Supporting Information

Control of C(20)-diastereoselectivity in the formation of C(21)-fluorinated thevinols

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Content

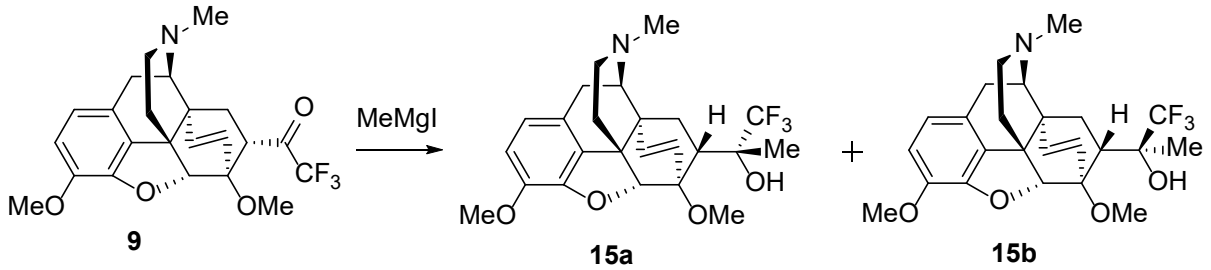
1. General

All reactions were performed in an argon atmosphere in dried glassware. All solvents were purified (dried and distilled) before use according to literature methods. All reagents were used as supplied by commercial sources unless otherwise stated. Thevinone (**2**) was obtained from thebaine (**1**) and methyl vinyl ketone according to the method **[1]**, 21,21,21-trifluorothevinone (**9**) was obtained from aldehyde **10** according to the method **[2]**, 21-methylthevinone (**19**) was obtained from thebaine (**1**) according to the method **[3]**

NMR spectra (^{1}H, ^{13}C, ^{19}F) were recordered using Brucker Avance^{TM} 400 spectrometer (400 MHz for ^{1}H, 376.5 MHz for ^{19}F) or Bruker Avance^{TM} 600 spectrometer (600.22 MHz for ^{1}H and 150.93 MHz for ^{13}C) in $CDCl_3$. Some ^{1}H, ^{19}F NMR spectra were recorded using Bruker Avance^{TM} 300 spectrometer (300 MHz for ^{1}H, 282 MHz for ^{19}F). $C^{19}F$ chemical shifts were measured relative to $CFCl_3$ as an external standard. Multiplicities are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants, *J*, are reported in Hz. HRMS were recorded on a Bruker maXis instrument using electrospray ionization. Microanalyses (C, H, N, F) were performed using the Carlo-Erba CE-1106. Melting points were determined with an Electrorthermal 1002 MELTEMP® capillary melting point apparatus and are uncorrected. TLC was performed with precoated TLC sheets of silica gel 60 F254 (Merck®) and visualized by UV and iodine. Column liquid chromatography was performed using silica gel (particle size no more then 80 μm).

2. Experimental Section and Spectra Data

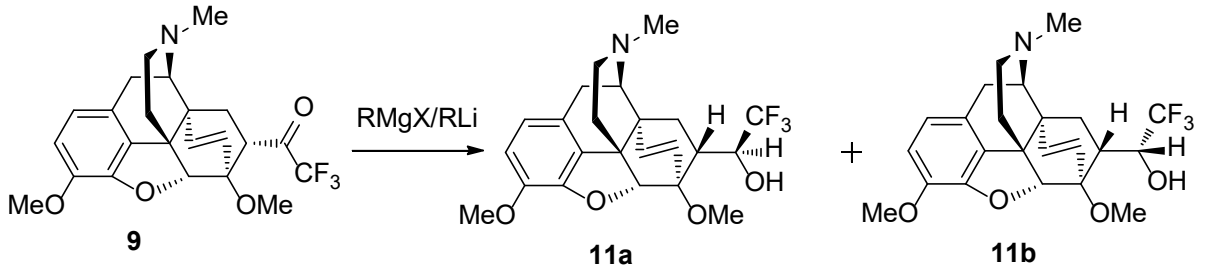
2.1 Reactions of MeMgI with 9. General procedure (Table 3).



An appropriate salt, if any (Table 3, entries 1-14, section 1.2.1.1 of the main text of the article), THF (if necessary) and ketone **9** (0.50 mmol) were added subsequently to a freshly prepared solution of MeMgI (1.05 mmol) in ether. The reaction mixture was stirred for an appropriate time and temperature (see Table 3). If necessary, it was allowed to warm to the room temperature, quenched with NH_4Cl (saturated aqueous solution), and extracted with ether, and the resulting layer was washed with water twice. The resulting ether solution was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue contains a mixture of isomers **15a** and **15b** in various ratios, which was determined by NMR (see Table 3, entries 1-14).

2.2 Reactions of RMgX or RLi (R = Bu^t, Bu^n, Pr^n, Pr^i, Et) with 9.

General procedure (Table 4).



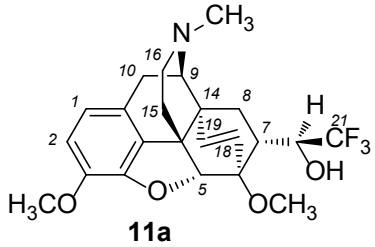
An appropriate salt, if any (Table 4, section 1.2.1.2 of the main text of the article) and ketone **9** (1 eq. in ether or THF) were added subsequently to a freshly prepared solution of RMgX or RLi[1]. The reaction mixture was stirred for an appropriate time and temperature (see Table 4), quenched with NH_4Cl (saturated aqueous solution), and extracted with ether or $CHCl_3$, and the resulting layer was washed with water twice. The resulting ether solution was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue contains a mixture of isomers **11a** and **11b** in various ratios, which was determined by NMR (see Table 4).

[1] 2.0 eq. of Bu^{t}MgCl in ether (Table 4, entries 1-3), 1.15 eq. of Bu^{n}MgBr in THF (Table 4, entry 4), 2.0 eq. of Pr^{i}MgBr in THF (Table 4, entries 5-6), 1.74 eq. of Pr^{n}MgBr in ether (Table4, entry 7), 1.15 eq. of EtMgBr in THF (Table 4, entry 8), 1.3 eq. of Bu^{t}Li in pentane (Table 4, entries 9-11), 1.1-2.0 eq. of Pr^{i}Li in pentane (Table 4, entries 12-14).

2.2.1 Synthesis of 11a,b by the reaction of 9 with Pr^{n}MgBr (Table 4, entry 7).

Pr^{n}Br (0.2 ml) was added dropwise to the mixture of ether (15 ml) and Mg (shavings, 0.14 g, 6.0 mmol) until complete dissolution of magnesium. The reaction mixture was allowed to warm to the room temperature and a solution of **9** (1.50 g, 3.45 mmol) in ether (5 ml) was added dropwise over 20 min. The reaction mixture was stirred for 20 min, quenched with NH_4Cl (saturated aqueous solution) and water. The resulted mixture was extracted with ether and the organic layer was washed with water twice. The resulting ether solution was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue contained a mixture of isomers **11a** and **11b** in 5:2 ratio. The products were separated by column chromatography on silica gel ($CHCl_3$: hexane : MeOH : NH_4OH = 1600:1600:15:1) affording 0.83 g of **11a** (55%) and 0.09 g of **11b** (6%) as colorless oils.

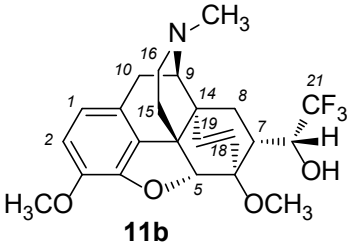
(5*R*,6*R*,7*R*,20*S*)-4,5-Epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (**11a**):



11a

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.04 (dd, 1H, H-8α), 1.83 (m, 1H, H-15$_{eq}$), 2.00 (ddd, ^2J = 12.8 Hz, ^3J = 12.8 Hz, ^3J = 5.6 Hz, 1H, H-15$_{ax}$), 2.15 (ddd, ^3J = 9.0 Hz, ^3J = 5.4 Hz, 1H, H-7β), 2.35 (s, 3H, NCH_3), 2.34-2.42 (m, 2H, H-10α + H-16$_{ax}$), 2.52 (m, 1H, H-16$_{eq}$), 2.89 (dd, ^2J = 13.7 Hz, ^3J = 9.0 Hz, 1H, H-8β), 3.14 (d, ^3J = 6.5 Hz, 1H, H-9), 3.21 (d, ^2J = 18.5 Hz, 1H, H-10β), 3.76 (s, 3H, 6-OCH_3), 3.76 (m, $^3J_{H\text{-}20,F\text{-}21}$ = 6.7 Hz, 1H, H-20), 3.81 (s, 3H, 3-OCH_3), 4.57 (d, $^4J_{H\text{-}5,H\text{-}18}$ = 0.9 Hz, 1H, H-5), 5.59 (d, ^3J = 8.9 Hz, 1H, H-19), 5.94 (s, 1H, OH), 5.95 (br d, 1H, H-18), 6.54 (br) + 6.62 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 22.31, 28.56, 33.03, 37.93, 42.36, 43.51, 45.38, 46.19, 54.95, 56.74, 59.90, 73.90 (q, $^2J_{C,F}$ = 28.5 Hz, C**H**-CF_3), 83.61, 96.63, 113.80, 119.74, 123.83, 125.12 (q, $^1J_{C,F}$ = 283.0 Hz, **C**F_3), 128.12, 134.15, 138.10, 141.99, 147.58; **^{19}F NMR** (282 MHz, $CDCl_3$): δ –74.67 (d, $^3J_{F,H}$ = 8.0 Hz, CF_3); **HRMS (ESI):** *m/z* calcd. for $C_{23}H_{27}F_3NO_4$: 438.1887 $(M+H)^+$, found: 438.1892.

(5*R*,6*R*,7*R*,20*R*)-4,5-Epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (**11b**):



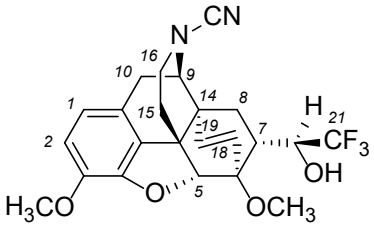
11b

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.50 (dd, ^2J = 13.5 Hz, ^3J = 6.7 Hz, 1H, H-8α), 1.86 (m, 1H, H-15$_{eq}$), 2.00-2.07 (m, 1H, H-15$_{ax}$), 2.21

(dd, ^3J = 9.6 Hz, ^3J = 6.5 Hz, 1H, H-7β), 2.40 (s, 3H, NCH_3), 2.35-2.46 (m, 2H, H-10α + H-16_{ax}), 2.57 (m, 1H, H-16_{eq}), 2.86 (dd, ^2J = 13.5 Hz, ^3J = 9.6 Hz, 1H, H-8β), 3.22 (d, ^3J = 6.0 Hz, 1H, H-9), 3.22 (d, ^2J = 18.5 Hz, 1H, H-10β), 3.60 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.47 (q, $^3J_{H\text{-}20,H\text{-}7\beta}$ < 1.0 Hz; $^3J_{H\text{-}20,F\text{-}21}$ = 8.0 Hz, 1H, H-20), 4.57 (d, $^4J_{H\text{-}5,H\text{-}18}$ = 1.1 Hz, 1H, H-5), 5.50 (d, ^3J = 8.7 Hz, 1H, H-19), 5.83 (br d, ^3J = 8.7 Hz, 1H, H-18), 6.54 (br) + 6.62 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (151 MHz, $CDCl_3$): δ 22.71, 29.38, 31.94, 36.43, 42.93, 43.51, 45.54, 47.21, 52.73, 56.56, 60.07, 67.25 (q, $^2J_{C,F}$ = 29.8 Hz, C-CF_3), 79.15, 94.47, 113.40, 119.54, 126.72, 127.08 (q, $^1J_{C,F}$ = 273.9 Hz, CF_3), 128.35, 133.88, 136.73, 141.93, 148.02; **^{19}F NMR** (282 MHz, $CDCl_3$): δ –76.48 (d, $^3J_{F,H}$ = 8.0 Hz, CF_3); **HRMS (ESI):** *m/z* calcd. for $C_{23}H_{27}F_3NO_4$ 438.1887 $(M+H)^+$, found: 438.1895.

2.2.2 (5*R*,6*R*,7*R*,20*S*)-17-Cyano-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-6,14-ethenoisomorphinan (11c).

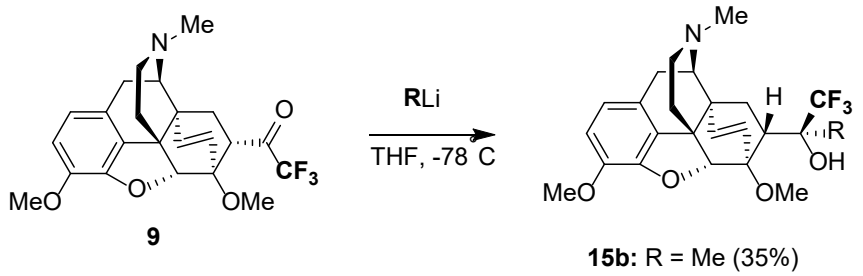
A solution of cyanogen bromide (1.37 ml, 0.8 M in $CHCl_3$) was added to **11a (**0.12 g, 0.27 mmol) and the resulted solution was allowed to stay at room temperature for 24 h. The reaction mixture was washed with diluted HCl and water, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. A crystallization of the residue from methanol delivered 0.030 g of **11c** (25%) as colorless crystals suitable for X-ray study.



11c

MP: 228-230°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.24 (m, 1H, H-8α), 1.93 (m, 1H, H-15_{eq}), 2.10 (m, 1H, H-15_{ax}), 2.20 (m, 1H, H-7β), 2.68 (dd, ^2J = 13.5 Hz, ^3J = 8.9 Hz, 1H, H-8β), 3.11 (dd, ^2J = 19.2 Hz, ^3J = 6.4 Hz, 1H, H-10α), 3.29 (d, ^2J = 19.2 Hz, 1H, H-10β), 3.37 (m, 2H, 2H-16), 3.79 (s, 3H, 6-OCH_3), 3.83 (s, 3H, 3-OCH_3), 3.80 (m, 1H, H-20), 3.89 (d, ^3J = 6.4 Hz, 1H, H-9), 4.59 (br d, 1H, H-5), 5.56 (d, ^3J = 9.0 Hz, 1H, H-19), 5.75 (s, 1H, OH), 6.07 (br d, 1H, H-18), 6.61 (br) + 6.70 (AB-system, J_{AB} = 8.2 Hz, 2H, H-1 + H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.31, 31.10, 31.71, 38.08, 41.14, 41.86, 45.66, 55.17, 56.64, 58.14, 73.43 (q, $^2J_{C,F}$ = 28.8 Hz, C-CF_3), 83.07, 96.29, 114.56, 117.62, 120.31, 124.82 (q, $^1J_{C,F}$ = 283.0 Hz, CF_3), 125.25, 125.27, 131.99, 135.59, 142.62, 147.79; **^{19}F NMR** (282 MHz, $CDCl_3$): δ –74.56 (s, CF_3); **HRMS (ESI)** calcd for $C_{23}H_{24}F_3N_2O_4$ $[M + H]^+$: 449.1683, found: 449.1680.

2.3 Reactions of RLi with 9. General procedure.



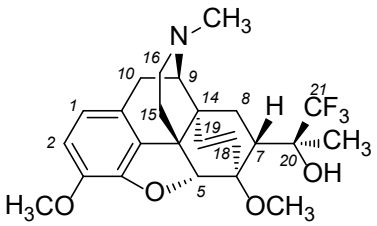
9

15b: R = Me (35%)
16b: R = Et (41%)
17b: R = Bu_n (61%)
18b: R = Pr_n (54%)

A solution of RLi was added dropwise to a solution of **9** in THF at -78 °C and the mixture was stirred for 15 min at -78 °C. The reaction mixture was allowed to warm to the room temperature, quenched with NH_4Cl (saturated aqueous solution), and extracted with $CHCl_3$ twice. The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo* to afford **15b-18b** as colorless solids after crystallization from methanol.

(5R,6R,7R,20S)-4,5-Epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (**15b**).

The reaction of ketone **9** (0.20 g, 0.46 mmol) with MeLi[2] (0.60 ml, 0.95 M solution in ether) afforded 0.073 g of **15b** (35%).



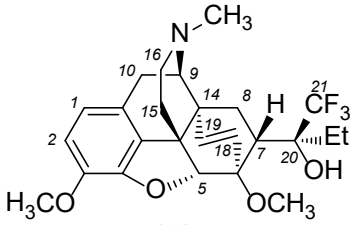
15b

MP: 196-198°C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.07 (dd, ^2J = 13.2 Hz, ^3J = 8.9 Hz, 1H, H-8α), 1.19 (s, 3H, CH_3), 1.81-1.88 (m, 1H, H-15_{eq}), 1.96 (ddd, ^2J = 12.5 Hz, ^3J = 5.6 Hz, 1H, H-15_{ax}), 2.28 (dd, ^3J = 8.9 Hz, ^3J = 9.2 Hz, 1H, H-7*β*), 2.36 (s, 3H, NCH_3), 2.32-2.41 (m, 2H, H-$10_α$ + H-16_{ax}), 2.51 (dd, ^2J = 12.1 Hz, ^3J = 5.4 Hz, 1H, H-16_{eq}), 2.91 (dd, ^2J = 13.2 Hz, ^3J = 9.2 Hz, 1H, H-8*β*), 3.15 (d, ^3J = 6.3 Hz, 1H, H-9), 3.23 (d, ^2J = 18.6 Hz, 1H, H-10*β*), 3.81 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.56 (br d, 1H, H-5), 5.53 (d, ^3J = 8.9 Hz, 1H, H-19), 5.65 (s, 1H, OH), 5.97 (br d, 1H, H-18), 6.62+6.53 (AB-system, J_{AB} = 8.2 Hz, 2H, H-1+H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 18.46, 22.39, 29.33, 33.31, 42.79, 43.40, 45.36, 46.73, 55.56, 56.72, 59.79, 76.11 (q, $^2J_{C,F}$ = 26.5 Hz, C-CF3), 83.29, 98.22, 113.86, 119.52, 123.92, 125.66 (q, $^1J_{C,F}$ = 285.9 Hz, CF_3), 128.01, 133.85, 136.63, 141.78, 147.80; **^{19}F NMR** (282 MHz, $CDCl_3$): δ –79.54 (s, 3F, CF_3); MS (ESI) (*m/z*): 452 $[M+1]^+$. Found (%): C 63.80, H 6.27, N 3.07, F 12.50; $C_{24}H_{28}F_3NO_4$. Calculated (%): C 63.85, H 6.25, N 3.10, F 12.62.

[2] To compare the stereochemical result, the reaction of **9** with MeLi was carried out under the same conditions at 20°C, 0°C, and -78°C. The ratio of products **15a:15b** was deduced from the NMR data. The results are shown in Table 3 (enries 15-17) of the main text of the article.

(5R,6R,7R,20S)-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)-6,14-ethenoisomorphinan (**16b**):

The reaction of ketone **9** (0.10 g, 0.23 mmol) with EtLi (1.00 ml, 0.33M solution in hexane) afforded 0.043 g of **16b** (41%).

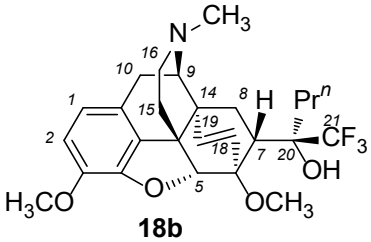


16b

MP: 198-200°C. **^{1}H NMR** (300 MHz, $CDCl_3$): 0.97 (t, ^2J= 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.11 (dd, ^2J = 13.5 Hz, ^3J= 8.7 Hz, 1H, H-8α), 1.36-1.51 and 1.55-1.70 (m + m, 2H, $C\underline{H}_2CH_3$), 1.84 (m, 1H, H-15$_{eq}$), 1.97 (ddd, ^2J = 12.5 Hz, ^3J = 5.4 Hz, 1H, H-15$_{ax}$), 2.31 (m, 1H, H-7β), 2.36 (s, 3H, NCH_3), 2.31-2.44 (m, 2H, H-10α + H-16$_{ax}$), 2.51 (dd, 1H, ^2J = 11.8 Hz, ^3J = 5.0 Hz, H-16$_{eq}$), 2.91 (dd, ^2J = 13.5 Hz, ^3J= 9.4 Hz, 1H, H-8β), 3.13 (d, ^3J = 6.3 Hz, 1H, H-9), 3.22 (d, ^2J =18.6 Hz, 1H, H-10β), 3.80 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.56 (br d, 1H, H-5), 5.25 (s, 1H, OH), 5.50 (d, ^3J= 8.9 Hz, 1H, H-19), 5.95 (br d, ^3J= 8.9 Hz, 1H, H-18), 6.63 + 6.53 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 7.62, 22.25, 25.55, 29.17, 33.50, 42.86, 43.48, 43.85, 45.30, 46.87, 55.62, 56.73, 59.73, 78.25 (q, $^2J_{C,F}$ = 25.2 Hz, $\underline{C}$-CF_3), 83.28, 98.56, 113.68, 119.44, 124.12, 125.63 (q, $^1J_{C,F}$ = 288.5 Hz, $\underline{C}F_3$), 128.29, 134.04, 136.50, 141.69, 147.80; **^{19}F NMR** (282 MHz, $CDCl_3$): δ -73.69 (s, 3F, CF_3); **HRMS (ESI)** calcd for $C_{25}H_{31}F_3NO_4$ $[M + H]^+$: 466.2205, found: 466.2208.

(5R,6R,7R,20S)-7-(1-Hydroxy-1-(trifluoromethyl)butyl)-4,5-epoxy-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (**18b**):

The reaction of ketone **9** (1.00 g, 2.30 mmol) with *n*-PrLi (9.00 ml, 0.34M solution in hexane) afforded 0.60 g of **18b** (54%).



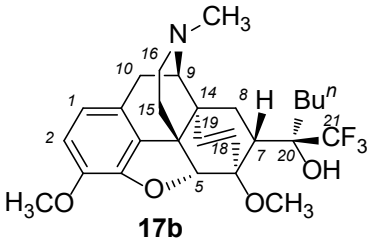
18b

MP: 193-196°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (t, ^2J= 6.5 Hz, 3H, $(CH_2)_2C\underline{H}_3$), 1.07-1.16 (m, 1H, H-8α), 1.24-1.38 and 1.52-1.67 (m + m, 2H + 2H, $(C\underline{H}_2)_2CH_3$), 1.84 (m, 1H, H-15$_{eq}$), 1.96 (ddd, ^2J = 12.6 Hz, ^3J = 5.5 Hz, 1H, H-15$_{ax}$), 2.29 (dd, ^3J = 8.7 Hz, ^3J = 9.2 Hz, 1H, H-7β), 2.36 (s, 3H, NCH_3), 2.33-2.42 (m, 2H, H-10α + H-16$_{ax}$), 2.51 (dd, 1H, ^2J = 11.7 Hz, ^3J = 4.9 Hz, H-16$_{eq}$), 2.90 (dd, ^2J = 13.1 Hz, ^3J= 9.2 Hz, 1H, H-8β), 3.14 (d, ^3J = 6.4 Hz, 1H, H-9), 3.22 (d, ^2J =18.6 Hz, 1H, H-10β), 3.80 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.55 (d, ^4J= 1.0 Hz, 1H, H-5), 5.32 (s, 1H, OH), 5.51 (d, ^3J= 8.9 Hz, 1H, H-19), 5.95 (br d, ^3J= 8.9 Hz, 1H, H-18), 6.63 + 6.53 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 14.97, 16.26, 22.23, 29.15, 33.51, 35.08, 42.85, 43.46, 43.86, 45.27, 46.85, 55.56, 56.76, 59.70, 78.13 (q, $^2J_{C,F}$ = 25.3 Hz, $\underline{C}$-CF_3), 83.28, 98.56, 113.81, 119.44, 124.04,

125.65 (q, $^{1}J_{C,F}$ = 288.5 Hz, <u>C</u>F_3), 128.32, 134.04, 136.53, 141.69, 147.82; **^{19}F NMR** (282 MHz, $CDCl_3$): δ -74.04 (s, 3F, CF_3); **HRMS (ESI)** calcd for $C_{26}H_{33}F_3NO_4$ $[M + H]^+$: 480.2362, found: 480.2370.

(5R,6R,7R,20S)-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)pentyl)-6,14-ethenoisomorphinan (**17b**):

The reaction of ketone **9** (0.10 g, 0.23 mmol) with *n*-BuLi (0.30 ml, 0.98 M solution in hexane) afforded 0.07 g of **17b** (61%).



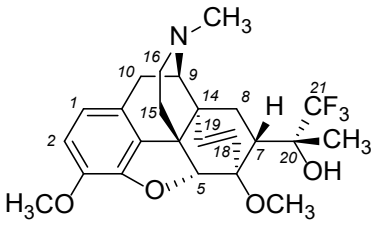
17b

MP: 165-167 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, ^{2}J = 6.9 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 1.06-1.17 (m, 1H, H-8*α*), 1.20-1.39 and 1.48-1.63 (m + m, 4H + 2H, $(C\underline{H}_2)_3CH_3$), 1.80-1.89 (m, 1H, H-15_{eq}), 1.97 (dd, ^{2}J = 12.5 Hz, ^{3}J = 5.5 Hz, 1H, H-15_{ax}), 2.37 (s, 3H, NCH_3), 2.24-2.44 (m, 3H, H-10*α* + H-16_{ax} + H-7*β*), 2.51 (dd, ^{2}J = 11.5 Hz, ^{3}J = 4.8 Hz, 1H, H-16_{eq}), 2.90 (dd, ^{2}J = 12.5 Hz, ^{3}J = 9.7 Hz, 1H, H-8*β*), 3.15 (d, ^{3}J = 6.2 Hz, 1H, H-9), 3.22 (d, ^{2}J =18.6 Hz, 1H, H-10*β*), 3.80 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.56 (br s, 1H, H-5), 5.31 (s, 1H, OH), 5.50 (d, ^{3}J = 8.9 Hz, 1H, H-19), 5.94 (br d, 1H, H-18), 6.63 + 6.53 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13.90, 22.24, 23.52, 24.97, 29.16, 32.47, 33.49, 42.86, 43.46, 43.91, 45.27, 46.84, 55.54, 56.75, 59.70, 78.09 (q, $^{2}J_{C,F}$ = 25.3 Hz, <u>C</u>-CF_3), 83.28, 98.57, 113.77, 119.45, 124.00, 125.66 (q, $^{1}J_{C,F}$ = 288.2 Hz, <u>C</u>F_3), 128.31, 134.04, 136.52, 141.69, 147.82; **^{19}F NMR** (282 MHz, $CDCl_3$): δ -74.01 (s, 3F, CF_3); **HRMS (ESI)** calcd for $C_{27}H_{35}F_3NO_4$ $[M + H]^+$: 494.2518, found: 494.2525.

2.4 Reactions of ketones 2, 19, 20 with $(CH_3)_3SiCF_3$.

(5R,6R,7R,20R)-4,5-Epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (**15a**):

A solution of **2** (0.20 g, 0.52 mmol) in THF (7 ml) and $(CH_3)_3SiCF_3$ (0.23 ml, 1.57 mmol) was added subsequently at room temperature to a freshly dried CsF (0.004 g, 0.26 mmol). The reaction mixture was stirred for 30 min, quenched with HCl (20% aq. solution, 15 ml) followed by vigorous stirring 3 min. The resulted mixture was treated with 25% aq. ammonia solution to pH 10 and extracted with $CHCl_3$ (3×12ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. A crystallization of the residue from methanol delivered 0.045 g of **15a** (19%) as colorless crystals.

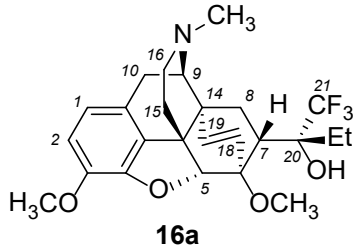


15a

MP: 162-163 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24-1.33 (m, 1H, H-8α), 1.34 (s, 3H, CH_3), 1.82-1.90 (m, 1H, H-15_{eq}), 1.89-2.00 (m, 1H, H-15_{ax}), 2.07-2.16 (m, 1H, H-7*β*), 2.37 (s, 3H, NCH_3), 2.34-2.44 (m, 2H, H-$10_α$ + H-16_{ax}), 2.52 (m, 1H, H-16_{eq}), 2.87 (dd, ^2J = 12.5 Hz, ^3J = 9.8 Hz, 1H, H-8*β*), 3.16 (d, ^3J = 6.4 Hz, 1H, H-9), 3.21 (d, ^2J =18.7 Hz, 1H, H-10*β*), 3.78 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.48 (br s, 1H, H-5), 5.50 (d, ^3J = 9.0 Hz, 1H, H-19), 5.94 (s, 1H, OH), 6.05 (br d, 1H, H-18), 6.63 + 6.53 (AB-system, J_{AB} = 8.1 , 2H, H-1+H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.19, 22.58, 28.78, 33.50, 42.36, 43.49, 45.42, 46.45, 47.15, 55.37, 56.77, 59.89, 75.53 (q, $^2J_{C,F}$ = 26.9 Hz, C-CF3), 83.39, 99.70, 113.83, 119.46, 123.18, 126.42 (q, $^1J_{C,F}$ = 288.0 Hz, CF_3), 128.15, 134.21, 135.81, 141.80, 147.84; **^{19}F NMR** (282 MHz, $CDCl_3$): δ – 74.52 (s, 3F, CF_3); Found (%): C 63.89, H 6.29, N 3.04, F 12.56; $C_{24}H_{28}F_3NO_4$ Calculated (%): C 63.85, H 6.25, N 3.10, F 12.62; **HRMS (ESI)** calcd for $C_{24}H_{29}F_3NO_4$ $[M + H]^+$: 452.2049, found: 452.2041

(5R,6R,7R,20R)-4,5-Epoxy-7-(1-hydroxy-1-(trifluoromethyl)ethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (**16a**):

A solution of **19** (0.036 g, 0.100 mmol) in THF (5 ml) and $(CH_3)_3SiCF_3$ (0.04 ml, 0.27 mmol) were added subsequently at room temperature to a freshly dried CsF (0.015 g, 0.100 mmol). The reaction mixture was stirred for 15 min, quenched with HCl (18% aq. solution, 3 ml) followed by vigorous stirring 3 min. The resulted mixture was treated with 25% aq. ammonia solution to pH 10 and extracted with $CHCl_3$ (3×7ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The products were separated by preparative TLC on silica gel ($CHCl_3$: hexane : MeOH : 25% aq. soln. of NH_3 = 800 : 800 : 15 : 1) affording 0.011 mg of **16a** (24%) as yellowish oil.



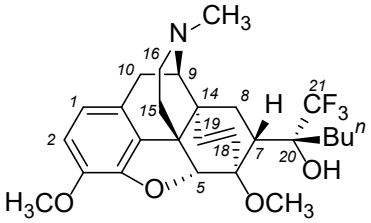
16a

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (t, ^2J = 7.4 Hz, 3H, CH_3CH_2), 1.31 (m, 1H, H-8*α*), 1.54-1.71 (m, 2H, CH_3CH_2), 1.82 - 1.92 (m, 2H, H-15_{eq} + H-15_{ax}), 2.15 (dd, ^3J = 8.7 Hz, ^3J = 10.5 Hz, 1H, H-7*β*), 2.36 (s, 3H, NCH_3), 2.31-2.44 (m, 2H, H-10*α* + H-16_{ax}), 2.51 (m, H-16_{eq}), 2.82 (dd, ^2J = 13.5 Hz, ^3J = 9.8 Hz, 1H, H-8*β*), 3.15 (d, ^3J = 6.5 Hz, 1H, H-9), 3.21 (d, ^2J =18.6 Hz, 1H, H-10*β*), 3.78 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.48 (br d, 1H, H-5), 5.48 (d, ^3J = 9.0 Hz, 1H, H-19), 5.91 (s, 1H, OH), 6.07 (br d, 1H, H-18), 6.63 + 6.52 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 7.05, 22.21, 25.76, 28.14, 29.69, 33.59, 42.29, 42.36, 43.55, 45.43, 55.39, 56.76, 59.88, 77.31 (q, $^2J_{C,F}$

= 25.5 Hz, C-CF_3), 83.23, 99.96, 113.77, 119.45, 123.59, 126.76 (q, $^1J_{C,F}$ = 288.6 Hz, CF_3), 128.23, 134.23, 135.48, 141.79, 147.90; **^{19}F NMR** (282 MHz, $CDCl_3$): δ -73.89 (s, 3F, CF_3); **HRMS (ESI)** calcd for $C_{25}H_{31}F_3NO_4$ $[M + H]^+$: 466.2205, found: 466.2210.

(5R,6R,7R,20R)-4,5-Epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)-6,14-ethenoisomorpninane (**17a**):

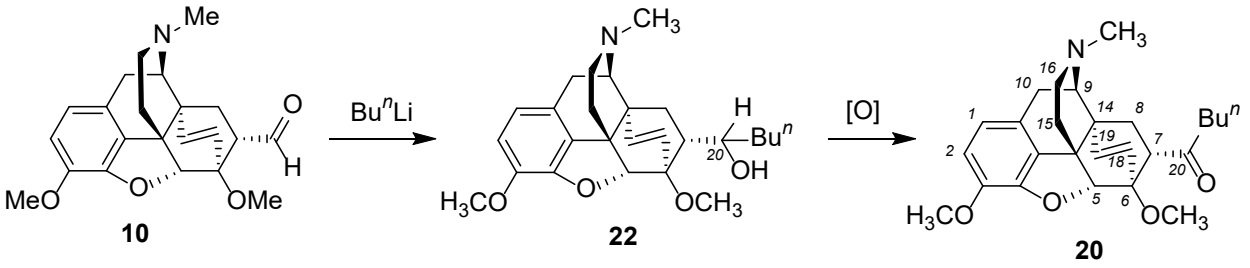
A solution of **20** (0.2 g, 0.47 mmol) in THF (15 ml), $(CH_3)_3SiCF_3$ (0.21 ml, 1.41 mmol) and HMPA (0.41 ml, 2.35 mmol) were added subsequently at room temperature to a freshly dried CsF (0.072 g, 0.47 mmol). The reaction mixture was stirred under reflux for 11 h. The reaction mixture was allowed to cool to the room temperature, quenched with HCl (18% aq. solution, 10 ml) followed by vigorous stirring 30 min. The resulted mixture was treated with 25% aq. ammonia solution to pH 10 and extracted with $CHCl_3$ (3×15ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The products were separated by preparative TLC on silica gel ($CHCl_3$: MeOH : 25% aq. soln. of NH_3 = 1500: 15 : 1) affording crude main product **17a** (0.065 g, 28%) as colourless solid. Pure colourless crystals of **17a** (0.030 g, 13 %) suitable for X-ray were obtained after crystallization from MeOH.



17a

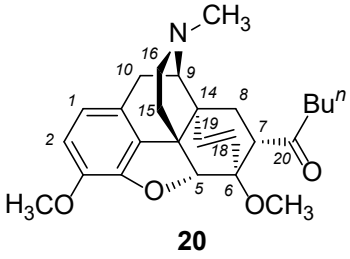
MP: 176-178 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): 0.97 (t, 3H, $(CH_2)_3C\underline{H}_3$, 1.32 (m, 1H, H-8*α*), 1.22-1.44 and 1.53-1.70 (m + m, 6H, $(C\underline{H}_2)_3CH_3$), 1.82-1.95 (m, 2H, H-15_{eq} + H-15_{ax}), 2.15 (m, 1H, H-7*β*), 2.38 (s, 3H, NCH_3), 2.30-2.47 (m, 2H, H-10*α* + H-16_{ax}), 2.54 (m, 1H, H-16_{eq}), 2.82 (m, 1H, H-8*β*), 3.15 (d, ^3J = 6.4 Hz, 1H, H-9), 3.22 (d, ^2J =18.6 Hz, 1H, H-10*β*), 3.77 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.47 (s, 1H, H-5), 5.48 (d, ^3J = 9.1 Hz, 1H, H-19), 5.94 (s, 1H, OH), 6.06 (br d, 1H, H-18), 6.52 + 6.63 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (101 MHz, CDCl3): δ 14.13, 22.29, 23.22, 24.53, 28.23, 33.02, 33.53, 42.31, 43.13, 43.55, 45.47, 46.47, 55.40, 56.78, 59.93, 77.23 (q $^2J_{C,F}$ = 25.8 Hz, C<u>H</u>-CF_3), 83.34, 99.90, 113.82, 119.48, 123.63, 126.70 (q, $^1J_{C,F}$ = 289.1 Hz, CF_3), 128.13, 134.24, 135.44, 141.84, 147.90; **^{19}F-NMR** (300 MHz, $CDCl_3$): -73.83 (s, 3F, CF_3); **HRMS (ESI)** calcd for $C_{27}H_{35}F_3NO_4$ $[M + H]^+$: 494.2518, found: 494.2523.

2.5 21-*n*-Propylthevinone (20).



A solution of Bu^{n}Li (0.73 ml, 1.2 M in hexane) was added in one portion to a solution of **10** (0.3 g, 0.8 mmol) in THF (12 ml) at room temperature. The resulted reaction mixture was stirred for 2 h. Water (20 ml) was added and the products were extracted with $CHCl_3$ (3×15ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. A mixture of the epimeric alcohols **22** (in 1:4 ratio according to the NMR data) was separated by flash column chromatography ($CHCl_3$: MeOH : 25% aq. soln. of NH_3 = 1500: 15 : 1) affording 0.24 g of **22** (70%) as colorless oil.

Dess-Martin periodinane (0.72 g, 1.70 mmol) was added in one portion to a stirred solution of **22** (0.24 g, 0.565 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred at room temperature for 2 h. The resulted mixture was treated with NaOH (20% aq. solution) and extracted with $CHCl_3$ (3×20 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* to afford 0.22 g of **20** (92%) as yellowish oil. Total yield of **20** from **10** is 65%.



^{1}H NMR (400 MHz, $CDCl_3$): 0.84 (t, 3H, $(CH_2)_3C\underline{H}_3$), 1.16-1.34 and 1.40-1.51 (m + m, 5H + 2H, $(C\underline{H}_2)_3CH_3$ + H-8α), 1.79 (m, 1H, H-15$_{eq}$), 1.94 (m, 1H, H-15$_{ax}$), 2.32 (s, 1H, NCH_3), 2.26-2.57 (m, 4H, H-10α + 2H-16 + H-7β), 2.86 (m, 1H, H-8β), 3.15 (d, ^3J = 6.0 Hz, 1H, H-9), 3.18 (d, ^2J =18.0 Hz, 1H, H-10β), 3.55 (s, 3H, 6-OCH_3), 3.77 (s, 3H, 3-OCH_3), 4.52 (s, 1H, H-5), 5.51 (d, ^3J= 8.8 Hz, 1H, H-19), 5.87 (d, ^3J= 8.8 Hz, 1H, H-18), 6.49 + 6.58 (AB-system, J_{AB} = 8.1 Hz, 2H, H-1 + H-2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13.90, 22.24, 22.42, 25.54, 29.68, 30.26, 33.43, 43.24, 43.50, 45.51, 47.40, 49.94, 53.76, 56.65, 59.99, 81.50, 95.85, 113.56, 119.32, 125.82, 128.25, 134.09, 135.55, 141.83, 148.04, 211.09; **HRMS (ESI)** calcd for $C_{26}H_{34}NO_4$ $[M + H]^+$: 424.2488, found: 424.2497.

3. Quantum chemical calculation details

The possible conformers for alcohols **15a** and **15b** were found by calculating the potential energy curve along to the rotation around C(7)-C(20) bond at the PBE0/Def2-TZVP level**.[4,5]** The geometry optimization of conformers for **2**, **9**, **10**, **15a**, and **15b** compounds was performed at the RIMP2/Def2-TZVP level of theory **[5,6]** using the ORCA program **[7]**. As the objects of calculation are huge, to accelerate the process, the RIJCOSX **[8]** approximation was utilized with Def2/J fitting basis set **[9]**.

xyz-Cartesian coordinates optimized at RIMP2/Def2-TZVP level

2 conformer **A** E_{tot}= -1245.792940314542 a.u.

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O	7.738429000	10.871946000	-2.727484000
O	7.387790000	11.584528000	-0.018932000
N	11.253121000	13.806358000	2.736466000
C	11.171574000	11.785116000	-1.600932000
H	12.193553000	11.712089000	-1.961374000
C	10.127941000	11.405159000	-2.457115000
H	10.375011000	11.092705000	-3.463741000
C	8.796460000	11.344779000	-2.016914000
C	8.557455000	11.754059000	-0.704607000
C	7.676287000	11.855909000	1.386247000
H	6.874543000	12.514532000	1.736589000
C	7.702475000	10.596162000	2.269107000
C	8.009715000	11.153512000	3.704028000
H	7.282982000	11.955577000	3.880428000
C	9.451826000	11.687610000	3.785555000
H	10.055715000	11.010845000	4.396170000
H	9.481241000	12.679102000	4.240124000
C	11.395354000	12.435218000	2.235610000
H	12.105897000	11.936990000	2.907509000
C	11.963196000	12.345909000	0.783806000
H	12.601485000	13.217582000	0.601980000
H	12.628945000	11.478253000	0.718835000
C	10.913427000	12.199032000	-0.291369000
C	9.576456000	12.262569000	0.071539000
C	9.067559000	12.511396000	1.448030000
C	10.037823000	11.731159000	2.362265000
C	9.006125000	13.992827000	1.816259000
H	8.390897000	14.517353000	1.077013000
H	8.520001000	14.104199000	2.791650000
C	10.395196000	14.604417000	1.871257000
H	10.807440000	14.695403000	0.849623000
H	10.343553000	15.616365000	2.284046000
C	12.529896000	14.459623000	2.956610000
H	12.359564000	15.413160000	3.460644000
H	13.089472000	14.667267000	2.030041000
H	13.152406000	13.836004000	3.601302000
C	8.844882000	9.714728000	1.859944000

H	8.689126000	8.668747000	1.623994000
C	10.050435000	10.304210000	1.897786000
H	10.975515000	9.779173000	1.677464000
C	7.753357000	10.038523000	4.713143000
C	8.025616000	10.408197000	-4.037551000
H	7.077044000	10.069727000	-4.446664000
H	8.734213000	9.575508000	-4.015428000
H	8.427296000	11.210897000	-4.662109000
C	5.933486000	9.395917000	1.158173000
H	5.170834000	8.678843000	1.458977000
H	6.705957000	8.884113000	0.579620000
H	5.490534000	10.171268000	0.532830000
C	6.427482000	10.063268000	5.421752000
H	5.623595000	10.136683000	4.688597000
H	6.311821000	9.172199000	6.036020000
H	6.381303000	10.954123000	6.055484000

2 conformer **B** E_{tot}= -1245.791594876890 a.u.

O	6.731287000	11.130442000	5.793798000
O	6.163013000	10.336025000	2.424948000
O	7.681069000	10.915956000	-2.705069000
O	7.321622000	11.757940000	-0.039810000
N	11.297796000	13.728946000	2.758886000
C	11.147520000	11.577319000	-1.512481000
H	12.168880000	11.403634000	-1.838454000
C	10.098766000	11.255706000	-2.385747000
H	10.344463000	10.885205000	-3.372797000
C	8.756401000	11.326478000	-1.982841000
C	8.518878000	11.806034000	-0.693929000
C	7.585228000	12.075489000	1.359389000
H	6.839834000	12.824142000	1.646408000
C	7.465327000	10.867006000	2.308294000
C	7.784993000	11.488679000	3.700295000
H	7.188960000	12.403735000	3.784638000
C	9.287197000	11.833488000	3.821155000
H	9.806650000	11.120252000	4.470045000
H	9.420322000	12.823511000	4.258611000
C	11.325840000	12.336060000	2.302407000
H	11.969890000	11.796509000	3.008953000
C	11.921598000	12.149651000	0.872181000
H	12.639338000	12.955533000	0.683526000
H	12.509604000	11.225411000	0.852060000
C	10.891113000	12.061000000	-0.226900000
C	9.555881000	12.257610000	0.094249000
C	9.032370000	12.601566000	1.445732000
C	9.904589000	11.766304000	2.413652000
C	9.100399000	14.092924000	1.770480000
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H	8.600410000	14.278183000	2.727343000
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H	10.984129000	14.598831000	0.837386000
H	10.569194000	15.599303000	2.232991000
C	12.623066000	14.269807000	2.996835000
H	12.527676000	15.248642000	3.471033000
H	13.222107000	14.399359000	2.080874000
H	13.169719000	13.611312000	3.674803000
C	8.523731000	9.866111000	1.939839000

H	8.266033000	8.845353000	1.680021000
C	9.783243000	10.331360000	1.986867000
H	10.652872000	9.720704000	1.759347000
C	7.342706000	10.625351000	4.868464000
C	7.959877000	10.386045000	-3.991802000
H	6.996093000	10.116267000	-4.416070000
H	8.593214000	9.497079000	-3.924184000
H	8.444580000	11.130484000	-4.629366000
C	5.567703000	9.861465000	1.218717000
H	4.715703000	9.257531000	1.527289000
H	6.261230000	9.246995000	0.638680000
H	5.228661000	10.684754000	0.589178000
C	7.718658000	9.165941000	4.876836000
H	8.762531000	9.016863000	4.598297000
H	7.525286000	8.753913000	5.865955000
H	7.104349000	8.647817000	4.137491000

9 conformer **A** E_{tot}= -1543.216214869761 a.u.

F	6.165508000	9.300358000	6.346121000
F	6.851072000	11.357706000	6.411041000
F	5.408223000	10.739155000	4.925158000
O	8.343864000	9.044736000	4.837618000
O	6.484173000	9.854186000	2.363456000
O	7.775159000	10.881848000	-2.779285000
O	7.406526000	11.509488000	-0.055776000
N	11.214885000	13.770344000	2.755570000
C	11.185555000	11.841276000	-1.623028000
H	12.209588000	11.800102000	-1.982477000
C	10.152550000	11.459625000	-2.491229000
H	10.407778000	11.179312000	-3.505254000
C	8.822179000	11.357157000	-2.055811000
C	8.572957000	11.726136000	-0.733642000
C	7.674271000	11.784159000	1.349121000
H	6.858993000	12.429237000	1.693402000
C	7.715941000	10.527265000	2.232974000
C	8.007727000	11.117216000	3.656329000
H	7.311054000	11.949628000	3.796511000
C	9.463900000	11.608753000	3.767288000
H	10.057714000	10.899749000	4.351115000
H	9.512503000	12.582379000	4.256941000
C	11.385836000	12.413050000	2.227472000
H	12.104567000	11.915379000	2.891212000
C	11.959016000	12.362526000	0.776489000
H	12.582644000	13.248773000	0.615615000
H	12.640110000	11.508106000	0.696714000
C	10.915574000	12.218576000	-0.304813000
C	9.576783000	12.243531000	0.056366000
C	9.056707000	12.460763000	1.434481000
C	10.039974000	11.683081000	2.339288000
C	8.967584000	13.933360000	1.831383000
H	8.344389000	14.461298000	1.101514000
H	8.477203000	14.017016000	2.807750000
C	10.344866000	14.569126000	1.902786000
H	10.758161000	14.687598000	0.884696000
H	10.272416000	15.571270000	2.335485000
C	12.477903000	14.444236000	2.995029000
H	12.285900000	15.383466000	3.517500000

H	13.036642000	14.681817000	2.075439000
H	13.110070000	13.820373000	3.629950000
C	8.869013000	9.659334000	1.824470000
H	8.721378000	8.615020000	1.576734000
C	10.068692000	10.261904000	1.859181000
H	10.999004000	9.750567000	1.628586000
C	7.690049000	10.047585000	4.669114000
C	6.491150000	10.342832000	5.596704000
C	8.068527000	10.471268000	-4.105967000
H	7.126184000	10.126616000	-4.524009000
H	8.795177000	9.654194000	-4.115123000
H	8.449993000	11.304823000	-4.701952000
C	5.942596000	9.301387000	1.164454000
H	5.167896000	8.606774000	1.484509000
H	6.701112000	8.762544000	0.591486000
H	5.511380000	10.075253000	0.529134000

9 conformer **B** E_{tot}= -1543.211149942889 a.u.

F	8.005100000	8.069375000	5.933413000
F	7.736926000	7.819964000	3.811272000
F	9.581774000	8.646464000	4.581786000
O	6.875660000	10.355068000	5.586956000
O	6.451371000	9.845171000	2.263614000
O	7.773411000	10.964773000	-2.849812000
O	7.399096000	11.533532000	-0.106741000
N	11.208696000	13.716065000	2.758337000
C	11.185099000	11.873938000	-1.658361000
H	12.210214000	11.832288000	-2.014688000
C	10.152367000	11.517217000	-2.537226000
H	10.409799000	11.255668000	-3.555637000
C	8.819218000	11.415596000	-2.109189000
C	8.567393000	11.758514000	-0.779895000
C	7.667754000	11.775711000	1.305376000
H	6.853138000	12.412719000	1.665630000
C	7.698747000	10.489609000	2.156059000
C	7.992672000	11.025528000	3.591928000
H	7.287275000	11.846883000	3.760474000
C	9.441408000	11.559618000	3.714843000
H	10.069261000	10.902085000	4.318583000
H	9.443591000	12.540469000	4.191008000
C	11.375644000	12.369604000	2.202179000
H	12.089612000	11.854302000	2.857499000
C	11.953212000	12.348288000	0.752027000
H	12.576812000	13.238120000	0.612024000
H	12.635150000	11.496345000	0.655490000
C	10.912367000	12.228889000	-0.334671000
C	9.572294000	12.255591000	0.021968000
C	9.049455000	12.447394000	1.402627000
C	10.025530000	11.644861000	2.294125000
C	8.966657000	13.913335000	1.824507000
H	8.354316000	14.457422000	1.097328000
H	8.466306000	13.985414000	2.796446000
C	10.347973000	14.537925000	1.917769000
H	10.768362000	14.675231000	0.904949000
H	10.279704000	15.531343000	2.370757000
C	12.473757000	14.377618000	3.019639000
H	12.283844000	15.306637000	3.560769000

H	13.039551000	14.631324000	2.108674000
H	13.098569000	13.736969000	3.645067000
C	8.848023000	9.637641000	1.699613000
H	8.703833000	8.611840000	1.383516000
C	10.048161000	10.237457000	1.770309000
H	10.975444000	9.739956000	1.500504000
C	7.627977000	10.049964000	4.687567000
C	8.248809000	8.621349000	4.750436000
C	8.072052000	10.585623000	-4.184780000
H	7.130094000	10.258568000	-4.617507000
H	8.793020000	9.763876000	-4.210578000
H	8.463305000	11.431050000	-4.757346000
C	5.910982000	9.310861000	1.056146000
H	5.120115000	8.629000000	1.363842000
H	6.663296000	8.759961000	0.486657000
H	5.500704000	10.096109000	0.420580000

10 conformer **A** E_{tot}=-1206.564395967521. a.u.

O	8.711649000	9.315548000	5.211563000
O	6.464780000	9.879986000	2.307056000
O	7.743589000	10.889373000	-2.748125000
O	7.380194000	11.589920000	-0.035799000
N	11.230304000	13.787824000	2.752854000
C	11.173354000	11.791092000	-1.599863000
H	12.196535000	11.721088000	-1.957428000
C	10.132685000	11.416994000	-2.462632000
H	10.383973000	11.110537000	-3.470044000
C	8.798570000	11.355901000	-2.029344000
C	8.554356000	11.758014000	-0.715861000
C	7.670262000	11.832755000	1.374144000
H	6.865781000	12.477914000	1.742882000
C	7.703555000	10.550726000	2.223116000
C	8.017822000	11.051048000	3.678693000
H	7.237499000	11.786441000	3.917570000
C	9.426263000	11.657378000	3.772428000
H	10.048639000	11.028213000	4.414682000
H	9.398874000	12.656490000	4.208606000
C	11.381753000	12.421595000	2.243123000
H	12.092256000	11.921756000	2.913712000
C	11.955104000	12.345841000	0.791326000
H	12.584016000	13.225917000	0.617515000
H	12.631219000	11.486610000	0.722088000
C	10.910187000	12.197362000	-0.288592000
C	9.571585000	12.257244000	0.068598000
C	9.058115000	12.492579000	1.445186000
C	10.028063000	11.709436000	2.358638000
C	8.988068000	13.971749000	1.820648000
H	8.376760000	14.496245000	1.078126000
H	8.492460000	14.078384000	2.791548000
C	10.374053000	14.588551000	1.888802000
H	10.792210000	14.689827000	0.870471000
H	10.315285000	15.597061000	2.308935000
C	12.502479000	14.445417000	2.985711000
H	12.325039000	15.393888000	3.496728000
H	13.066097000	14.663468000	2.063930000
H	13.124660000	13.819731000	3.628671000
C	8.857885000	9.689453000	1.799521000

H	8.712955000	8.650222000	1.527185000
C	10.058189000	10.287154000	1.876605000
H	10.990716000	9.776500000	1.653340000
C	7.813159000	9.883615000	4.624081000
C	8.035806000	10.433583000	-4.059874000
H	7.088771000	10.098400000	-4.475186000
H	8.743606000	9.600163000	-4.040415000
H	8.440657000	11.239641000	-4.677962000
C	5.940994000	9.373839000	1.079453000
H	5.191940000	8.634431000	1.359292000
H	6.716855000	8.896358000	0.476356000
H	5.480740000	10.163598000	0.485623000
H	6.767171000	9.558672000	4.746151000

10 conformer **B** E_{tot}= -1206.564163099856 a.u.

O	7.201050000	10.103656000	5.707968000
O	6.468224000	9.864501000	2.351196000
O	7.768136000	10.884475000	-2.776523000
O	7.394552000	11.538433000	-0.056147000
N	11.218035000	13.767345000	2.757675000
C	11.183533000	11.816408000	-1.613937000
H	12.208256000	11.762688000	-1.969856000
C	10.149177000	11.438895000	-2.482190000
H	10.405142000	11.147851000	-3.492969000
C	8.816051000	11.354748000	-2.050742000
C	8.565177000	11.736199000	-0.731844000
C	7.666341000	11.802323000	1.353368000
H	6.857103000	12.451528000	1.703052000
C	7.701105000	10.539261000	2.229935000
C	7.996224000	11.082952000	3.658132000
H	7.265796000	11.866583000	3.883513000
C	9.442735000	11.623326000	3.761980000
H	10.065450000	10.958179000	4.371578000
H	9.456988000	12.603458000	4.239325000
C	11.381247000	12.408605000	2.232094000
H	12.095560000	11.907169000	2.897900000
C	11.956214000	12.352822000	0.781586000
H	12.578490000	13.239613000	0.618317000
H	12.639084000	11.499592000	0.704220000
C	10.913004000	12.206209000	-0.299550000
C	9.573316000	12.246503000	0.057820000
C	9.053103000	12.470095000	1.434747000
C	10.030946000	11.687874000	2.342111000
C	8.973618000	13.944395000	1.827111000
H	8.358003000	14.473997000	1.092022000
H	8.478064000	14.034776000	2.799875000
C	10.355174000	14.570506000	1.901683000
H	10.772571000	14.685079000	0.884701000
H	10.288717000	15.573805000	2.332666000
C	12.484572000	14.432958000	2.999743000
H	12.297751000	15.374106000	3.520644000
H	13.047800000	14.665494000	2.081465000
H	13.110756000	13.805667000	3.637297000
C	8.851912000	9.672386000	1.802304000
H	8.699399000	8.638704000	1.512789000
C	10.055402000	10.267586000	1.854535000
H	10.982791000	9.761113000	1.601286000

C	7.805111000	9.980355000	4.663951000
C	8.065816000	10.458223000	-4.097199000
H	7.122901000	10.119446000	-4.518762000
H	8.784044000	9.633576000	-4.094059000
H	8.460275000	11.281644000	-4.698895000
C	5.911718000	9.355565000	1.140131000
H	5.140804000	8.648813000	1.442811000
H	6.661980000	8.840208000	0.534941000
H	5.471048000	10.150998000	0.538397000
H	8.315479000	9.029048000	4.408788000

15a conformer ***t*** E_{tot}= -1583.632156198033 a.u.

O	8.763114000	9.289245000	4.903012000
O	6.243416000	10.180438000	2.160738000
O	7.741093000	10.875765000	-2.753279000
O	7.348163000	11.736591000	-0.081511000
N	11.242255000	13.777075000	2.744633000
C	11.189411000	11.605896000	-1.537758000
H	12.215038000	11.451050000	-1.859853000
C	10.149934000	11.259424000	-2.413471000
H	10.408191000	10.887765000	-3.396894000
C	8.801782000	11.308428000	-2.022253000
C	8.547051000	11.791458000	-0.738131000
C	7.626301000	12.005823000	1.327640000
H	6.850474000	12.701763000	1.662732000
C	7.537757000	10.730767000	2.201268000
C	7.817143000	11.219399000	3.670620000
H	7.067511000	11.996529000	3.861709000
C	9.251846000	11.824566000	3.748092000
H	9.860873000	11.260277000	4.453303000
H	9.223619000	12.852154000	4.107779000
C	11.320079000	12.388900000	2.283471000
H	11.974131000	11.865771000	2.992604000
C	11.934114000	12.228724000	0.852270000
H	12.609424000	13.071813000	0.669686000
H	12.570924000	11.337508000	0.834712000
C	10.916621000	12.093258000	-0.256163000
C	9.574943000	12.260081000	0.050495000
C	9.040170000	12.584164000	1.398539000
C	9.918337000	11.771432000	2.368641000
C	9.056352000	14.078495000	1.715479000
H	8.515569000	14.609366000	0.924324000
H	8.525416000	14.259591000	2.655623000
C	10.476838000	14.604616000	1.823045000
H	10.941027000	14.646889000	0.820539000
H	10.468467000	15.627287000	2.211404000
C	12.545963000	14.354502000	3.012407000
H	12.412812000	15.331275000	3.481600000
H	13.162855000	14.498604000	2.110364000
H	13.093986000	13.712774000	3.705014000
C	8.042682000	10.336784000	-4.031461000
H	7.088765000	10.042437000	-4.461553000
H	8.693652000	9.462028000	-3.948256000
H	8.517848000	11.083522000	-4.673436000
C	5.799828000	9.628326000	0.921070000
H	5.043499000	8.886870000	1.179933000
H	6.611229000	9.142599000	0.374690000

H	5.364539000	10.391772000	0.276888000
C	9.883656000	10.336442000	1.924418000
C	8.653913000	9.797005000	1.824036000
C	7.630391000	10.141080000	4.783240000
H	9.066482000	9.106324000	3.999594000
H	8.466590000	8.771383000	1.521761000
H	10.792306000	9.781255000	1.705399000
C	6.373207000	9.276710000	4.698536000
H	6.464684000	8.593150000	3.859890000
H	6.297446000	8.692357000	5.615278000
H	5.471295000	9.869859000	4.561570000
C	7.560806000	10.868694000	6.141283000
F	6.463202000	11.646642000	6.199060000
F	7.488503000	10.002768000	7.157954000
F	8.610028000	11.661866000	6.390245000

15a conformer g^1 E_{tot}= -1583.634365629981 a.u.

O	8.236443000	11.121297000	5.988562000
O	6.260371000	10.304915000	2.402164000
O	7.526788000	11.129564000	-2.719756000
O	7.329405000	11.835593000	0.004299000
N	11.494643000	13.547402000	2.692250000
C	11.066924000	11.638123000	-1.677722000
H	12.064761000	11.455013000	-2.065552000
C	9.966018000	11.391429000	-2.510471000
H	10.149492000	11.068602000	-3.527371000
C	8.648575000	11.473755000	-2.034137000
C	8.490829000	11.889953000	-0.711416000
C	7.676552000	12.069152000	1.402355000
H	6.965000000	12.815754000	1.770142000
C	7.567204000	10.807323000	2.286801000
C	7.965490000	11.336808000	3.701110000
H	7.423000000	12.278961000	3.837195000
C	9.482445000	11.643472000	3.743727000
H	10.019080000	10.889487000	4.323695000
H	9.666037000	12.600736000	4.230053000
C	11.456786000	12.182058000	2.159767000
H	12.118173000	11.585975000	2.801985000
C	11.975784000	12.060723000	0.692017000
H	12.705931000	12.857142000	0.511010000
H	12.535350000	11.124138000	0.591420000
C	10.890284000	12.059760000	-0.357142000
C	9.579170000	12.274865000	0.041869000
C	9.135970000	12.555644000	1.435241000
C	10.026648000	11.644451000	2.309432000
C	9.262267000	14.023059000	1.841160000
H	8.695749000	14.638322000	1.133726000
H	8.818328000	14.162862000	2.832784000
C	10.715488000	14.463457000	1.870907000
H	11.109115000	14.532373000	0.840083000
H	10.795049000	15.463011000	2.308591000
C	12.845926000	14.035968000	2.890907000
H	12.805135000	14.990369000	3.419726000
H	13.404192000	14.196743000	1.954142000
H	13.403451000	13.326246000	3.505450000
C	7.721716000	10.679350000	-4.051056000
H	6.729564000	10.459472000	-4.437242000

H	8.334657000	9.774104000	-4.076982000
H	8.189816000	11.453490000	-4.665367000
C	5.613110000	9.897116000	1.199935000
H	4.777545000	9.273065000	1.514731000
H	6.279961000	9.319653000	0.554674000
H	5.243875000	10.753059000	0.634240000
C	9.851090000	10.238202000	1.812799000
C	8.580703000	9.803193000	1.813293000
C	7.574438000	10.460362000	4.910984000
H	7.969905000	10.682392000	6.808826000
H	8.281933000	8.803905000	1.516274000
H	10.693232000	9.621592000	1.510231000
C	8.016281000	9.009556000	4.808322000
H	9.093164000	8.965255000	4.653104000
H	7.776367000	8.482649000	5.735977000
H	7.513042000	8.505415000	3.984817000
C	6.061205000	10.485308000	5.265335000
F	5.343433000	9.516171000	4.699201000
F	5.927011000	10.286380000	6.604663000
F	5.477650000	11.655137000	4.996806000

15a conformer ***g²*** *without H-bond* E_{tot}= -1583.628980541434 a.u.

O	5.956413000	10.860856000	4.981651000
O	6.029165000	10.635532000	2.306857000
O	7.321708000	11.570108000	-2.744516000
O	7.271211000	12.135222000	0.018456000
N	11.670452000	13.117941000	2.693910000
C	10.917320000	11.542446000	-1.767047000
H	11.874352000	11.250674000	-2.189807000
C	9.778073000	11.491998000	-2.583366000
H	9.898877000	11.205881000	-3.620437000
C	8.492039000	11.721699000	-2.070162000
C	8.414998000	12.077403000	-0.722805000
C	7.672399000	12.231073000	1.418558000
H	7.070033000	13.038316000	1.848029000
C	7.396323000	10.939613000	2.227047000
C	7.894161000	11.332674000	3.667016000
H	7.479097000	12.334557000	3.843541000
C	9.440869000	11.435523000	3.681050000
H	9.890038000	10.577215000	4.183229000
H	9.765497000	12.333080000	4.209838000
C	11.442409000	11.803177000	2.084162000
H	12.029788000	11.087423000	2.674045000
C	11.915740000	11.703615000	0.599378000
H	12.741926000	12.406646000	0.446239000
H	12.344533000	10.709340000	0.432514000
C	10.822430000	11.907418000	-0.421394000
C	9.559085000	12.269085000	0.021920000
C	9.180911000	12.521647000	1.439434000
C	9.955546000	11.451671000	2.236409000
C	9.508455000	13.934054000	1.920764000
H	9.019006000	14.657441000	1.259644000
H	9.100967000	14.076860000	2.927790000
C	11.007646000	14.175634000	1.942409000
H	11.391692000	14.249932000	0.908568000
H	11.227631000	15.129029000	2.432127000
C	13.078834000	13.413773000	2.881249000

H	13.175189000	14.330450000	3.466693000
H	13.631992000	13.560207000	1.939408000
H	13.552622000	12.600491000	3.434647000
C	7.432605000	11.157841000	-4.097941000
H	6.414028000	11.089951000	-4.471558000
H	7.917954000	10.180899000	-4.175288000
H	7.991055000	11.888694000	-4.689492000
C	5.375829000	10.298503000	1.086708000
H	4.480771000	9.748792000	1.376094000
H	5.997156000	9.666109000	0.447591000
H	5.097127000	11.187538000	0.519839000
C	9.584516000	10.109912000	1.673032000
C	8.268960000	9.841388000	1.683084000
C	7.337881000	10.559180000	4.883897000
H	5.654295000	10.536534000	5.842815000
H	7.845797000	8.898093000	1.360425000
H	10.334093000	9.403099000	1.327856000
C	8.042562000	11.051047000	6.150917000
H	7.962508000	12.138169000	6.186137000
H	7.549087000	10.640013000	7.033472000
H	9.093280000	10.769829000	6.190013000
C	7.476172000	9.029059000	4.828434000
F	8.759799000	8.633341000	4.772048000
F	6.958762000	8.496075000	5.960781000
F	6.833882000	8.455561000	3.816653000

15a conformer ***g²*** *with H-bond* E_{tot}= -1583.642528197173 a.u.

O	5.929701000	10.751954000	4.963787000
O	6.034995000	10.653275000	2.316971000
O	7.311260000	11.577222000	-2.735050000
O	7.273594000	12.147587000	0.028312000
N	11.690966000	13.112871000	2.683000000
C	10.910164000	11.526991000	-1.770021000
H	11.863836000	11.229326000	-2.196108000
C	9.767850000	11.482552000	-2.582311000
H	9.883669000	11.194370000	-3.619338000
C	8.484865000	11.721024000	-2.065104000
C	8.416146000	12.079029000	-0.718376000
C	7.683199000	12.242810000	1.424381000
H	7.088707000	13.053332000	1.858593000
C	7.417396000	10.955005000	2.233008000
C	7.912437000	11.337321000	3.673230000
H	7.491729000	12.335845000	3.857849000
C	9.456050000	11.453052000	3.688774000
H	9.912433000	10.612288000	4.211851000
H	9.768032000	12.364463000	4.200571000
C	11.454742000	11.797641000	2.079301000
H	12.040733000	11.080820000	2.668911000
C	11.920312000	11.690504000	0.592185000
H	12.747279000	12.391199000	0.432744000
H	12.346160000	10.694828000	0.426405000
C	10.823190000	11.894531000	-0.424525000
C	9.563456000	12.263795000	0.022697000
C	9.194172000	12.524104000	1.440889000
C	9.967517000	11.453889000	2.241309000
C	9.529956000	13.937213000	1.914439000
H	9.042650000	14.660027000	1.251121000

H	9.125875000	14.087020000	2.921668000
C	11.030681000	14.171117000	1.930857000
H	11.411888000	14.241358000	0.895630000
H	11.256069000	15.124838000	2.417268000
C	13.100971000	13.402020000	2.867827000
H	13.202886000	14.318770000	3.452078000
H	13.653447000	13.543933000	1.924889000
H	13.570996000	12.587135000	3.421976000
C	7.415190000	11.180257000	-4.094040000
H	6.395119000	11.123908000	-4.465381000
H	7.893488000	10.201098000	-4.184779000
H	7.976850000	11.914699000	-4.677897000
C	5.365272000	10.312517000	1.100231000
H	4.476640000	9.756289000	1.395185000
H	5.991839000	9.687091000	0.462649000
H	5.083441000	11.205325000	0.543189000
C	9.589841000	10.111938000	1.683101000
C	8.273234000	9.848917000	1.687304000
C	7.323623000	10.543381000	4.865385000
H	5.588411000	10.658546000	4.054155000
H	7.845933000	8.905859000	1.370308000
H	10.335303000	9.398423000	1.343524000
C	7.917399000	11.080388000	6.161663000
H	7.822104000	12.166720000	6.163912000
H	7.350931000	10.682549000	7.002318000
H	8.966910000	10.813247000	6.278057000
C	7.548460000	9.021413000	4.832279000
F	8.848323000	8.686509000	4.714073000
F	7.109459000	8.460232000	5.967912000
F	6.895013000	8.420615000	3.828543000

15b conformer ***t*** E_{tot}= -1583.633543192024 a.u.

O	8.740884000	9.269341000	4.822087000
O	6.194702000	10.256742000	2.075433000
O	7.739278000	10.920196000	-2.778779000
O	7.330259000	11.769204000	-0.104975000
N	11.213439000	13.793097000	2.753998000
C	11.181937000	11.642608000	-1.541562000
H	12.208863000	11.488828000	-1.860114000
C	10.146252000	11.302359000	-2.424363000
H	10.409372000	10.936042000	-3.408530000
C	8.795804000	11.349573000	-2.040306000
C	8.532957000	11.825109000	-0.754799000
C	7.609360000	12.029274000	1.305572000
H	6.827778000	12.715519000	1.645444000
C	7.511641000	10.743991000	2.163535000
C	7.773807000	11.218028000	3.634621000
H	7.012300000	11.981985000	3.833777000
C	9.200862000	11.840580000	3.734029000
H	9.803391000	11.274336000	4.446693000
H	9.161136000	12.870910000	4.086950000
C	11.291032000	12.405608000	2.288292000
H	11.942065000	11.879603000	2.998205000
C	11.912033000	12.247394000	0.859213000
H	12.597468000	13.083963000	0.684636000
H	12.540307000	11.350010000	0.844049000
C	10.902305000	12.122802000	-0.258733000

C	9.559285000	12.288223000	0.040494000
C	9.018859000	12.608498000	1.386074000
C	9.887749000	11.789845000	2.362746000
C	9.036516000	14.102322000	1.706266000
H	8.503344000	14.635920000	0.911992000
H	8.497869000	14.283928000	2.641955000
C	10.457350000	14.624577000	1.826823000
H	10.930834000	14.665207000	0.828905000
H	10.449635000	15.646976000	2.216001000
C	12.518796000	14.366204000	3.026403000
H	12.387514000	15.342715000	3.496726000
H	13.137974000	14.509857000	2.126073000
H	13.063382000	13.721269000	3.718813000
C	8.044945000	10.402156000	-4.064698000
H	7.092038000	10.116227000	-4.502577000
H	8.694520000	9.525348000	-3.993567000
H	8.523152000	11.159489000	-4.691842000
C	5.926729000	9.312568000	1.044177000
H	4.842300000	9.276734000	0.953792000
H	6.284918000	8.316751000	1.319205000
H	6.357608000	9.619675000	0.090068000
C	9.855578000	10.359510000	1.905123000
C	8.629480000	9.815993000	1.785134000
C	7.648635000	10.172646000	4.781715000
C	7.666697000	10.930010000	6.106970000
H	6.738047000	11.486467000	6.241970000
H	7.783626000	10.226122000	6.928756000
H	8.501774000	11.627139000	6.127278000
C	6.373568000	9.307119000	4.785891000
F	5.258841000	10.031416000	4.632355000
F	6.397785000	8.342188000	3.855777000
F	6.255164000	8.670229000	5.966464000
H	8.919736000	8.987902000	3.910302000
H	8.456788000	8.801461000	1.444113000
H	10.765626000	9.812297000	1.673472000

15b conformer g^1 E_{tot}= -1583.633759368920 a.u.

O	8.018324000	11.126221000	6.102852000
O	6.183640000	10.387796000	2.299538000
O	7.505004000	11.190414000	-2.725604000
O	7.308225000	11.874347000	0.008104000
N	11.482435000	13.523119000	2.720029000
C	11.048601000	11.653718000	-1.672217000
H	12.044963000	11.464333000	-2.060837000
C	9.946102000	11.425676000	-2.508433000
H	10.128271000	11.110588000	-3.528022000
C	8.628163000	11.516210000	-2.034014000
C	8.471287000	11.920742000	-0.707458000
C	7.665591000	12.084584000	1.406835000
H	6.953536000	12.823595000	1.787423000
C	7.530630000	10.807886000	2.270601000
C	7.926744000	11.321996000	3.700538000
H	7.396459000	12.276179000	3.820973000
C	9.446082000	11.635893000	3.743554000
H	10.001173000	10.877566000	4.302230000
H	9.626944000	12.600997000	4.218892000
C	11.435569000	12.163164000	2.173210000

H	12.091044000	11.555026000	2.810264000
C	11.955940000	12.050169000	0.704723000
H	12.692292000	12.842851000	0.532542000
H	12.509206000	11.110529000	0.598635000
C	10.873646000	12.065676000	-0.348296000
C	9.563901000	12.288514000	0.049237000
C	9.121905000	12.563556000	1.443132000
C	10.000482000	11.637999000	2.313060000
C	9.259374000	14.027212000	1.858556000
H	8.702942000	14.651540000	1.151180000
H	8.808942000	14.166872000	2.847553000
C	10.716349000	14.453601000	1.901085000
H	11.117317000	14.525487000	0.873544000
H	10.803551000	15.448988000	2.346602000
C	12.838140000	13.997858000	2.926954000
H	12.804490000	14.946559000	3.466302000
H	13.398707000	14.163835000	1.992848000
H	13.388402000	13.276256000	3.534114000
C	7.697194000	10.761643000	-4.064794000
H	6.703411000	10.558450000	-4.455668000
H	8.301310000	9.851199000	-4.106100000
H	8.173382000	11.542451000	-4.664207000
C	5.765782000	9.521204000	1.247065000
H	4.677450000	9.563086000	1.244506000
H	6.076573000	8.491142000	1.442216000
H	6.140056000	9.849735000	0.276924000
C	9.813531000	10.237801000	1.808920000
C	8.543281000	9.803330000	1.800524000
C	7.443923000	10.529405000	4.944667000
C	5.943502000	10.633304000	5.171907000
H	5.388351000	10.076370000	4.423933000
H	5.711414000	10.265958000	6.170866000
H	5.655672000	11.682999000	5.113170000
C	7.833726000	9.044177000	4.967269000
F	7.306852000	8.353135000	3.947516000
F	9.169384000	8.862948000	4.919968000
F	7.413147000	8.461439000	6.097002000
H	8.980750000	11.129052000	5.997927000
H	8.261327000	8.806502000	1.489424000
H	10.651510000	9.619201000	1.500261000

15b conformer ***g²*** *with H-bond* E_{tot}= -1583.633662566085 a.u.

O	5.961618000	10.916141000	4.972175000
O	6.052625000	10.521660000	2.319997000
O	7.316691000	11.543498000	-2.717418000
O	7.259738000	12.100820000	0.039318000
N	11.643709000	13.119591000	2.732936000
C	10.912841000	11.570860000	-1.744917000
H	11.874380000	11.294991000	-2.168082000
C	9.774764000	11.504125000	-2.561827000
H	9.899784000	11.221397000	-3.599344000
C	8.486513000	11.713758000	-2.046701000
C	8.405964000	12.065987000	-0.698998000
C	7.653778000	12.190151000	1.440205000
H	7.040143000	12.985490000	1.875005000
C	7.407951000	10.891020000	2.242061000
C	7.902459000	11.304278000	3.682282000

H	7.507308000	12.312993000	3.852514000
C	9.446800000	11.371563000	3.697833000
H	9.879128000	10.482618000	4.161241000
H	9.790272000	12.236531000	4.266869000
C	11.437968000	11.811454000	2.104283000
H	12.036104000	11.096639000	2.684353000
C	11.913387000	11.743056000	0.618119000
H	12.717583000	12.473110000	0.474542000
H	12.372187000	10.764919000	0.436544000
C	10.813606000	11.930710000	-0.398134000
C	9.545386000	12.272663000	0.049069000
C	9.161782000	12.501776000	1.470575000
C	9.957445000	11.432722000	2.251025000
C	9.466377000	13.909639000	1.978922000
H	8.961076000	14.638367000	1.335898000
H	9.062678000	14.022440000	2.991222000
C	10.960988000	14.176969000	2.000094000
H	11.341217000	14.275199000	0.966613000
H	11.165163000	15.125884000	2.504849000
C	13.046270000	13.436605000	2.926876000
H	13.126233000	14.343090000	3.530190000
H	13.597083000	13.610679000	1.988168000
H	13.533988000	12.621434000	3.465130000
C	7.428919000	11.129376000	-4.069998000
H	6.410106000	11.044093000	-4.439508000
H	7.929558000	10.160078000	-4.146664000
H	7.973089000	11.867350000	-4.665877000
C	5.394954000	10.254946000	1.083375000
H	4.511073000	9.672367000	1.341651000
H	6.022593000	9.680488000	0.397004000
H	5.094879000	11.175253000	0.581705000
C	9.608320000	10.094763000	1.667540000
C	8.296525000	9.810684000	1.688415000
C	7.299982000	10.471098000	4.827363000
C	7.384643000	8.967199000	4.611700000
H	8.405224000	8.650249000	4.396452000
H	7.040612000	8.434528000	5.502031000
H	6.742333000	8.708557000	3.772262000
C	7.978635000	10.818121000	6.169879000
F	9.181592000	10.246003000	6.333808000
F	8.131332000	12.135991000	6.338645000
F	7.215387000	10.376408000	7.191609000
H	5.533107000	10.348288000	5.628417000
H	7.877726000	8.869333000	1.349988000
H	10.365501000	9.404501000	1.305292000

15b conformer g^2 *without H-bond* E_{tot}= -1583.642354540677 a.u.

O	5.921811000	10.810218000	4.962633000
O	6.027496000	10.692876000	2.333797000
O	7.269862000	11.662946000	-2.683838000
O	7.261035000	12.196664000	0.082421000
N	11.709305000	13.081602000	2.723976000
C	10.878462000	11.590238000	-1.758464000
H	11.826890000	11.295643000	-2.198172000
C	9.728328000	11.561217000	-2.560331000
H	9.832699000	11.287689000	-3.602563000
C	8.451870000	11.796838000	-2.026361000

C	8.397832000	12.136862000	-0.674546000
C	7.685608000	12.265184000	1.474645000
H	7.095153000	13.066894000	1.928042000
C	7.422167000	10.968380000	2.267880000
C	7.930531000	11.351488000	3.707013000
H	7.554309000	12.364994000	3.890873000
C	9.475317000	11.392379000	3.708315000
H	9.894058000	10.498793000	4.175079000
H	9.836166000	12.252543000	4.273876000
C	11.461480000	11.784554000	2.089140000
H	12.049299000	11.050065000	2.654765000
C	11.913507000	11.714019000	0.594811000
H	12.735718000	12.422475000	0.445523000
H	12.342909000	10.725009000	0.400421000
C	10.806433000	11.938465000	-0.406767000
C	9.552898000	12.306725000	0.059503000
C	9.198035000	12.538410000	1.487086000
C	9.974045000	11.444339000	2.255594000
C	9.545410000	13.934883000	1.999441000
H	9.053563000	14.680506000	1.365504000
H	9.154506000	14.052430000	3.016119000
C	11.046933000	14.162282000	2.007190000
H	11.419081000	14.259868000	0.970720000
H	11.280328000	15.101073000	2.518028000
C	13.121858000	13.358831000	2.906130000
H	13.232368000	14.258529000	3.514616000
H	13.668072000	13.523894000	1.963140000
H	13.591862000	12.527041000	3.434545000
C	7.356021000	11.290760000	-4.051037000
H	6.331253000	11.243316000	-4.410521000
H	7.831046000	10.312515000	-4.165820000
H	7.911857000	12.034890000	-4.628008000
C	5.447893000	10.012015000	1.216676000
H	4.377450000	10.200926000	1.275720000
H	5.620562000	8.934863000	1.284806000
H	5.834483000	10.397357000	0.274116000
C	9.582109000	10.122059000	1.667429000
C	8.264304000	9.865363000	1.698018000
C	7.299331000	10.504217000	4.833398000
C	7.505796000	9.004087000	4.665991000
H	8.555070000	8.739620000	4.534477000
H	7.110281000	8.483490000	5.539086000
H	6.948840000	8.671523000	3.789806000
C	7.863060000	10.946253000	6.193628000
F	9.121057000	10.510050000	6.393607000
F	7.886446000	12.281741000	6.316888000
F	7.127382000	10.465876000	7.199125000
H	5.578691000	10.764410000	4.051493000
H	7.831983000	8.941213000	1.335338000
H	10.313778000	9.418692000	1.279525000

4. Crystal structure data

4.1. General

Single crystals of **15b, 17a** and **18b** were crystallized from MeOH. Suitable crystals were selected and mounted on a needle on a Bruker SMART APEX II (**15b, 17a**), a Bruker SMART 1000 (**15b**) or a Bruker Quest D8 CMOS diffractometer (**11c**, **16b**), using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Using Olex2 **[10]**, the structures were solved with the ShelXS **[11]** structure solution program using Direct Methods (**15b** and **18b**) or XT **[12]** structure solution program using Intrinsic Phasing (**11c, 16b, 17a**) and refined with the ShelXL2014 **[11]** refinement package using Least Squares minimization against F^2 in anisotropic approximation for non-hydrogen atoms. The crystal of **18b** was disordered, with the $CH_3C(O)CF_3$ group occupying two close positions with occupancies of 0.61 and 0.29. Hydrogen atoms of hydrogen groups in **16b** and **11c** were located from difference Fourier synthesis while the positions of other hydrogen atoms were calculated, and they all were refined in isotropic approximation within the riding model.

The CIF files of all studied compounds were deposited with CCDC, deposition numbers **2217268 (11c)**, **2221023** (**15b**), **2217267** (**16b**), **2221036** (**17a**), **2221027** (**18b**).

4.2 Crystal structure data for compounds 11c, 15b, 16b, 17a, 18b

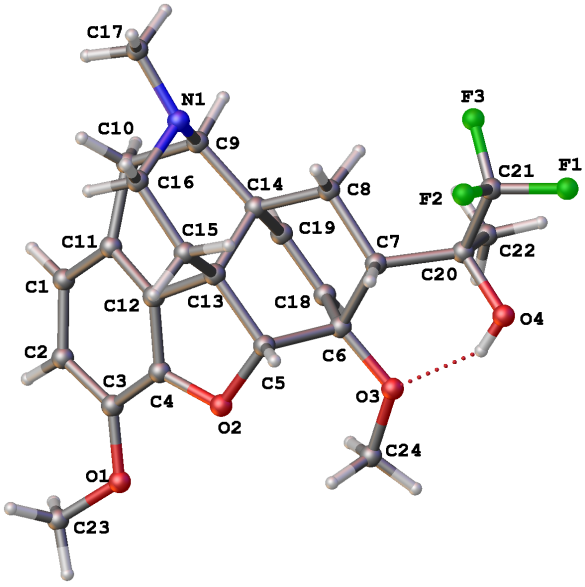


Figure 1. The general view of **15b** in crystal. Atoms are represented by anisotropic thermal displacement ellipsoids (p=50%). Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as S. The dotted line shows an intramolecular hydrogen bond (O…O 2.625(3) Å, OHO 148(3)°).

Crystal Data for $C_{24}H_{28}F_3NO_4$ (**15b**) (M =451.47 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.0266(17) Å, b = 11.611(2) Å, c = 20.467(3) Å, V = 2145.1(7) Å^3, Z = 4, T = 100 K, μ(MoKα) = 0.111 mm^{-1}, *Dcalc* = 1.398 g/cm^3, 16410 reflections measured (3.98° ≤ 2Θ ≤ 60.054°), 6255 unique (R_{int} = 0.0476, R_{sigma} = 0.0573) which were used in all calculations. The final R_1 was 0.0458 (I > 2σ(I)) and wR_2 was 0.1003 (all data).

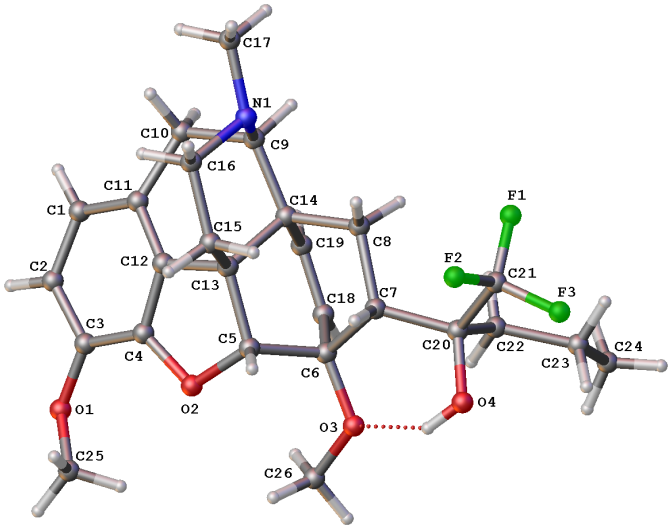


Figure 2. General view of the compound **18b** in representation of atoms *via* thermal ellipsoids at 50% probability level. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as S. The dotted line shows an intramolecular hydrogen bond (O…O 2.671(6) Å, OHO 142.2(4)°).

Crystal Data for $C_{26}H_{32}F_3NO_4$ (**18b**) (M =479.52 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 7.0711(13) Å, b = 10.670(2) Å, c = 15.423(3) Å, β = 100.581(4)°, V = 1143.9(4) Å^3, Z = 2, T = 120 K, μ(MoKα) = 0.109 mm^{-1}, *Dcalc* = 1.392 g/cm^3, 13376 reflections measured (4.668° ≤ 2Θ ≤ 60.002°), 6467 unique (R_{int} = 0.0225, R_{sigma} = 0.0333) which were used in all calculations. The final R_1 was 0.0414 (I > 2σ(I)) and wR_2 was 0.1102 (all data).

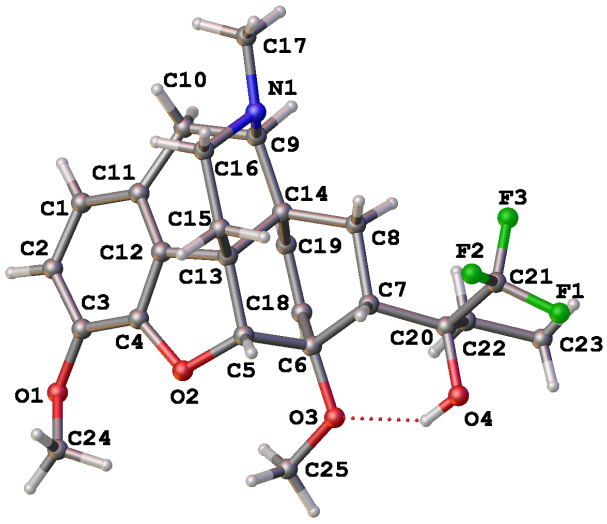


Figure 3. General view of the compound **16b** in representation of atoms *via* thermal ellipsoids at 50% probability level. The second symmetry-independent molecule is omitted for clarity. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as S. The dotted line shows an intramolecular hydrogen bond (O…O 2.668(3) Å, OHO 144(5)°).

Crystal Data for $C_{25}H_{30}F_3NO_4$ (**16b**) (M =465.50 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 13.5849(3) Å, b = 10.6443(3) Å, c = 15.6105(4) Å, β = 100.4980(10)°, V = 2219.52(10) Å^3, Z = 4, T = 100.00 K, μ(MoKα) = 0.110 mm^{-1}, *Dcalc* = 1.393 g/cm^3, 33721 reflections measured (3.66° ≤ 2Θ ≤ 61.15°), 13076 unique (R_{int} = 0.0721, R_{sigma} = 0.1037) which were used in all calculations. The final R_1 was 0.0580 (I > 2σ(I)) and wR_2 was 0.1151 (all data).

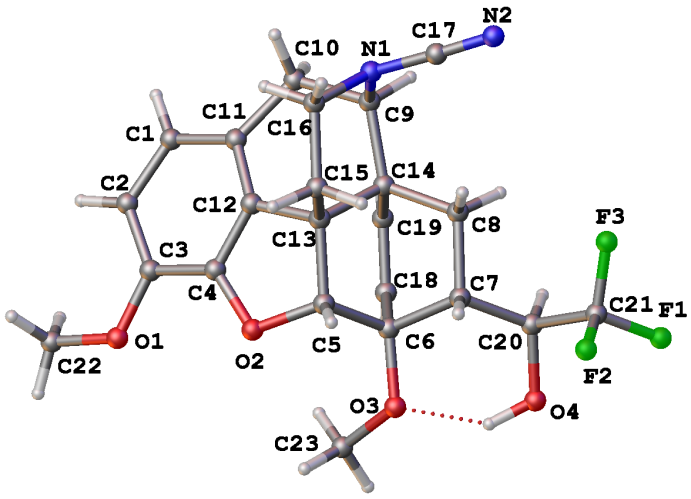


Figure 4. General view of the compound **11c** in representation of atoms *via* thermal ellipsoids at 50% probability level. The second symmetry-independent molecule is omitted for clarity. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as S. The dotted line shows an intramolecular hydrogen bond (O…O 2.545(8) Å, OHO 142.3(4)°).

Crystal Data for $C_{23}H_{23}F_3N_2O_4$ (**11c**) (M =448.43 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 10.0899(7) Å, b = 7.6365(5) Å, c = 26.1261(17) Å, β = 98.814(3)°, V = 1989.3(2) Å^3, Z = 4, T = 100.00 K, μ(MoKα) = 0.121 mm^{-1}, *Dcalc* = 1.497 g/cm^3, 55164 reflections measured (4.084° ≤ 2Θ ≤ 57.992°), 9514 unique (R_{int} = 0.0592, R_{sigma} = 0.0490) which were used in all calculations. The final R_1 was 0.0997 (I > 2σ(I)) and wR_2 was 0.2900 (all data)

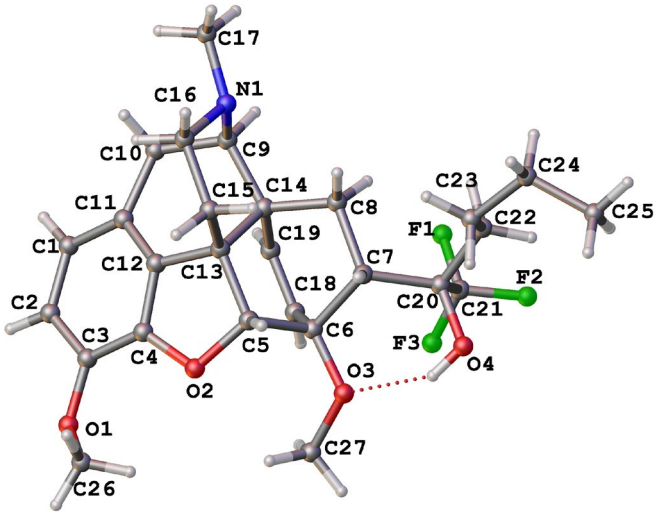
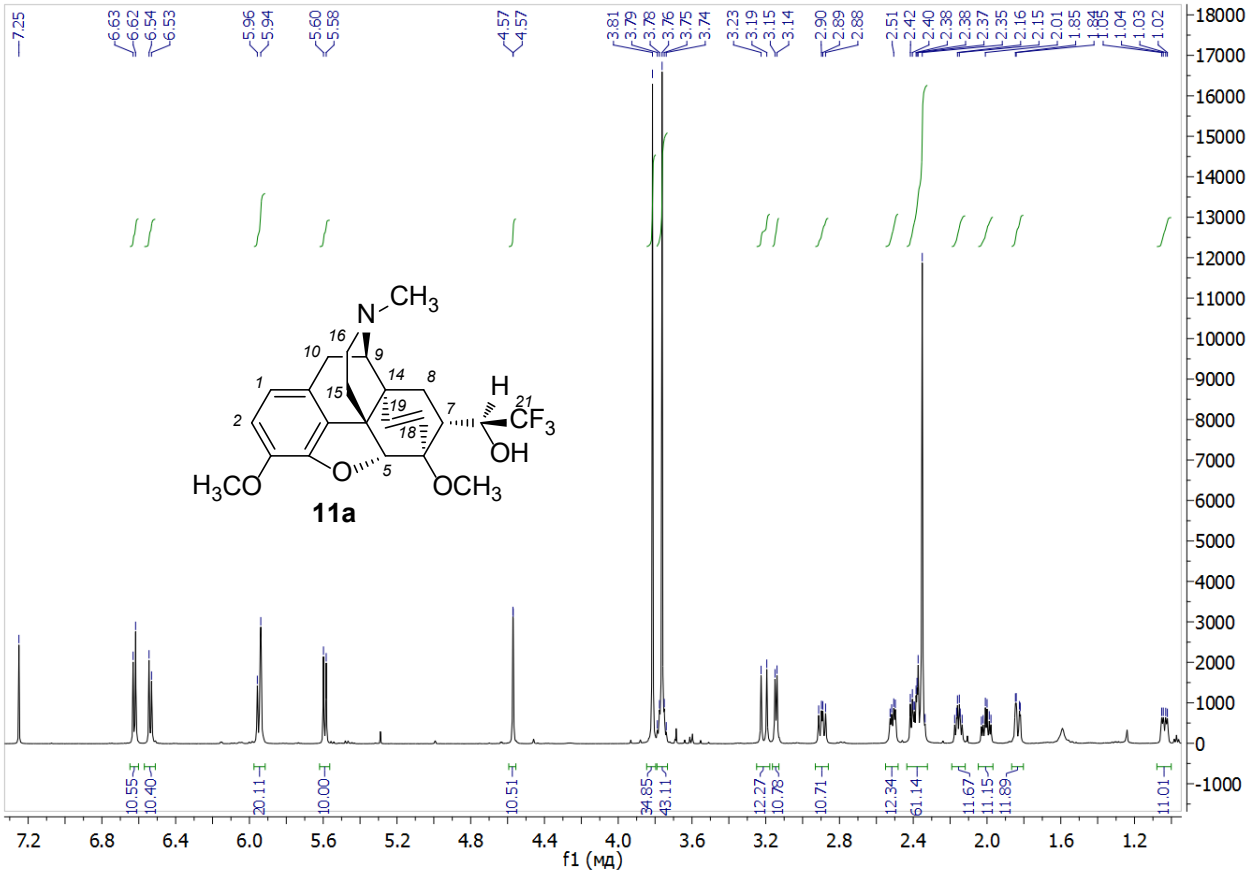


Figure 5. General view of the compound **17a** in representation of atoms *via* thermal ellipsoids at 50% probability level. Based on the absolute configuration of the asymmetric centres in the parent compound, the absolute configuration of the atom C(20) was identified as S. The dotted line shows an intramolecular hydrogen bond (O…O 2.622(2) Å, OHO 144.88(11)°).

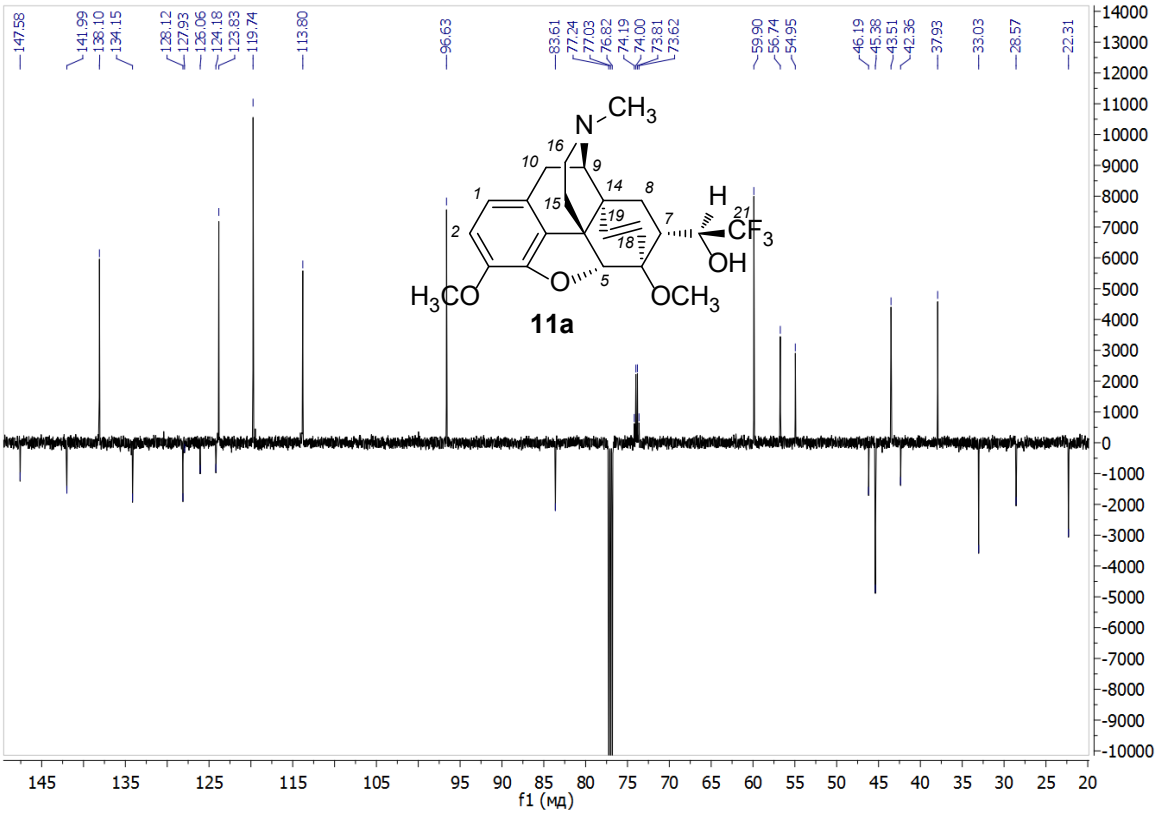
Crystal Data for $C_{27}H_{34}F_3NO_4$ (**17a**) (M =493.55 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.9944(2) Å, b = 11.8989(3) Å, c = 25.1140(6) Å, V = 2388.96(10) Å^3, Z = 4, T = 100 K, μ(MoKα) = 0.106 mm^{-1}, *Dcalc* = 1.372 g/cm^3, 25264 reflections measured (3.788° ≤ 2Θ ≤ 52°), 4694 unique (R_{int} = 0.0415, R_{sigma} = 0.0318) which were used in all calculations. The final R_1 was 0.0315 (I > 2σ(I)) and wR_2 was 0.0779 (all data).

5. NMR Spectra.

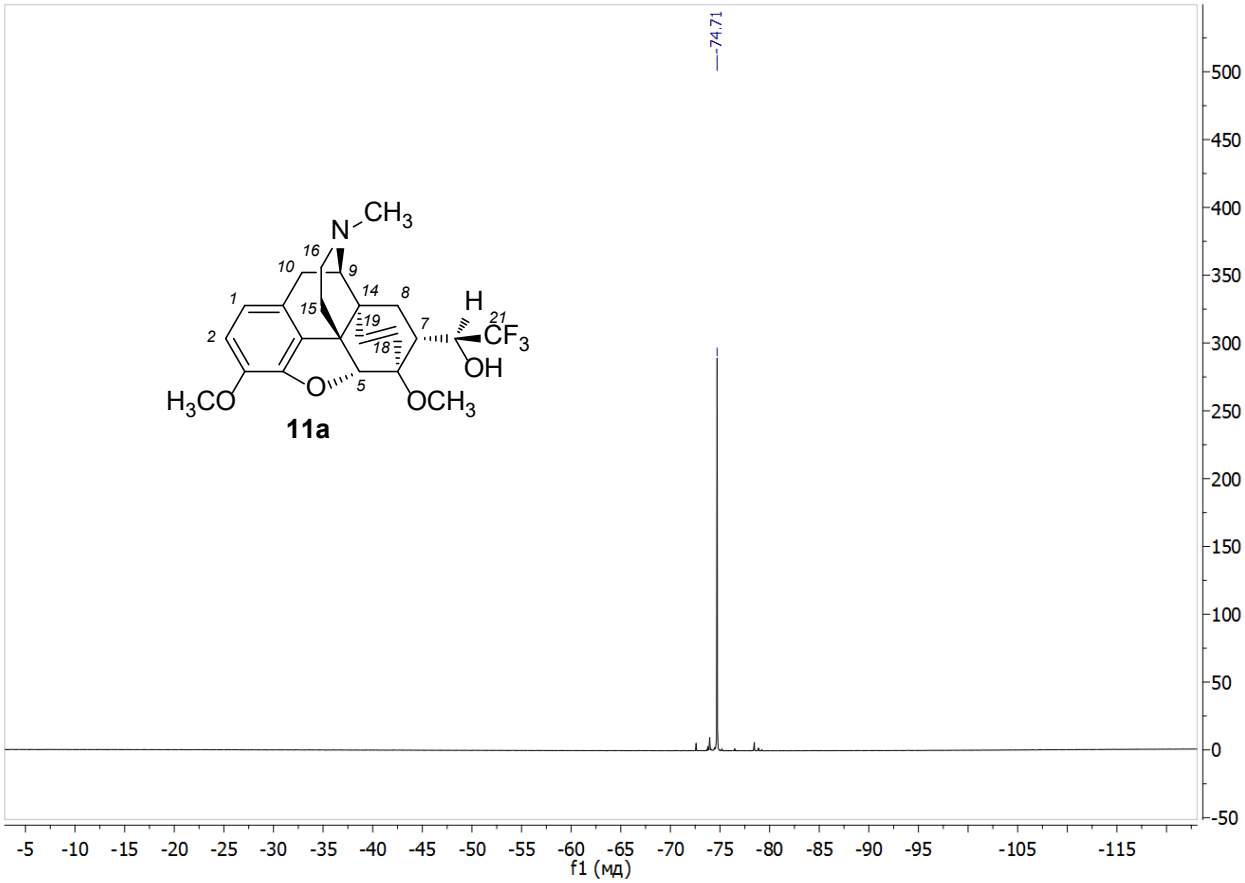
^{1}H NMR Spectrum of (5*R*,6*R*,7*R*,20*S*)-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (11a)



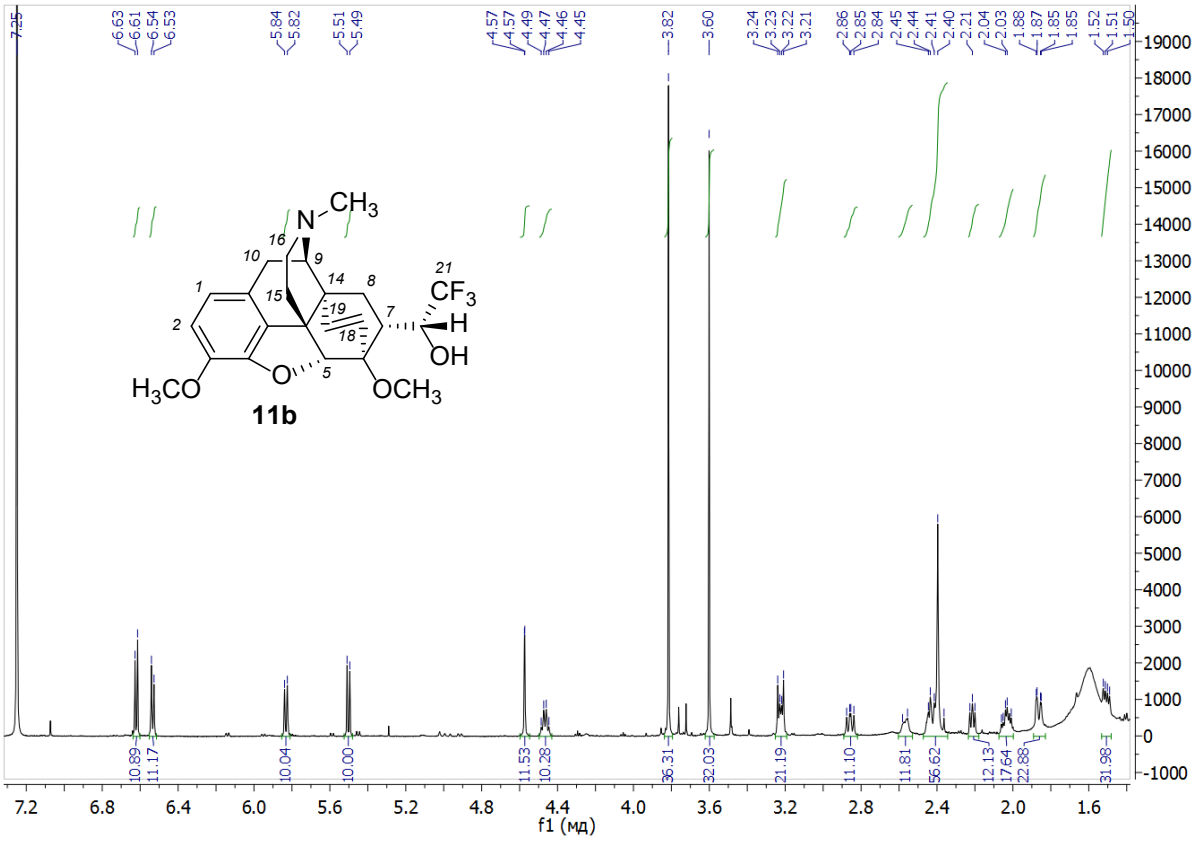
^{13}C (JMODECHO) NMR Spectrum of (5*R*,6*R*,7*R*,20*S*)-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (11a)



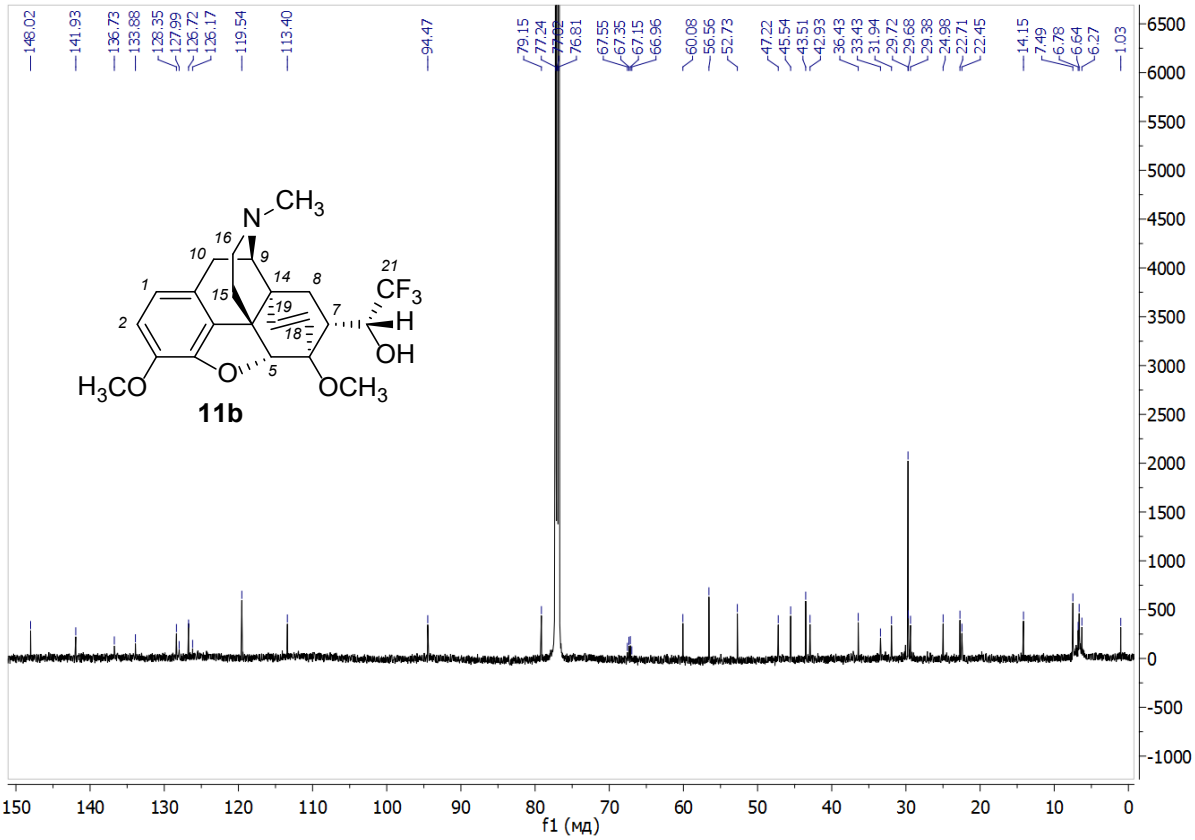
$^{19}F\{^{1}H\}$ NMR Spectrum of (5*R*,6*R*,7*R*,20*S*)-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (11a)



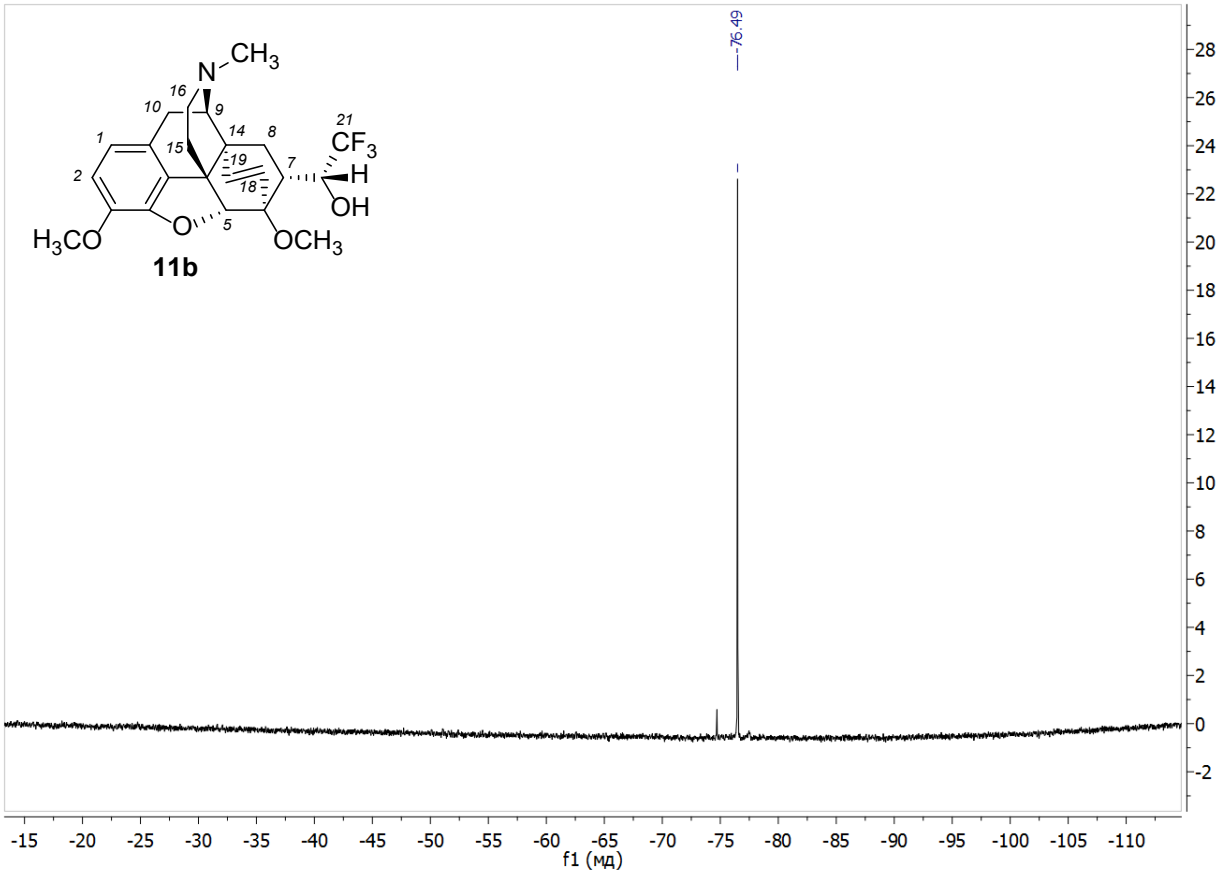
^{1}H NMR Spectrum of (5*R*,6*R*,7*R*,20*R*)-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (11b)



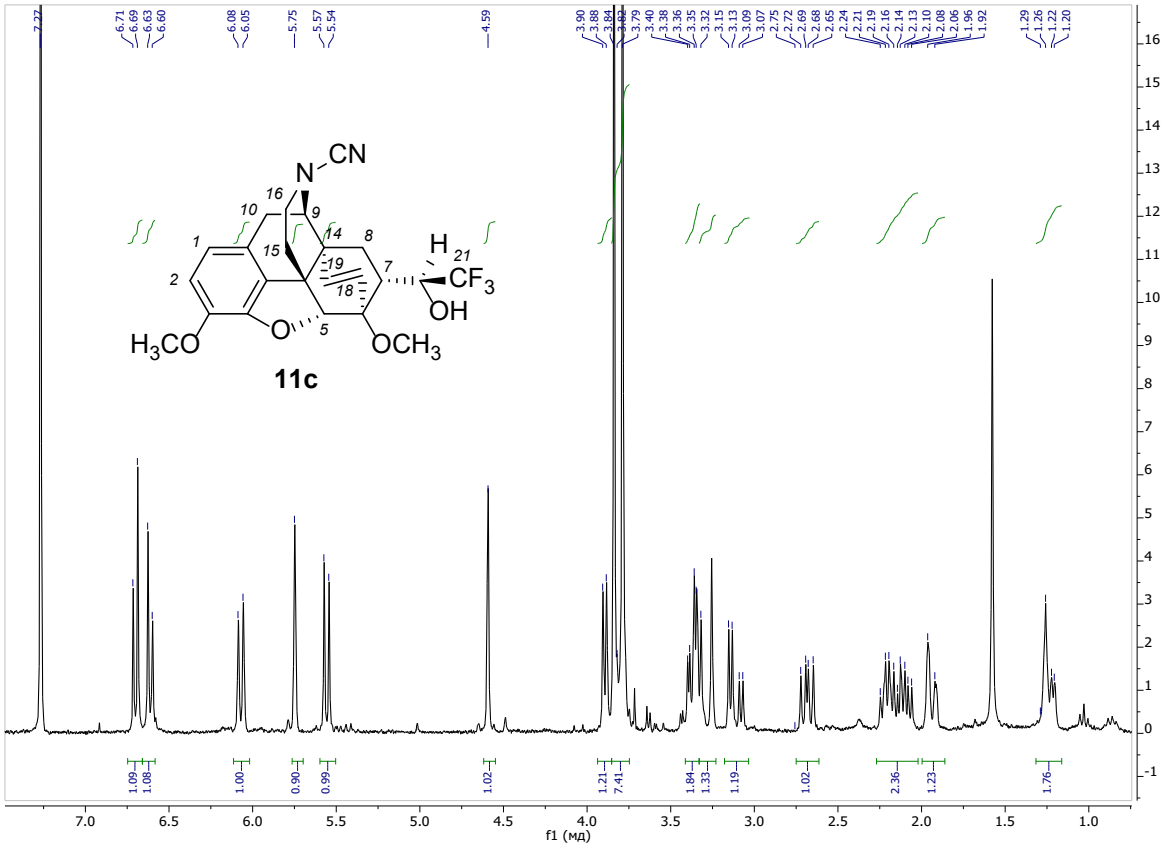
^{13}C NMR Spectrum of (5*R*,6*R*,7*R*,20*R*)-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (11b)



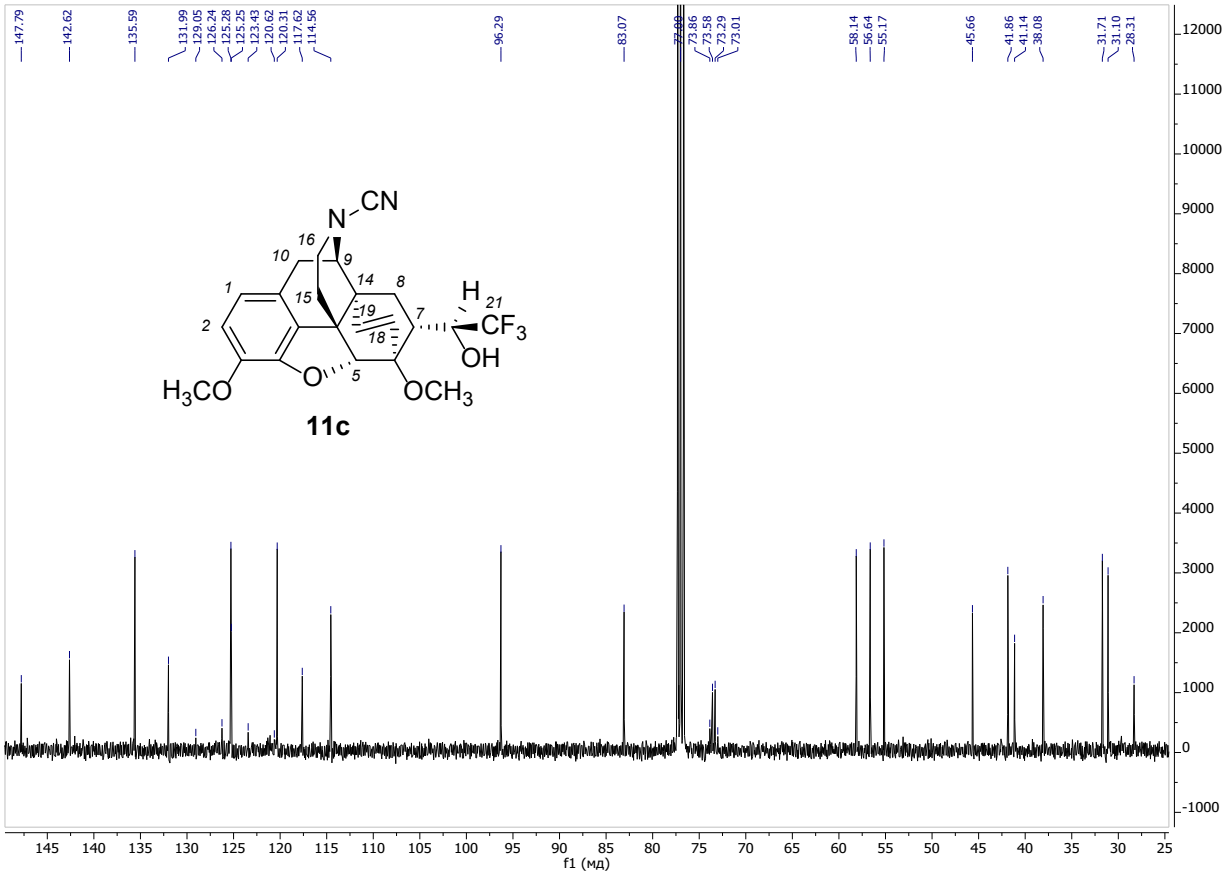
^{19}F{^{1}H} NMR Spectrum of (5*R*,6*R*,7*R*,20*R*)-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (11b)



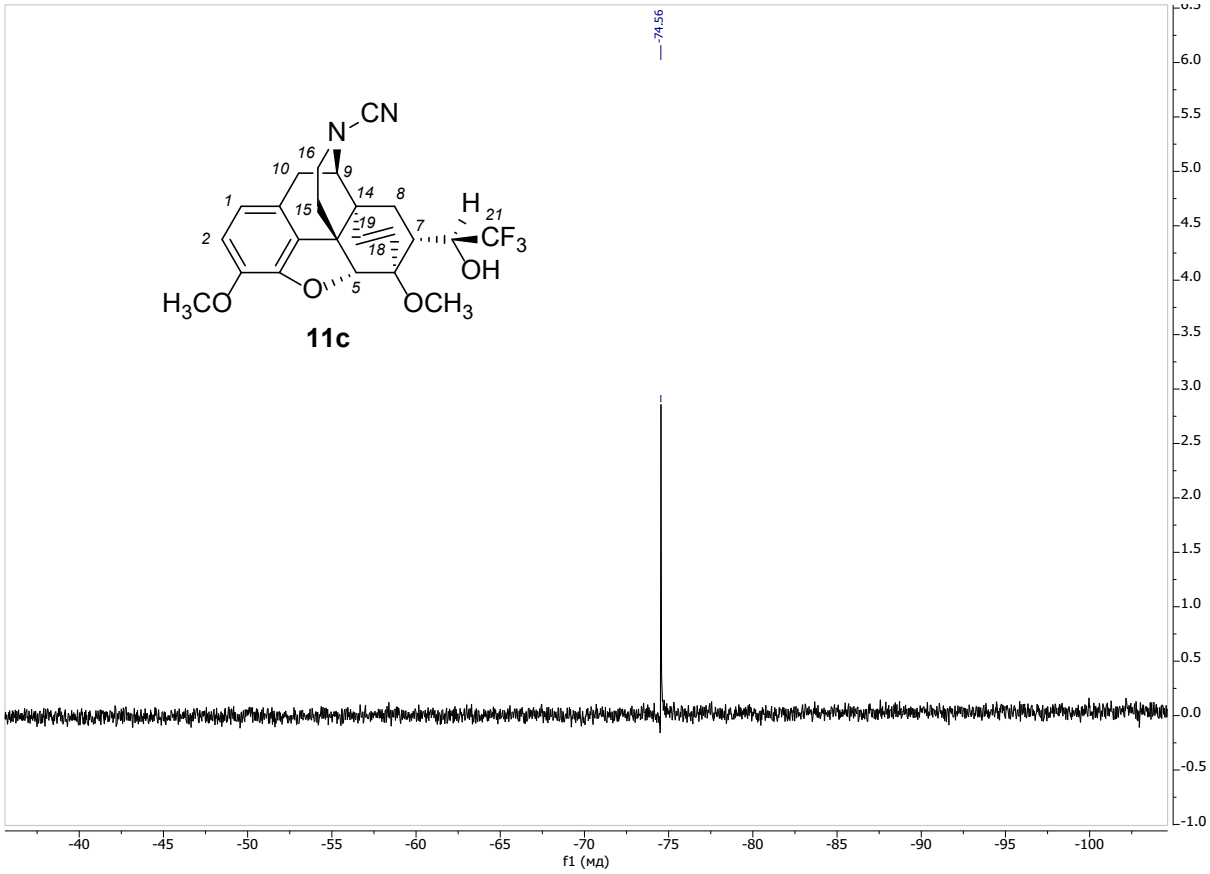
^{1}H NMR Spectrum of (5*R*,6*R*,7*R*,20*S*)-17-cyano-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-6,14-ethenoisomorphinan (11c):



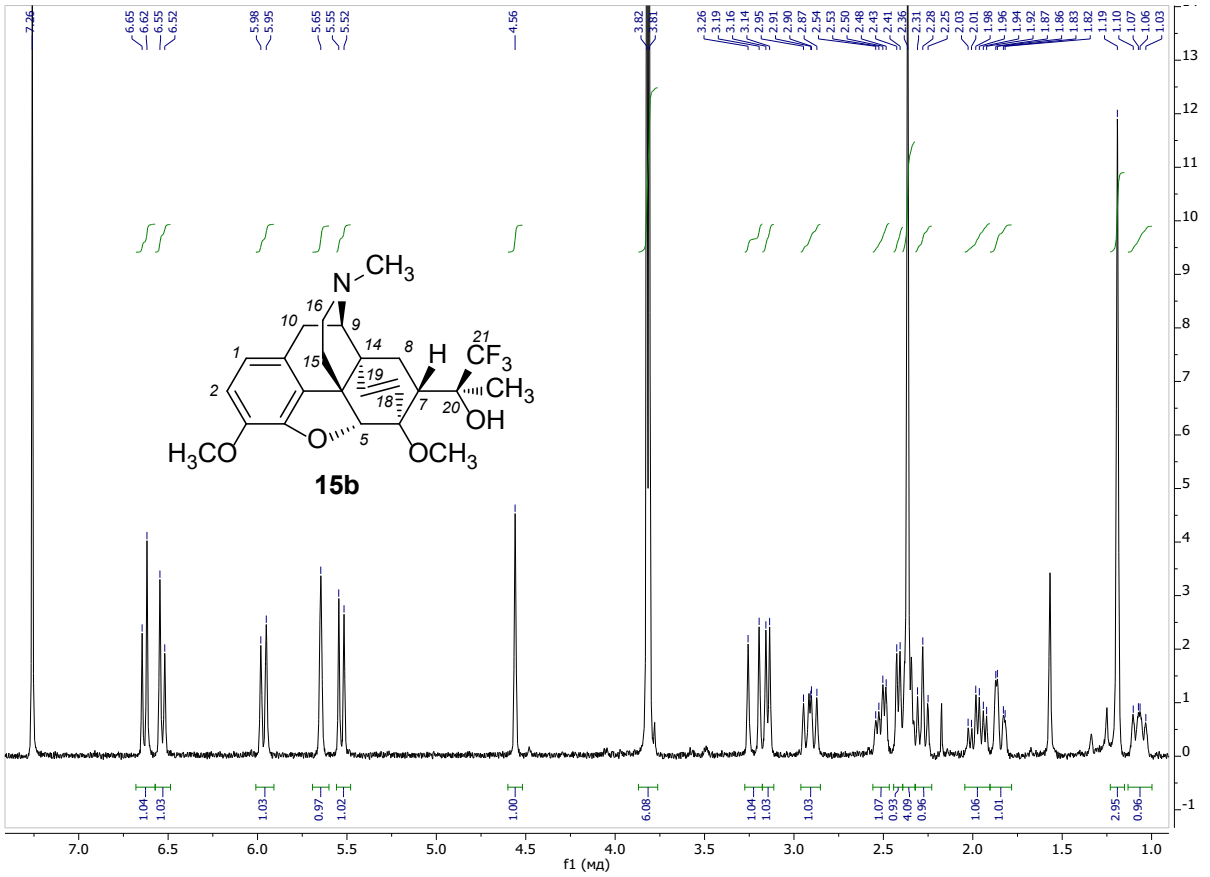
^{13}C NMR Spectrum of (5*R*,6*R*,7*R*,20*S*)-17-cyano-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-6,14-ethenoisomorphinan (11c):



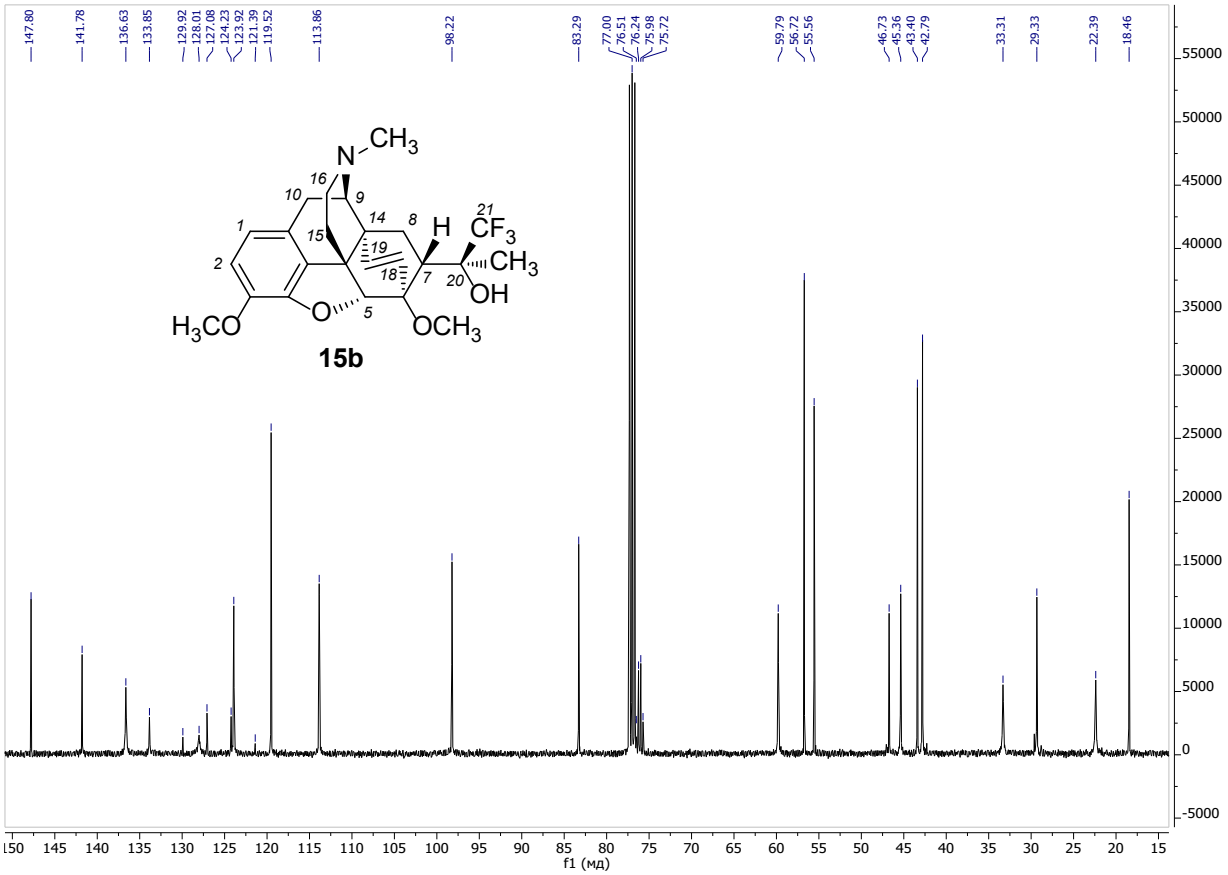
^{19}F NMR Spectrum of (5*R*,6*R*,7*R*,20*S*)-17-cyano-4,5-epoxy-7-(1-hydroxy-2,2,2-trifluoroethyl)-3,6-dimethoxy-6,14-ethenoisomorphinan (11c):



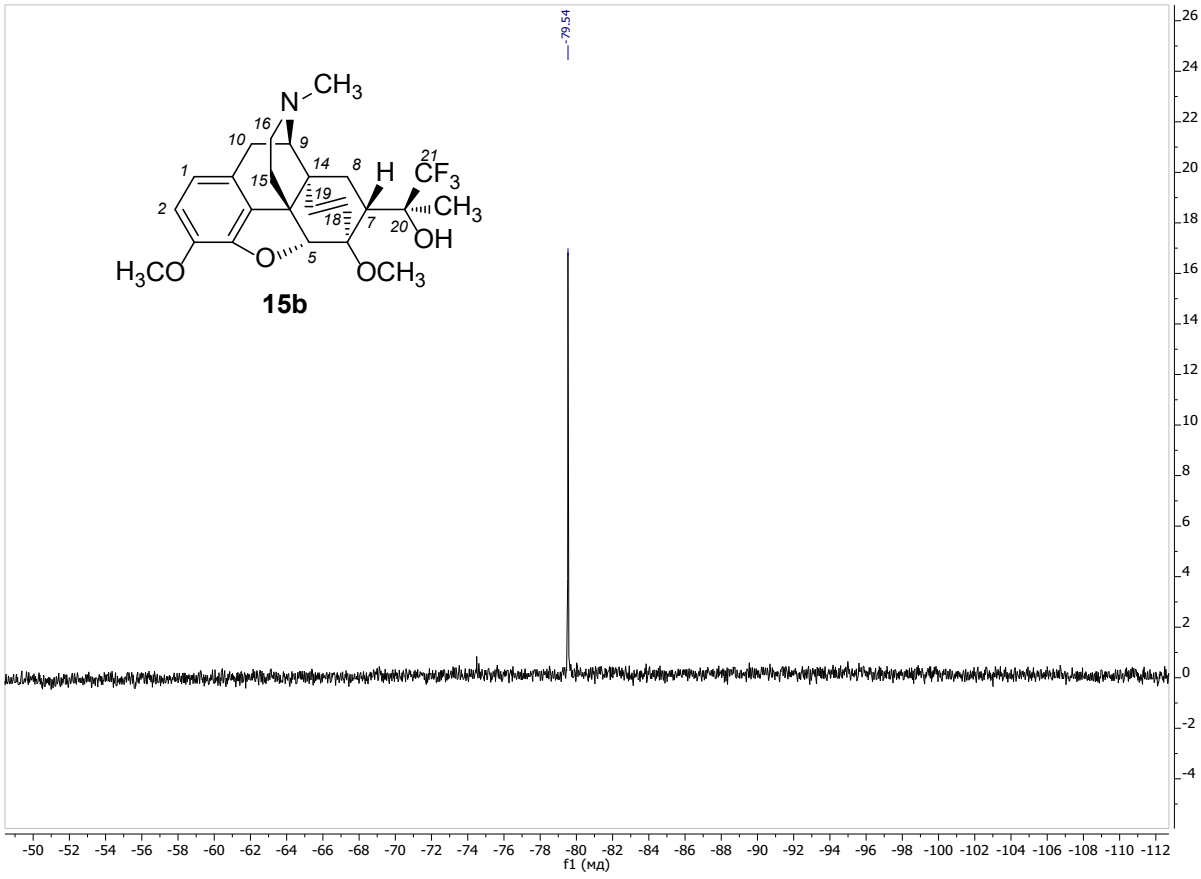
^{1}H NMR Spectrum of (5R,6R,7R,20S)-4,5-epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (15b):



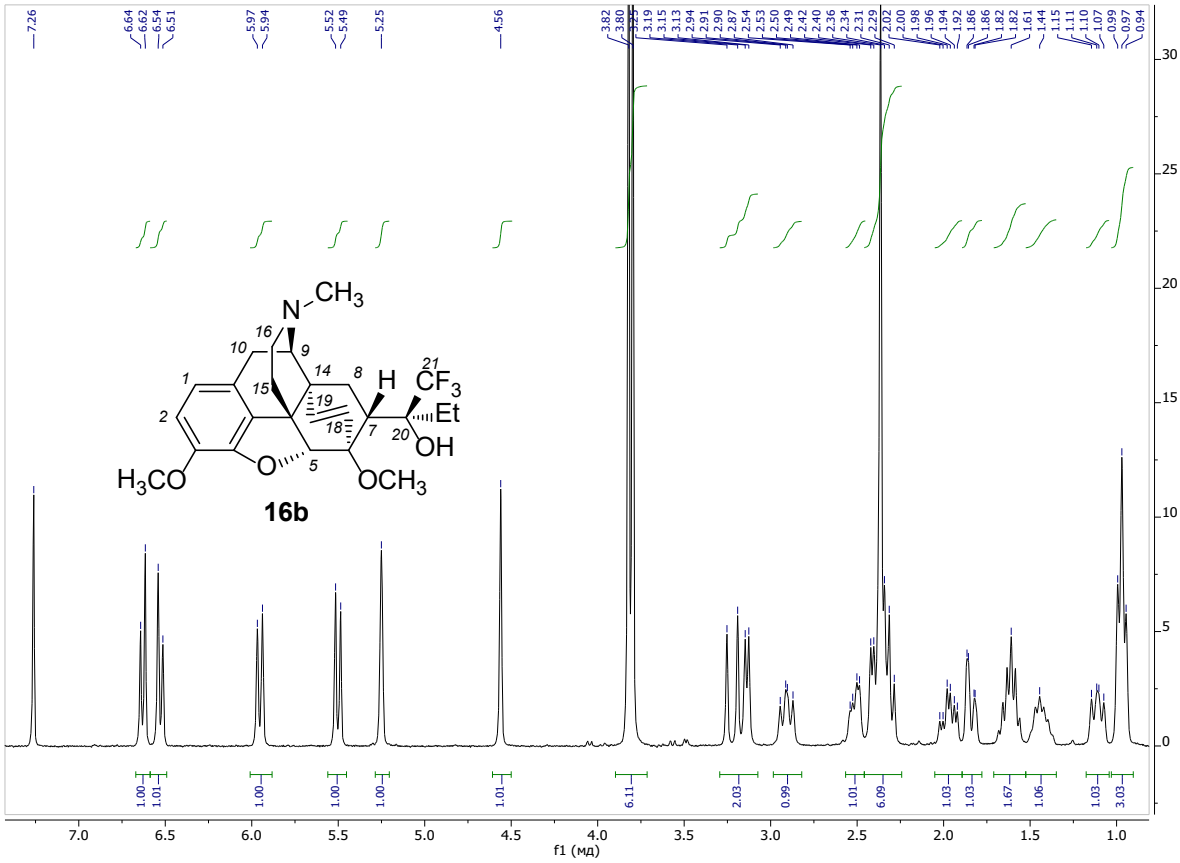
^{13}C NMR Spectrum of (5R,6R,7R,20S)-4,5-epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (15b):



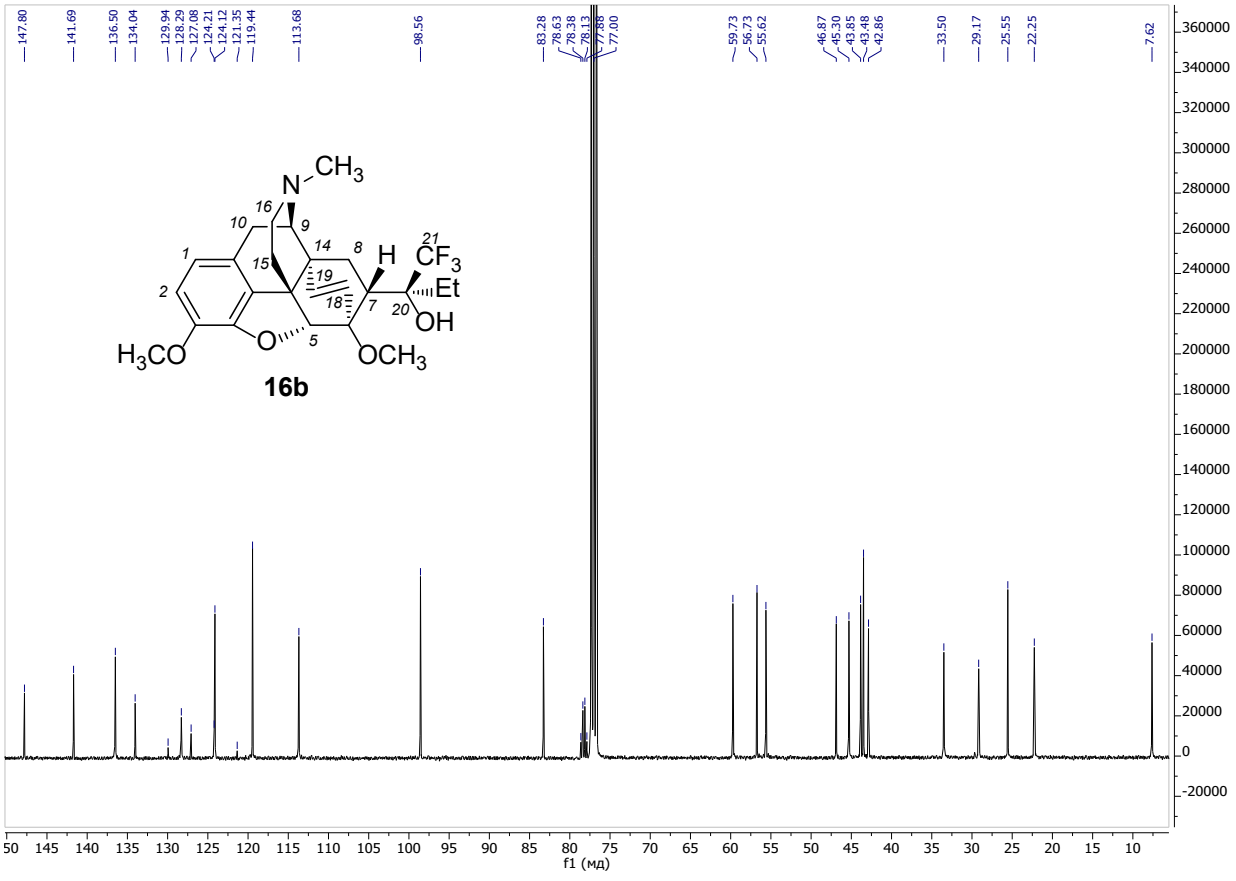
^{19}F NMR Spectrum of (5R,6R,7R,20S)-4,5-epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (15b):



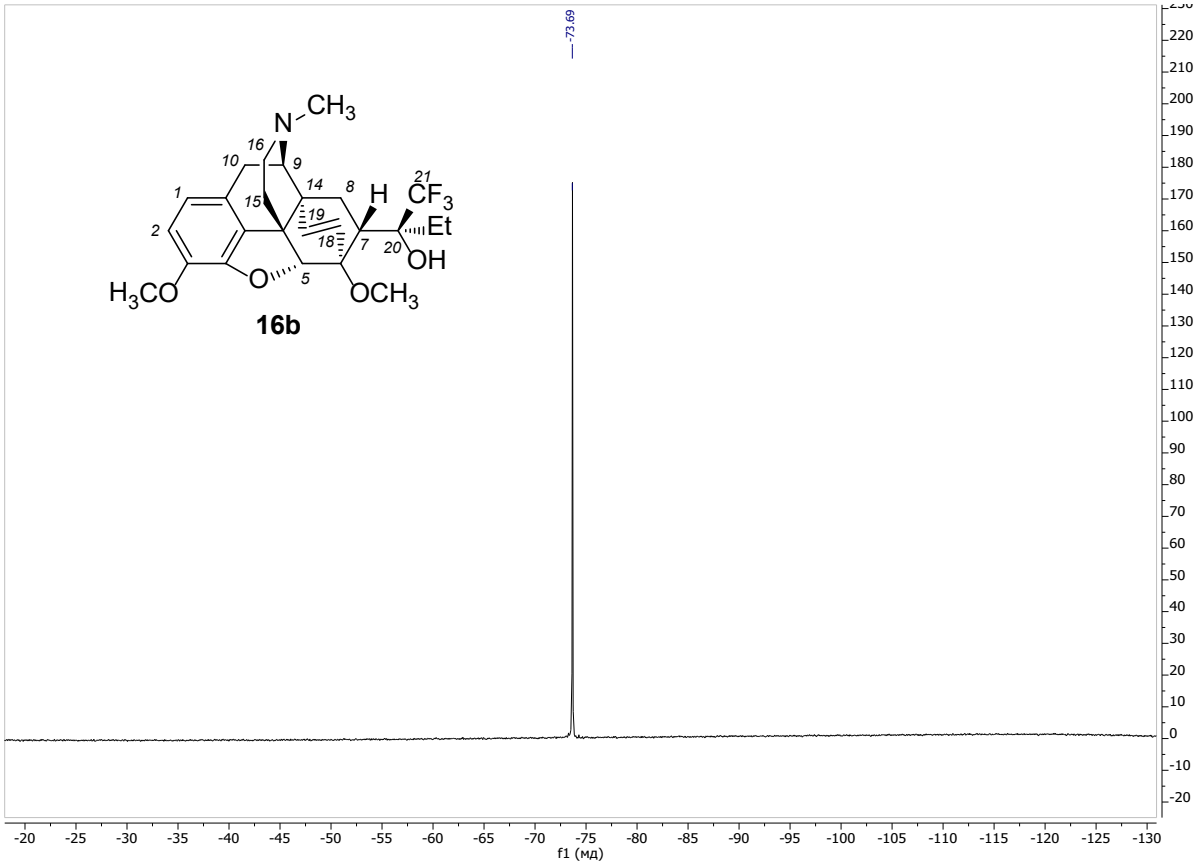
^{1}H NMR Spectrum of *(5R,6R,7R,20S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)- 6,14-ethenoisomorphinan (16b):



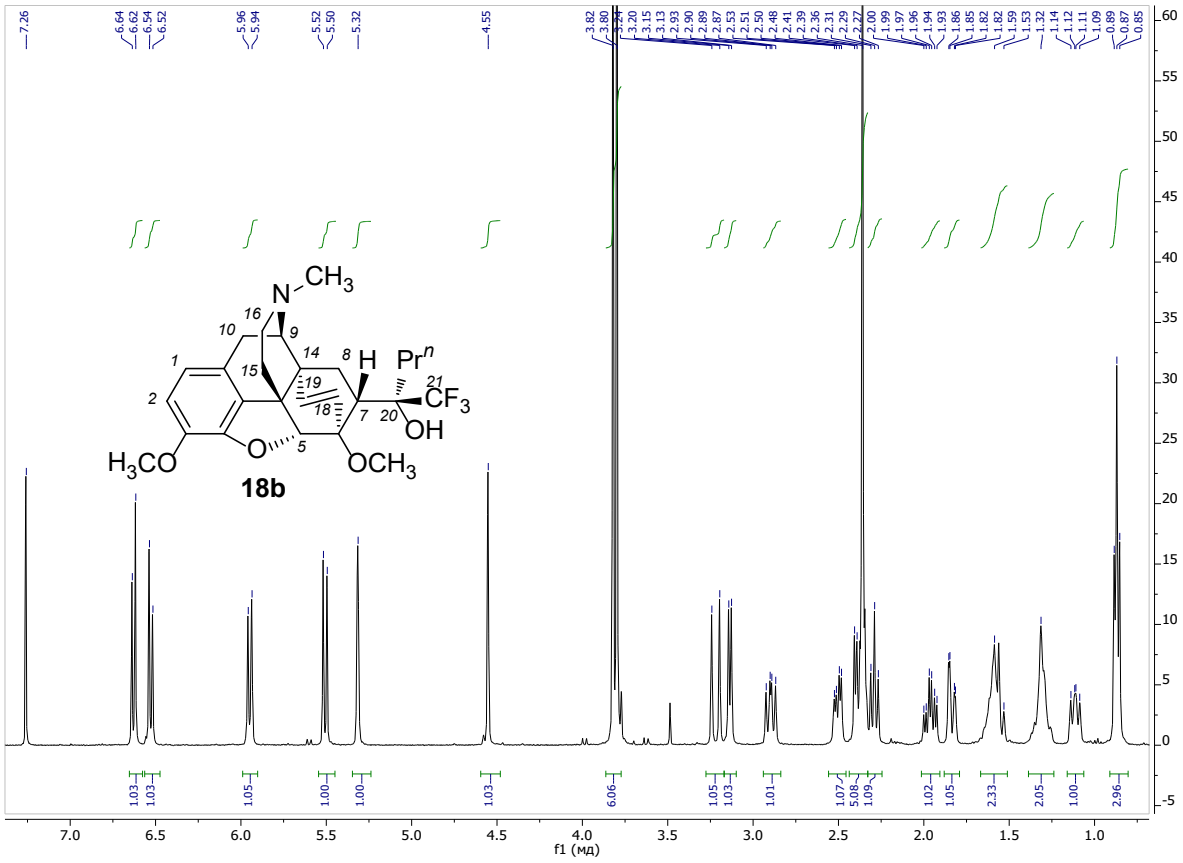
^{13}C NMR Spectrum of *(5R,6R,7R,20S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)- 6,14-ethenoisomorphinan (16b):



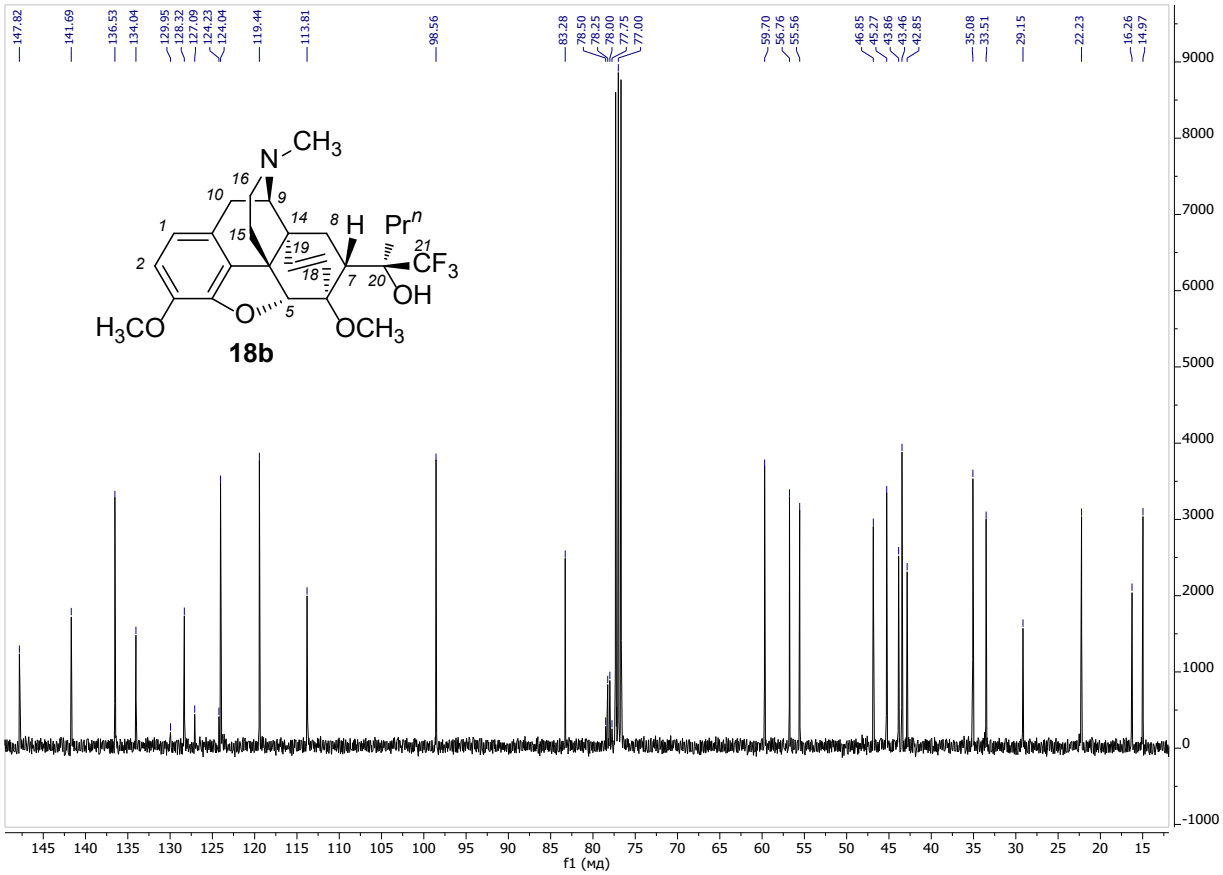
^{19}F NMR Spectrum of *(5R,6R,7R,20S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)- 6,14-ethenoisomorphinan (16b):



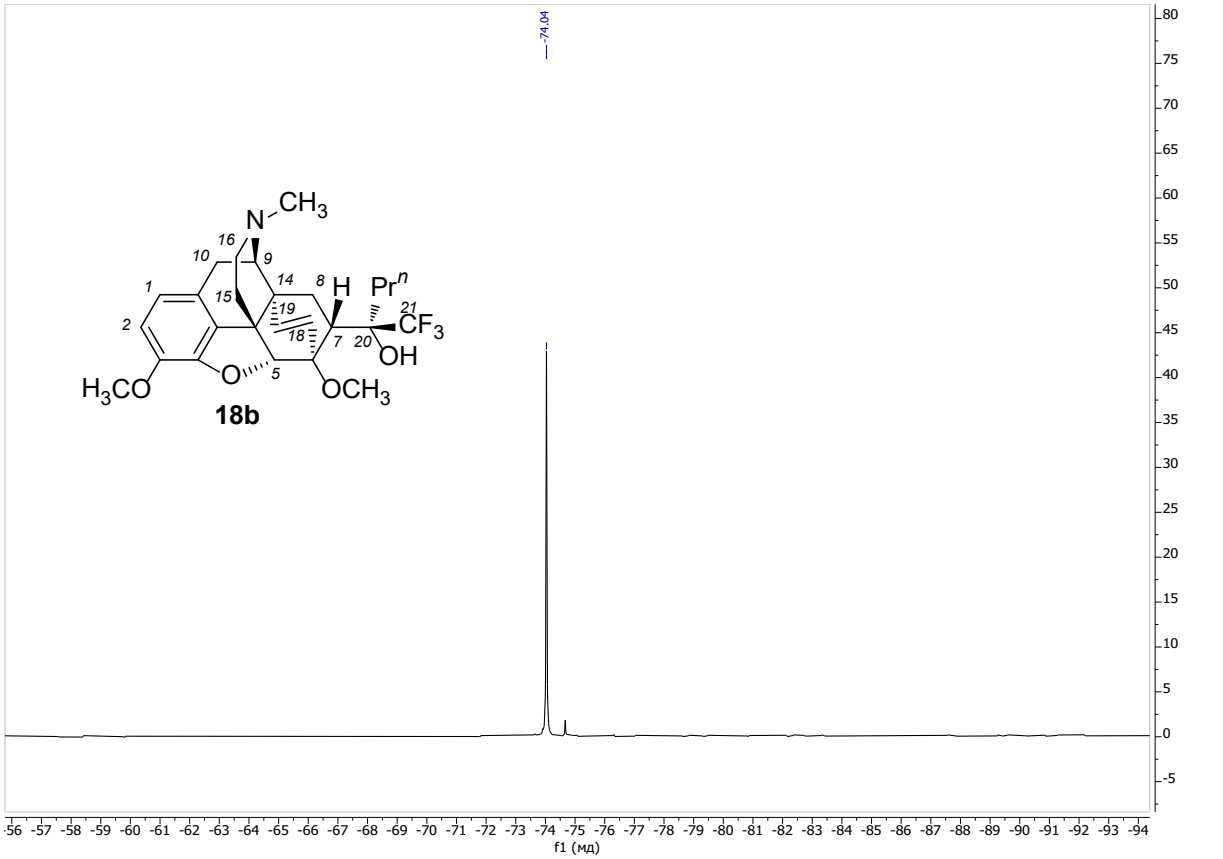
^{1}H NMR Spectrum of *(5R,6R,7R,20S)*-7-(1-hydroxy-1-(trifluoromethyl)butyl)-4,5-epoxy-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (18b):



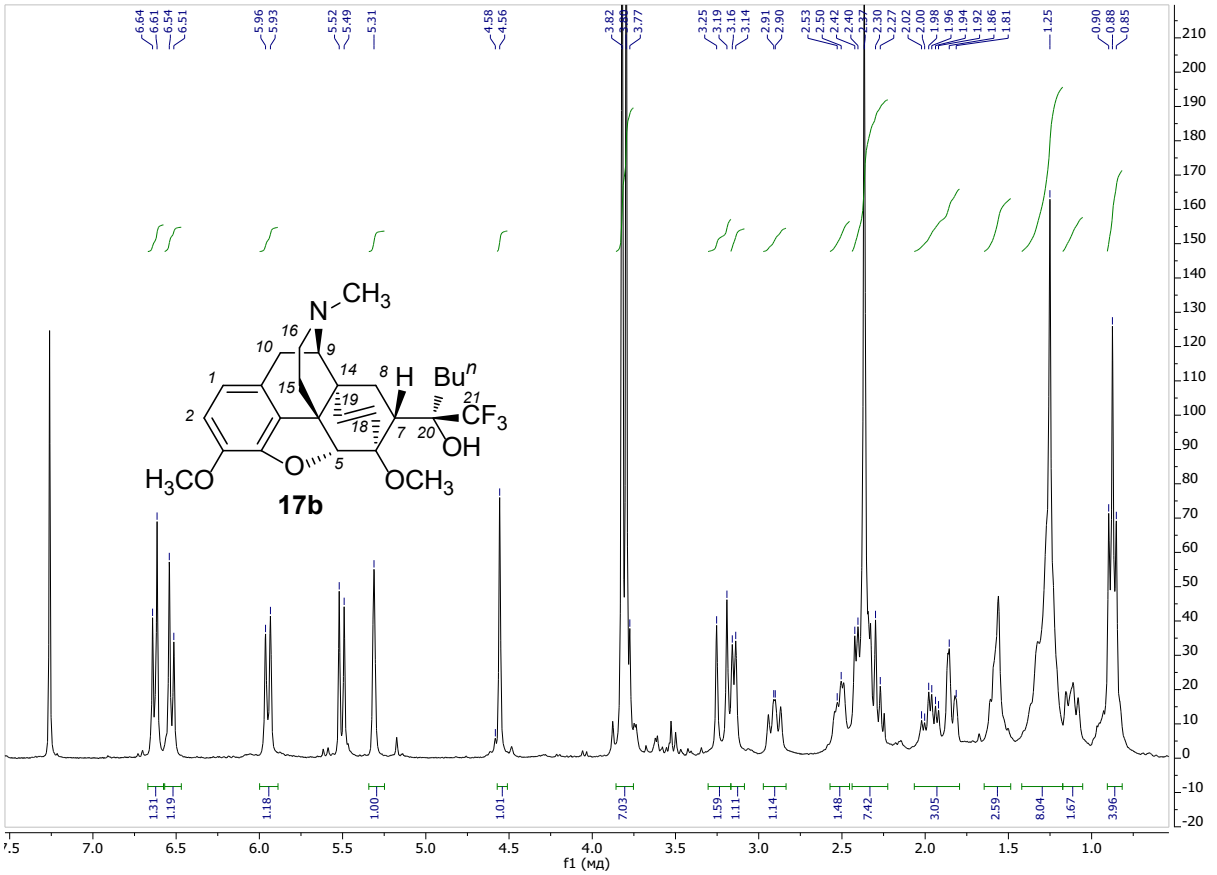
^{13}C NMR Spectrum of *(5R,6R,7R,20S)*-7-(1-hydroxy-1-(trifluoromethyl)butyl)-4,5-epoxy-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (18b):



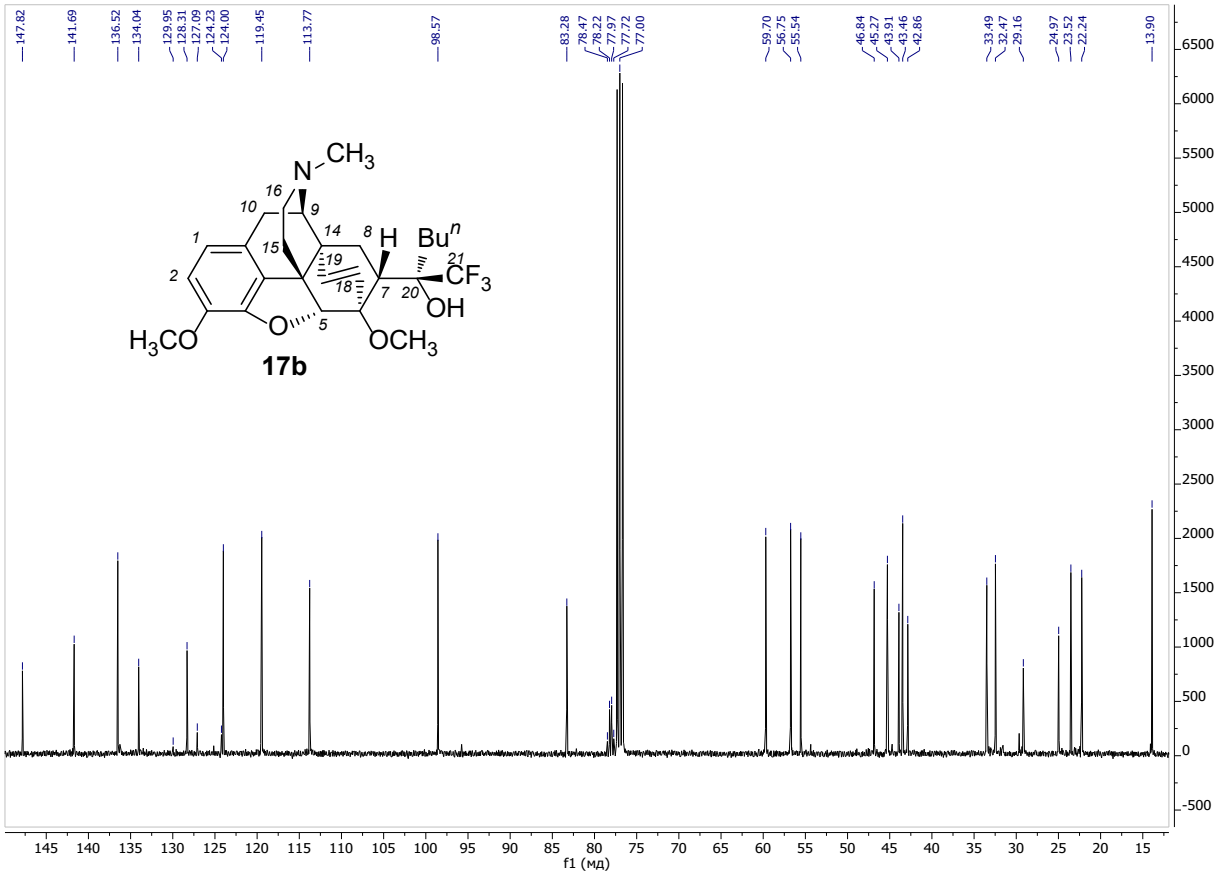
^{19}F NMR Spectrum of *(5R,6R,7R,20S)*-7-(1-hydroxy-1-(trifluoromethyl)butyl)-4,5-epoxy-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (18b):



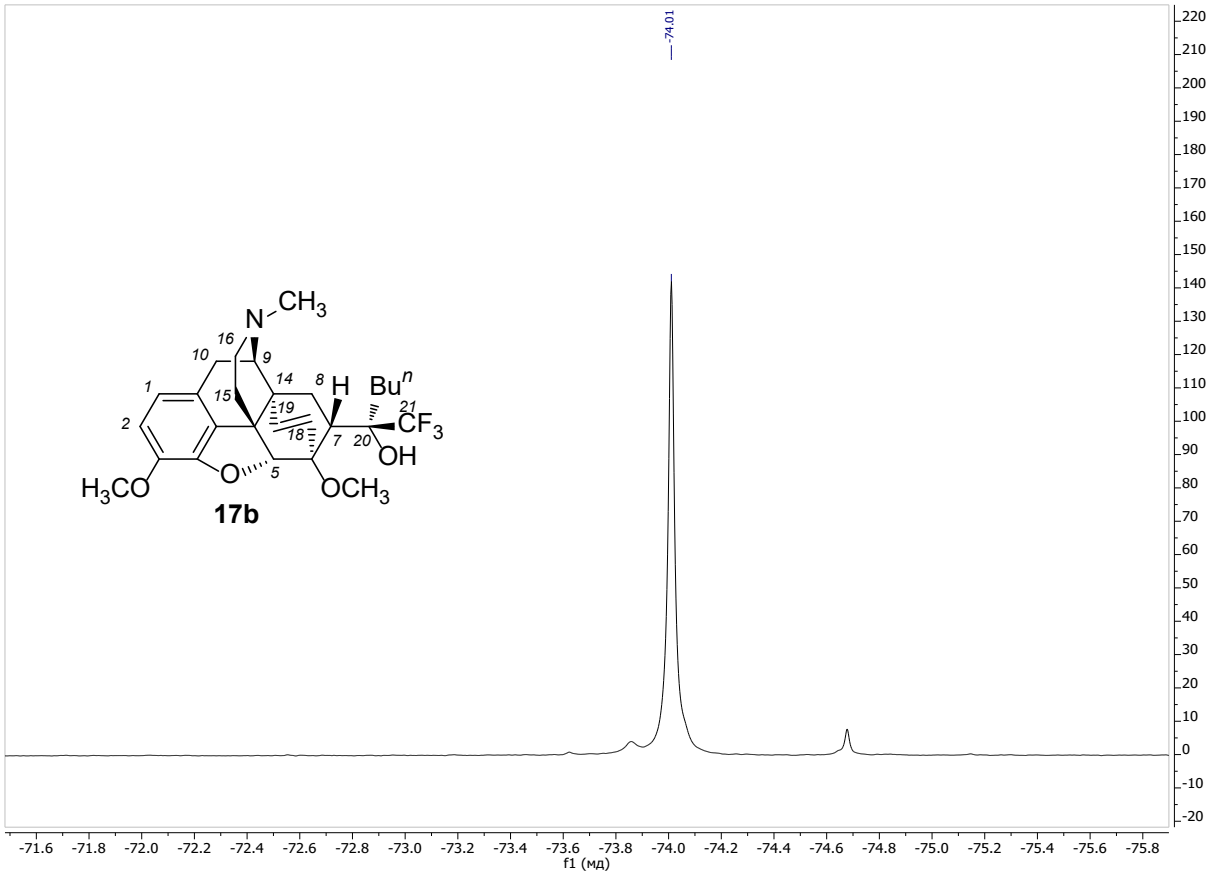
^{1}H NMR Spectrum of *(5R,6R,7R,20S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)pentyl)-6,14-ethenoisomorphinan (17b):



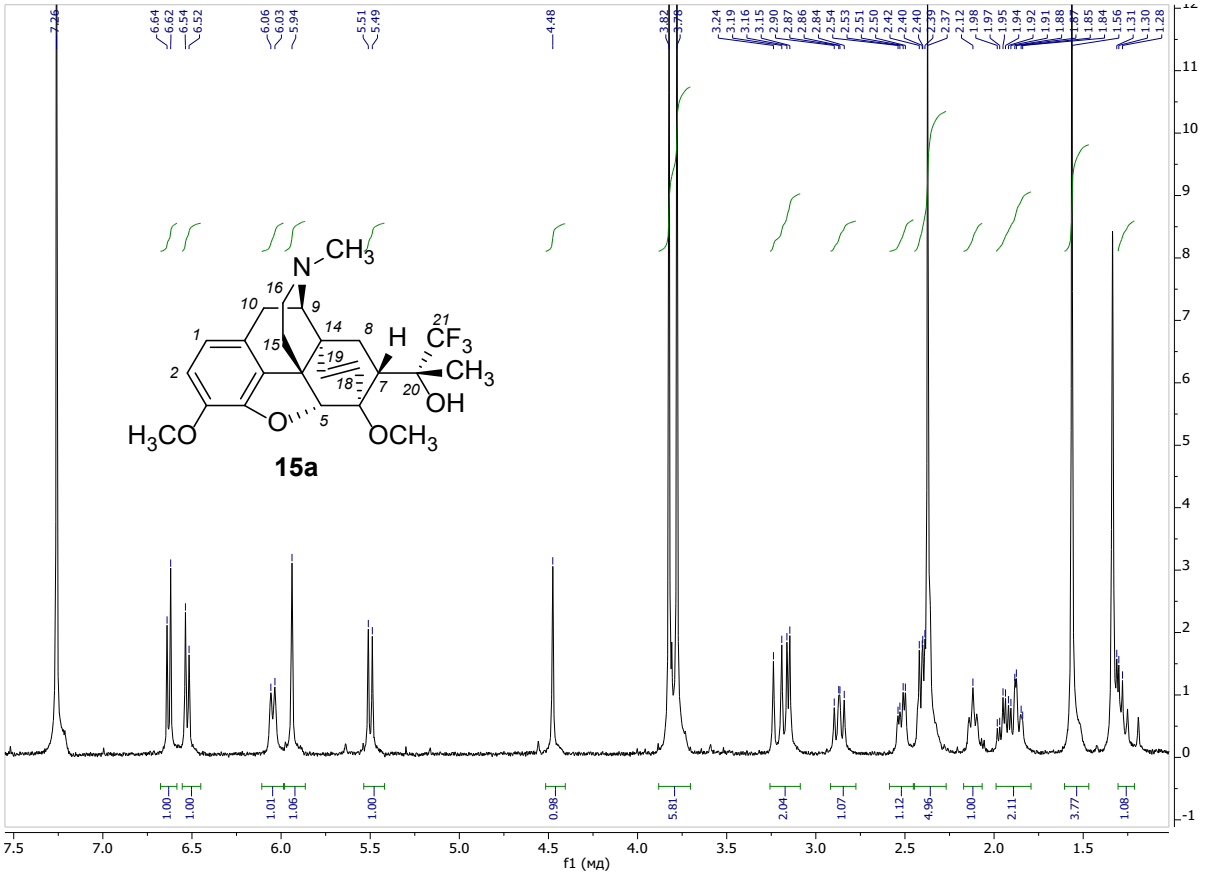
^{13}C NMR Spectrum of *(5R,6R,7R,20S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)pentyl)-6,14-ethenoisomorphinan (17b):



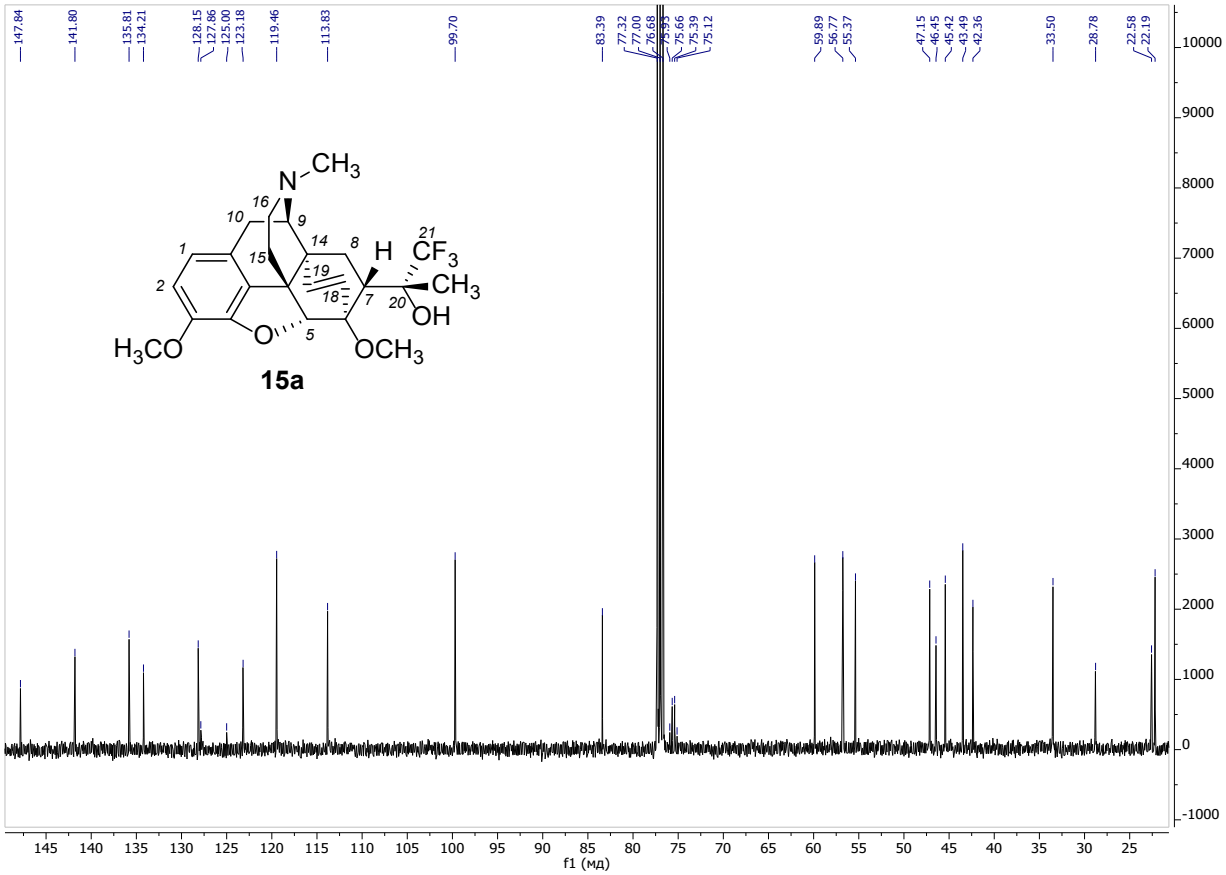
^{19}F NMR Spectrum of *(5R,6R,7R,20S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)pentyl)-6,14-ethenoisomorphinan (17b):



^{1}H NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (15a):

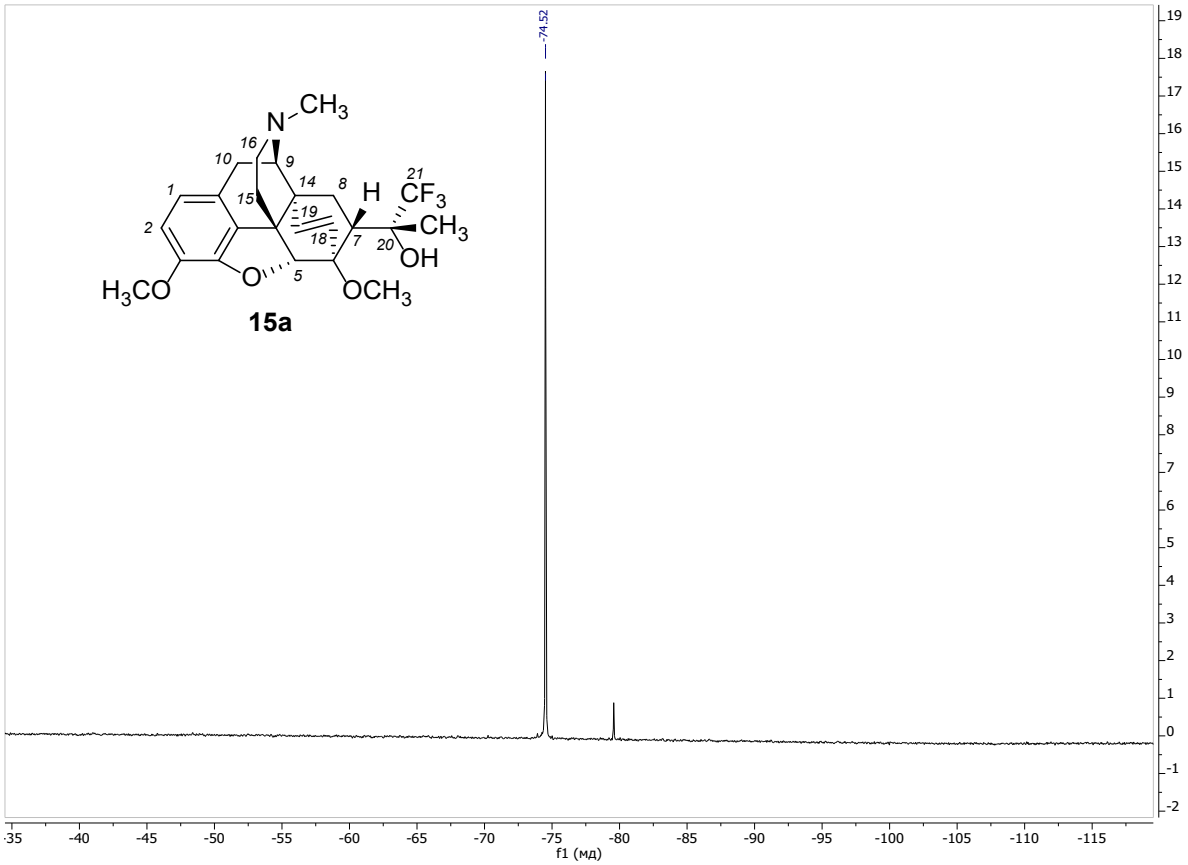


^{13}C NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (15a):



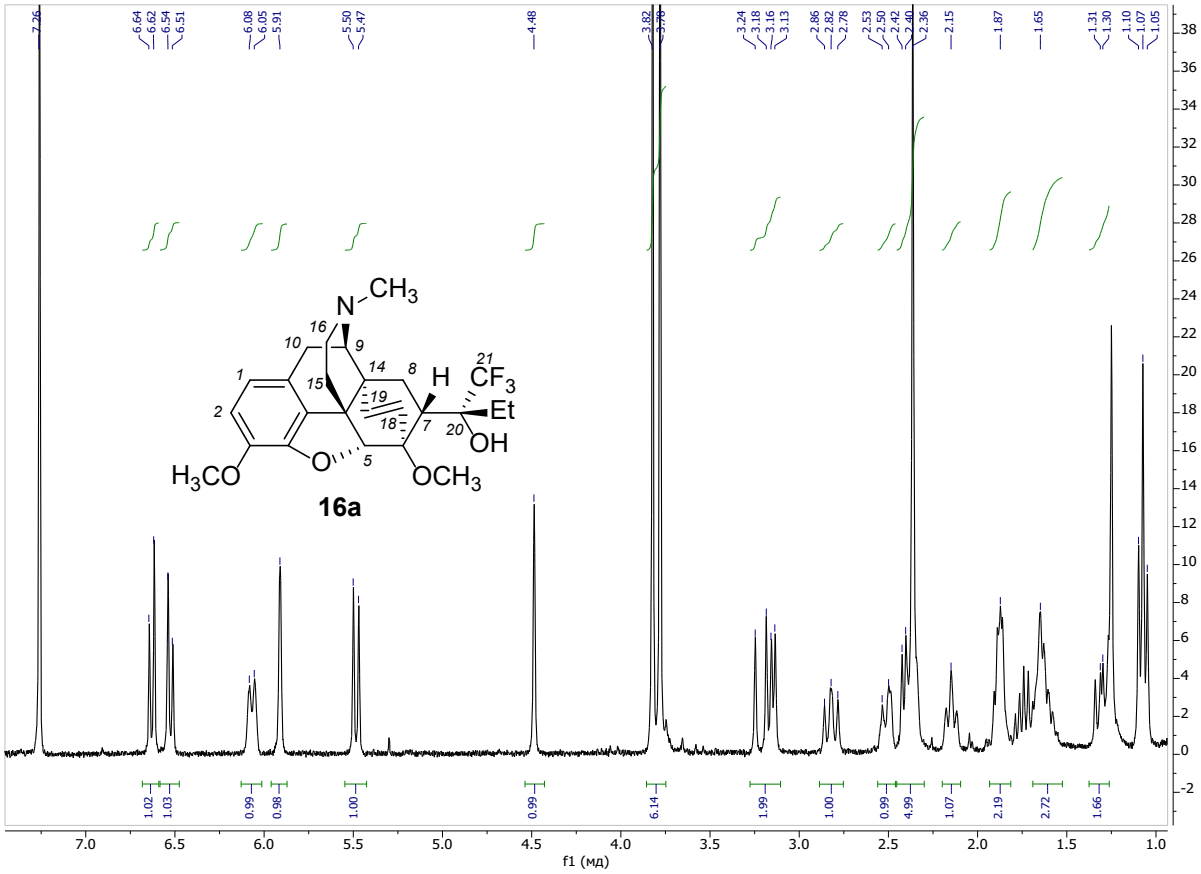
15a

^{19}F NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-7-(1-hydroxy-1-methyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (15a):

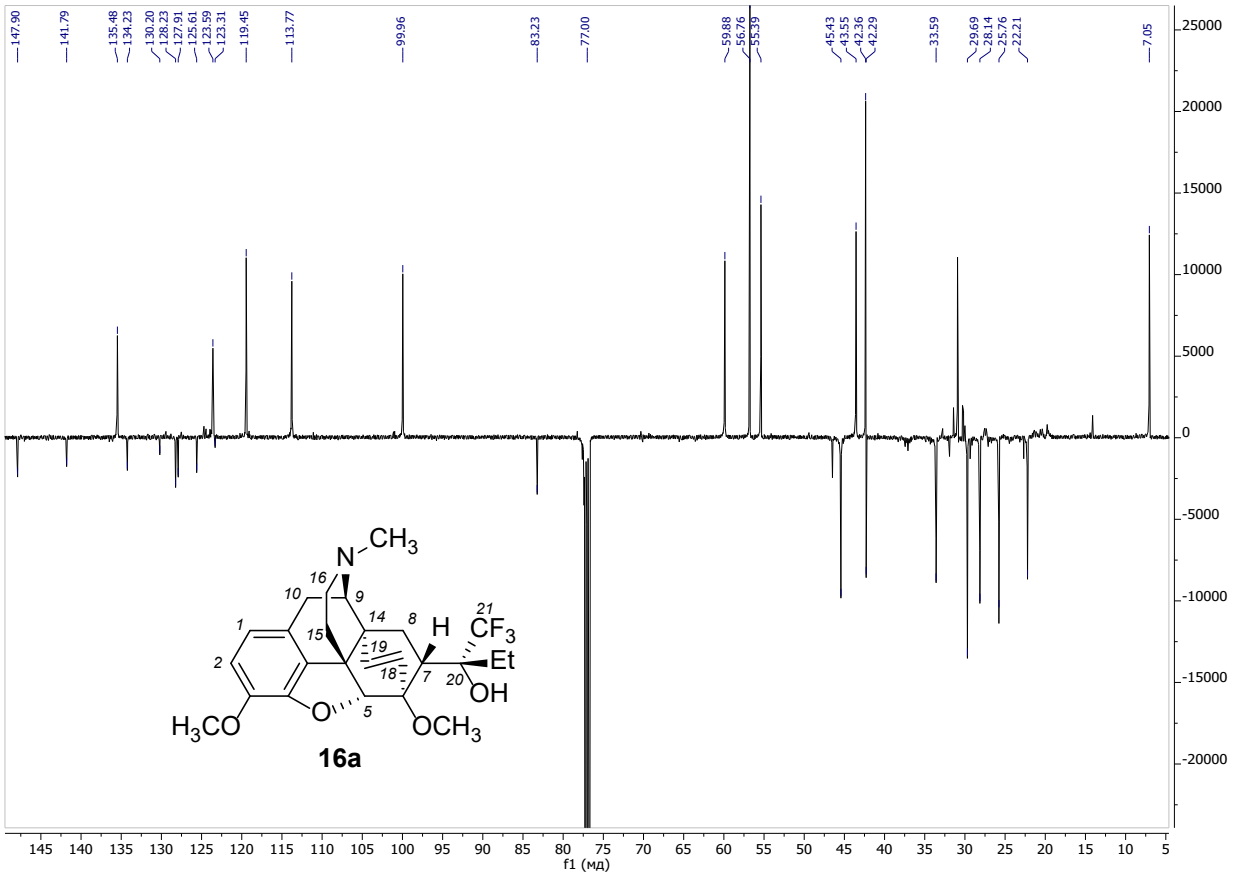


15a

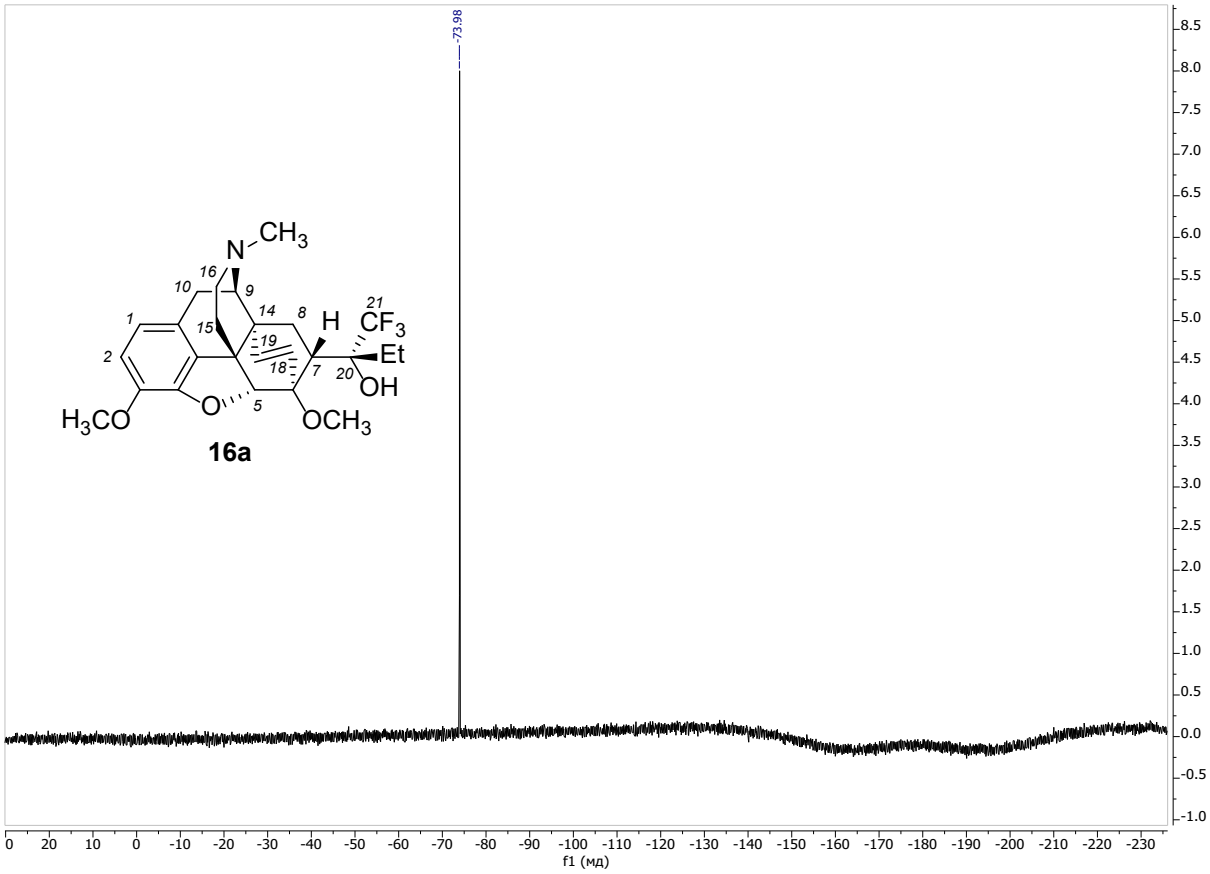
^{1}H NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-7-(1-hydroxy-1-(trifluoromethyl)ethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (16a):



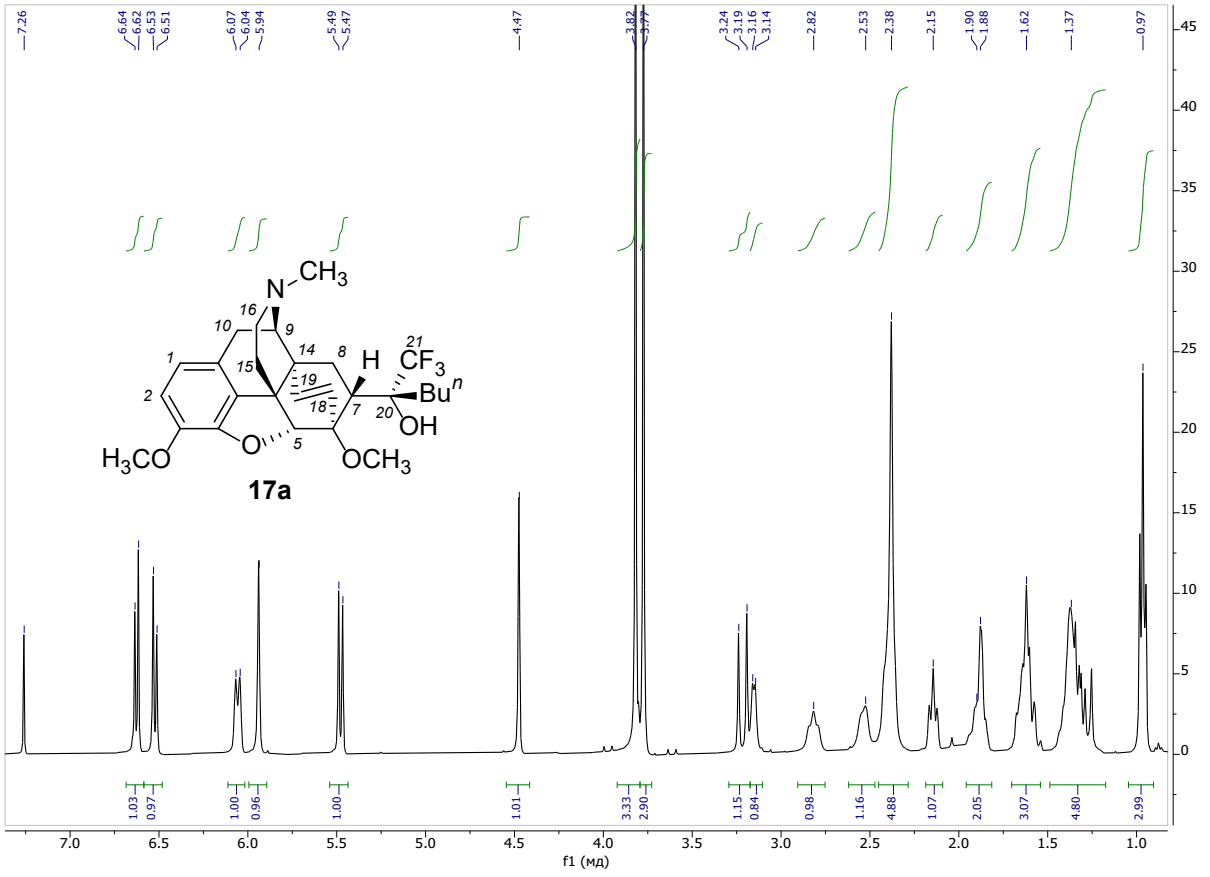
^{13}C (JMODECHO) NMR Spectrum of*(5R,6R,7R,20R)*-4,5-epoxy-7-(1-hydroxy-1-(trifluoromethyl)ethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (16a):



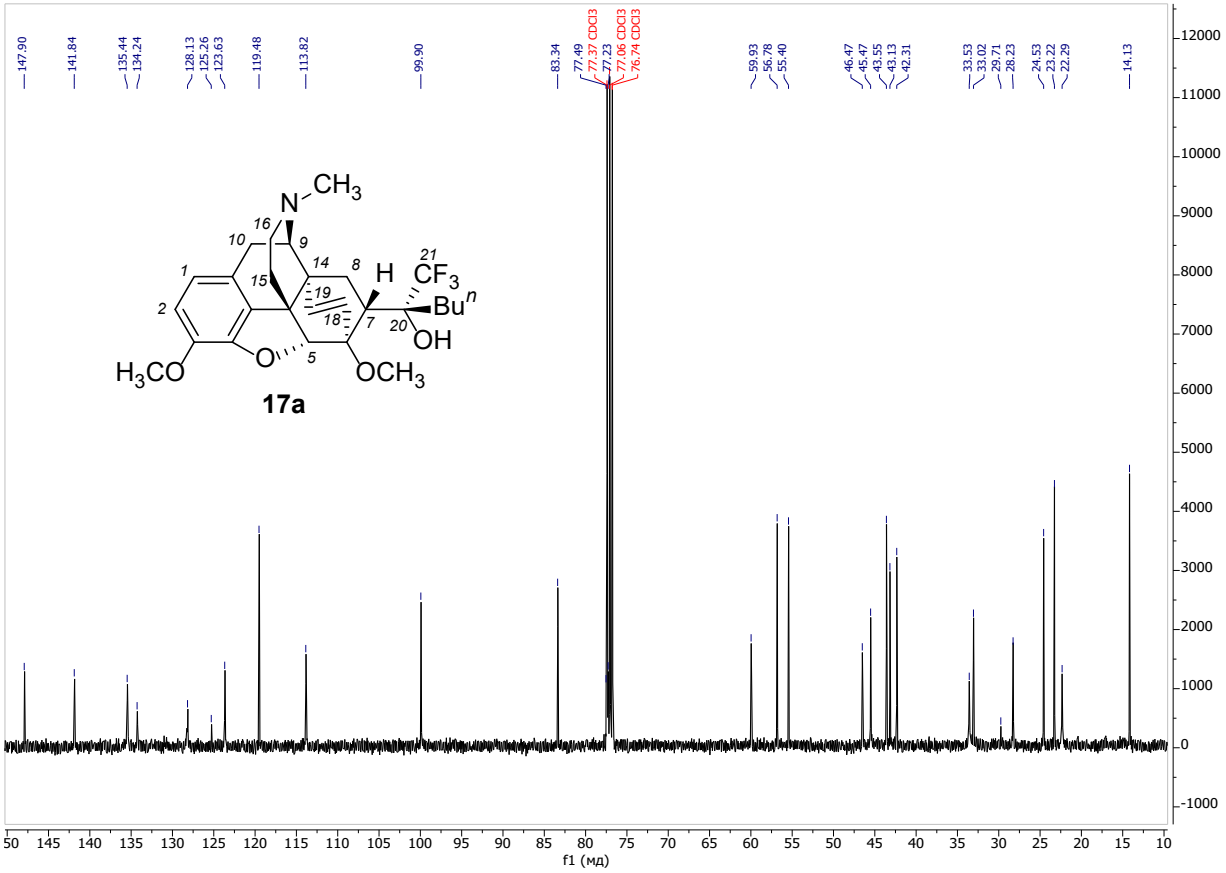
^{19}F NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-7-(1-hydroxy-1-(trifluoromethyl)ethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (16a):



^{1}H NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)- 6,14-ethenoisomorpninane (17a):

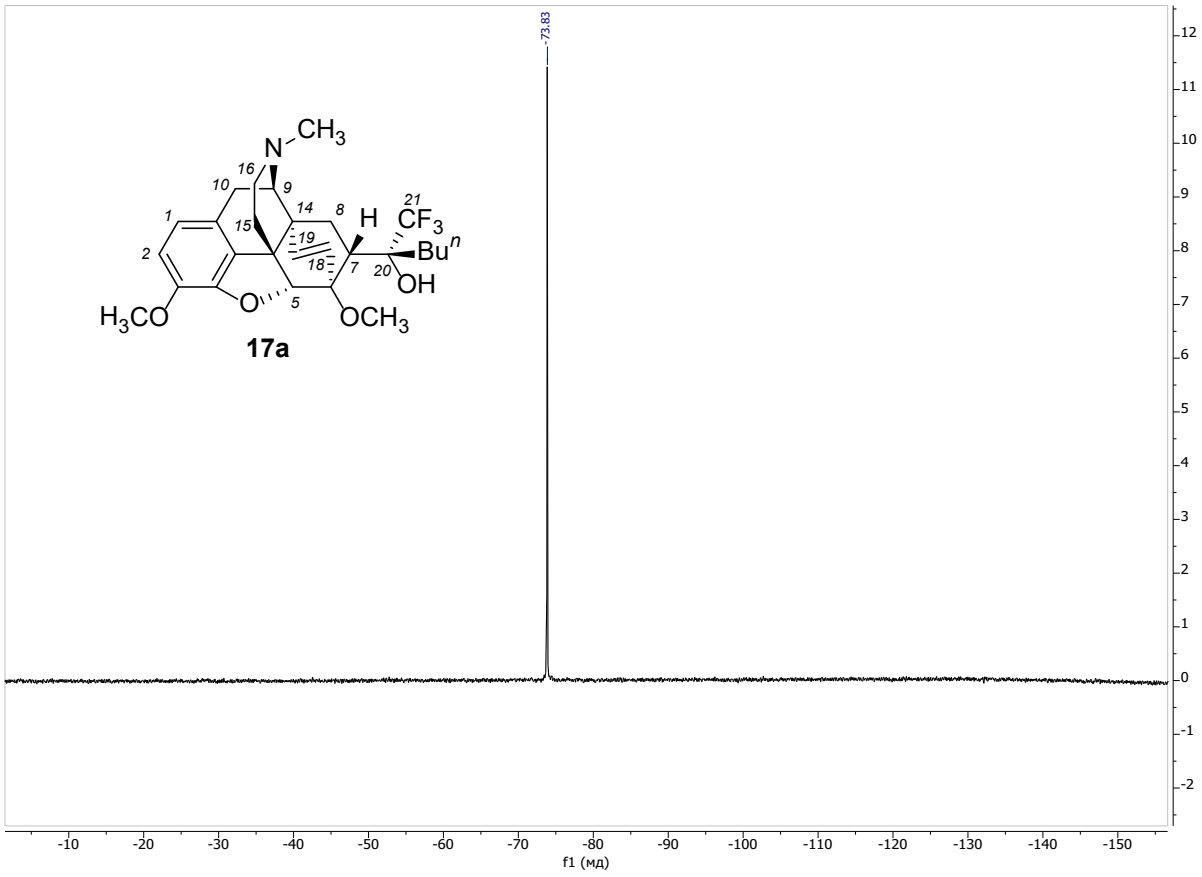


^{13}C NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)- 6,14-ethenoisomorpninane (17a):



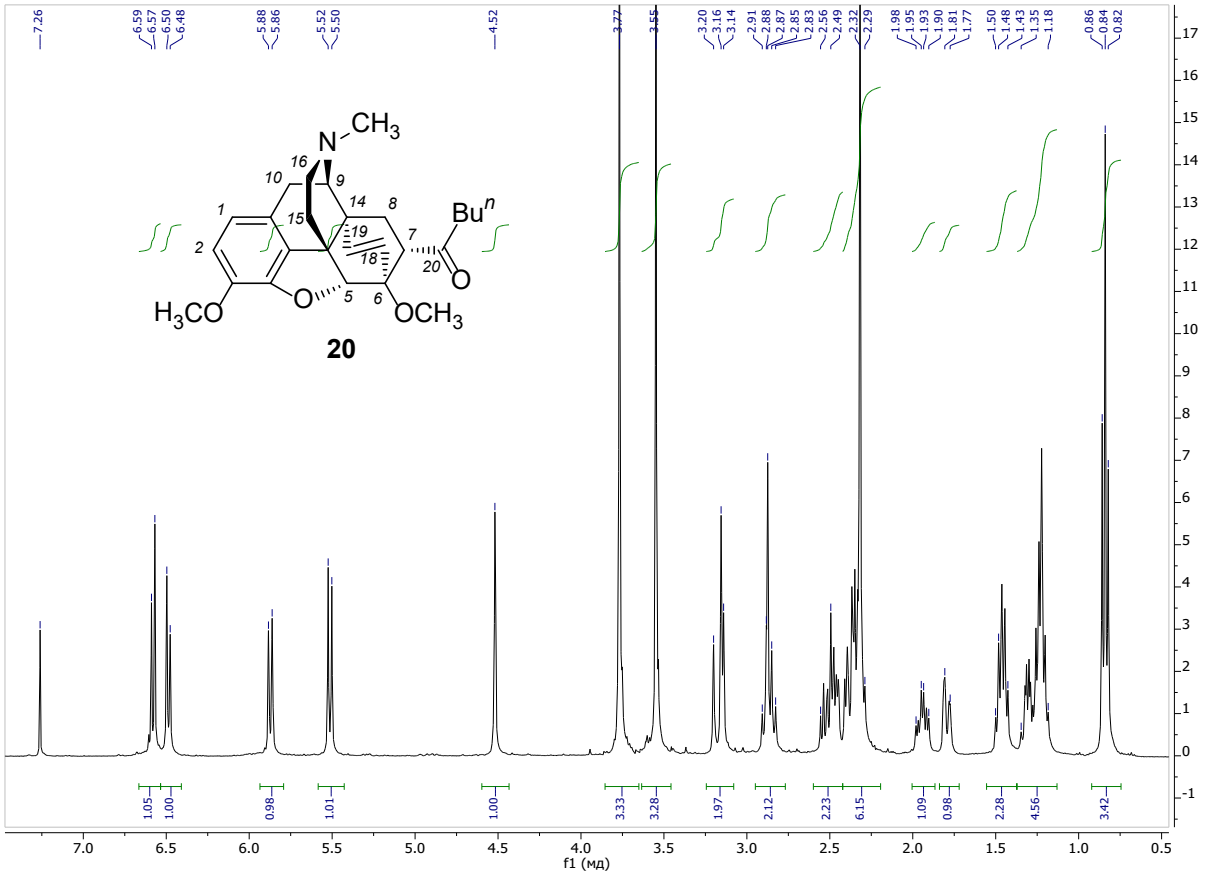
17a

^{19}F NMR Spectrum of *(5R,6R,7R,20R)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(1-hydroxy-1-(trifluoromethyl)propyl)- 6,14-ethenoisomorpninane (17a):



17a

^{1}H NMR Spectrum of *(5R,6R,7S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-pentanoyl-6,14-ethenoisomorphinan [21-*n*-propylthevinone] (20):



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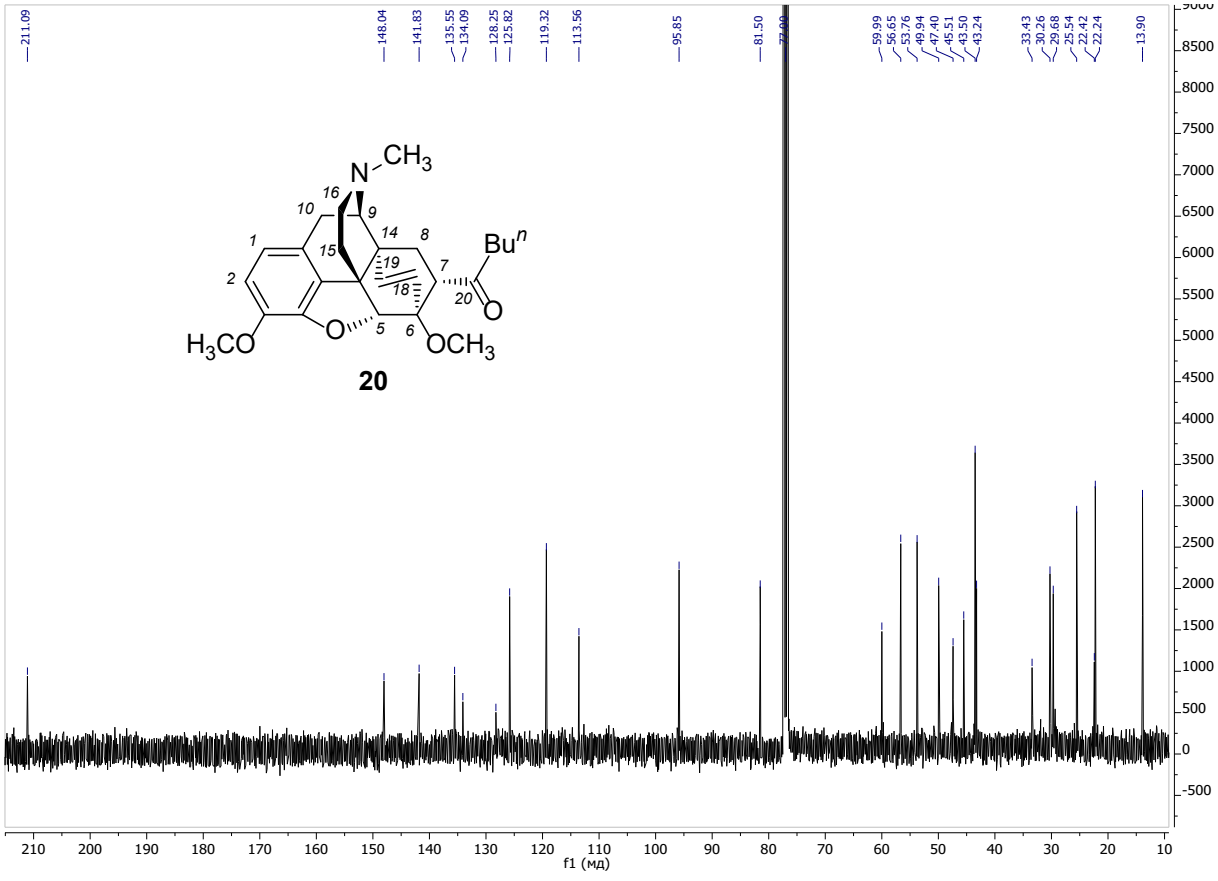
^{13}C NMR Spectrum of *(5R,6R,7S)*-4,5-epoxy-3,6-dimethoxy-17-methyl-7-pentanoyl-6,14-ethenoisomorphinan [21-*n*-propylthevinone] (20):



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