Supplementary Material
Structure-reactivity study of O-tosyl *Cinchona* alkaloids in their new synthesis and in hydrolysis to 9-epibases. Unexpected formation of cinchonicine enol tosylate accelerated by microwave activation

Teodozja M. Lipińska,*[a] Katarzyna Piechocka[a], Monika Denisiuk[a], Beata Chmiel[b], and Agnieszka Skórska-Stania[b]

[a]Institute of Chemistry, University of Siedlce. ul. 3 Maja 54, 08-110 Siedlce, Poland
[b]Faculty of Chemistry, Jagiellonian University, ul. R. Ingardena 3, 30-060 Kraków, Poland
E-mail: tlip@uph.edu.pl

1. Supplementary experimental informations

1.1 General procedure of Method B: liguid-solid phase tosylation of Cinchona alkaloids: Tosyl chloride (0.57 g, 3 mmol), tributylamine (0.10 mL, 0.4 mmol) and a powdered potassium hydroxide (1,12 g,.20 mmol) were added to a stirred solution ofcinchonine **2b** (0.59 g, 2 mmol) in dichloromethane (50 mL). The resulting mixture was stirred for 24 h at 20 ºC. Additional portion of potassium hydroxide (0.56g,10 mmol) was added and stirred for the next day. Water (50 mL) was added and stirred for 5 min. Organic phase was separated, washed with three portions of water and dried. Pure product **4b** (0.63 g, 79 %) was isolated

by column chromatography from unchanged started alkaloid (0.09 g, 15 %) Yields: **3a** 0.72 g (75 % from **1a**), **3b** 0.67 g (70 %) from **1b**; **4a**: 0.63 g (70 % from **2a**); **4b**: 0.71 (79 % from **2b).** Characterization data are given in the main text.

1.2 Hydrolysis of *O*-tosyl derivatives to 9-eipibases by conventional Procedure 1

Tosylate **3a**, **3b**, or **4a**, **4b** (4.78 g or 4.48 g, 10 mmol) and L-(+)- tartaric acid (2.25 g. 15 mmol) were added to 150 mL water and heated in water bath (temperature of the reaction mixture was 90-92 ºC. Conversion of tosylates was controlled by TLC (ethyl acetate - methanol system 10:1). This way, the times of heating of the reaction mixtures to the moment of the substrates disappearance were optimized as 15 min for **3a**, 30 min for **3b**, 6 h for **4a** and 20 h for **4b**. Next, solid sodium hydroxide 1.2 g (30 mmol) was added to the cooled reaction mixture and extracted with dichloromethane. Organic layer was dried with anhydrous sodium sulphate, solvent was removed under reduced pressure and oily residue was obtained in all cases. The trace of unchanged tosylates (2-4 %) were isolated as first during separation by column chromatography with the use of ethyl acetate. Then, in the cases reaction of tosylates **3a,b**, **4a** the starting alkaloids **1a,b**, **2a** were eluted (2-4 %) as the second compounds with pure 2-methoxyetanol or with the mixture ethyl acetate- methanol (up to 5 %) and next 9-epibases **1c,d**, **2c** were eluted with the mixture of 2-methoxyethanol and methanol (5-8 %).

In the case hydrolysis of tosylate **4b**, its remaining is as first isolated (with ethyl acetate), next the starting alkaloid **2b** (with pure methoxyethanol), then a new product **5** and 9-epicinchonine **2d** were carefully eluted (with the mixture methoxyetkanol – methanol up to 2 :1). In the Table 2 are given the yields of products **1c** (entry 1), **1d** (entry 2), **2c** (entry 3), **2d**, **5** (entry 4) together with their R_f values.

1.3 Procedure 2: Hydrolysis of tosylate 4b under microwave irradiation in the medium of tartaric acid : Tosylate **4b** (1.80 g, 4 mmol), L-(+)- tartaric acid (0.9 g, 6 mmol) to 20 mL and distilled water were added to a Pyrex cylindrical vessel and irradiated in Prolabo microwave reactor (Synthewave 402) in open system. The temperature set point was programmed at the temperature 80 ºC which was controlled continuously by changeable power. The full conversion of substrate **4b** was observed after 20 minutes which was found by monitoring of the reaction course by TLC analysis of the reaction mixture (silica-gel TLC plates eluting with ethyl acetate –methanol system 10:1) The analytical samples of the reaction mixture were collected after 5, 10, 15, 20, 25, 30 minutes. In the final procedure, the reaction was finished after 20 min. The reaction mixture was extracted with dichloromethane in the presence of an excess of 20 % solution sodium hydroxide (cooled). The organic phase was dried with anhydrous calcium chloride and the organic solvent was removed under reduced pressure. The pure product **5** (0.54 g, 30 %) was isolated by silica gel column chromatography eluted first with ethyl acetate first for removing trace of starting material **4b**. Product **5** was eluted with methanol/ethyl acetate - 3:100 or alternatively, by 2-methoxyethanol. Cinchonine **2b** (0.27 g, 23 %) and next 9-epicinchonine **2d** (0.36 g. 30 %) were eluted with the use of mixtures 2-

methoxyethanol and methanol (up to 8%). The characterization data for **5** are listed in the main text, ^{1}H NMR and ^{13}C NMR spectra NMR of 9-epicinchonine **2d** are given as **Figures SI. 3.7 and 3.8**.

2. Crystal data and the structure refinement from X-ray measurements of compound 6

Single crystals of compound **6** (CCDC 836794) were obtained from ethanol solution. The crystals were grown by slow evaporation of the solvent, at a temperature of about 293 K. The phase problem was solved by direct methods using SIR[1] and refined by full matrix least-squares method using SHELX97[2]. Hydrogen atoms were located in difference Fourier maps and refined isotropically, using riding model.

The details of the crystal data, data collection and refinement are listed in Table 1, while the asymmetric units of these structures together with atom numbering are shown in Figure 1. All projections were generated using ORTEP[3].

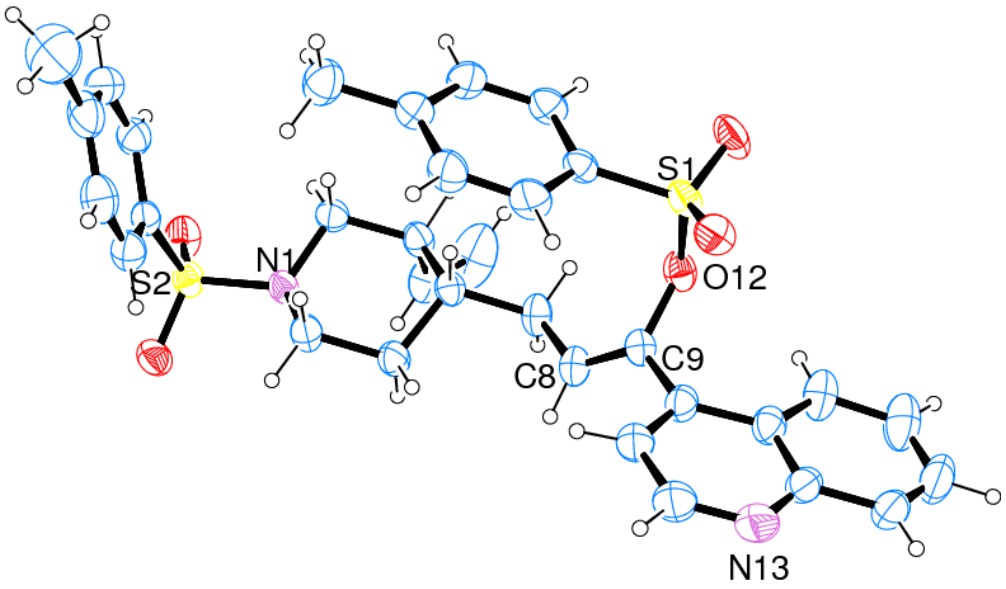

Figure 1. Ortep drawing of **6** with displacement ellipsoids shown at the 30% probability level

Table 1. Crystal data and structure refinement for compound **6**.

Identification code	Compound **6**
Empirical formula	C33 H34 N2 O5 S2
Formula weight	602.74
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, $P2_1$
Unit cell dimensions	a = 10.3964(3) Å α = 90° b = 12.9497(4) Å β = 111.465(1)° c = 12.6200(4) Å γ = 90°
Volume	1581.19(8) $Å^3$
Z, Calculated density	2, 1.266 Mg/m^3
Absorption coefficient	0.211 mm^{-1}
F(000)	636
Crystal size	0.25 x 0.12 x 0.07 mm
Theta range for data collection	2.10 to 27.53°
Limiting indices	-13<=h<=13, -16<=k<=16, -15<=l<=16
Reflections collected / unique	12347 / 6947 [R(int) = 0.0345]
Completeness to theta = 27.53°	99.7 %
Diffractometer	Bruker Nonius KappaCCD
Max. and min. transmission	0.9854 and 0.9492
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6947 / 1 / 381
Goodness-of-fit on F^2	1.033
Final R indices [I>2δ(I)]	R1 = 0.0464, wR2 = 0.0933
R indices (all data)	R1 = 0.0764, wR2 = 0.1069
Absolute structure parameter	-0.10(6)
Largest diff. peak and hole	0.171 and -0.233 $e.Å^{-3}$

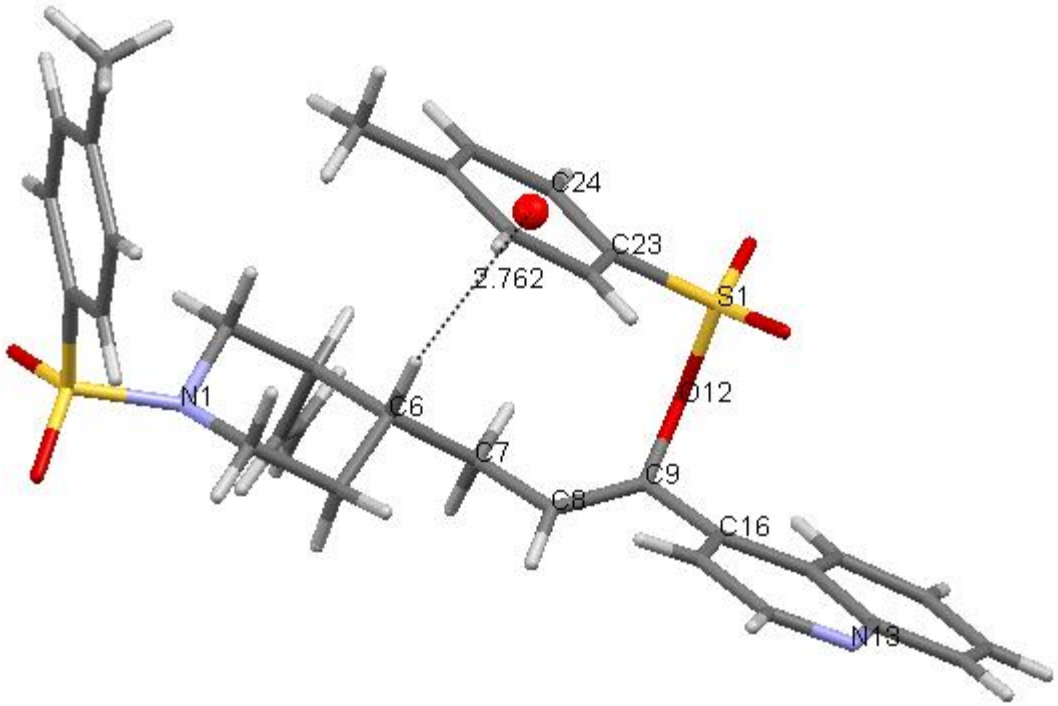

Figure 2. Projection of intramolecular interactions in crystals of **6.**

As shown in the projection of the molecule of the compound **6** (Fig.2), the configuration *Z* should be assigned to the double bond C8=C9. The shape of the molecule seems to be determined by the intramolecular C-H···π interactions (Table 2), which are most probably responsible for the conformation of the whole molecule. The carbon atom C6 interacts with the phenyl ring (C23-C28, the centre , Ctr, presented by the red ball) of the O-tosylate moiety. This interaction leads to the formation of a pseudo-ring: C6-H6···Ctr··· C23-S1-O12-C9-C8-C7-C6. A relatively short contact (3.988 Å), of a C-H···π character, occurs also between the atom C40 (in the methyl substituent of C23-C28 ring) and the phenyl ring of the N-tosylate group. The phenyl ring of the O-tosylate group and the quinoline ring are almost planar and almost parallel to each other, the angle between their planes being about 8°. The N-tosylate moiety is strongly deviated from the O-tosylate group (the angle between the two planes equals 56°).

The classical intermolecular hydrogen bonds do not exist in the crystal structure of the compound **6**, however the weak hydrogen bonds, C-H···O (Table 3) play a crucial part in controlling the crystal packing.

Table 2. Intramolecular C-H…π geometry (Å, °)

D-H…Ctr	D-H	H…Ctr	D…Ctr	D-H…Ctr
C6-H6…Cg(4)	0.98	2.76	3.710(3)	163
Ctr - centroid of the ring C26, C27, C28, C23, C24, C25				

Table 3. Intermolecular hydrogen-bond geometry (Å, °)

D-H…A	D-H	H…A	D…A	D-H..A
C4-H4A...O14 [1]	0.97	2.41	3.343(4)	161
C27-H27...O21 [2]	0.93	2.46	3.364(4)	164
C29-H29C...O13 [3]	0.96	2.44	3.375(4)	165
Symmetry codes:				
[1] -1+x,y,z				
[2] -x,1/2+y,1-z				
[3] 1-x,-1/2+y,1-z				

References

1. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.; Burla, M.; Polidori, G.; Camalli, M.; Spagna R. *J. Appl. Crystallogr.* **1994**, *27*, 436.
2. Sheldrick G.M., *SHELXL97. Program for crystal structure refinement,* University of Göttingen **1997**
3. Farrugia, L.J. J. *Appl. Crystallogr*. **1997**, *30*, 565.

3. NMR spectra of 9-epibases 1c,d, 2c,d

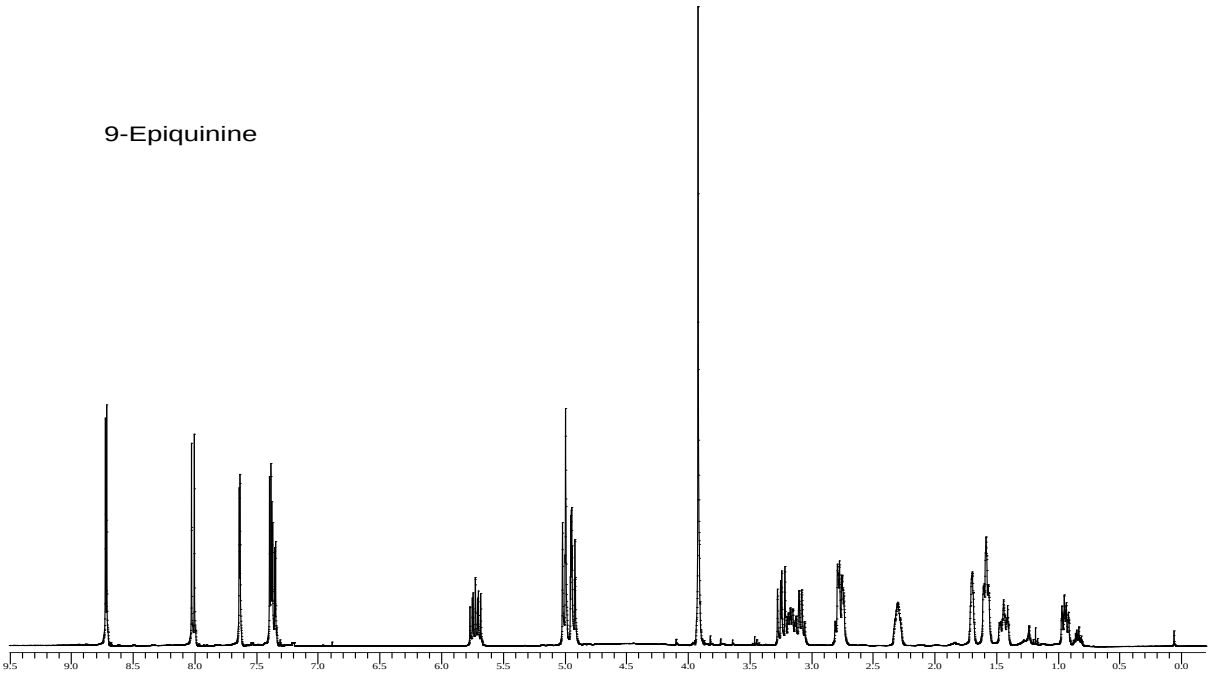

Figure SM. 3.1. ^{1}H NMR of 9-epiquinine **1c.**

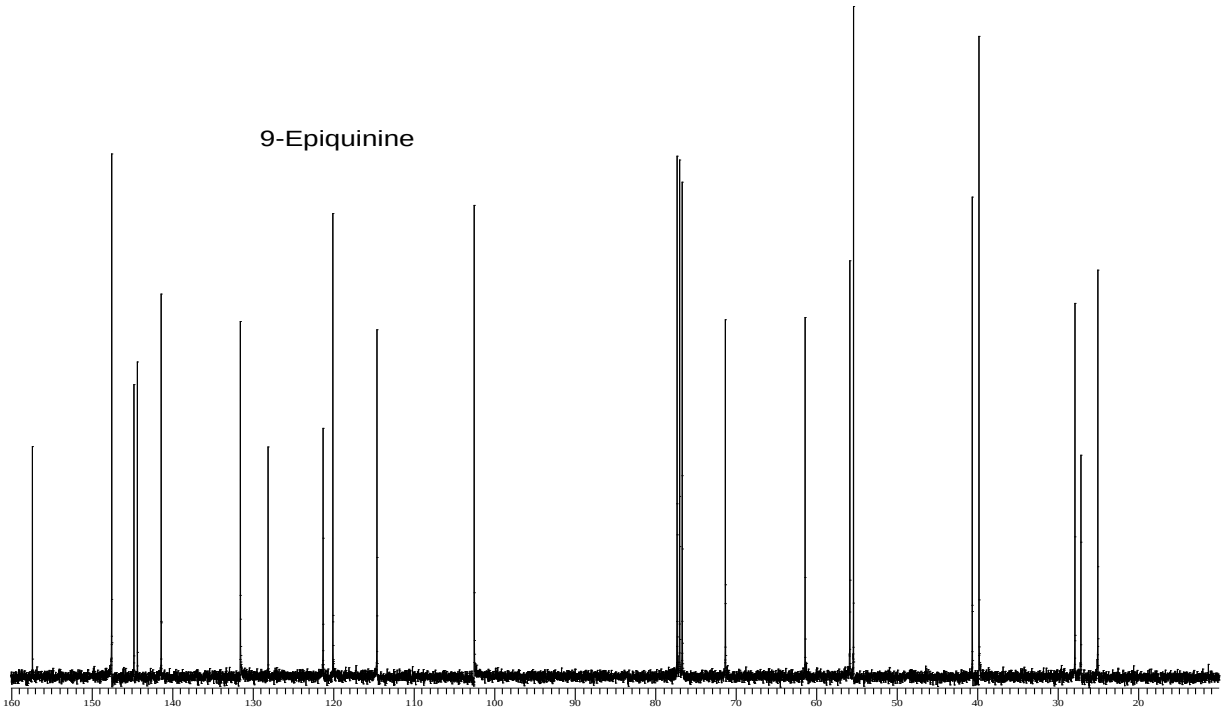

Figure SM. 3.2. ^{13}C NMR spectrum of epiquinine **1c.**

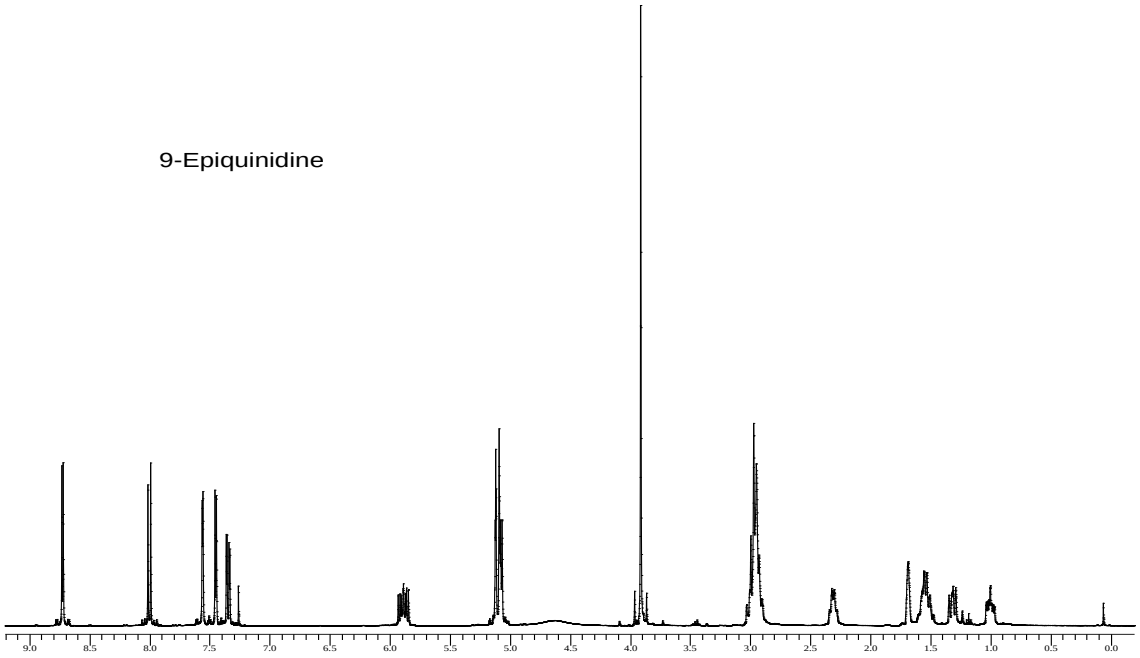

Figure SI. 3.3. ^{1}H NMR spectrum of 9-epiquinidine **1d**.

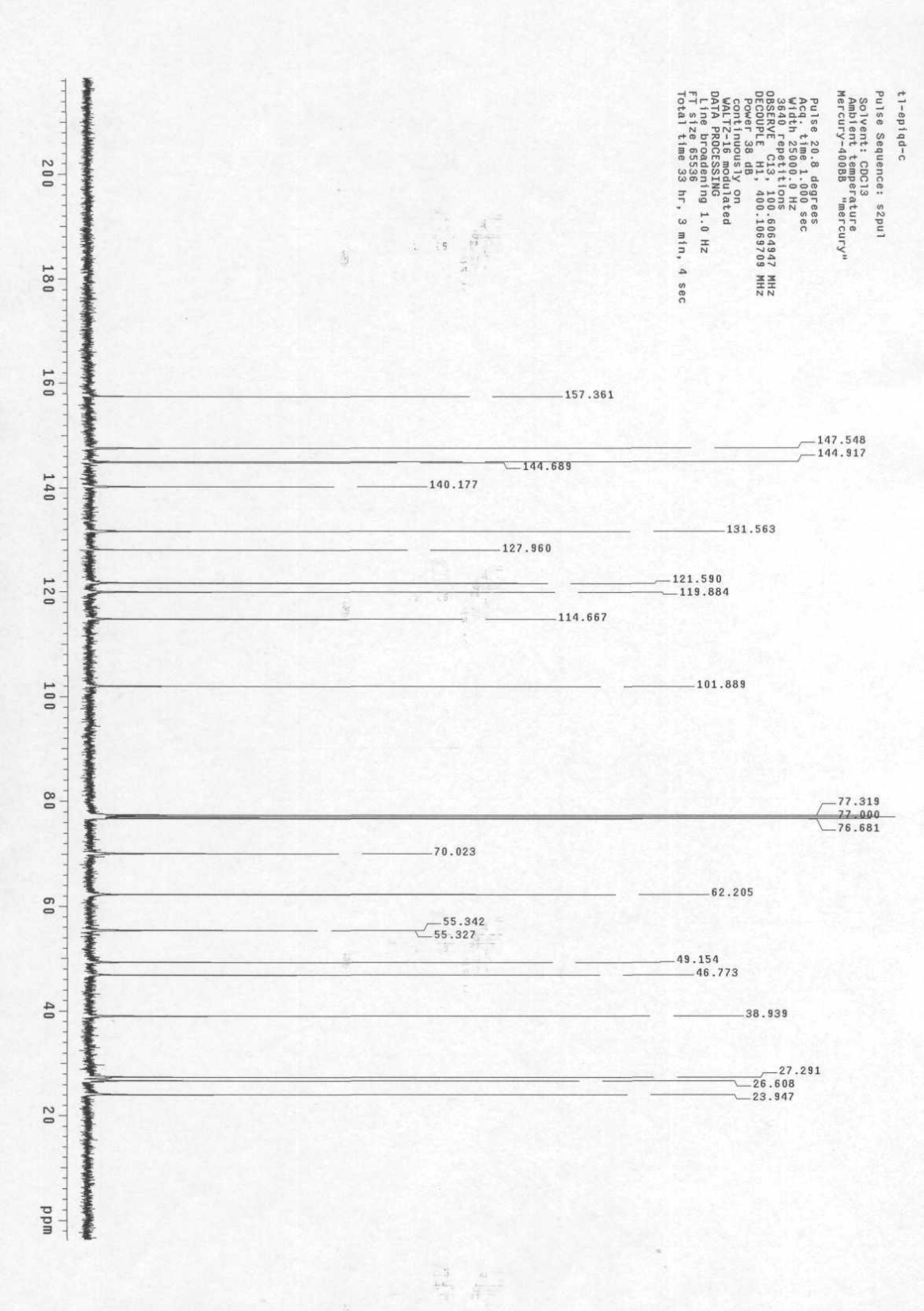

Figure SI. 3.4. ^{13}C NMR spectrum of 9-epiquinidine **1d**.

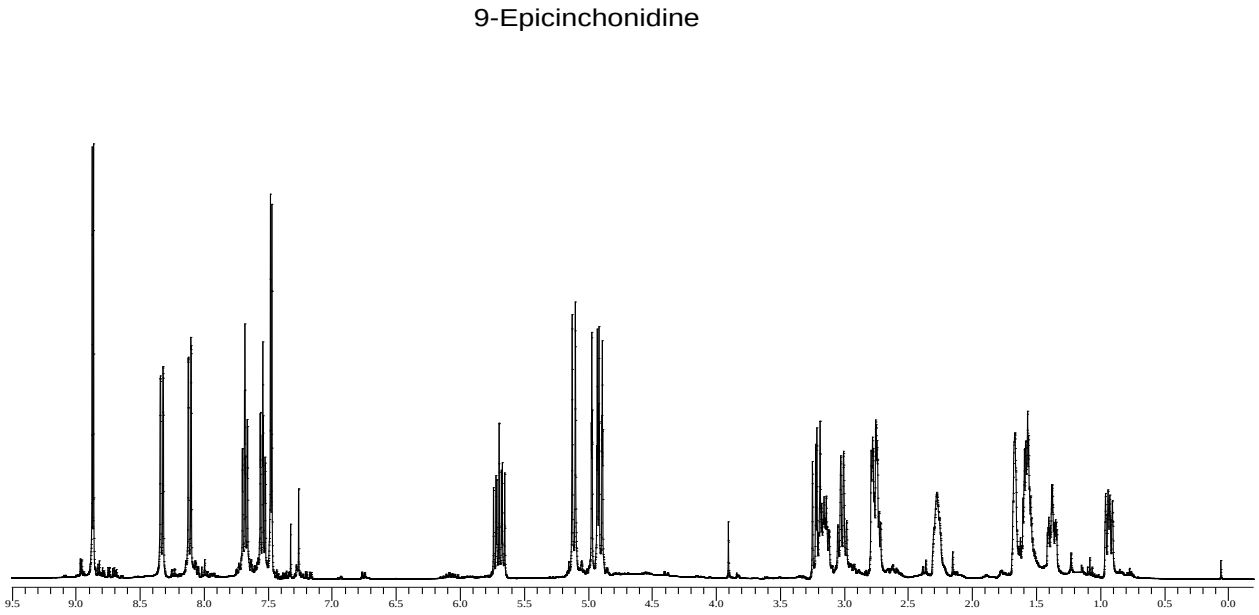

Figure SM. 3.5. ^{1}H NMR spectrum of 9-epicinchonidine **2c.**

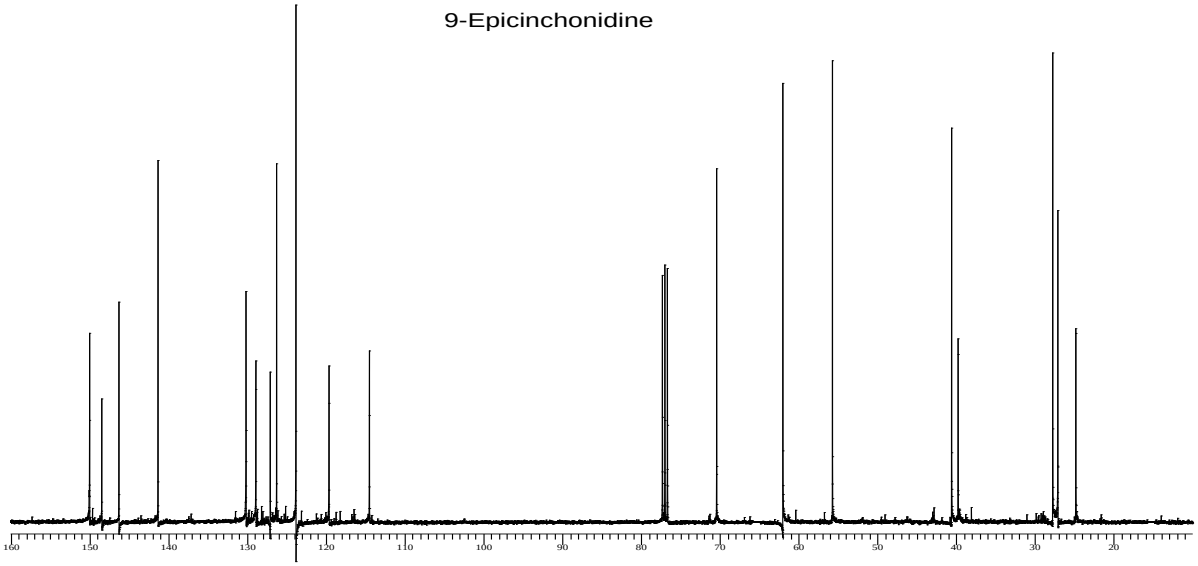

Figure SM. 3.6. ^{13}C NMR spectrum of 9-epicinchonidine **2c**.

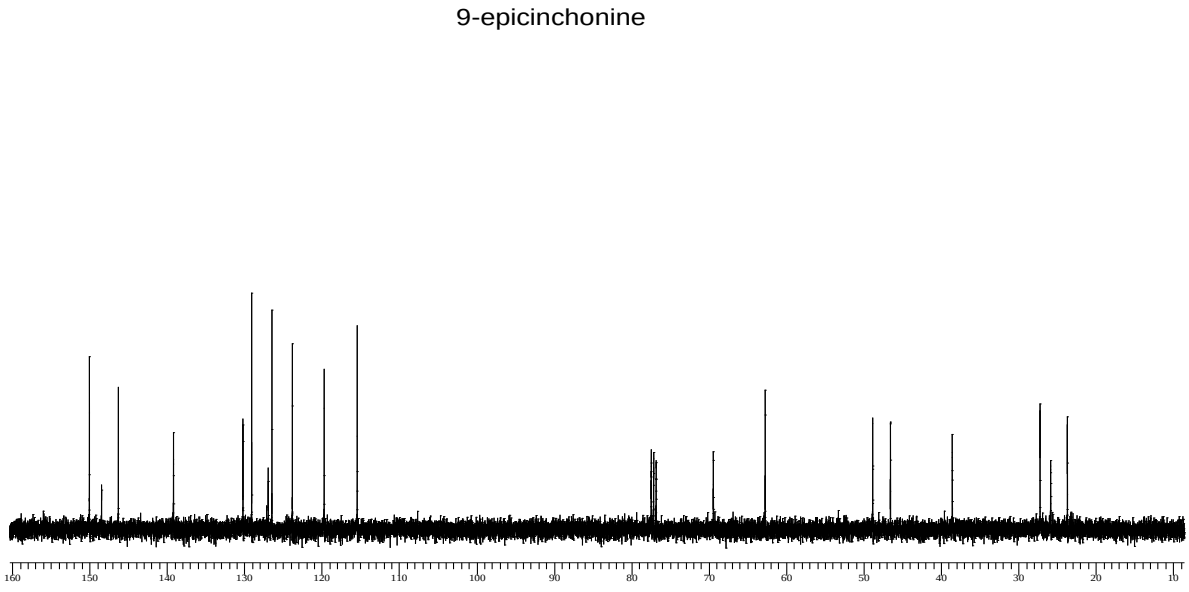

Figure SM.3. 7. ^{1}H NMR spectrum of 9-epicinchonine **2d.**

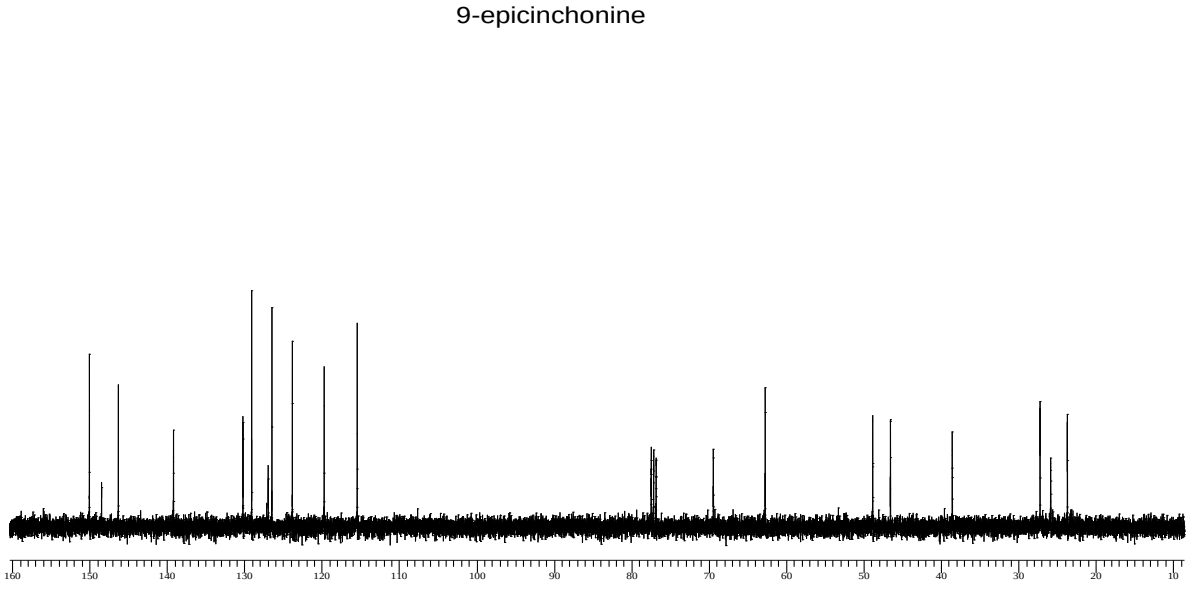

Figure SM 3.8. ^{13}C NMR spectrum of 9-epicinchonine **2d.**

