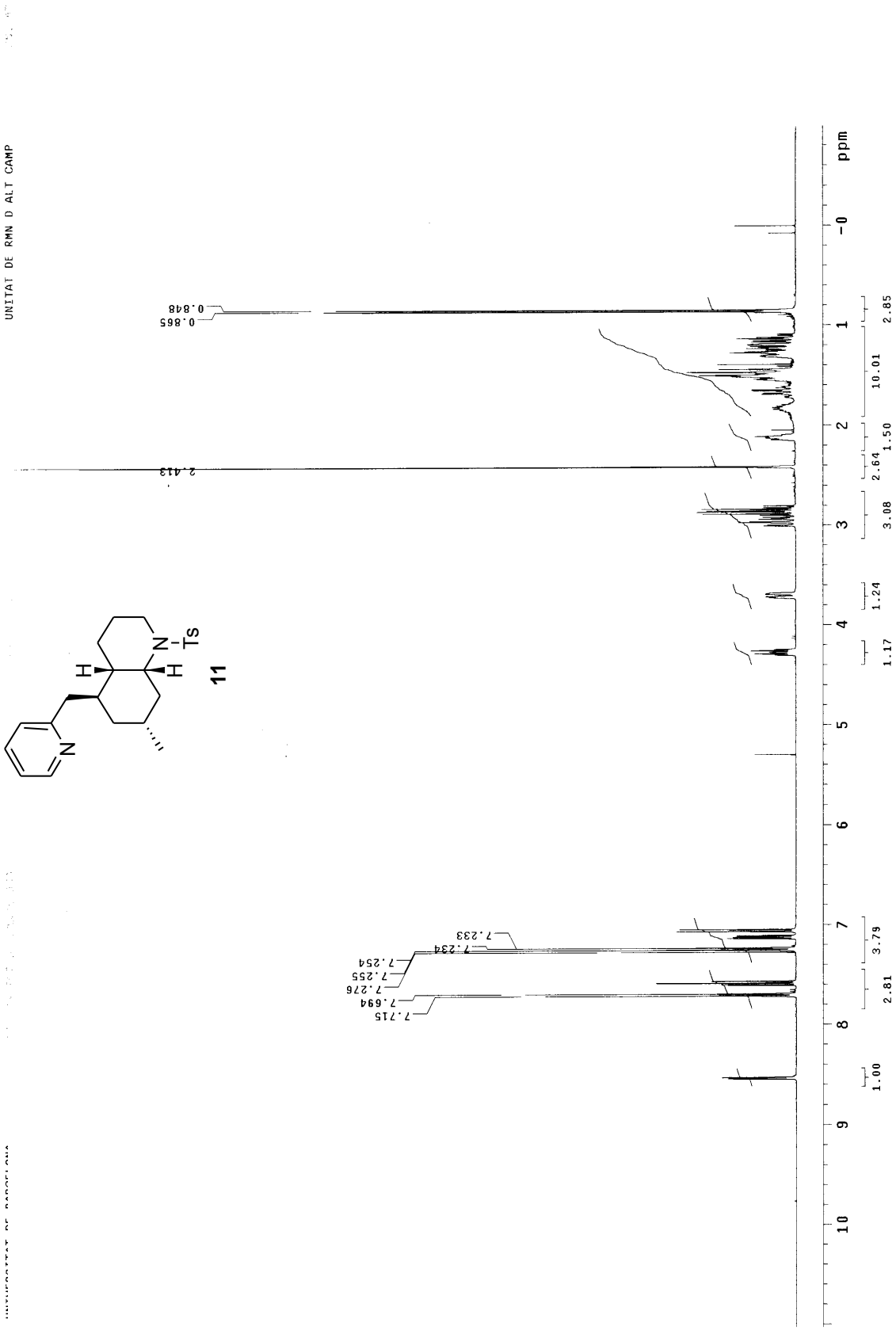
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **10 (*Z* isomer)**



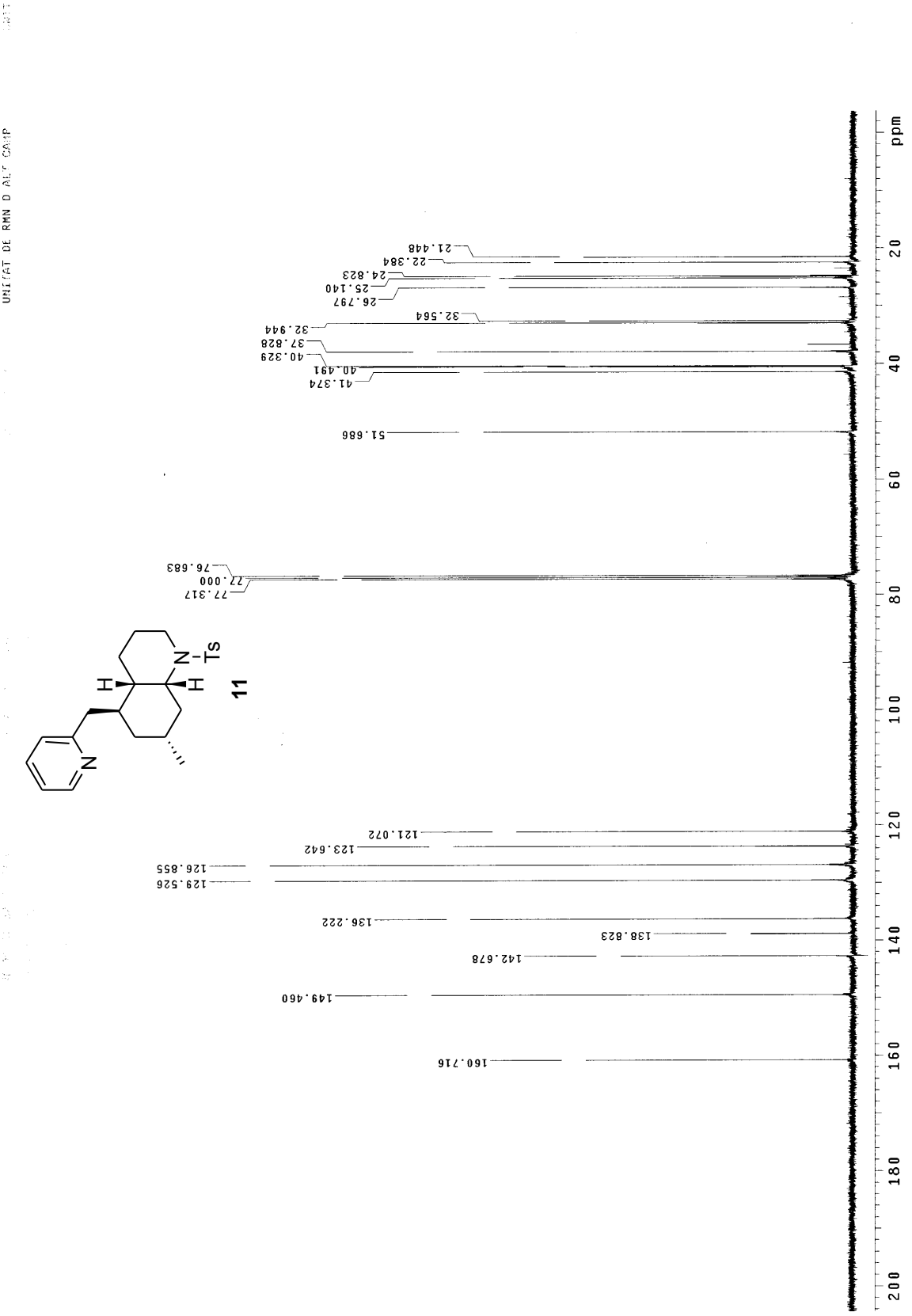
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **10 (*Z* isomer)**



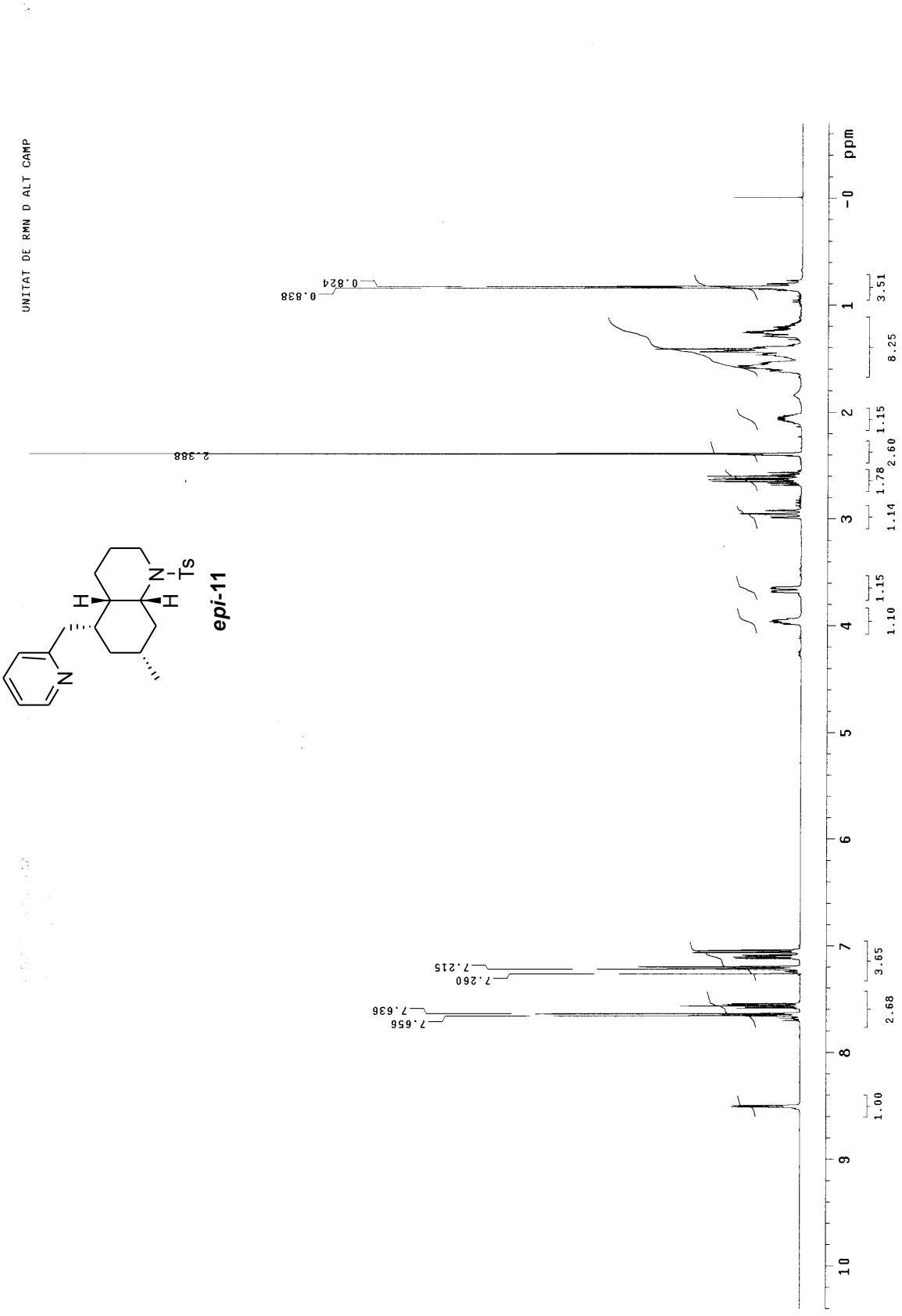
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **11**



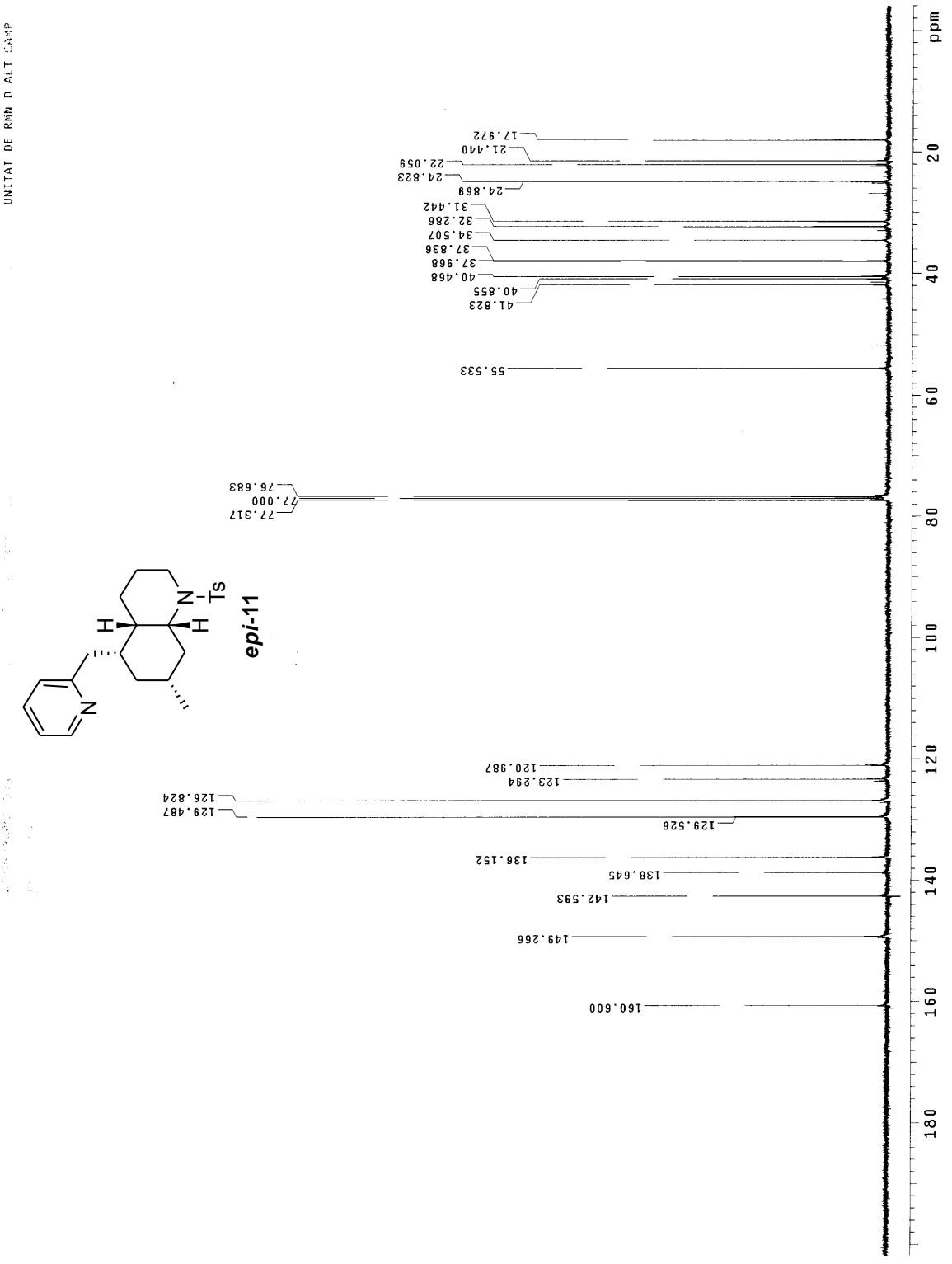
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **11**



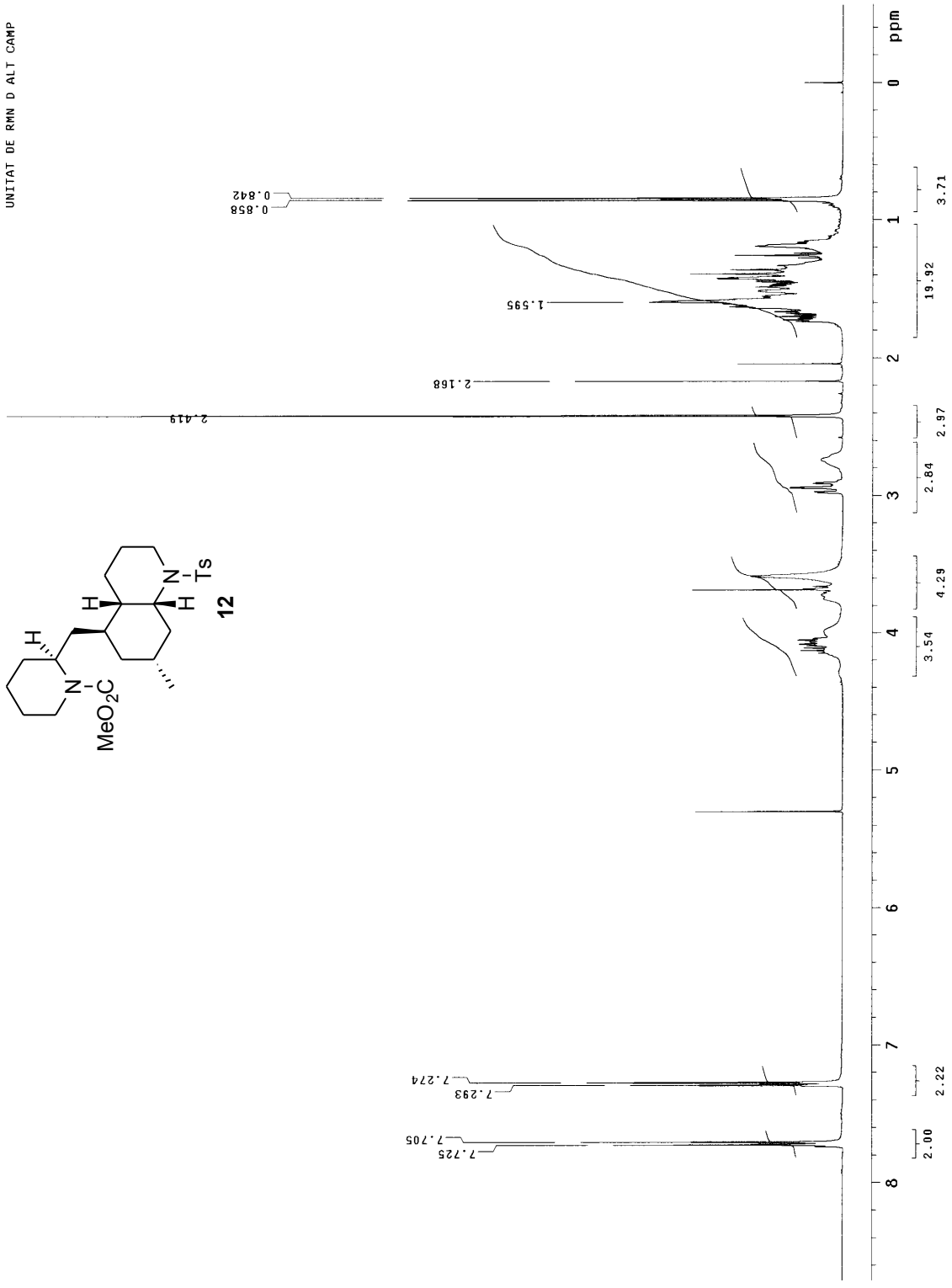
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for ***epi*-11**



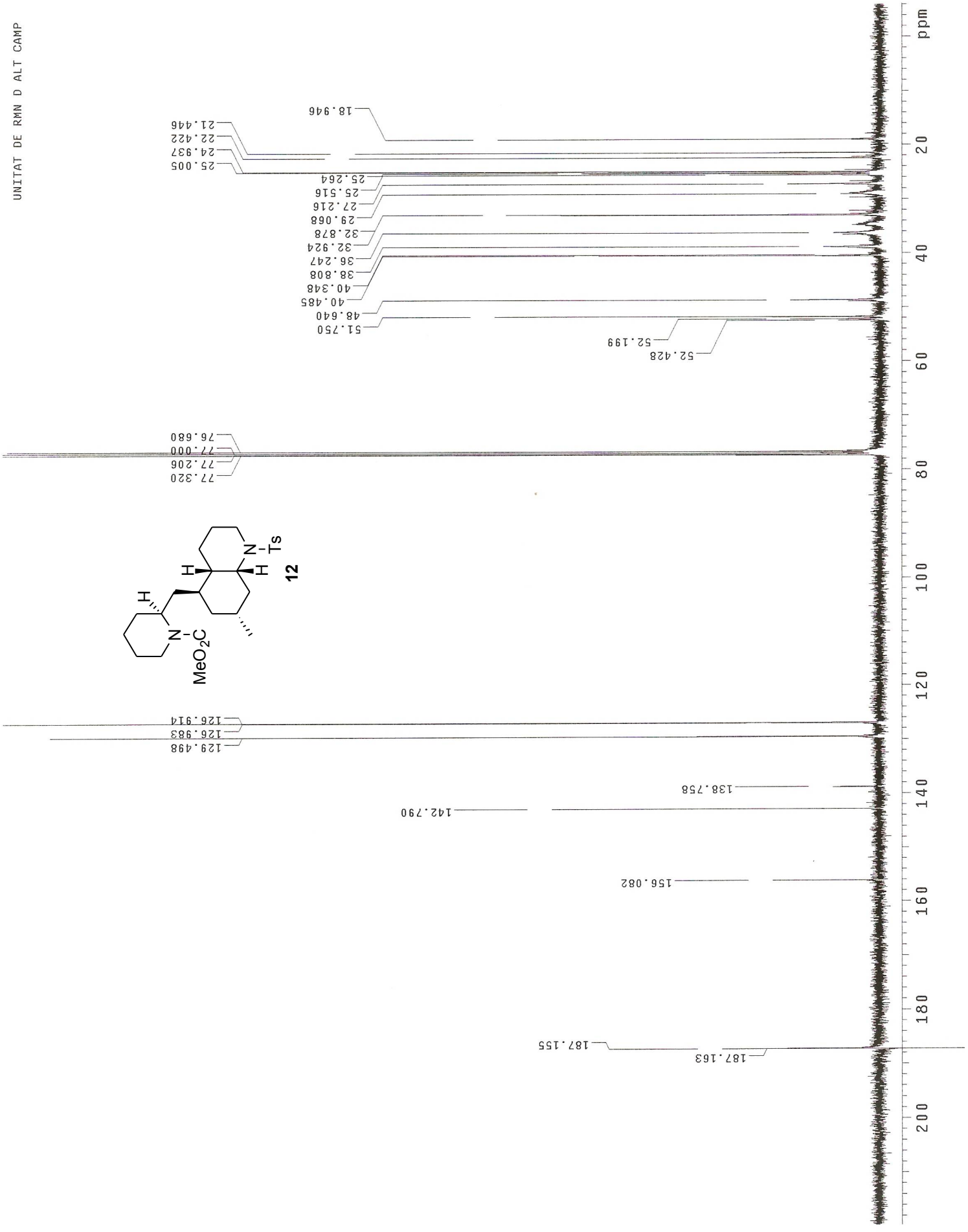
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for ***epi*-11**



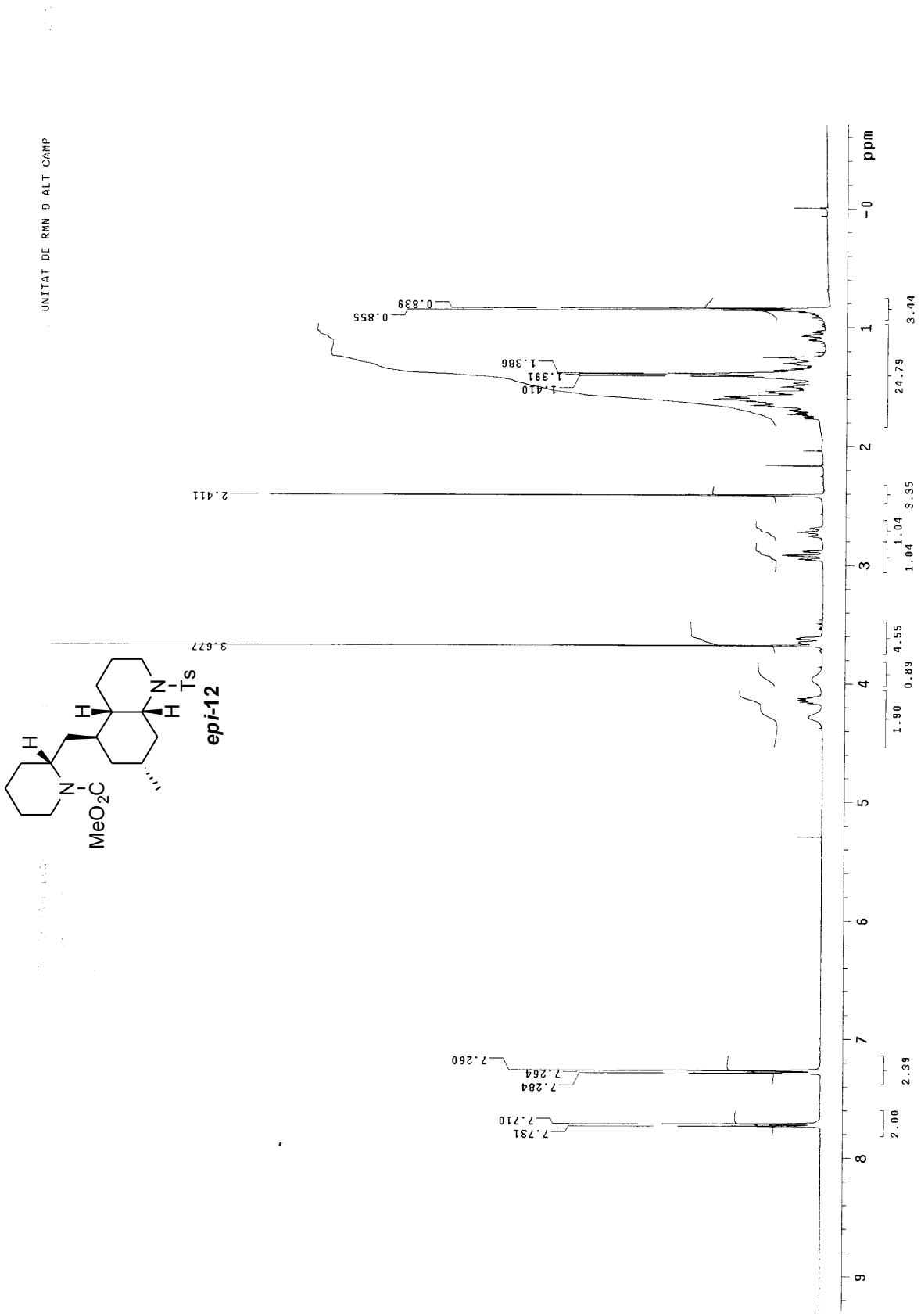
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **12**



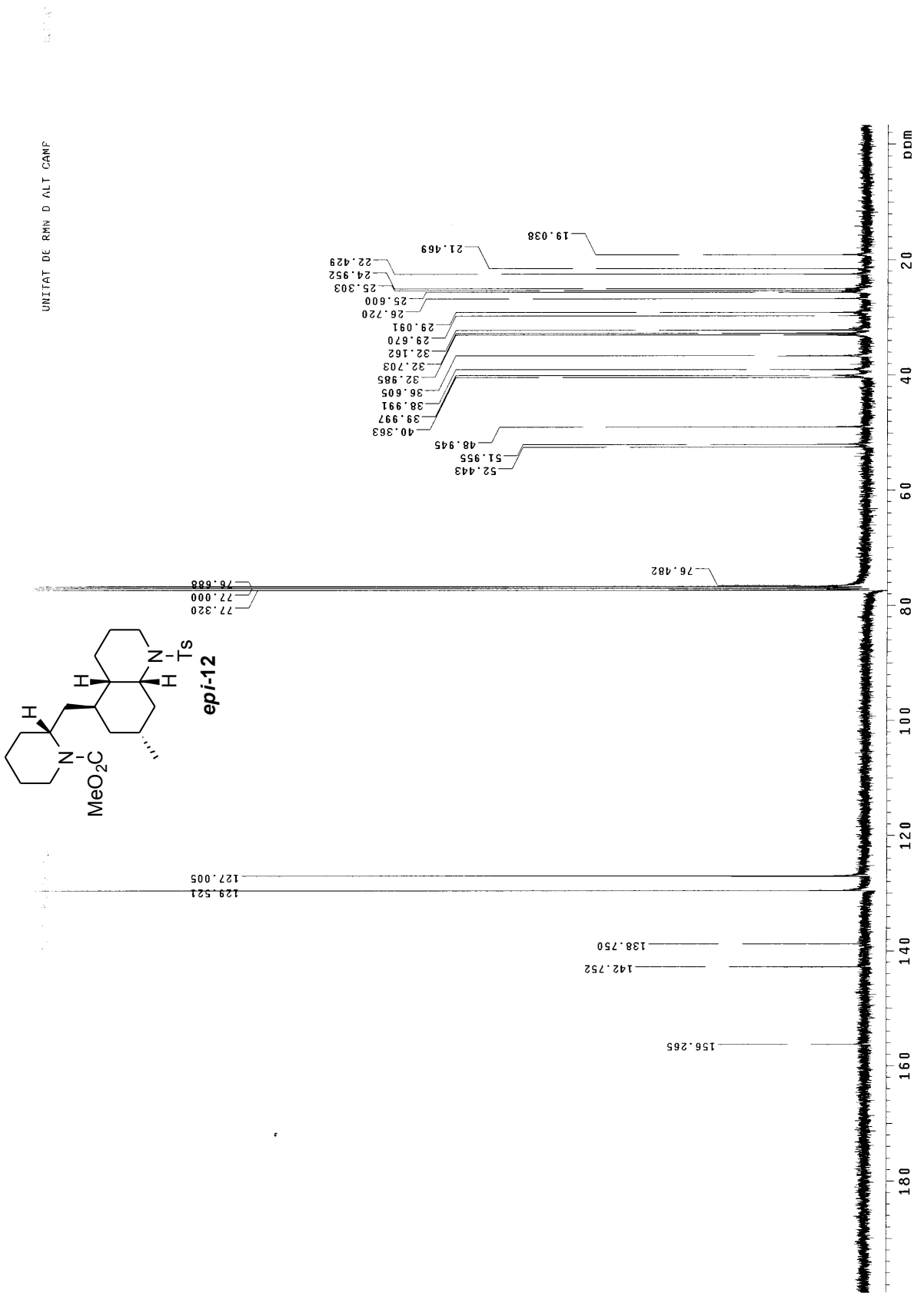
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **12**



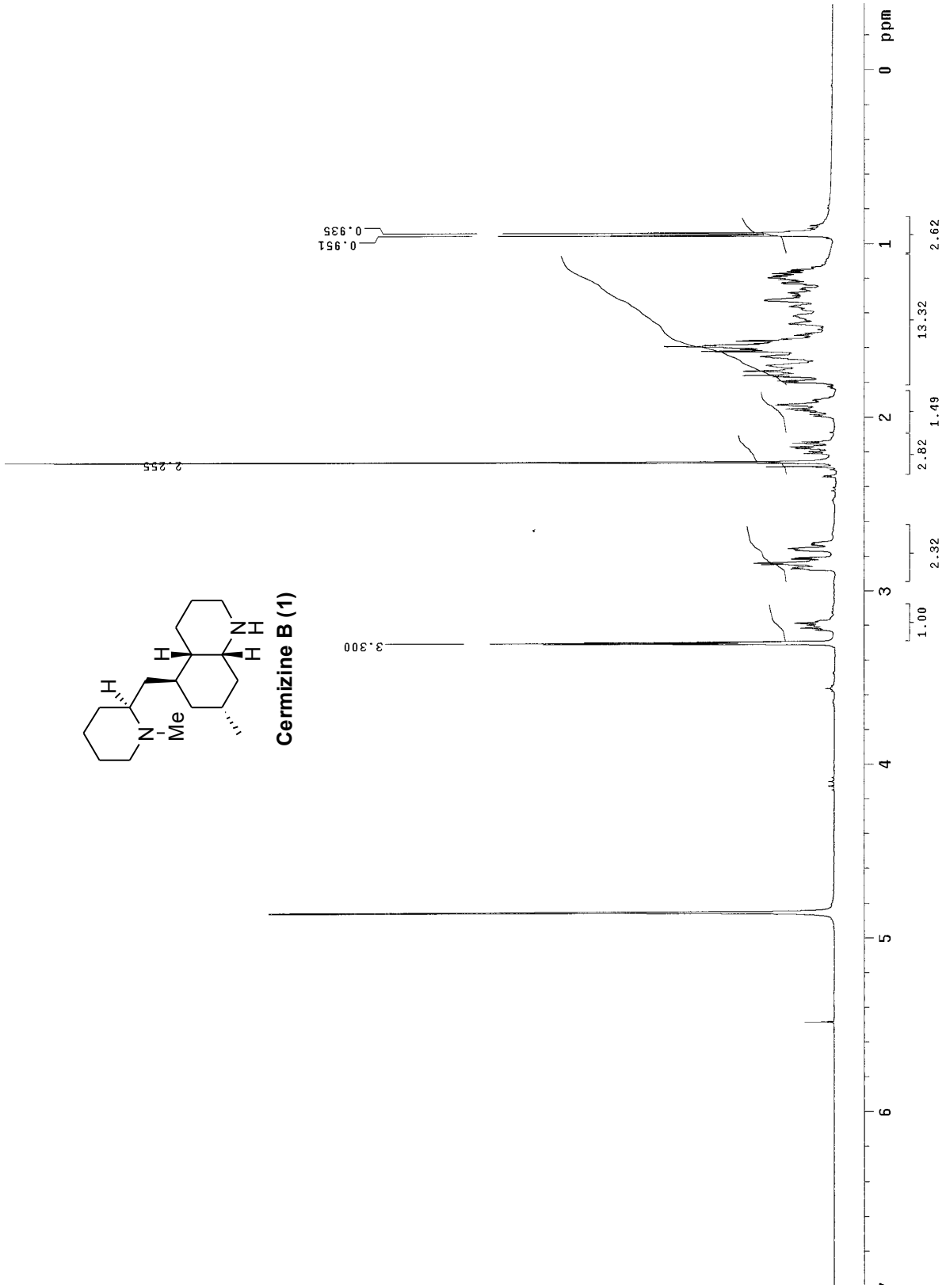
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for ***epi*-12**



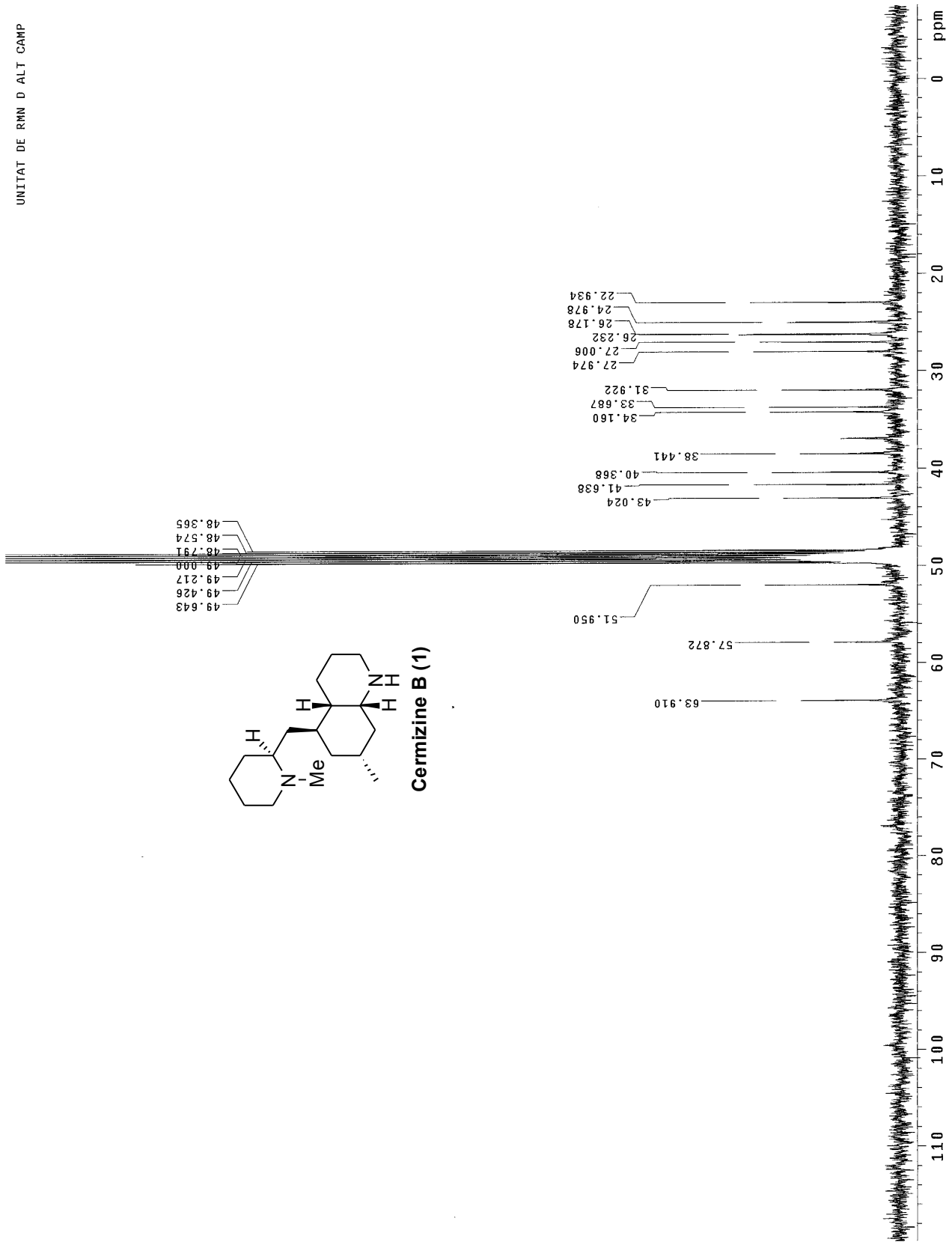
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for ***epi*-12**



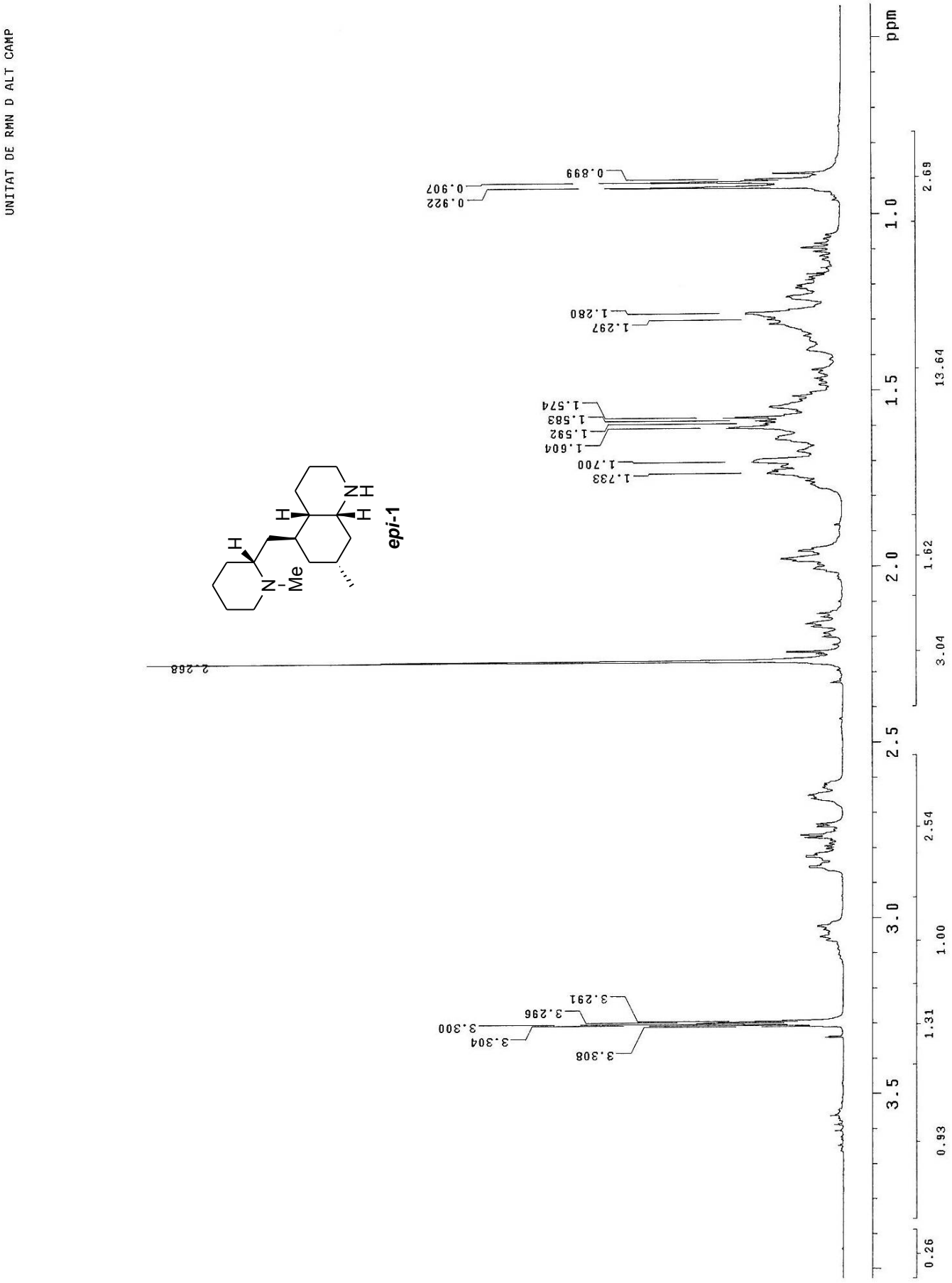
^{1}H NMR (400 MHz, CD_3OD) spectrum for **1 – Cermizine B**



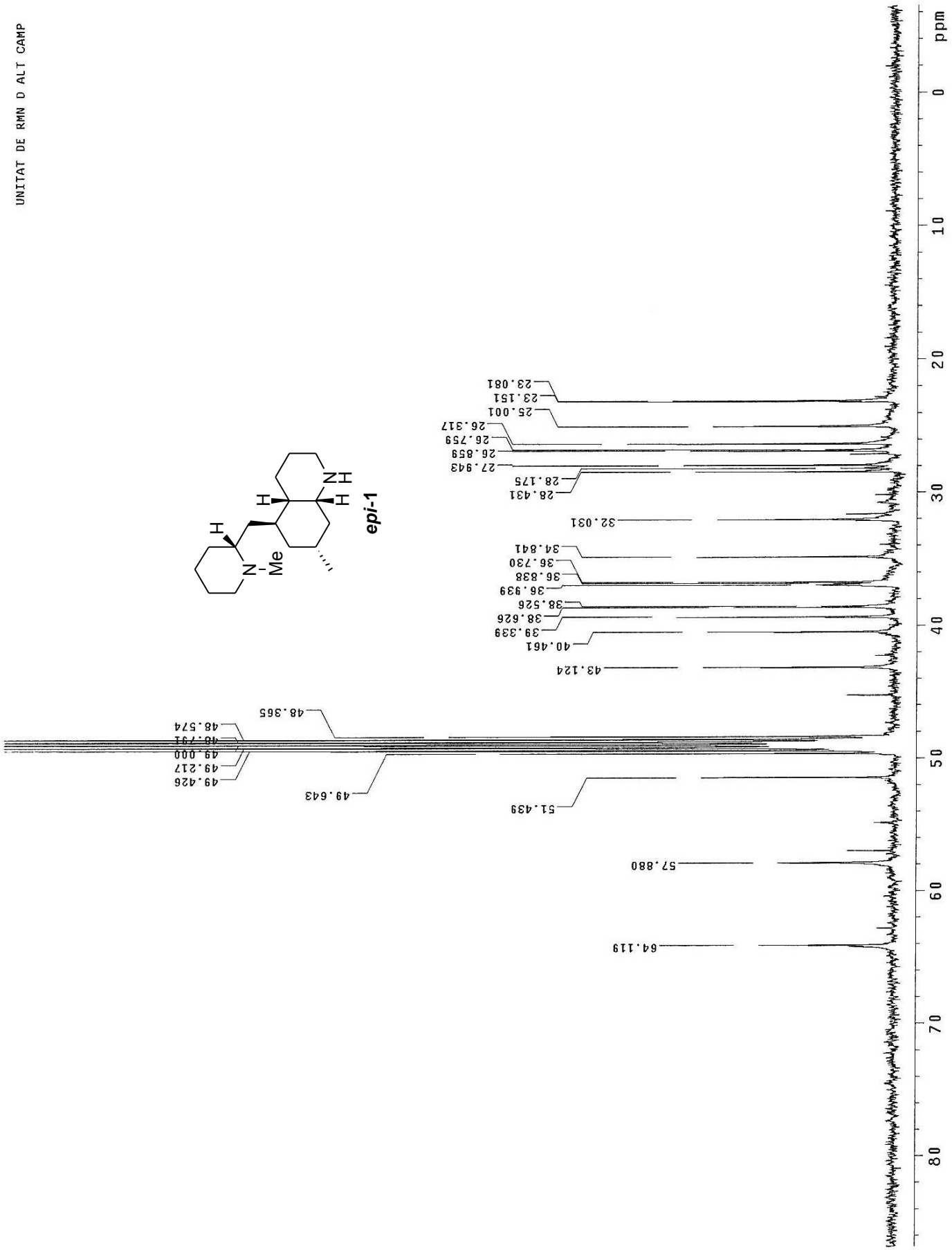
^{13}C NMR (100 MHz, CD_3OD) spectrum for **1 – Cermizine B**



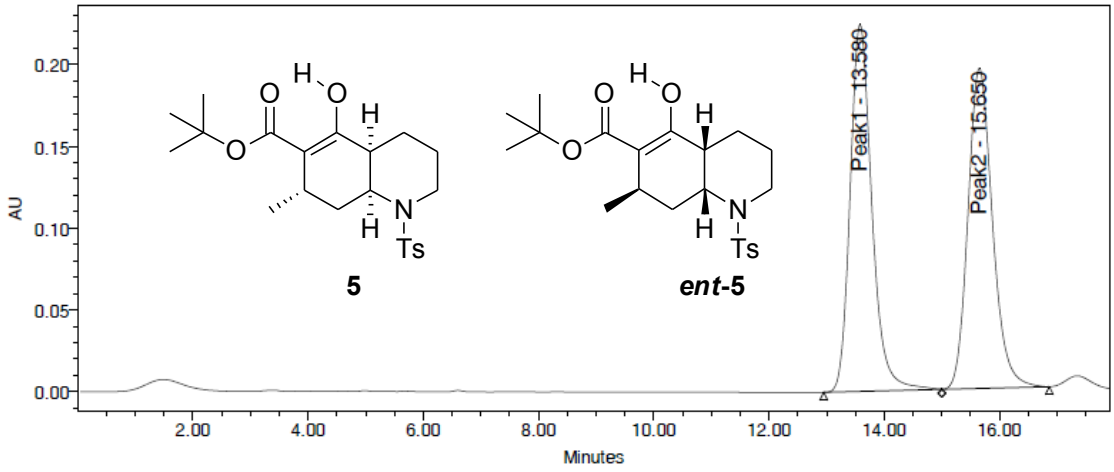
^{1}H NMR (400 MHz, CD_3OD) spectrum for ***epi*-1**



^{13}C NMR (100 MHz, CD_3OD) spectrum for ***epi*-1**



HPLC of a racemic sample of β-keto ester 5

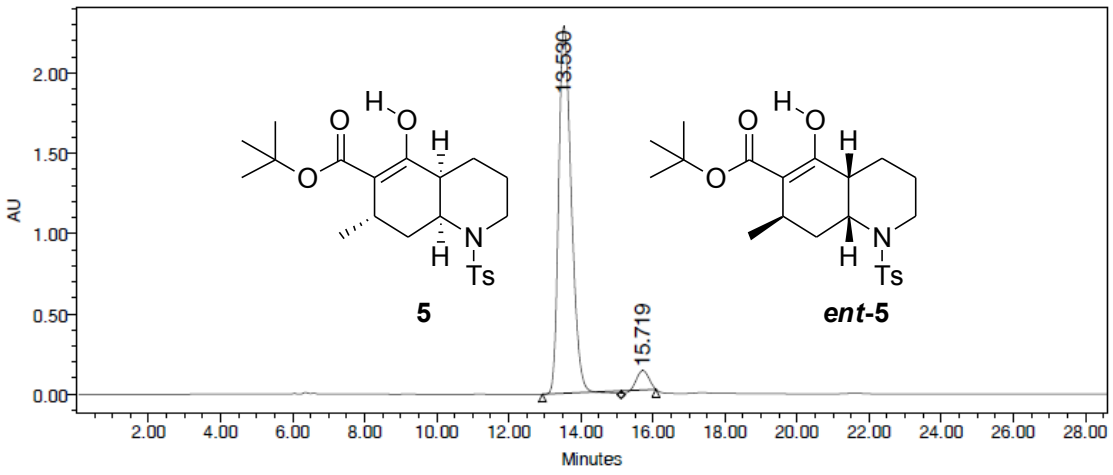


Channel: 2487Channel 1; Processed Channel: ; Result Id: 4244; Processing Method: a

Processed Channel Descr.:

	Peak Name	RT	Area	% Area	Height
1	Peak1	13.580	5872613	50.45	224308
2	Peak2	15.650	5767916	49.55	195800

HPLC of organocatalysed reaction



Channel: 2487Channel 1; Processed Channel: ; Result Id: 4151; Processing Method: a

Processed Channel Descr.:

	RT	Area	% Area	Height
1	13.530	55847434	94.96	2283645
2	15.719	2965265	5.04	121234