# Total Synthesis of (–)-Lycorine and (–)-2-*epi*-Lycorine by Asymmetric Conjugate Addition Cascade

*Ken-ichi Yamada, Mitsuaki Yamashita, Takaaki Sumiyoshi, Katsumi Nishimura, and Kiyoshi Tomioka**

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto 606-8501, Japan.

tomioka@pharm.kyoto-u.ac.jp

**Contents**

Experimental Procedures..... S2

NMR Charts of the Products ..... S19

HPLC Traces of **7** and **9** ..... S51

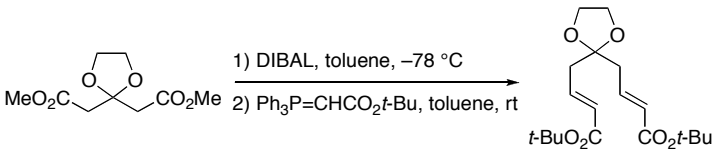
## Supporting Information

### General.

All melting points are uncorrected. Silica gel was used for column chromatography. NMR (500 MHz for $^{1}H$ and 125 MHz for $^{13}C$) was measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts and coupling constants are presented in ppm δ relative to tetramethylsilane and Hz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. $^{13}C$ peak multiplicity assignments were made based on DEPT data. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in $cm^{-1}$. $POCl_3$ and *m*-CPBA were purified by standard protocols prior to use.[1] Other reagents were purchased from chemical companies and used as received. Except for MeOH and MeCN, dehydrated solvents were purchased for the reactions and used without further desiccation.

### Total Synthesis of Lycorine.

***tert*-Butyl (2*E*,2'*E*)-4,4'-(1,3-dioxolane-2,2-diyl)dibut-2-enoate (5):**




To a solution of dimethyl 1,3-dioxolane-2,2-diacetate[2] (21.8 g, 100 mmol) in toluene (500 mL) was added DIBAL (1.0 M in hexane, 200 mL, 200 mmol) over 1 h at –78 °C, and the mixture was stirred at the same temperature for 1 h. MeOH (8.1 mL) was added at –78 °C, and the mixture was stirred at the same temperature for additional 15 min. $H_2O$ (11 mL) in MeOH (16 mL) was added at –78 °C, and the mixture was allowed to warm up to room temperature. The mixture was filtered through Celite, and the filtrate was dried over $Na_2SO_4$. Concentration gave brown oil (16.0 g), which was then dissolved in toluene (400 mL). To the solution, was added (*t*-butoxycarbonylmethylene)triphenylphosphorane (82.7

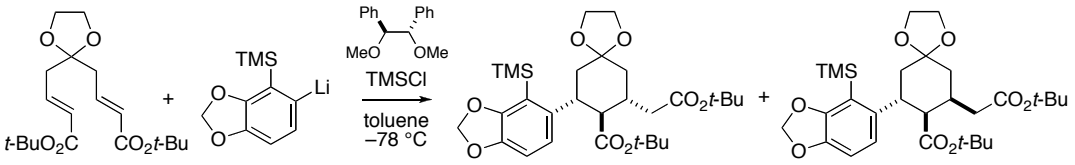
---

1 D. D. Perrin, W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press, Oxford, UK, **1988**.

2 R. J. Davenport. A. C. Regan, *Tetrahedron Lett*. **2000**, *41*, 7619–7622.

g, 220 mmol), and the mixture was stirred for 3 h at room temperature. After addition of hexane (200 mL), the reaction mixture was filtered through Celite, and the filtrate was dried over $Na_2SO_4$. Concentration and column chromatography (hexane/$Et_2O$ = 4/1) gave the titled dialkenoate (18.2 g, 51% yield in 2 steps) as colorless gum. $^1$H NMR: 1.48 (s, 18H), 2.50 (dd, *J* = 1.3, 7.6, 4H), 3.97 (s, 4H), 5.82 (dd, *J* = 1.3, 15.2, 2H), 6.82 (dt, *J* = 7.6, 15.2, 2H). $^{13}$C NMR: 28.1 ($CH_3$), 40.5 ($CH_2$), 65.4 ($CH_2$), 80.2 (C), 109.4 (C), 126.6 (CH), 141.1 (CH), 165.4 (C). IR (neat): 2978, 2936, 2889, 1710, 1477, 1458, 1393, 1366, 1655, 1157, 984. FABMS *m/z*: 355 (MH), 243, 213, 157. Anal. Calcd. for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.31; H, 8.44.

***tert*-Butyl (1*R*,2*R*,3*R*)- and (1*S*,2*R*,3*R*)-2-*tert*-butoxycarbonyl-3-(4-trimethylsilyl-1,3-benzodioxol-5-yl)-5,5-ethylenedioxycyclohexaneacetate (7 and its isomer):**

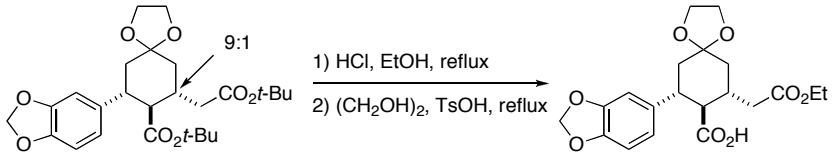



To a solution of **3** (1.02 g, 4.21 mmol) and 5-bromo-4-(trimethylsilyl)-1,3-benzodioxole[3] (819 mg, 3.00 mmol) in toluene (27 mL) was added *t*-BuLi (1.66 mL, 1.7 M pentane solution, 2.8 mmol) over 10 min at –78 °C, the mixture was stirred for 1 h. A solution of dialkenoate **5** (354 mg, 1.00 mmol) and TMSCl (0.63 mL, 5.0 mmol) in toluene (3.0 mL) was added over 10 min at –78 °C. The resulting solution was stirred at –78 °C for 10 min and then quenched with sat. $NH_4Cl$. The mixture was extracted with $Et_2O$. The organic extracts were washed with sat. $NaHCO_3$ and brine, and then dried over $Na_2SO_4$. Concentration and column chromatography (hexane/$Et_2O$ = 4/1) gave a 9:1 mixture of **7** and its isomer (532 mg, 97% yield) as colorless gum: $[\alpha]_D^{25}$ –17.3 (*c* 1.02, $CHCl_3$). The enantiomeric excess of **7** was determined to be 92% ee by HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 100/1, 1 mL/min, 254 nm, major 11.0 min and minor 15.4 min). $^1$H NMR, **7**: 0.40 (s, 9H), 1.10 (s, 9H), 1.46 (s, 9H), 1.51 (dd, *J* =

3 R. J. Mattson, C. P. Sloan, C. C. Lockhart, J. D. Catt, Q. Gao, S. Huang, *J. Org. Chem.* **1999**, *64*, 8004–8007.

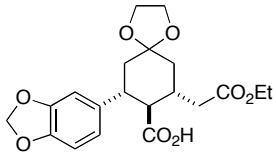
13.1, 13.1, 1H), 1.60 (dd, *J* = 13.3, 13.3, 1H), 1.89 (ddd, *J* = 2.8, 2.8, 13.3, 1H), 1.95 (m, 1H), 2.10 (dd, *J* = 8.9, 15.3, 1H), 2.33 (dd, *J* = 2.5, 15.3, 1H), 2.37–2.50 (m, 2H), 3.39 (ddd, *J* = 3.4, 10.7, 12.8, 1H), 3.89–4.00 (m, 4H), 5.84 (d, *J* = 11.3, 1H), 5.85 (d, *J* = 11.3, 1H), 6.78 (d, *J* = 8.2, 1H), 6.80 (d, *J* = 8.2, 1H); its isomer: 0.44 (s, 9H), 1.21 (s, 9H), 1.45 (s, 9H), 1.55–1.63 (m, 1H), 1.87–1.97 (m, 2H), 2.07–2.14 (m, 1H), 2.28–2.50 (m, 2H), 2.78–2.88 (m, 2H), 3.34–3.42 (m, 1H), 3.83–4.00 (m, 4H), 5.84–8.85 (m, 2H), 6.70 (d, *J* = 7.9, 1H), 3.73 (d, *J* = 7.9, 1H). $^{13}$C NMR, **7**: 1.3 ($CH_3$), 27.6 ($CH_3$), 28.0 ($CH_3$), 34.8 (CH), 39.2 ($CH_2$), 39.3 ($CH_2$), 42.4 (CH), 43.8 ($CH_2$), 54.8 (CH), 64.2 ($CH_2$), 64.3 ($CH_2$), 79.8 (C), 80.2 (C), 99.5 ($CH_2$), 107.8 (CH), 108.6 (C), 119.4 (C), 120.5 (CH), 141.0 (C), 144.1 (C), 152.2 (C), 170.8 (C), 173.0 (C). IR: 2978, 2878, 1728, 1620, 1580, 1450, 1416, 1396, 1369, 1153, 1076, 1053. EIMS *m*/*z*: 548 ($M^+$), 421, 329, 243. Anal. Calcd. for $C_{29}H_{44}O_8Si$: C, 63.47; H, 8.08. Found: C, 63.77; H, 8.28. The diasteromeric ratio was determined based on the ratio of the integration aria of the $^1$H NMR signals at 0.40 and 0.44 ppm where the methyl protons of the TMS of the each isomer appear. The relative configuration of **7** was confirmed after conversion to **8**.

**Ethyl (1*R*,2*R*,3*R*)-3-(1,3-benzodioxol-5-yl)-2-carboxy-5,5-ethylenedioxycyclohexaneacetate (8):**

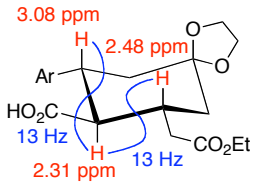



To a solution of the 9:1 mixture of dialkanoates **7** and its isomer (20.8 g, 379 mmol) in EtOH (6 mL) was added 40% HCl in EtOH (60 mL) at 0 °C. The mixture was heated under reflux for 1 h. After addition of cold $H_2O$ (100 mL), the mixture was extracted with $Et_2O$ three times. The combined organic extracts were washed with brine and dried over $Na_2SO_4$. Concentration gave brown oil (25.7 g), which was then dissolved in benzene (100 mL). To a solution was added and ethylene glycol (8.5 mL, 150 mmol) *p*-toluenesulfonic acid monohydrate (217 mg, 1.14 mmol), and the mixture was heated under reflux for 2 h. After cooled to room temperature, the mixture was washed with brine and then dried over

$Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 1/1) gave the titled carboxylic acid (11.5 g, 77% yield) as colorless gum.

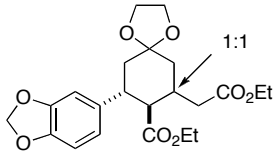



**8**: $[\alpha]_D^{25}$ –12.4 (*c* 0.95, $CHCl_3$). $^1$H NMR: 1.24 (t, *J* = 7.1, 3H), 1.46 (dd, *J* = 12.8, 12.8, 1H), 1.71 (dd, *J* = 12.8, 12.8, 1H), 1.86 (dd, *J* = 3.4, 12.8, 1H), 1.94 (dd, *J* = 3.4, 12.8, 1H), 2.18 (dd, *J* = 8.9, 15.6, 1H), 2.31 (dd, *J* = 12.8, 12.8, 1H), 2.39 (dd, *J* = 3.4, 15.6, 1H), 2.48 (m, 1H), 3.08 (ddd, *J* = 3.4, 12.8, 12.8, 1H), 3.96 (m, 4H), 4.10 (q, *J* = 7.1, 2H), 5.91 (s, 2H), 6.61 (d, *J* = 8.0, 1H), 6.67 (s, 1H), 6.68 (d, *J* = 8.0, 1H). $^{13}$C NMR: 14.1 ($CH_3$), 34.5 (CH), 38.5 ($CH_2$), 39.0 ($CH_2$), 43.8 (CH), 54.6 ($CH_2$), 60.4 ($CH_2$), 64.3 ($CH_2$), 64.5 ($CH_2$), 100.8 ($CH_2$), 107.5 (C), 107.5 ($CH_2$), 108.2 (CH), 120.6 (CH), 128.3 (C), 135.9 (C), 146.4 ($CH_2$), 147.7 (C), 171.6 (C), 179.0 (C). IR: 3300, 2955, 2893, 1732, 1713, 1609, 1489, 1443, 1377, 1072, 1042. EIMS *m*/*z*: 392 ($M^+$), 346, 259, 219, 185, 148, 115, 99. HRMS-EI (*m*/*z*): $[M]^+$ Calcd. for $C_{20}H_{24}O_8$: 392.1471. Found: 392.1479. Anal. Calcd. for $C_{20}H_{24}O_8$: C, 61.22; H, 6.16. Found: C, 61.33; H, 5.95. The relative configuration of **8** was assigned based on the coupling constants shown below.

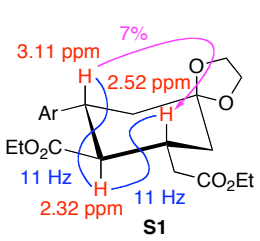


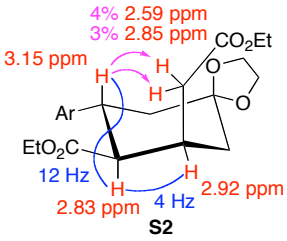

**Ethyl (1*R*,2*R*,3*R*)-3-(1,3-benzodioxol-5-yl)-2-carboxy-5,5-ethylenedioxycyclohexaneacetate (8), and ethyl (1*R*,2*R*,3*R*)- and (1*S*,2*R*,3*R*)-3-(1,3-benzodioxol-5-yl)-2-ethoxycarbonyl-5,5-ethylene-dioxycyclohexaneacetate (S1 and S2):**

The same procedure as above, except that the first reaction was conducted for 3 h, gave **8** in 50% yield as well as a 1:1 diastereomeric mixture of diethyl esters **S1** and **S2** in 25% yield as colorless oil.

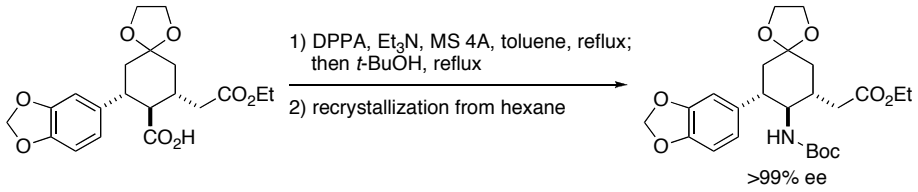



the 1:1 mixture of **S1** and **S2**: $^{1}$H NMR, **S1**: 0.98 (t, *J* = 7.0, 3H), 1.25 (t, *J* = 7.0, 3H), 1.49 (dd, *J* = 13.0, 13.0, 1H), 1.73 (dd, *J* = 13.1, 13.1, 1H), 1.89 (m, 1H), 1.98 (ddd, *J* = 3.1, 3.1, 13.0, 1H), 2.18 (dd, *J* = 9.2, 15.6, 1H), 2.32 (dd, *J* = 11.3, 11.3, 1H), 2.36 (dd, *J* = 4.0, 15.6, 1H), 2.52 (m, 1H), 3.11 (ddd, *J* = 3.7, 11.3, 13.1, 1H), 3.85–4.01 (m, 6H), 4.10–4.16 (m, 2H), 5.904 (s, 2H), 6.63–6.71 (m, 3H); **S2**: 1.04 (t, *J* = 7.2, 3H), 1.26 (t, *J* = 7.2, 3H), 1.65 (dd, *J* = 13.1, 13.1, 1H), 1.84 (dd, *J* = 5.2, 14.4, 1H), 1.87–1.94 (m, 2H), 2.59 (dd, *J* = 5.8, 16.5, 1H), 2.83 (dd, *J* = 4.3, 12.2, 1H), 2.85 (dd, *J* = 8.6, 16.5, 1H), 2.92 (m, 1H), 3.15 (ddd, *J* = 3.1, 12.2, 13.1, 1H), 3.85–4.01 (m, 6H), 4.10–4.16 (m, 2H), 5.902 (s, 2H), 6.63–6.71 (m, 3H). $^{13}$C NMR, **S1**: 13.93 ($CH_3$), 14.1 ($CH_3$), 34.6 (CH), 38.6 ($CH_2$), 39.3($CH_2$), 41.9($CH_2$), 44.2 (CH), 55.1 (CH), 60.1 ($CH_2$), 60.3 ($CH_2$), 64.4 ($CH_2$), 64.6 ($CH_2$), 100.84 ($CH_2$), 107.7 (C), 107.78 (CH), 108.12 (CH), 120.7 (CH), 136.3 (C), 146.3 (C), 147.62 (C), 171.9 (C), 173.5 (C); **S2**: 13.86 ($CH_3$), 14.2 ($CH_3$), 32.4 (CH), 34.0 ($CH_2$), 37.4 ($CH_2$), 38.8 (CH), 43.3 ($CH_2$), 51.4 (CH), 60.15 ($CH_2$), 60.17($CH_2$), 63.8($CH_2$), 64.7($CH_2$), 100.82 ($CH_2$), 107.81 (CH), 108.08 (CH), 108.2 (C), 120.4 (CH), 137.3 (C), 146.1 (C), 147.57 (C), 172.9 (C), 173.3 (C). IR (neat): 2978, 2893, 1728, 1612, 1489, 1443, 1381, 1250, 1173, 1080, 1034, 984, 864, 810, 733, 640. FABMS *m/z*: 421 (MH), 420 ($M^+$), 419 (M–1), 375 (M – OEt), 347 (M – $CO_2$Et). HRMS-FAB (*m/z*): $[M]^+$ Calcd. for $C_{22}H_{28}O_8$: 420.1784. Found: 420.1783. The relative configurations of **S1** and **S2** were assigned based on the coupling constants (blue) and the NOE (magenta) shown below.



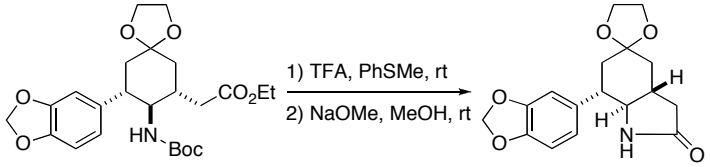




**Ethyl (1*R*,2*R*,3*S*)-3-(1,3-benzodioxol-5-yl)-2-(*tert*-butoxycarbonylamino)-5,5-ethylenedioxycyclohexaneacetate (9):**



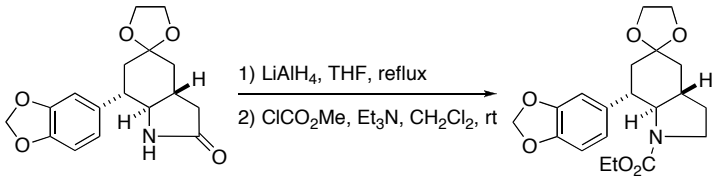

Carboxylic acid **8** (4.31 g, 11.0 mmol) was dried by azeotropic distillation with toluene (3 × 50 mL) and dissolved in toluene (50 mL). To the solution were added crushed molecular sieves 4Å (20 g), and the mixture was stirred for 30 min under argon atmosphere at room temperature. To the mixture were added $Et_3N$ (6.1 mL, 44 mmol) and DPPA (4.8 mL, 22 mmol), and the mixture was heated under reflux for 1.5 h. After addition of *t*-BuOH (40 mL), the mixture was further heated under reflux for 4 days. The mixture was filtered through Celite, and the filtrate was dried over $Na_2SO_4$. Concentration and silica gel column chromatography (hexane/acetone = 4/1) gave the titled carbamate (4.70 g, 80% yield) as colorless needles. Recrystallization from hexane gave almost enantiomerically pure colorless needles (4.12 g, 88% yield) of mp 155–157 °C (>99% ee; HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, 1 mL/min, 254 nm, major 10.1 min and minor 8.2 min): $[\alpha]_D^{25}$ –8.0 (*c* 2.28, $CHCl_3$). $^1$H NMR: 1.21 (s, 9H), 1.25 (t, *J* = 7.1, 3H), 1.57 (dd, *J* = 12.8, 12.8, 1H), 1.86 (dd, *J* = 12.8, 12.8, 1H), 1.92 (m, 2H), 2.18 (dd, *J* = 8.0, 15.6, 1H), 2.25 (m, 1H), 2.61 (dd, *J* = 4.7, 15.6, 1H), 2.75 (ddd, *J* = 3.7, 12.8, 12.8, 1H), 3.48 (dd, *J* = 12.8, 12.8, 1H), 3.94 (m, 4H), 4.09 (brs, 1H), 4.10 (m, 2H), 5.89 (d, *J* = 9.2, 2H), 6.67 (d, *J* = 8.0, 1H), 6.71(s, 1H), 6.72 (d, *J* = 8.0, 1H). $^{13}$C NMR: 14.2 ($CH_3$), 28.0 ($CH_3$), 37.6 (CH), 38.0 ($CH_2$), 40.0 ($CH_2$), 42.4 ($CH_2$), 47.6 (CH), 57.4 (CH), 60.3 ($CH_2$), 64.4 ($CH_2$), 64.5 ($CH_2$), 79.0 (C), 100.8 ($CH_2$), 107.5 (C), 108.0 (CH), 108.3 (CH), 121.0 (CH), 135.9 (C), 146.2 (C), 147.5 (C), 155.5 (C), 173.1 (C). IR: 3360, 2978, 2932, 2885, 1720, 1710, 1609, 1504, 1443, 1366, 1246, 1169, 1038. EIMS *m*/*z*: 463 ($M^+$), 346, 259, 221, 148, 135. Anal. Calcd. for $C_{24}H_{33}NO_8$: C, 62.19; H, 7.18; N, 3.02. Found: C, 62.11; H, 7.19; N, 3.17.

**(3a*R*,7*S*,7a*R*)-7-(1,3-Benzodioxol-5-yl)-5,5-ethylenedioxyhexahydro-1*H*-indol-2(3*H*)-one (S3):**




A mixture of carbamate **9** (2.32 g, 5.00 mmol), TFA (7.70 mL, 100 mmol) and thioanisole (1.17 mL, 10.0 mmol) was stirred at room temperature for 1 h. The mixture was poured into sat. $NaHCO_3$ (50 mL) at 0 °C and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried over $Na_2SO_4$, and then concentrated to give brown oil (3.56 g). To a solution of the oil in MeOH (25 mL) was added NaOMe (1.35 g, 25.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 days. The reaction mixture was diluted with AcOEt, washed with brine, and then dried over $Na_2SO_4$. Concentration and column chromatography (AcOEt) gave the titled lactam (1.28 g, 81% yield) as colorless needles of mp 192.5–193.5 °C: $[\alpha]_D^{25}$ –51.3 (*c* 1.01, $CHCl_3$). $^1$H NMR: 1.69 (dd, *J* = 12.8, 12.8, 1H), 1.82 (dd, *J* = 12.8, 12.8, 1H), 1.95–2.05 (m, 2H), 2.12 (dd, *J* = 12.8, 15.0, 1H), 2.30 (m, 1H), 2.38 (dd, *J* = 6.8, 15.0, 1H), 2.81 (dd, *J* = 3.2, 11.6, 11.6, 1H), 3.20 (dd, *J* = 11.6, 11.6, 1H), 3.93–4.00 (m, 4H), 5.33 (brs, 1H), 5.95 (s, 2H), 6.65 (d, *J* = 8.0, 1H), 6.68 (s, 1H), 6.76 (d, *J* = 8.0, 1H). $^{13}$C NMR: 37.5 ($CH_2$), 37.7 ($CH_2$), 40.9 (CH), 41.5 ($CH_2$), 45.3 (CH), 64.5 ($CH_2$), 64.6 ($CH_2$), 64.6 (CH), 101.1 ($CH_2$), 107.0 (CH), 108.6 (CH), 120.1 (CH), 134.7 (C), 146.8 (C), 148.2 (C), 177.6 (C). IR (nujol): 3300, 1720, 1693, 1609, 1099, 1069, 1038. EIMS *m/z*: 317 ($M^+$), 221, 135. Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.32; H, 5.90; N, 4.37.

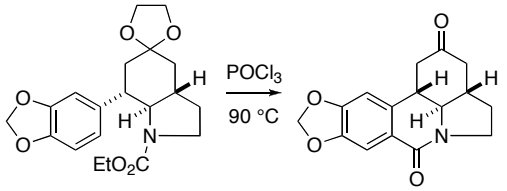
**Ethyl (3a*S*,7*S*,7a*R*)-7-(1,3-benzodioxol-5-yl)-5,5-ethylenedioxyoctahydroindole-1-carboxylate (10):**




A suspension of lactam **S3** (317 mg, 1.00 mmol) and $LiAlH_4$ (190 mg, 5.00 mmol) in THF (10 mL) was heated under reflux for 3 h and then quenched by sequential dropwise addition of $H_2O$ (0.2 mL),

15% NaOH (0.2 mL), and $H_2O$ (0.6 mL). The mixture was filtered through Celite, and the filtrate was dried over $Na_2SO_4$ and concentrated to give pale brown oil (710 mg). To a solution of the oil and $Et_3N$ (152 mg, 1.50 mmol) in $CH_2Cl_2$ (5 mL) was added ethyl chloroformate (162 mg, 1.50 mmol) at 0 °C. The mixture was stirred at room temperature for 8 h and diluted with AcOEt. The mixture was washed with sat. $NaHCO_3$ and brine, and then dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 2/1) gave the titled carbamate (258 mg, 69% yield in 2 steps) as a colorless gum: $[\alpha]_D^{25}$ +4.7 (*c* 3.26, $CHCl_3$). $^1$H NMR: 0.90 (t, *J* = 7.0, 3H), 1.45 (m, 1H), 1.69 (dd, *J* = 12.8, 12.8, 1H), 1.79 (m, 1H), 1.9–2.0 (m, 3H), 2.20 (m, 1H), 2.87 (ddd, *J* = 4.0, 12.8, 12.8, 1H), 3.19 (dd, *J* = 12.8, 12.8, 1H), 3.32–3.39 (m, 2H), 3.77–3.83 (m, 2H), 3.94–4.00 (m, 4H), 5.90 (d, *J* = 9.0, 2H), 6.62 (d, *J* = 8.0, 1H), 6.69 (s, 1H), 6.70 (d, *J* = 8.0, 1H). $^{13}$C NMR: 14.2 ($CH_3$), 29.8 ($CH_2$), 38.9 ($CH_2$), 42.0 ($CH_2$), 45.5 (CH), 47.5 (CH), 50.3 ($CH_2$), 60.7 ($CH_2$), 64.4 ($CH_2$), 64.6 ($CH_2$), 67.8 (CH), 100.6 ($CH_2$), 107.6 (CH), 108.2 (CH), 109.1 (C), 120.7 (CH), 137.9 (C), 145.7 (C), 147.3 (C), 157.6 (C). IR (nujol): 1693, 1065, 1038. EIMS *m/z*: 375 ($M^+$), 330, 221, 147, 135. HRMS-EI (*m/z*): $[M]^+$ Calcd. for $C_{20}H_{25}O_6N$: 375.1682. Found: 375.1689. Anal. Calcd. for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.88; H, 6.71; N, 3.73.

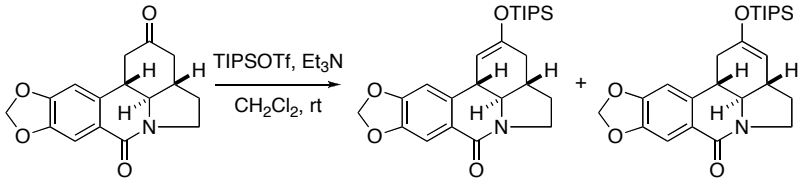
**(12*S*,15*S*,16*S*)-9,10-Methylenedioxygalanthan-2,7-dione (11):**



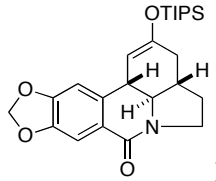

A mixture of carbamate **10** (29 mg, 0.077 mmol) and freshly distilled $POCl_3$ (1.0 mL) was heated at 90 °C for 8 h. The mixture was slowly poured into ice-water being stirred. The aqueous layer was basified (pH 11) with 8% NaOH and extracted with $CHCl_3$. The organic extracts were washed with brine and dried over $Na_2SO_4$. Concentration followed by column chromatography (hexane/AcOEt = 1/2) gave the titled product (21 mg, 95% yield) as colorless needles of mp 270–273 °C: $[\alpha]_D^{25}$ –4.9 (*c* 1.03,

$CHCl_3$). $^1$H NMR: 1.71 (m, 1H), 2.18 (m, 1H), 2.27 (m, 1H), 2.35 (dd, *J* = 13.2, 13.2, 1H), 2.44 (dd, *J* = 13.2, 13.2, 1H), 2.83 (dd, *J* = 4.0, 13.2, 1H), 3.10 (m, 1H), 3.39 (dd, *J* = 13.2, 13.2, 1H), 3.73 (m 1H), 3.94 (m, 1H), 6.02 (d, *J* = 3.0, 2H), 6.55 (s, 1H), 7.60 (s, 1H). $^{13}$C NMR: 29.0 ($CH_2$), 38.1 (CH), 42.5 ($CH_2$), 43.0 (CH), 45.0 ($CH_2$), 45.3 ($CH_2$), 64.5 (CH), 101.8 ($CH_2$), 103.6 (CH), 108.8 (CH), 125.0 (C), 134.7 (C), 147.2 (C), 150.9 (C), 162.3 (C), 206.8 (C). IR (nujol): 1705, 1651, 1605, 1258, 1038. EIMS *m/z*: 285 ($M^+$). HRMS-EI (*m/z*): $[M]^+$ Calcd. for $C_{16}H_{15}O_4N$: 285.1001. Found: 285.0995. Anal. Calcd. for $C_{16}H_{15}NO_4$•1/4$H_2O$: C, 66.31; H, 5.39; N, 4.83. Found: C, 66.60; H, 5.33; N, 4.78.

**(12*S*,15*S*,16*S*)-9,10-Methylenedoxy-2-triisopropylsiloxy-1,2-didehydrogalanthan-7-one (12) and (12*S*,15*S*,16*S*)-9,10-Methylenedioxy-2-triisopropylsiloxy-2,3-didehydrogalanthan-7-one (13):**

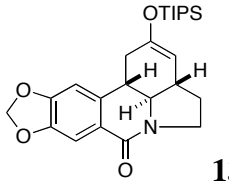



To a solution of ketone **11** (140 mg, 0.490 mmol) and $Et_3N$ (0.40 mL, 2.9 mmol) in $CH_2Cl_2$ (4.0 mL) was added TIPSOTf (0.66 mL, 2.5 mmol) at 0 °C, and the mixture was stirred at room temperature. After 24 h, the reaction was quenched with sat. $NaHCO_3$, and the whole was extracted with $Et_2O$. The organic extracts were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 3/1) gave silyl enol ether **12** (125 mg, 58%) and regioisomer **13** (90 mg, 41%).



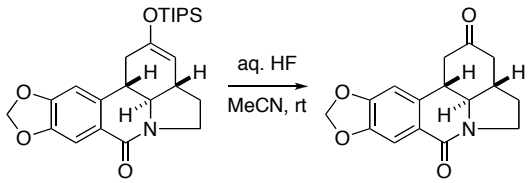

**12**: colorless oil. $[\alpha]_D^{25}$ –33.0 (*c* 0.67, $CHCl_3$). $^1$H NMR: 1.11 (d, *J* = 3.4, 9H), 1.12 (d, *J* = 3.4, 9H), 1.22 (dd, *J* = 3.4, 3.4, 3H), 1.64 (m, 1H), 2.13–2.29 (m, 3H), 2.49 (m, 1H), 3.10 (dd, *J* = 10.7, 11.9, 1H), 3.44 (d, *J* = 11.9, 1H), 3.67 (m, 1H), 3.91 (m, 1H), 5.34 (s, 1H), 6.01 (s, 2H), 6.67 (s, 1H), 7.59 (s, 1H). $^{13}$C NMR: 12.6, 17.9, 29.4, 35.4, 38.7, 41.1, 45.5, 63.7, 100.6, 101.5, 103.2, 109.0,

125.7, 136.0, 146.4, 150.4, 153.7, 162.8. IR (neat): 2943, 2866, 1651, 1504, 1454, 1385, 1350, 1265, 1196, 1038, 880, 680. EIMS *m*/*z*: 442 ($M^+$), 398, 268, 275, 241, 171, 103, 75. HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{25}H_{35}NO_4Si$, 441.2336; found, 441.2333.



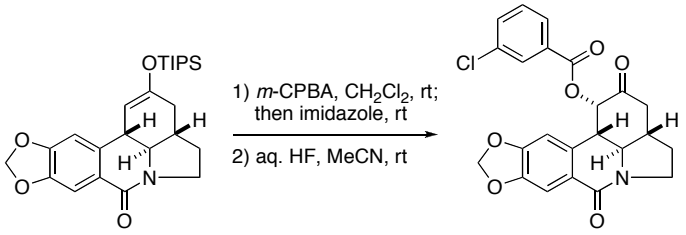

**13:** colorless needles of mp 105–108 °C. $[\alpha]_D^{25}$ –108 (*c* 1.00, $CHCl_3$). $^1H$ NMR: 1.10 (d, *J* = 3.7, 9H), 1.11 (d, *J* = 4.0, 9H), 1.20 (dd, *J* = 3.7, 4.0, 3H), 1.59 (m, 1H), 2.20 (m, 1H), 2.41 (m, 1H), 2.56 (m, 1H), 2.81 (dd, *J* = 5.8, 16.5, 1H), 3.04–3.15 (m, 2H), 3.70 (m, 1H), 3.87 (m, 1H), 5.12 (s, 1H), 6.01 (s, 2H), 6.64 (s, 1H), 7.61 (s, 1H). $^{13}C$ NMR: 12.5, 17.9, 28.5, 34.6, 36.6, 42.6, 45.8, 63.9, 101.6, 103.2, 104.3, 108.5, 125.3, 136.1, 146.7, 150.6, 151.7, 162.1. IR (KBr): 2943, 3866, 1654, 1504, 1462, 1385, 1350, 1261, 1038, 883, 737. EIMS *m*/*z*: 442 ($M^+$), 398, 268, 275, 241, 171, 75. HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{25}H_{35}NO_4Si$, 441.2335; found, 441.2341.

**Conversion of 13 to 11.**




Silyl enol ether **13** (90 mg, 0.20 mmol) was dissolved in HF–MeCN (48% HF:MeCN = 5:95, 0.5 mL), and the mixture was stirred at room temperature. After 12 h, the reaction was quenched with sat. $NaHCO_3$, and the whole was extracted with AcOEt. The organic extracts were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 1/9) gave **11** (52 mg, 92%).

**(1*S*,15*S*,16*S*)-1-(3-Chlorobezoyloxy)-9,10-methylenedioxygalanthan-2,7-dione (14):**

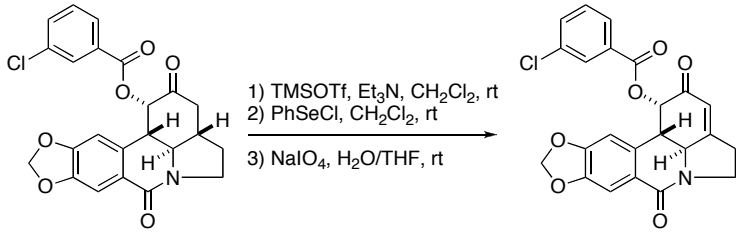



To a solution of silyl enol ether **12** (90 mg, 0.20 mmol) in $CH_2Cl_2$ (1.0 mL) was added purified *m*-CPBA (41 mg, 0.24 mmol) in $CH_2Cl_2$ (1.0 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. Imidazole (30 mg, 0.16 mmol) was added to the mixture, which was then stirred for additional 1 h at the same temperature. The reaction was quenched with sat. $NaHCO_3$, and the whole was extracted with AcOEt. The organic extracts were washed with sat. $NH_4Cl$ and brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/THF = 2/1) gave benzoyloxy silyl enol ether (80 mg, 67% yield) as colorless needles of mp 192–193 °C: $[\alpha]_D^{25}$ –10.2 (*c* 1.00, $CHCl_3$). $^1$H NMR: 1.12 (d, *J* = 6.8, 9H), 1.15 (d, *J* = 6.7, 9H), 1.53 (dd, *J* = 6.7, 6.8, 1H), 1.70 (m, 1H), 2.16–2.26 (m, 2H), 3.45–3.48 (m, 2H), 3.57 (dd, *J* = 11.0, 13.7, 1H), 3.72 (m, 1H), 3.91 (m, 1H), 5.74 (brs, 1H), 5.93 (s, 1H), 5.95 (s, 1H), 6.54 (s, 1H), 7.34 (dd, *J* = 7.9, 8.0, 1H), 7.53 (dd, *J* = 1.2, 8.0, 1H), 7.61 (s, 1H), 7.75 (d, *J* = 7.9, 1H), 7.83 (d, *J* = 1.2, 1H). $^{13}$C NMR: 12.9, 18.2, 28.1, 39.1, 41.1, 41.6, 45.4, 60.5, 74.5, 98.8, 101.6, 103.2, 109.0, 126.0, 128.0, 129.9, 130.9, 132.0, 133.8, 134.8, 147.0, 150.8, 162.0, 166.9. IR (KBr): 2924, 2866, 1728, 1643, 1608, 1604, 1462, 1385, 1254, 1126, 1038, 736. EIMS *m*/*z*: 457 (M – $ClC_6H_4CO_2$), 439 (M – $C_9H_{21}Si$), 283, 228, 131, 103, 75.

A solution of the above silyl enol ether (60 mg, 0.10 mmol) in HF–MeCN (48% HF:MeCN = 5:95, 0.6 mL) was stirred at room temperature. After 12 h, the reaction was quenched with sat. $NaHCO_3$, and the whole was extracted with AcOEt. The organic extracts were washed with brine, and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 1/9) gave the titled ketone (42 mg, 95% yield) as colorless needles of mp 118–119 °C: $[\alpha]_D^{25}$ –33.6 (*c* 0.830, $CHCl_3$). $^1$H NMR: 1.82 (m, 1H), 2.17–2.25 (m, 1H), 2.31 (m, 1H), 2.75 (dd, *J* = 13.2, 13.4, 1H), 2.83 (m, 1H), 3.37 (dd, *J* = 2.8, 13.4, 1H), 3.76 (m, 1H), 3.96–4.00 (m, 2H), 5.91 (d, *J* = 2.8, 1H), 5.98 (s, 1H), 5.99 (s, 1H), 6.64 (s, 1H),

7.37 (dd, *J* = 7.9, 8.0, 1H), 7.55 (d, *J* = 7.9, 1H), 7.63 (s, 1H), 7.79 (d, *J* = 8.0, 1H), 7.85 (s, 1H). $^{13}$C NMR: 28.7, 42.1, 44.1, 44.1, 45.2, 59.7, 73.8, 101.9, 103.7, 109.2, 125.7, 128.0, 129.8, 129.8, 130.0, 130.3, 134.0, 134.9, 147.6, 151.0 161.8, 163.9, 202.0. IR (neat): 2924, 1728, 1643, 1601, 1385, 1358, 1258, 1130, 1258, 1130, 1038, 740. EIMS *m*/*z*: 441 (M+2), 439 ($M^+$), 283, 255, 139, 111, 75. HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{18}NO_6Cl$, 439.0823; found, 439.0828.

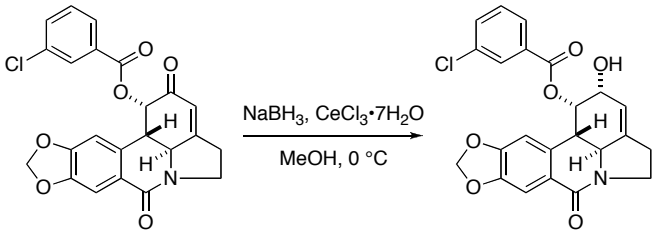
**(1*S*,15*S*,16*S*)-1-(3-Chlorobezoyloxy)-9,10-methylenedioxy-3,12-didehydrogalanthan-2,7-dione (15):**




To a solution of ketone **14** (80 mg, 0.18 mmol) and $Et_3N$ (0.30 mL, 2.2 mmol) in $CH_2Cl_2$ (1.0 mL) was added TMSOTf (0.33 mL, 1.8 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with sat. $NaHCO_3$, and the whole was extracted with $Et_2O$ three times. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration gave the corresponding TMS enol ether, which was used in the next step without further purification. To a solution of the crude enol ether in $CH_2Cl_2$ (2.0 mL) was added PhSeCl (104 mg, 0.54 mmol) in $CH_2Cl_2$ (2.0 mL) and stirred at 0 °C for 1 h. The reaction was quenched with sat. $NaHCO_3$, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated. The resulting pale yellow oil (210 mg) was passed through silica gel column with a 1:1 mixture of hexane and AcOEt as an eluent to give white amorphous (75 mg), a part of which (20 mg) was then dissolved in $H_2O$–THF (1:1, 1.0 mL). $NaIO_4$ (15 mg, 0.068 mmol) was added to the solution at 0 °C, and the mixture was stirred for 12 h at room temperature. The reaction was quenched with sat. $NaHCO_3$, and the whole was extracted with AcOEt three times. The combined organic layers were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 1/2) gave

the titled enone (11.0 mg, 52% yield) as colorless needles of mp 130–132 °C: $[\alpha]_D^{25}$ –170 (*c* 0.29, $CHCl_3$). $^1$H NMR: 3.07–3.20 (m, 2H), 3.57 (dd, *J* = 3.1, 11.9, 1H), 3.95 (m, 1H), 4.07 (m, 1H), 4.80 (d, *J* = 11.9, 1H), 5.98 (s, 1H), 6.00 (s, 1H), 6.14 (s, 1H), 6.29 (d, *J* = 3.1, 1H), 6.79 (s, 1H), 7.36 (dd, *J* = 7.6, 8.3, 1H), 7.53 (dd, *J* = 1.2, 8.3, 1H), 7.58 (s, 1H), 7.85 (dd, *J* = 1.3, 7.6, 1H), 7.86 (dd, *J* = 1.2, 1.3, 1H). $^{13}$C NMR: 29.4, 43.3, 45.8, 56.5, 68.3, 101.9, 103.8, 109.2, 121.3, 125.6, 128.3, 129.9, 130.4, 130.6, 133.8, 134.7, 147.7, 151.3, 162.4, 164.1, 165.5, 191.1. IR (neat): 1728, 1651, 1466, 1420, 1373, 1250, 1119, 1034. EIMS *m*/*z*: 298 (M – $ClC_6H_4CO$), 281, 253, 240, 225, 156, 139, 111, 75. HRMS–FAB (*m*/*z*): $[M+H]^+$ Calcd for $C_{23}H_{17}NO_6Cl$, 438.0744. Found, 438.0747.

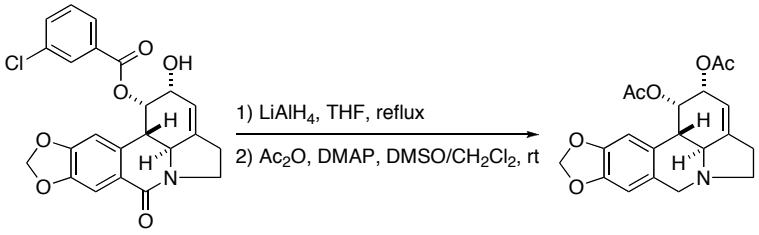
**(1*S*,2*R*,15*S*,16*S*)-1-(3-Chlorobezoyloxy)-2-hydroxy-9,10-methylenedioxy-3,12-didehydrogalanthan-7-one (16):**




To a solution of enone **15** (6.0 mg, 0.014 mmol) and $CeCl_3$•$7H_2O$ (5.1 mg, 0.014 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (1.0 mg, 0.026 mmol) at 0 °C. After stirred for 10 min, the reaction mixture was quenched with water and extracted with AcOEt. The organic extracts were washed with brine and dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 1/2) gave the titled alcohol (5.5 mg, 90% yield) as colorless needles of mp 150–152 °C: $[\alpha]_D^{21}$ –116 (*c* 1.01, $CHCl_3$). $^1$H NMR: 2.78 (m, 1H), 2.87 (m, 1H), 3.10 (ddd, *J* = 1.2, 1.2, 12.2, 1H), 3.78 (ddd, *J* = 8.6, 8.6, 11.9, 1H), 3.88 (ddd, *J* = 2.9, 10.9, 11.9, 1H), 4.48 (d, *J* = 12.2, 1H), 4.80 (dd, *J* = 2.2, 4.0, 1H), 5.64 (d, *J* = 2.2, 1H), 5.93 (d, *J* = 1.5, 1H), 5.97 (d, *J* = 1.5, 1H), 6.31 (d, *J* = 4.0, 1H), 6.78 (d, *J* = 0.9, 1H), 7.31 (dd, *J* = 7.9, 8.0, 1H), 7.48 (ddd, *J* = 1.3, 1.9, 7.9, 1H), 7.51 (s, 1H), 7.82 (ddd, *J* = 1.3, 1.5, 7.7, 1H), 7.88 (dd, *J* = 1.5, 1.9, 1H). $^{13}$C NMR: 28.2 ($CH_2$), 43.7 ($CH_2$), 44.2 (CH), 55.7 (CH), 67.8 (CH), 69.9 (CH), 101.7

($CH_2$), 103.3 (CH), 108.9 (CH), 120.2 (CH), 126.2 (C), 128.0 (CH), 129.7 (CH), 129.8 (CH), 131.1 (C), 131.9 (C), 133.4 (CH), 134.6 (C), 140.8 (C), 147.1 (C), 150.9 (C), 162.6 (C), 165.6 (C). IR (KBr): 3402, 1720, 1651, 1481, 1420, 1373, 1258, 1126, 1034, 926, 748. EIMS *m*/*z*: 441 (M+2), 439 ($M^+$), 423 (M+2 – $H_2O$), 421 (M – $H_2O$), 283, 266, 241, 226, 139, 111. HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{18}NO_6Cl$, 439.0823; found, 439.0817.

**1*O*,2*O*-Diacetyl-2-*epi*-lycorine (17):**

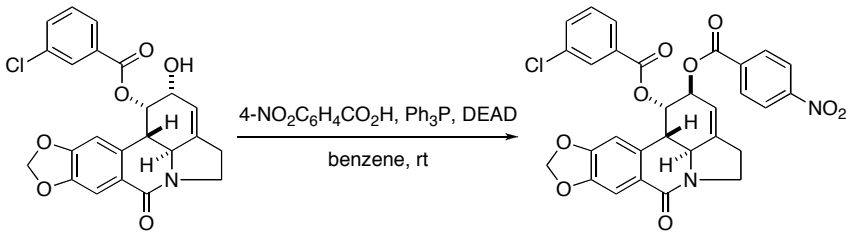



A suspension of lactam **16** (2.0 mg, 4.6 μmol) and $LiAlH_4$ (13 mg, 0.36 mmol) in THF (1.5 mL) was heated under reflux for 4 h, and then the reaction was quenched by sequential dropwise addition of $H_2O$ (0.02 mL), 15% NaOH (0.02 mL), and $H_2O$ (0.06 mL). The mixture was filtered through Celite, and the filtrate was dried over $Na_2SO_4$ and concentrated to give white solids (1.8 mg). To a solution of the white solids and DMAP (1.0 mg, 0.010 mmol) in $CH_2Cl_2$ (0.5 mL) and DMSO (0.5 mL) was added $Ac_2O$ (162 mg, 1.50 mmol) at room temperature. The mixture was stirred at room temperature for 12 h and sat. $NaHCO_3$ was added. The mixture was stirred for additional 0.5 h at room temperature and extracted with AcOEt. The organic extracts were washed with brine and then dried over $Na_2SO_4$. Concentration and column chromatography (hexane/AcOEt = 1/4) gave the titled product (0.8 mg, 47% in 2 steps) as colorless needles of mp >192 °C (dec.) and $[\alpha]_D^{25}$ –65 (*c* 0.11, $CHCl_3$); lit.[4] 192–194.5 and $[\alpha]_D$ –158.2 (*c* 1.04, $CHCl_3$). $^1$H NMR: 1.99 (s, 3H), 2.05 (s, 3H), 2.41 (m, 1H), 2.61–2.66 (m, 2H), 2.92–3.00 (m, 2H), 3.37 (m, 1H), 3.52 (d, *J* = 14.4, 1H), 4.14 (d, *J* = 14.4, 1H), 5.36 (m, 1H), 5.79 (m, 1H), 5.92 (s,

4 Y. Nakagawa, S. Uyeo, *J. Chem. Soc.* **1959**, 3736–3740.

2H), 6.09 (d, *J* = 4.9, 1H), 6.56 (s, 1H), 6.72 (s, 1H). IR (KBr): 2940, 1744, 1660, 1435, 1373, 1240, 1034. EIMS *m/z*: 371 ($M^+$), 311 (M – AcOH), 252, 226.

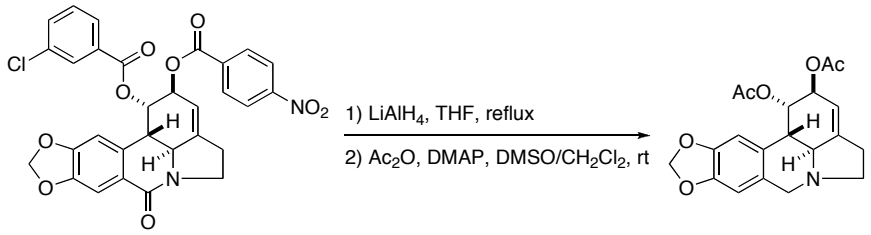
**(1*S*,2*S*,15*S*,16*S*)-1-(3-Chlorobezoyloxy)-9,10-methylenedioxy-2-(4-nitrobezoyloxy)-3,12-didehydro-galanthan-7-one (S4):**




To a solution of alcohol **16** (14.2 mg, 0.032 mmol) in dry benzene (0.6 mL), was added 4-nitrobenzoic acid (7 mg, 0.04 mmol) and triphenylphosphine (11 mg, 0.04 mmol). To the resulting pale yellow solution, was dropwise added a 40% solution of diethyl azodicarboxylate in toluene (0.02 mL, 0.4 mmol), and the whole was stirred at room temperature. After 2 h, 4-nitrobenzoic acid (7 mg, 0.04 mmol), triphenylphosphine (11 mg, 0.04 mmol), and a 40% solution of diethyl azodicarboxylate in toluene (0.02 mL, 0.4 mmol) were added again to the mixture. The mixture was stirred for additional 1 h at room temperature and concentrated in vacuo. The resulting pale yellow oil (72.8 mg) was purified by column chromatography (hexane/EtOAc = 35/65) to give the titled 4-nitrobenzoate (15.9 mg, 84%) as pale yellow oil: $[\alpha]_D^{21}$ +130 (*c* 0.610, $CHCl_3$). $^1$H NMR: 2.91 (m, 1H), 2.99 (m, 1H), 3.21 (ddd, *J* = 0.9, 2.1, 12.5, 1H), 3.88–3.98 (m, 2H), 4.49 (1H, d, *J* = 12.5 Hz), 5.73 (br, 1H), 5.80 (br, 1H), 5.97 (d, *J* = 1.2, 1H), 5.99 (d, *J* = 1.2, 1H), 6.19 (br, 1H), 6.76 (br, 1H), 7.38 (dd, *J* = 7.8, 8.1, 1H), 7.56 (ddd, *J* = 1.1, 2.1, 8.1, 1H), 7.59 (s, 1H), 7.85 (ddd, *J* = 1.1, 1.5, 7.8, 1H), 7.89 (dd, *J* = 1.5, 2.1, 1H), 8.24 (d, *J* = 9.0, 2H), 8.31 (d, *J* = 9.0, 2H). $^{13}$C NMR: 28.7 ($CH_2$), 40.9 (CH), 43.6 ($CH_2$), 55.4 (CH), 68.2 (CH), 71.4 (CH), 101.8 ($CH_2$), 103.5 (CH), 109.2 (CH), 115.0 (CH), 123.7 (CH), 126.4 (C), 128.1 (CH), 129.9 (CH), 130.0 (CH), 130.7 (C), 131.1 (CH), 131.3 (C), 133.9 (CH), 134.8 (C), 144.9 (C), 147.4 (C), 150.9 (C), 151.0 (C), 162.7 (C), 163.4 (C), 164.3 (C). IR (KBr): 2926, 1730, 1651, 1603, 1526, 1418, 1373,

1265, 1097, 1036, 746, 718. FABMS *m/z*: 591 (MH+2), 590 (MH+1), 589 (MH). HRMS–FAB (*m/z*): $[MH]^+$ calcd for $C_{30}H_{22}ClNO_9$, 589.1014; found, 589.1015.

**1*O*,2*O*-Diacetyl-lycorine (18):**

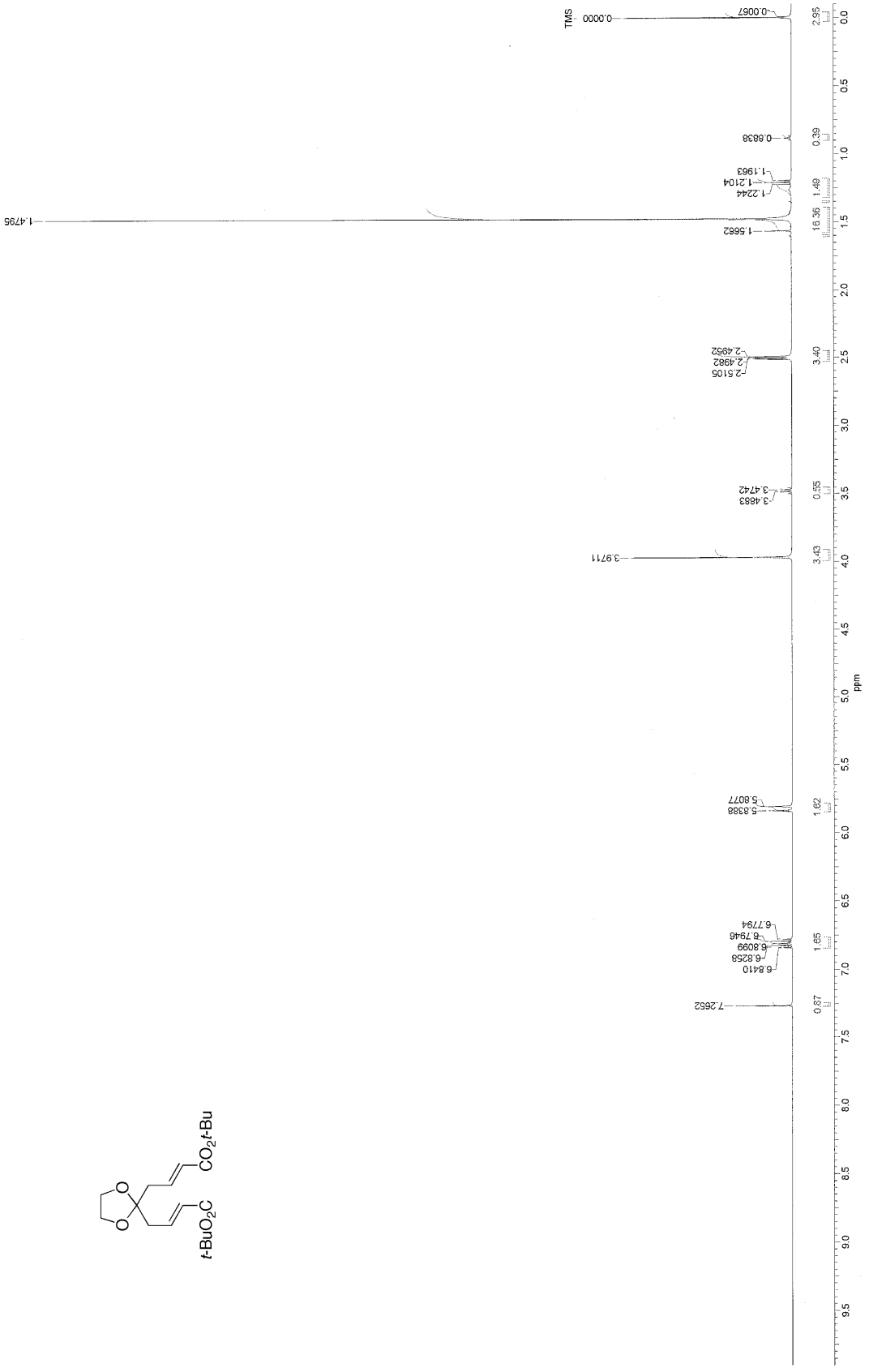



To a solution of dibenzoate **S4** (12 mg, 0.021 mmol) in dry THF (4.1 mL), was dropwise added a 1 M solution of $LiAlH_4$ (2.1 mL, 2.1 mmol) at room temperature. The mixture was heated under reflux for 4 h and then cooled to room temperature. $H_2O$ (0.08 mL), 15% NaOH (0.08 mL), and then another $H_2O$ (0.24 mL) were successively added to the mixture. The mixture was filtered through celite, and the residue was washed with distilled THF. The filtrate was concentrated in vacuo to give pale yellow solids (9.4 mg), whose comparison of TLC, and $^1H$ and $^{13}C$ NMR with those of an authentic sample indicated the existence of lycorine: $R_f$ 0.6 EtOAc/$CH_2Cl_2$/MeOH (2/2/1). $^1H$ NMR (DMSO-$d_6$): 2.19 (m, 1H), 2.42 (m, 1H), 2.45–2.53 (m, 2H), 2.59 (d, $J$ = 10.4, 1H), 3.17 (m, 1H), 3.31 (d, $J$ = 14.0, 1H), 3.96 (m, 1H), 4.00 (d, $J$ = 14.0, 1H), 4.25 (m, 1H), 4.79 (m, 1H), 4.91 (m, 1H), 5.35 (brs, 1H), 5.90–5.96 (m, 2H), 6.66 (s, 1H), 6.79 (s, 1H). $^{13}C$ NMR (DMSO-$d_6$): 28.2 ($CH_2$), 40.2 (CH), 53.4 ($CH_2$), 56.8 ($CH_2$), 60.8 (CH), 70.3 (CH), 71.8 (CH), 100.7 ($CH_2$), 105.2 (CH), 107.2 (CH), 118.6 (CH), 129.7 (CH), 129.9 (CH), 141.9 (C), 145.4 (C), 145.8 (C). To a solution of the lycorine-containing solids in DMSO-$d_6$ (0.5 mL), were added $CH_2Cl_2$ (2 mL), 4-(dimethylamino)pyridine (10 mg, 0.082 mmol), and then $Ac_2O$ (0.5 mL, 5 mmol), and the whole was stirred at room temperature for 3.5 h. To the mixture sat. $NaHCO_3$ (5 mL) was added, and the whole was stirred for 0.5 h and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc 5 times. The combined organic layers were washed with water 5 times, dried over $Na_2SO_4$, and concentrated in vacuo. The resulting brown oil (14.9

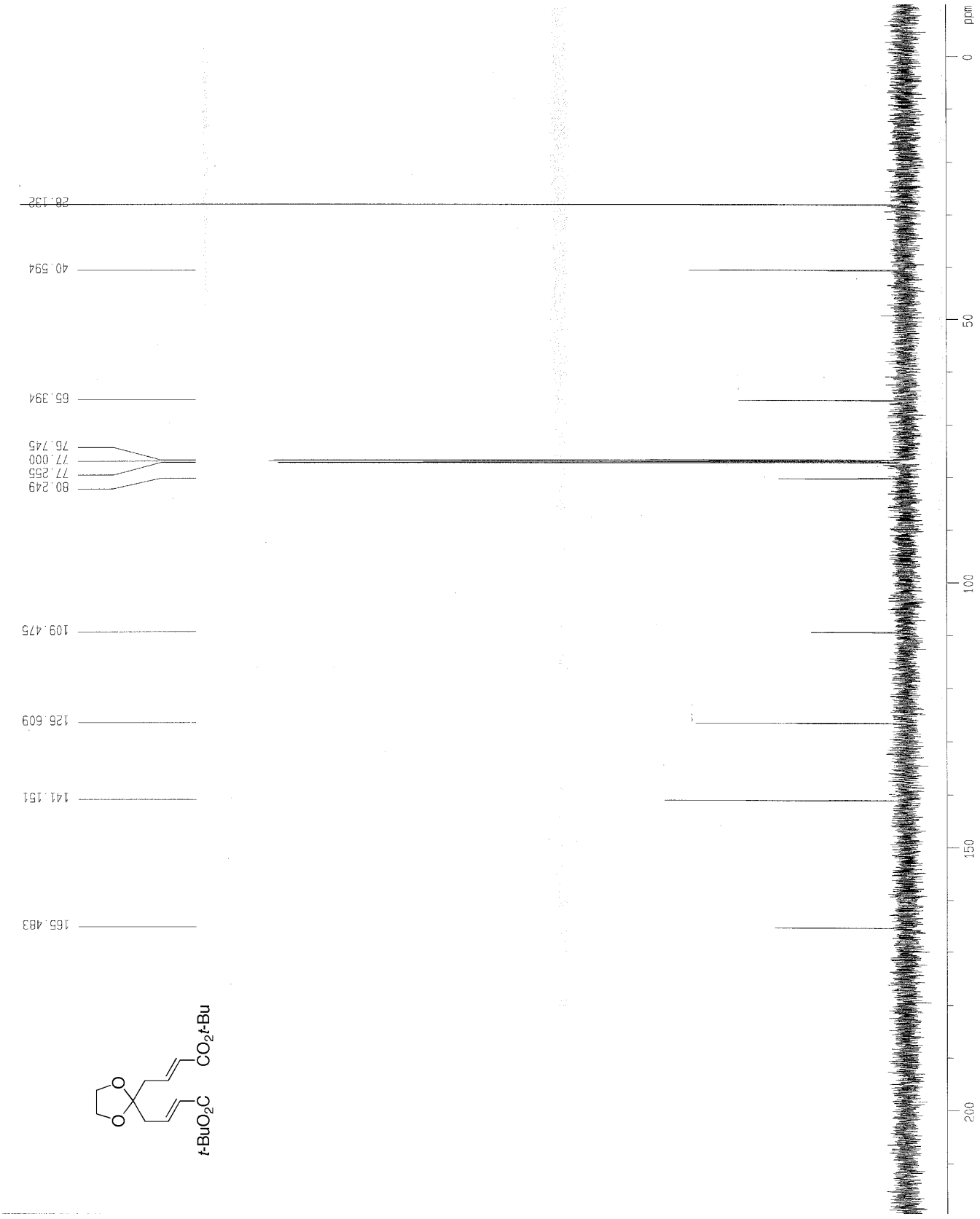
mg) was purified by column chromatography (hexane/EtOAc = 1/1) to give the titled diacetyl lycorine (4.8 mg, 62% over 2 steps) as pale brown solids of mp 207–208 °C (dec) and $[\alpha]_D^{27}$ +22 (*c* 0.48, $CHCl_3$) (an authentic sample $[\alpha]_D^{26}$ +23 (*c* 0.43, $CHCl_3$); lit.[5] mp 207–209 (dec) and $[\alpha]_D^{23}$ +25.6 (*c* 0.39, $CHCl_3$)). $^1$H NMR: 1.95 (s, 3H), 2.08 (s, 3H), 2.42 (m, 1H), 2.63–2.70 (m, 2H), 2.79 (m, 1H), 2.89 (d, *J* = 10.3, 1H), 3.38 (m, 1H), 3.55 (d, *J* = 14, 1H), 4.16 (d, *J* = 14, 1H), 5.25 (m, 1H), 5.53 (m, 1H), 5.74 (m, 1H), 5.92 (s, 2H), 6.58 (s, 1H), 6.74 (s, 1H). $^{13}$C NMR: 20.9 ($CH_3$), 21.1 ($CH_3$), 28.7 ($CH_2$), 40.5 ($CH_2$), 53.6 ($CH_2$), 56.9 ($CH_2$), 61.2 (CH), 69.3 (CH), 70.9 (CH), 101.0 ($CH_2$), 105.1 (CH), 107.3 (CH), 113.8 (CH), 126.6 (C), 129.4 (C), 146.1 (C), 146.3 (C), 146.4 (C), 169.7 (C), 170.0 (C). IR (KBr): 2931, 2856, 1745, 1726, 1510, 1489, 1367, 1253, 1240, 1219, 1038, 1018, 966, 932, 901. FABMS *m*/*z*: 372 (MH), 370, 252 (MH – 2AcOH), 250. HRMS–FAB (*m*/*z*): MH calcd for $C_{20}H_{22}NO_6$, 372.1447; found, 372.1446. $R_f$ 0.3 hexane/EtOAc (1/1, 3 times) was identical to that of the authentic sample. The spectroscopic data were identical to those of the authentic sample, prepared by reported procedure, and in good agreement with those reported in the literatures.[5]

5 A. G. Schultz, M. A. Holoboski, M. S. Smyth, *J. Am. Chem. Soc.* **1996**, *118*, 6210–3219.

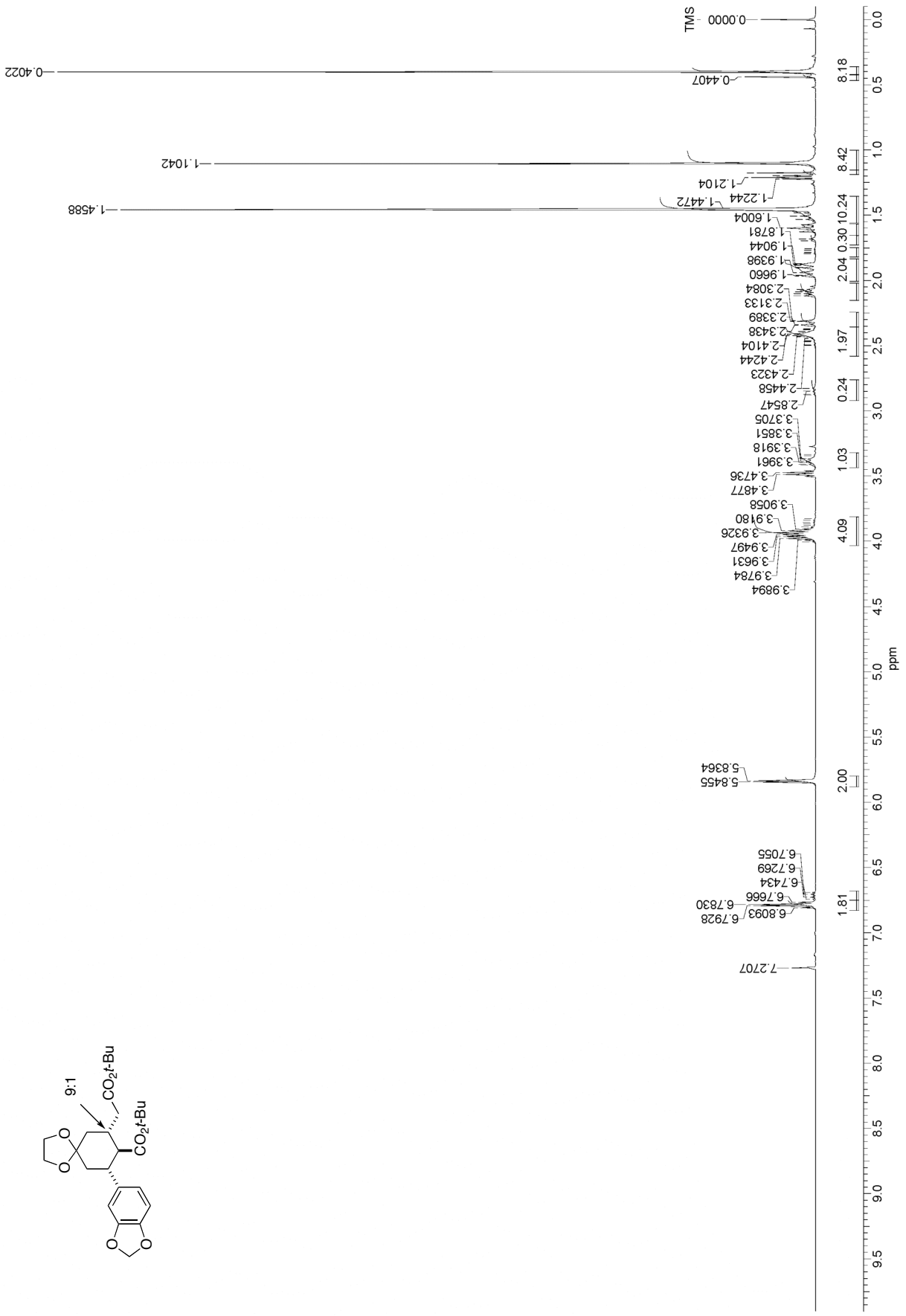
$^1$H NMR of **5**


TMS
0.0000
-0.0067
0.8838
1.1963
1.2104
1.2244
1.4795
1.5662
2.4852
2.4982
2.5105
3.4742
3.4883
3.9711
5.8077
5.8388
6.7794
6.7946
6.8099
6.8258
6.8410
7.2652
ppm
t-BuO2C
CO2t-Bu

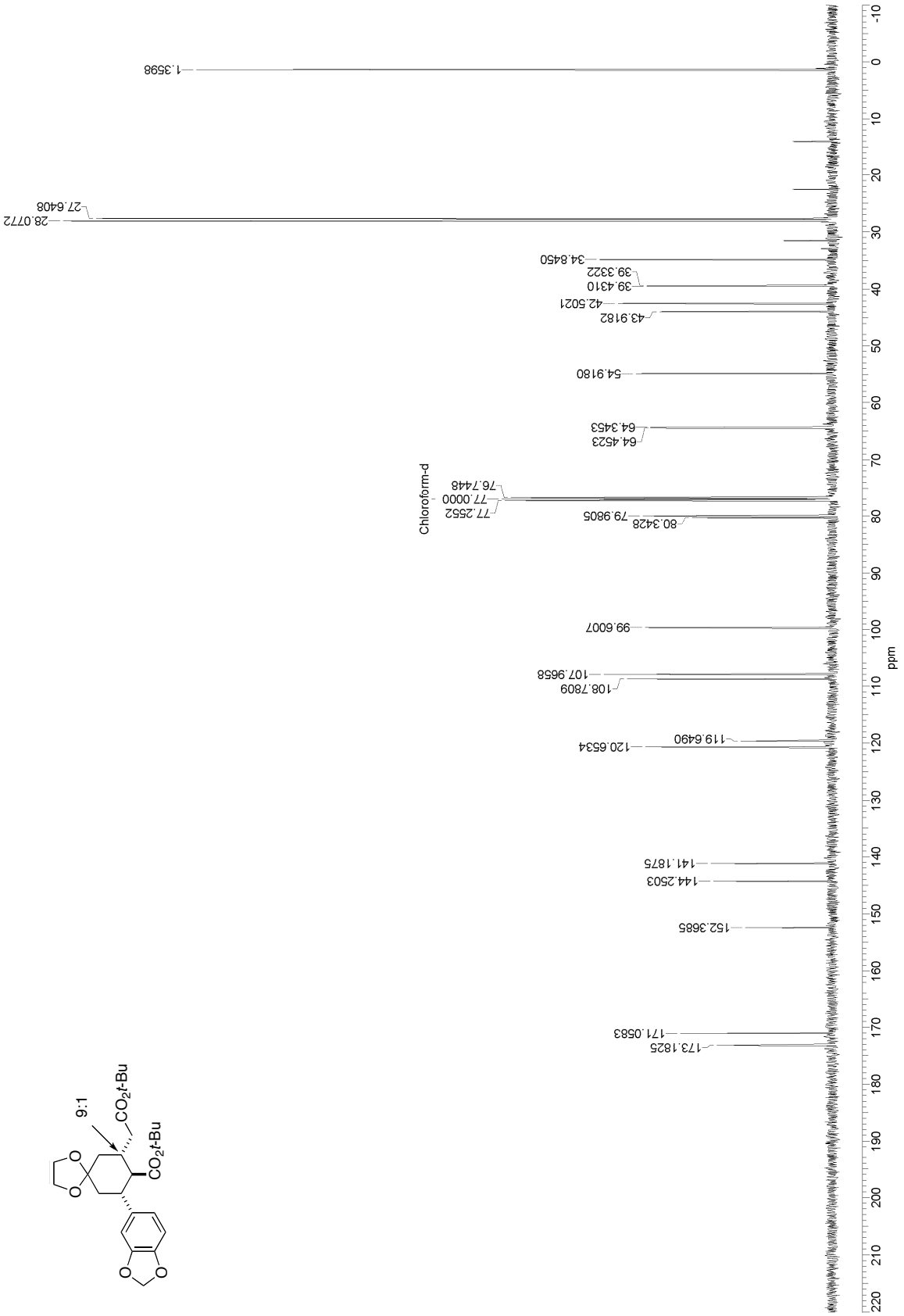
$^{13}$C NMR of **5**


28.132
40.594
65.394
76.745
77.000
77.255
80.249
109.475
126.609
141.151
165.483
ppm
0
50
100
150
200
CO2t-Bu
t-BuO2C

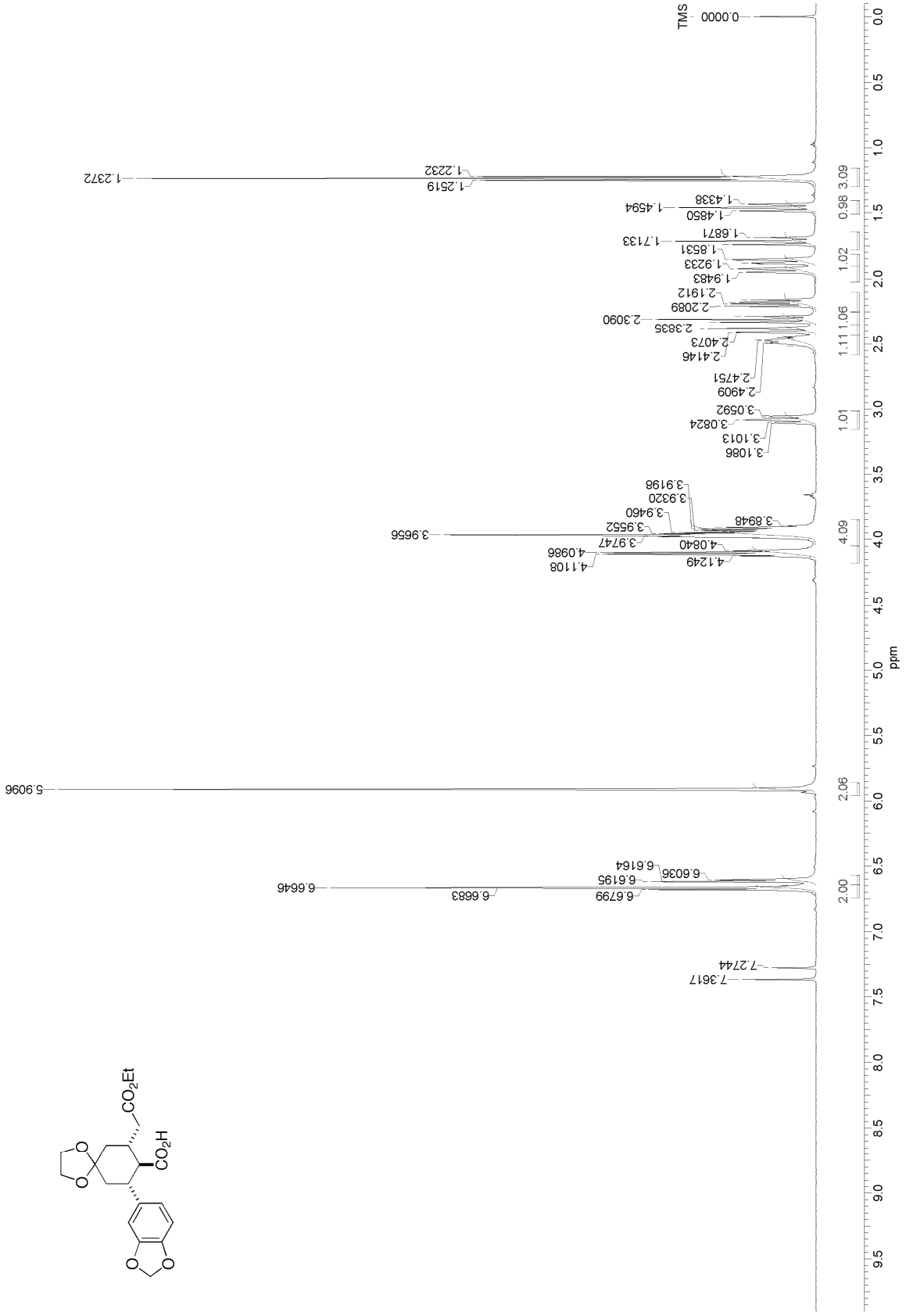
$^1$H NMR of **7**


TMS
0.0000
0.4022
0.4407
1.1042
1.2104
1.2244
1.4472
1.4588
1.6004
1.8781
1.9044
1.9398
1.9660
2.3084
2.3133
2.3389
2.3438
2.4104
2.4244
2.4323
2.4458
2.8547
3.3705
3.3851
3.3918
3.3961
3.4736
3.4877
3.9058
3.9180
3.9326
3.9497
3.9631
3.9784
3.9894
5.8455
5.8364
6.7055
6.7269
6.7434
6.7666
6.7830
6.7928
6.8093
7.2707
8.18
8.42
10.24
0.30
2.04
1.97
0.24
1.03
4.09
2.00
1.81
ppm
9:1
$CO_2t$-Bu
$CO_2t$-Bu

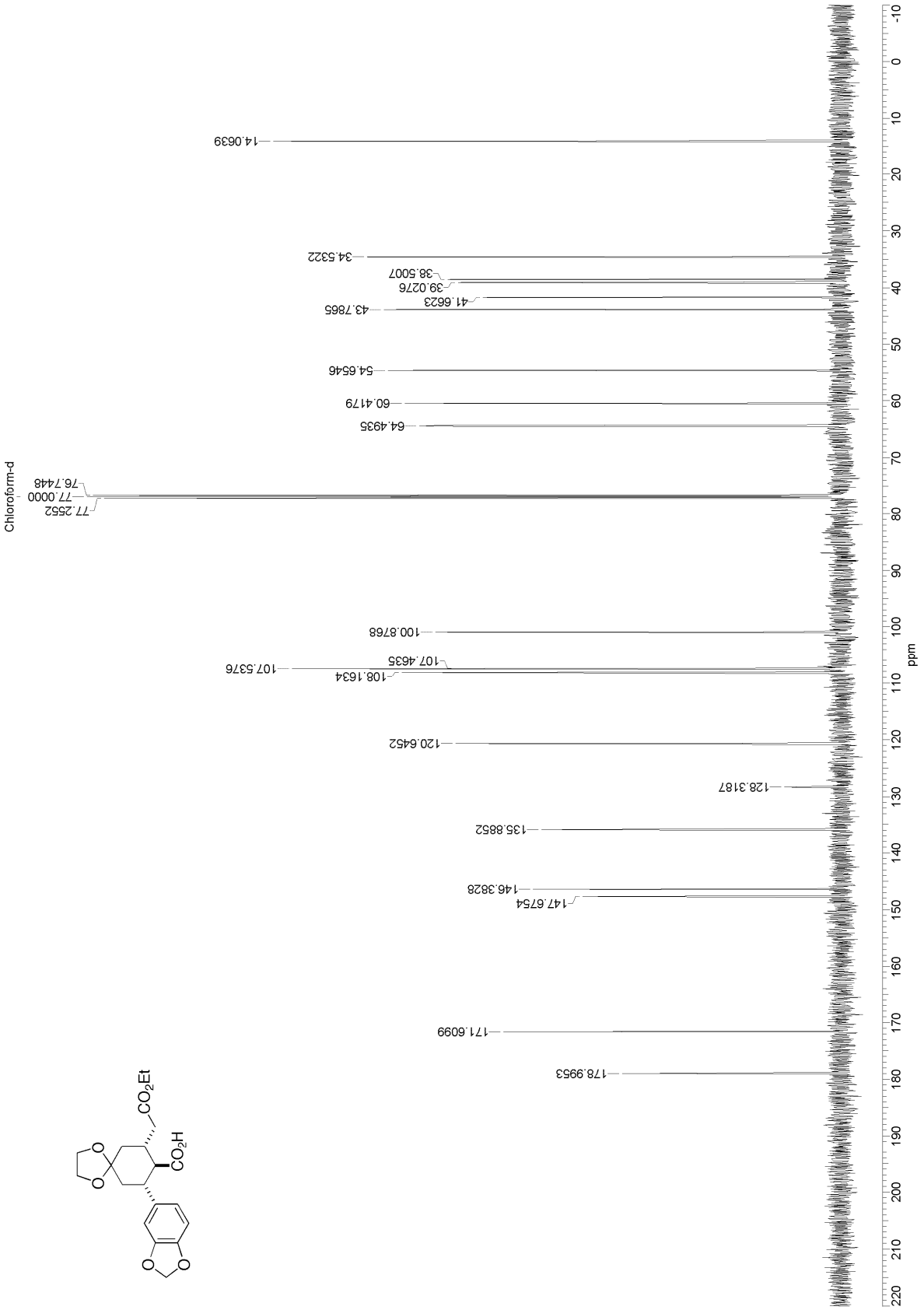
$^{13}$C NMR of **7**


1.3598
27.6408
28.0772
34.8450
39.3322
39.4310
42.5021
43.9182
54.9180
64.4523
64.3453
Chloroform-d
76.7448
77.0000
77.2552
79.9805
80.3428
99.6007
107.9658
108.7809
119.6490
120.6534
141.1875
144.2503
152.3685
171.0583
173.1825
ppm
9:1
CO2t-Bu
CO2t-Bu

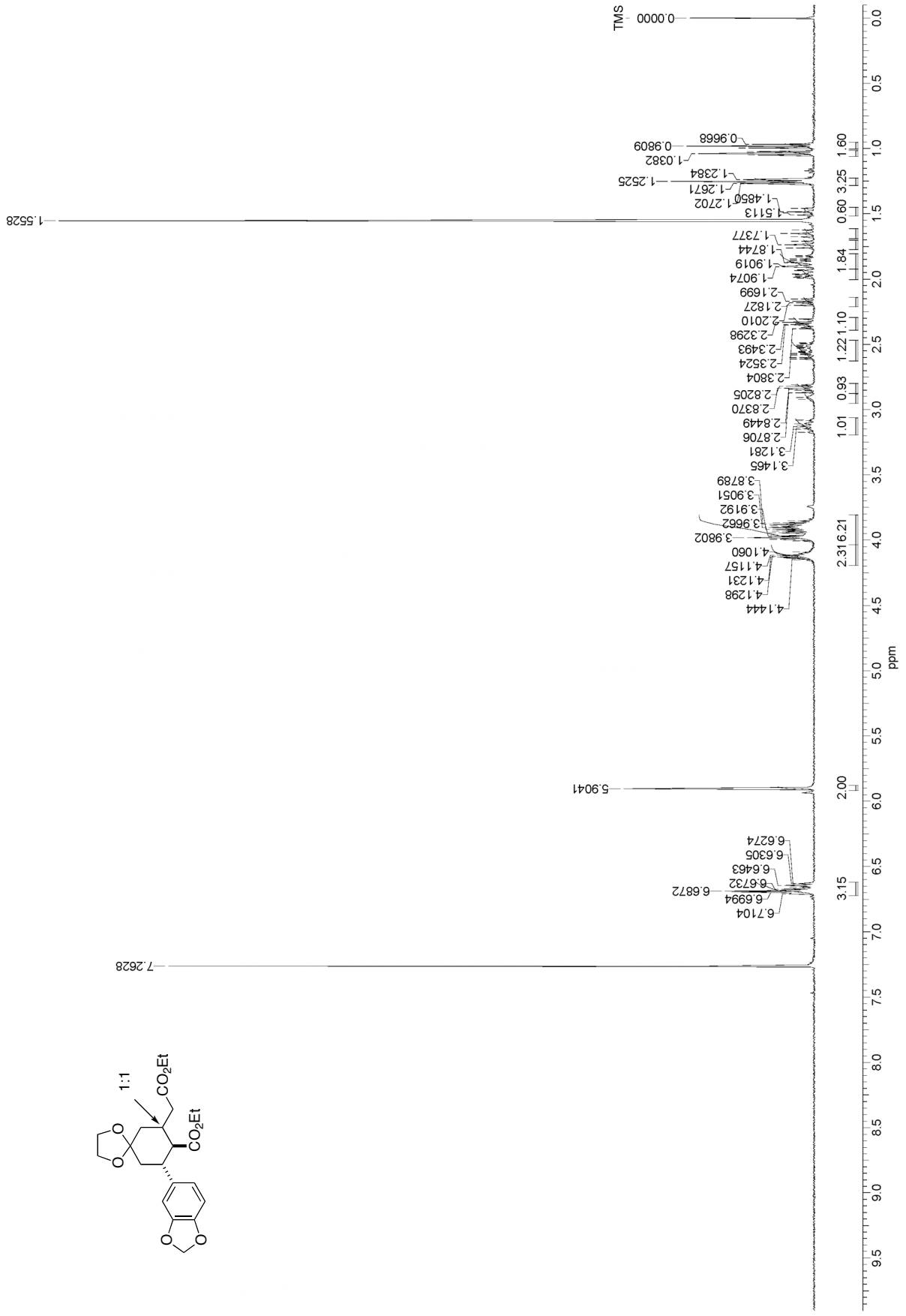
$^1$H NMR of **8**


TMS
0.0000
1.2372
1.2232
1.2519
1.4338
1.4594
1.4850
1.6871
1.7133
1.8531
1.9233
1.9483
2.1912
2.2089
2.3090
2.3835
2.4073
2.4146
2.4751
2.4909
3.0592
3.0824
3.1013
3.1086
3.8948
3.9198
3.9320
3.9460
3.9552
3.9656
3.9747
4.0840
4.0986
4.1108
4.1249
5.9096
6.6036
6.6164
6.6195
6.6683
6.6799
6.6846
7.2744
7.3617
3.09
0.98
1.02
1.06
1.11
1.01
4.09
2.06
2.00
ppm
CO2Et
CO2H

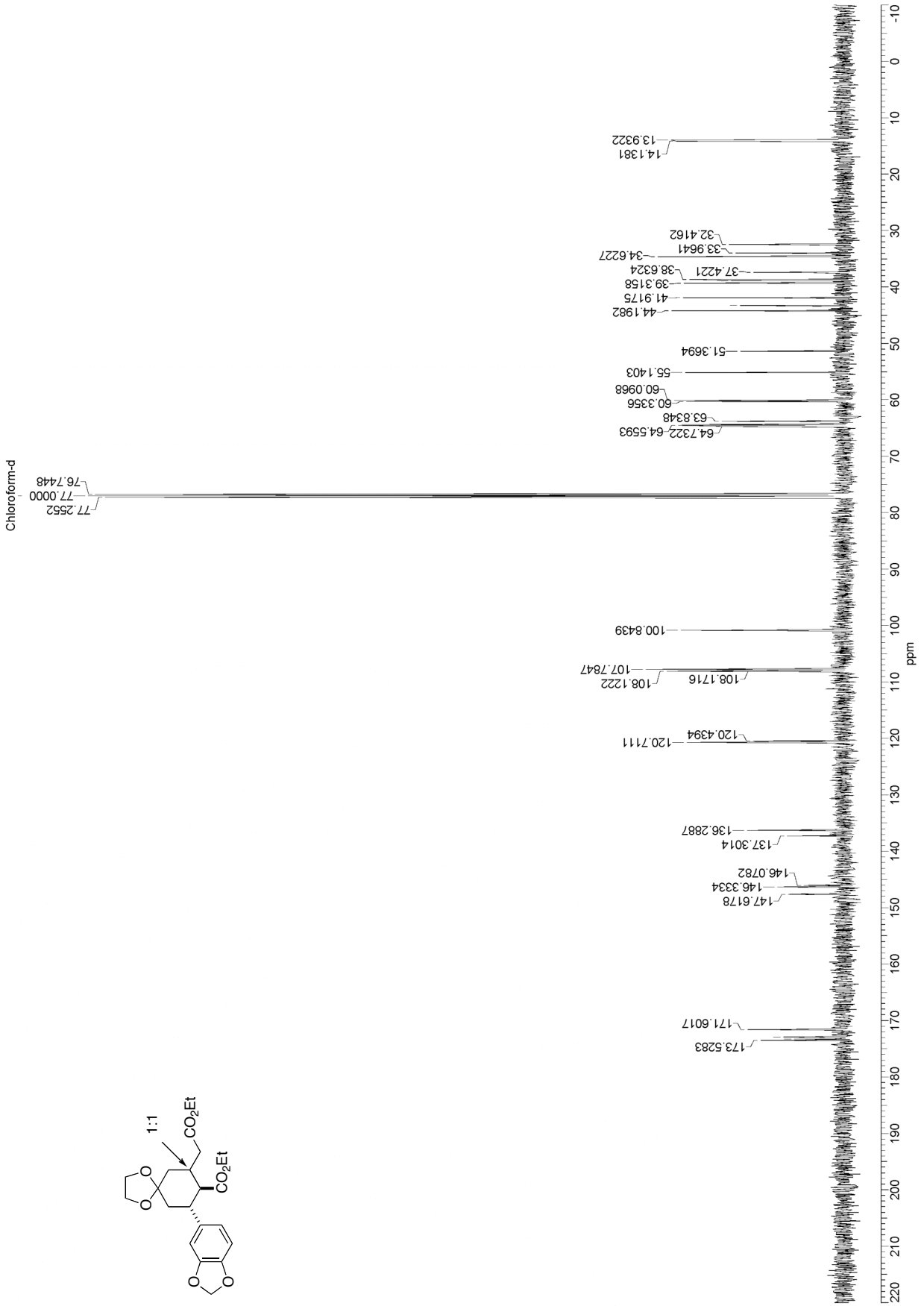
$^{13}$C NMR of **8**


14.0639
34.5322
38.5007
39.0276
41.6623
43.7865
54.6546
60.4179
64.4935
Chloroform-d
76.7448
77.0000
77.2552
100.8768
107.4635
107.5376
108.1634
120.6452
128.3187
135.8852
146.3828
147.6754
171.6099
178.9953
ppm
CO2Et
CO2H

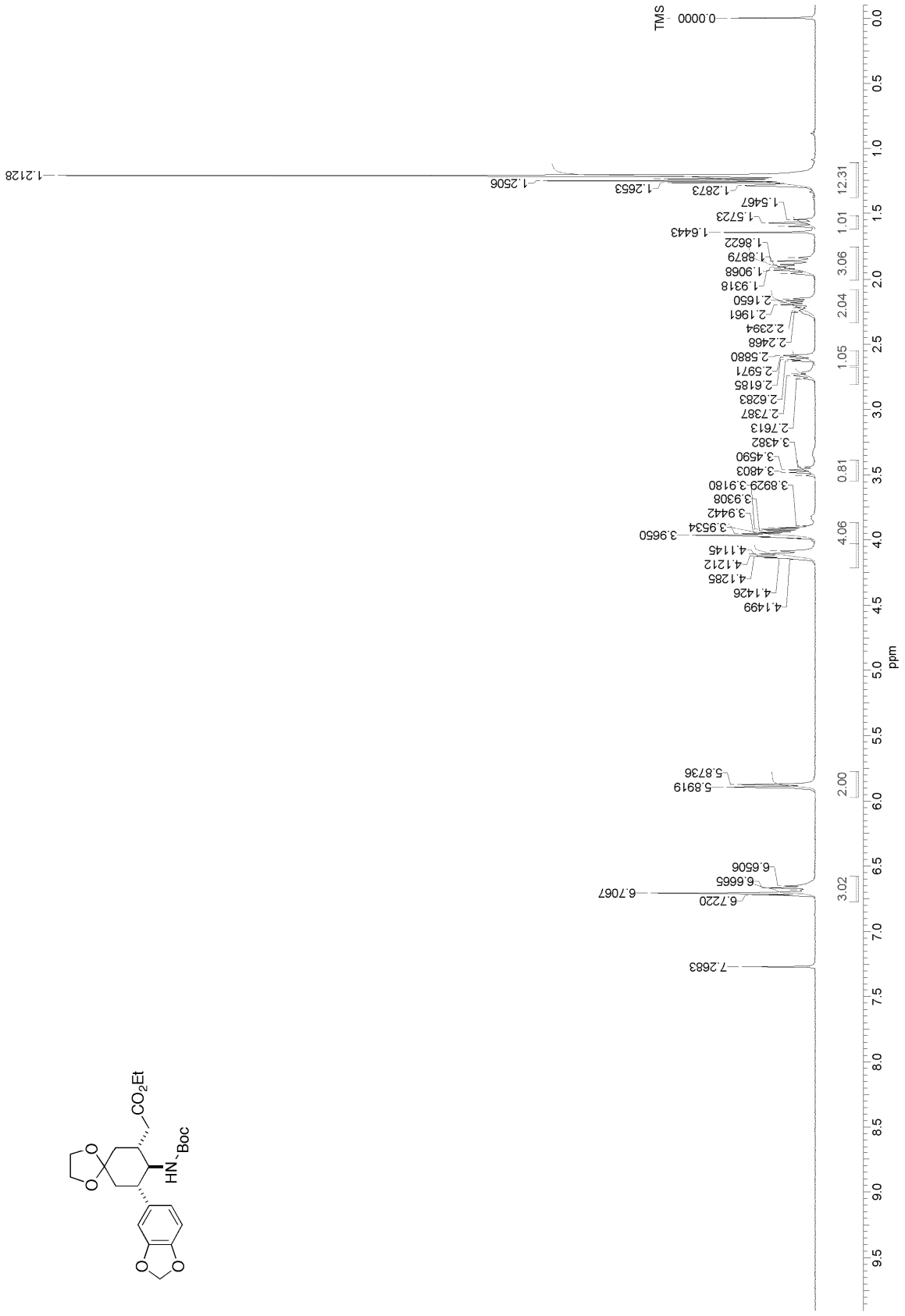
$^{1}$H NMR of **S1/S2**



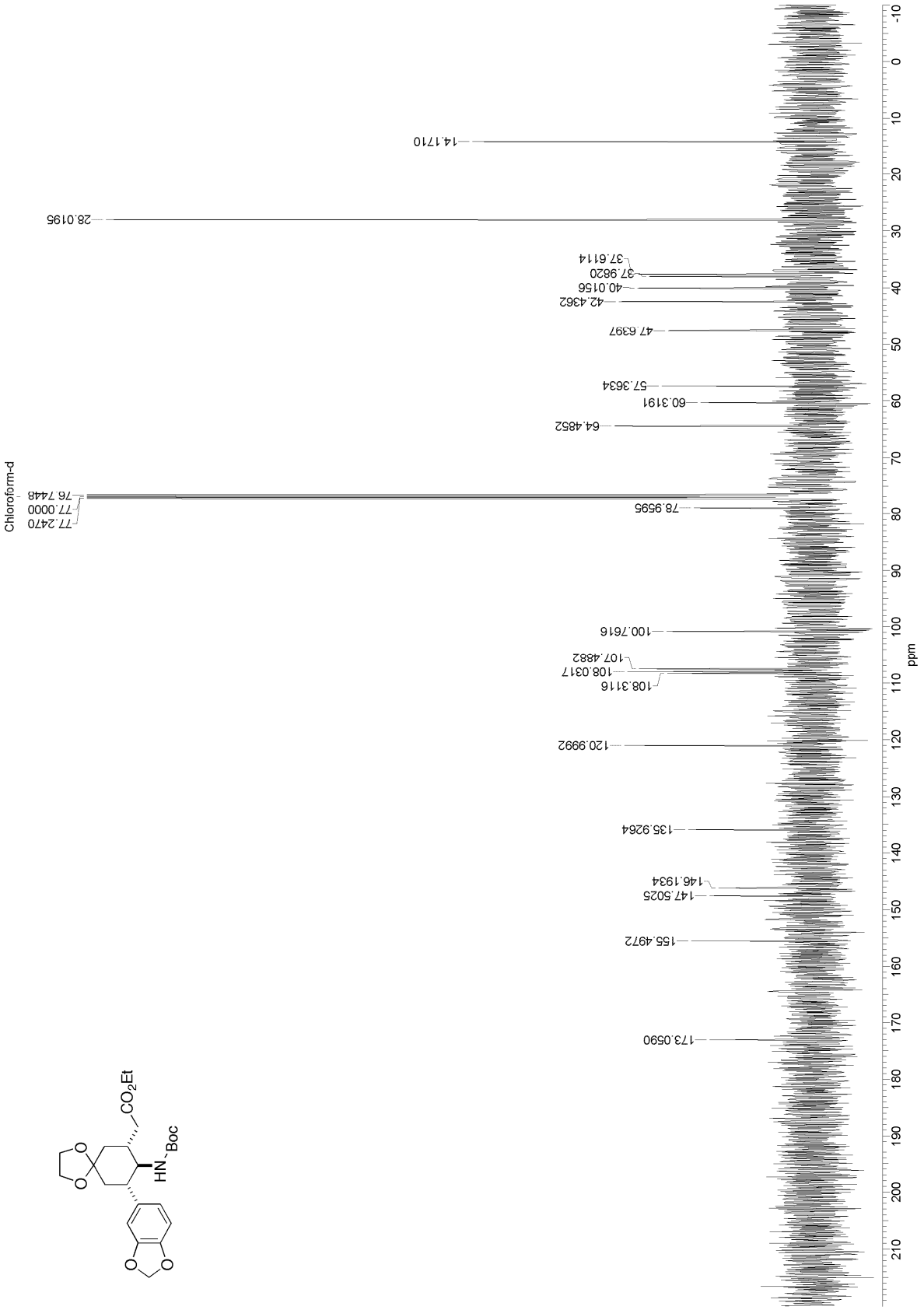
$^{13}$C NMR of **S1/S2**



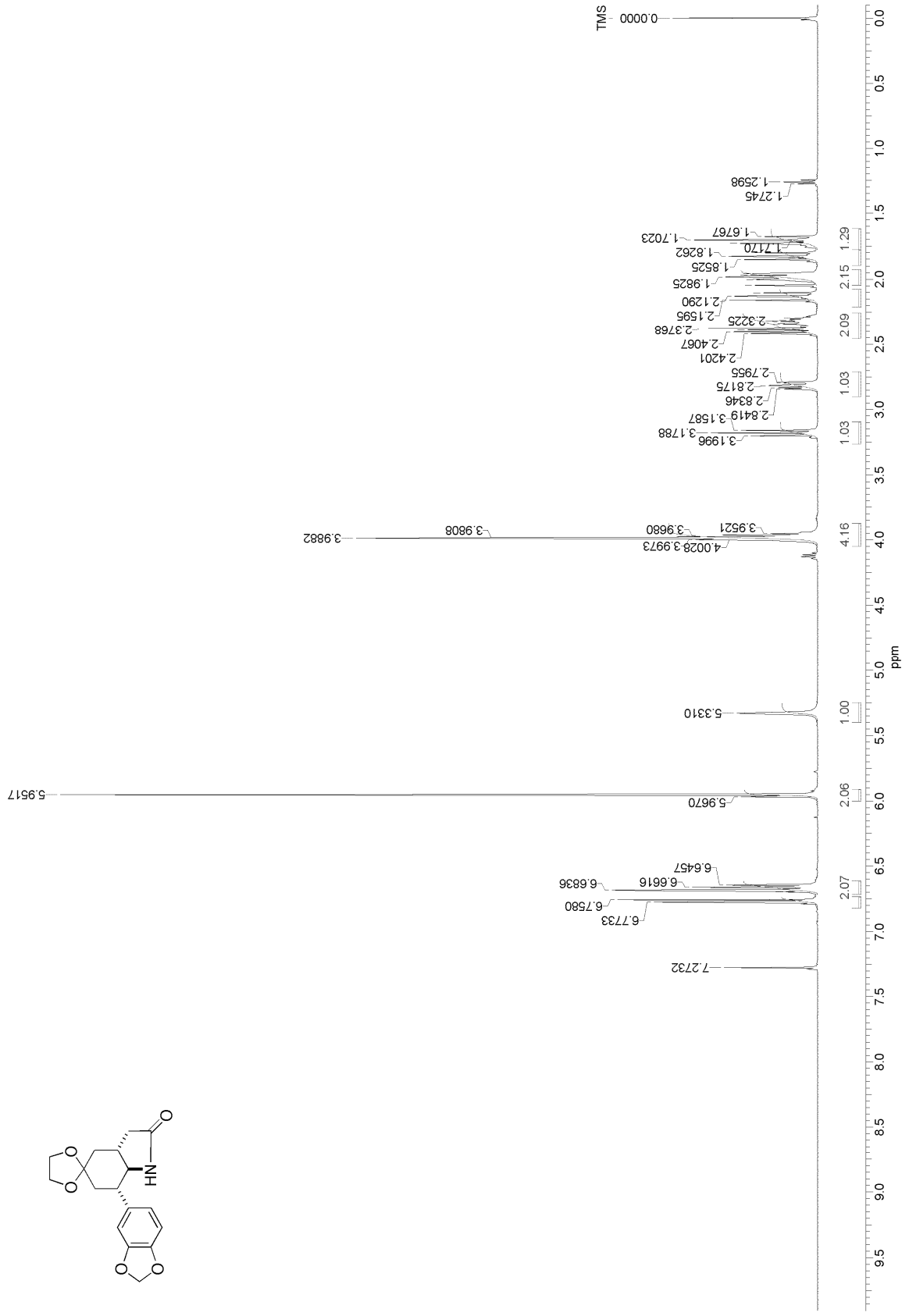
$^1$H NMR of **9**


TMS
0.0000
1.2128
1.2506
1.2653
1.2873
1.5467
1.5723
1.6443
1.8622
1.8879
1.9068
1.9318
2.1650
2.1961
2.2394
2.2468
2.5880
2.5971
2.6185
2.6283
2.7387
2.7613
3.4382
3.4590
3.4803
3.8929-3.9180
3.9308
3.9442
3.9534
3.9650
4.1145
4.1212
4.1285
4.1426
4.1499
5.8736
5.8919
6.6506
6.6665
6.7067
6.7220
7.2683
12.31
1.01
3.06
2.04
1.05
0.81
4.06
2.00
3.02
ppm
CO2Et
HN
Boc
O
O
O
O
O

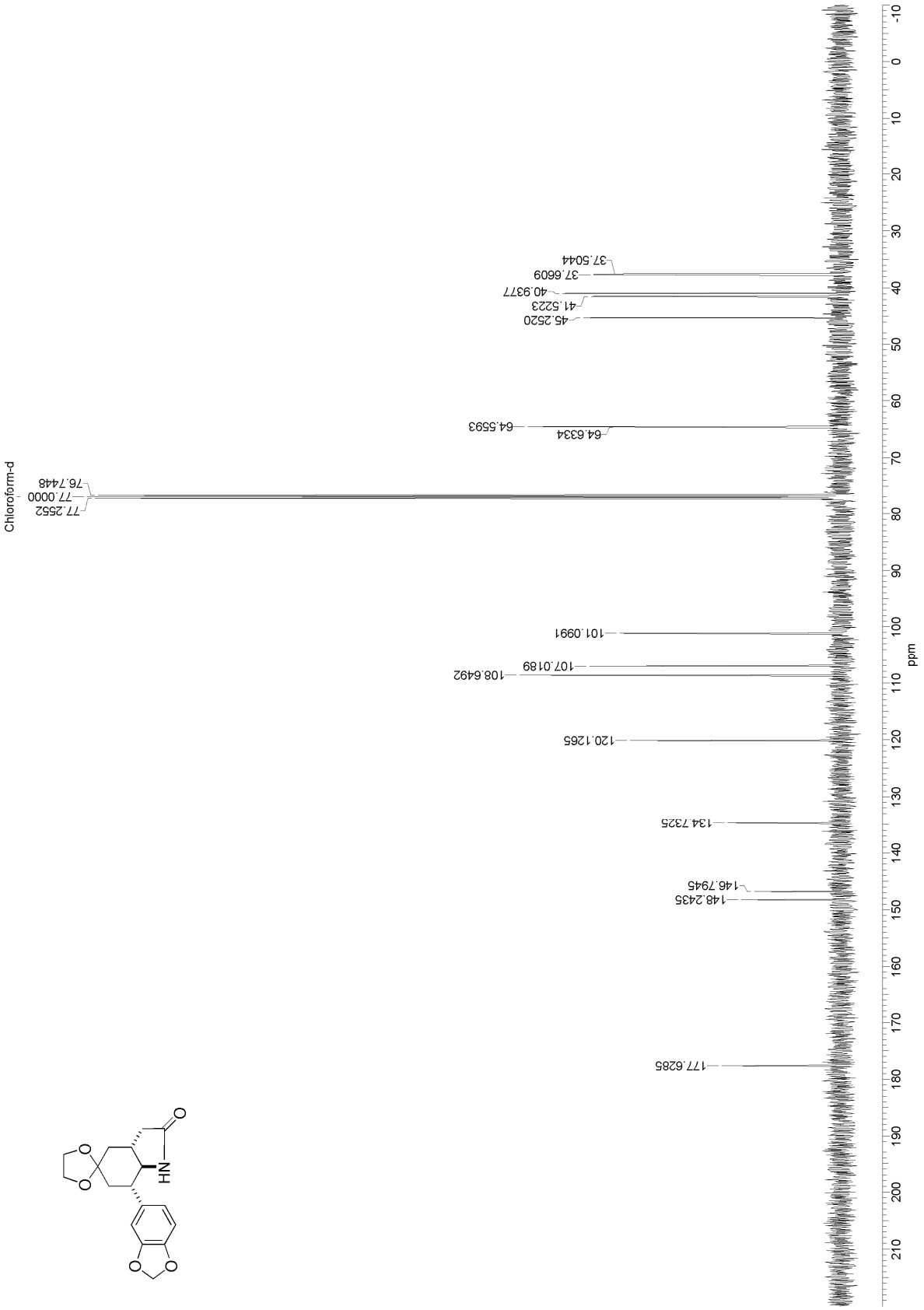
$^{13}$C NMR of **9**


14.1710
28.0195
37.6114
37.9820
40.0156
42.4362
47.6397
57.3634
60.3191
64.4852
Chloroform-d
77.2470
77.0000
76.7448
78.9595
100.7616
107.4882
108.0317
108.3116
120.9992
135.9264
146.1934
147.5025
155.4972
173.0590
CO2Et
HN
Boc
ppm

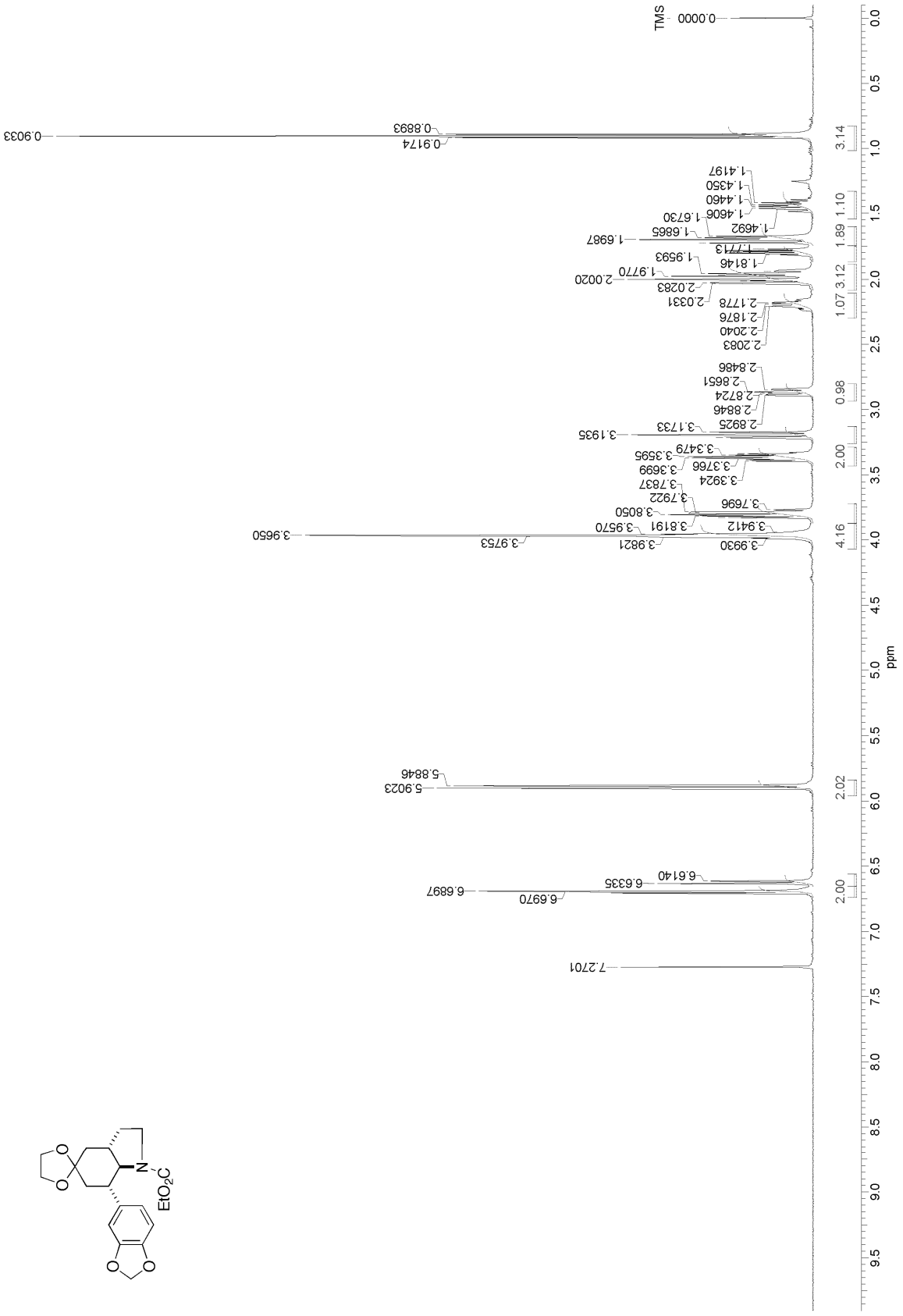
$^1$H NMR of **S3**


TMS
0.0000
1.2745
1.2598
1.6767
1.7023
1.7170
1.8262
1.8525
1.9825
2.1290
2.1595
2.3225
2.3768
2.4067
2.4201
2.7955
2.8175
2.8346
2.8419
3.1587
3.1788
3.1996
3.9521
3.9680
3.9808
3.9882
4.0028
3.9973
5.3310
5.9670
5.9517
6.6457
6.6616
6.6836
6.7580
6.7733
7.2732
1.29
2.15
2.09
1.03
1.03
4.16
1.00
2.06
2.07
ppm
NH
O

$^{13}$C NMR of **S3**

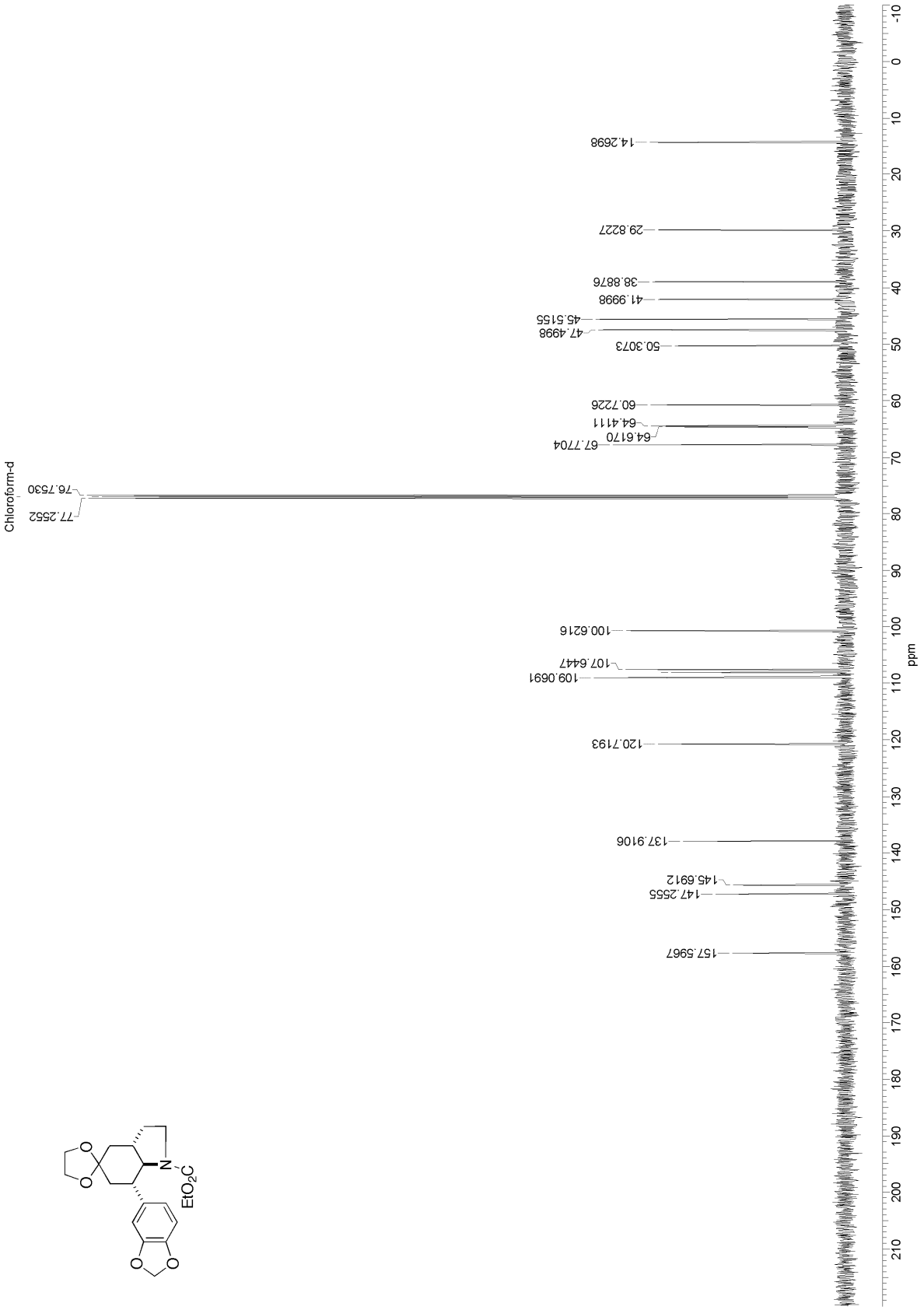

Chloroform-d
77.2552
77.0000
76.7448
64.6334
64.5593
45.2520
41.5223
40.9377
37.6609
37.5044
101.0991
107.0189
108.6492
120.1265
134.7325
146.7945
148.2435
177.6285
ppm
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
O
O
O
O
NH
O

$^1$H NMR of **10**

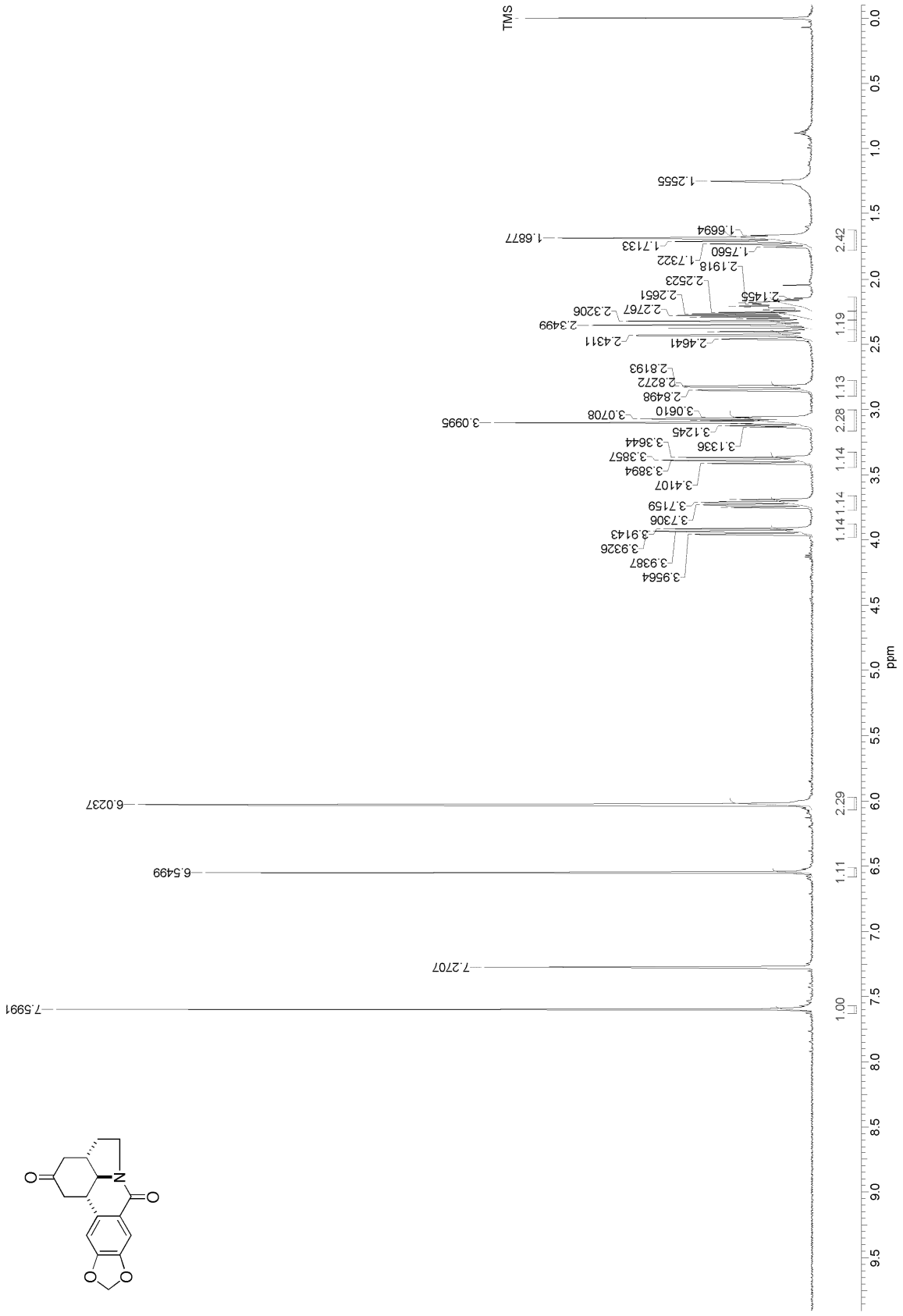

TMS
0.0000
0.9033
0.8893
0.9174
1.4197
1.4350
1.4460
1.4606
1.4692
1.6730
1.6865
1.6987
1.7713
1.8146
1.9593
1.9770
2.0020
2.0283
2.0331
2.1778
2.1876
2.2040
2.2083
2.8486
2.8651
2.8724
2.8846
2.8925
3.1733
3.1935
3.3479
3.3595
3.3699
3.3766
3.3924
3.7837
3.7922
3.7696
3.8050
3.8191
3.9412
3.9570
3.9650
3.9753
3.9821
3.9930
5.8846
5.9023
6.6140
6.6335
6.6897
6.6970
7.2701
3.14
1.10
1.89
3.12
1.07
0.98
2.00
4.16
2.02
2.00
ppm


O
O
N
EtO2C
O
O

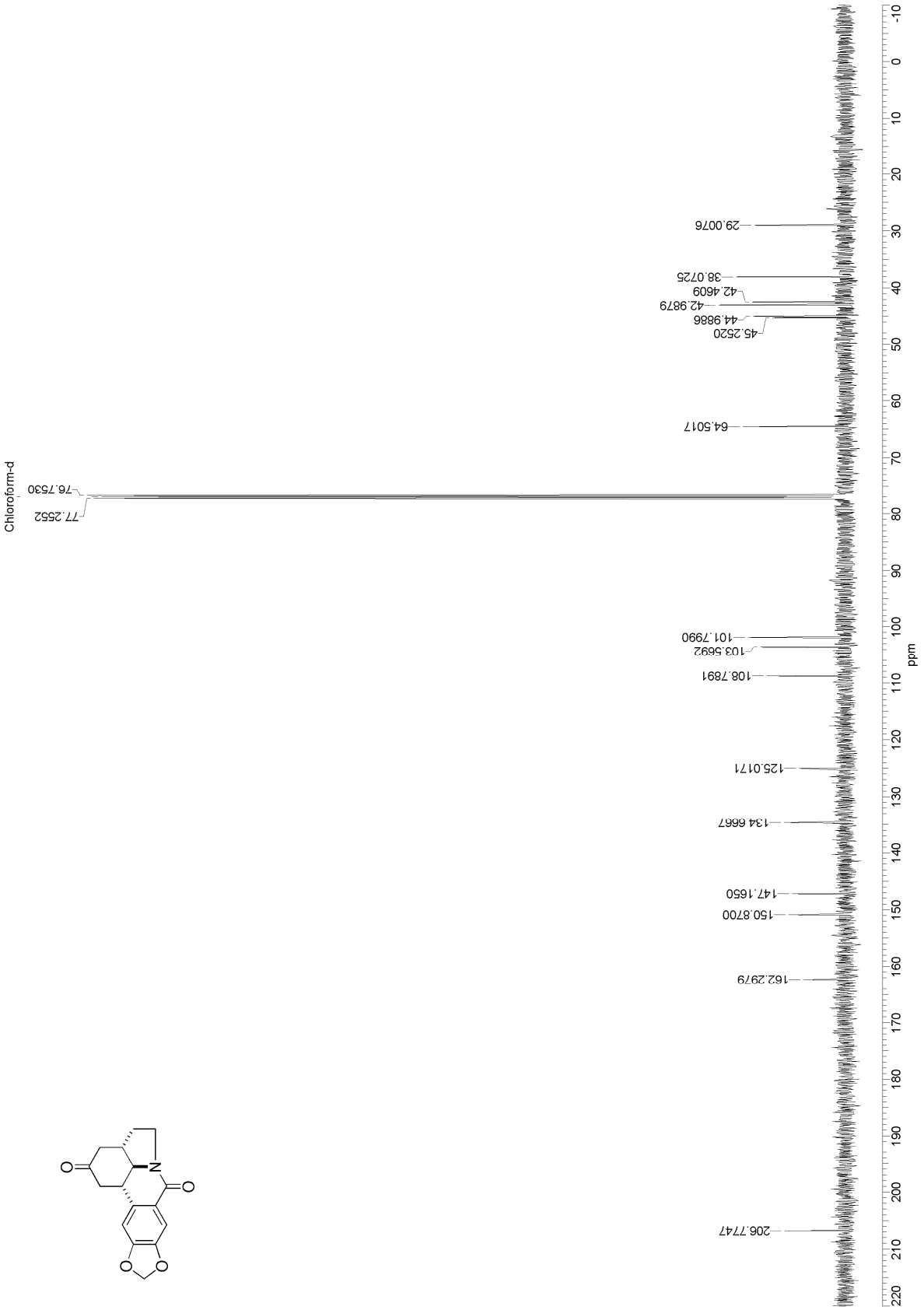
$^{13}$C NMR of **10**


14.2698
29.8227
38.8876
41.9998
45.5155
47.4998
50.3073
60.7226
64.4111
64.6170
67.7704
Chloroform-d
76.7530
77.2552
100.6216
107.6447
109.0691
120.7193
137.9106
145.6912
147.2555
157.5967
ppm
EtO2C

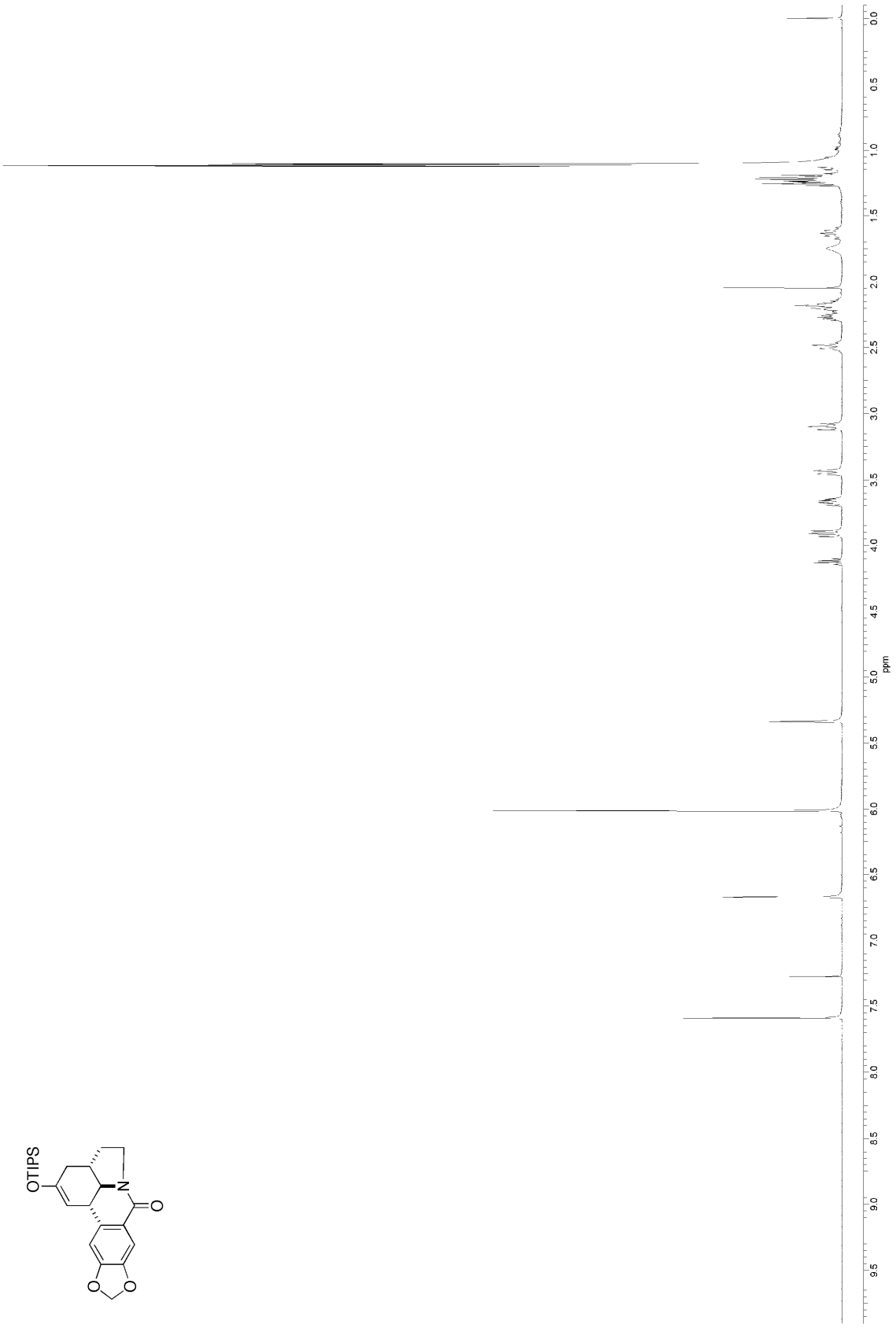
$^{1}$H NMR of **11**


TMS
1.2555
1.6694
1.6877
1.7133
1.7560
1.7322
2.1918
2.2523
2.1455
2.2651
2.2767
2.3206
2.3499
2.4641
2.4311
2.8193
2.8272
2.8498
3.0610
3.0708
3.0995
3.1245
3.1336
3.3644
3.3857
3.3894
3.4107
3.7159
3.7306
3.9143
3.9326
3.9387
3.9564
6.0237
6.5499
7.2707
7.5991
1.00
1.11
2.29
1.14
1.14
1.14
2.28
1.13
1.19
2.42
ppm

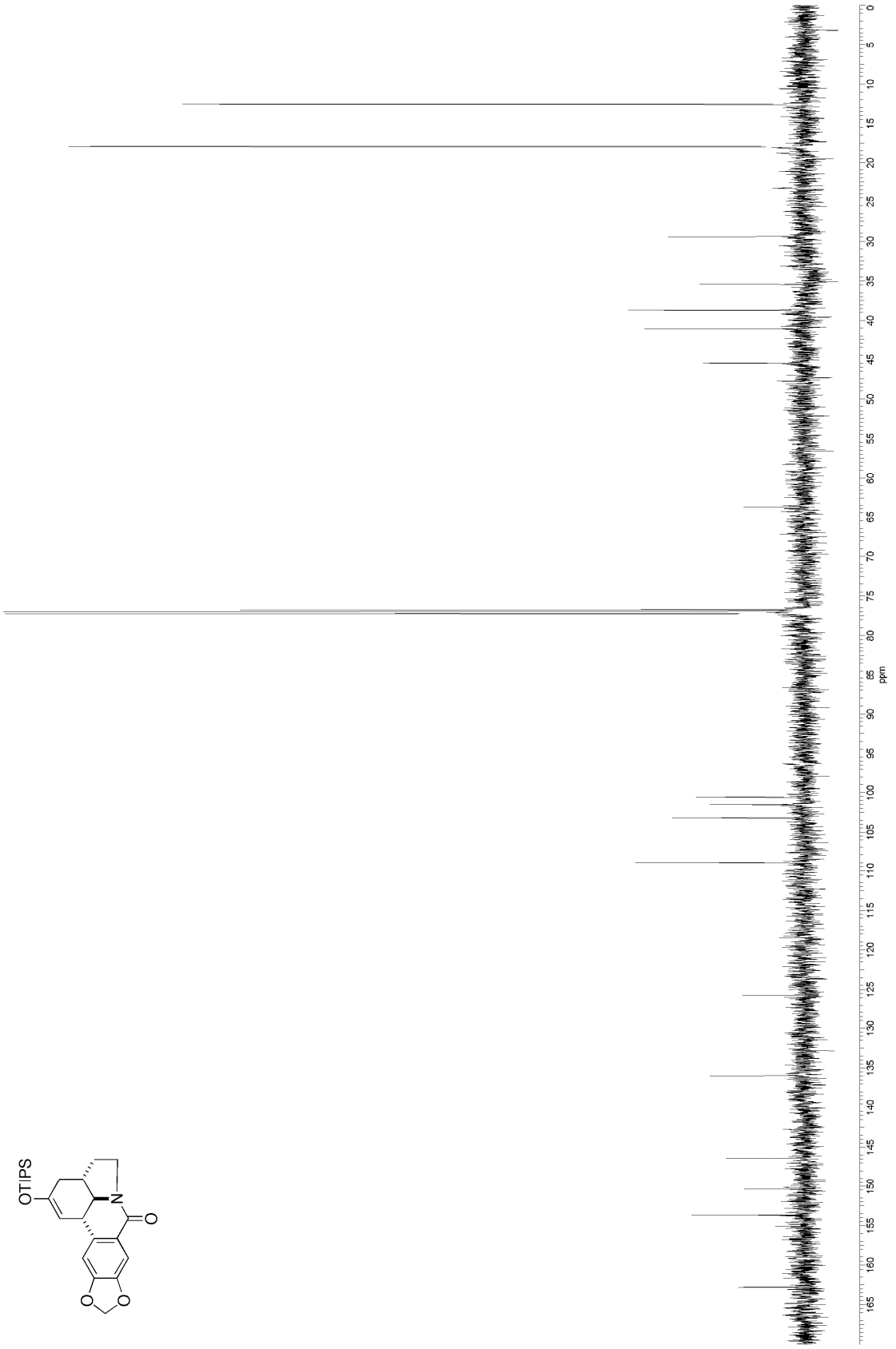
$^{13}$C NMR of **11**


Chloroform-d
76.7530
77.2552
29.0076
38.0725
42.4609
42.9879
44.9886
45.2520
64.5017
101.7990
103.5692
108.7891
125.0171
134.6667
147.1650
150.8700
162.2979
206.7747
ppm

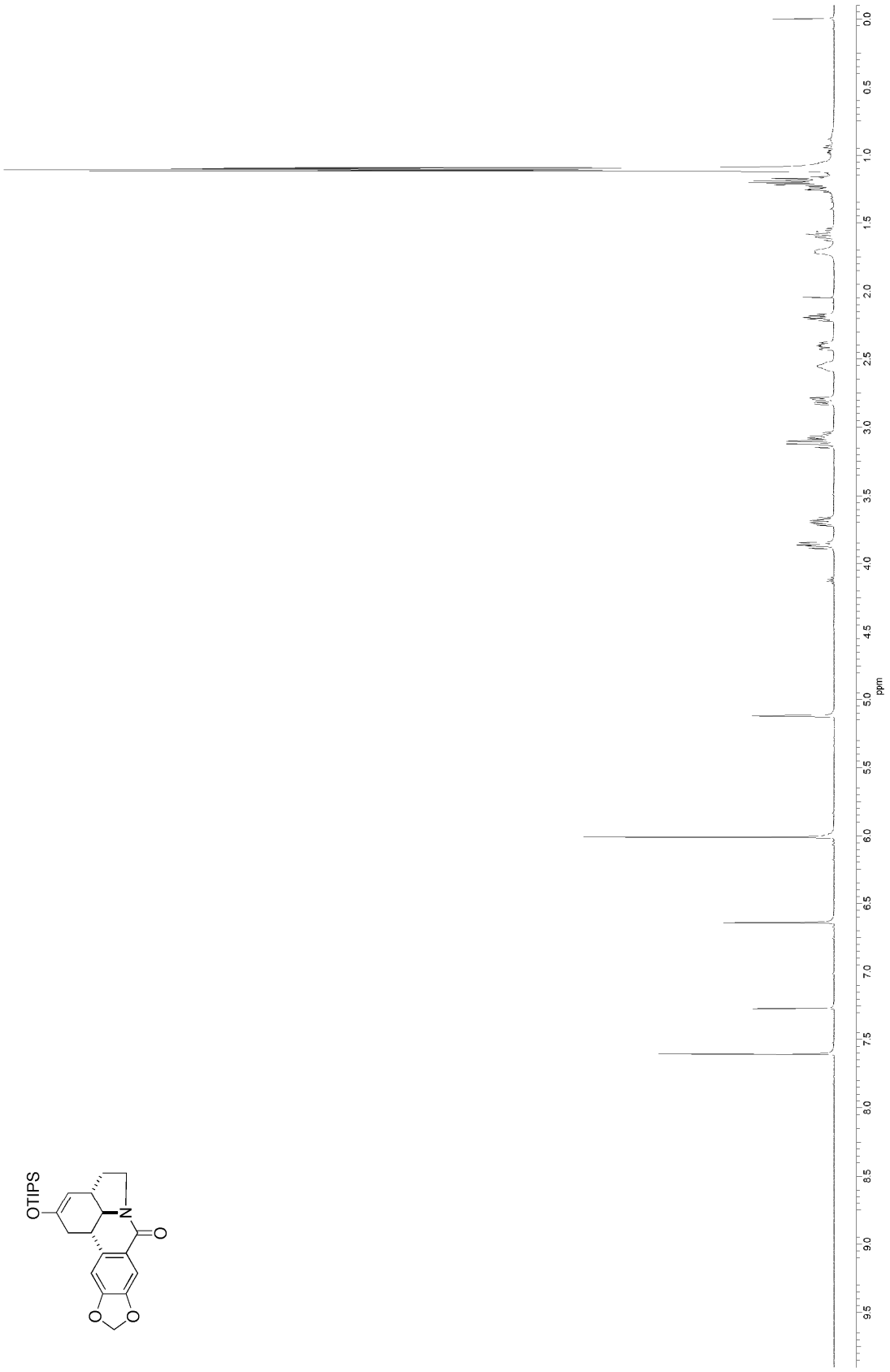
$^1$H NMR of **12**



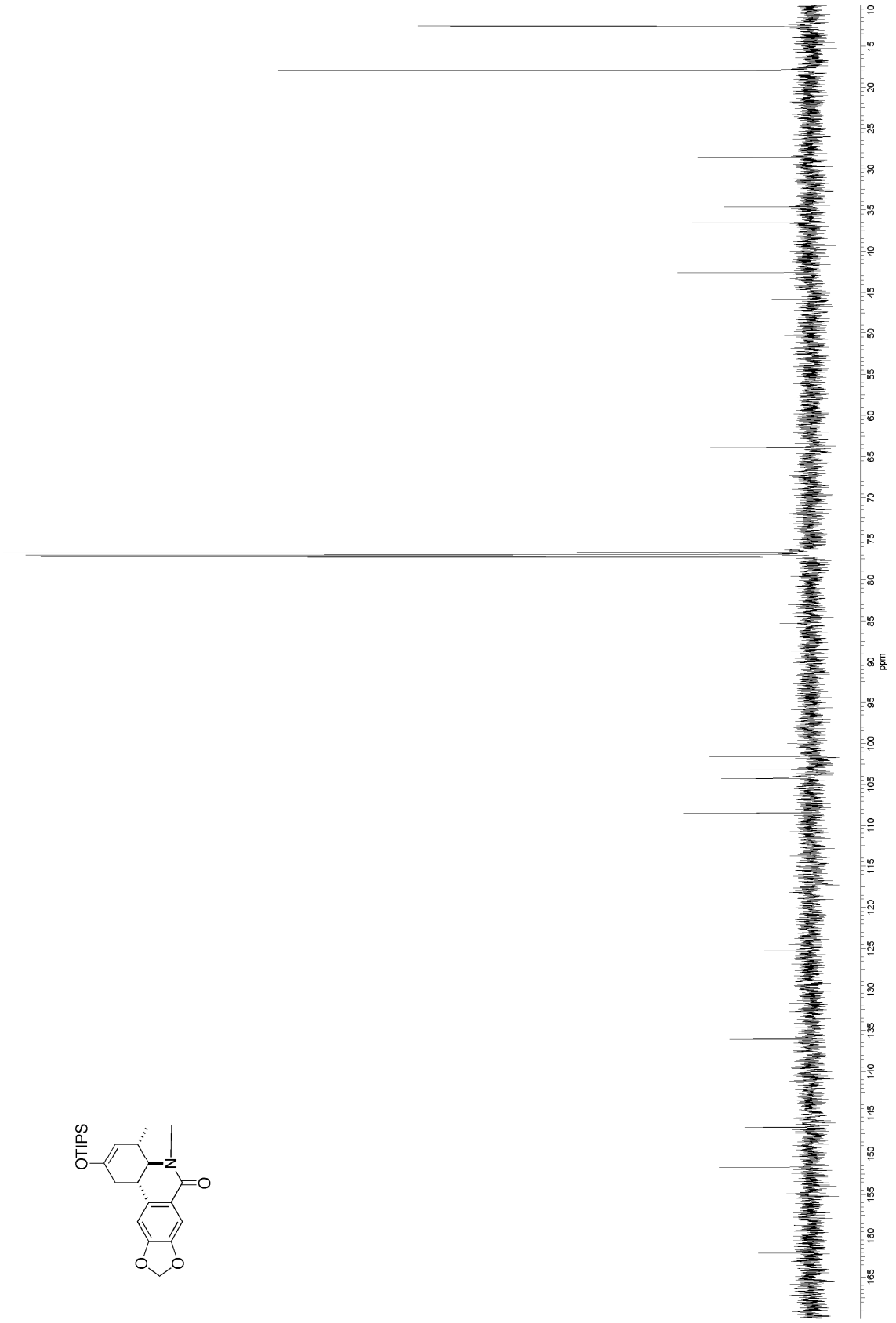
$^{13}$C NMR of **12**



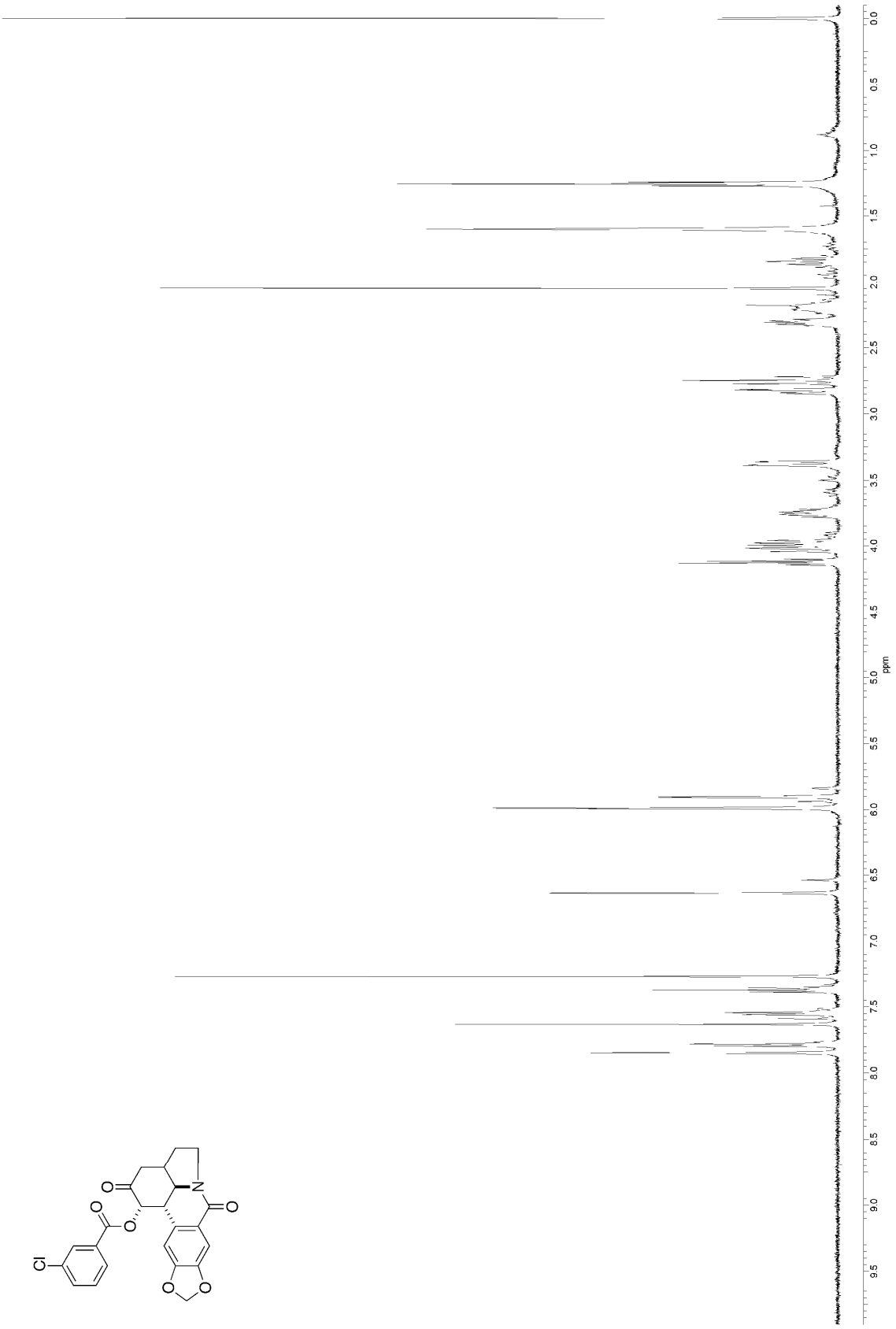
$^1$H NMR of **13**



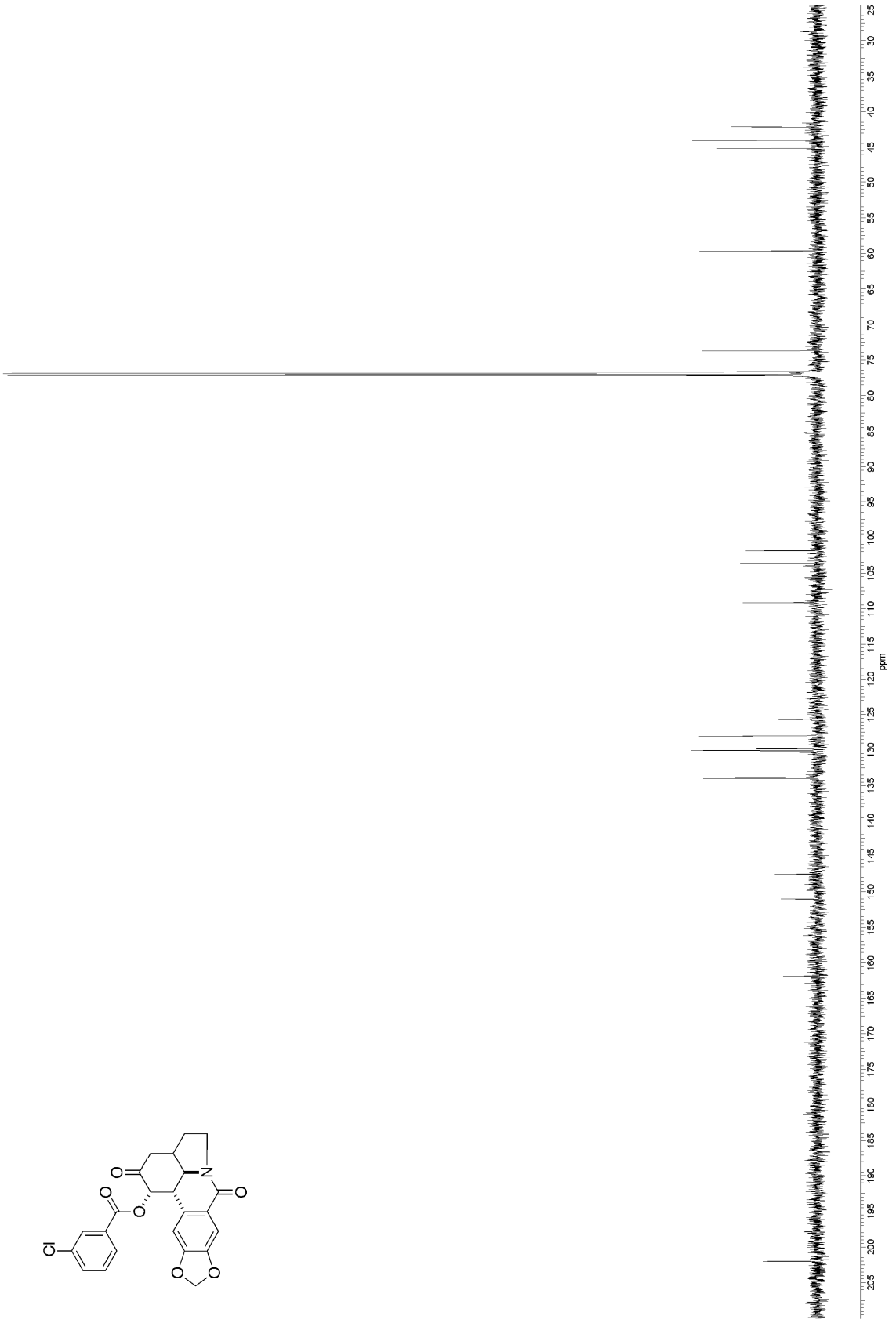
$^{13}$C NMR of **13**



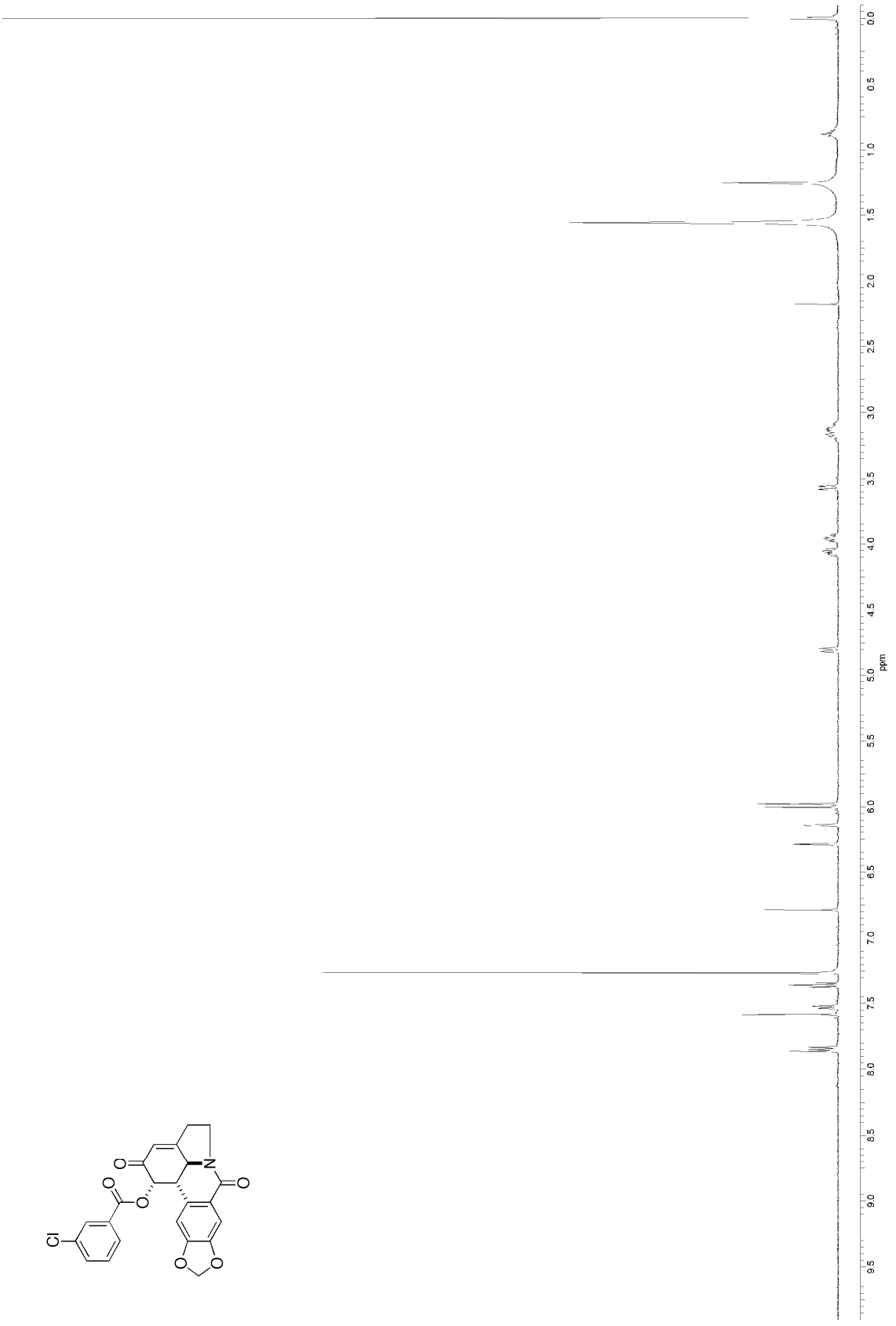
$^{1}$H NMR of **14**


ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
O
O
O
N
O
Cl
O
O

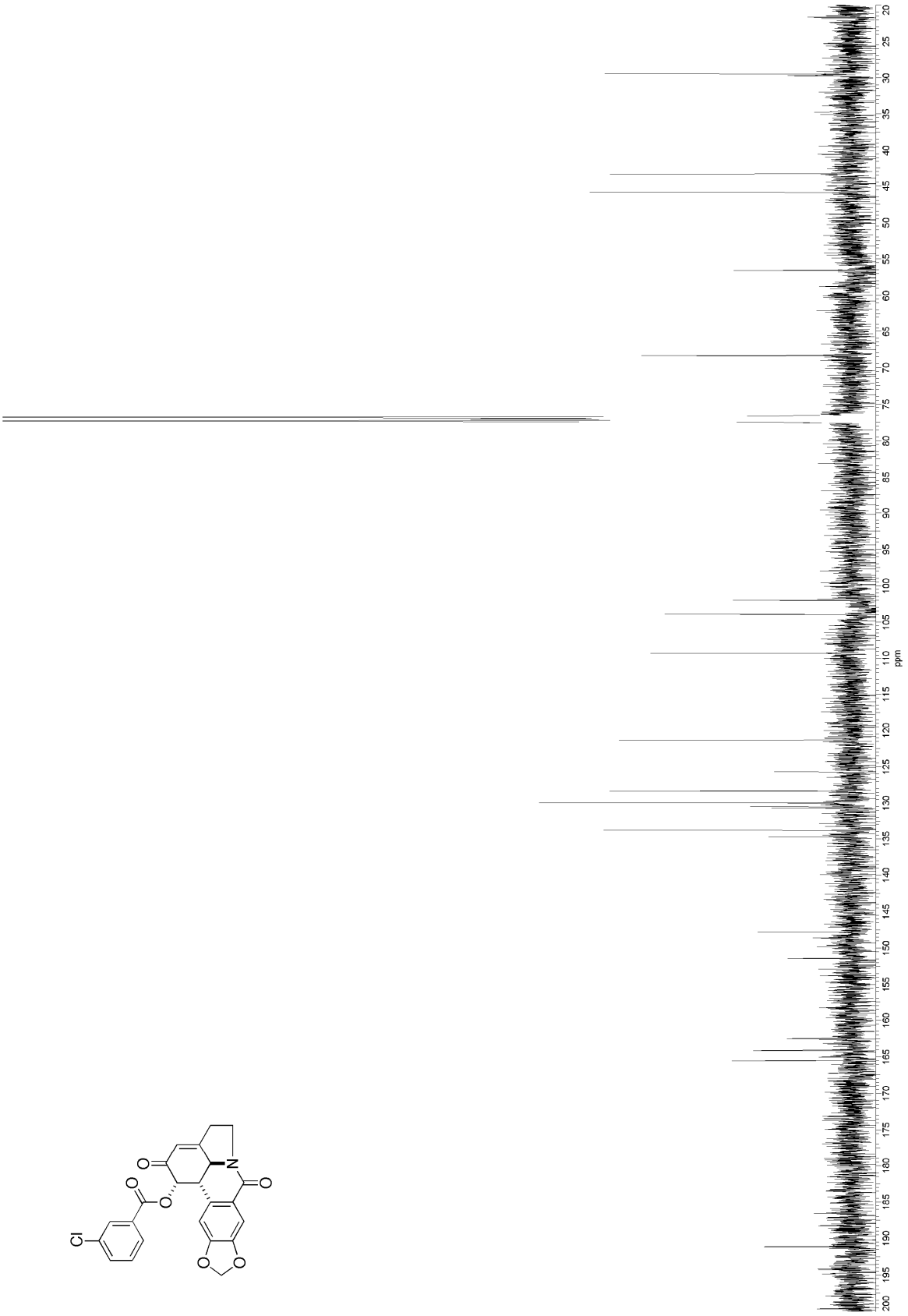
$^{13}$C NMR of **14**



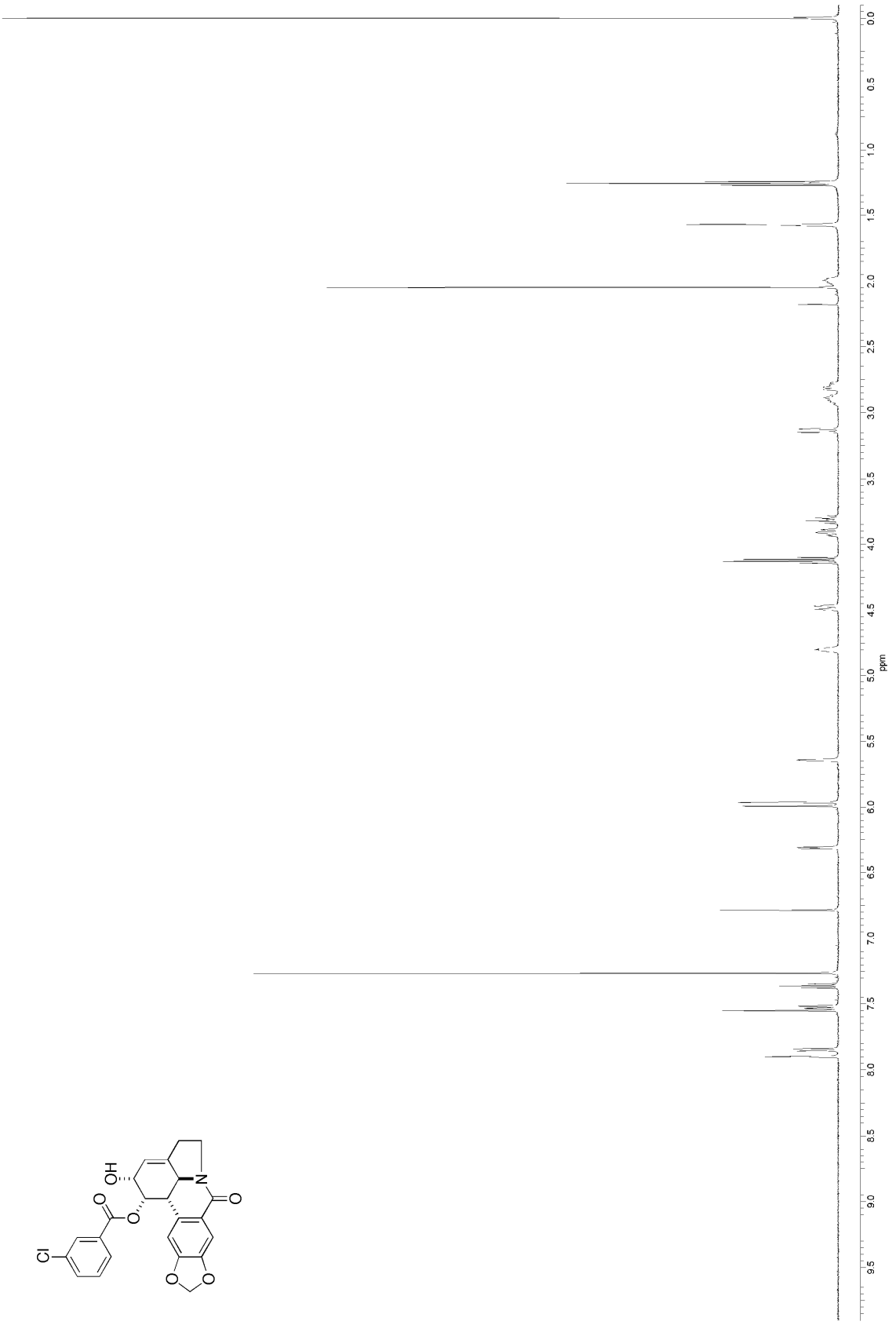
$^{1}$H NMR of **15**


0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
ppm
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
O
O
O
N
O
Cl
O
O

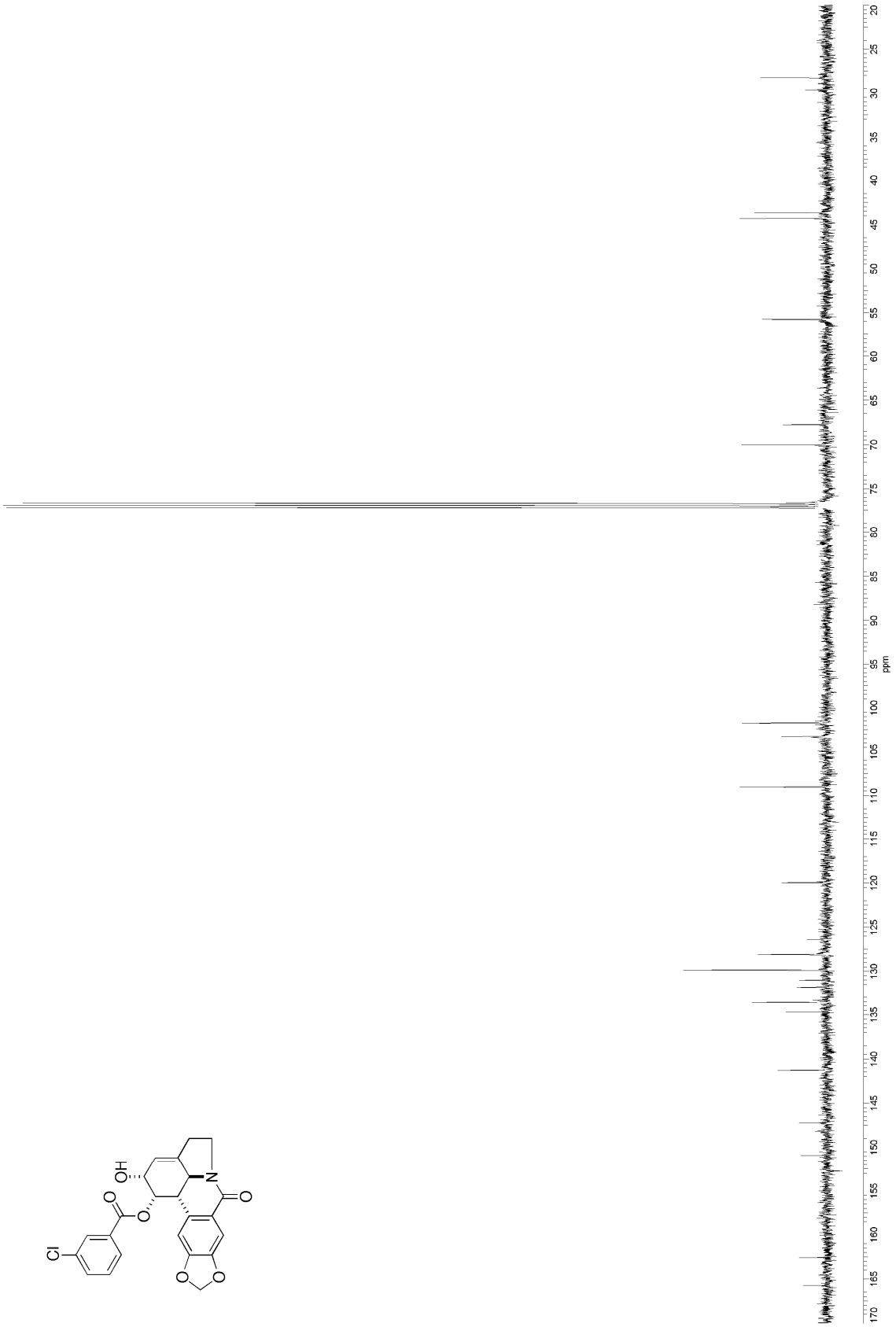
$^{13}$C NMR of **15**



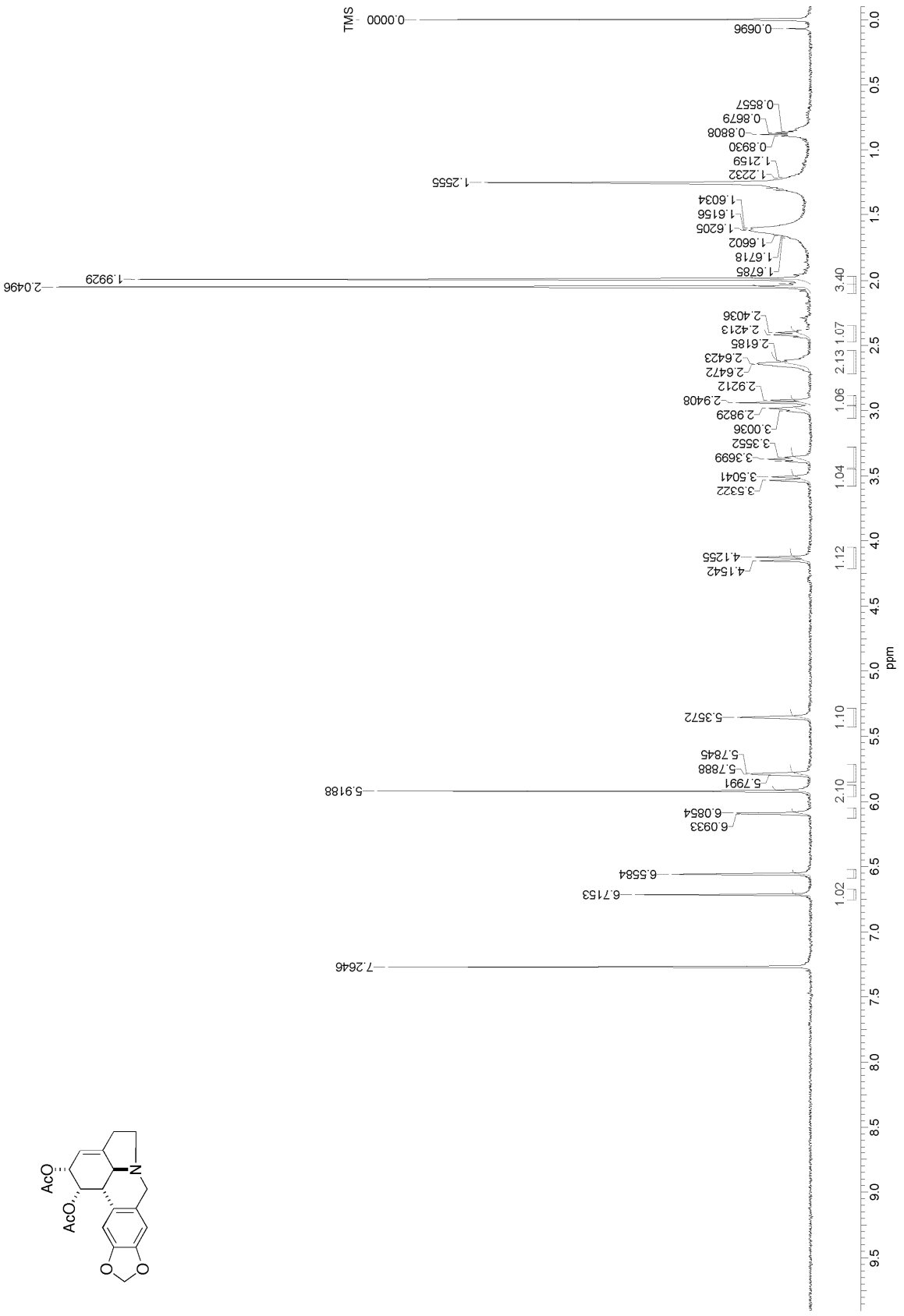
$^{1}$H NMR of **16**



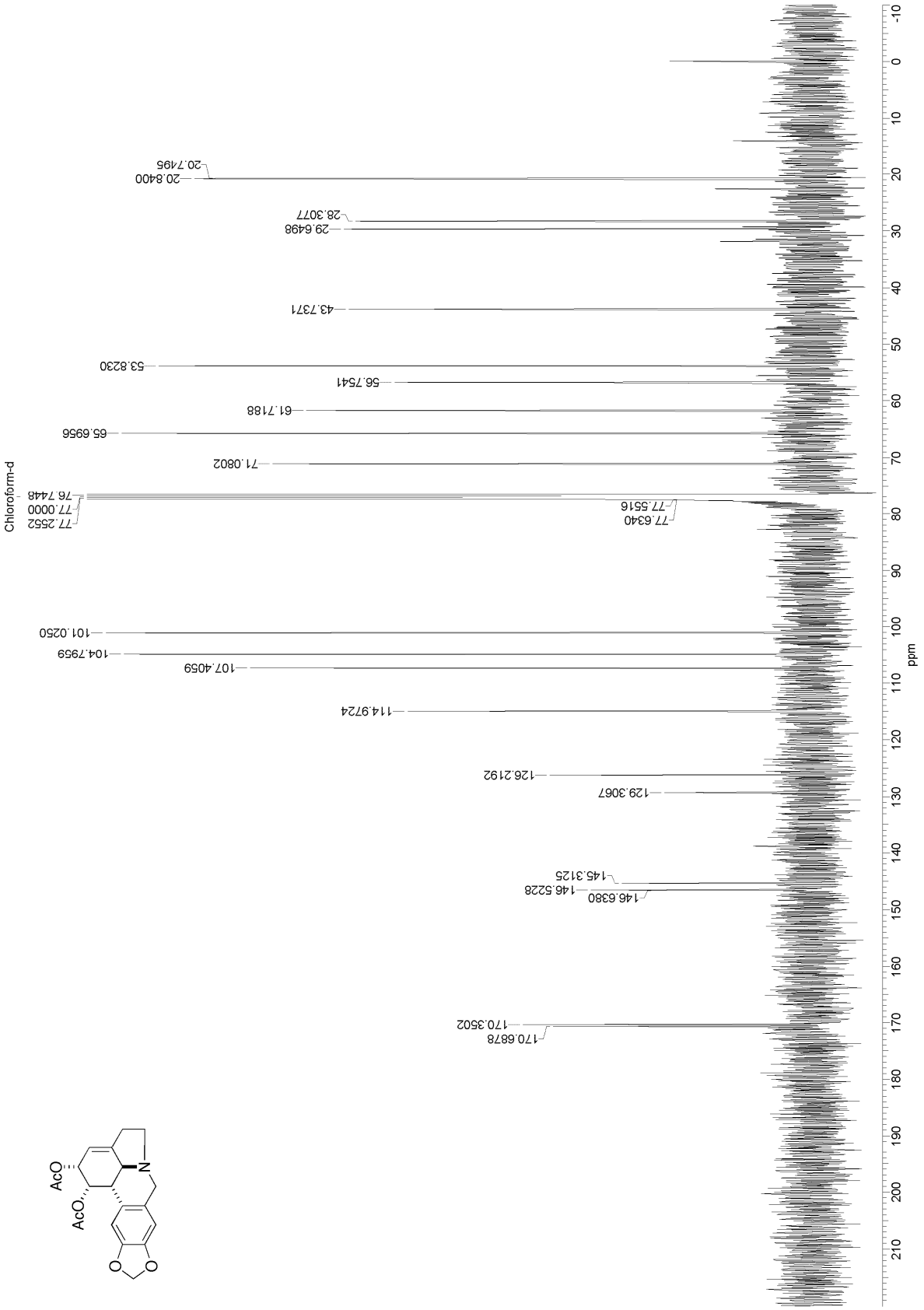
$^{13}$C NMR of **16**



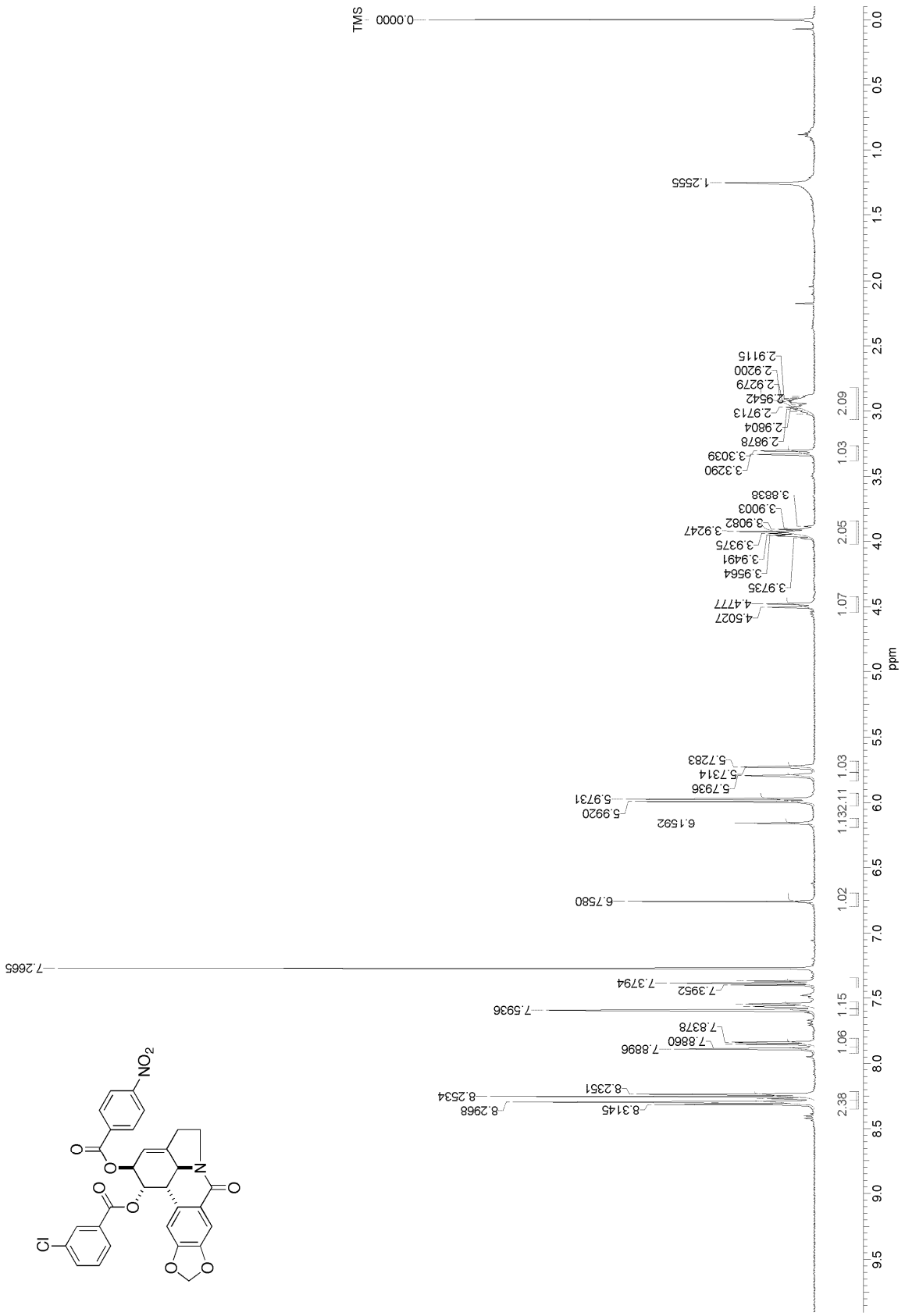
$^1$H NMR of **17**


TMS
0.0000
0.0696
0.8557
0.8679
0.8808
0.8930
1.2159
1.2232
1.2555
1.6034
1.6156
1.6205
1.6602
1.6718
1.6785
1.9929
2.0496
2.4036
2.4213
2.6185
2.6423
2.6472
2.9212
2.9408
2.9829
3.0036
3.3552
3.3699
3.5041
3.5322
4.1255
4.1542
5.3572
5.7845
5.7888
5.7991
5.9188
6.0854
6.0933
6.5584
6.7153
7.2646
3.40
1.07
2.13
1.06
1.04
1.12
1.10
2.10
1.02
ppm
AcO
AcO
N
O
O

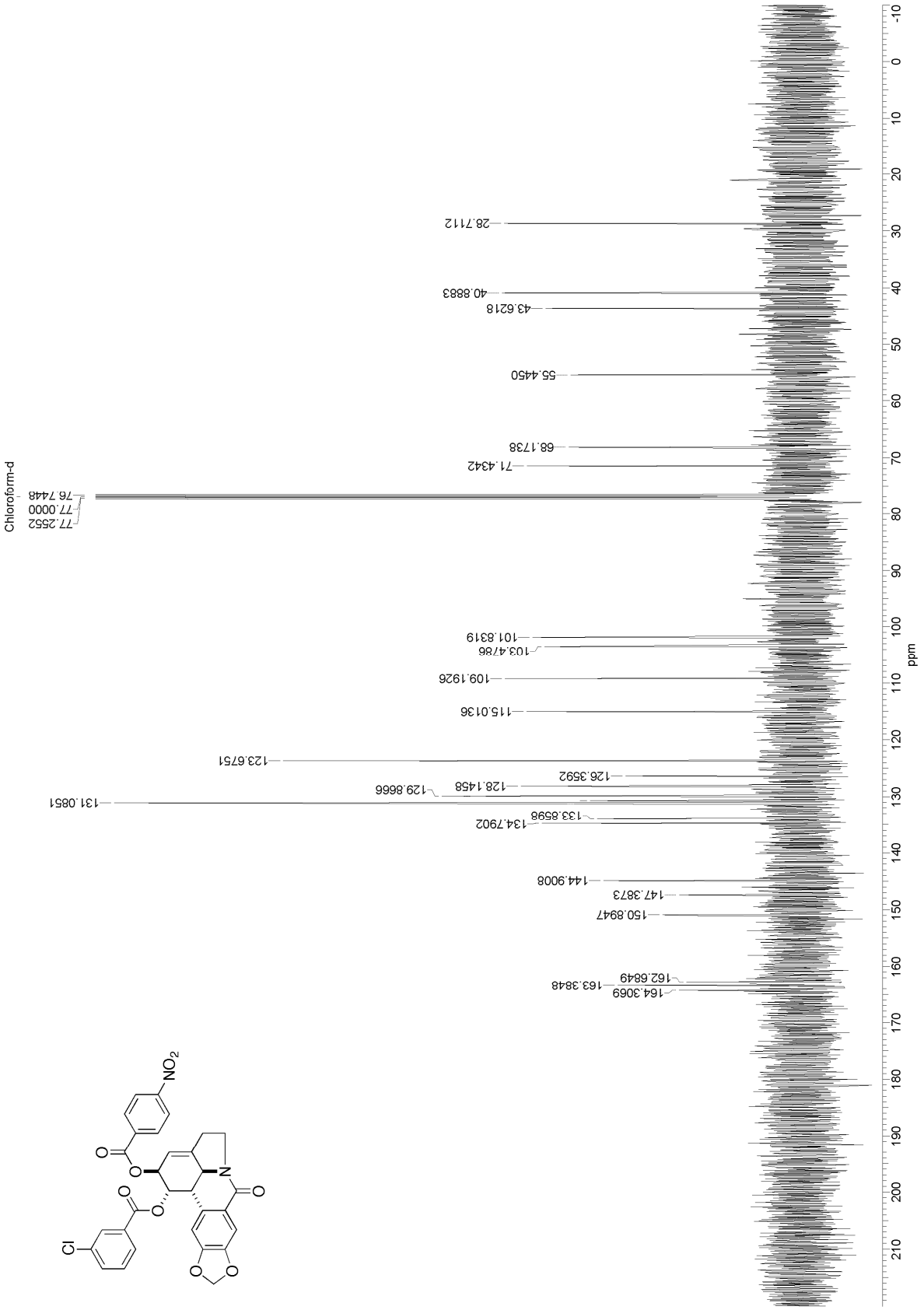
$^{13}$C NMR of **17**


Chloroform-d
77.2552
77.0000
76.7448
77.6340
77.5516
71.0802
65.6956
61.7188
56.7541
53.8230
43.7371
29.6498
28.3077
20.8400
20.7495
101.0250
104.7959
107.4059
114.9724
126.2192
129.3067
145.3125
146.5228
146.6380
170.6878
170.3502
AcO
AcO
N
O
O
ppm

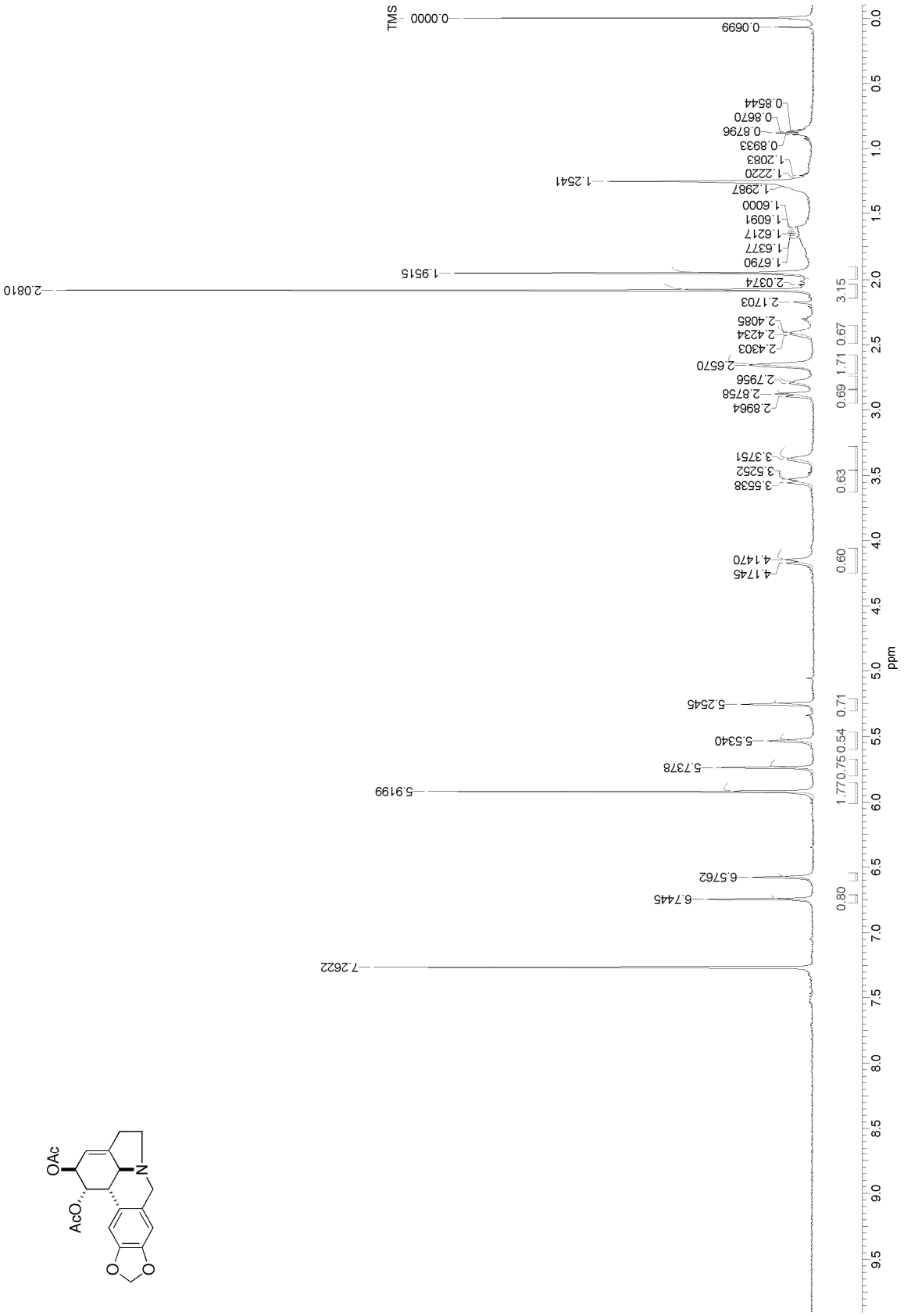
$^1$H NMR of **S4**


TMS
0.0000
1.2555
2.9115
2.9200
2.9279
2.9542
2.9713
2.9804
2.9878
3.3039
3.3290
3.8838
3.9003
3.9082
3.9247
3.9375
3.9491
3.9564
3.9735
4.4777
4.5027
5.7283
5.7314
5.7936
5.9731
5.9920
6.1592
6.7580
7.2665
7.3794
7.3952
7.5936
7.8378
7.8660
7.8896
8.2351
8.2534
8.2968
8.3145
2.38
1.06
1.15
1.02
1.13
2.11
1.03
2.05
1.07
1.03
2.09
ppm
Cl
O
O
O
O
N
O
O
O
$NO_2$

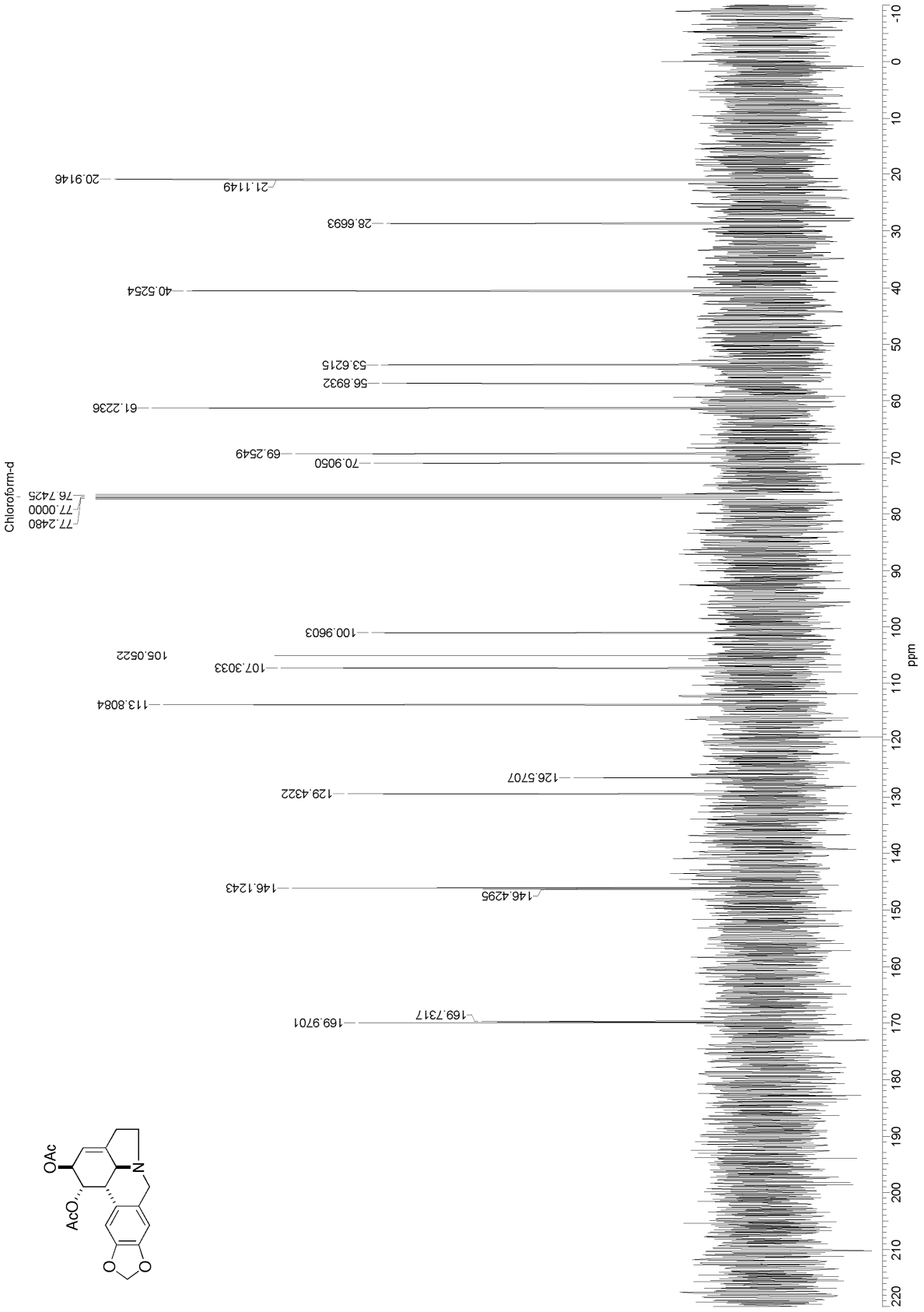
$^{13}$C NMR of **S4**


Chloroform-d
77.2552
77.0000
76.7448
71.4342
68.1738
55.4450
43.6218
40.8883
28.7112
101.8319
103.4786
109.1926
115.0136
123.6751
126.3592
128.1458
129.8666
131.0851
133.8596
134.7902
144.9008
147.3873
150.8947
162.6849
163.3848
164.3069
ppm

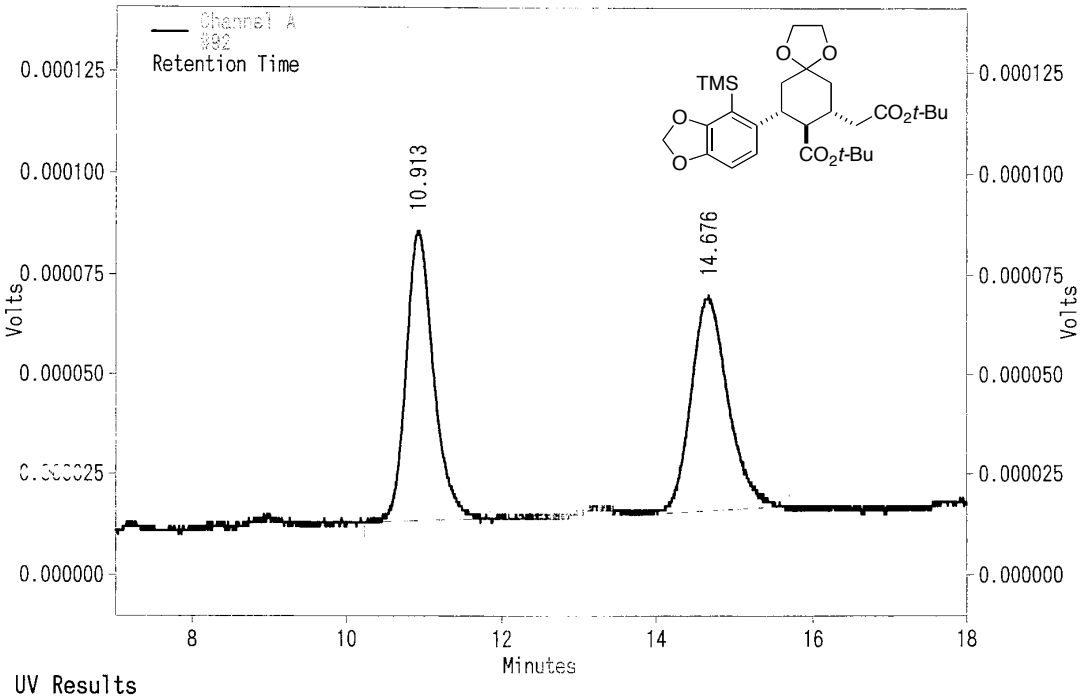
$^1$H NMR of **18**


TMS
0.0000
0.0699
0.8544
0.8670
0.8796
0.8933
1.2083
1.2220
1.2541
1.2987
1.6000
1.6091
1.6217
1.6377
1.6790
1.9515
2.0374
2.0810
2.1703
2.4085
2.4234
2.4303
2.6570
2.7956
2.8758
2.8964
3.3751
3.5252
3.5538
4.1470
4.1745
5.2545
5.5340
5.7378
5.9199
6.5762
6.7445
7.2622
3.15
0.67
1.71
0.69
0.63
0.60
0.71
0.54
1.77
0.75
0.80
ppm
OAc
AcO
N
O
O

$^{13}$C NMR of **18**


20.9146
21.1149
28.6693
40.5254
53.6215
56.8932
61.2236
69.2549
70.9050
76.7425
77.0000
77.2480
Chloroform-d
100.9603
105.0522
107.3033
113.8084
126.5707
129.4322
146.1243
146.4295
169.7317
169.9701
OAc
AcO
O
O
N
ppm

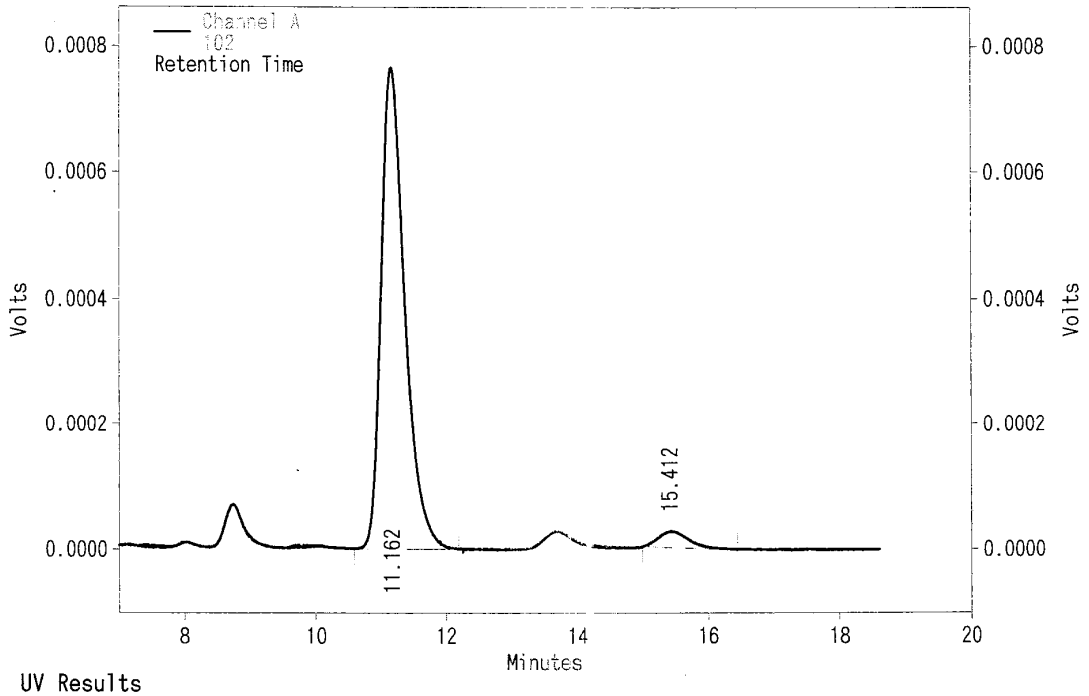
HPLC Trace of (±)-**7**




UV Results

| ﾋﾟｰｸ番号 | 名前 | 保持時間 | 面積 | 面積 % | 高さ | ｺｰﾄﾞ |
|---|---|---|---|---|---|---|
| 1 | | 10.913 | 1765 | 50.242 | 73 | MM |
| 2 | | 14.676 | 1748 | 49.758 | 54 | MM |
| Totals | | | 3513 | 100.000 | 127 | |

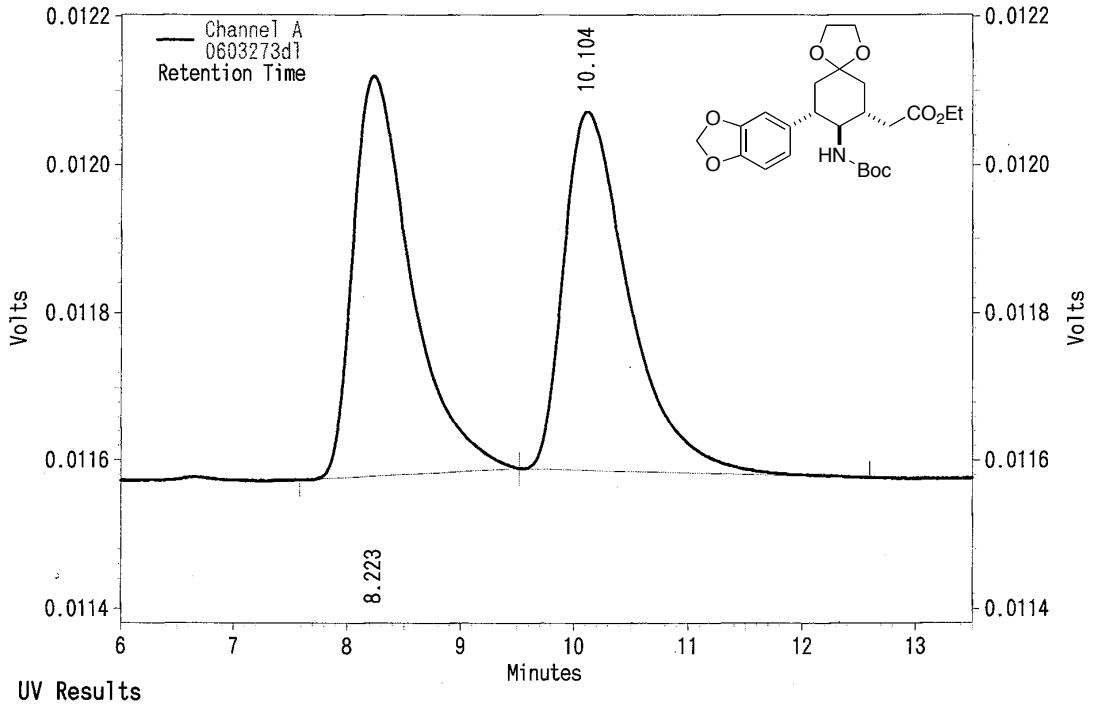
HPLC Trace of (–)-**7** with 92% ee




UV Results

| ﾋﾟｰｸ番号 | 名前 | 保持時間 | 面積 | 面積 % | 高さ | ｺｰﾄﾞ |
|---|---|---|---|---|---|---|
| 1 | | 11.162 | 19443 | 95.816 | 765 | BV |
| 2 | | 15.412 | 849 | 4.184 | 26 | BV |
| Totals | | | 20292 | 100.000 | 791 | |

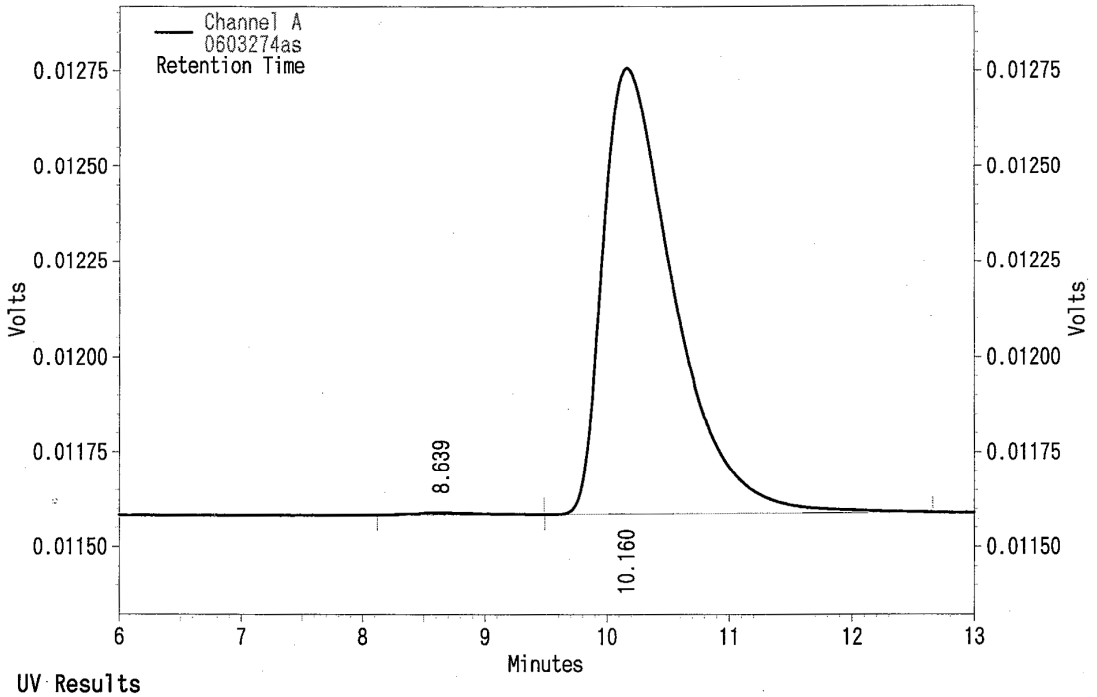
HPLC Trace of (±)-**9**




UV Results

| ピーク番号 | 名前 | 保持時間 | 面積 | 面積 % | 高さ | コード |
|---|---|---|---|---|---|---|
| 1 | | 8.223 | 19221 | 49.667 | 542 | MM |
| 2 | | 10.104 | 19479 | 50.333 | 485 | MM |
| Totals | | | 38700 | 100.000 | 1027 | |

HPLC Trace of (–)-**9** with >99% ee




UV Results

| ピーク番号 | 名前 | 保持時間 | 面積 | 面積 % | 高さ | コード |
|---|---|---|---|---|---|---|
| 1 | | 8.639 | 219 | 0.459 | 6 | MM |
| 2 | | 10.160 | 47486 | 99.541 | 1170 | MM |
| Totals | | | 47705 | 100.000 | 1176 | |