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^{19}F NMR determination of the C^{20} absolute configuration of C^{21}-fluorinated arylthevinols

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Experimental

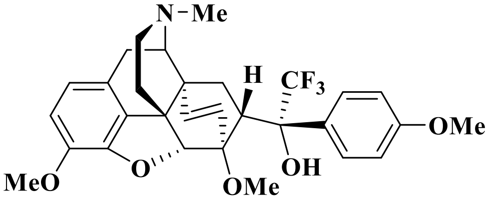
General considerations

All reactions were performed in an argon atmosphere in dried glassware. All solvents were purified (dried and distilled) before use according to the reported methods. All reagents were used as supplied by commercial sources unless otherwise stated. (5*R*,6*R*,7*S*)-4,5-Epoxy-7-(2,2,2-trifluoro-1-oxoethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan [21,21,21-trifluorothevinone] **3**, (5*R*,6*R*,7*R*,20*S*)-4,5-epoxy-7-(1-hydroxy-1-phenyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (20*S*)-**4e** and (5*R*,6*R*,7*R*,20*R*)-4,5-epoxy-7-(1-hydroxy-1-phenyl-2,2,2-trifluoroethyl)-3,6-dimethoxy-17-methyl-6,14-ethenoisomorphinan (20*R*)-**4e** were prepared as described [K. W. Bentley, D. G. Hardy and B. Meek, *J. Am. Chem. Soc.*, 1967, **89**, 3273]. NMR spectra (^{1}H, ^{13}C, ^{19}F) were recorded using Brucker Avance 400 spectrometr (^{1}The ^{19}F NMR experiments were recorded on Bruker AvanceTM 400 spectrometer (376.5 MHz). The spectrometer was equipped with BBFO+ probe-head. 19F chemical shifts were measured relative to $CFCl_3$ as an external standard. Multiplicites 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 on Merck UV-254 plates; the spots were visualized in camera with iodine. Column liquid chromatography was performed using silica gel (particle size no more then 80 μm).

General procedure for the preparation of 21,21,21-trifluoroarylthevinols 2a-d *via* the Grignard reaction

A solution of Grignard reagent (0.4 M in THF, 1.70 ml, 0.69 mmol) was added to a solution of ketone **3** (0.15 g, 0.35 mmol) in THF (5 ml). After stirring for 2 h at 25ºC, the mixture was quenched with a saturated aqueous solution of NH_4Cl (25 ml) and water (25 ml) and extracted with ether (25 ml). The organic layer was separated, washed with water (2×15 ml) and dried over Na_2SO_4. Pure (20*S*)-epimer was obtained after recrystallization from MeOH as colourless crystals.

(5*R*,6*R*,7*R*,20*S*)-4,5*α*-epoxy-7-[1-hydroxy-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (4a):



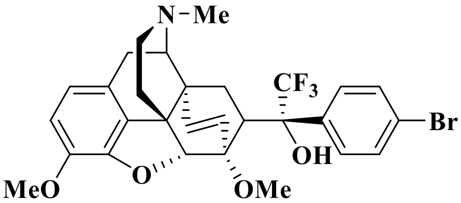
Yield: 69 mg (37%). Colourless crystals. R_f 0.6 ($CHCl_3$:MeOH:NH_4OH 10:1:0.07), m.p. 153-155 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.31 (m, 1H, H-8α), 1.71 (m, 2H, H-15aq, H-15ex), 2.12-2.38 (m, 5H, H-7β, H-8β, H-10α, H-16aq, H-16ex), 2.24 (s, 3H, NCH_3), 3.06 (d, 1H, $^3J_{H-9,H-10\alpha}$ = 6.6 Hz, H-9), 3.15 (br. d., 1H, H-10β), 3.82 (m, 9H, 3-OCH_3, 6-OCH_3, *p*-OCH_3), 4.46 (br. s., 1H, H-5), 5.53 (d, $^3J_{H-18,H-19}$ = 9 Hz, 1H, H-19), 6.11 (br. d., 1H, H-18), 6.51+6.62 (AB-system, J_{AB} = 8.2 Hz, 2H, H-1 + H-2), 6.62 (br. s., 1H, OH), 6.89+7.50 (AB-system, J_{AB} = 8.9 Hz, 4H, $C_6\underline{H_4}$).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 1.00, 15.26, 22.21, 29.22, 33.21, 42.40, 43.35, 45.22, 46.28, 48.90, 55.21, 55.33, 55.42, 56.74, 59.78, 65.85, 83.65, 99.59, 113.43, 113.69, 114.13, 119.47, 123.10, 127.62, 127.64, 128.24, 134.34, 136.26, 141.82, 147.76.

^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.74 (s, CF_3).

Found (%): C 66.39, H 6.01, N 2.56, F 9.22; $C_{30}H_{32}F_3NO_4$. Calculated (%): C 66.29, H 5.89, N 2.58, F 10.49.

(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-[1-hydroxy-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (4b):



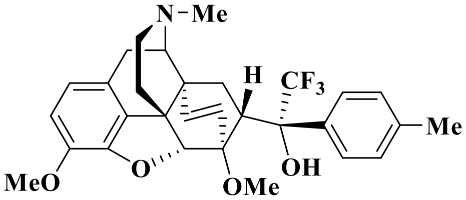
Yield: 57 mg (28%). Colourless crystals. R_f 0.5 ($CHCl_3$:MeOH:NH_4OH 10:1:0.07), m.p. 192-194 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (m, 1H, H-8α), 1.70 (ddd, $^2J_{H\text{-}15ax,H\text{-}15eq}$ = 12.7 Hz, $^3J_{H\text{-}15ax,H\text{-}16eq}$ = 12,3 Hz, $^3J_{H\text{-}15ax,H\text{-}16eq}$ = 6,2 Hz, 1H, H-15ax), 1.79 (m, 1H, H-15eq), 2.18-2.42 (m, 5H, H-7β, H-8β, H-10α, H-16ax, H-16eq), 2.28 (s, 3H, NCH_3), 3.10 (d, 1H, $^3J_{H\text{-}9,H\text{-}10\alpha}$ = 6.5 Hz, H-9), 3.20 (br. d., 1H, H-10β), 3.85 (d, 6H, 3-OCH_3, 6-OCH_3), 4.49 (s., 1H, H-5), 5.57 (d, $^3J_{H\text{-}18,H\text{-}19}$ = 9.8 Hz, 1H, H-19), 6.15 (br. d., 1H, H-18), 6.55+6.65 (AB-system, J_{AB} = 8.5 Hz, 2H, H-1 + H-2), 6,72 (s, 1H, OH), 7.52 (m, 4H, 4H-$C_6\underline{H_4}$).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 22.21, 29.14, 29.28, 33.23, 42.41, 43.35, 45.16, 46.27, 48.59, 55.44, 56.73, 59.75, 77.21, 83.70, 99.45, 113.71, 119.56, 122.29, 122.98, 126.41, 127.97, 128.13, 128.18, 128.26, 131.29, 134.21, 136.44, 141.85, 147.75.

^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.65 (s, CF_3).

HMRS (ESI): m/z calcd for $C_{29}H_{29}BrF_3NO_4$ $[M+H]^+$: 592.1310, found: 594.1289.

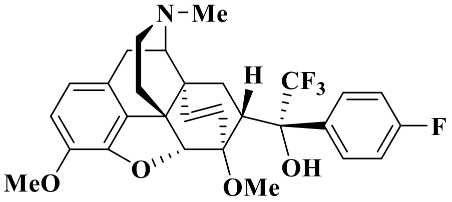
(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-[1-hydroxy-1-(4-methylphenyl)-2,2,2-trifluoroethyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (4c):



Yield: 73 mg (40%). Colourless crystals. R_f 0.6 ($CHCl_3$:MeOH:NH_4OH 10:1:0.07), m.p. 187-188 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (dd, $^2J_{H\text{-}8\alpha,H\text{-}8\beta}$ = 12.6 Hz, $^3J_{H\text{-}8\alpha,H\text{-}7\beta}$ = 5.9 Hz, 1H, H-8α), 1.73 (m, 2H, H-15eq, H-15ax), 2.13-2.38 (m, 5H, H-7β, H-8β, H-10α, H-16ax, H-16eq), 2.24 (s, 3H, NCH_3), 2.35 (s, 3H, CH_3), 3.08 (d, 1H, $^3J_{H\text{-}9,H\text{-}10\alpha}$ = 6.6 Hz, H-9), 3.17 (br. d., 1H, H-10β), 3.81 (s, 3H, 6-OCH_3), 3.82 (s, 3H, 3-OCH_3), 4.47 (s., 1H, H-5), 5.53 (d, $^3J_{H\text{-}18,H\text{-}19}$ = 9.6 Hz, 1H, H-19), 6.12 (br. d., 1H, H-18), 6.51+6.62 (AB-system, J_{AB} = 8 Hz, 2H, H-1 + H-2), 6.63 (br. s., 1H, OH), 7.17+7.47 (AB-system, J_{AB} = 8.1 Hz, 4H, $C_6\underline{H_4}$).

^{13}C NMR (100.62 MHz, $CDCl_3$): δ 0.99, 21.04, 22.20, 29.15, 29.68, 33.17, 42.40, 43.34, 45.23, 46.26, 48.67, 55.38, 56.74, 59.79, 77.20, 79.45, 83.71, 99.53, 113.71, 119.47, 123.12, 126.26, 127.50, 128.23, 128.82, 134.35, 136.25, 137.58, 141.82, 147.75.
^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.61 (s, CF_3).
HRMS (ESI): *m/z* calcd. for $C_{30}H_{32}F_3NO_4$: 528.2362 $[M+H]^+$, found: 528.2208.

(5*R*,6*R*,7*R*,20*S*)-4,5α-Epoxy-7-[1-hydroxy-1-(4-fluorophenyl)-2,2,2-trifluoroethyl]-3,6-dimethoxy-17-methyl-6,14-*endo*-ethenoisomorphinan (4d):



Yield: 81 mg (33%). Colourless crystals. R$_f$ 0.6 ($CHCl_3$:MeOH:NH_4OH 10:1:0.07), m. p. 218-218 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.30 (dd, $^{2}J_{\text{H-8}\alpha,\text{H-8}\beta}$ = 10,9 Hz, $^{3}J_{\text{H-8}\alpha,\text{H-7}\beta}$ = 5,2 Hz, 1H, H-8α), 1.72 (ddd, $^{2}\mathrm{J}_{\text{H-15ax,H-15eq}}$ = 12,1 Hz, $^{3}J_{\text{H-15ax,H-16ax}}$ = 15,6 Hz, $^{3}J_{\text{H-15ax,H-16eq}}$ = 5,9 Hz, 2H, H-15ax, H-15eq), 2.13 (m, 2H, H-7β, H-8β), 2.25 (s, 3H, NCH_3), 2.33 (m, 3H, H-10α, H-16ax, H-16eq), 3.07 (d, 1H, $^{3}J_{\text{H-9,H-10}\alpha}$ = 6,7 Hz, H-9), 3.16 (br. d., 1H, H-10β), 3.82 (s, 6H, 3-OCH_3, 6-OCH_3), 4.46 (s., 1H, H-5), 5.54 (d, $^{3}J_{\text{H-18,H-19}}$ = 9,0 Hz, 1H, H-19), 6.12 (d., 1H, *J* = 8.9 Hz, H-18), 6.51+6.62 (AB-system, J_{AB} = 8,1 Hz, 2H, H-1 + H-2), 6.68 (s, 1H, OH), 7.06+7.57 (AA'XX'-system, $^{3}J_{\text{H,F}}$ = 8.2 Hz, $^{4}J_{\text{H,F}}$ = 5.7 Hz, 4H, $C_6\underline{H_4}$).
^{13}C NMR (100.62 MHz, $CDCl_3$): δ 22.20, 29.17, 29.68, 33.23, 42.38, 43.33, 45.17, 46.26, 47.44, 48.78, 55.45, 56.71, 59.74, 79.19, 83.67, 99.48, 113.69, 114.91, 115.12, 119.53, 123.00, 128.17, 128.23, 128.32, 134.22, 135.07, 136.37, 141.83, 147.71.
^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.71 (s, 3F, CF_3), -114.44 (s, 1F, C_6H_4F).
HRMS (ESI): *m/z* calcd. for $C_{29}H_{29}F_4NO_4$: 532.2111 $[M+H]^+$, found: 532.2035.

Crystallographic data for (20*S*)-4a-d

Crystal data for (20*S*)-**4a**. $C_{30}H_{32}F_3NO_5$, M = 543.56, monoclinic, space group $P\ 2_1$, 120 K: a = 8.914(14) Å, b = 12.336(18) Å, c = 11.692(16) Å, β = 93.03(4)°, Z = 2, V = 1284(3) Å^3, d_{calc} = 1.406 g cm^{-3}, F(000) = 572. Intensities of 16383 reflections were measured using a Bruker APEX2 DUO CCD diffractometer (ω and φ scans, λ[Mo-Kα] = 0.71073 Å, μ = 1.09 mm^{-1}, $2\theta_{\max}$ = 60°). After merging of equivalents and absorption correction, 7497 independent reflections were used for the structure solution and refinement. Final R factors: R_1 = 0.0545 [4029 reflections with $I>2\sigma(I)$], wR_2 = 0.1069 (all reflections), GOF = 0.939.

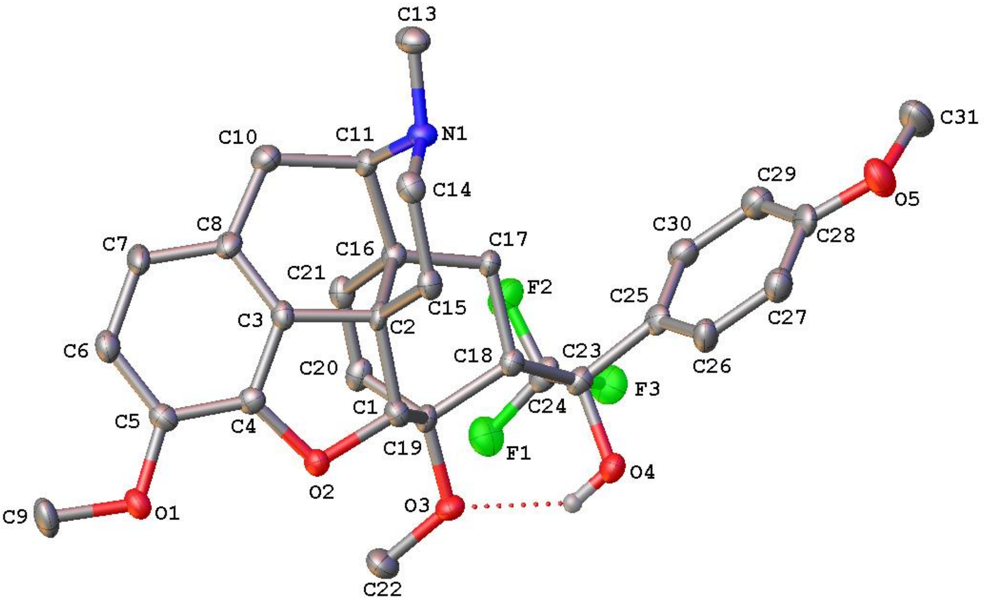


Figure S1. *General view of the compound (20S)-**4a** in representation of non-hydrogen atoms as thermal ellipsoids at 50% probability level. Hydrogen atoms except for that of the OH group are omitted for clarity.*

Crystal data for (20*S*)-**4b**. $C_{29}H_{29}BrF_3NO_4$, M = 592.44, orthorhombic, space group $P\ 2_12_12_1$, 120 K: a = 9.1057(2) Å, b = 11.4867(3) Å, c = 24.5136(5) Å, Z = 4, V = 2563.99(10) Å^3, d_{calc} = 1.535 g cm^{-3}, F(000) = 1216. Intensities of 35878 reflections were measured using a Bruker APEX2 DUO CCD diffractometer (ω and φ scans, λ[Cu-Kα] = 1.54178 Å, μ = 27.00 mm^{-1}, $2\theta_{max}$ = 129.62°). After merging of equivalents and absorption correction, 4329 independent reflections were used for the structure solution and refinement. Final R factors: R_1 = 0.0201 [4292 reflections with $I > 2\sigma(I)$], wR_2 = 0.0564 (all reflections), GOF = 1.068.

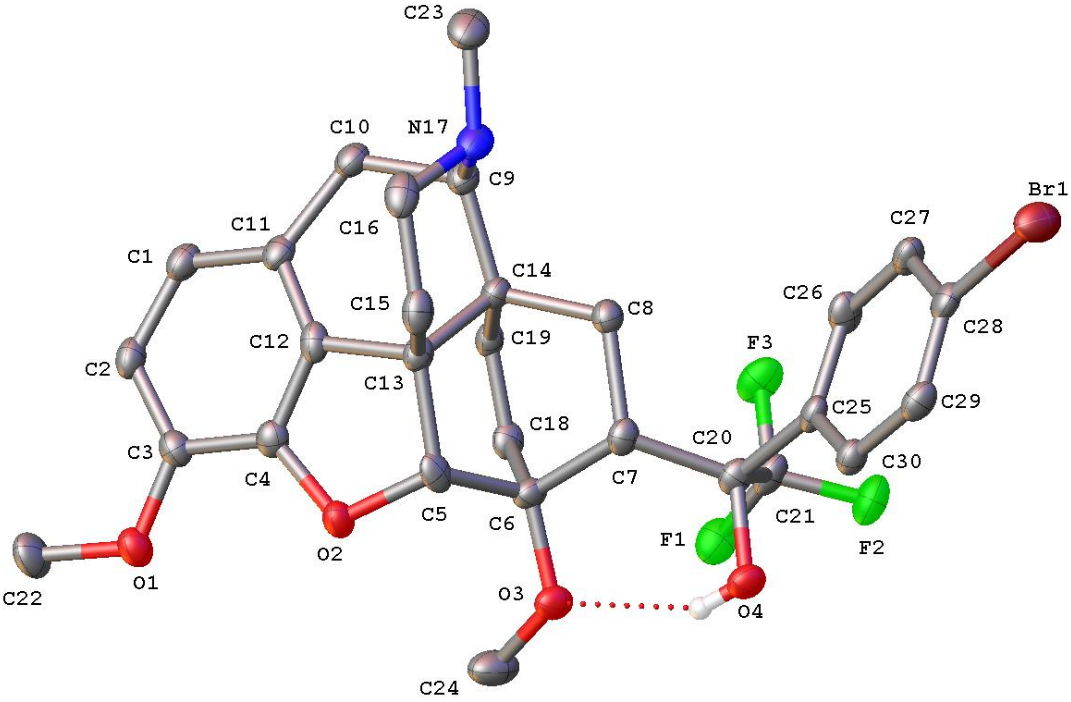


Figure S2. *General view of the compound (20S)-**4b** in representation of non-hydrogen atoms as thermal ellipsoids at 50% probability level. Hydrogen atoms except for that of the OH group are omitted for clarity.*

Crystal data for (20*S*)-**4c**. $C_{30}H_{32}F_3NO_4$, M = 527.56, triclinic, space group *P*1, 120 K: *a* = 7.3665(7) Å, *b* = 8.0075(11) Å, *c* = 11.3133(11) Å, α = 87.794(3)°, β = 84.653(2)°, γ = 70.923(2), Z = 1, *V* = 627.92(12) $Å^3$, d_{calc} = 1.395 g cm^{-3}, F(000) = 278. Intensities of 13492 reflections were measured using a Bruker APEX2 DUO CCD diffractometer (ω and φ scans, sealed tube, λ[Mo-Kα] = 0.71073 Å, μ = 1.07 mm^{-1}, $2\theta_{max}$ = 60.686°). After merging of equivalents and absorption correction, 7384 independent reflections were used for the structure solution and refinement. Final *R* factors: R_1 = 0.0428 [6574 reflections with $I>2\sigma(I)$], wR_2 = 0.1069 (all reflections), GOF = 1.035.

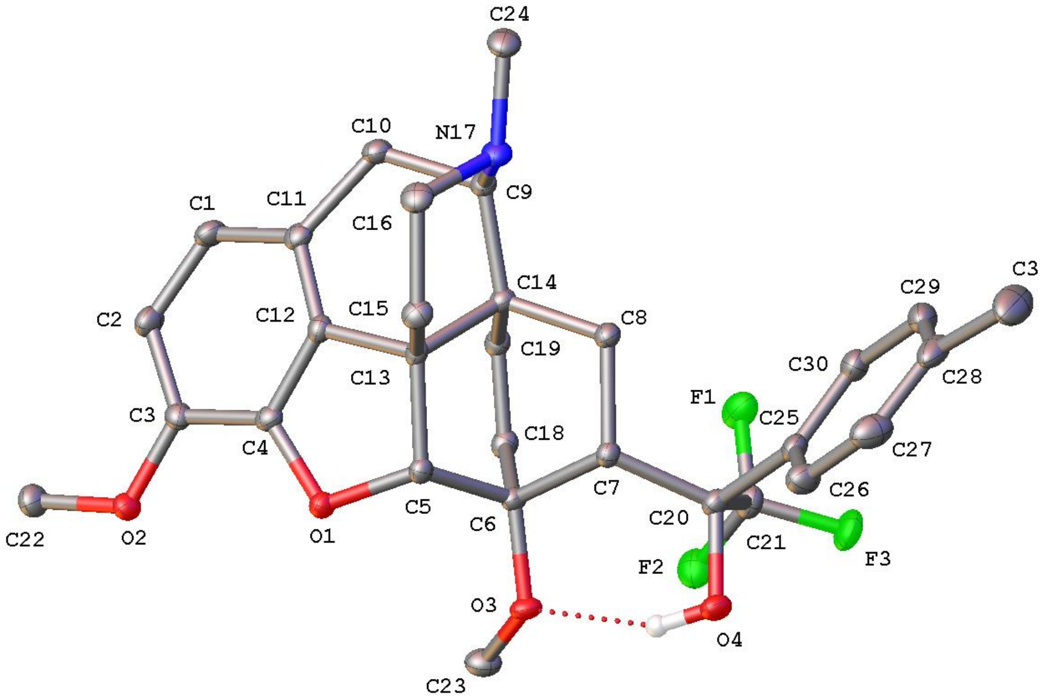


Figure S3. *General view of the compound (20S)-**4c** in representation of non-hydrogen atoms as thermal ellipsoids at 50% probability level. Hydrogen atoms except for that of the OH group are omitted for clarity.*

Crystal data for (20*S*)-**4d**. $C_{29}H_{29}F_4NO_4$, M = 531.53, orthorhombic, space group $P\,2_12_12_1$, 120 K: a = 8.8127(14) Å, b = 11.8505(18) Å, c = 23.497(4) Å, Z = 4, V = 2454.0(7) Å^3, d_{calc} = 1.439 g cm^{-3}, F(000) = 1112. Intensities of 33139 reflections were measured using a Bruker APEX2 DUO CCD diffractometer (ω and φ scans, λ[Mo-Kα] = 0.71073 Å, μ = 1.15 mm^{-1}, $2\theta_{\max}$ = 60.84°). After merging of equivalents and absorption correction, 7392 independent reflections were used for the structure solution and refinement. Final R factors: R_1 = 0.0699 [4197 reflections with $I>2\sigma(I)$], wR_2 = 0.1385 (all reflections), GOF = 0.978.

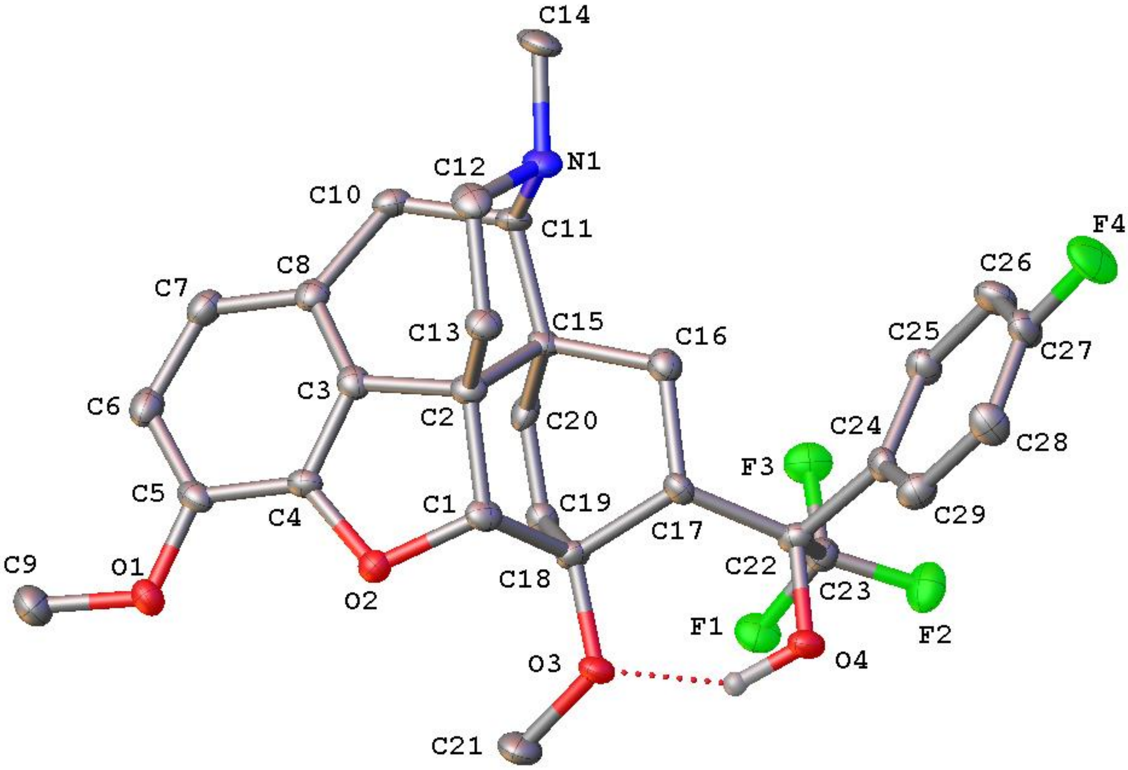


Figure S4. *General view of the compound (20S)-**4d** in representation of non-hydrogen atoms as thermal ellipsoids at 50% probability level. Hydrogen atoms except for that of the OH group are omitted for clarity.*

Using Olex2 [O. V. Dolomanov et al, *J. Appl. Cryst*., 2009, **42**, 339], the structures were solved with the ShelXT structure solution program [G. M. Sheldrick, *Acta Cryst*., 2015, **A71**, 3] using Intrinsic Phasing and refined against F^2 with the SHELXTL PLUS 5.0 refinement package using full-matrix least-squares technique. The positions of hydrogen atoms of OH groups in all compounds were found in difference Fourier synthesis. Positions of other hydrogen atoms were calculated, and they all were refined in isotropic approximation in riding model. Molecular graphics were drawn using Olex2 program.

CCDC 2088140–2088143 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.

^{1}H, ^{13}C, ^{19}F NMR spectra

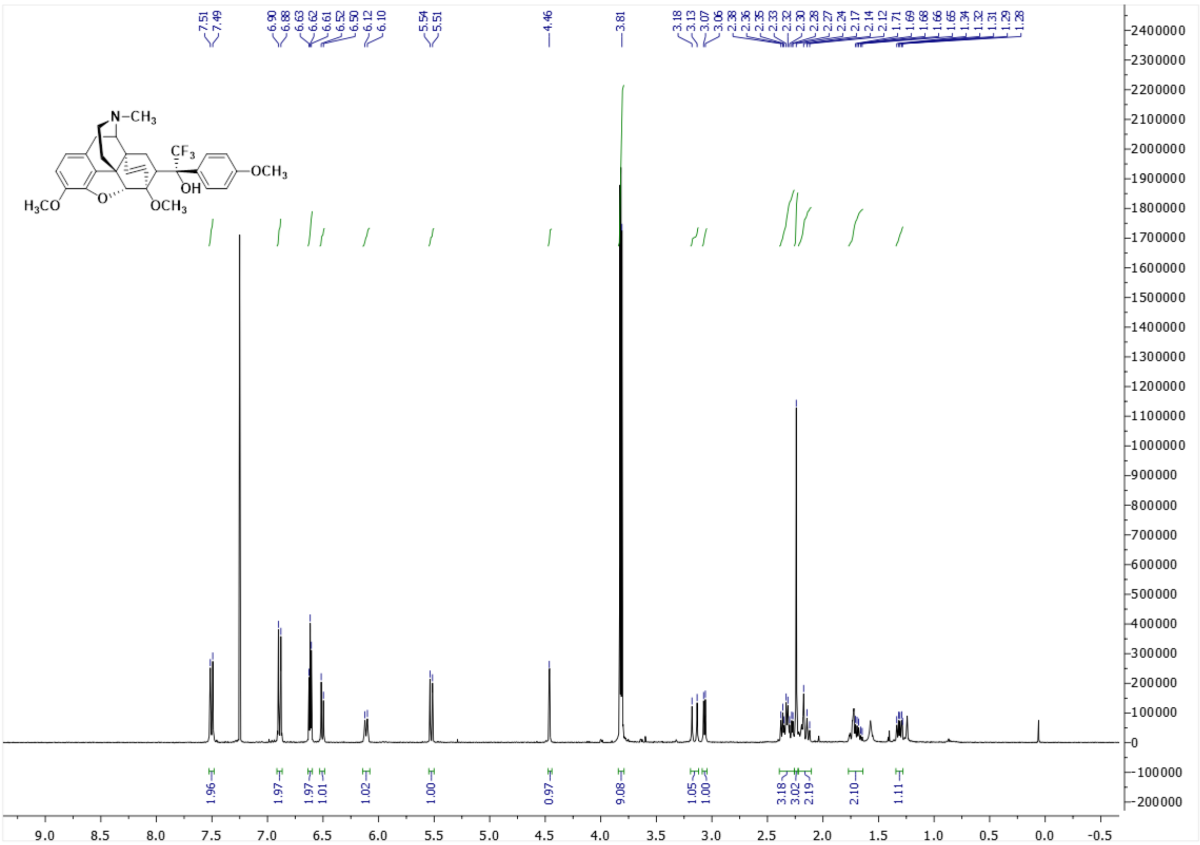


Figure S5. ^{1}H NMR spectrum of compound *(20S)*-**4a**

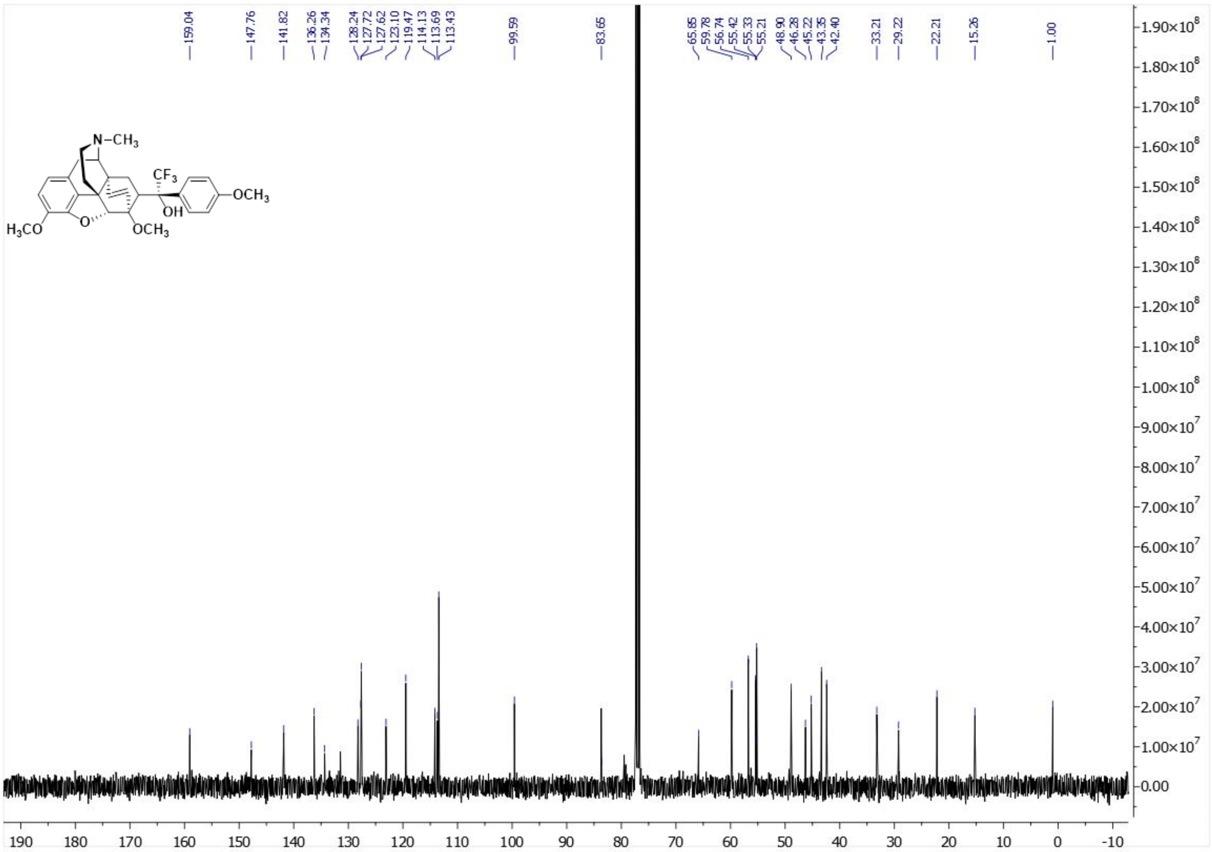


Figure S6. ^{13}C NMR spectrum of compound *(20S)*-**4a**

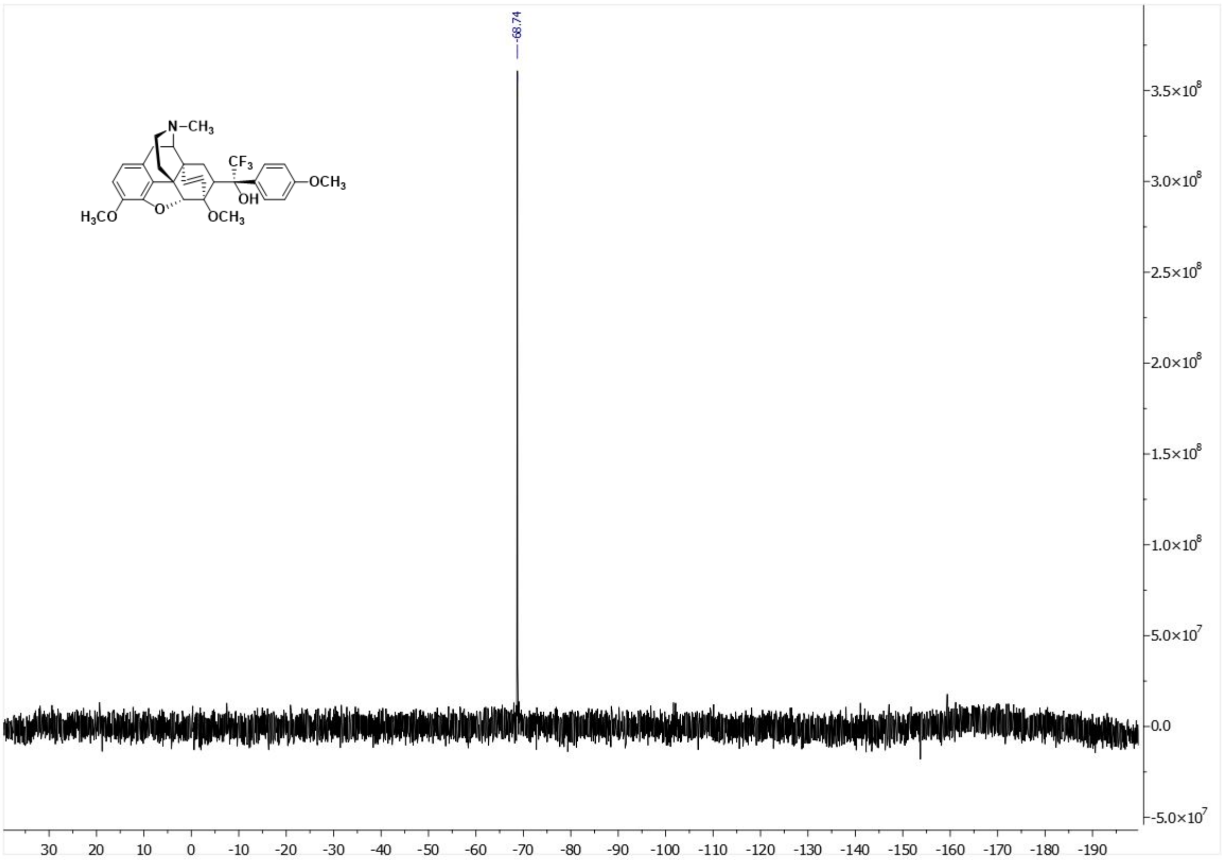


Figure S7. ^{19}F NMR spectrum of compound *(20S)*-**4a**

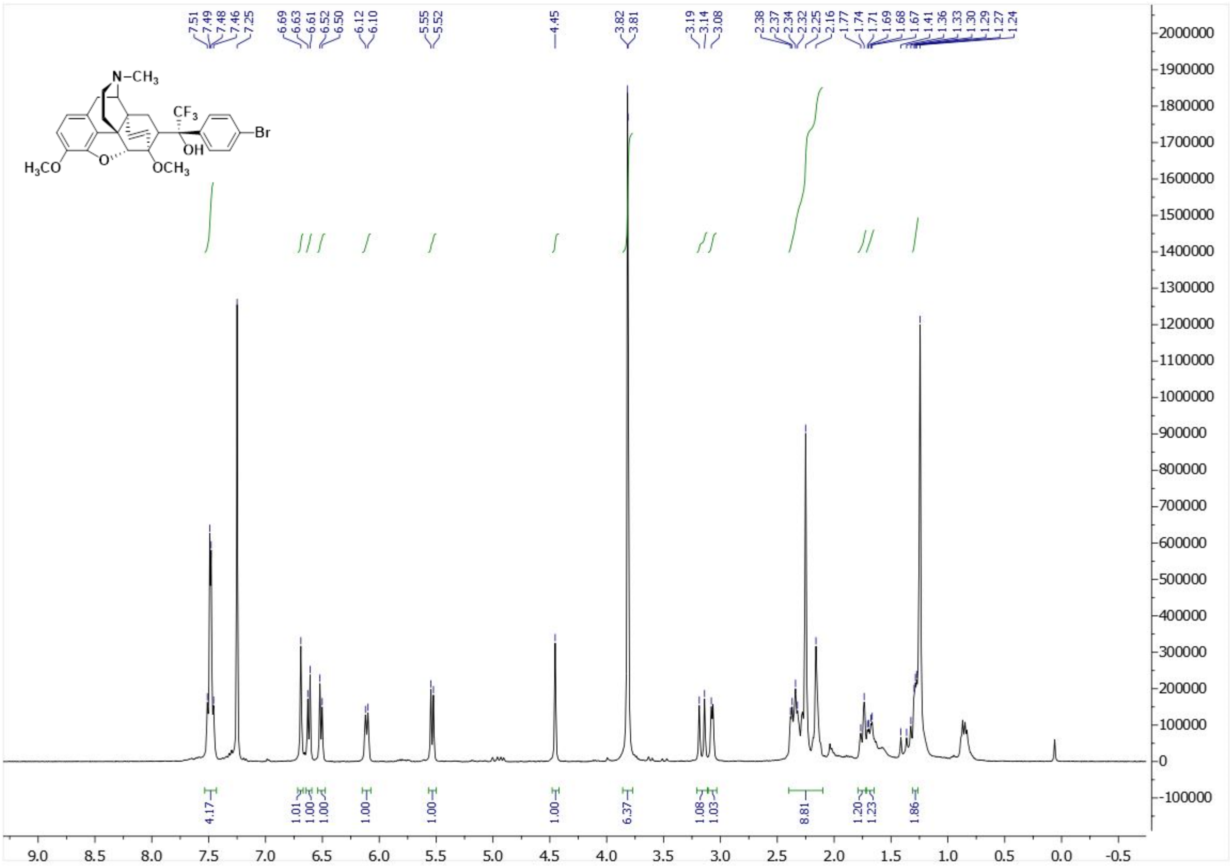


Figure S8. ^{1}H NMR spectrum of compound *(20S)*-**4b**

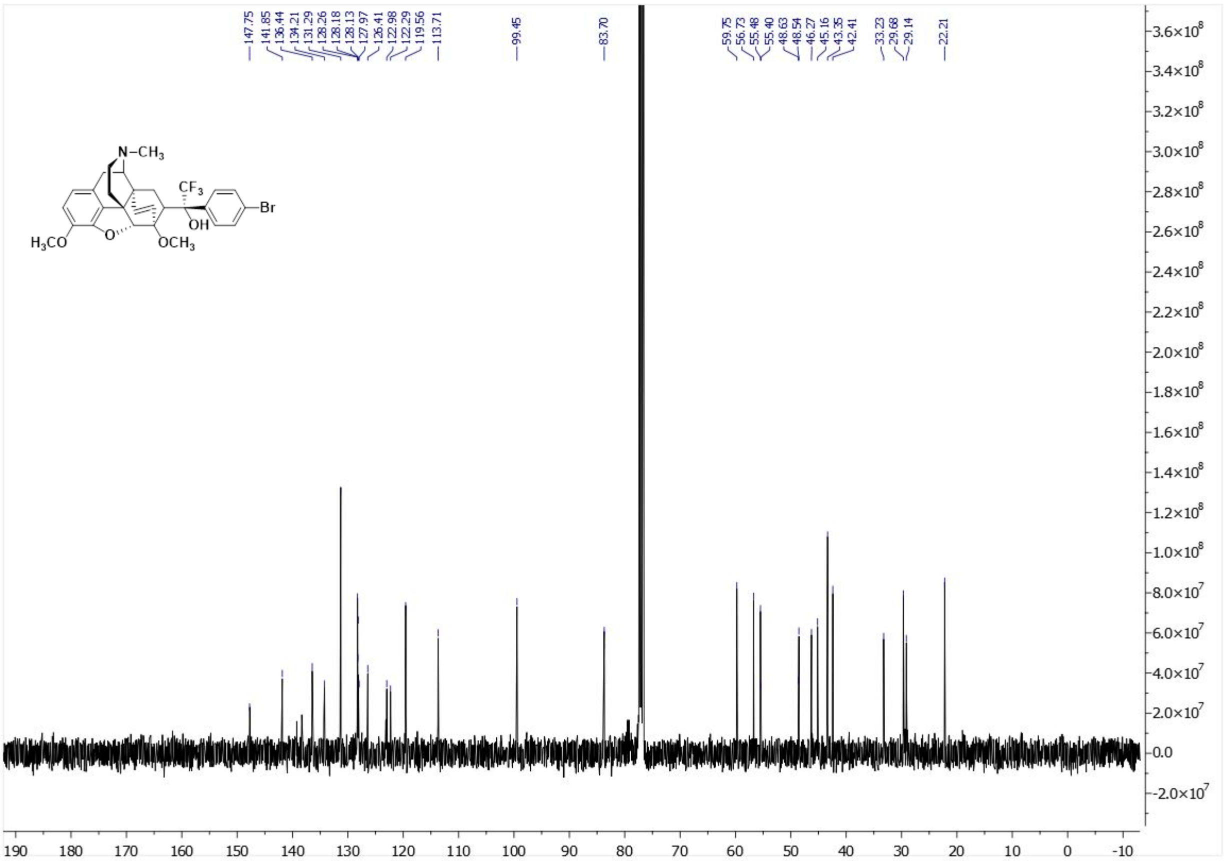


Figure S9. ^{13}C NMR spectrum of compound *(20S)*-**4b**

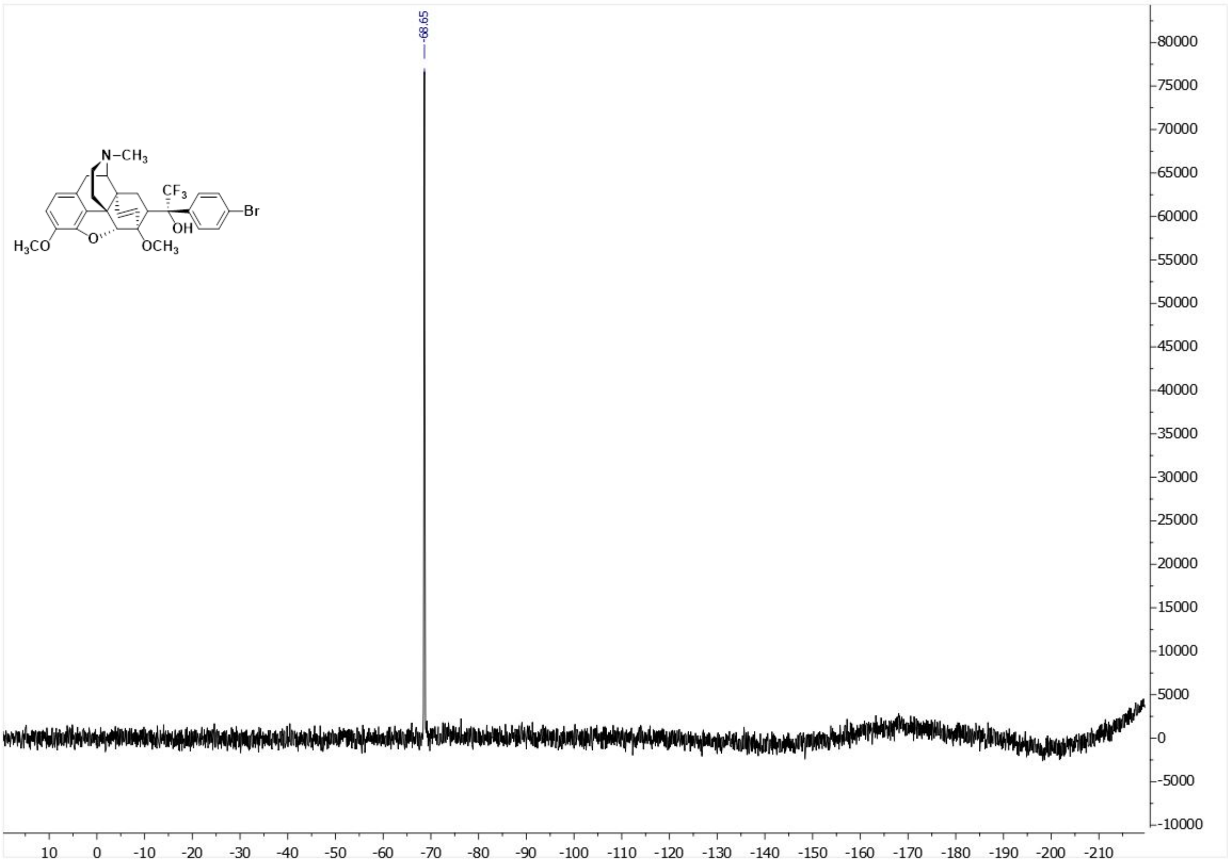


Figure S10. ^{19}F NMR spectrum of compound *(20S)*-**4b**

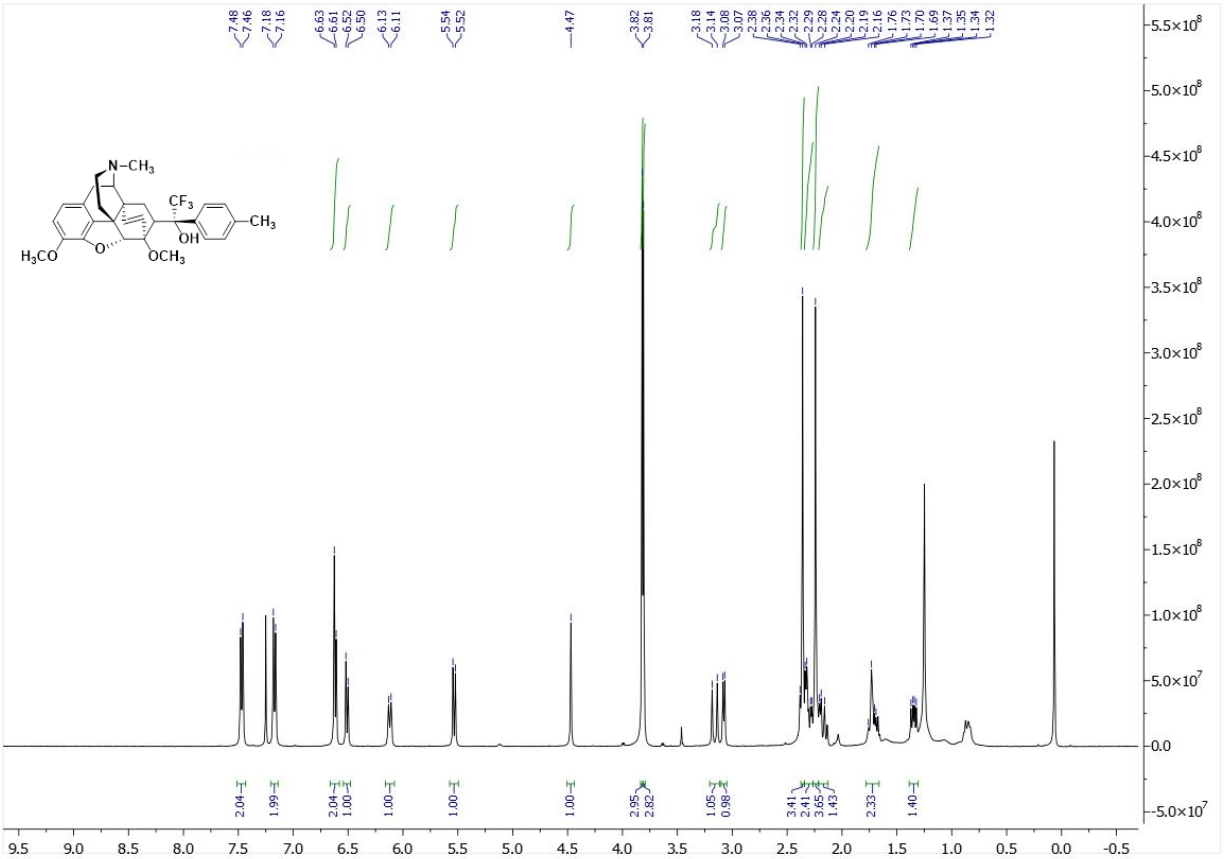


Figure S11. ^{1}H NMR spectrum of compound *(20S)*-**4c**

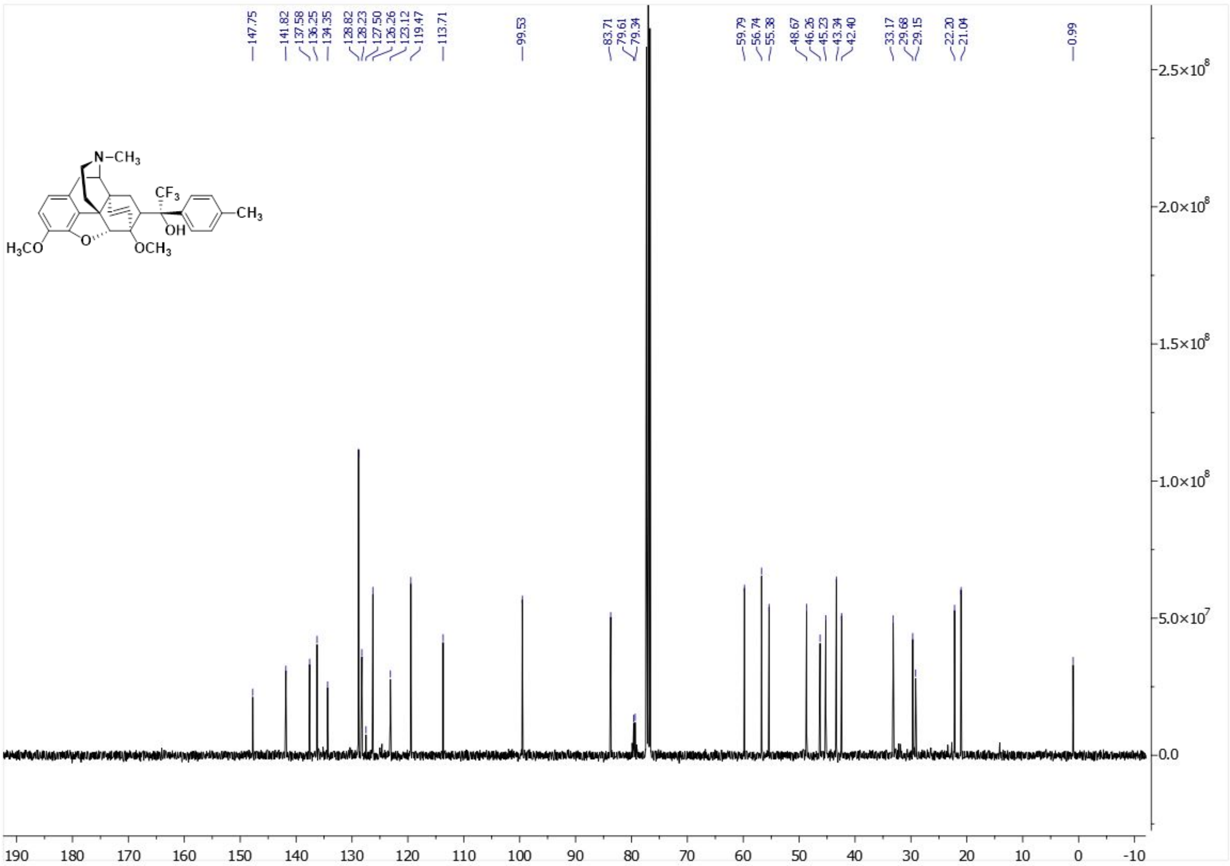


Figure S12. ^{13}C NMR spectrum of compound *(20S)*-**4c**

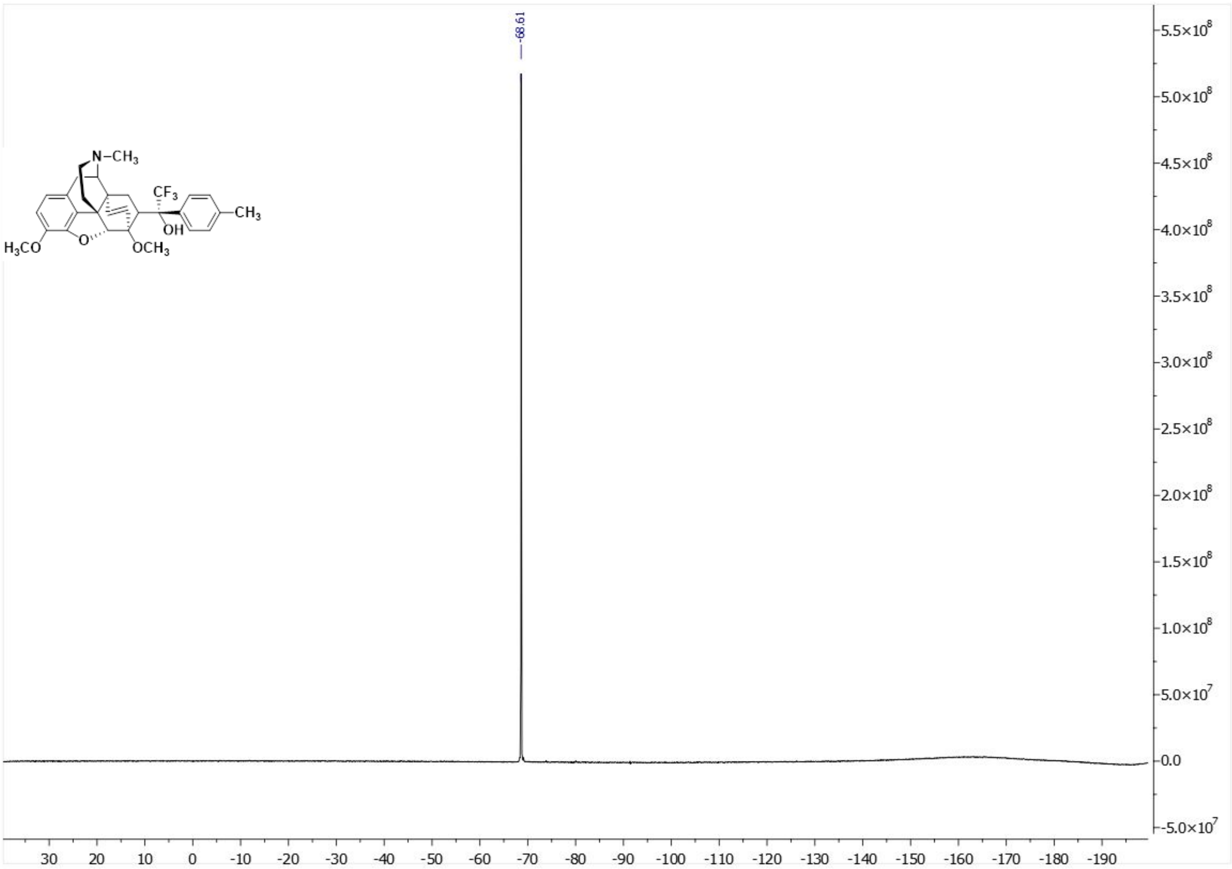


Figure S13. ^{19}F NMR spectrum of compound *(20S)*-**4c**

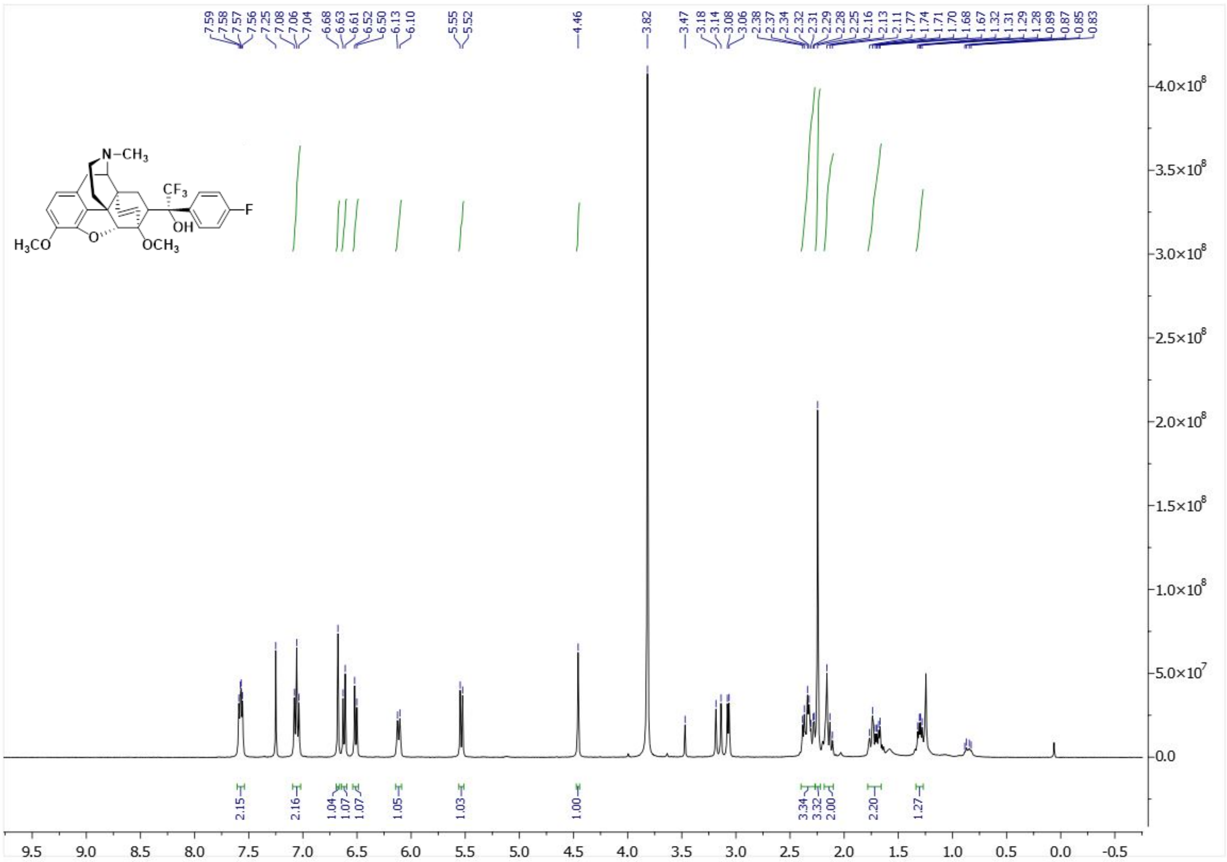


Figure S14. ^{1}H NMR spectrum of compound *(20S)*-**4d**

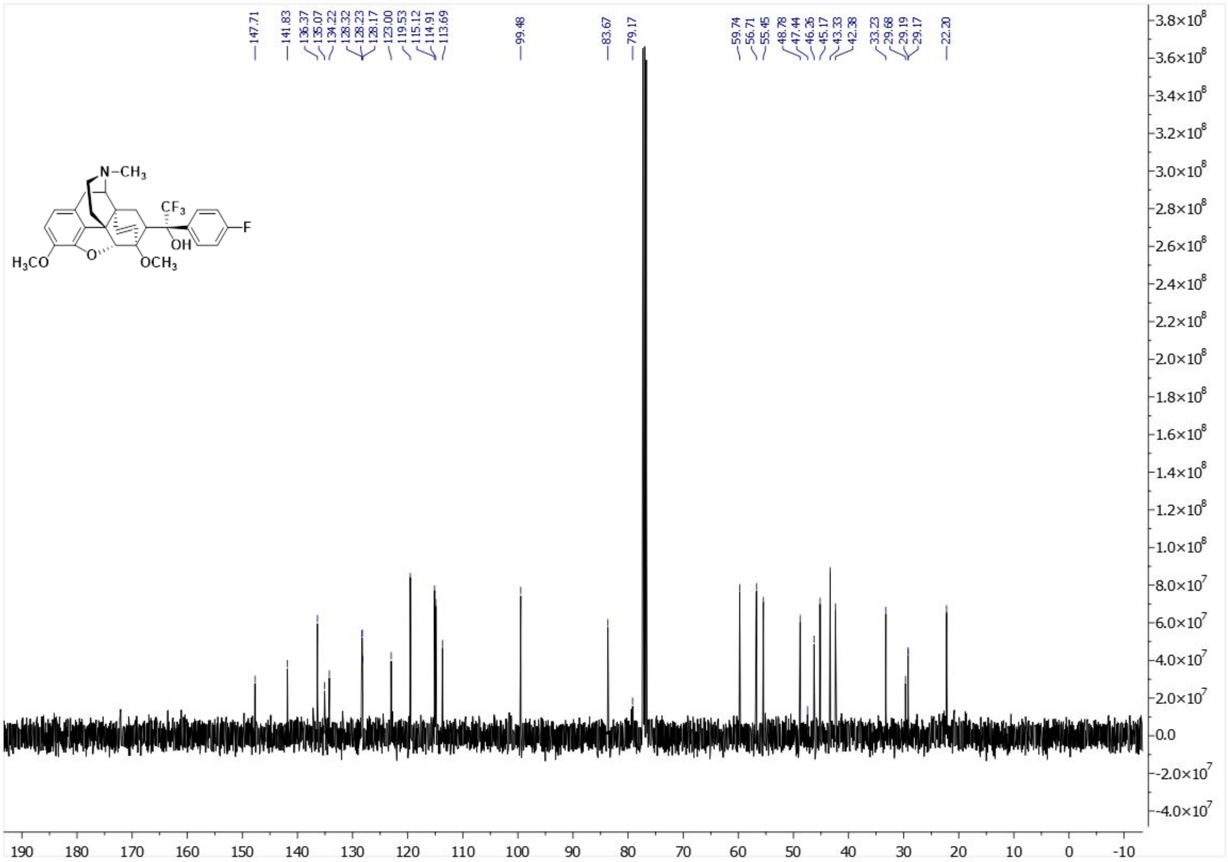


Figure S15. ^{13}C NMR spectrum of compound *(20S)*-**4d**

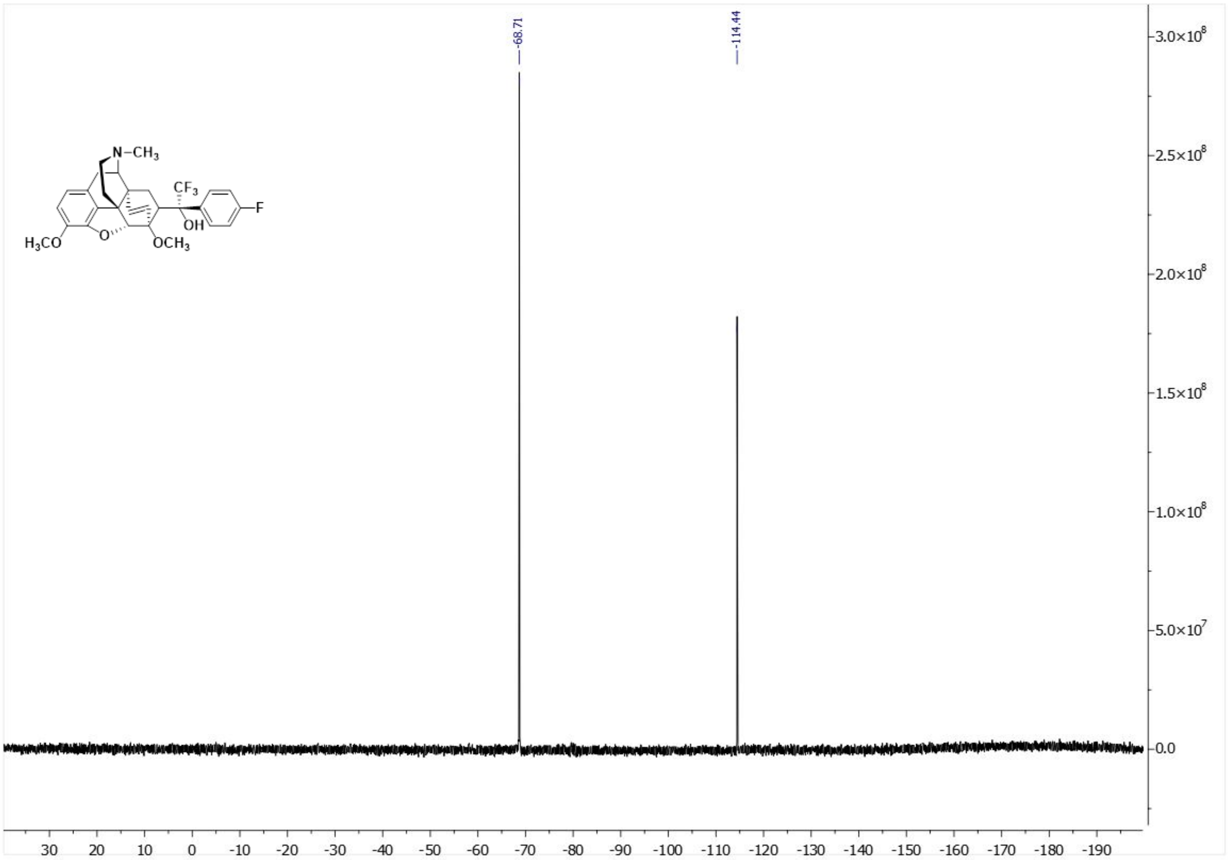


Figure S16. ^{19}F NMR spectrum of compound *(20S)*-**4d**