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Recyclization of glaucine as a new route to litebamine derivatives

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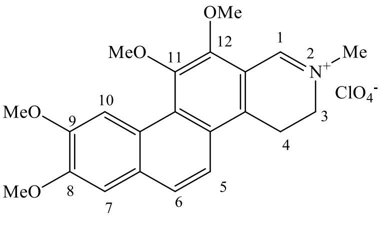
Content

1. General methods

The starting compounds were presented by InterBioscreen Ltd. (Russia). Solvents were purified using the standard procedures. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 spectrometer (600 MHz) in DMSO-d_6 at 25°C. The chemical shifts of ^{1}H and ^{13}C nuclei (δ, ppm) are given against the signals of deuterated solvent (δ = 2.49 ppm for protons and δ = 39.5 ppm for carbon nuclei). The melting points were measured on a Fisher – Johns Melting Point Apparatus (Fisher Scientific) (USA). The elemental analysis was carried out by the classic method for microanalysis. The course of reaction and the purity of the compounds obtained were controlled by the TLC method (plates with Al_2O_3 of III degree of activity, eluent $CHCl_3$, staining with iodine vapor at the wet chamber).

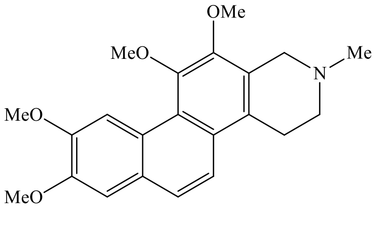
2. Synthesis and characteristics of compounds 6, 8-11

8,9,11,12-Tetramethoxy-2-methyl-3,4-dihydronaphtho[2,1-f]isoquinolin-2-ium perchlorate ***(6)***



The mixture of glaucine hydrochloride (7.83 g, 0.02 mol), anhydrous AcONa (1.64 g, 0.02 mol), and Ac_2O (6.12 g, 0.06 mol) in absolute DMF (8 mL) was boiled for 1.5 h, then poured into water (150 mL), the precipitate formed was filtered off, washed with water (4×15 mL), and dried at 100°C for 4 h. The yield was 7.3 g (95%). Then the compound was mixed with a KOH alcohol solution (7.4 g of 85% KOH in 20 mL of alcohol) and boiled for 8 h. The mixture was poured into water (150 mL), the precipitate was filtered off, washed with water (4×15 mL), and dried at 100°C for 4 h. The yield was 6.4 g (95%). The seco-alkaloid **2** (35.5 g, 0.1 mol) obtained in several experiments without additional purification was formylated by treatment with 99.7% formic acid solution (14 mL) in absolute DMF (50 mL), and this mixture was boiled for 45 min. The mixture was poured into water (200 mL) on stirring, the formyl derivative **5** was filtered off, washed with water (5×20 mL), and dried at 100°C for 5 h. The yield was 35.6 g (93%). Previously, this formyl derivative was prepared by reaction of glaucine with $POCl_3$ in DMF in the yield of 49% [S1]. In the final cyclization, compound **5** was used without additional purification. For this purpose, formyl derivative **5** (10.7 g, 0.03 mol) was added to a solution of $POCl_3$ (3.8 mL, 0.04 mol) in dry $CHCl_3$ (30 mL), and the mixture was kept at 28-30°C for 24 h. Then ethanol (60 mL) and 40% $HClO_4$ (6 mL) were added on stirring. Perchlorate **6** was filtered off and washed with ethanol (4×15 mL). The yield was 12.6 g (97%), mp 215-220°C with decomposition (EtOH). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 3.64 (t, 3H, CH_2, J = 8.4 Hz), 3.86 (s, 3H, Me), 3.95 (s, 3H, OMe), 3.97 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.12-4.14 (m, 5H, CH_2, OMe), 7.56 (s, 1H, H-1), 7.89 (d, 1H, H-5, J = 8.4 Hz), 7.94 (d, 1H, H-6, J = 8.4 Hz), 9.09 (s, 1H, H-7), 9.38 (s, 1H, H-10). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 22.24, 47.01, 48.96, 55.40, 55.57, 60.16, 62.68, 108.54, 108.76, 117.04, 120.51, 122.81, 125.74, 127.64, 129.94, 130.03, 131.63, 148.68, 149.09, 150.17, 150.54, 161.59. Found, %: C 56.49, H 5.00, Cl 7.74, N 2.69. $C_{22}H_{24}ClNO_8$. Calculated, %: C 56.72, H 5.19, Cl 7.61, N 3.01.

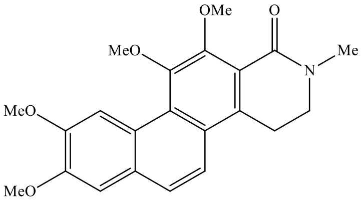
8,9,11,12-Tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-f]isoquinoline ***(8)***



Sodium borohydride (0.5 g, 13.2 mmol) was added in small portions at 0°C to a stirred solution of perchlorate **6** (10.3 g, 22.2 mmol) and NaOH (1.0 g, 25 mmol) in a mixture of EtOH (50 mL) and water (5 mL). The mixture was agitated at 3-5°C for 1 h and poured into water (120 mL), the precipitate of tetrahydro derivative **8** formed was filtered off and washed with water (20 mL). The yield was 7.5 g (92%), mp 146-150°C (EtOAc) (64-68 ºC [S2]). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.42 (s, 3H, Me), 2.69 (t, 2H, CH_2, J = 6.0 Hz), 3.10 (t, 2H, CH_2, J = 5.4 Hz), 3.60

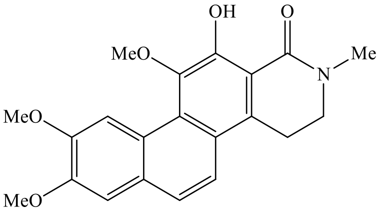
(s, 2H, CH_2), 3.88 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.95 (s, 3H, OMe), 7.42 (s, 1H, H-7), 7.68-7.71 (m, 2H, H-5,6), 9.06 (s, 1H, H-10). ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ: 26.52, 45.75, 52.02, 53.04, 55.22, 55.27, 59.72, 60.30, 17.91, 108.32, 119.66, 122.02, 123.63, 125.68, 126.66, 127.12, 127.45, 128.01, 147.77, 147.90, 148.43. Found, %: C 71.60, H 6.52, N 3.56. $C_{22}H_{25}NO_4$. Calculated, %: C 71.91, H 6.86, N 3.81.

8,9,11,12-Tetramethoxy-2-methyl-3,4-dihydronaphtho[2,1-f]isoquinolin-1(2H)-one ***(9)***



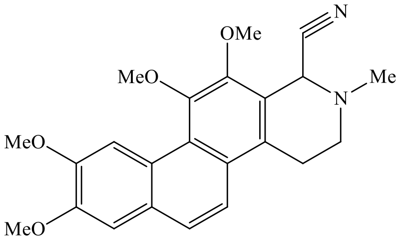
Finely powdered iodine (2.7 g, 10.6 mmol) was added on stirring to a mixture of perchlorate **6** (4.7 g, 10 mmol) in $CHCl_3$ (30 mL) at 25-30°C. The mixture was vigorously agitated at 25-30°C for 1.5 h, then saturated solution of K_2CO_3 (20 mL) was added to complete decolouration. The organic layer was separated, washed with water (2×5 mL), aqueous solution of Na_2SO_3, with water (2×5 mL), 5% H_2SO_4 (2×5 mL), and finally again with water (2×5 mL). A chloroform solution was dried over K_2CO_3, chloroform was evaporated, the residue was recrystallized from EtOAc – EtOH mixture (1 : 1). The yield was 3.0 g (79%), mp 187-190°C (146-149 °C [S2]). ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ: 3.09 (s, 3H, Me), 3.28 (t, 2H, CH_2, J = 6.3 Hz), 3.58 (t, 2H, CH_2, J = 6.6 Hz), 3.88 (s, 3H, OMe), 3.94 (s, 3H, OMe), 3.96 (s, 3H, OMe), 4.96 (s, 3H, OMe), 7.45 (s, 1H, H-7), 7.73 (d, 1H, H-5, J = 9.0 Hz,), 7.81 (d, 1H, H-6, J = 9.0 Hz), 9.08 (s, 1H, H-10). ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ: 25.18, 34.08, 46.77, 55.27, 55.34, 59.94, 61.54, 108.29, 108.38, 120.40, 122.50, 123.01, 125.37, 125.39, 126.39, 128.49, 134.02, 148.70, 149.26, 150.00, 150.60, 161.65. Found, %: C 69.47, H 5.84, N 3.31. $C_{22}H_{23}NO_5$. Calculated, %: C 69.28, H 6.08, N 3.67.

12-Hydroxy-8,9,11-trimethoxy-2-methyl-3,4-dihydronaphtho[2,1-f]isoquinolin-1(2H)-one ***(10)***



The mixture of compound **9** (1.0 g, 2.6 mmol), AcOH (3 mL), and HCl conc. (1.5 mL) was boiled for 1 h. After cooling, the precipitate of hydroxy derivative **10** was filtered off, washed with 50% AcOH (2×3 mL) and water (4×5 mL). The yield was 0.78 g (84%), mp 234-237°C (5% AcOH) (240-242 °C [S2]). ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ: 3.11 (s, 3H, Me), 3.40 (d, 2H, CH$_2$, *J* = 6.9 Hz), 3.70 (d, 2H, CH$_2$, *J* = 7.2 Hz), 3.90 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.94 (s, 3H, OMe), 7.41 (s, 1H, H-7), 7.61 (d, 1H, H-5, *J* = 9.0 Hz), 7.77 (d, 1H, H6, *J* = 9.0 Hz), 9.13 (s, 1H, H-10), 13.26 (s, 1H, OH). ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ: 23.31, 34.11, 46.99, 55.25, 55.36, 58.96, 108.40, 108.80, 11.61, 120.62, 121.32, 122.67, 124.46, 126.74, 128.90, 132.03, 142.42, 148.25, 149.38, 151.00, 167.96. Found, %: C 68.49, H 5.43, N 3.40. $C_{21}H_{21}NO_5$. Calculated, %: C 68.65, H 5.76, N 3.81.

8,9,11,12-Tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-f]isoquinoline-1-carbonitrile ***(11)***



Acetone cyanohydrin (0.23 g, 2.7 mmol) was added to a solution of perchlorate **6** (0.93 g, 2 mmol) and NaOH (0.1 g, 2.5 mmol) in aqueous alcohol (5 mL EtOH, 2 mL of water) on stirring. The mixture was agitated for 30 min, the precipitate formed was filtered off and washed with water (3×3 mL). The yield of nitrile **11** was 0.7 g (90%), mp 184-186°C (EtOAc). ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ: 2.57 (s, 3H, Me), 3.61-2.65 (m, 1H, CH), 3.09-3.20 (m, 3H, CH$_2$, CH), 3.91 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.96 (s, 3H, OMe), 4.09 (s, 3H, OMe), 5.27 (s, 1H, H-1), 7.46 (s, 1H, H-7), 7.74 (d, 1H, H-5, *J* = 9.0 Hz), 7.76 (d, 1H, H-6, *J* = 9.6 Hz), 9.07 (s, 1H, H-10). ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ: 25.66, 42.44, 47.41, 51.71, 55.27, 55.33, 59.69, 60.74, 107.98, 108.38, 116.35, 119.59, 122.94, 123.30, 123.60, 126.26, 127.05, 127.17, 127.98, 147.38, 147.93, 148.72, 148.90. Found, %: C 70.41, H 5.32, N 6.68. $C_{23}H_{22}N_2O_4$. Calculated, %: C 70.75, H 5.68, N 7.17.

4. XRD-Data

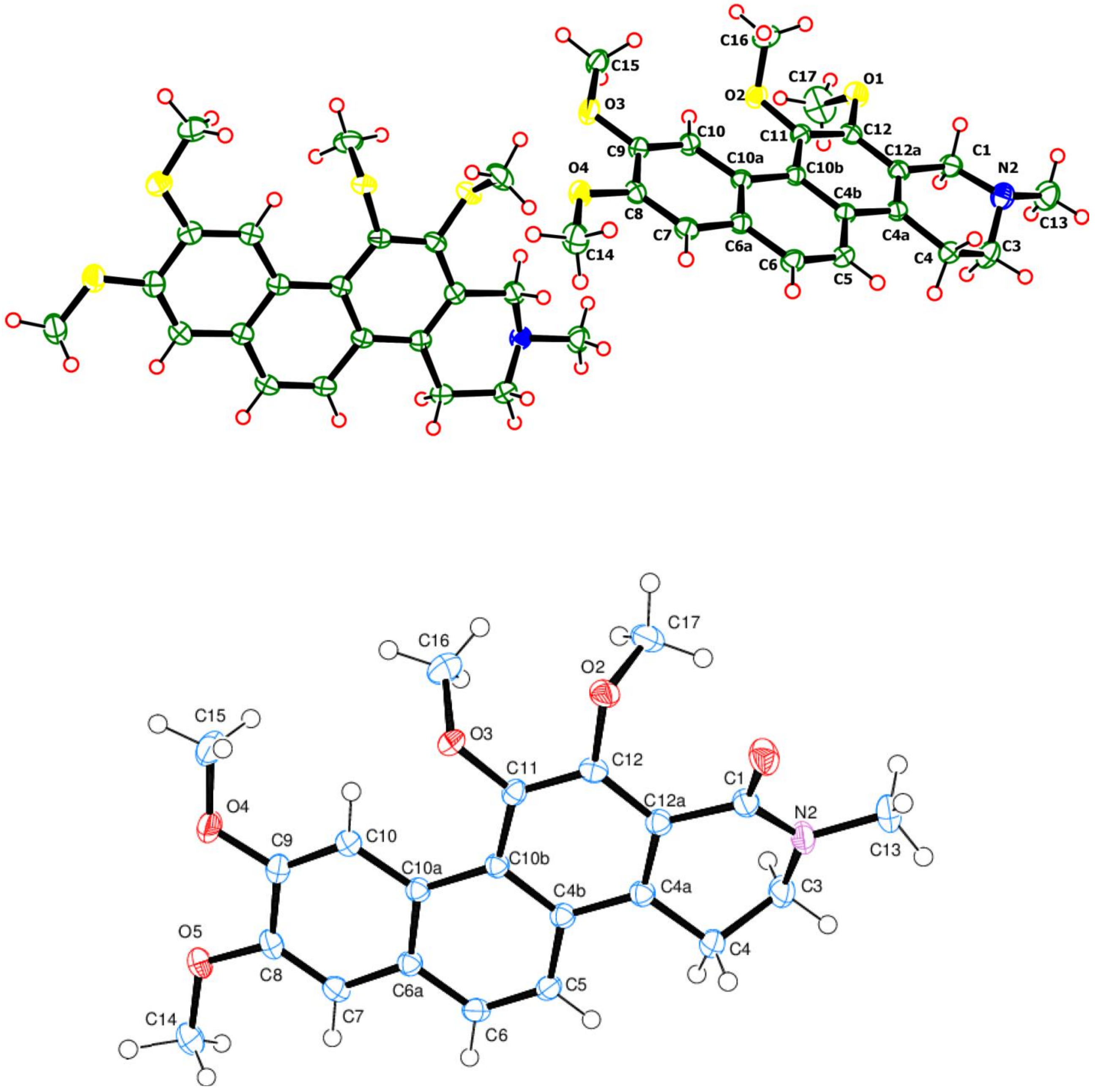


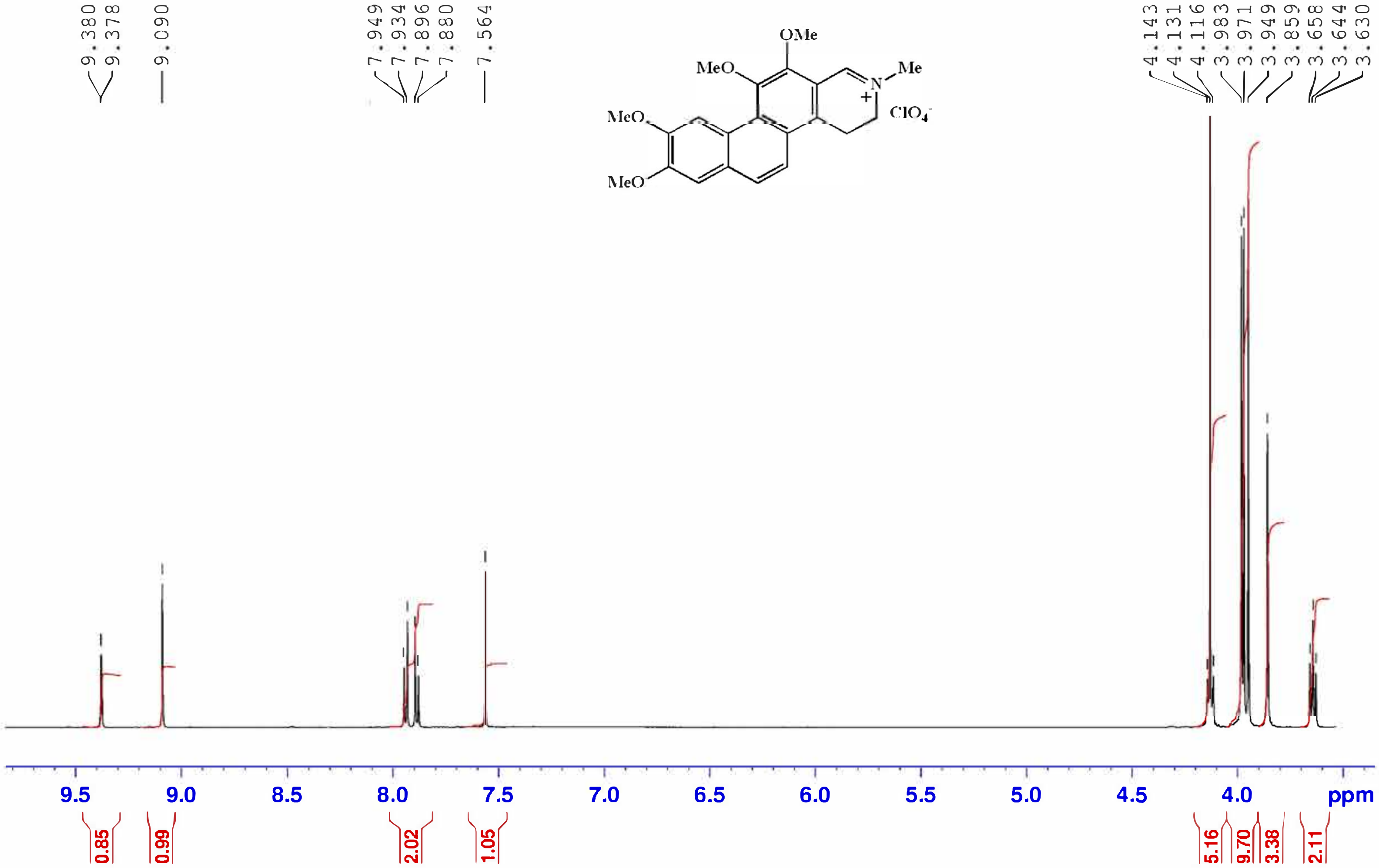
Figure S1 Molecular structure of *O*,*O*-dimethyllitebamine **8** (top) and its oxo derivative **9** (bottom). The ellipsoids of heat vibrations are depicted with probability of 30%.

References

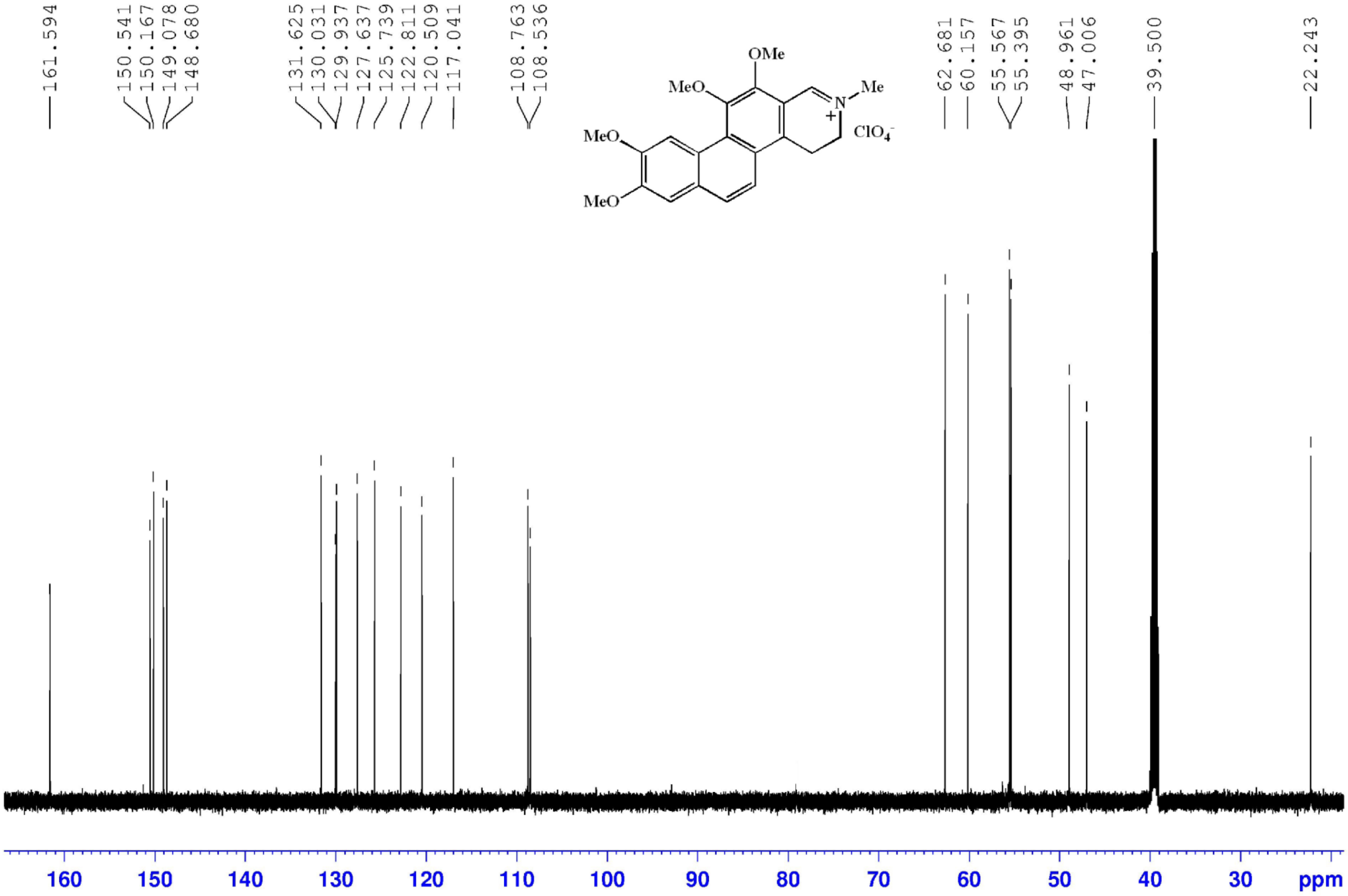
[S1] N. Mollov, S. Philipou and H. Dutschewska, *Chem. Ber.*, 1978, **111**, 554.

[S2] M. C. Pampín, J. C. Estévez, R. J. Estévez and L. Castedo, *ARKIVOC*, 2003, (xv), 29.

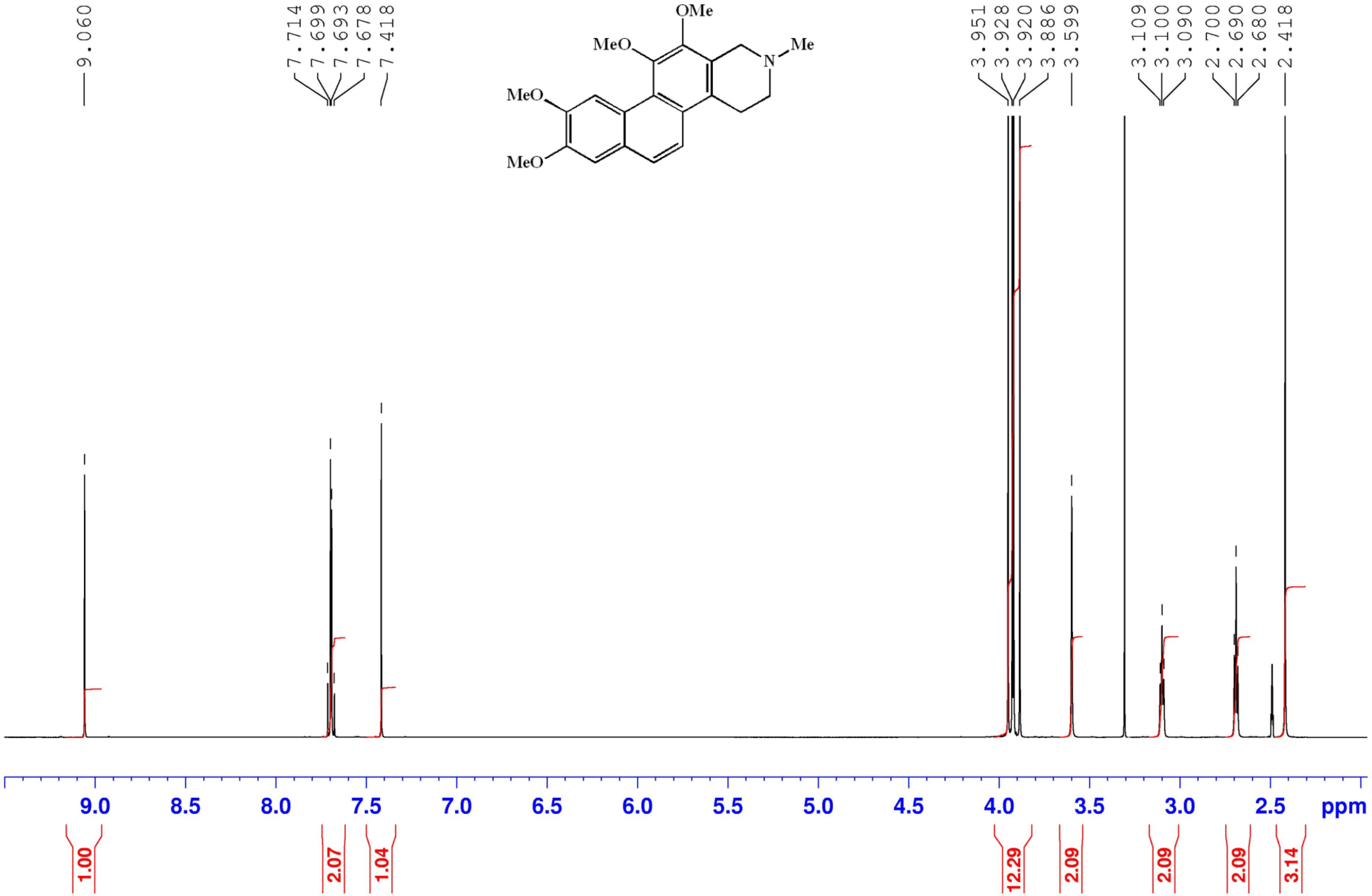
8,9,11,12-Tetramethoxy-2-methyl-3,4-dihydronaphto[2,1-*f*]isoquinolin-2-ium perchlorate (6)



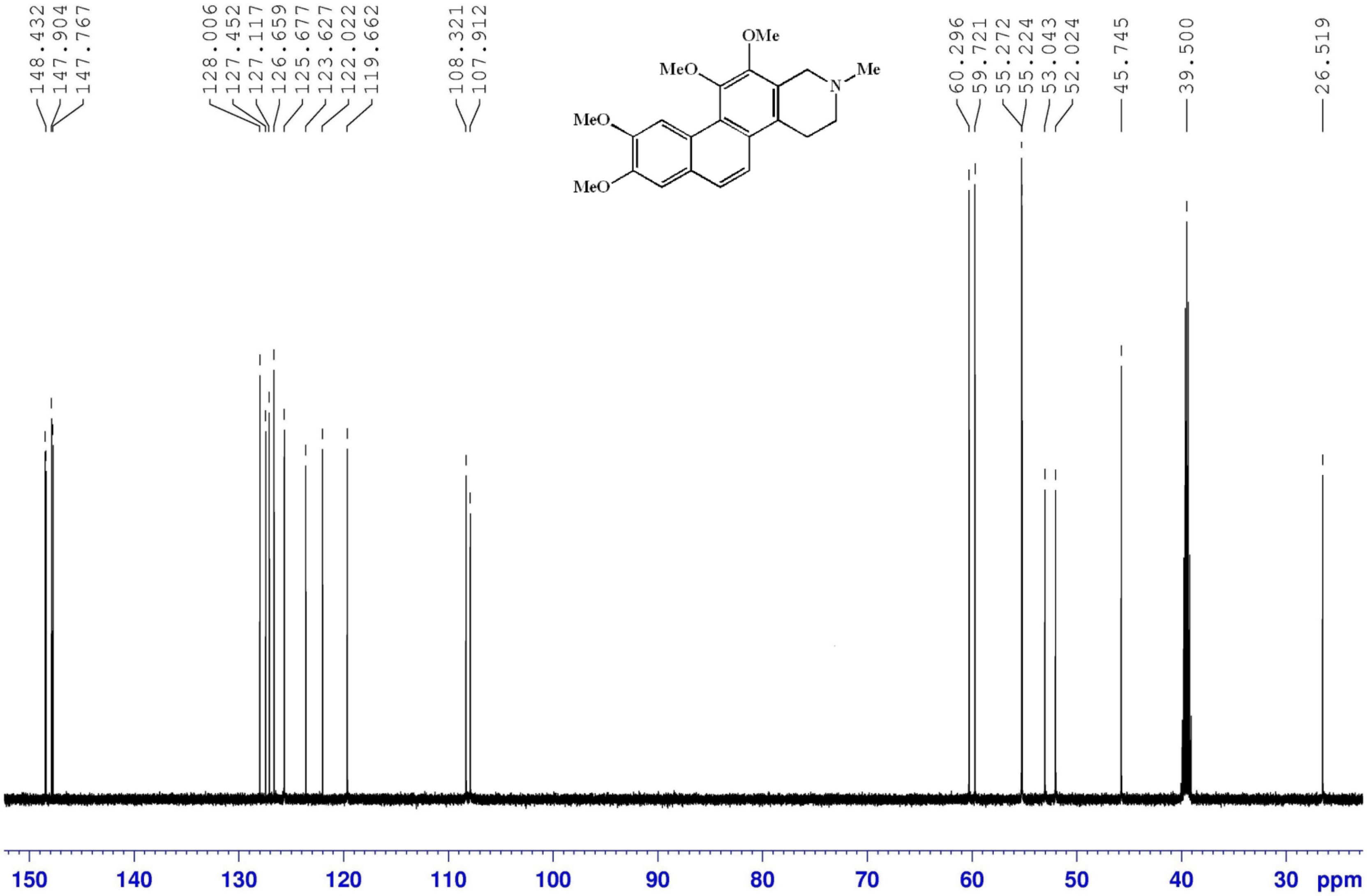
8,9,11,12-Tetramethoxy-2-methyl-3,4-dihydronaphto[2,1-*f*]isoquinolin-2-ium perchlorate (6)



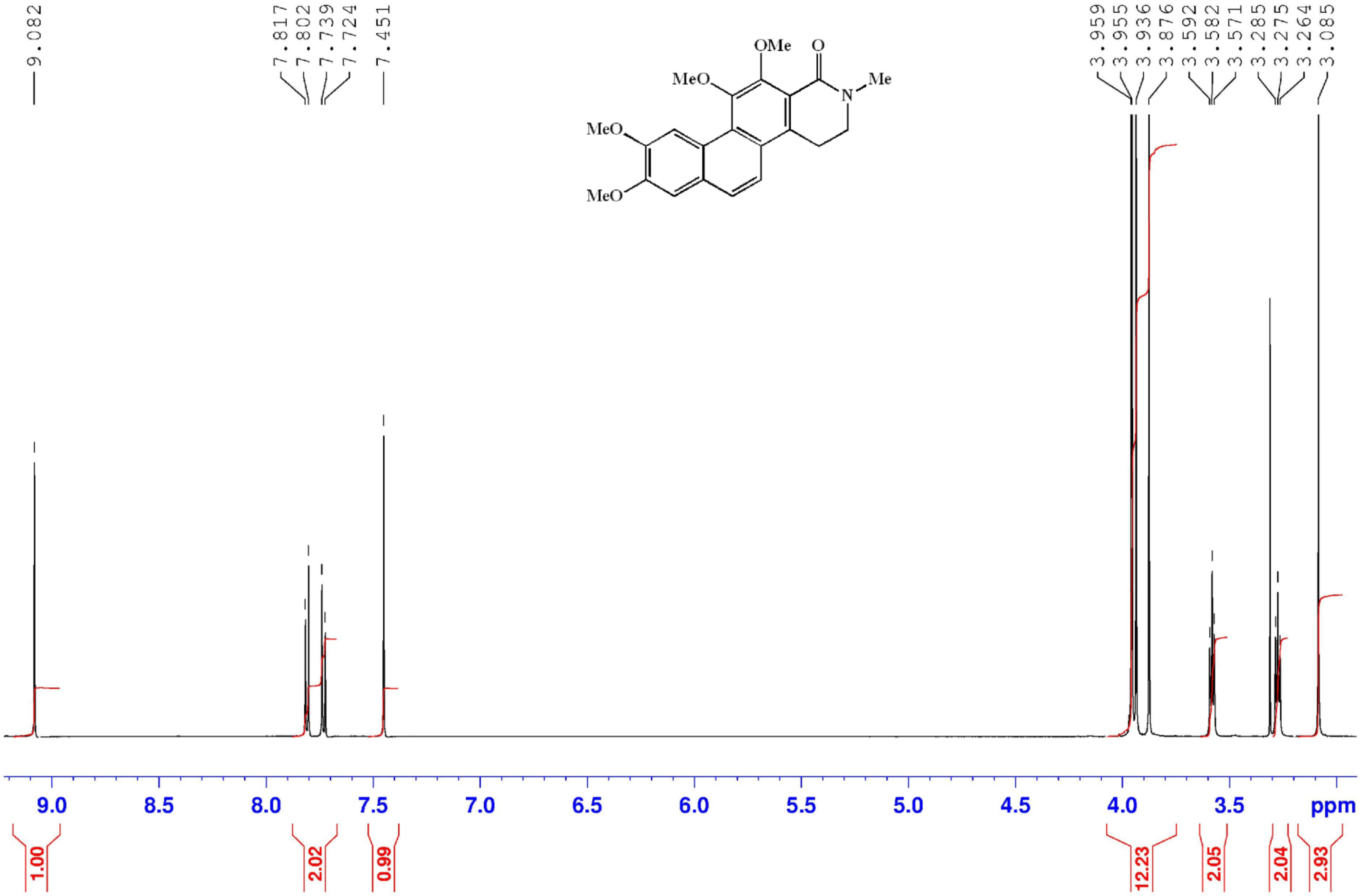
8,9,11,12-Tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphto[2,1-*f*]isoquinoline (8)



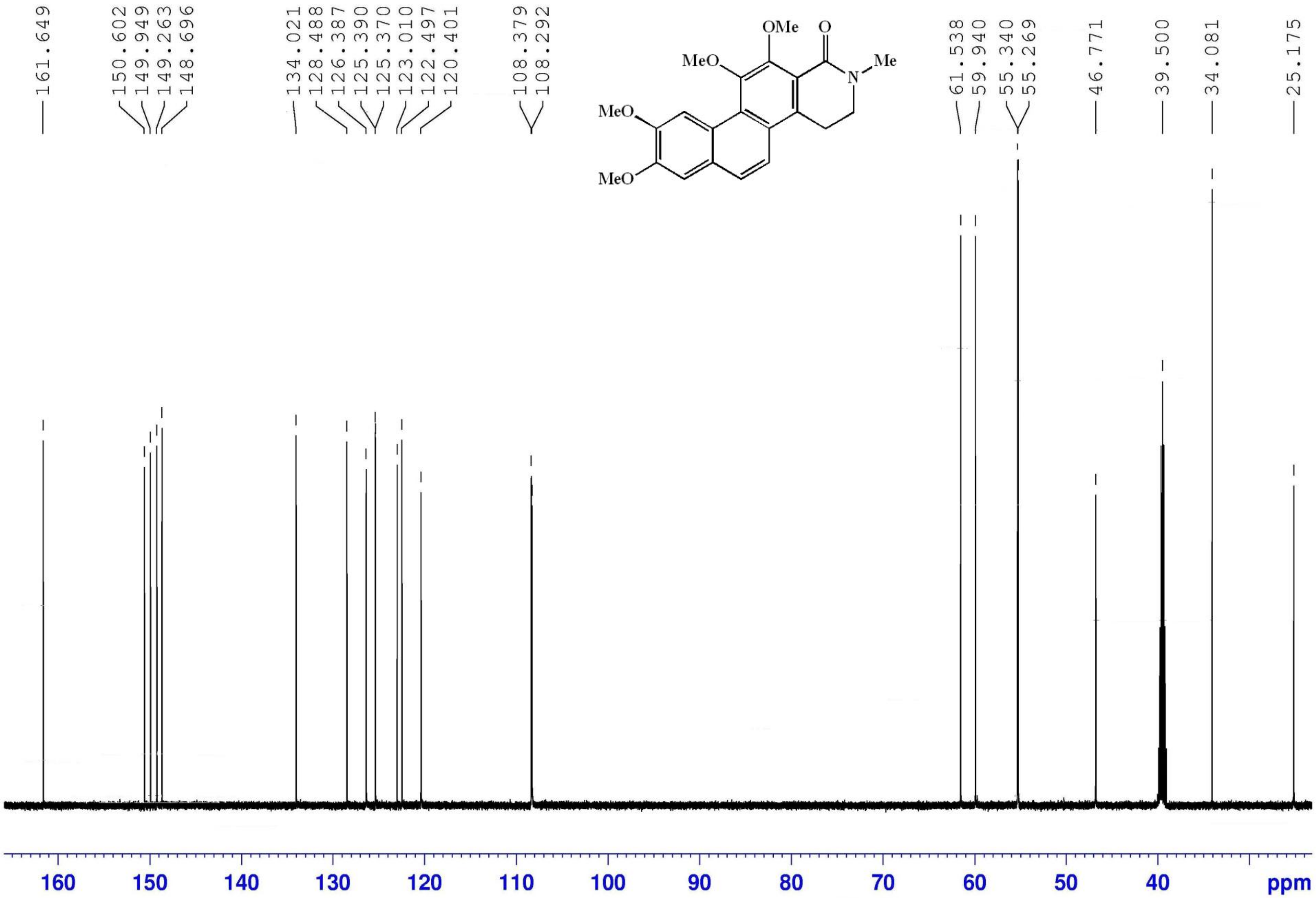
8,9,11,12-Tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphto[2,1-*f*]isoquinoline (8)



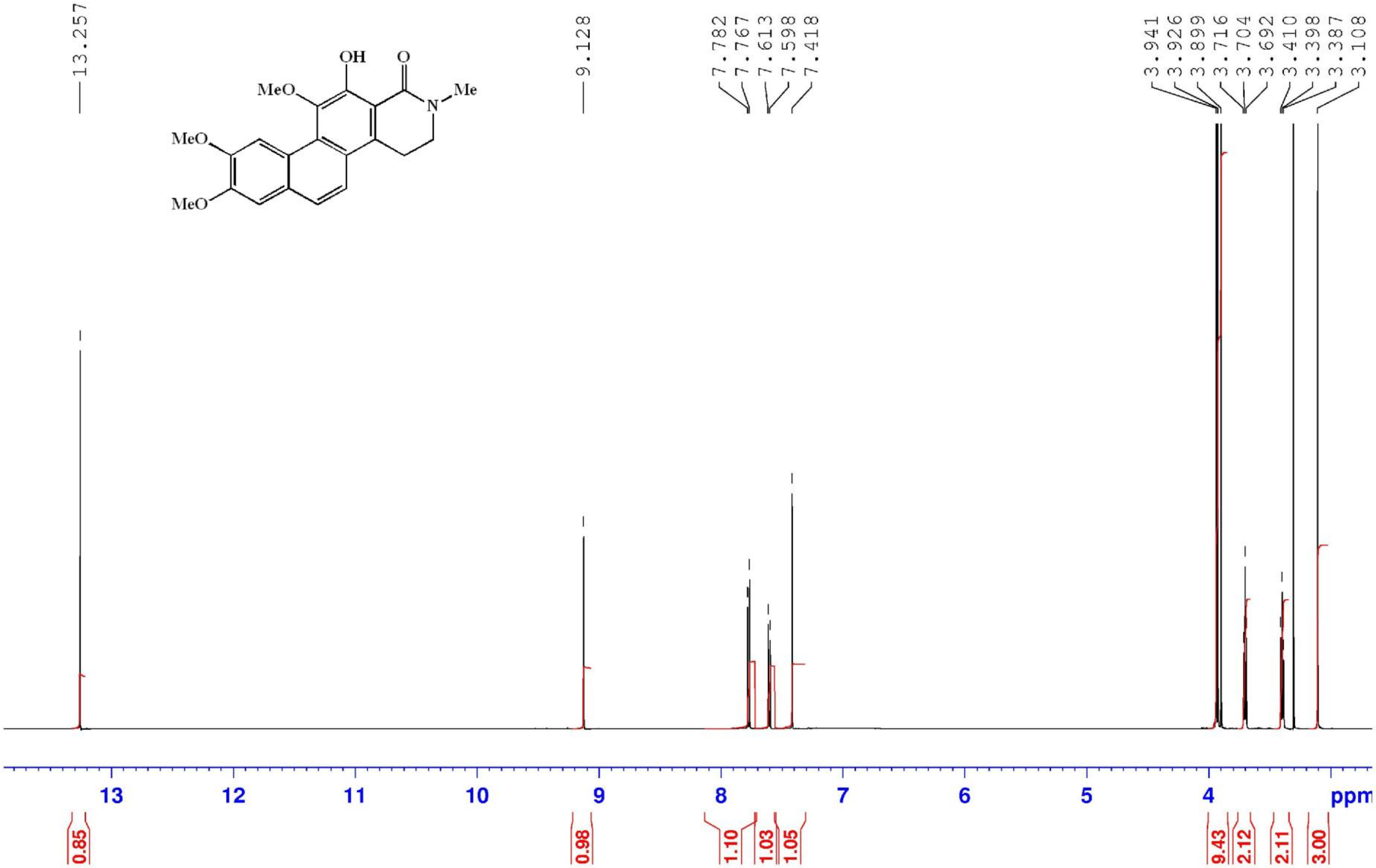
8,9,11,12-Tetramethoxy-2-methyl-3,4-dihydronaphto[2,1-*f*]isoquinolin-1(2*H*)-one (9)



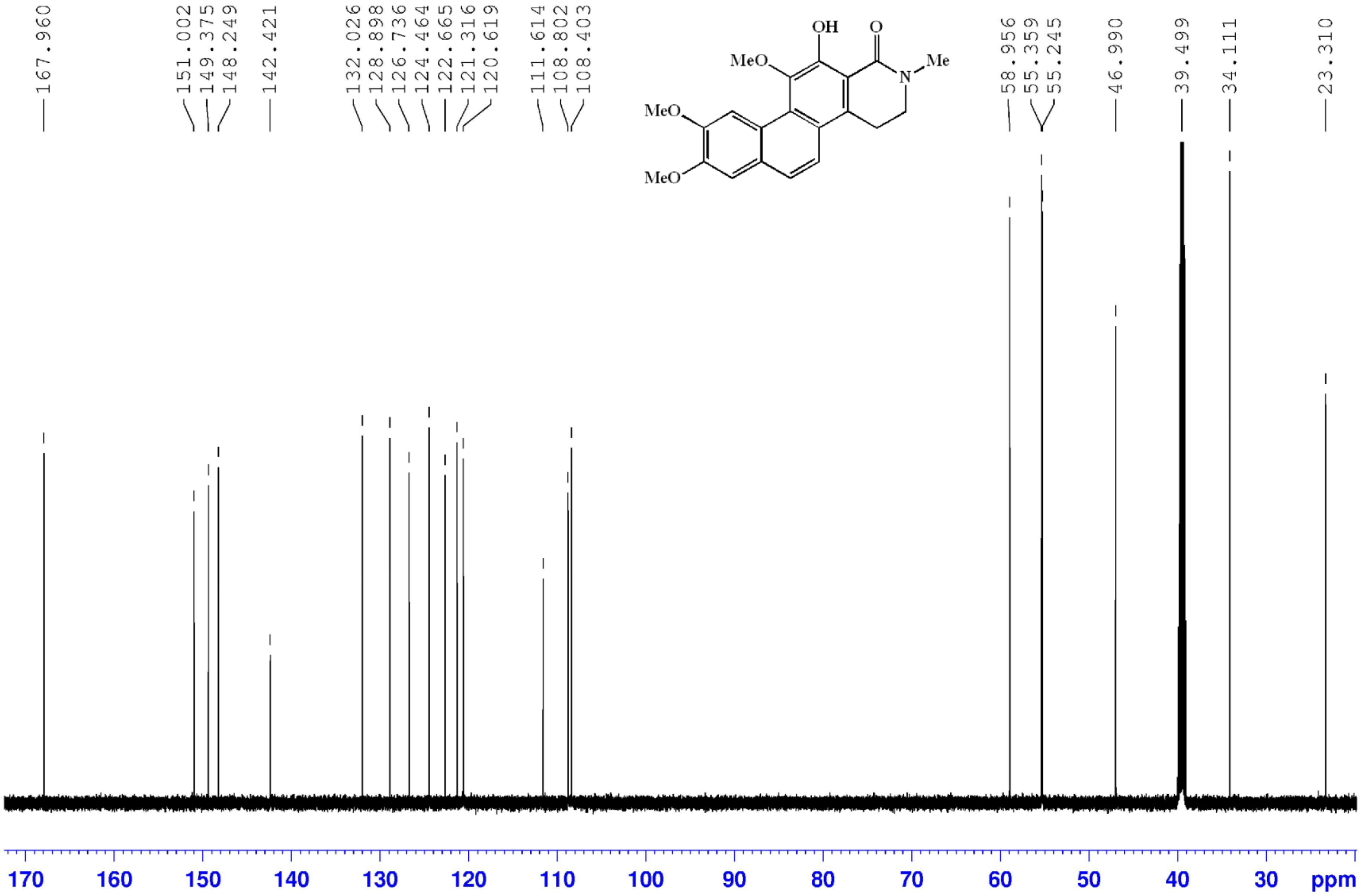
8,9,11,12-Tetramethoxy-2-methyl-3,4-dihydronaphto[2,1-*f*]isoquinolin-1(2*H*)-one (9)



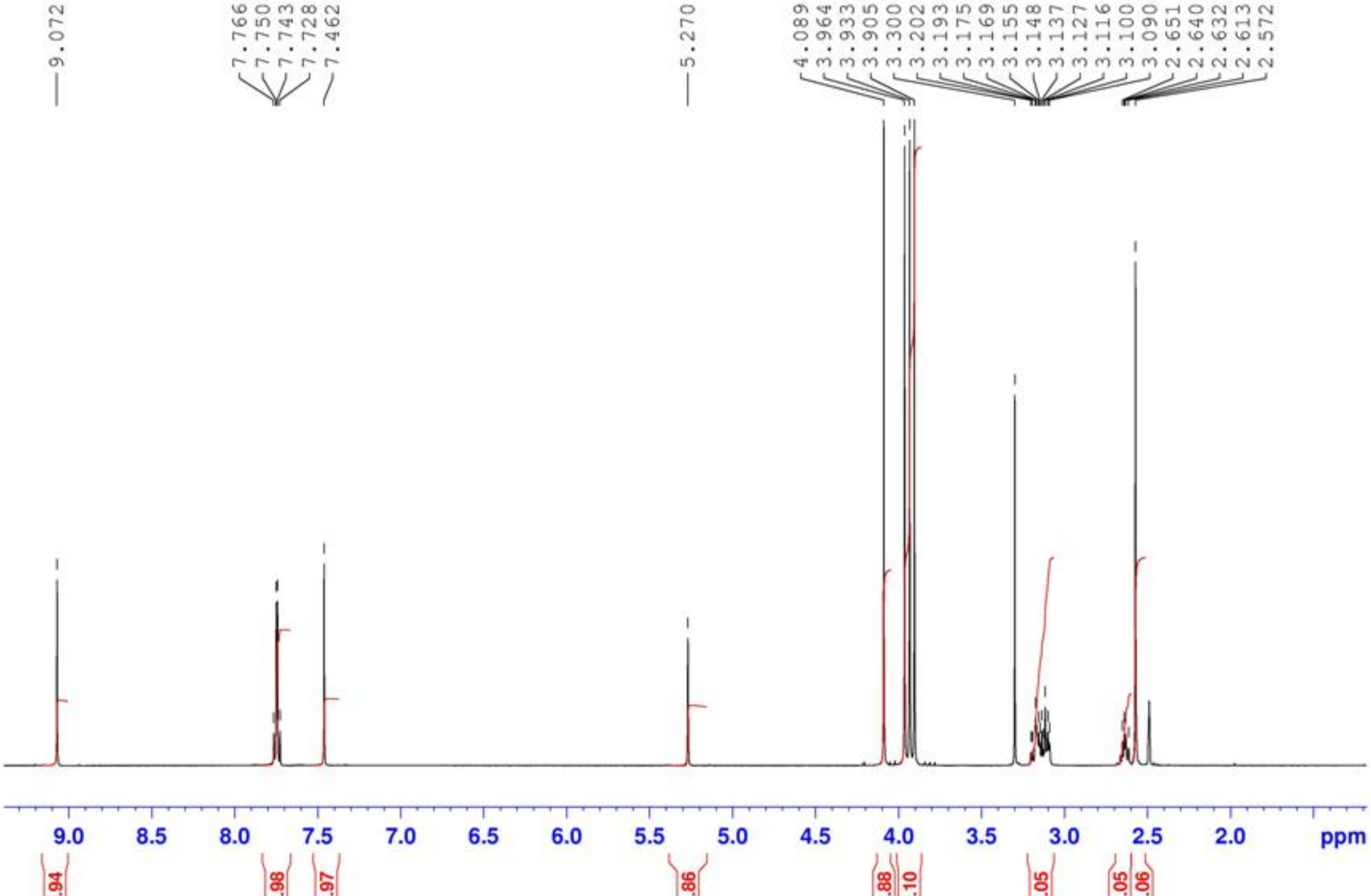
12-Hydroxy-8,9,11-trimethoxy-2-methyl-3,4-dihydronaphto[2,1-*f*]isoquinolin-1(2*H*)-one (10)



12-Hydroxy-8,9,11-trimethoxy-2-methyl-3,4-dihydronaphto[2,1-*f*]isoquinolin-1(2*H*)-one (10)



8,9,11,12-Tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphto[2,1-*f*]isoquinoline-1-carbonitrile (11)



8,9,11,12-Tetramethoxy-2-methyl-1,2,3,4-tetrahydronaphto[2,1-*f*]isoquinoline-1-carbonitrile (11)