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New trifluoromethylated sesquiterpenoids: synthesis, rearrangement, biological activity

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Contents

1. Materials and Instrumentation

All chemicals and materials were obtained from commercial suppliers and were used as received: (-)-caryophyllene oxide (purity 95%, Sigma-Aldrich), tetracyanoethylene TCNE (purity 96%, Sigma-Aldrich), (trifluoromethyl)trimethylsilane $TMSCF_3$ (purity 98%, Alfa Aesar), cesium fluoride CsF (purity 98%, Alfa Aesar), tetra-*n*-butylammonium fluoride trihydrate $TBAF{\cdot}3H_2O$ (purity 98%, Alfa Aesar), silica gel (mesh 0.06-0.2 mm) from Alfa Aesar, TCL plates "Sorbfil". If necessary, the reactions were carried out in dry solvents and in an argon flow. ^{1}H, ^{13}C Jmod NMR and 2D NMR ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HSQC, ^{1}H-^{1}H COSY and ^{1}H-^{1}H NOESY spectra were recorded with a Bruker Avance II 300 MHz (300.17 MHz for ^{1}H NMR, 75.5 MHz for ^{13}C NMR, 262 MHz for ^{19}F NMR). Data are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak, and scalar coupling constants (*J*) are reported in units of Hertz (Hz). Infrared spectra were recorded using a Shimadzu IR Prestige 21 spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). Mass spectra (MS, *m/z*) were recorded on a Thermo Finnigan LCQ Fleet HPLC/MS spectrometer in positive mode (ESI^+, 10-40 eV). Specific optical rotation angles were determined on an Optical Activity polAAr 3001 polarimeter. The melting points of solid samples of the synthesized compounds were determined on a Gallenkamp-Sanyo MPD350BM3.5 instrument and were not corrected.

The X-ray diffraction data for compound **15** were collected on a Xcalibur 3, for compounds **18**, **27** and **29** were collected on a Bruker D8 Quest (**18** and **29**) and Oxford Xcalibur Eos (**27**) diffractometers (Mo-K_α radiation, ω-scan technique, λ = 0.71073 Å). The intensity data were integrated by SAINT[1] (**18** and **29**) and CrysAlisPro[2] programs. SADABS[3] program (**18** and **29**) and SCALE3 ABSPACK algorithm[2] (**27**) were used to perform absorption corrections. All compounds were solved by dual method[4] and refined on F_{hkl}^2 using SHELXTL package.[5] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms except H(1) atoms in **18**, **27** and **29** were placed in calculated positions and were refined using a riding model ($U_{iso}(H) = 1.5U_{eq}(C)$ for CH_3-group and $U_{iso}(H) = 1.2U_{eq}(C)$ for other groups). In turn, the hydrogen atoms H(1) in **18**, **27** and **29** were localized from the difference Fourier synthesis and were refined in the isotropic approximation.

The fluorine atoms in the CF_3-group of the complex **27** are disordered in three positions with occupancies ~0.48/0.47/0.05. Two carbon atoms (C(2A) and C(3A)) in complex **29** are disordered over two positions (~0.72/0.28). Identical anisotropic displacement parameters for disordered

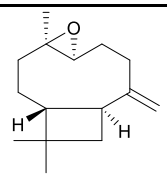
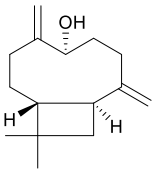
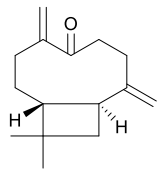
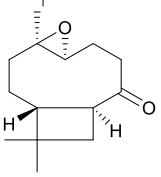
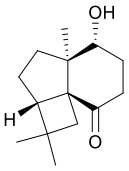
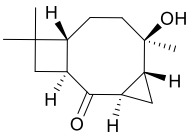
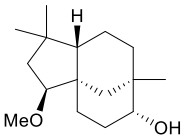
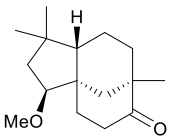
atoms were received with EADP instruction. SADI, DFIX and ISOR instructions were used to refine disordered fragments. The absence of heavy atoms in structures **18**, **27** and **29** leads to a high s.u. in determining absolute structure parameter. The error value exceeds its own value of the absolute parameter (Table 5), which means that the experimental data do not support the determination of the absolute structure. The main crystallographic data and structure refinement details for compounds **15**, **18**, **27** and **29** are given in Table S5. CCDC 2167152 (**15**) 2169284 (**18**), 2169285 (**27**) and 2169286 (**29**) contain the supplementary crystallographic data for this paper. These data can also be obtained free of charge at ccdc.cam.ac.uk/getstructures from the Cambridge Crystallographic Data Centre.

2. General methods

2.1. Chemistry

2.1.1. Preparation of substrates

Table S1 Terpenic substrates

Compound	Structure	Name	References
1		Caryophyllene oxide	Commercial aviable from Sigma-Aldrich
2		(1*S*,5*S*,9*R*)-10,10-dimethyl-2,6-dimethylenebicyclo[7.2.0]undecan-5-ol, α-betulenol	6
3		(1*S*,9*R*)-10,10-dimethyl-2,6-dimethylenebicyclo[7.2.0]undecan-5-one, betulenone	7
5		(1*R*,4*R*,6*R*,10*S*)-4,12,12-trimethyl-5-oxatricyclo[6.2.0.$0^{4,6}$]dodecan-9-one, kobusone	8
6		(2a*S*,4a*R*,5*R*,8a*S*)-5-5-hydroxy-2,2,4a-trimethyloctahydrocyclobuta[c]inden-8(1*H*)-one, 5*α*-hydroxynorpanasinsan-8-one	9,10
7		(1*S*,3*S*,5*R*,6*R*,9*R*)-6-hydroxy-6,10,10-trimethyltricyclo[7.2.0.$0^{3,5}$]undecan-2-one, rumphellolide F	9,11
8		(3*S*,3a*S*,6*R*,7*R*,9a*S*)-3-methoxy-1,1,7-trimethyldecahydro-3a,7-methanocyclopenta[8]annulen-6-ol, 2*β*-methoxyclovan-9*α*-ol	12
9		(3*S*,3a*S*,7*R*,9a*S*)-3-methoxy-1,1,7-trimethyloctahydro-3a,7-methanocyclopenta[8]annulen-6(1*H*)-one, 2*β*-methoxyclovan-9-on	

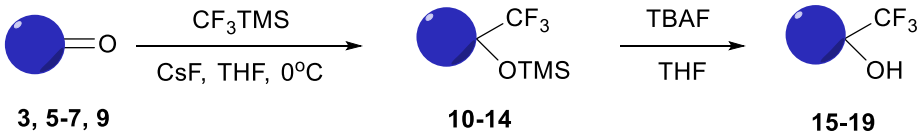
8-Methoxyisocaryolan-9-one 4. Alcohol **2** (1.5 g, 6.81 mmol) was dissolved in 20 mL MeOH, 20 mol% TCNE (173 mg, 1.35 mmol) was added and stirred at room temperature. The progress of the reaction was monitored by TLC (chloroform as eluent). After 5–7 days, when no changes were observed by TLC, excess MeOH was removed under vacuum, the residue was extracted with EtOAc, washed with brine, and the organic layer was dried over Na_2SO_4. The mixture was separated by column chromatography on silica gel eluting with petroleum ether (PE):EtOAc 5:1 (developer 5% phosphomolybdic acid, PMA). The fraction containing 2-methoxyclovan-9-ol and 8-methoxyisocaryolan-9-ol was re-separated by silica gel column chromatography eluting with $CHCl_3$:Et_2O 10:1 (v/v). The yield of pure 2-methoxyclovan-9-ol and 8-methoxyisocaryolan-9-ol was 11% and 37%, respectively.

Purified 8-methoxyisocaryolan-9*α*-ol (250 mg, 0.99 mmol) was dissolved in DCM (25-30 mL), PCC (235 mg, 1.09 mmol, 1.1 equiv.) was added. The mixture was stirred at room temperature. The reaction progress was monitored by TLC (PE: EtOAc 5:1, developer 5% PMA). Upon completion of the reaction, the mixture was diluted with DCM, washed with brine, dried over Na_2SO_4. The resulting ketone **4** was purified by column chromatography eluting with PE:EtOAc 5:1 (v/v), 34% yield. Colorless oil, α_D^{24} -62.8 (*c* = 0.200, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.12 (s, 3H, Me-16), 2.73 (ddd, 1H, H-7B, *J* = 16.4, 11.2, 5.6 Hz), 2.24-2.45 (m, 2H, H-7A, 10B), 1.86-2.01 (m, 2H, H-12A, 12B), 1.76 (td, 1H, H-3B, *J* = 12, 4.1 Hz), 1.37-1.69 (m, 6H, H-2, 3A, 5, 6B, 11A, 11B), 1.03-1.34 (m, 2H, H-6A, 10A), 0.96 (s, 3H, Me-15), 0.90 (s, 3H, Me-14), 0.87 (s, 3H, Me-13). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 210.4 (C-9), 79.0 (C-8), 50.8 (C-16), 49.2 (C-12), 45.4 (C-5), 42.1 (C-2), 36.7 (C-11), 35.8 (C-3), 34.2 (C-7), 33.3 (C-1), 31.8 (C-10), 30.4 (C-15), 30.1 (C-4), 26.0 (C-13), 24.3 (C-6), 21.1 (C-14). IR (v, sm^{-1}): 2953, 2864. 1710 (C=O), 1458, 1382, 1369, 1286, 1255, 1180, 1159, 1124, 1103, 1064 (C-O-C), 1004, 970, 940, 948, 914, 821, 802, 738, 653, 590, 545, 499, 476. MS (ESI, 20 eV, I_{rel}, %): 251.16 (100) $[M+H]^+$. Calculated: $C_{16}H_{26}O_2$, MW = 250.31.

2*β*-Methoxyclovan-9-on 9. A solution of 0.5 g (2.27 mmol) of caryophyllene oxide **1** in 10 mL of methanol was stirred at room temperature with 20% TCNE for 7 days. Next, the resulting mixture was separated by column chromatography on silica gel eluting with PE:EtOAc 10:1 (v/v) with an increase in the proportion of the latter to a ratio of 2:1 (v/v). The yield of 2*β*-methoxyclovan-9*α*-ol **8** was 40-45%. To a solution of 0.99 mmol of alcohol **8** in 25 mL of DCM, 1.09 mmol of PCC was added. The mixture was

stirred at room temperature. The progress of the reaction was monitored by TLC (PE: EtOAc 5:1, v/v). Upon completion of the reaction, the mixture was diluted with DCM, washed with brine, dried over Na_2SO_4. Product **9** was purified by column chromatography on silica gel eluting with PE:EtOAc 5:1 (v/v). Colorless oil, average yield 55-58%. Spectral characteristics correspond to the literature.[13]

2.1.2. Synthetic procedure for CF_3-containing terpenoids



3, 5-7, 9 **10-14** **15-19**

In a two-necked flask, 0.45 mmol (1 equiv.) of ketone, 1.35 mmol (3 equiv.) of CF_3TMS, and 2 mL of dry THF were placed in a flow of argon. For trifluoromethylation of ketones **6** and **7**, 6 equiv. CF_3TMS and 3 equiv. TBAF, since the reactions proceeded simultaneously on the C=O and OH groups. Next, 0.23 mmol (0.5 equiv.) of CsF was added to the mixture in the cold and left under stirring. The progress of the reaction was monitored by TLC using $CHCl_3$ as eluent and 5% vanillin solution as developer. Upon completion of the reaction, the mixture was extracted with Et_2O or EtOAc (3×10 ml), the combined organic layers were washed with saturated NaCl solution, then dried over Na_2SO_4, the solvent was removed under vacuum. Silyl ethers were purified by column chromatography using the following eluents: **10**, **11** – $CHCl_3$; **13** – PE:EtOAc 50:1; **14** – PE:EtOAc 10:1.

Purified silyl ethers **10**-**14** (1.76 mmol) were dissolved in 2 mL of THF, 2.67 mmol (2.67 mL) of 1M TBAF in THF was added. The mixture was stirred for 8–10 min, the course of the reaction was monitored by TLC with $CHCl_3$ eluted. Then extracted with Et_2O or EtOAc (3×20 ml), the combined organic layers were washed with saturated NaCl solution, then dried over Na_2SO_4, the solvent was removed under vacuum. The residue was chromatographed on silica gel. Compound **15** was purified using the eluent $CHCl_3$:Et_2O 10:1; **16** – PE:EtOAc 3:1; **17** – $CHCl_3$:*i*-PrOH 50:2; **18** – $CHCl_3$:Et_2O 20:1; **19** – PE:Et_2O 10:1. The trifluoromethylation reaction of betulenone **3** was carried out in one stage without isolation of intermediate silyl ethers. A similar synthesis in one-pot was carried out for the rest of the ketones as a control.

2.1.3. General procedure for acid-catalyzed isomerization of compounds 10 and 15

Acid catalysis. To a solution of 0.34 mmol of ether **10** or alcohol **15** in 2 mL of dry benzene was added 0.02 mmol (5 mol.%) of PTSA·H_2O or CSA. The mixture was stirred at room temperature or at the boil. The progress of the reaction was monitored by TLC on $CHCl_3$:Et_2O 10:1 (v/v). Upon completion of the reaction, the mixture after reflux was cooled to room temperature, diluted with 15–20 ml of benzene, washed with brine, then dried over Na_2SO_4, the solvent was removed under vacuum. The residue was chromatographed on silica gel, eluent $CHCl_3$:Et_2O. R_f (**25**+**26**) = 0.82, R_f (**23**+**24**) = 0.13. The eluents used are indicated in the description of each of the products.

Rearrangement of 15 with $ZnCl_2$. A solution of 100 mg (0.34 mmol) of **15** in 5 mL of dried DCM and 3 mg (0.02 mmol, 5 mol %) of anhydrous $ZnCl_2$ was placed in a two-necked flask under argon, and the mixture was stirred at reflux. TLC control for $CHCl_3$: Et_2O 10:1. Upon completion of the reaction (40-60 min), the mixture was cooled to room temperature, diluted with 15-20 mL DCM, washed with brine, the organic layer was dried over Na_2SO_4, the solvent was removed under vacuum. The residue was chromatographed on silica gel using $CHCl_3$:*i*-PrOH 50:1 eluent, developing with vanillin. Two fractions were isolated: 1 - a mixture of **27**+**28**, 2 - **23**+**24**. Fraction 1 was re-separated by eluting with DCM with obtaining individual components.

Isomerization with LDA. Substrates **10** or **15** (0.62 mmol) in dry THF (5 mL) and 2M LDA (0.31 mL) in THF (0.62 mmol) were placed in a two-necked flask, and the mixture was refluxed under argon. The progress of the reaction was monitored by TLC using the $CHCl_3$:Et_2O 10:1 (v/v) eluent. Upon completion of the reaction, the mixture was extracted with Et_2O (3×10 ml), the combined organic layers were washed with brine, then dried over Na_2SO_4, the solvent was removed under vacuum. The residue was chromatographed on silica gel eluting with $CHCl_3$:Et_2O 10:1 (to isolate the transformation products of alcohol **15**) or PE:EtOAc 10:1 (to isolate the transformation products of ether **10**).

2.2. Biological Activity Study

2.2.1. Antiviral activity

Cytotoxicity Assay. MDCK cells were seeded onto 96-well culture plates (10^4 cells per well) and incubated at 36 °C in 5% CO_2 until continuous monolayer formation. To assess the toxicity of compounds, a series of their three-fold dilutions at concentrations of 300 to 3.7 μg/mL in Eagle's MEM medium were prepared. The dilutions were added to the wells of the plates. Cells were incubated for 72 h at 36 °C in a CO_2 incubator under 5% CO_2. Further, a microtetrazolium (MTT) assay was performed on 96-well plates. The cells were washed 2 times with saline (0.9% NaCl) and 100 μL/well of MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) at a concentration of 0.5 μg/mL in MEM was added. The plates were incubated for 1 h at 36 °C, the liquid was removed and DMSO (0.1 mL per well) was added. The optical density of the cells was measured on a Thermo Multiskan FC spectrophotometer (Thermo Fisher Scientific, USA) at a wavelength of 540 nm. Based on the obtained data, the CC_{50}, the concentration of the compound that destroys 50% of the cells in culture, was calculated for each specimen.

CPE Reduction Assay. The compounds in appropriate concentrations were added to MDCK cells (0.1 mL per well). MDCK cells were further infected with A/Puerto Rico/8/34 (H1N1) influenza virus (m.o.i 0.01). Plates were incubated for 72 h at 36 °C at 5% CO_2. After that, cell viability was assessed by MTT test as described above. The cytoprotective activity of compounds was considered as their ability to increase the values of OD compared to control wells (with virus only, no drugs). Based on the results obtained, the values of IC_{50}, i.e., the concentration of compounds that results in 50% cells protection, were calculated using GraphPad Prism software. Values of IC_{50} obtained in micrograms/mL were then calculated into micromoles. Based on the obtained data, the selectivity index (SI), the ratio of CC_{50} to IC_{50}, was calculated for each compound.

2.2.2. Antibacterial activity assay

The antibacterial activity of compoundshas been tested on methicillin sensitive *Staphylococcus aureus* ATCC®29213 (MSSA), *Staphylococcus aureus* MRSA clinical isolate, *Pseudomonas aeruginosa* (ATCC 27853D-5). *Candida albicans* 706 (clinical isolate from mucous membranes of the tonsils) was used to assess antifungal activity. Clinical isolates were

obtained from the Kazan Institute of Epidemiology and Microbiology (Kazan, Russia). Strains were stored in 10% (v/v) glycerol stocks at -80 °C and freshly streaked on LB-agar plates (or Sabouraudagar for *C.albicans*) and grown overnight at 37 °C before use. The 18 h cultures of microorganisms were adjusted to 10^8 cells/mL in full MH-broth (Sigma-Aldrich) and used as a working suspension.

The MIC of compounds was determined by the broth microdilution method in 96-well microtiter plates (Eppendorf) according to the EUCAST rules for antimicrobial susceptibility testing[14]. The reference antimicrobials were purchased from Sigma-Aldrich. The microbial culture adjusted to 3-9×10^5 cells/mL in the MH broth was seeded into 96-well polystyrol culture plates (Eppendorf). The concentrations of treated compounds ranged from 1 to 1024 μg/mL. The minimal inhibitory concentration was determined as the lowest concentration of compound for which no visible growth could be observed after 24 h of incubation.

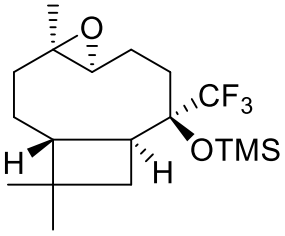
***Cytotoxicity*.** The cytotoxicity of compounds was evaluated on HEK 293by MTT assay. Cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum, 2 mM *L*-glutamine, 100 μg/mL penicillin and 100 μg/mL streptomycin. Cells were seeded in 96-well plates at the density of 3000 cells per well and grown overnight at 37 °C and 5% CO_2 in humidified atmosphere. Then the medium was changed to the fresh one containing compounds in concentration of 0-1024 μg/mL. After 24 h of cultivation the medium was replaced with a fresh one and MTT solution (in Dulbecco's phosphate-buffered saline) was added to the wells until final concentration of 0.5 mg/mL. After 3 h incubation the liquid was removed and formazan crystals were dissolved in dimethyl sulfoxide, and absorption was measured on Tecan Infinite 200Pro at 557 nm with reference 700 nm. Based on data obtained, the CC_{50} values (concentrations decreasing the proliferative activity by 2-fold) were calculated.

***Genotoxicity*.** The Ames test was carried out using *S. typhimurium*TA98, TA100, TA102 strains was performed as described in [15]. Due to compounds toxicity to *S. typhimurium*, the spot test modification has been applied. For that, 5 μL of sample (10 mg/mL solution in water) was dropped onto 5-mm filter disk placed on the top agar surface (see Table S6). The amount of revertants was then calculated by using the in-house developed software[16]. The tested compound was considered to be mutagenic if the count of revertants in the experiment was more than 2 times

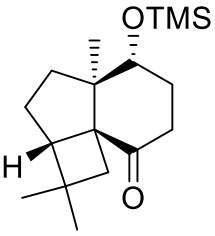
higher than that in the negative control (DMSO) and increased at higher concentrations of compound.

Statistics and data analysis. All experiments were performed in biological triplicates (i.e. newly prepared cultures and medium) with three repeats in each run. Comparison against negative control using the non-parametric Kruskal–Wallis one-way analysis of variance test has been performed in each experiment. Significant differences against respective controls were considered at $p<0.05$ and specified in the corresponding figure captions

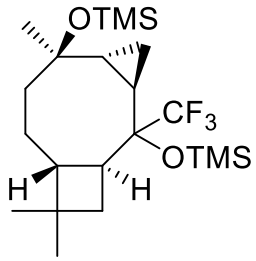
3. Characteristics of the synthesized compounds



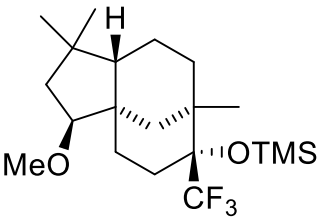
Trimethyl(((1*R*,4*R*,6*S*,9*R*,10*S*)-4,12,12-trimethyl-9-(trifluoromethyl)-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-yl)oxy)silane 10. Yield 95%, yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.09 (1H, dd, *J* = 9.5, 4.8, H-5), 2.34-2.01 (4H, m, H-3A, H-6A, H-7A, H-9), 1.93-1.57 (4H, m, H-1, H-2A, H-10A, H-10B), 1.51-1.41 (2H, m, H-2B, H-7B), 1.27-1.23 (1H, m, H-6B), 1.27 (3H, s, Me-14), 1.10-0.95 (1H, m, H-3B), 0.96 (3H, s, Me-12), 0.93 (3H, s, Me-13), 0.26 (s, 9H, Me-16, Me-17, Me-18). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 126.9 (C-15, q, *J* = 292.10 Hz), 78.8 (C-8, q, *J* = 24.55 Hz), 60.5 (C-5), 59.0 (C-4), 48.6 (C-9), 46.2 (C-1), 40.2 (C-3), 36.2 (C-10), 33.3 (C-11), 31.4 (C-7), 29.5 (C-13), 28.0 (C-2), 24.4 (C-6), 22.3 (C-12), 16.1 (C-14), 1.9 (C-16, C-17, C-18). ^{19}F (282 MHz, $CDCl_3$, δ, ppm): -75.67 (s, CF_3). IR (v, sm^{-1}): 2954, 2864, 1456, 1377, 1292, 1255 (CF_3), 1211, 1159, 1136, 1066, 1047, 1020, 958, 893, 842 ($(CH_3)_3Si$), 758 (C-O-C), 713, 688, 478. Mass spectrum, *m/z* (ESI, 10 eV, I_{rel}, %): 365.30 (100) $[M+H]^+$. Calculated: $C_{18}H_{31}F_3O_2Si$, MW = 364.51.



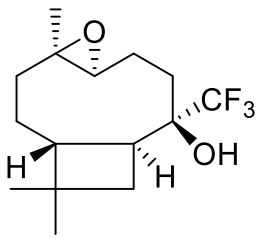
(2a*S*,4a*R*,5*R*,8a*S*)-2,2,4a-trimethyl-5-((trimethylsilyl)-oxy)octahydro-cyclobuta[c]inden-8(1*H*)-one 11. Yield 93%, yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.89-3.75 (m, 1H, H-5), 2.63-2.44 (m, 2H, H-1, H-8A), 2.41-2.26 (m, 2H, H-2a, H-8B), 2.06-1.73 (m, 5H, H-3A, H-3B, H-4A, H-6A, H-6B), 1.64-1.50 (m, 1H, H-4B), 1.40 (d, 1H, H-1, *J* = 12 Hz), 1.02 (s, 3H, Me-10), 0.91 (s, 3H, Me-11), 0.83 (s, 3H, Me-9), 0.17 (s, 9H, Me-12, Me-13, Me-14). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 212.2 (C-8), 70.9 (C-5), 58.2 (C-8a), 55.0 (C-2a), 53.9 (C-4a), 37.4 (C-4), 36.3 (C-8), 33.3 (C-1), 31.2 (C-2), 30.7 (C-6), 29.9 (C-10), 25.2 (C-3), 24.5 (C-11), 12.4 (C-9), 0.4 (C-12, C-13, C-14). IR (v, sm^{-1}): 2953, 2872, 1697 (C=O), 1462, 1431, 1375, 1323, 1253, 1174, 1114, 1093, 1039, 977, 952, 896, 842 (Me_3Si), 750, 684, 628, 572, 464, 401. Mass spectrum, *m/z* (ESI, 10 eV, I_{rel}, %): 297.28 (55) $[M+3H]^+$, 263.30 (100) $[M-2CH_3-H]^+$. Calculated: $C_{17}H_{30}O_2Si$, MW = 294.50.



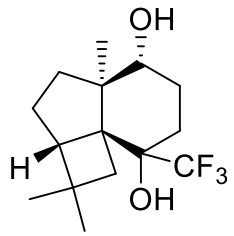
(((1*S*,2*S*,3*R*,5*R*,6*R*,9*R*)-6,10,10-trimethyl-2-(trifluoromethyl)tricyclo[7.2.0.0^{3,5}]undecane-2,6-diyl)bis(oxy))bis(trimethylsilane) 13. Yield 74%, yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 2.35-2.19 (m, 1H, H-1), 1.94-1.44 (m, 6H, H-8B, H-9, H-7A, H-7B, H-11A, H-11B), 1.03-1.20 (m, 2H, H-5, H-8A), 0.98 (s, 3H, Me-12), 0.96 (s, 3H, Me-13), 0.82 (s, 3H, Me-14), 0.63-0.73 (m, 1H, H-3), 0.49-0.63 (m, 2H, H-4A, H-4B), 0.17 (s, 9H, Me-19, Me-20, Me-21), 0.14 (s, 9H, Me-16, Me-17, Me-18). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 126.5 (C-15, q, *J* = 287.36 Hz), 89.1 (C-2, q, *J* = 9.95 Hz), 75.8 (C-6), 48.3 (C-7), 46.8 (C-1), 46.5 (C-9), 35.3 (C-10), 33.8 (C-11), 29.5 (C-5), 26.8 (C-8), 21.6 (C-13), 21.0 (C-12), 20.7 (C-3), 20.6 (C-14), 4.2 (C-4), 2.8 (C-16, C-17, C-18), 2.0 (C-19, C-20, C-21). ^{19}F NMR (282 MHz, $CDCl_3$): -76.62 (s, CF_3). IR (v, sm^{-1}): 3010, 2954, 2864, 1458, 1406, 1379, 1298, 1253, 1172, 1132, 1103 (CF3), 1047, 1029 (Si-O-C), 981, 912, 887, 840, 754 (Me_3Si), 719, 682, 638, 511, 470. Mass spectrum, *m/z* (ESI, 10 eV, I_{rel}, %): 437.30 (100) $[M+H]^+$. Calculated: $C_{21}H_{39}F_3O_2Si_2$, MW = 436.69.



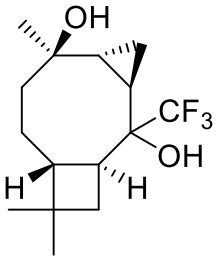
(((3*S*,3a*S*,6*S*,7*R*,9a*S*)-3-methoxy-1,1,7-trimethyl-6-(trifluoromethyl)decahydro-3a,7-methanocyclopenta[8]annulen-6-yl)oxy)trimethylsilane 14. Yield 93%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.33 (s, 3H, Me-16), 3.40-3.24 (m, 1H, H-2), 2.15-2.02 (m, 1H, H-7B), 1.87-1.85 (m, 5H, H-3B, H-7A, H-10B, H-11B, H-12B), 1.52-1.10 (m, 7H, H-3A, H-5, H-6A, H-6B, H-10A, H-11A, H-12A), 1.05 (s, 3H, Me-14), 1.02 (d, 3H, Me-15, *J* = 2.06 Hz), 0.87 (s, 3H, Me-13), 0.15 (s, 9H, Me-18, Me-19, Me-20). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 127.3 (C-17, q, *J* = 289.54 Hz), 89.2 (C-2), 80.5 (C-8, q, *J* = 24.82 Hz), 58.2 (C-16), 51.7 (C-5), 44.4 (C-3), 43.2 (C-1), 39.0 (C-12, d, *J* = 2.21 Hz), 38.1 (C-4), 37.2 (C-8), 32.9 (C-10), 31.3 (C-14), 29.6 (C-11), 28.6 (C-7), 26.3 (C-15, d, *J* = 2.21 Hz), 25.4 (C-13), 20.1 (C-6), 2.1 (C-18, C-19, C-20). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -67.95 (s, CF_3). Mass spectrum, *m/z* (ESI, 10 eV, I_{rel}, %): 392.40 (100) $[M]^+$. Calculated: $C_{20}H_{35}F_3O_2Si$, MW = 392.5714.



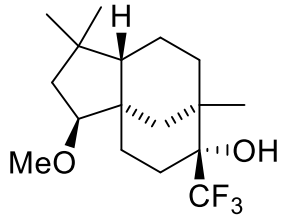
(1*R*,4*R*,6*S*,9*R*,10*S*)-4,12,12-trimethyl-9-(trifluoromethyl)-5-oxatricyclo[8.2.0.0^{4,6}]dodecan-9-ol 15. Yield 87%, white powder, α_D^{24} -81.0 (*c* = 0.200, $CHCl_3$), M.P. = 142-143 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.24 (dd, 1H, H-5, *J* = 9.8, 4.8 Hz), 2.39 (s, 1H, OH), 2.36-2.17 (m, 3H, H-6B, H-7B, H-9), 2.16-2.02 (m, 1H, H-3B), 1.90 (t, 1H, H-1, *J* = 9.2 Hz), 1.82-1.62 (m, 3H, H-2B, H-10A, H-10B), 1.58-1.30 (m, 3H, H-2A, H-6A, H-7A), 1.30 (s, 3H, Me-14), 1.11-0.97 (m, 1H, H-3A), 0.99 (s, 3H, Me-12), 0.95 (s, 3H, Me-13). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 127.0 (q, C-15, *J* = 288.6 Hz), 74.6 (q, C-8, *J* = 25.43 Hz), 60.8 (C-5), 59.0 (C-4), 47.4 (C-9), 46.4 (C-1), 40.1 (C-3), 35.8 (C-10), 33.7 (C-11), 30.2 (C-7), 29.2 (C-13), 27.8 (C-2), 23.5 (C-6), 21.7 (C-12), 16.1 (C-14). ^{19}F (282 MHz, $CDCl_3$, δ, ppm): -79.70 (s, CF_3). IR (v, sm^{-1}): 3429 (OH), 2947, 2868, 1463 (CF_3), 1384, 1363, 1282, 1230, 1168, 1155, 1112, 1070, 1043, 983, 960, 914, 862 (C-O-C, epoxyde), 796, 734, 673, 632, 580, 557, 542, 482, 424. Mass spectrum, *m/z* (ESI, 10 eV, I_{rel}, %): 293.18 (100) $[M+H]^+$. Calculated: $C_{15}H_{33}F_3O_2$, MW = 292.33.



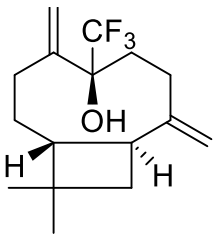
(2a*S*,4a*R*,5*R*,8*S*,8a*S*)-2,2,4a-trimethyl-8-(trifluoromethyl)decahydro-cyclobuta[c]indene-5,8-diol 16. Yield 50%, white powder, α_D^{27} -40.6 (*c* = 0.182, $CHCl_3$), M.P. = 113-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.55-3.42 (m, 1H, H-5), 2.57 (d, 1H, H-2a, *J* = 6.50 Hz), 2.40-2.20 (m, H-2H, H-7B, OH), 2.14-1.94 (m, 2H, H-1B, H-4B), 1.96-1.61 (m, 6H, H-3B, H-4A, H-6A, H-6B, H-7A, OH), 1.61-1.36 (m, 2H, H-1A, H-3A), 1.22 (s, 3H, Me-10), 0.94 (s, 3H, Me-11), 0.90 (d, 3H, Me-9, *J* = 2.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 126.9 (C-12, q, *J* = 291.67 Hz), 75.5 (C-2, q, *J* = 25.84 Hz), 73.0 (C-5), 52.6 (C-8a), 50.9 (C-2a), 49.3 (C-4a), 39.9 (C-7), 36.7 (C-7), 31.1 (C-1), 29.3 (C-10), 29.0 (C-2), 26.8 (C-6), 24.8 (C-11), 23.8 (C-3), 13.4 (C-9, q, *J* = 5.53 Hz). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -69.97 (s, CF_3). IR (v, sm^{-1}): 3385 (OH), 2949, 2873, 1707, 1460, 1384, 1336, 1269, 1228, 1170, 1147, 1116, 1082, 1062 (CF_3), 1033, 1004, 977, 950, 904, 879, 811, 734, 698, 673, 651, 619, 596, 538, 468, 455. Mass spectrum, *m/z* (ESI, 40 eV, I_{rel}, %): 315.23 (100) $[M+Na]^+$, 293.10 (37) $[M+H]^+$. Calculated: $C_{15}H_{23}F_3O_2$, MW = 292.33.



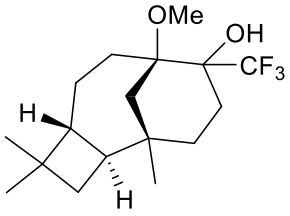
(1*S*,2*S*,3*R*,5*R*,6*R*,9*R*)-6,10,10-trimethyl-2-(trifluoromethyl)tricyclo[7.2.0.0^{3,5}]undecane-2,6-diol 17. Yield 69%, yellow liquid, α_D^{26} +6,2 (*c* = 0.450, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 2.36 (q, 1H, H-1, *J* = 9.39 Hz), 2.04 (br.s., 2H, OH), 1.95-1.78 (m, 2H, H-8B, H-9), 1.77-1.62 (m, 2H, H-7A, H-7B), 1.62-1.50 (m, 2H, H-11A, H-11B), 1.36-1.08 (m, 2H, H-5, H-8A), 1.00 (s, 3H, Me-13), 0.98 (s, 3H, Me-12), 0.84 (s, 3H, Me-14), 0.76-0.55 (m, 3H, H-3, H-4A, H-4B). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 126.6 (C-15, q, *J* = 282.52 Hz), 72.8 (C-6), 71.5 (C-2, q, *J* = 28.60 Hz), 46.5 (C-7), 48.4 (C-9), 45.7 (C-1), 35.5 (C-10), 33.2 (C-11), 29.3 (C-12), 26.7 (C-8), 21.2 (C-13), 20.4 (C-14), 20.2 (C-5), 18.7 (C-3), 2.2 (C-4). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -80.36 (s, CF_3). IR (v, sm^{-1}): 3387 (OH), 2951, 2927, 2864, 1707, 1460, 1375, 1284, 1224, 1155, 1097, 1072 (CF_3, br. absorption band), 1026, 1001, 975, 941, 894, 840, 759, 682, 657, 592, 549, 472, 422. Mass spectrum, *m/z* (ESI, 40 eV, I_{rel}, %): 291.01 (100) $[M-H]^+$. Calculated: $C_{15}H_{23}F_3O_2$, MW = 292.33.



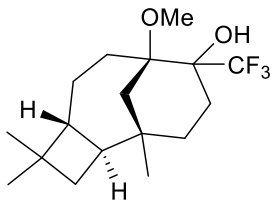
(3*S*,3a*S*,6*S*,7*R*,9a*S*)-3-methoxy-1,1,7-trimethyl--6-(trifluoromethyl)decahydro-3a,7-methanocyclopenta[8]annulen-6-ol 18. Yield 76%, white powder, M.P. = 78 ^{o}C, α_D^{25} +2.00 (*c* = 0.200, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.37 (d, 1H, H-2, *J* = 5.9 Hz), 3.33 (s, 3H, Me-17), 1.99-2.12 (m, 1H, H-7B), 1.96 (s, 1H, OH), 1.90-1.61 (m, 5H, H-3B, H-7B, H-10B, H-11B, H-12B), 1.52-1.14 (m, 7H, H-3A, H-5, H-6A, H-6B, H-10A, H-11A, H-12A), 1.07 (t, 3H, Me-15, *J* = 2.05, 2.96 Hz), 1.05 (s, 3H, Me-14), 0.87 (s, 3H, Me-13). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 127.5 (C-15, q, *J* = 281.60 Hz), 89.0 (C-2), 76.9 (C-9, q, *J* = 26.05 Hz), 58.2 (C-17), 51.5 (C-5), 44.3 (C-3), 43.3 (C-1), 39.2 (C-12, d, *J* = 2.21 Hz), 37.1 (C-8), 37.0 (C-4), 32.0 (C-10), 31.2 (C-14), 29.3 (C-11), 27.5 (C-7), 26.0 (C-15, d, *J* = 2.21 Hz), 25.3 (C-13), 19.9 (C-6). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -69.69 (s, CF_3). IR (v, sm^{-1}): 3423 (OH), 2954, 2877, 1458, 1382, 1359, 1340, 1303, 1271, 1244 (CF_3), 1199, 1145 (C-O-C), 1099 (CF_3), 1033, 987, 974, 925, 900, 617, 590, 570, 545, 491, 470, 447. Mass spectrum, *m/z* (ESI, 40 eV, I_{rel}, %): 343.34 (100) $[M+Na]^+$, 321.42 (43) $[M+H]^+$. Calculated: $C_{17}H_{27}F_3O_2$, MW = 320.20.



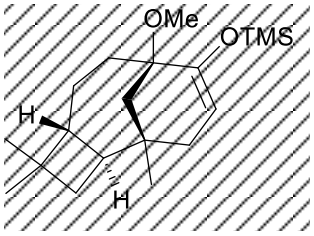
(1*S*,9*R*)-10,10-dimethyl-2,6-dimethylene-5-(trifluoromethyl)bicyclo[7.2.0]undecan-5-ol 19a,b. Yield 89%, colorless oil, mixture of isomers with *dr* = 5:1. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 5.54 (t, 1H, H-14'B, *J* = 2.42, 1.57 Hz), 5.41 (d, 1H, H-14A, *J* = 1.38 Hz), 5.29 (d, 2H, H-14'A, H-14'B, *J* = 18.93 Hz), 4.86 (d, 2H, H-15'A, H-15'B, *J* = 13.44 Hz), 4.75 (d, 2H, H-15A, H-15B, *J* = 17.61 Hz), 2.57-2.32 (m, H, H-2B, 2'B, 7B, 7'B, 9, 9'), 2.28 (s, 2H, 2OH), 2.21-2.03 (m, H, H-2A, H-2'A), 2.03-1.77 (m, H, H-3B, H-3'B, H-6B, H-6'B), 1.74-1.48 (m, 10H, H-1, H-1', H-3A, H-3'A, H-6A, H-6'A, H-10A, H-10B, H-10'A, H-10'B), 1.01 (s, 12H, Me-12, Me-12', Me-13, Me-13'). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): *major signals* 153.1 (C-8), 145.5 (C-4), 125.3 (C-16, q, *J* = 285.12 Hz), 117.1 (C-14), 110.3 (C-15), 78.9 (C-5, q, *J* = 26.45 Hz), 53.8 (C-1), 44.8 (C-9), 38.1 (C-10), 33.7 (C-11), 32.0 (C-3), 29.9 (C-13(12)), 29.8 (C-6), 29.6 (C-7), 28.8 (C-2), 22.0 (C-12(13)); *minor signals* 152.6, 144.5, 118.4, 109.9, 53.3, 43.0, 37.5, 33.3, 31.3, 30.2, 30.1, 29.9. ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -78.81 (s, CF_3, major), -80.37 (s, CF_3, minor signals). IR (v, sm^{-1}): 3599, 3489 (OH), 2953, 2931, 2866, 1716, 1637, 1460, 1409, 1367, 1284, 1259, 1224 (CF_3), 1159, 1101, 1058, 1004, 968, 918, 889, 827, 736, 665, 623, 553, 462. Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 287.00 (100) $[M-H]^+$. Calculated: $C_{16}H_{23}F_3O_2$, MW = 288.34.



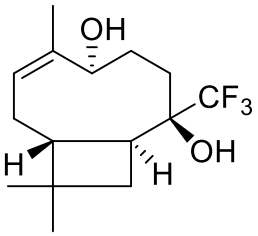
(1*S*,2*S*,5*R*,8*R*)-8-methoxy-1,4,4-trimethyl-9-(trifluoromethyl)tricyclo[6.3.1.0^{2,5}]dodecan-9-ol 20a. Yield 40 %, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 3.28 (s, 3H, MeO-16), 2.71 (s, 1H, OH), 2.14-1.88 (m, 5H, H-2, H-10A, H-10B, H-11A, H-12A), 1.83-1.43 (m, 7H, H-3A, H-5, H-6A, H-6B, H-7A, H-11B, H-12B), 1.39-1.30 (m, 2H, H-3B, H-7A), 1.00 (s, 3H, Me-14(15)), 0.99 (s, 3H, Me-15(14)), 0.85 (s, 3H, Me-13). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 126.4 (q, *J* = 288.6 Hz, C-17), 81.5 (C-8), 79.2 (C-9, q, *J* = 25.60 Hz), 49.8 (C-16), 44.4 (C-5), 39.6 (d, *J* = 2.2 Hz, C-12), 37.2 (C-2), 35.6 (C-3), 34.9 (C-4), 34.3 (C-7), 32.1 (C-1), 32.0 (C-11), 30.6 (C-15), 28.2 (C-10), 26.0 (C-13), 22.2 (C-6), 20.7 (C-14). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -67.45 (s, CF_3). Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 662.91 (100) $[2M+Na-H]^+$, 343.22 (37) $[M+Na]^+$. Calculated: $C_{17}H_{27}F_3O_2$, MW = 320.20.



(1*S*,2*S*,5*R*,8*R*)-8-methoxy-1,4,4-trimethyl-9-(trifluoromethyl)tricyc-lo[6.3.1.0^{2,5}]dodecan-9-ol 20b. Yield 21 %, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 4.01 (s, 1H, OH), 3.29 (s, 3H, MeO), 2.04-1.50 (m, 5H, H-2, H-5, H-3A, H-6A, H-7A, H-10A, H-10B, H-11, H-12A), 1.45-1.33 (m, H-3B, H-6B, H-12B), 1.23-1.29 (m, H-7A), 1.01 (s, 3H, Me-14), 1.00 (s, 3H, Me-15), 0.86 (s, 3H, Me-13). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 126.6 (q, *J* = 287.79 Hz, C-17. CF_3), 80.1 (C-8), 75.9 (q, *J* = 26.16 Hz, C-9), 48.9 (C-16), 46.5 (C-5), 41.0 (C-12), 40.1 (C-2), 36.5 (C-3), 34.6 (C-4), 33.0 (C-7), 31.8 (C-1), 31.2 (C-11), 30.6 (C-14), 26.6 (C-13), 25.3 (C-10), 24.0 (C-6), 20.6 (C-15). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -75.19 (s, CF_3). Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 319.20 (70) $[M-H]^+$. Calculated: $C_{17}H_{27}F_3O_2$, MW = 320.23.



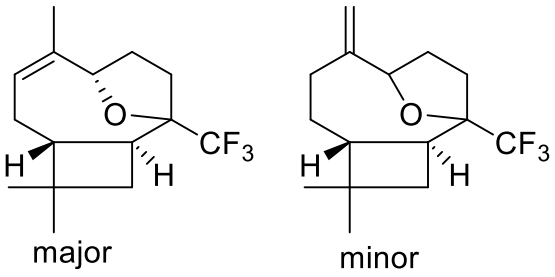
(((1*S*,2*S*,5*R*,8*R*)-8-methoxy-1,4,4-trimethyltricyclo[6.3.1.0^{2,5}]dodec-9-en-9-yl)oxy)trimethylsilane 22. Yield 56 %, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 4.92 (d, 1H, H-10, *J* = 6.5 Hz), 3.11 (s, 3H, Me-16), 2.11 (d, 1H, H-6B, *J* = 12.6 Hz), 2.03-1.86 (m, 2H, H-2, H-11B), 1.82-1.69 (m, 1H, H-11A), 1.66 (s, 2H, H-12A, H-12B), 1.59-1.35 (m, 4H, H-5, H-3B, H-7A, H-7B), 1.30-1.15 (m, 1H, H-6A), 1.14-1.06 (m, 1H, H-3A), 0.98 (s, 3H, Me-15), 0.94 (s, 3H, Me-12), 0.86 (s, 3H, Me-13), 0.25 (s, 9H, Me-17, Me-18, Me-19). ^{13}C NMR (75 MHz, $CDCl_3$): 150.3 (C-9), 107.2 (C-10), 79.2 (C-8), 49.0 (C-16), 47.0 (C-5), 44.4 (C-2), 44.0 (C-12), 40.4 (C-11), 37.4 (C-3), 36.8 (C-7), 33.4 (C-4), 32.5 (C-1), 30.4 (C-15), 26.2 (C-13), 25.5 (C-6), 21.1 (C-12), 0.5 (C-17, C-18, C-19). IR (ν, sm^{-1}): 1651 (C=C), 1253 (Me_3Si), 1078 (Si-O-C), 894, 844 (Me_3Si). Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 323.23 (18) $[M+H]^+$, 263.34 (100) $[M-3Me-O]^+$. Calculated: $C_{19}H_{36}O_2Si$, MW = 322.23.



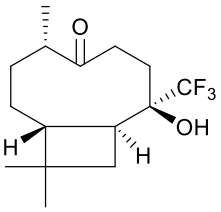
(1*S*,2*R*,5*S*,9*R*,*Z*)-6,10,10-trimethyl-2-(trifluoromethyl)bicyclo[7.2.0]undec-6-ene-2,5-diol 23. Yield 69%, colorless oil. ^{1}H NMR (300 MHz, C_6D_6, δ, ppm, *J*, Hz): 5.26 (t, 1H, H-3, *J* = 8.1 Hz), 4.07 (dd, 1H, H-5, *J* = 8.5, 3.8 Hz), 2.49 (q, 1H, H-9, *J* = 9.4 Hz), 2.10-1.80 (m, 4H, H-1, H-2A, H-2B, OH), 1.65 (s, 3H, Me-14), 1.76-1.36 (m, 6H, H-6A, H-6B, H-7A, H-7B, H-10A, H-10B), 0.88 (s, 3H, Me-12), 0.83 (s, 3H, Me-13). ^{13}C NMR (75 MHz, C_6D_6, δ, ppm, *J*, Hz): 138.8 (C-4), 128.3 (C-15, q, *J* = 82.4 Hz), 124.9 (C-3), 86.1 (C-8, q, *J* = 32.38 Hz), 44.1 (C-1), 73.2 (C-5), 38.5 (C-9), 34.6 (C-11), 34.2 (C-10), 31.3 (C-7), 30.0 (C-13), 29.7 (C-6),

27.5 (C-2), 23.3 (C-12), 20.8 (C-14). ^{19}F NMR (282 MHz, C_6D_6, δ, ppm): -78.00 (s, CF_3). IR (ν, sm^{-1}): 3402, 3387 (OH), 2951, 2866, 1456, 1371, 1317, 1284, 1261 (CF_3), 1166, 1120, 1095, 1053, 1029, 1006, 968, 854, 759, 671, 611, 569, 538, 460. Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 291.32 (72) $[M-H]^+$, 273.27 (100) $[M-F]^+$. Calculated: $C_{15}H_{23}F_3O_2$, MW = 292.34.

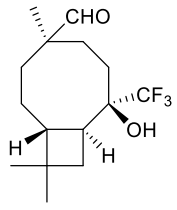
(1*S*,2*R*,5*S*,9*R*)-10,10-dimethyl-6-methylene-2-(trifluoromethyl)-bicyclo[7.2.0]undecane-2,5-diol 24. Not isolated in pure form.



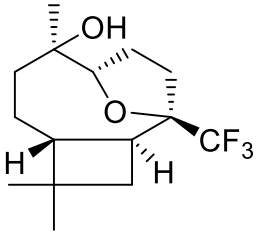
(1*R*,2*S*,5*R*,9*R*,*Z*)-4,4,8-trimethyl-1-(trifluoromethyl)-12-oxatricyclo[7.2.1.0^{2,5}]dodec-7-ene 25, **(1*R*,2*S*,5*R*,9*R*)-4,4-dimethyl-8-methylene-1-(trifluoromethyl)-12-oxatricyclo[7.2.1.0^{2,5}]dodecane 26**. Indivisible mixture. Yield 74%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): *major signals* 5.39 (t, 1H, H-3, *J* = 5.6 Hz), 4.65-4.50 (m, 1H, H-5), 2.41-2.08 (m, 6H, H-1, H-2B, H-7B, H-6B, H-9, OH), 2.02-1.75 (m, 4H, H-2A, H-6A, H-7A, H-10A, H-2'A, H-6'A, H-7'A, H-10'A), 1.69 (s, 3H, Me-14), 1.74-1.62 (m, 1H, H-10A, H-7'A), 1.02 (s, 6H, Me-13, Me-13'), 0.96 (s, 3H, Me-12); *minor signals* 4.88 (d, 2H, H-14'A, H-14'B, *J* = 21.33 Hz), 4.79-4.70 (m, 1H, H-5'), 2.41-2.08 (m, 5H, H-1', H-2'B, H-6'B, H-10'B, OH), 2.02-1.75 (m, 6H, H-2'A, H-3'A, H-3'B, H-6'A, H-7'A, H-10'A), 1.74-1.62 (m, 2H, H-7'A, H-9'), 1.02 (s, 3H, Me-13'), 0.98 (s, 3H, Me-12'). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): *major signals* 137.0 (C-4), 125.3 (C-15, q, *J* = 284.14 Hz), 123.7 (C-3), 83.7 (C-8, q, *J* = 29.53 Hz), 81.8 (C-5), 45.6 (C-1), 43.3 (C-9), 36.2 (C-10), 34.7 (C-6), 34.1 (C-11), 31.1 (C-7), 29.7 (C-13), 28.7 (C-2), 26.3 (C-14), 20.9 (C-12); *minor signals* 141.7 (C-4'), 125.3 (C-15, q, *J* = 284.14 Hz), 110.5 (C-14'), 83.7 (C-8, q, *J* = 29.53 Hz), 80.9 (C-5'), 47.3 (C-1'), 43.8 (C-9'), 40.7 (C-3'), 36.2 (C-7'), 34.1 (C-10'), 32.1 (C-11'), 31.1 (C-2'), 30.1 (C-13'), 29.5 (C-6'), 22.4 (C-12'). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -76.15 (s, CF_3, major signals), -75.66 (s, CF_3, minor signals). IR (ν, sm^{-1}): 2949, 2883, 1458 ($C=CH_2$), 1386, 1367, 1338, 1301, 1265 (epoxyde), 1157, 1128 (CF_3), 1078, 1043, 943, 879, 835 (epoxyde), 779, 740, 719, 638, 530. Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 309.27 (100) $[M+2NH_4-H]^+$, 279.33 (38) $[M+3H]^+$, 255.44 (14) $[M-F]^+$. Calculated: $C_{15}H_{21}F_3O$, MW = 274.33.



(1*S*,2*R*,6*S*,9*R*)-2-hydroxy-6,10,10-trimethyl-2-(trifluoro-methyl)bicyclo[7.2.0]undecan-5-one 27. Yield 25-27%, white powder, M.P. = 122 °C, α_D^{27} +31.8 (*c* = 0.380, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 2.92-2.71 (m, 2H, H-4, H-3B), 2.45 (s, 1H, OH), 2.41-2.28 (m, 2H, H-3A, H-6B), 2.28-2.15 (m, 1H, H-9), 2.14-2.00 (m, 1H, H-6A), 1.94-1.78 (m, 3H, H-1, H-7A, H-7B), 1.71-1.55 (m, 2H, H-10A, H-10B), 1.53-1.41 (m, 1H, H-2B), 1.38-1.21 (m, 1H, H-2A), 1.05 (d, 3H, *J* = 6.7 Hz, Me-14), 0.94 (s, 3H, Me-13), 0.93 (s, 3H, Me-12). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 214.3 (C-5), 126.5 (q, C-15, *J* = 288.37 Hz), 75.2 (q, C-8, *J* = 25.18 Hz), 46.5 (C-1), 45.5 (C-4), 40.1 (C-9), 34.8 (C-3), 34.7 (C-10), 34.5 (C-11), 33.4 (C-7), 29.2 (C-13), 28.2 (C-6), 23.4 (C-2), 23.3 (C-12), 15.7 (C-14). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -78.04 (s, CF_3). IR (v, sm^{-1}): 3458 (OH), 2978, 2945, 2870, 1705 (C=O), 1463, 1450, 1406, 1384, 1278, 1249, 1224, 1166, 1147, 1112 (CF_3), 1056, 1029, 989, 954, 914, 877, 812, 698, 642, 594, 524, 507, 470, 437. Mass spectrum, *m/z* (ESI, 40 eV, I_{rel}, %): 315.39 (100) $[M+Na]^+$, 293.24 (20) $[M+H]^+$. Calculated: $C_{15}H_{21}F_3O$, MW = 292.33.

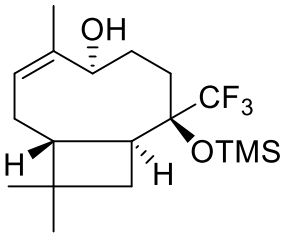


(1*R*,4*R*,7*R*,8*S*)-7-hydroxy-4,10,10-trimethyl-7-(trifluoro-methyl)bicyclo[6.2.0]decane-4-carbaldehyde 28. Yield 32%, colorless oil, α_D^{28} -22.9 (*c* = 0.549, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 9.42 (s, 1H, CHO), 2.36-2.53 (m, 1H, H-8), 1.91-2.13 (m, 3H, H-1, H-5A, OH), 1.90-1.70 (m, 3H, H-3A, H-3B, H-6A), 1.68-1.52 (m, 3H, H-6A, H-9A, H-9B), 1.45-1.28 (m, 3H, H-2A, H-2B, H-5B), 1.02 (s, 3H, Me-13), 1.00 (s, 6H, Me-11, Me-12). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 205.6 (C-14), 126.9 (q, C-15, *J* = 285.23 Hz), 73.7 (q, C-7, *J* = 29.87 Hz), 48.7 (C-4), 43.7 (C-1), 37.7 (C-8), 34.6 (C-10), 33.5 (C-3), 30.5 (C-9), 29.5 (C-13), 27.1 (C-6), 24.5 (C-5), 22.5 (C-12(11)), 22.3 (C-11(12)), 20.0 (C-2). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -80.66 (s, CF_3). IR (v, sm^{-1}): 3479 (OH), 2951, 2866, 2711, 1720 (CHO), 1465, 1371, 1319, 1292, 1153 (CF_3), 1107, 1031, 997, 921, 867, 829, 694, 669, 599. 530. Mass spectrum, *m/z* (ESI, 40 eV, I_{rel}, %): 315.28 (75) $[M+Na]^+$, 293.24 (33) $[M+H]^+$. Calculated: $C_{15}H_{21}F_3O$, MW = 292.33.

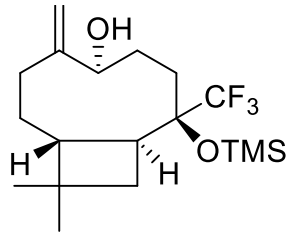


(1*R*,2*S*,5*R*,8*R*,9*S*)-4,4,8-trimethyl-1-(trifluoro-methyl)-12-oxatricyclo[7.2.1.0^{2,5}]dodecan-8-ol 29. Yield 80%. white powder, M.P. = 76-77 °C, α_D^{25} -38.0 (*c* = 0.200, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 4.16 (t, 1H, H-5), 2.48 (br.s., 1H, OH), 2.28-2.04 (m,

4H, H-1, H-7B, H-9, H-10B), 1.95-1.46 (m, 7H, H-2B, H-3A, H-3B, H-6A, H-6B, H-7A, H-10A), 1.39-1.22 (m, 1H, H-2A), 1.05 (s, 3H, Me-12), 1.01 (s, 3H, Me-13), 0.95 (s, 3H, Me-14). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 125.9 (q, *J* = 284.17 Hz, C-15), 87.6 (C-5), 83.5 (q, *J* = 27.64 Hz, C-8), 73.9 (C-4), 43.6 (C-1), 39.2 (C-9), 35.4 (C-3), 34.3 (C-10), 34.1 (C-11), 32.0 (C-6), 30.2 (C-13), 26.9 (C-12), 26.4 (C-7), 21.4 (C-14), 19.5 (C-2). ^{19}F (282 MHz, $CDCl_3$, δ, ppm): -75.67 (s, CF_3). IR (v, sm^{-1}): 3446 (OH), 2949, 2868, 1458 (CF_3), 1375, 1325, 1300, 1265, 1182, 1159, 1143, 1085, 1033, 962, 912 (C-O-C, epoxyde), 829, 732, 651, 540, 447. Mass spectrum, *m/z* (ESI, 10 eV, I_{rel}, %): 293.18 (100) [M+1]. Calculated: $C_{15}H_{23}F_3O_2$, MW = 292.34.



(1*R*,5*S*,8*R*,9*S*,*Z*)-4,11,11-trimethyl-8-(trifluoromethyl)-8-((trimethyl-silyl)oxy)bicyclo[7.2.0]undec-3-en-5-ol 30. Yield 9-67%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 5.59-5.43 (m, 1H, H-3), 4.40-4.23 (m, 1H, H-5), 2.50 (q, 1H, H-9, *J* = 9.1 Hz), 2.22-1.91 (m, 5H, H-1, H-2A, H-2B, H-7B, H-10B), 1.84-1.72 (m, 2H, H-6A, H-6B), 1.79 (s, 3H, Me-14), 1.68-1.43 (m, 2H, H-7A, H-10A), 1.02 (s, 3H, Me-12), 0.97 (s, 3H, Me-13), 0,19 (s, 9H, Me-16, Me-17, Me-18). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 137.8 (C-4), 125.6 (C-15, q, *J* = 129.33 Hz), 125.6 (C-3), 78.1 (C-8, q, *J* = 26.40 Hz), 73.7 (C-5), 43.5 (C-1), 38.7 (C-9), 34.2 (C-11), 33.7 (C-10), 31.6 (C-7), 29.8 (C-13), 29.7 (C-6), 26.3 (C-2), 23.2 (C-12), 21.4 (C-14), 2.1 (C-16, C-17, C-18). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -76.81 (s, CF_3). IR (v, sm^{-1}): 3346 (OH), 2953, 2866, 1456 (Me_3Si), 1409, 1373, 1317, 1255, 1203, 1159 (CF_3), 1080, 1053, 1029, 1001 (Si-O-C), 914, 881, 844 (Me_3Si), 756, 692, 669, 626, 569, 540, 526. Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 365.30 (100) $[M+H]^+$. Calculated: $C_{18}H_{31}F_3O_2Si$, MW = 364.51.



(1*S*,2*R*,5*S*,9*R*)-10,10-dimethyl-6-methylene-2-(trifluoromethyl)-2-((trimethylsilyl)oxy)bicyclo[7.2.0]undecan-5-ol 31. Yield 9%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 5.12 (d, 2H, H-14A, H-14B, *J* = 10.6 Hz), 4.26 (br.s., 1H, H-5), 2.37-2.54 (m, 1H, H-7B), 2.15 (q, 1H, H-1, *J* = 8.7 Hz), 2.00-1.70 (m, 6H, H-2A, H-2B, H-3B, H-6B, H-9, OH), 1.70-1.45 (m, 5H, H-3A, H-6A, H-7A, H-10A, H-10B), 0.95 (s, 3H, Me-13), 0.94 (s, 3H, Me-12), 0.20 (s, 9H, Me-16, Me-17, Me-18). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 151.2 (C-4), 128.7 (q, *J* = 298.42 Hz, C-15), 110.8 (C-14), 77.8 (q, *J* = 12.11 Hz, C-8), 74.7 (C-5), 43.8 (C-1), 42.5 (C-9), 34.6 (C-3), 33.8 (C-11), 31.9 (C-10), 30.8 (C-7), 29.7 (C-

12), 25.0 (C-6), 23.8 (C-2), 23.2 (C-13), 1.6 (C-16-18). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -77.14 (s, CF_3). IR (v, sm^{-1}): 3363 (OH), 2953, 2864, 1454, 1408, 1367 (CF_3), 1286, 1255, 1163, 1116, 1074, 1035, 985, 960, 916, 844, 756 (Me_3Si), 711, 688, 621, 736. Mass spectrum, *m/z* (ESI, 20 eV, I_{rel}, %): 365.30 (100) $[M+H]^+$. Calculated: $C_{18}H_{31}F_3O_2Si$, MW = 364.52.

4. Spectral data of synthesized compounds

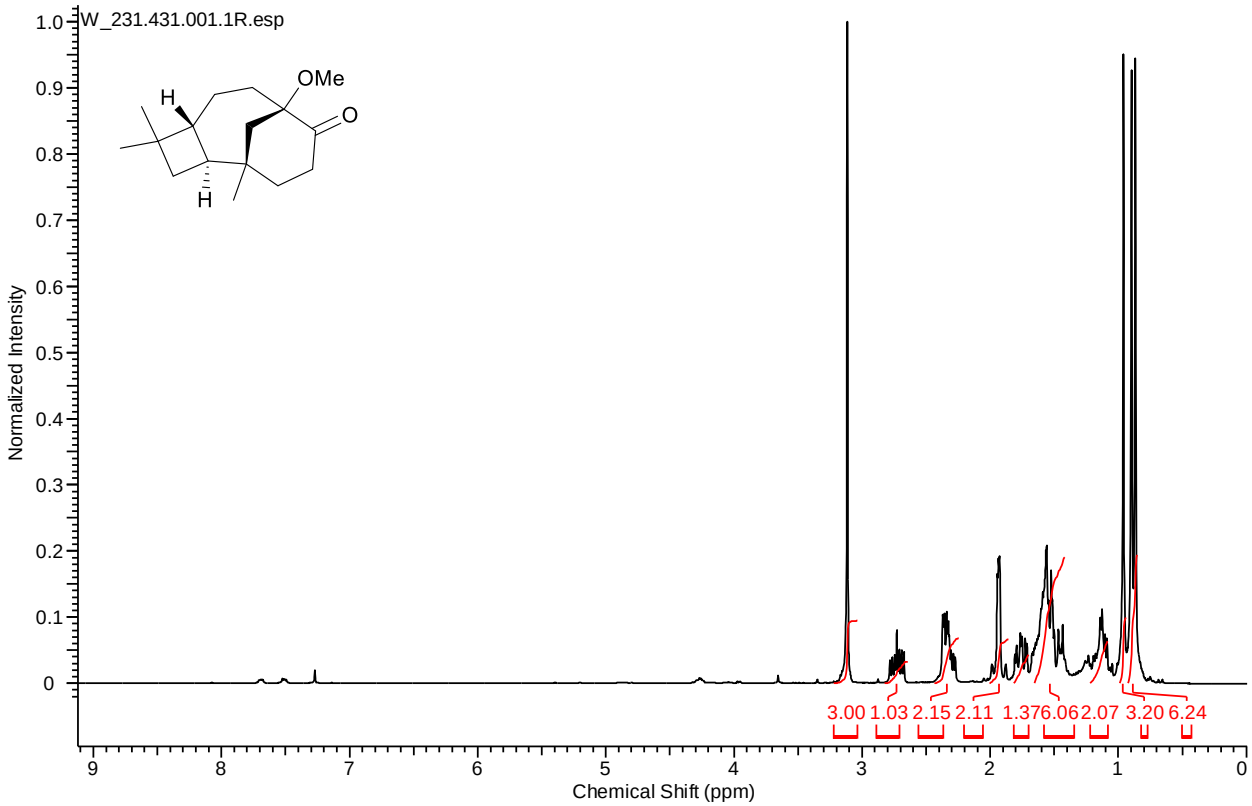


Figure S1. ^{1}H NMR spectra (300 MHz) of 8*β*-Methoxyisocaryolan-9-one **4** in $CDCl_3$

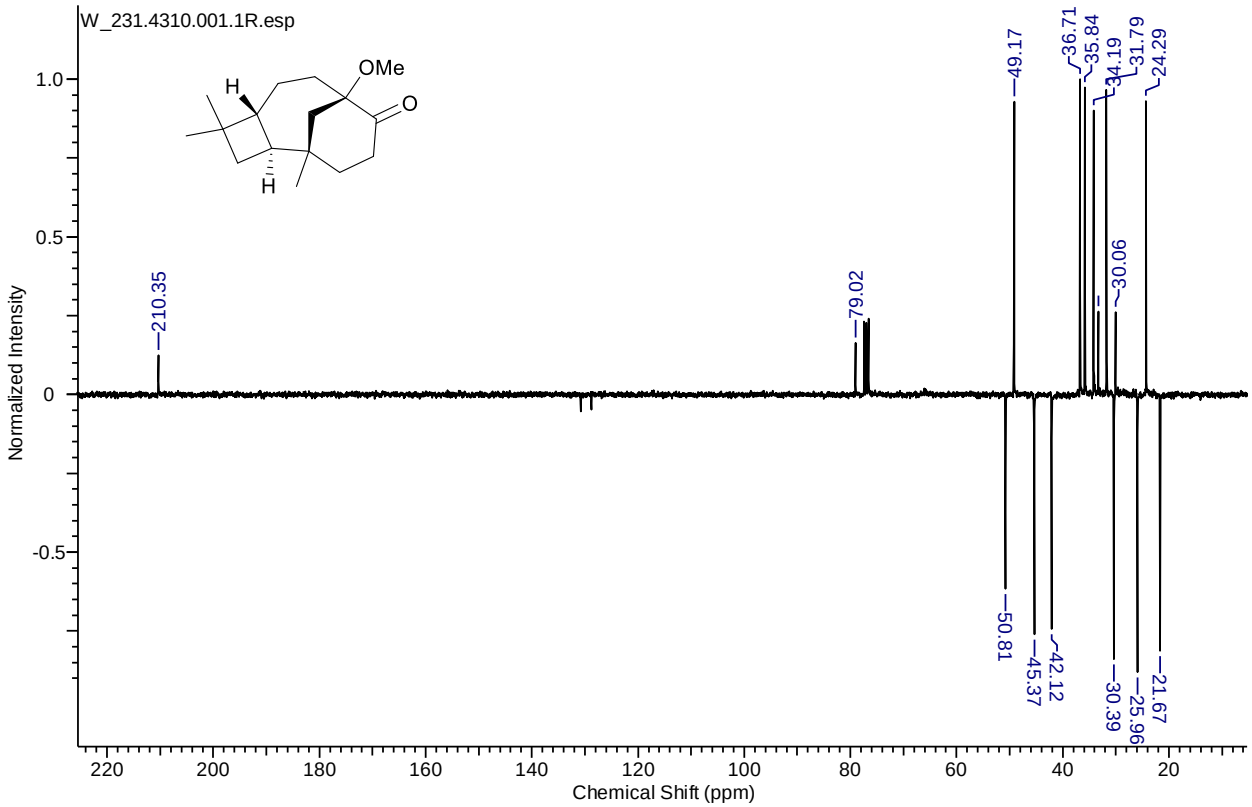


Figure S2. ^{13}C NMR spectra (75 MHz) of **4** in $CDCl_3$

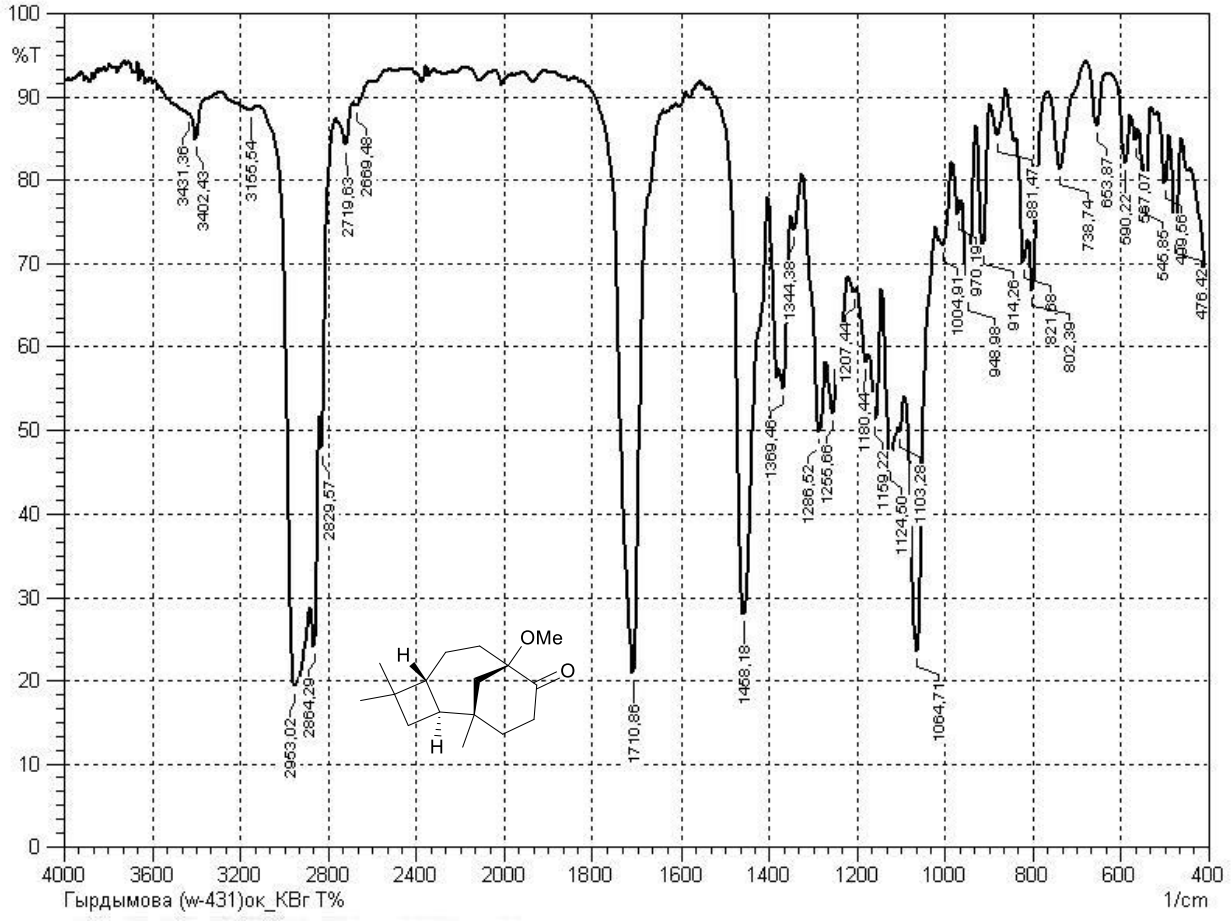


Figure S3. IR spectra of **4**

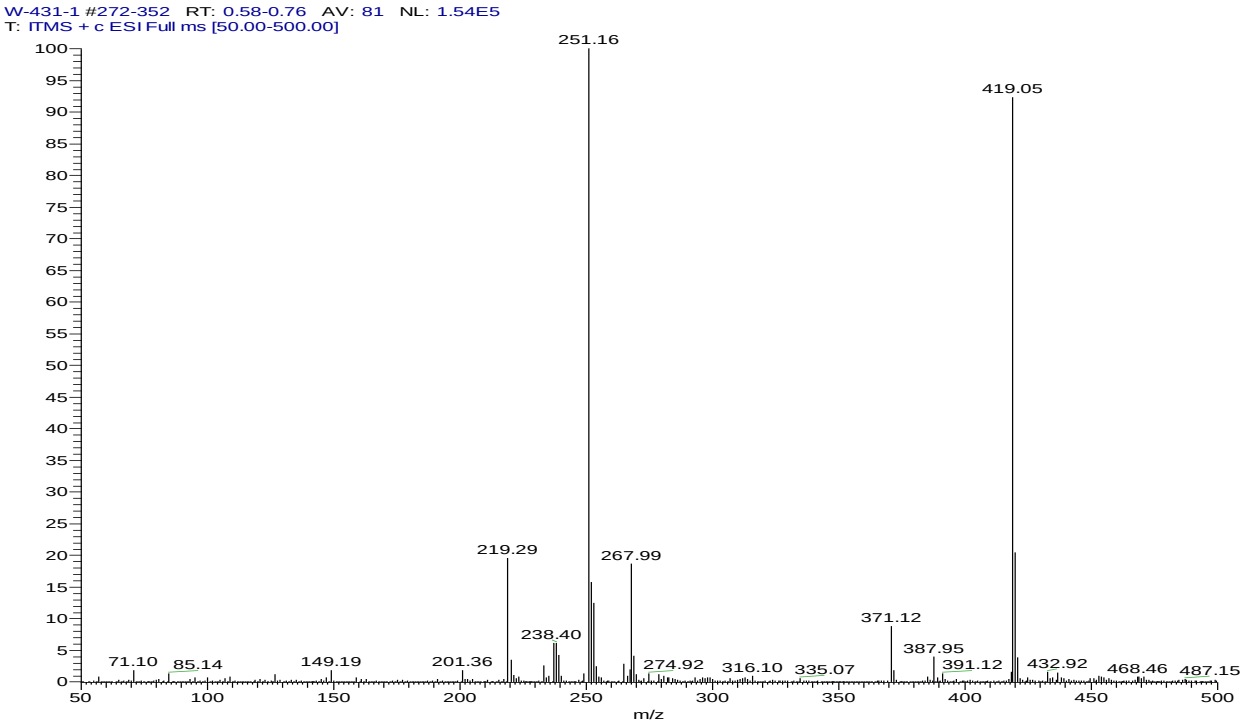


Figure S4. ESI-MS spectra of ketone **4**

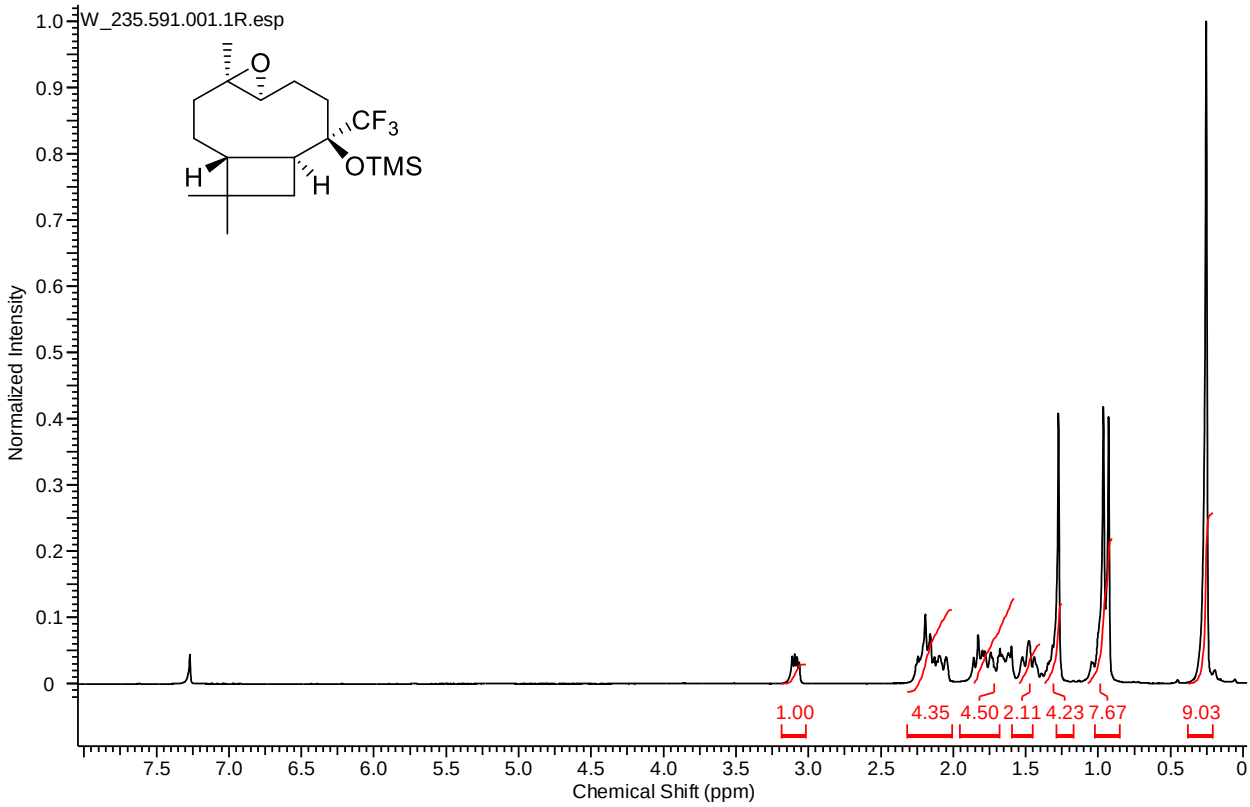


Figure S5. ^{1}H NMR spectra (300 MHz) of silyl ether **10** in $CDCl_3$

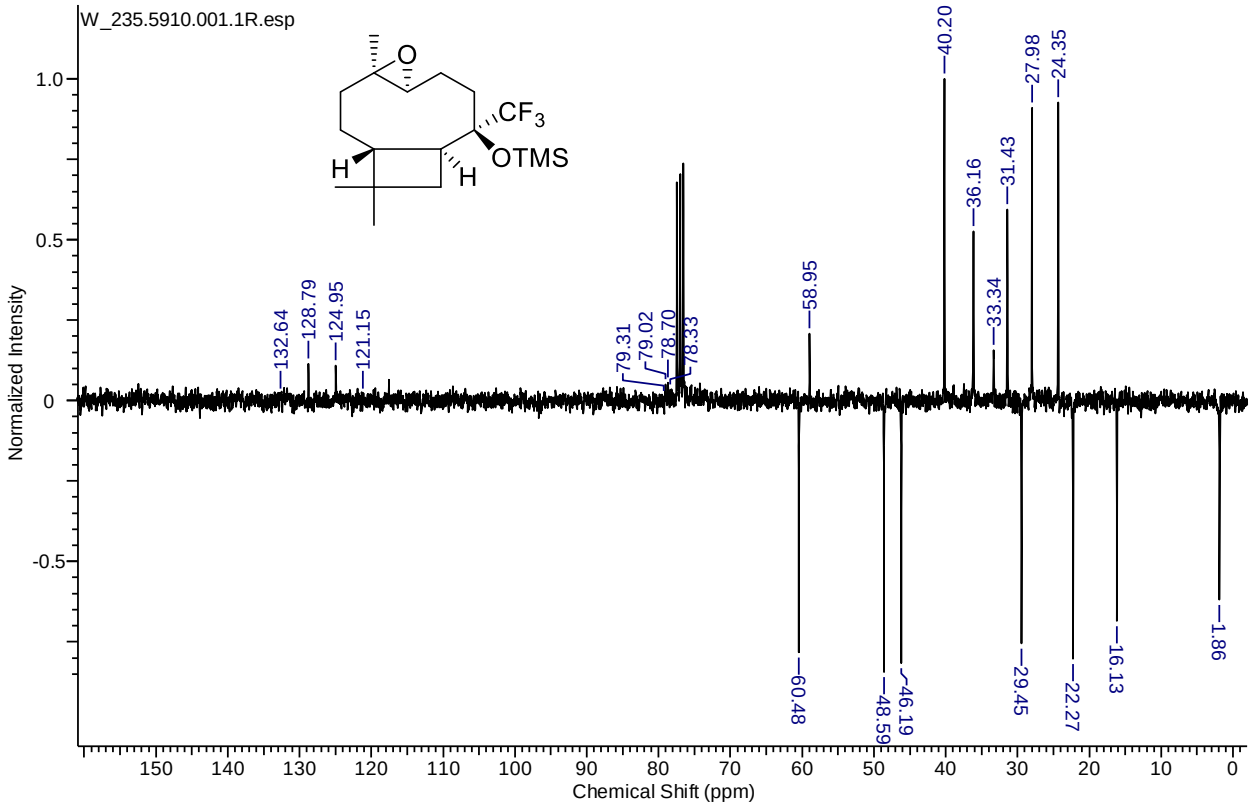


Figure S6. ^{13}C NMR spectra (75 MHz) of silyl ether **10** in $CDCl_3$

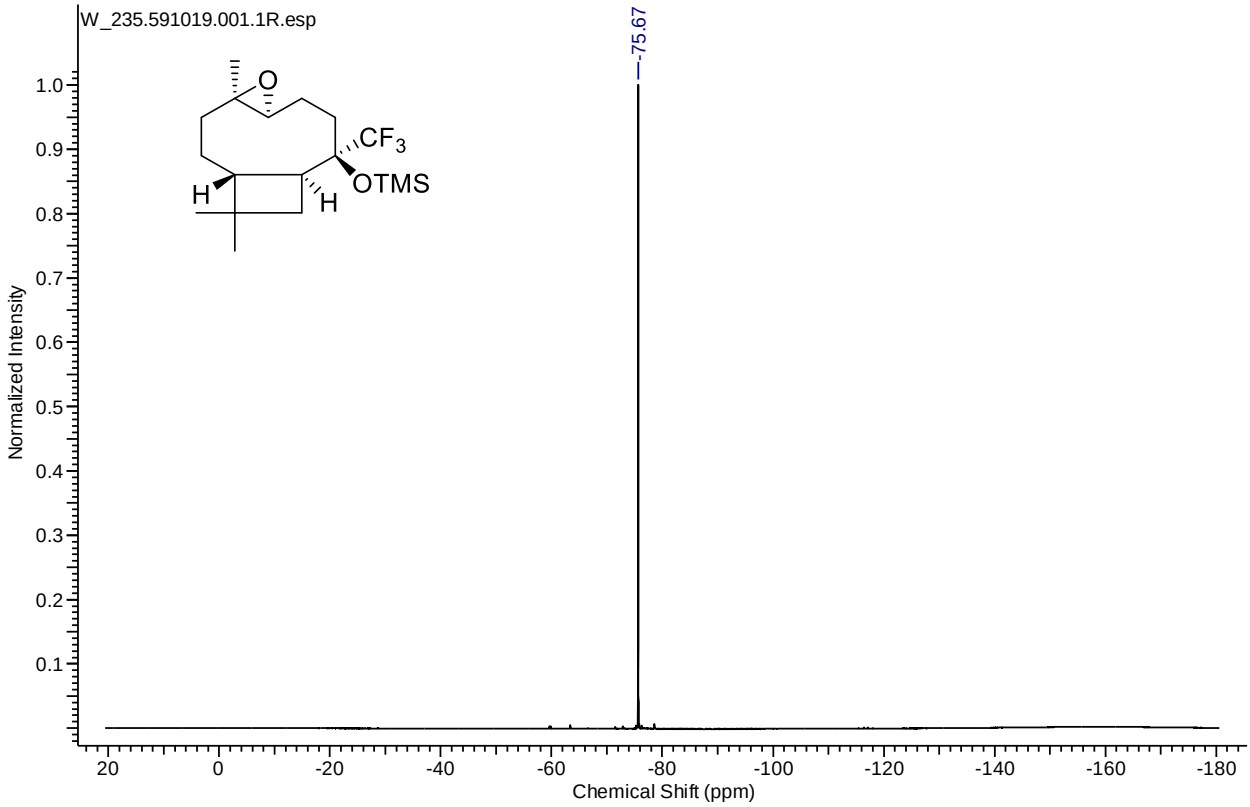


Figure S7. ^{19}F NMR spectra (282 MHz) of silyl ether **10** in $CDCl_3$

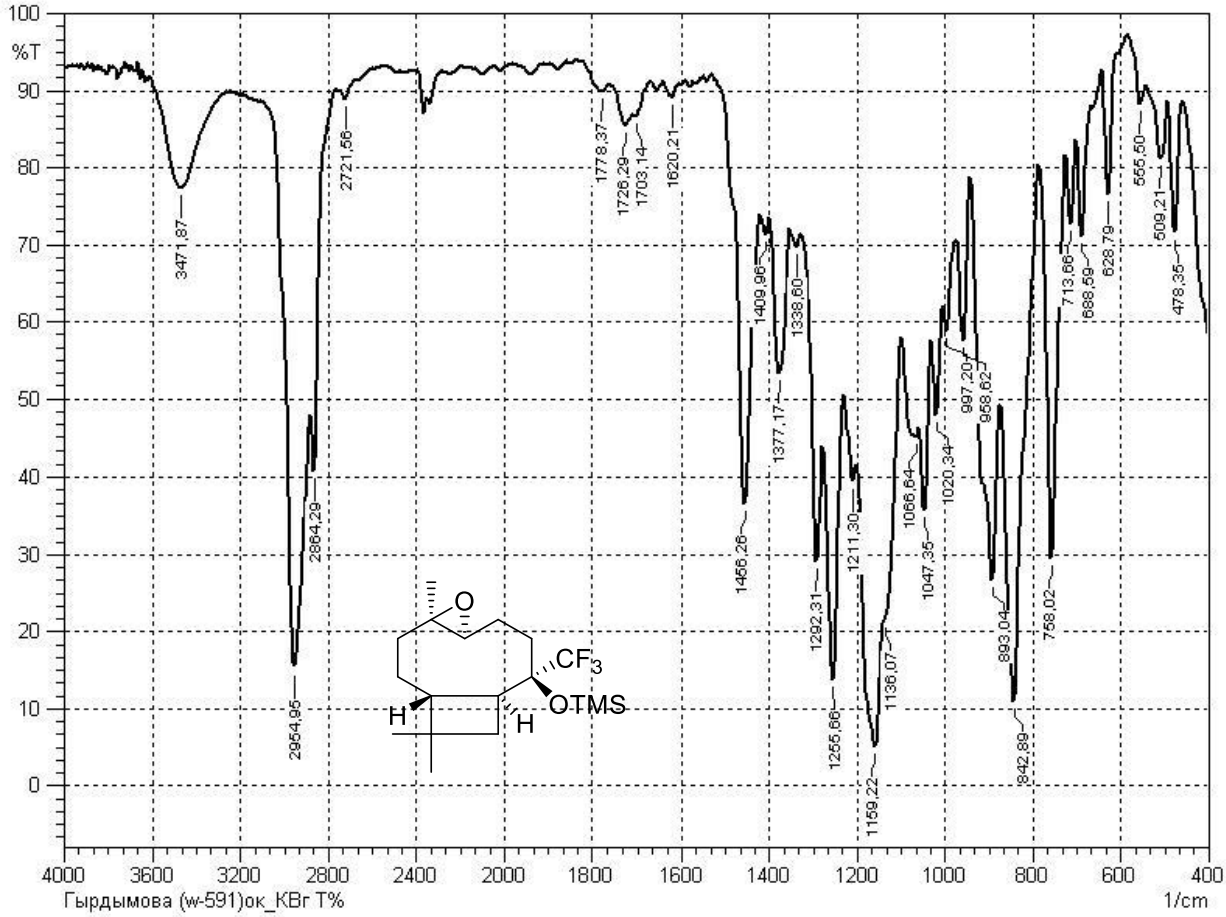


Figure S8. IR spectra of silyl ether **10**

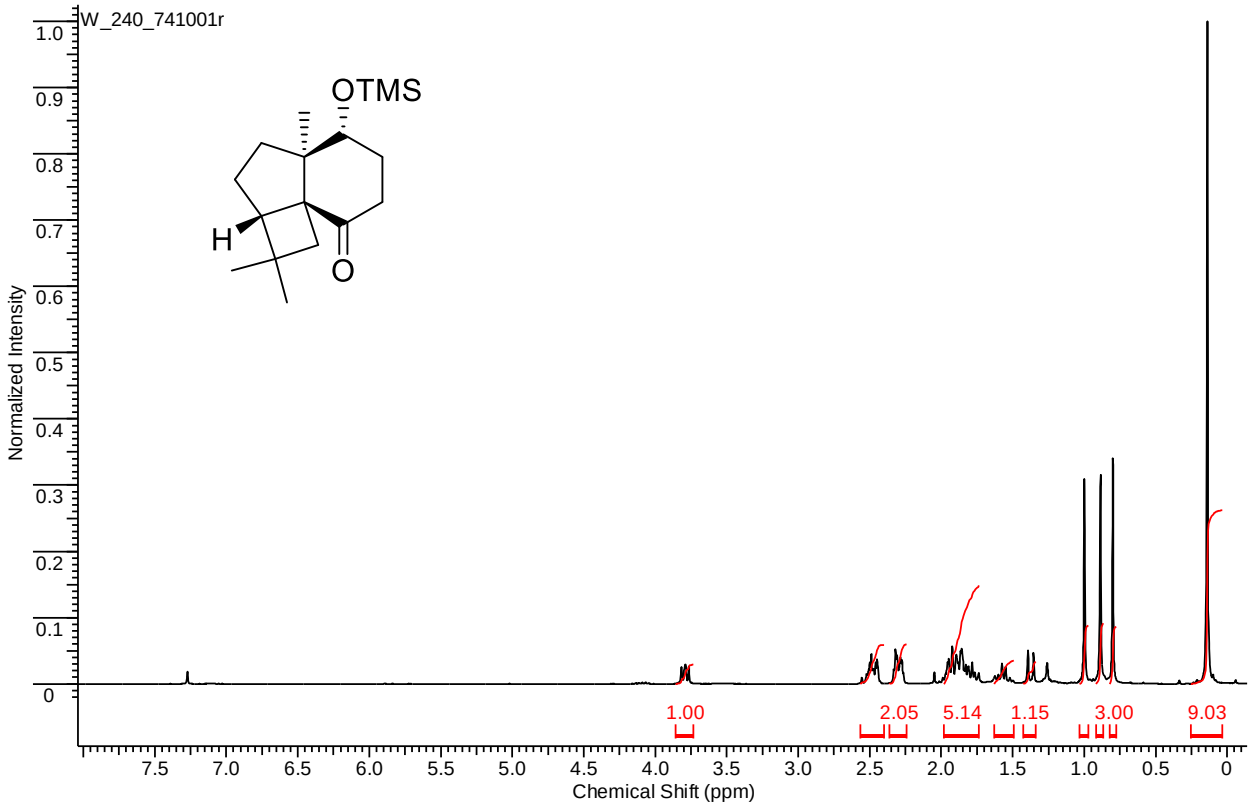


Figure S9. ^{1}H NMR spectra (300 MHz) of **11** in $CDCl_3$

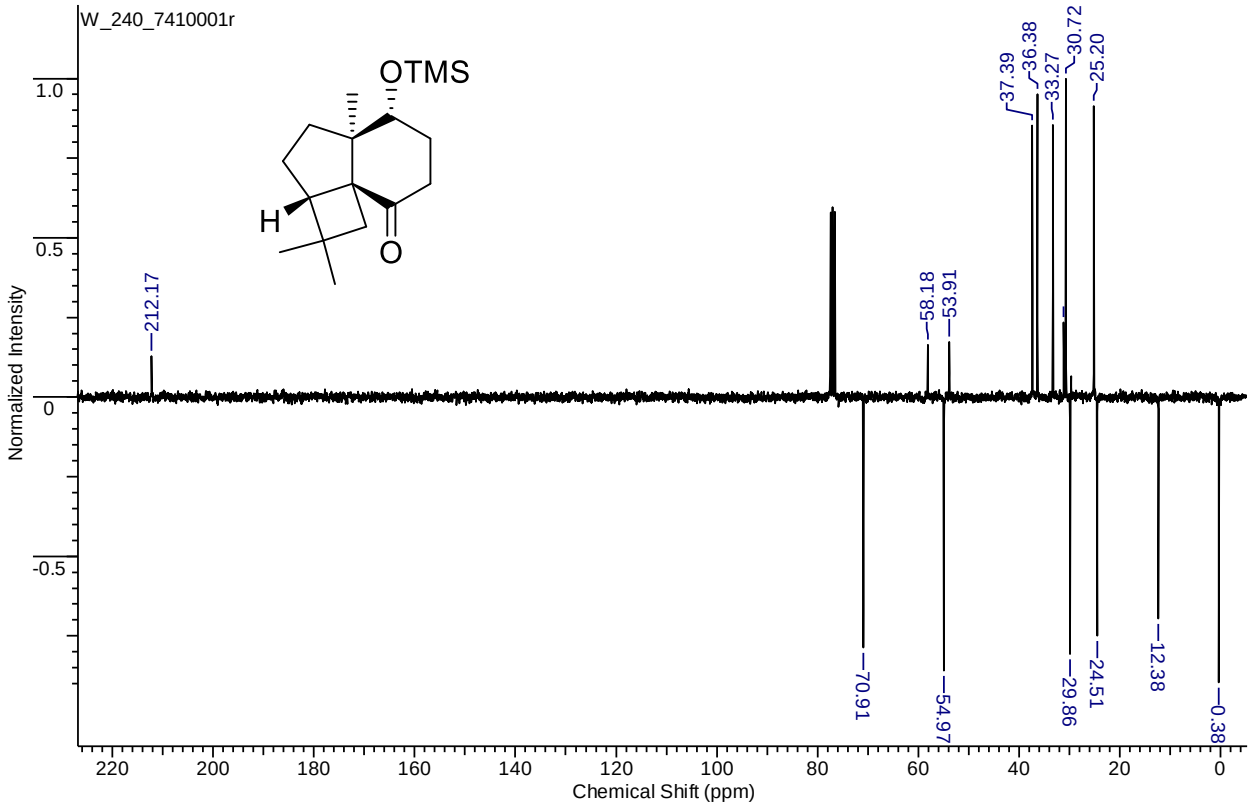


Figure S10. ^{13}C NMR spectra (75 MHz) of **11** in $CDCl_3$

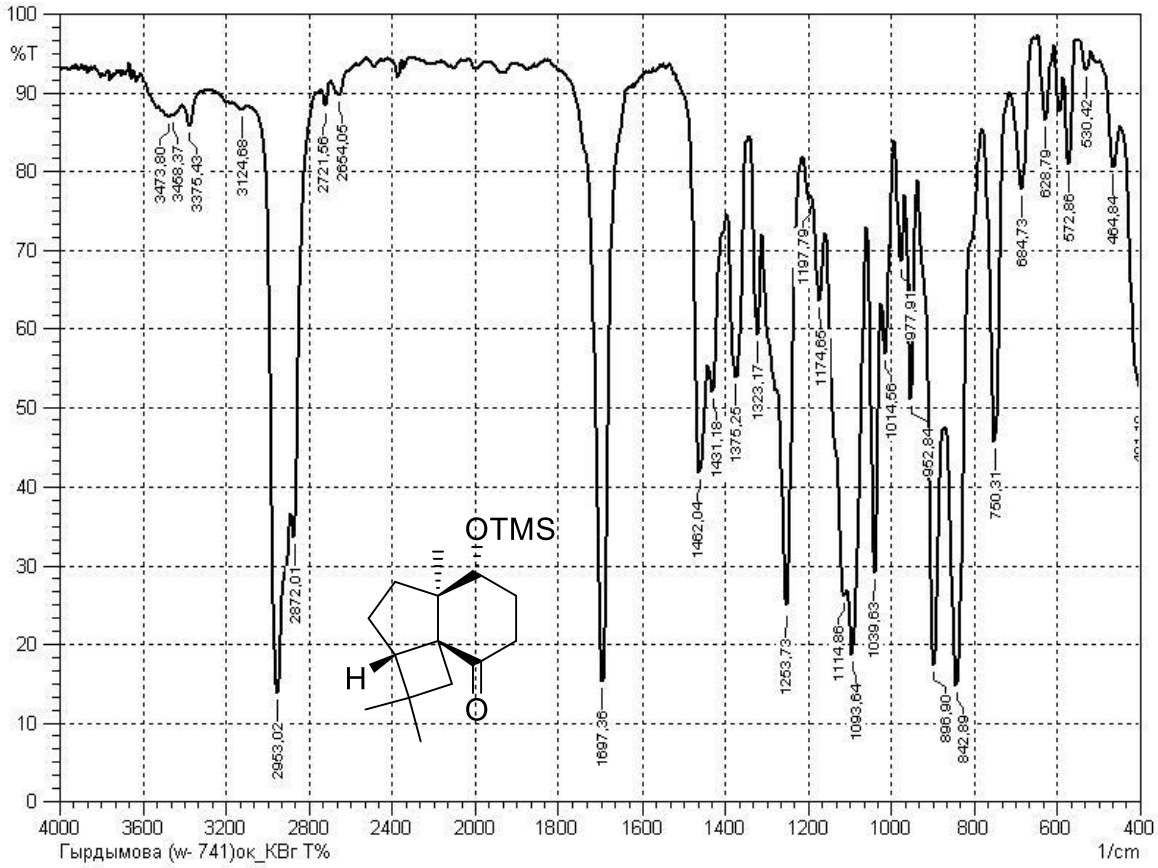


Figure S11. IR spectra of **11**

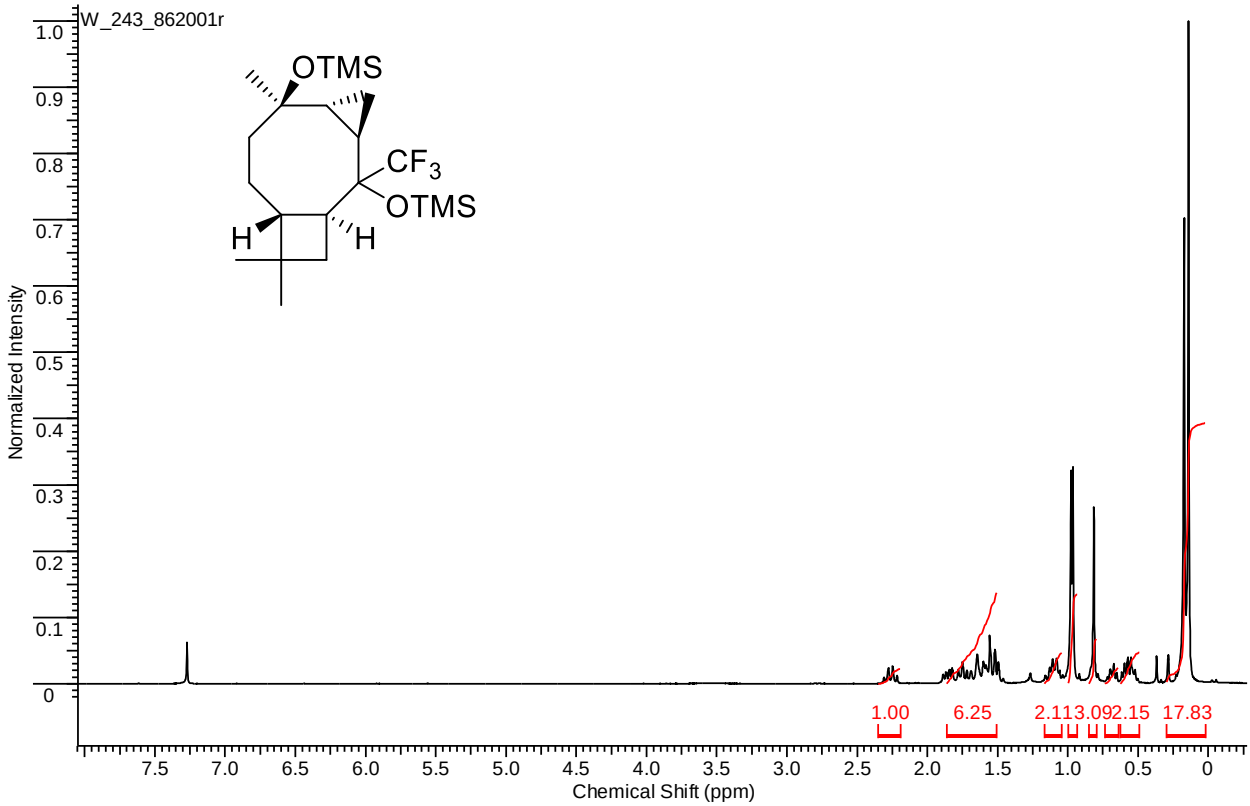


Figure S12. ^{1}H NMR spectra (300 MHz) of silyl ether **13** in $CDCl_3$

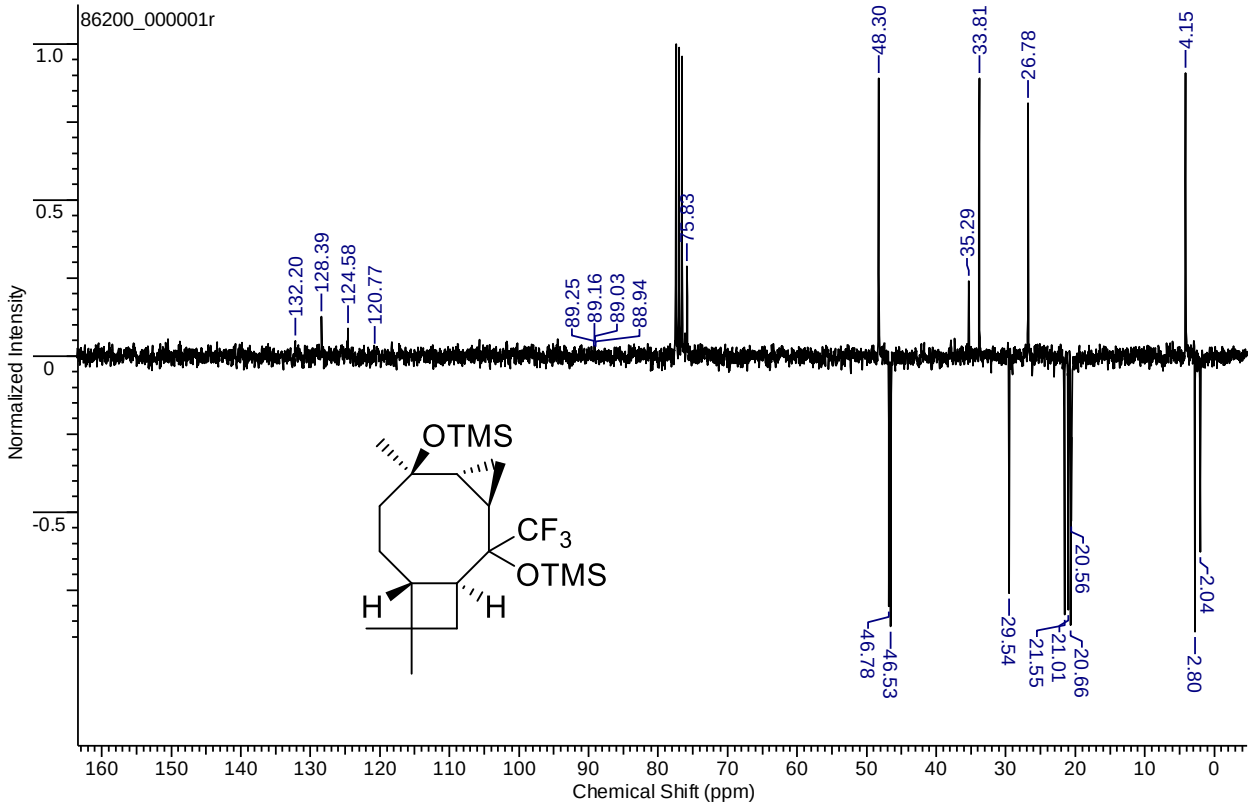


Figure S13. ^{13}C NMR spectra (75 MHz) of silyl ether **13** in $CDCl_3$

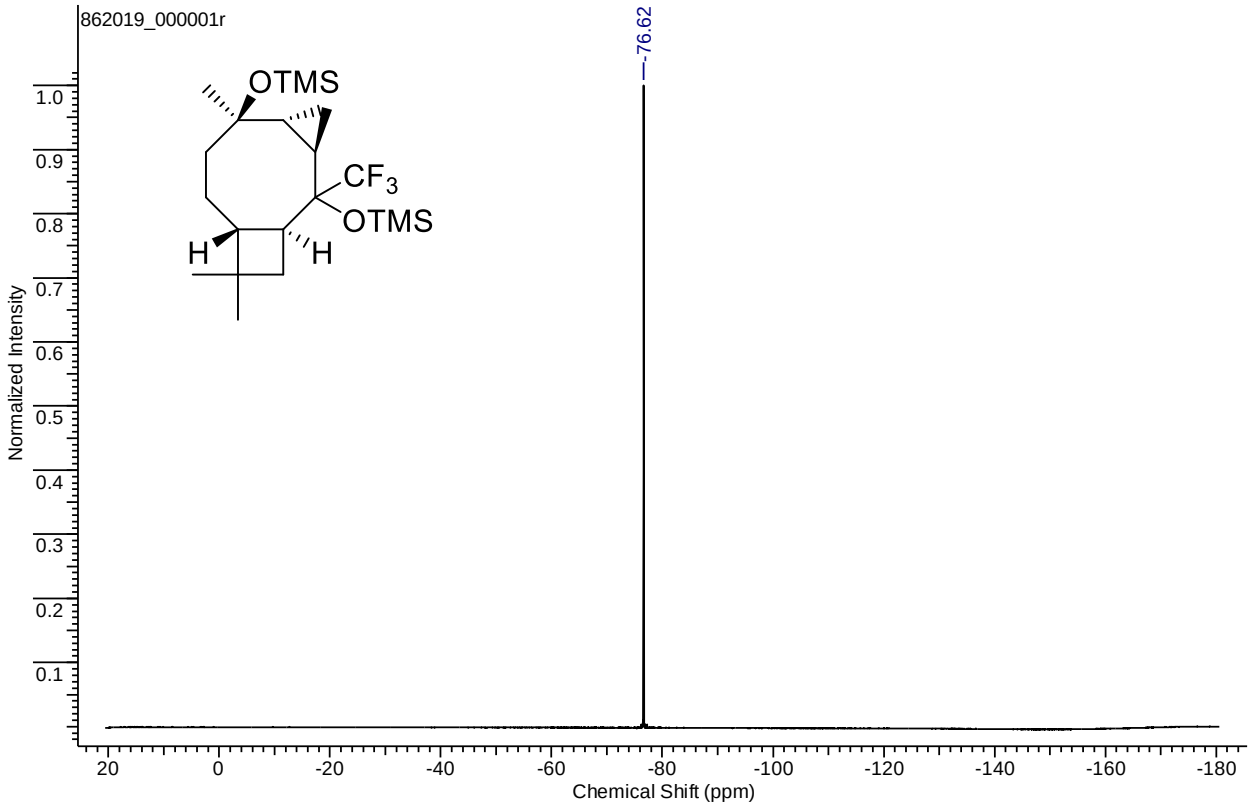


Figure S14. ^{19}F NMR spectra (282 MHz) of silyl ether **13** in $CDCl_3$

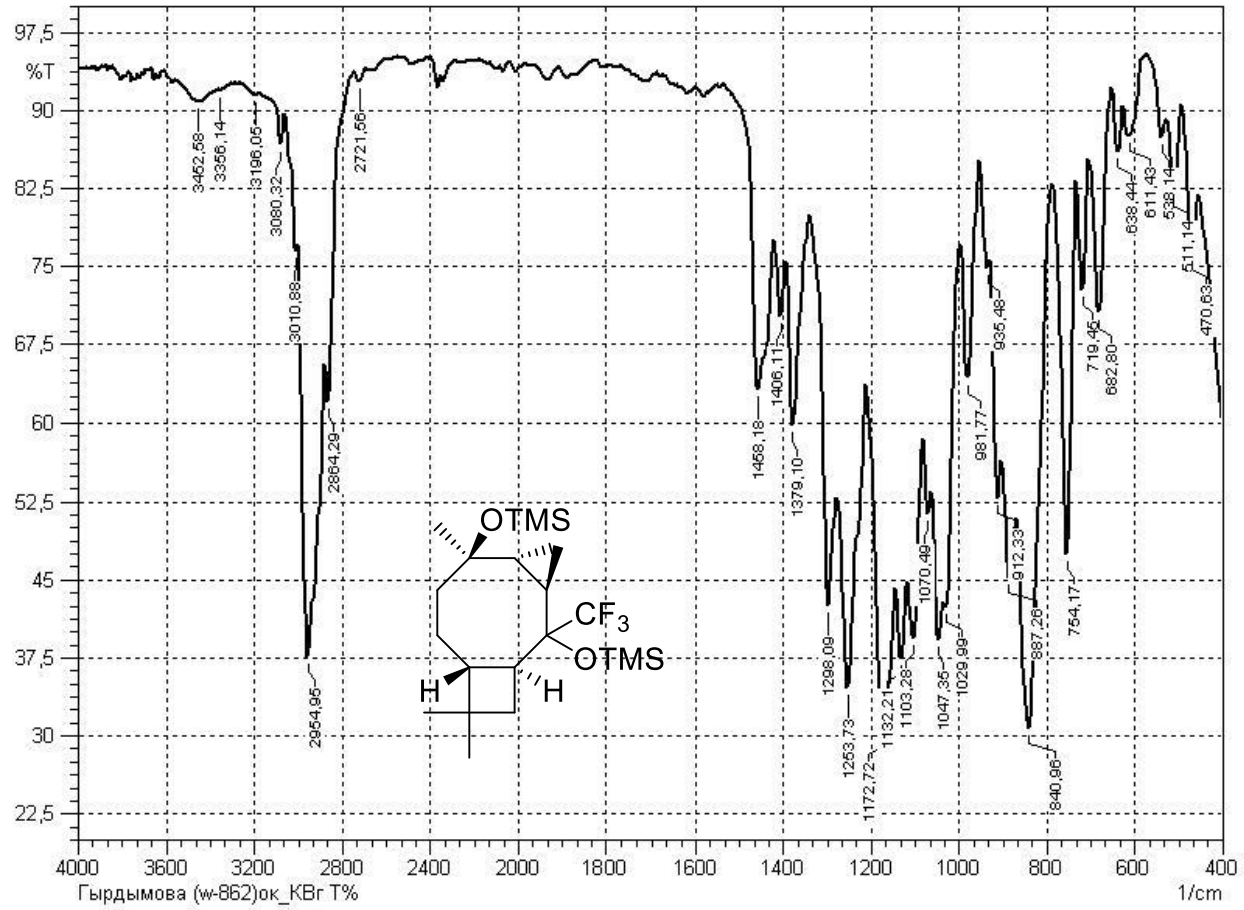


Figure S15. IR spectra of silyl ether **13**

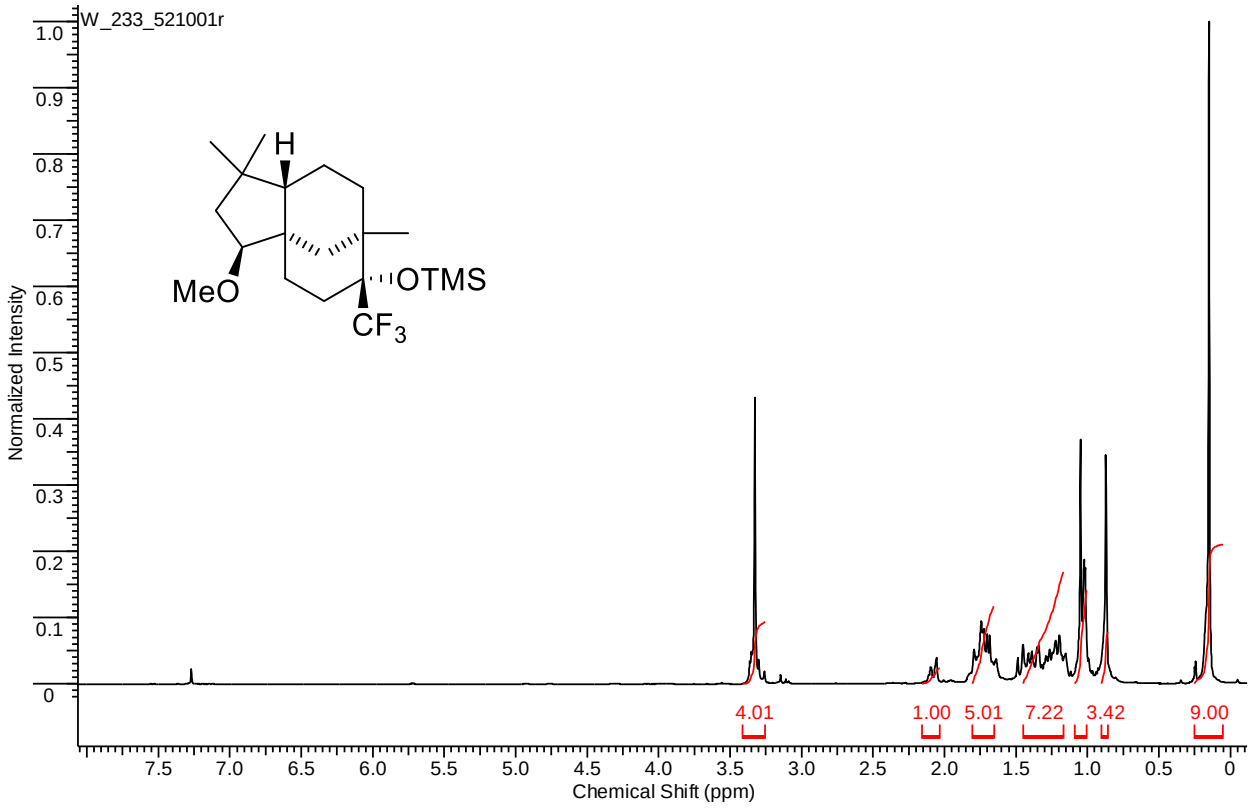


Figure S16. ^{1}H NMR spectra (300 MHz) of silyl ether **14** in $CDCl_3$

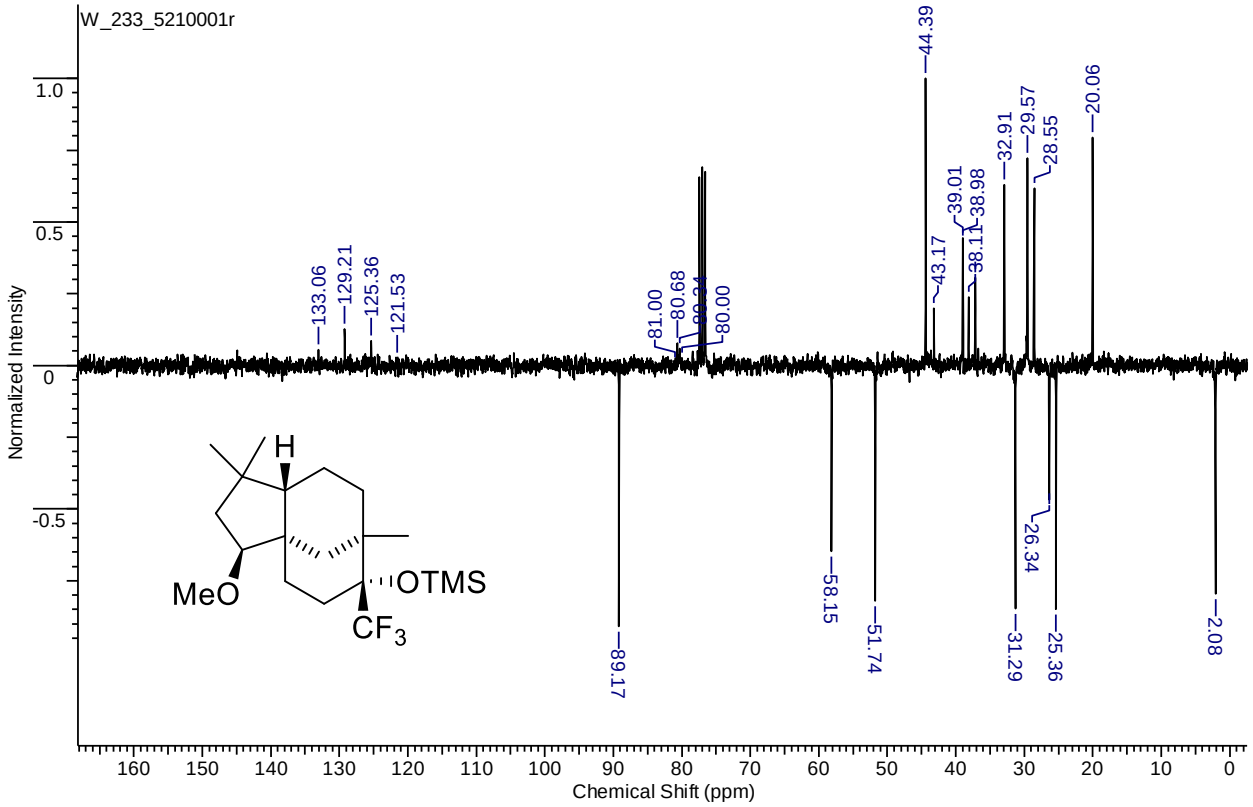


Figure S17. ^{13}C NMR spectra (75 MHz) of silyl ether **14** in $CDCl_3$

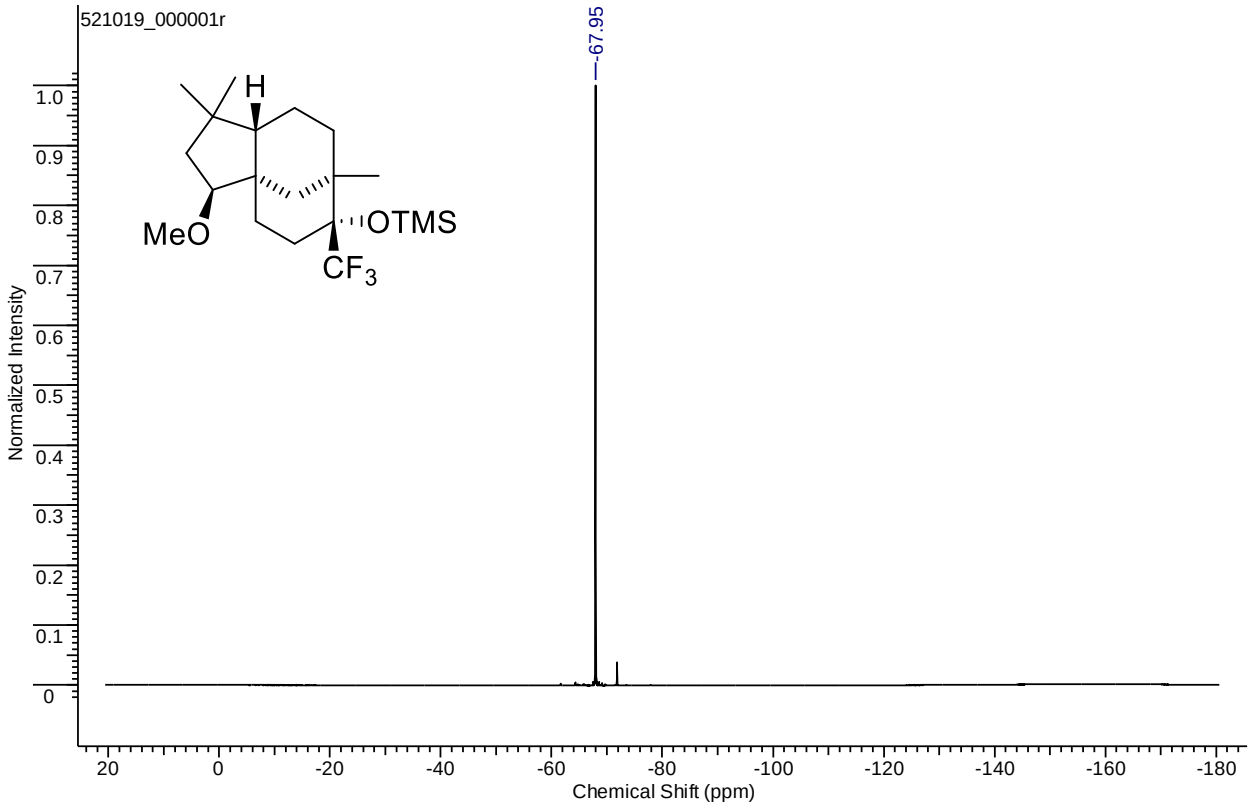


Figure S18. ^{19}F NMR spectra (282 MHz) of silyl ether **14** in $CDCl_3$

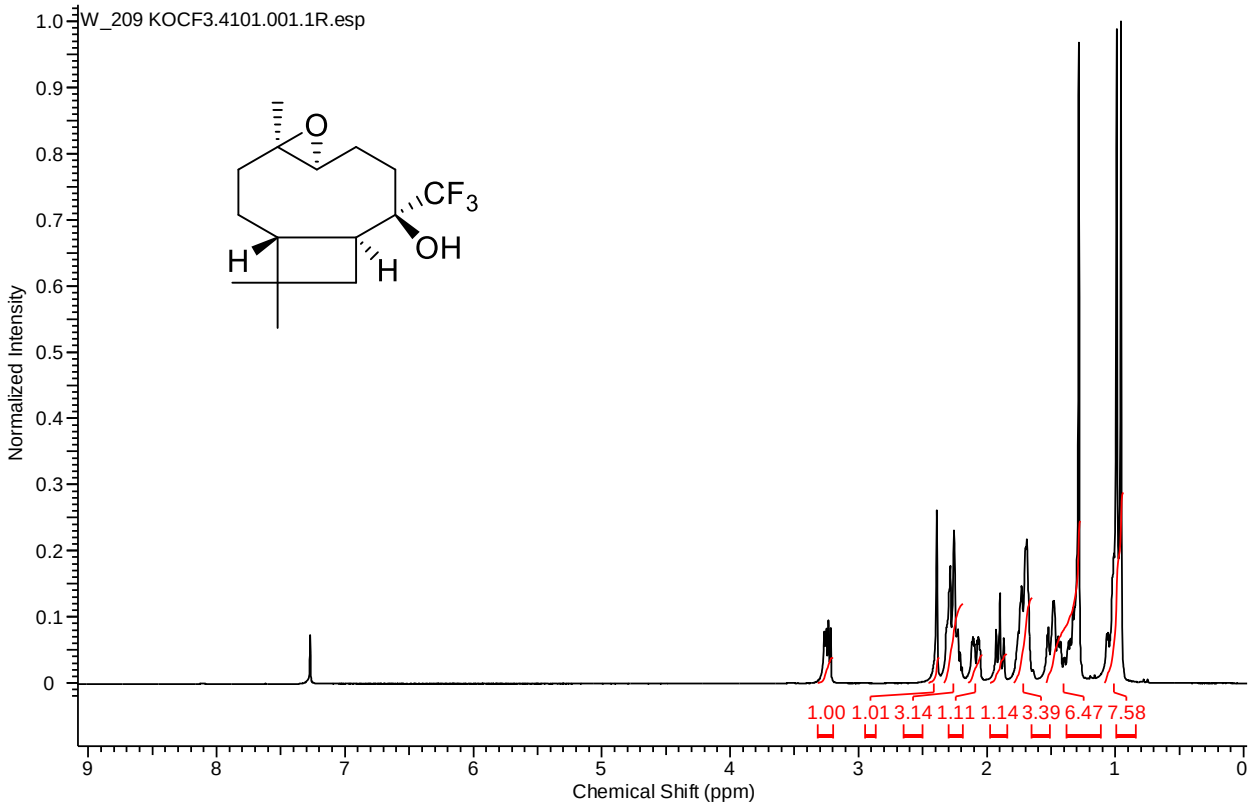


Figure S19. ^{1}H NMR spectra (300 MHz) of **15** in $CDCl_3$

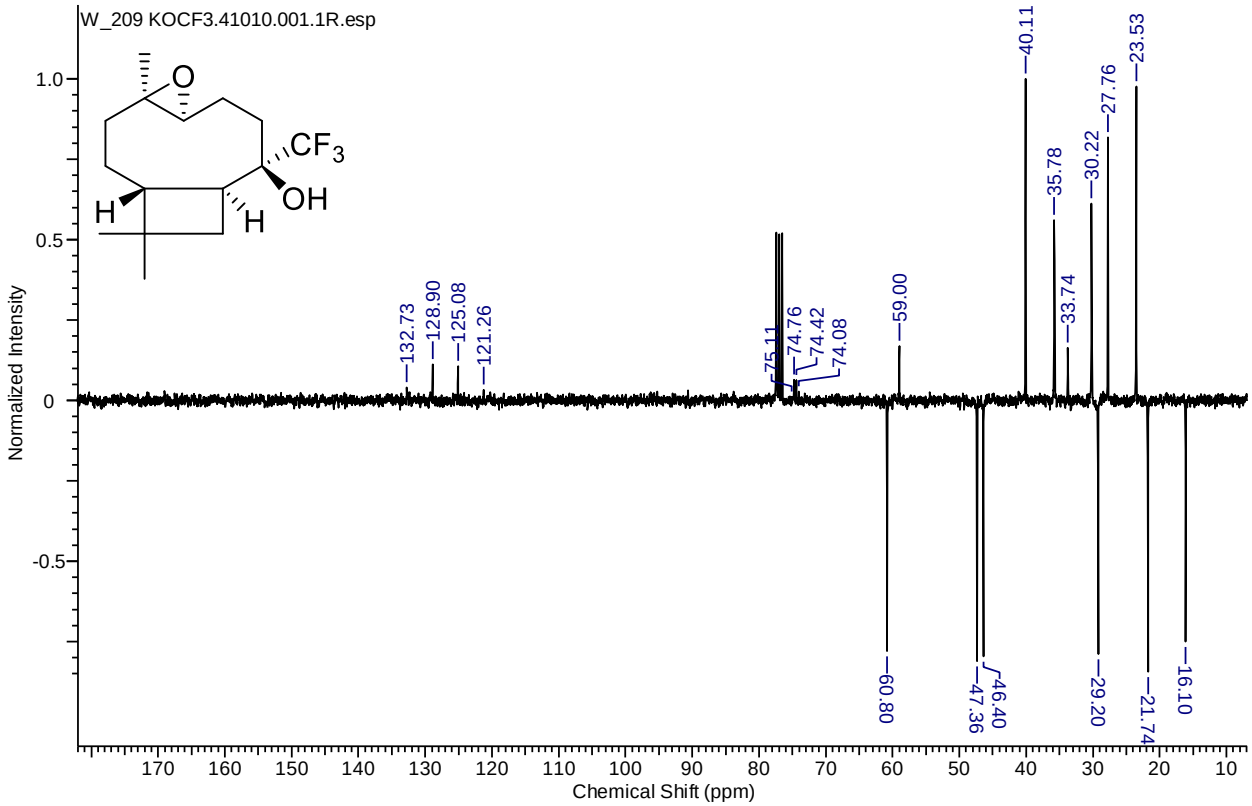


Figure S20. ^{13}C NMR spectra (75 MHz) of **15** in $CDCl_3$

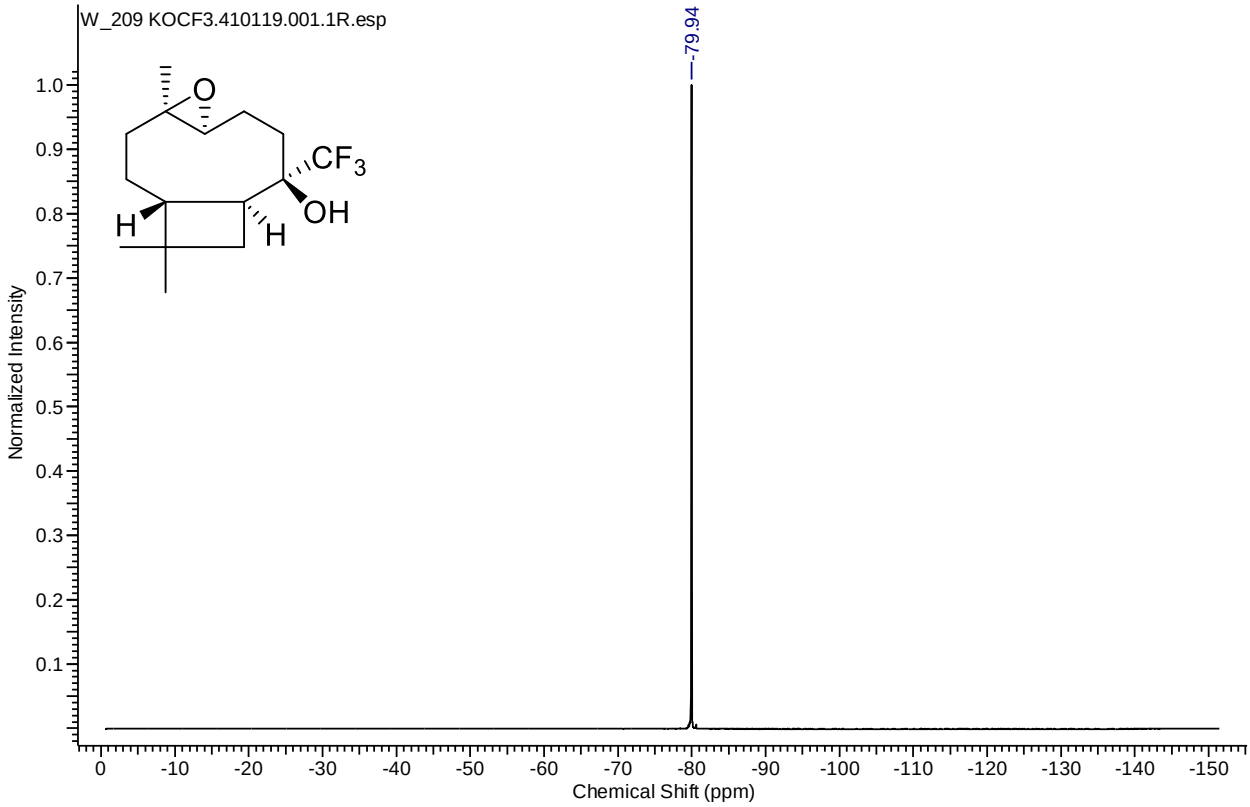


Figure S21. ^{19}F NMR spectra (282 MHz) of **15** in $CDCl_3$

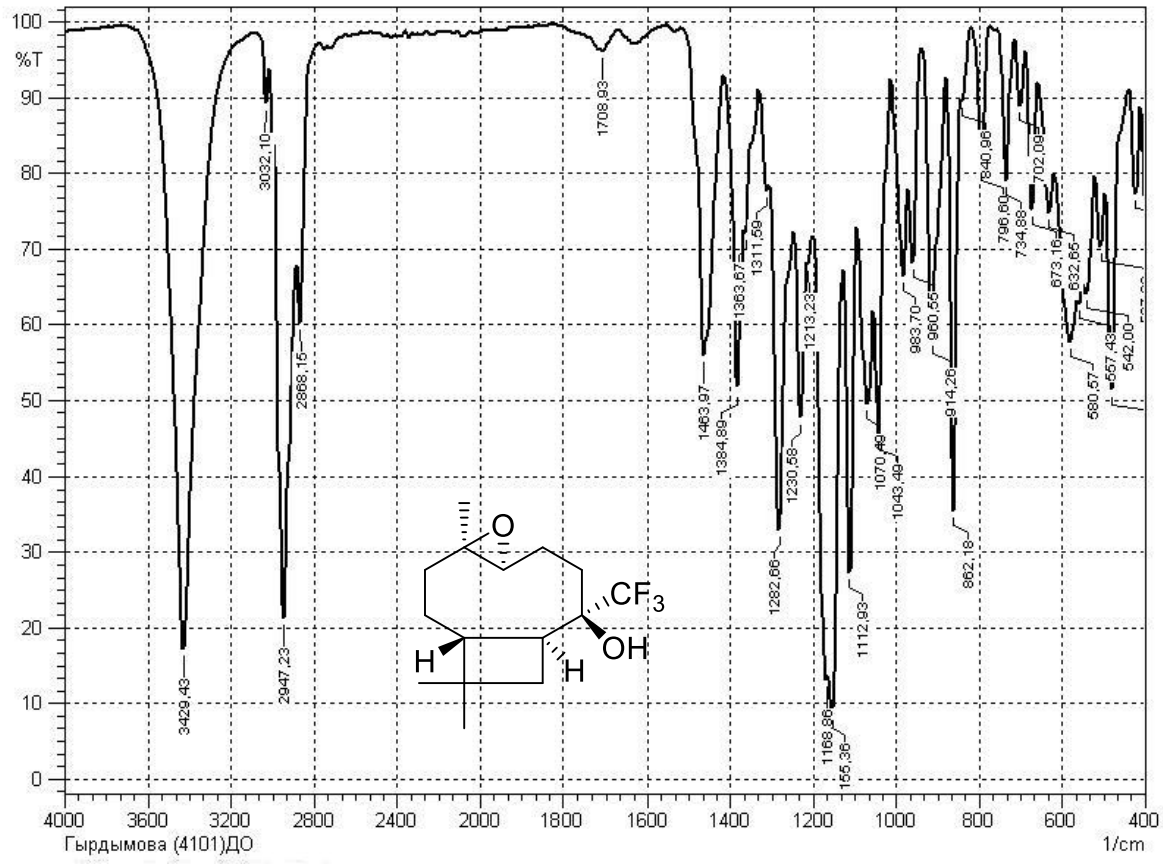


Figure S22. IR spectra of **15**

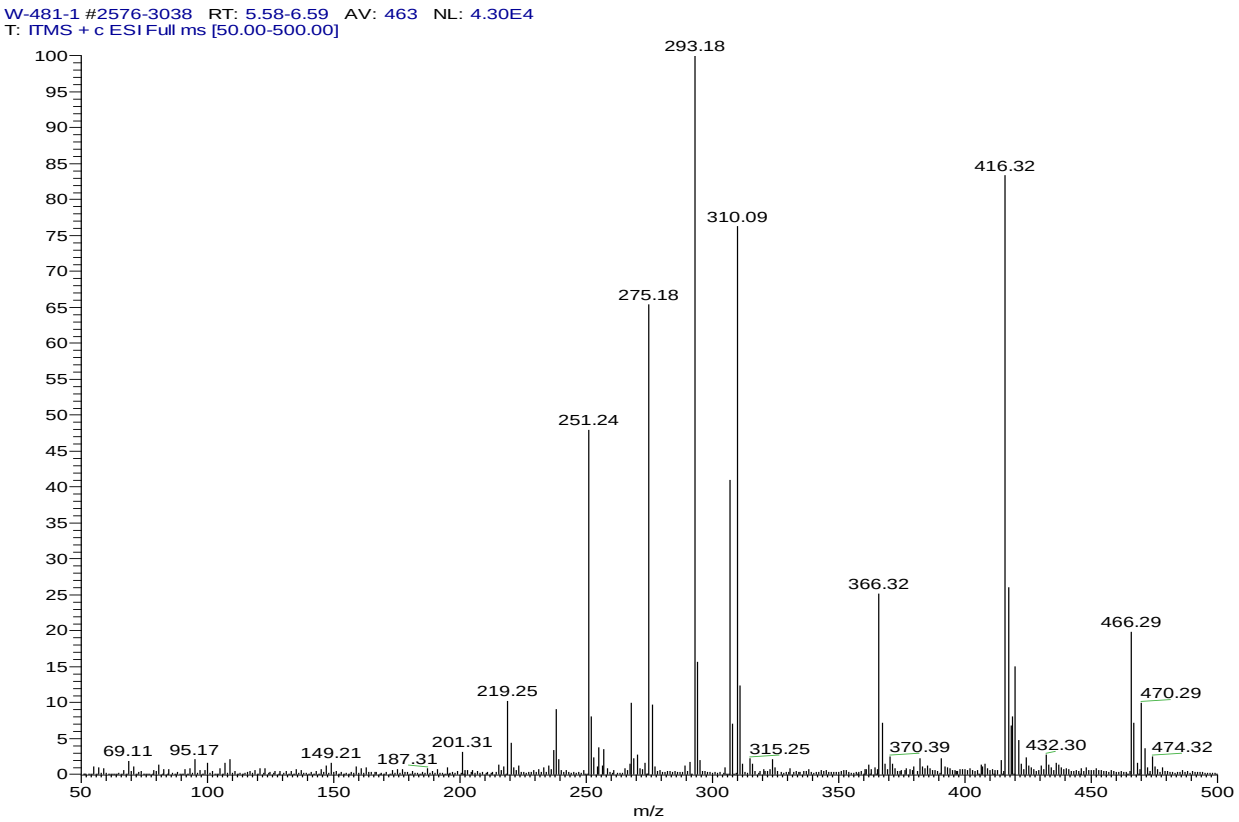


Figure S23. ESI-MS spectra of **15**

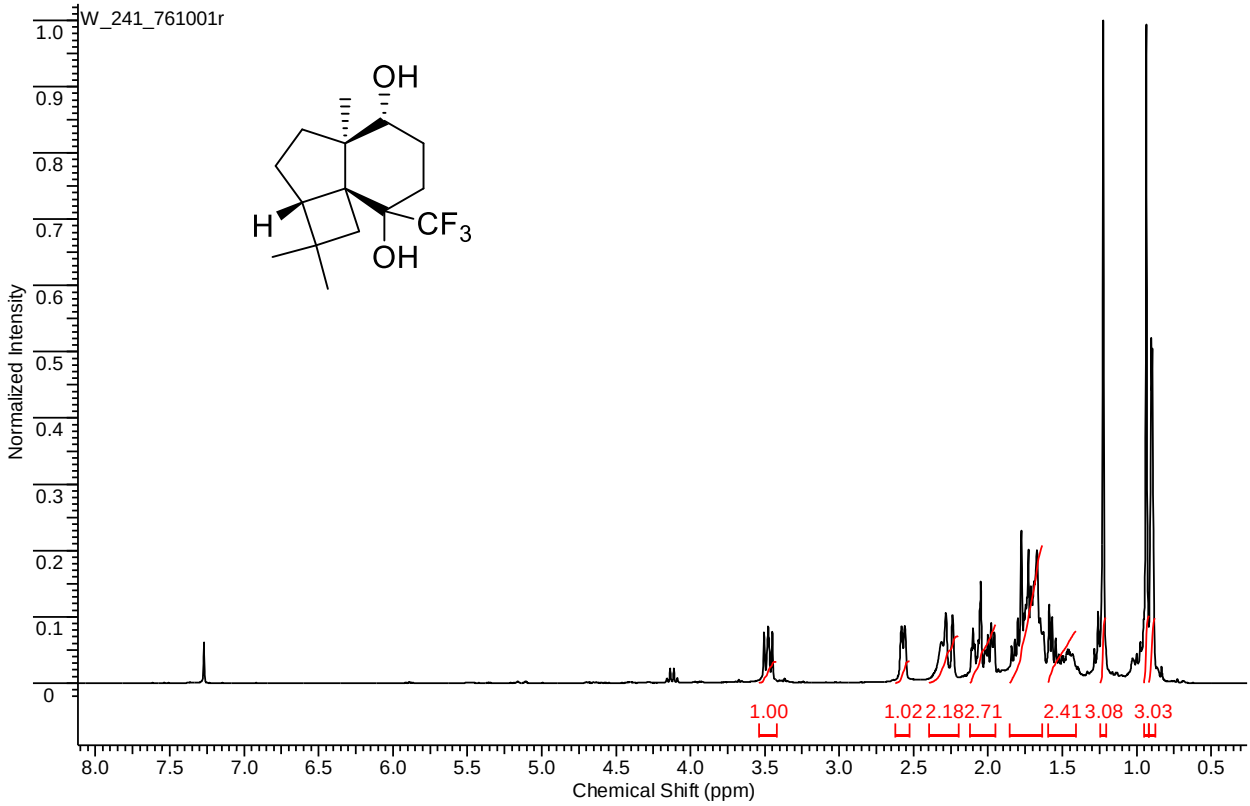


Figure S24. ^{1}H NMR spectra (300 MHz) of **16** in $CDCl_3$

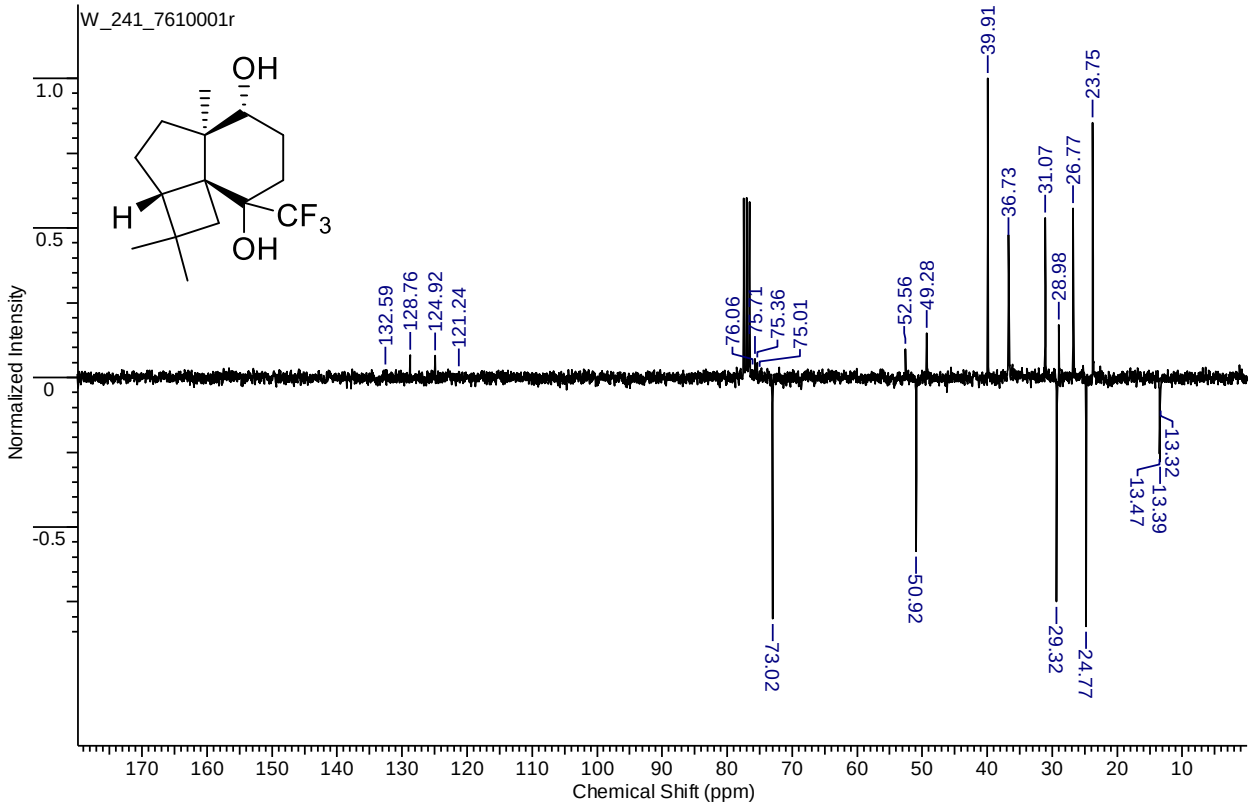


Figure S25. ^{1}H NMR spectra of **16** in $CDCl_3$

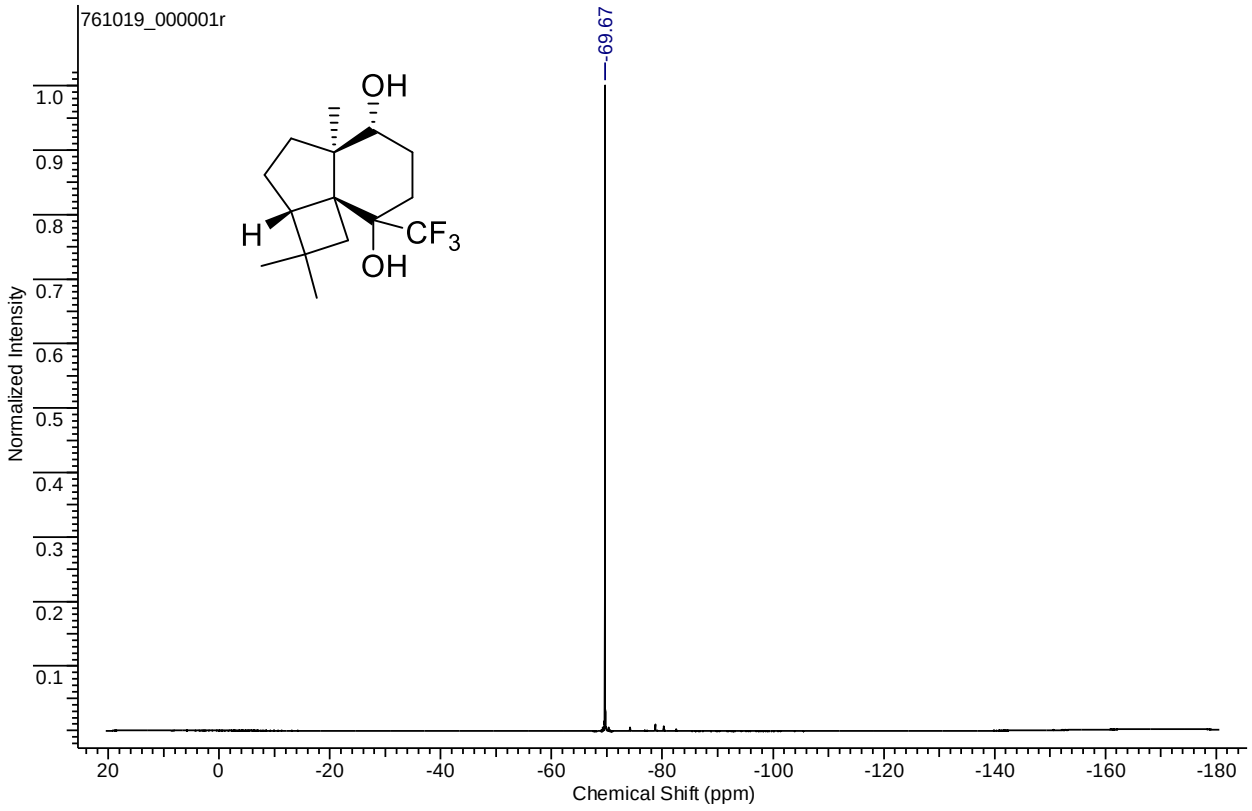


Figure S26. ^{19}F NMR spectra (282 MHz) of **16** in $CDCl_3$

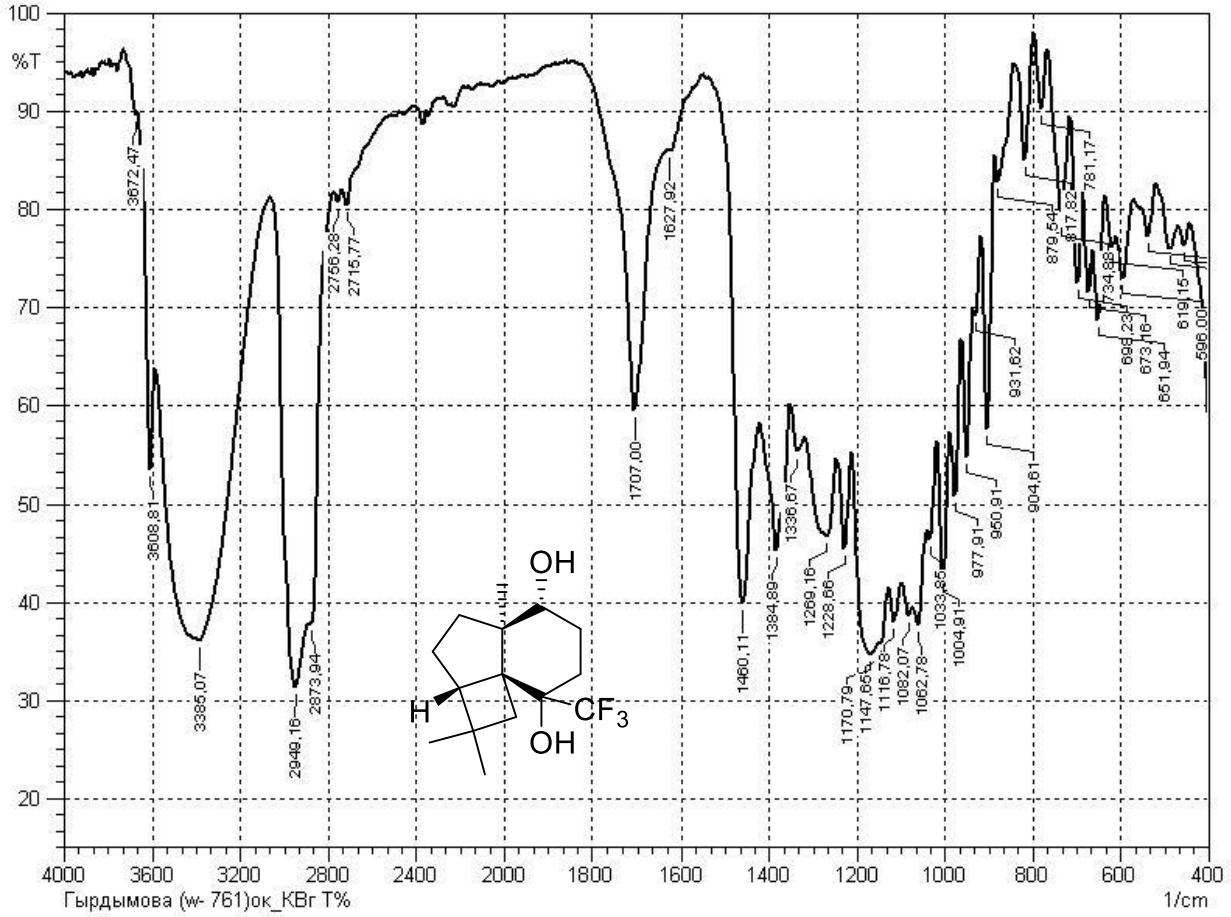


Figure S27. IR spectra of **16**

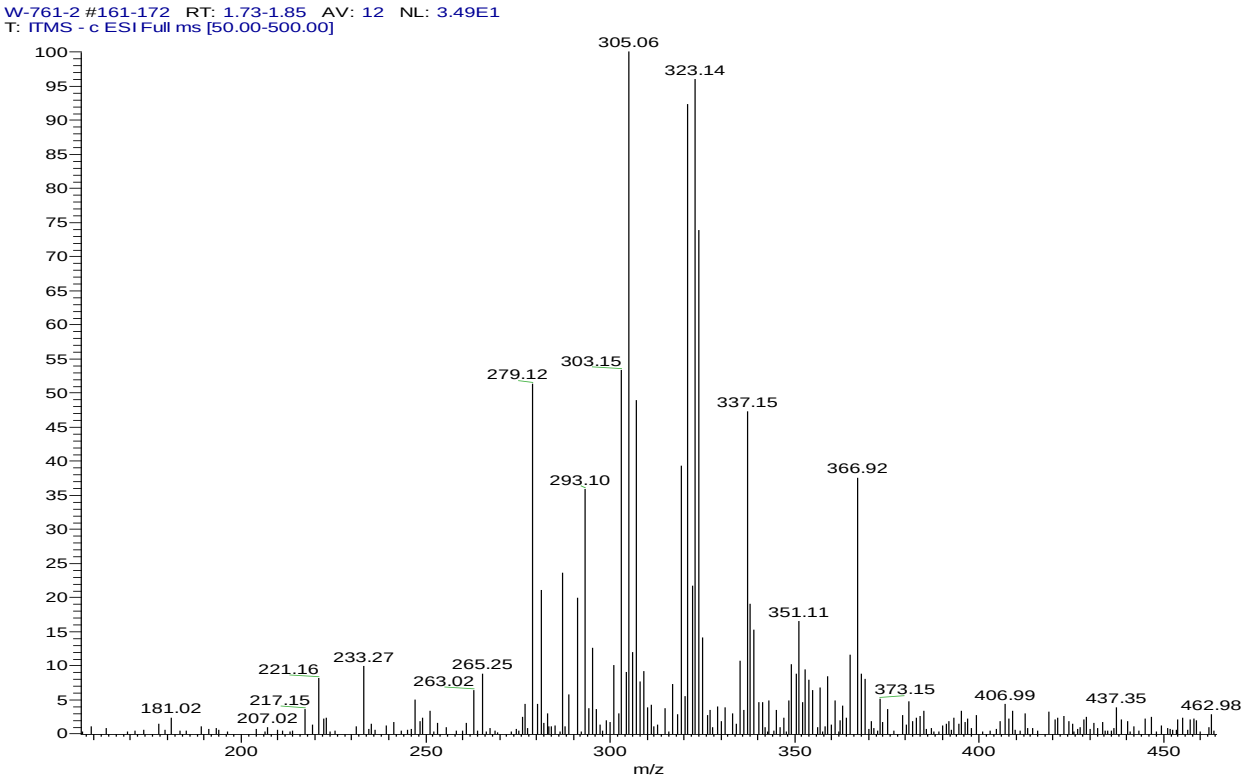


Figure S28. ESI-MS spectra of **16**

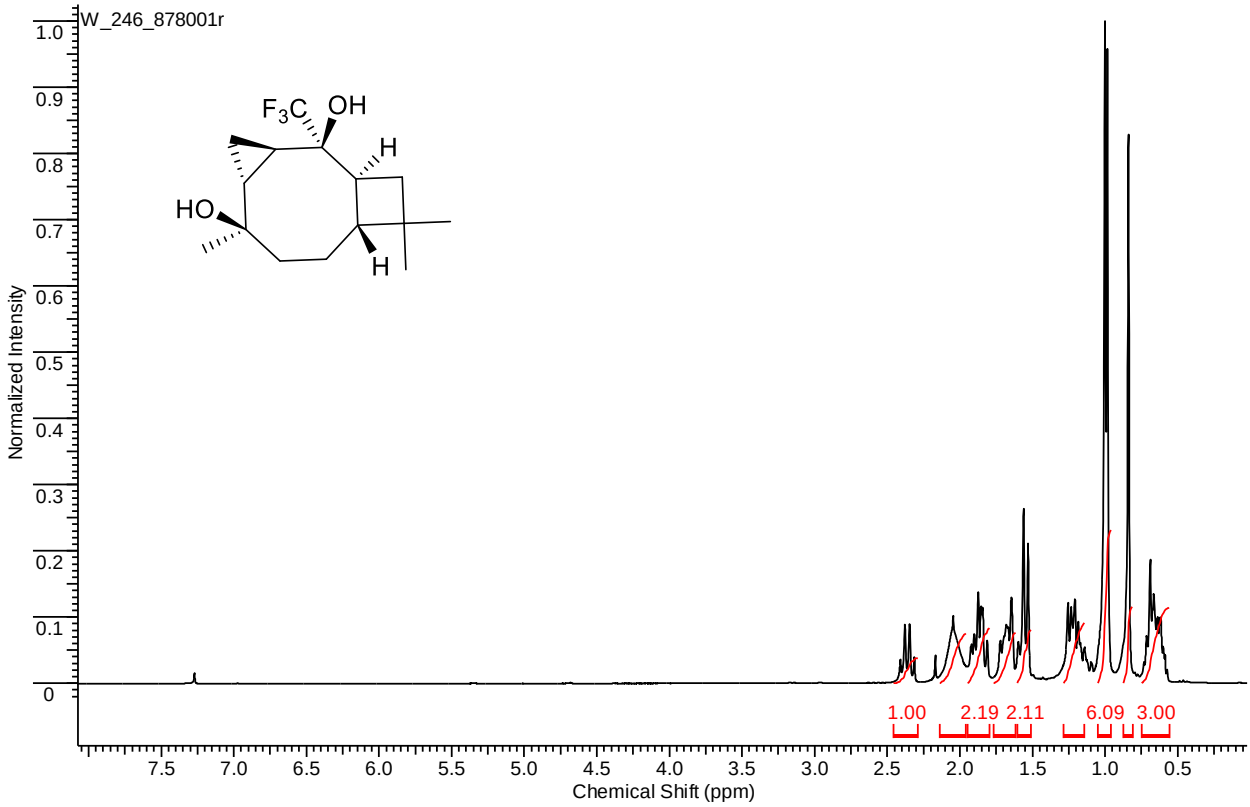


Figure S29. ^{1}H NMR spectra (300 MHz) of **17** in $CDCl_3$

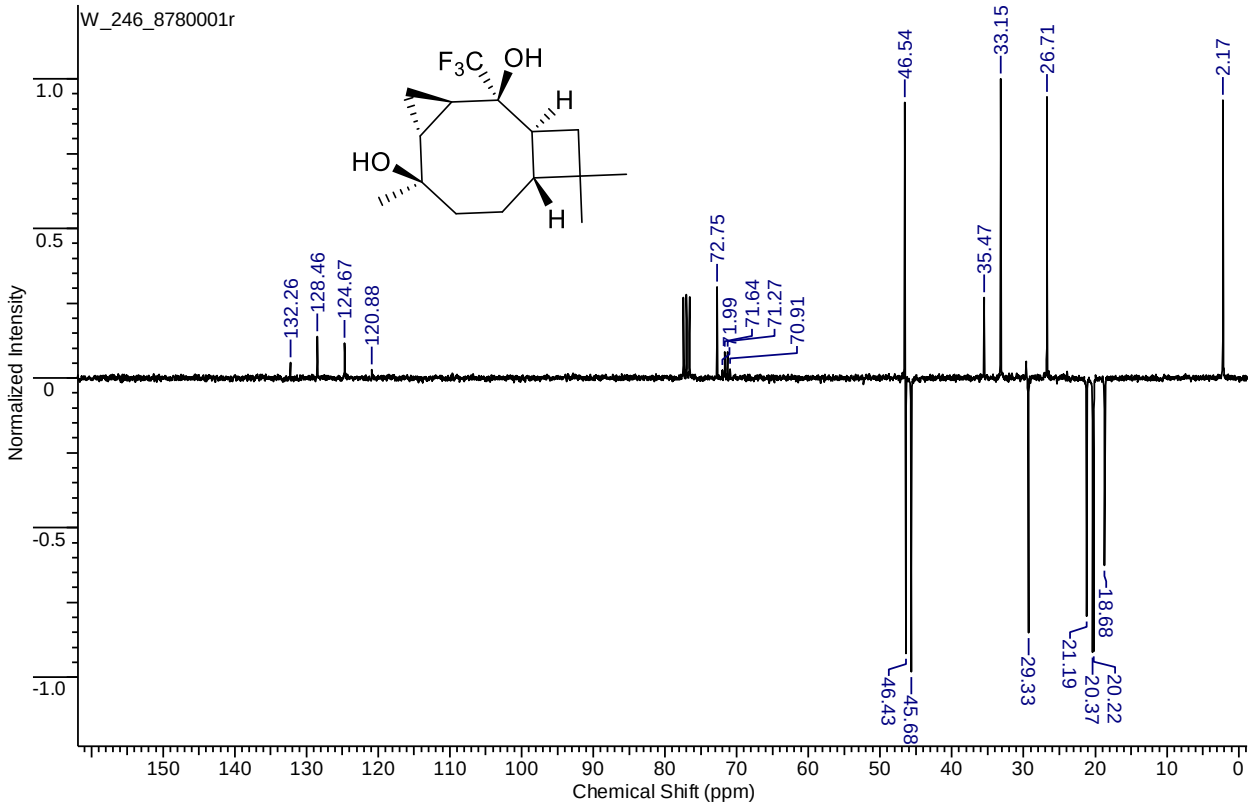


Figure S30. ^{13}C NMR spectra (75 MHz) of **17** in $CDCl_3$

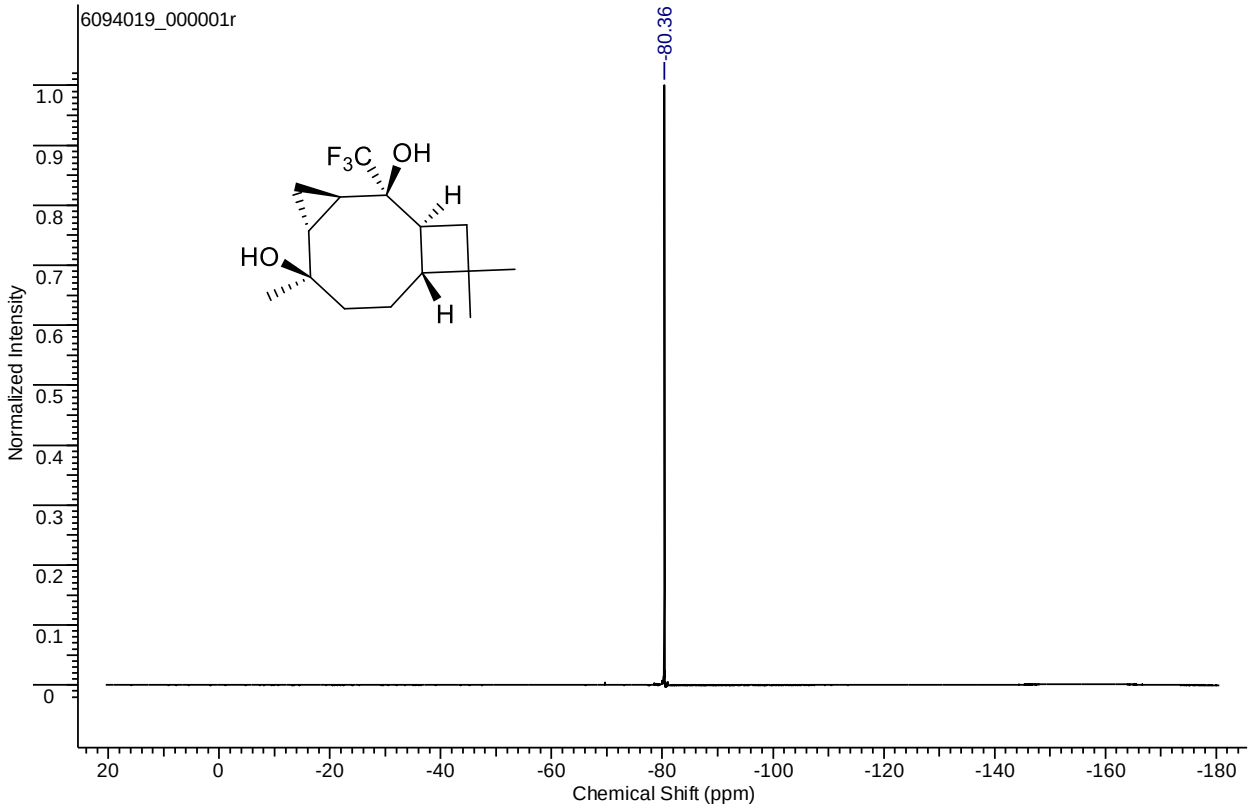


Figure S31. ^{19}F NMR spectra (282 MHz) of **17** in $CDCl_3$

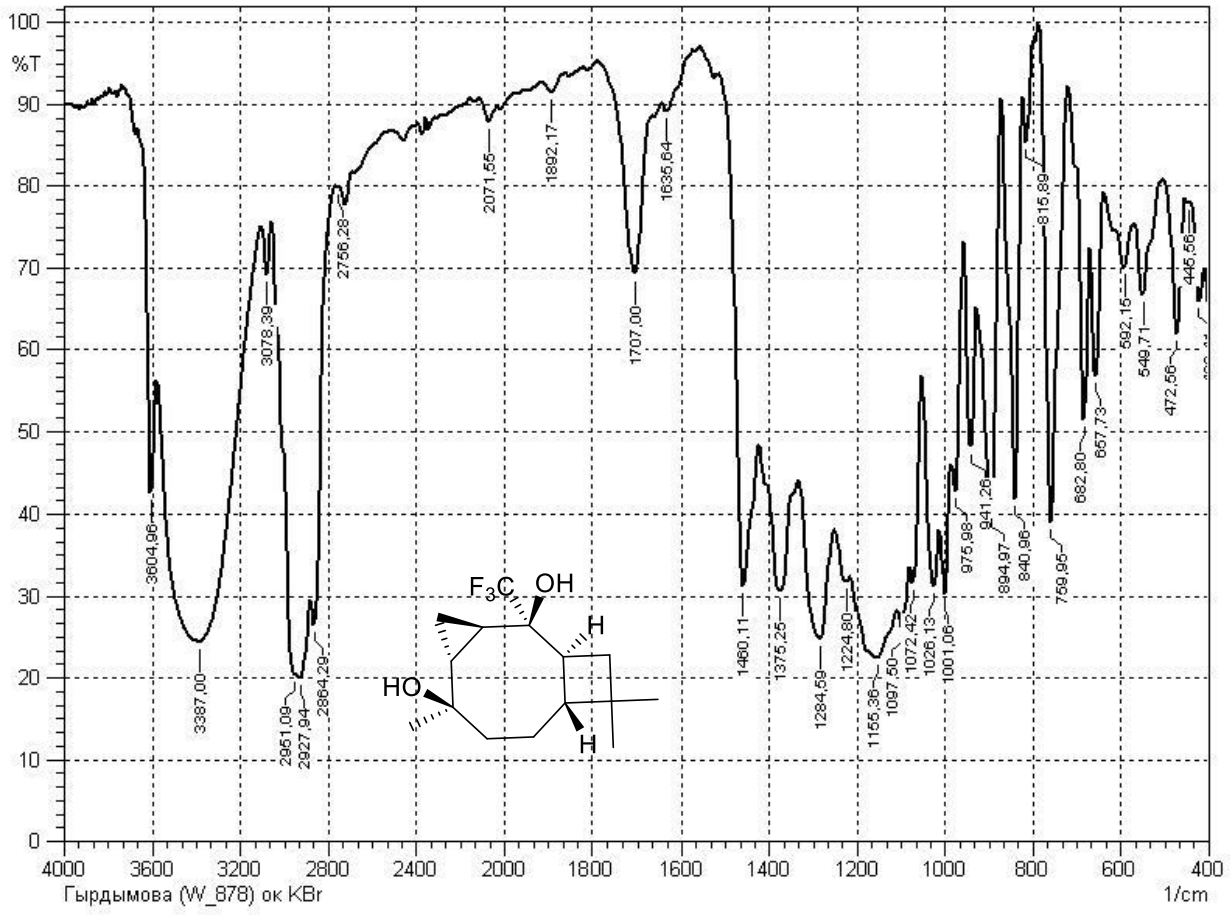


Figure S32. IR spectra of **17**

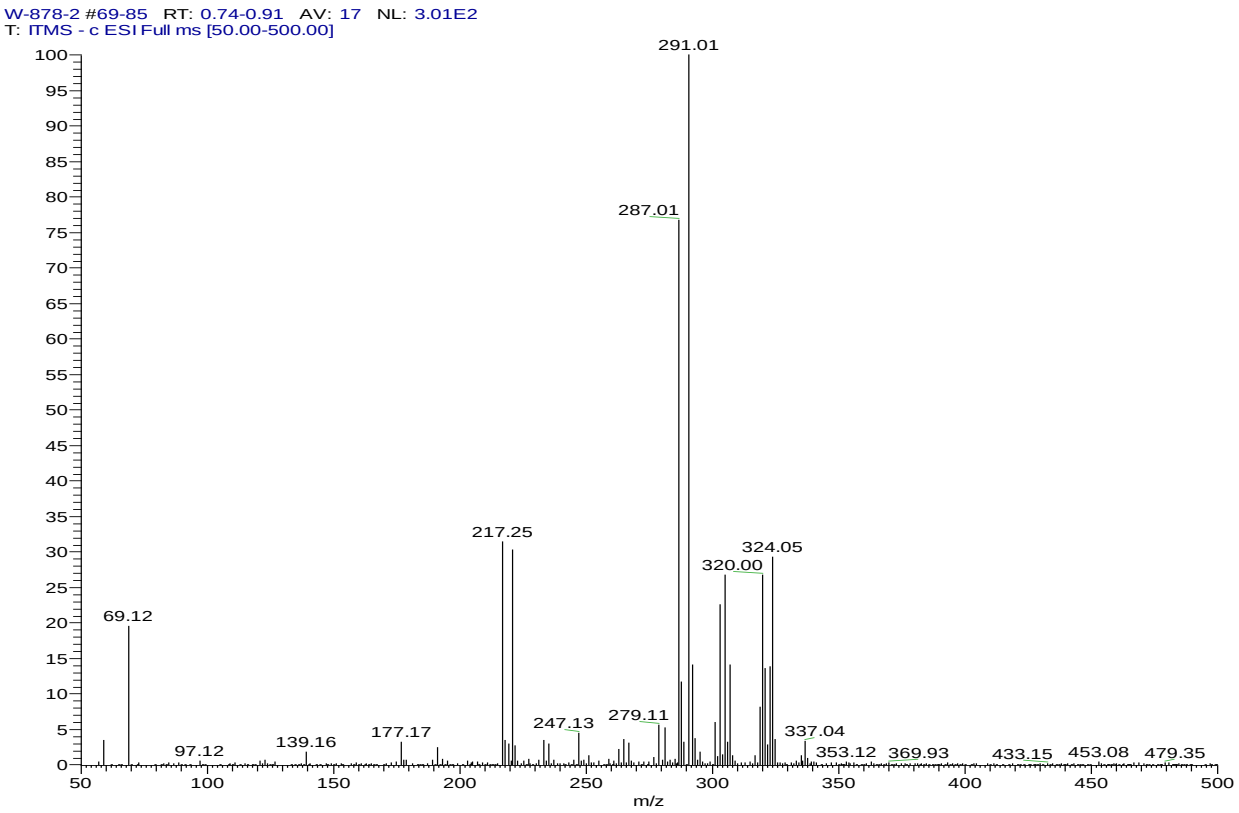


Figure S33. ESI-MS spectra of **17**

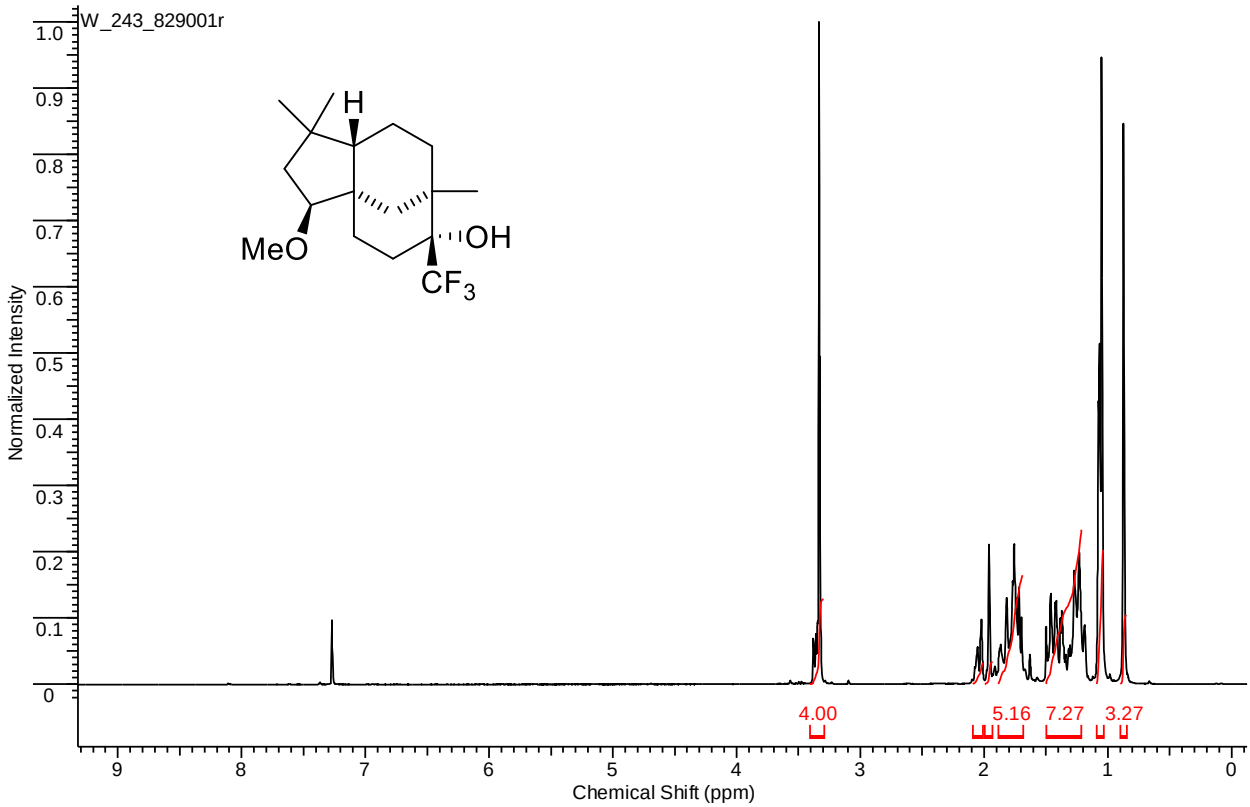


Figure S34. ^{1}H NMR spectra (300 MHz) of **18** in $CDCl_3$

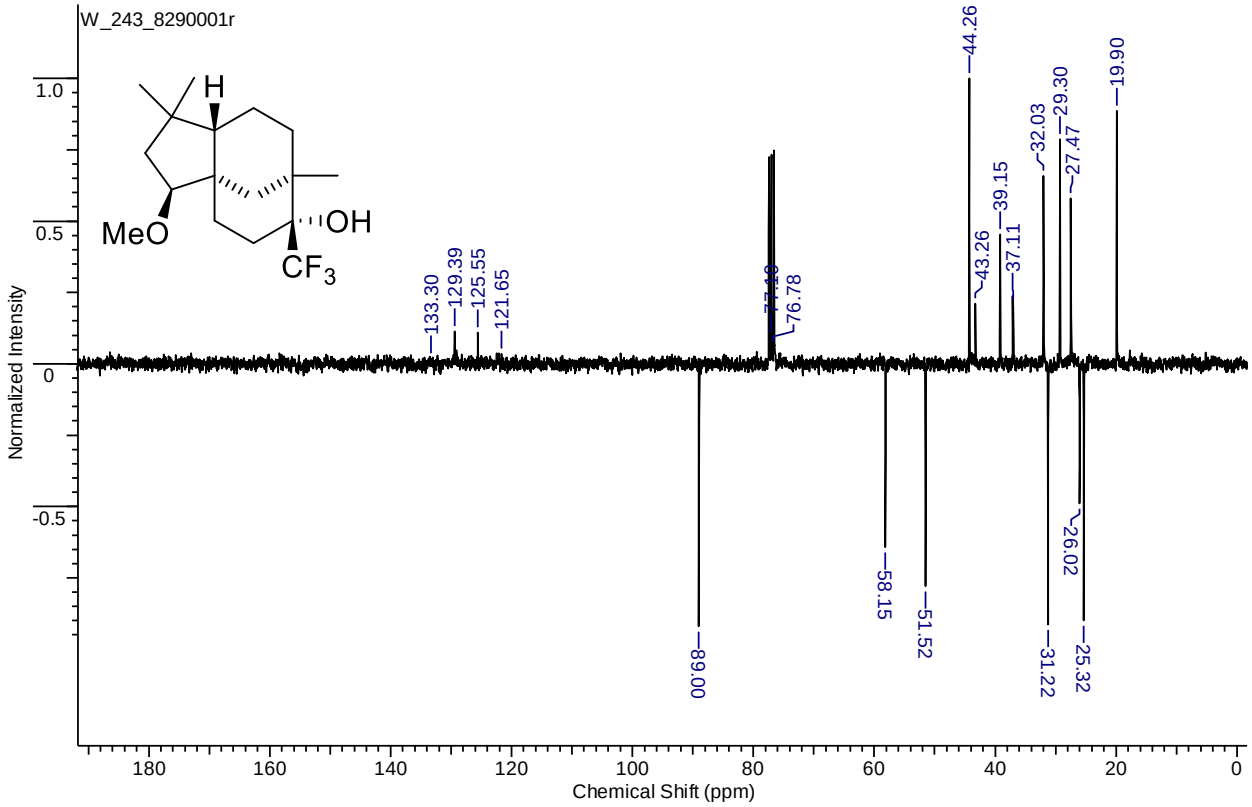


Figure S35. ^{13}C NMR spectra (75 MHz) of **18** in $CDCl_3$

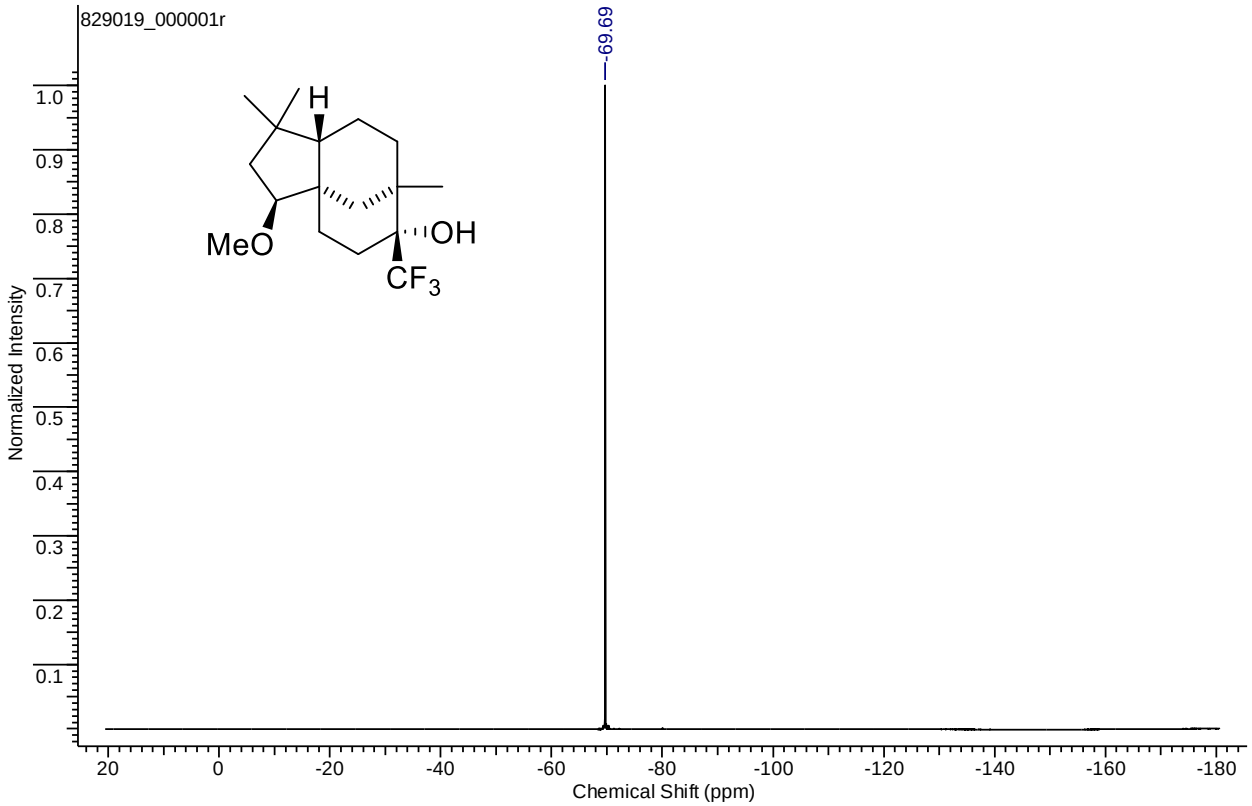


Figure S36. ^{19}F NMR spectra (282 MHz) of **18** in $CDCl_3$

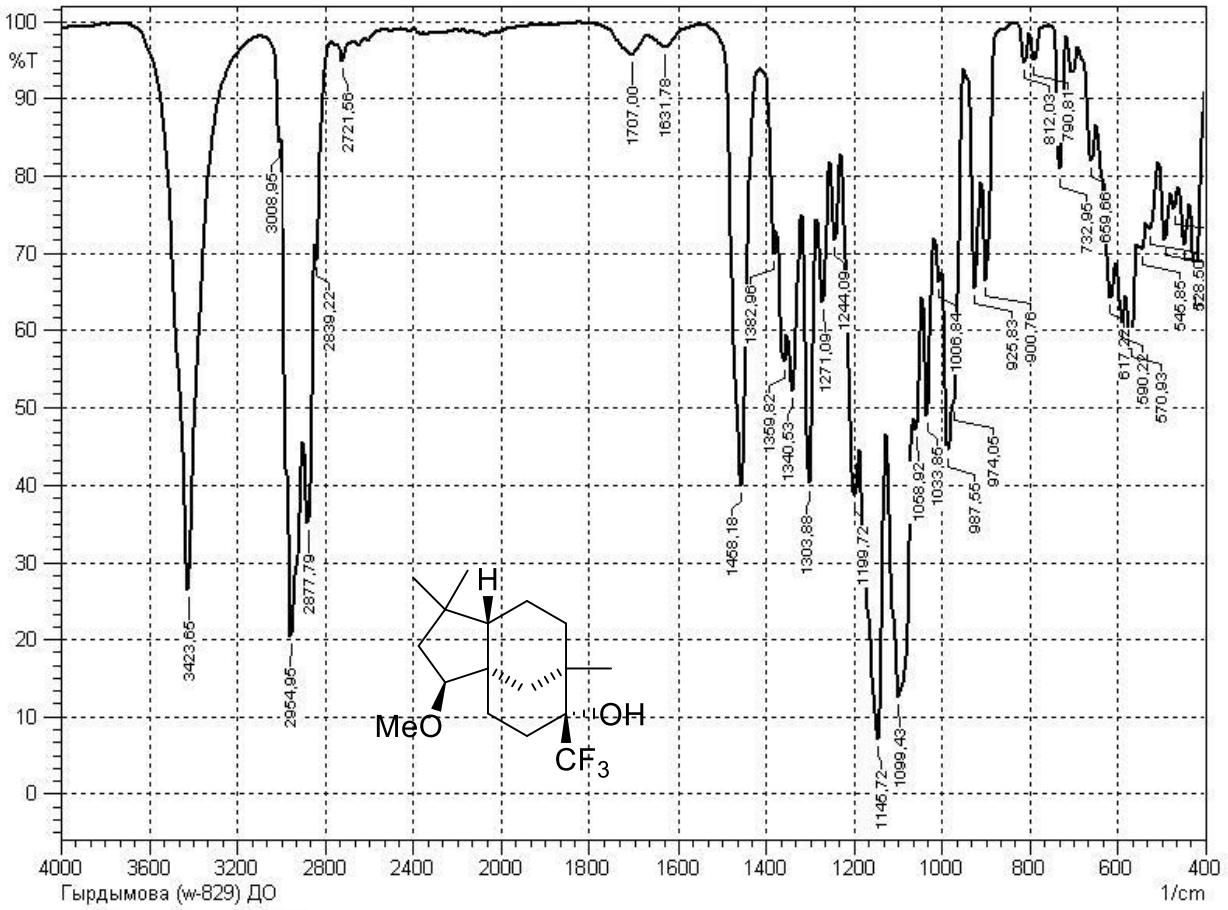


Figure S37. IR spectra of **18**

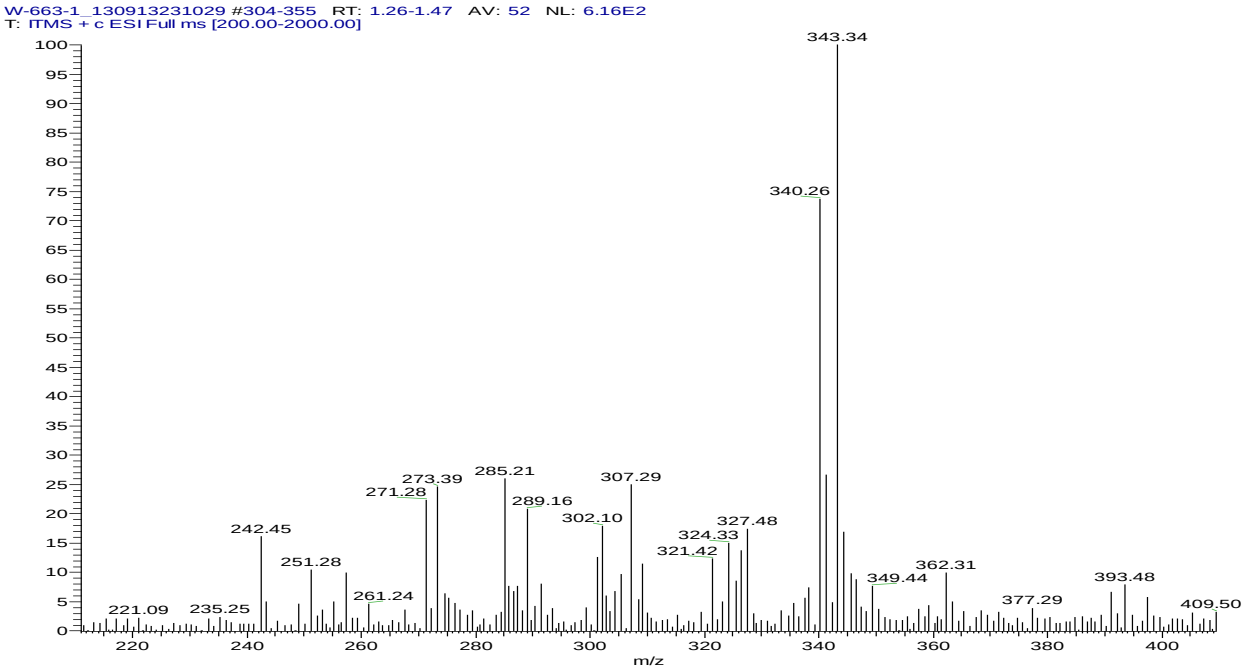


Figure S38. ESI-MS spectra of **18**

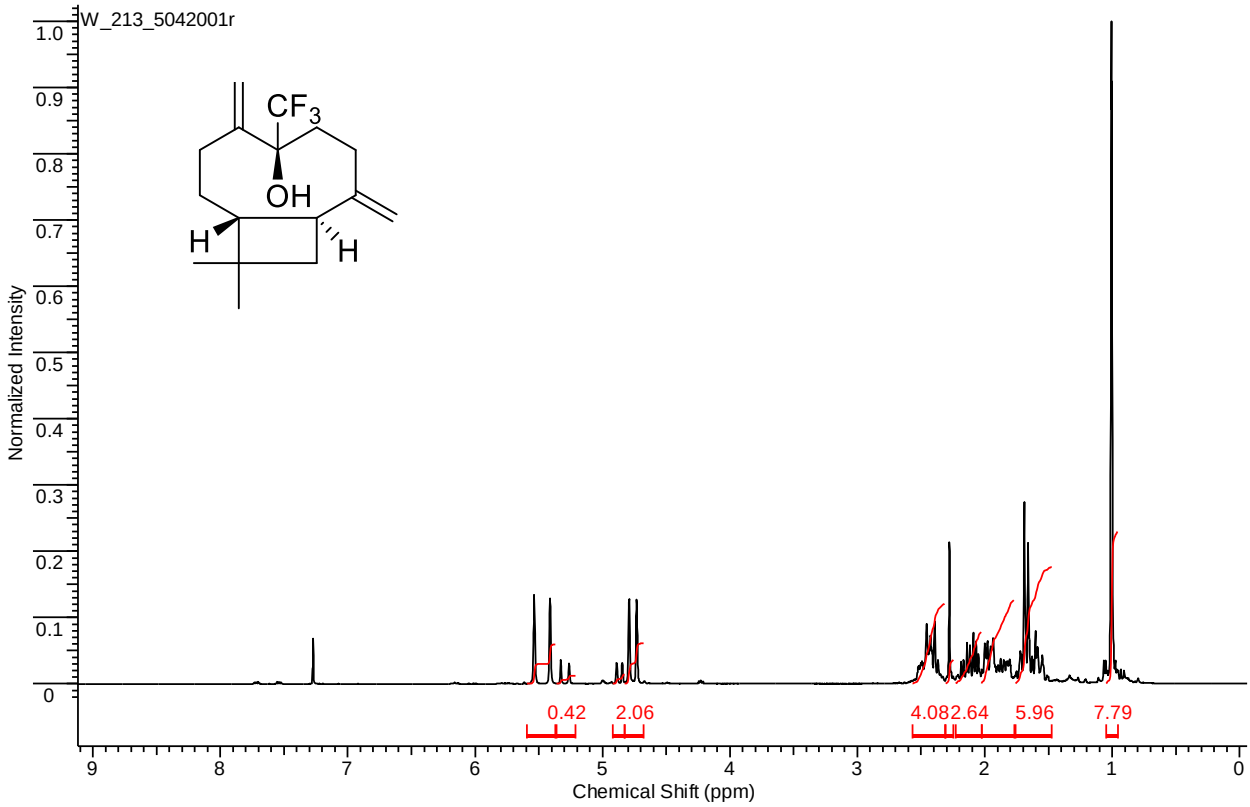


Figure S39. ^{1}H NMR spectra (300 MHz) of **19** in $CDCl_3$

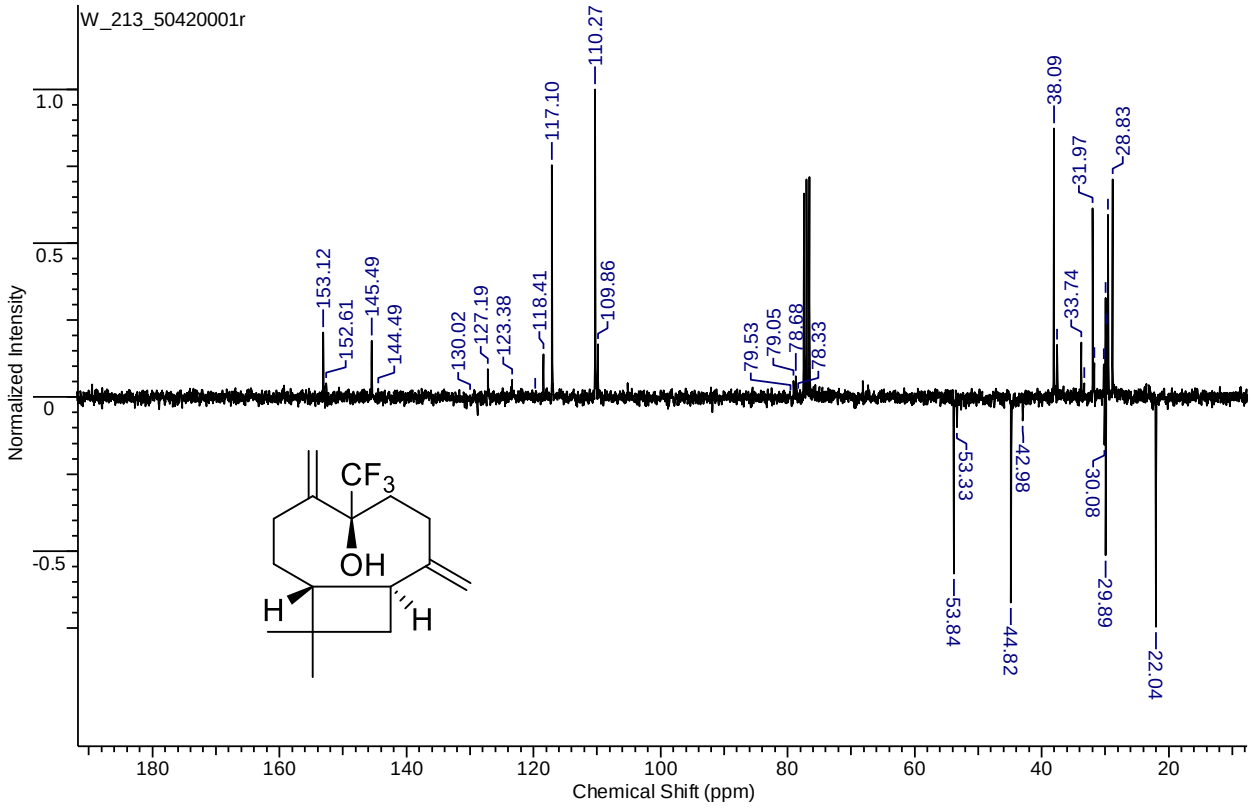


Figure S40. ^{13}C NMR spectra (75 MHz) of **19** in $CDCl_3$

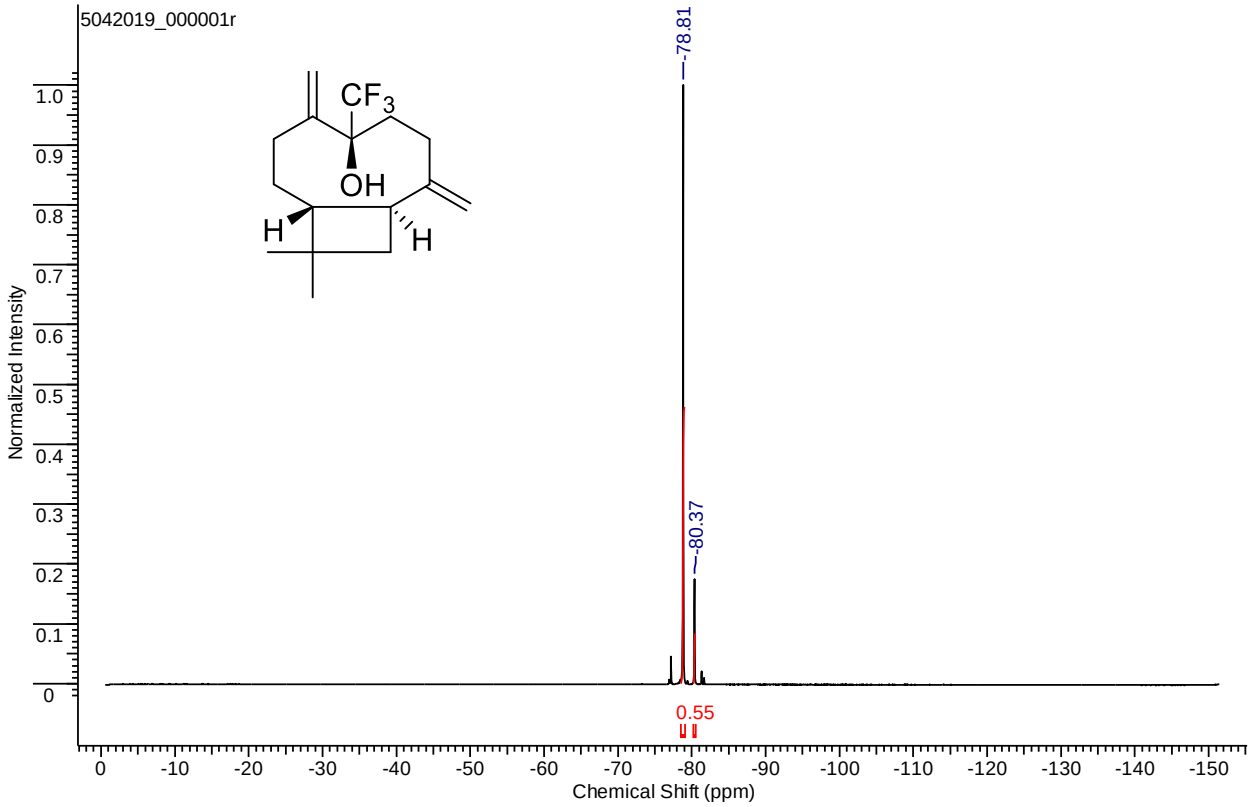


Figure S41. ^{19}F NMR spectra (282 MHz) of **19** in $CDCl_3$

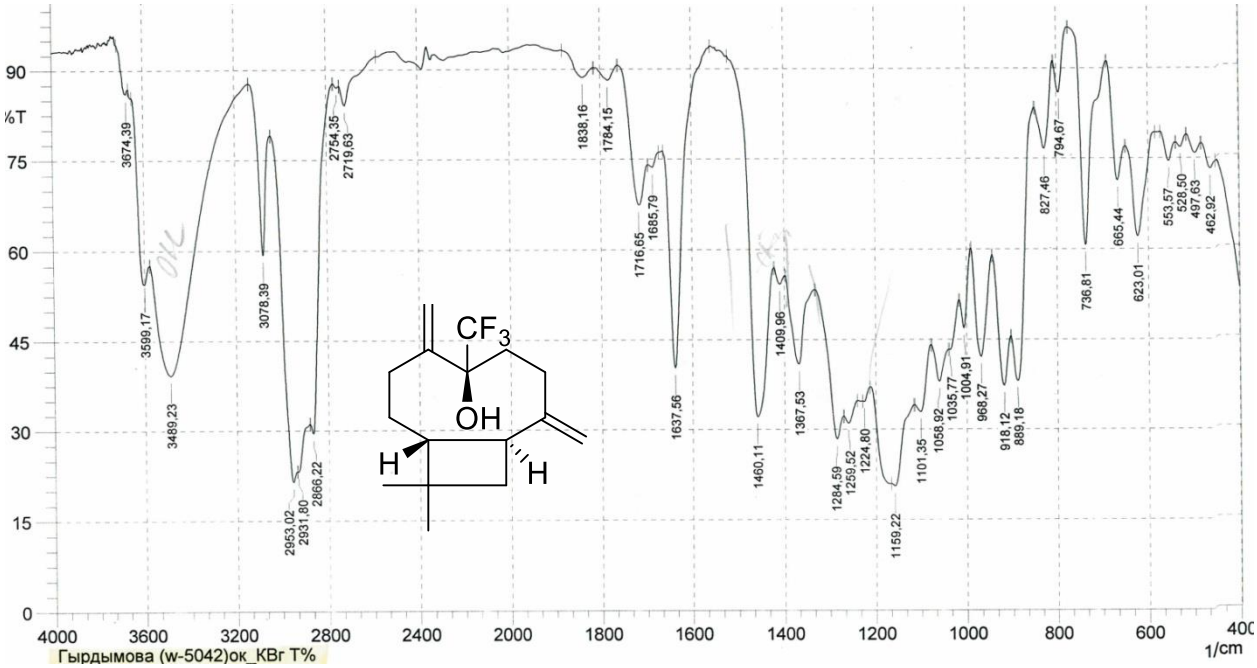


Figure S42. IR spectra of **19**

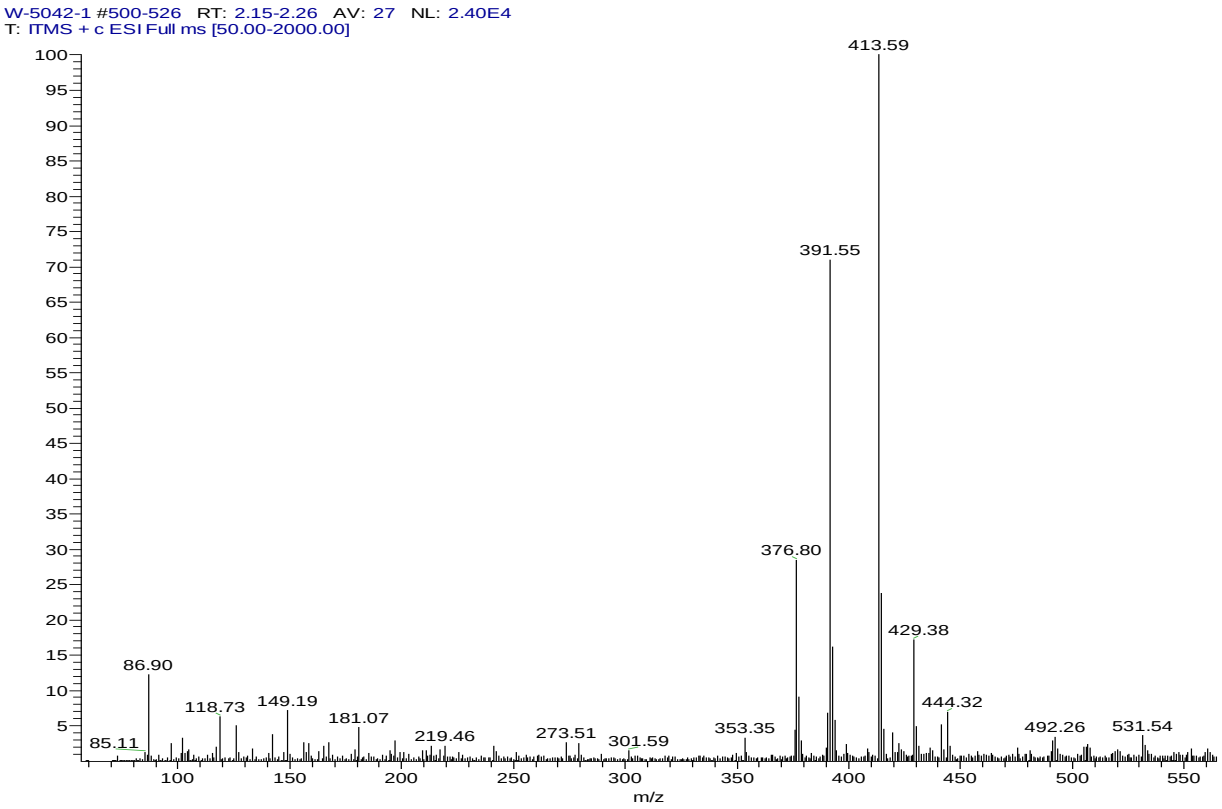


Figure S43. ESI-MS spectra of **19**

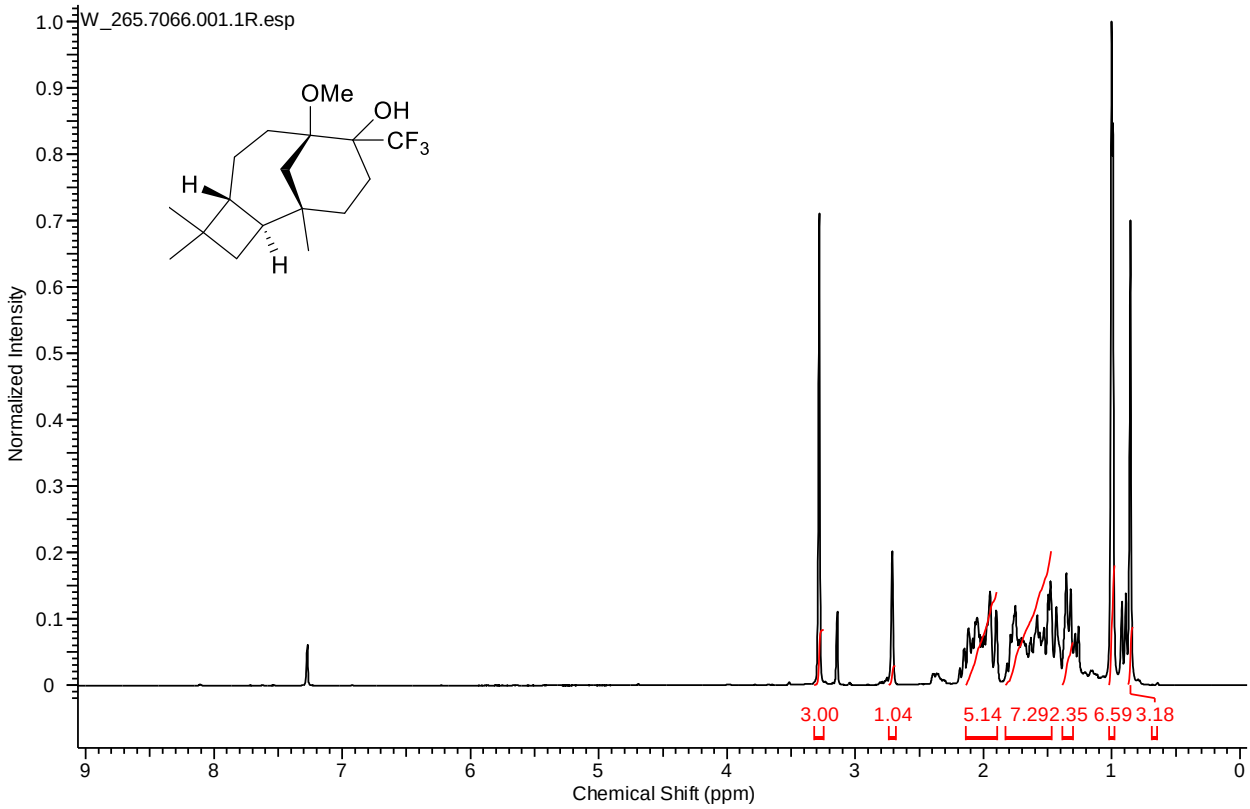


Figure S44. ^{1}H NMR spectra (300 MHz) of **20a** in $CDCl_3$

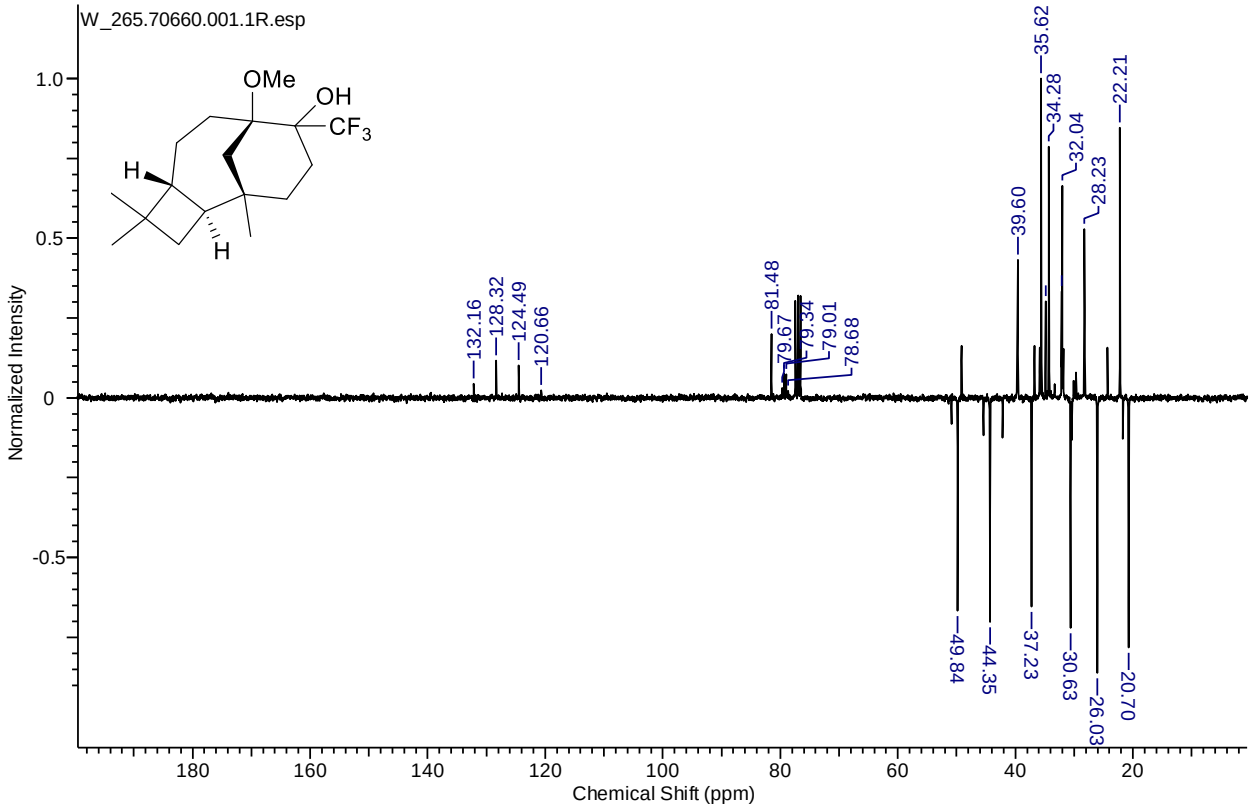


Figure S45. ^{13}C NMR spectra (75 MHz) of **20a** in $CDCl_3$

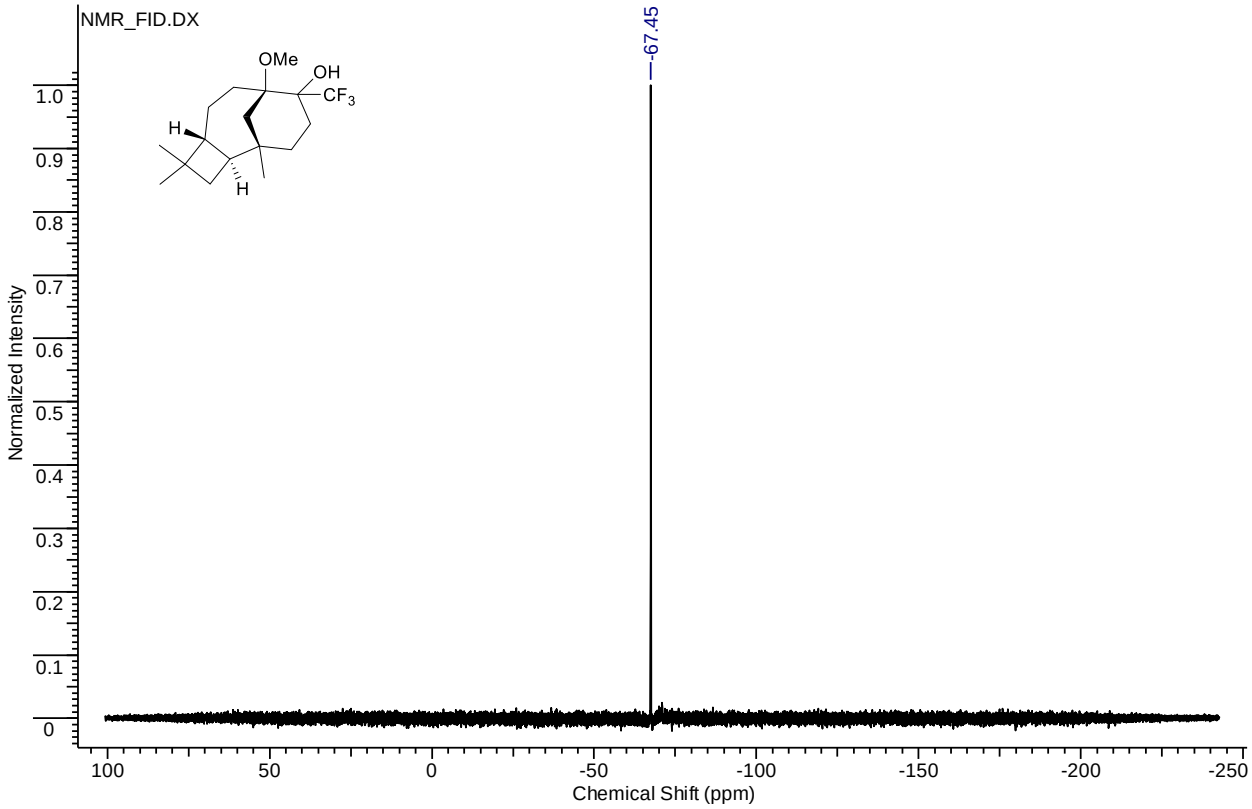


Figure S46. ^{19}F NMR spectra (282 MHz) of **20a** in $CDCl_3$

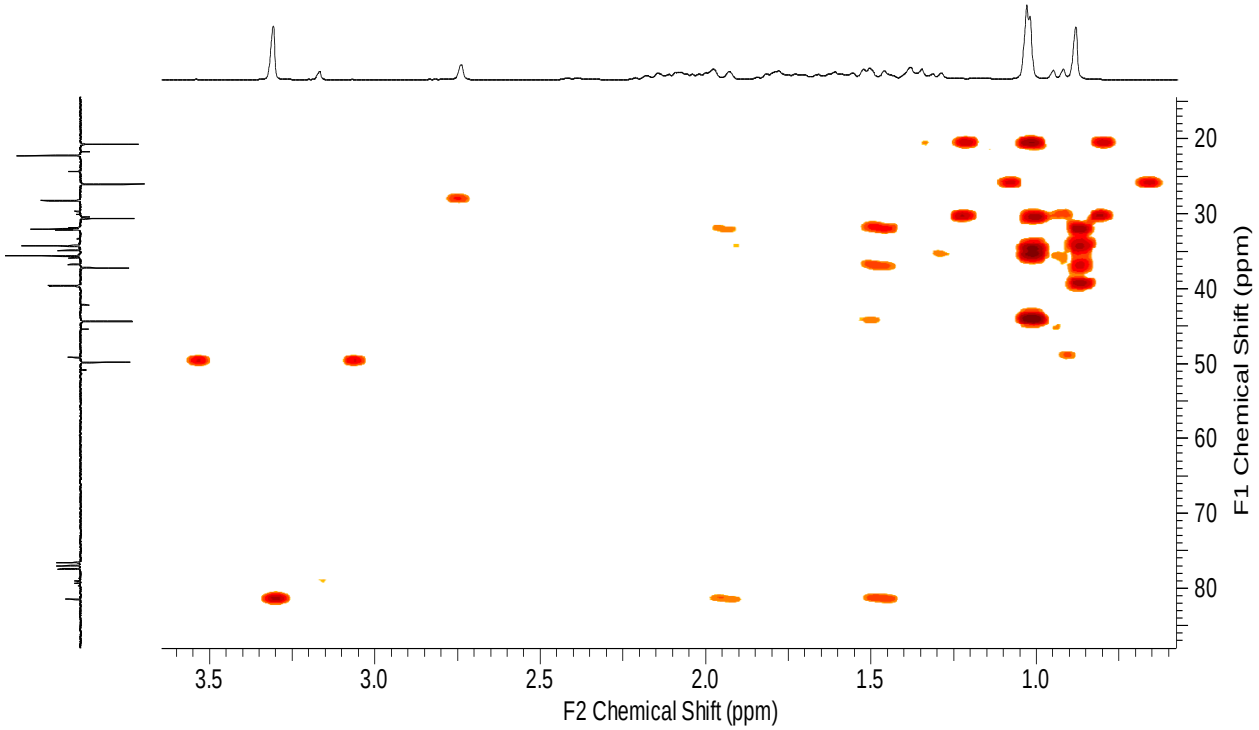


Figure S47. HMBC NMR spectra of **20a** in $CDCl_3$

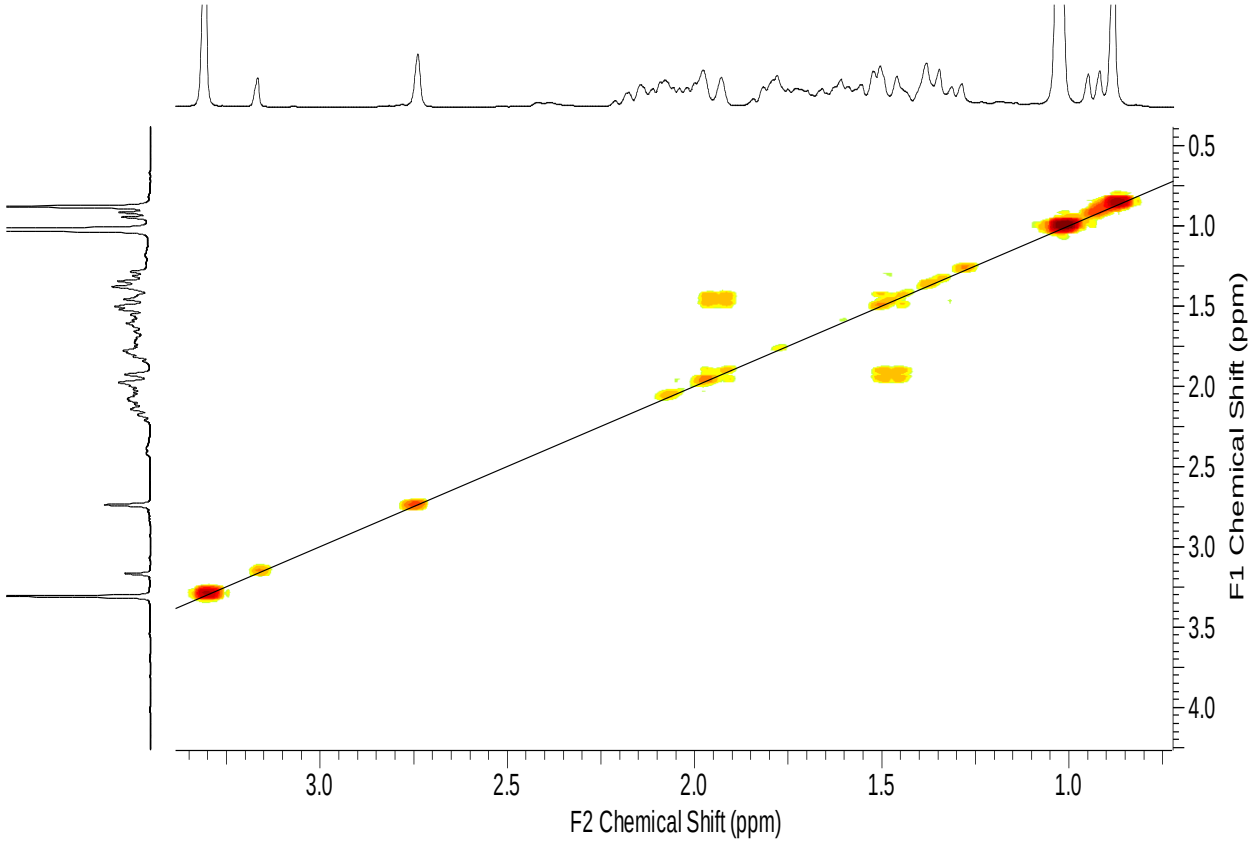


Figure S48. COSY NMR spectra of **20a** in $CDCl_3$

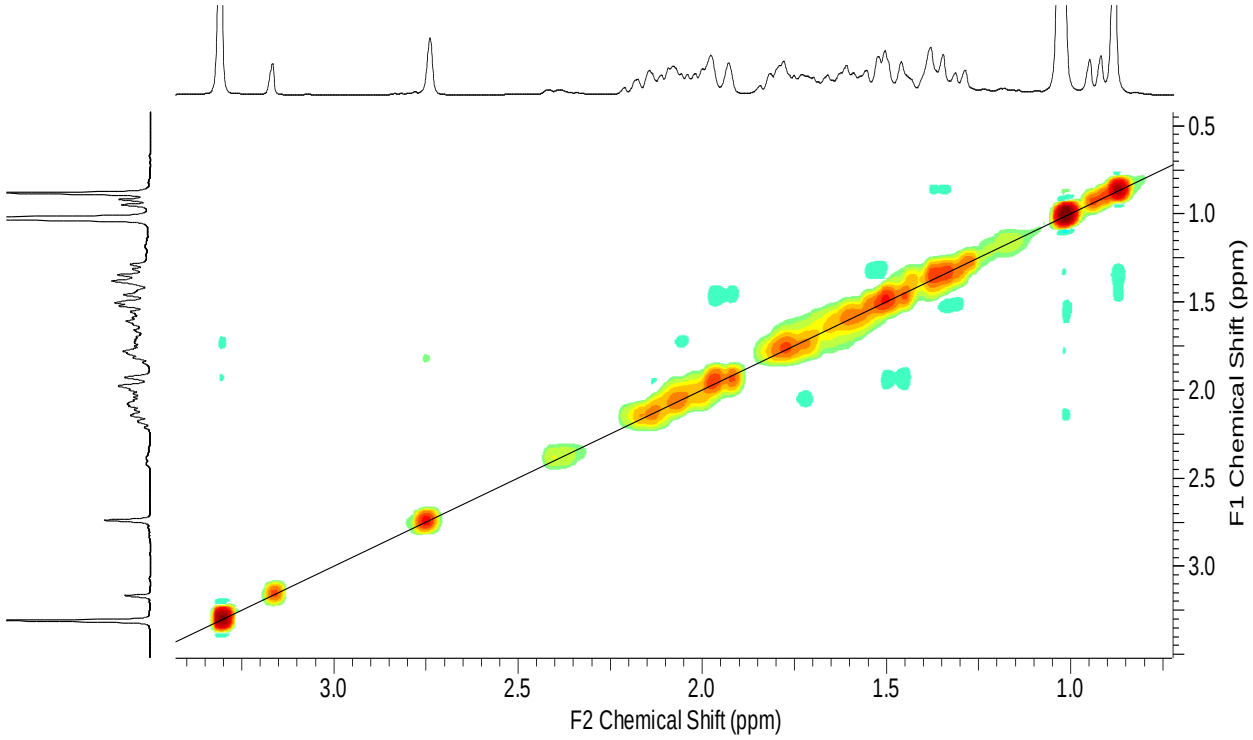


Figure S49. NOESY NMR spectra of **20a** in $CDCl_3$

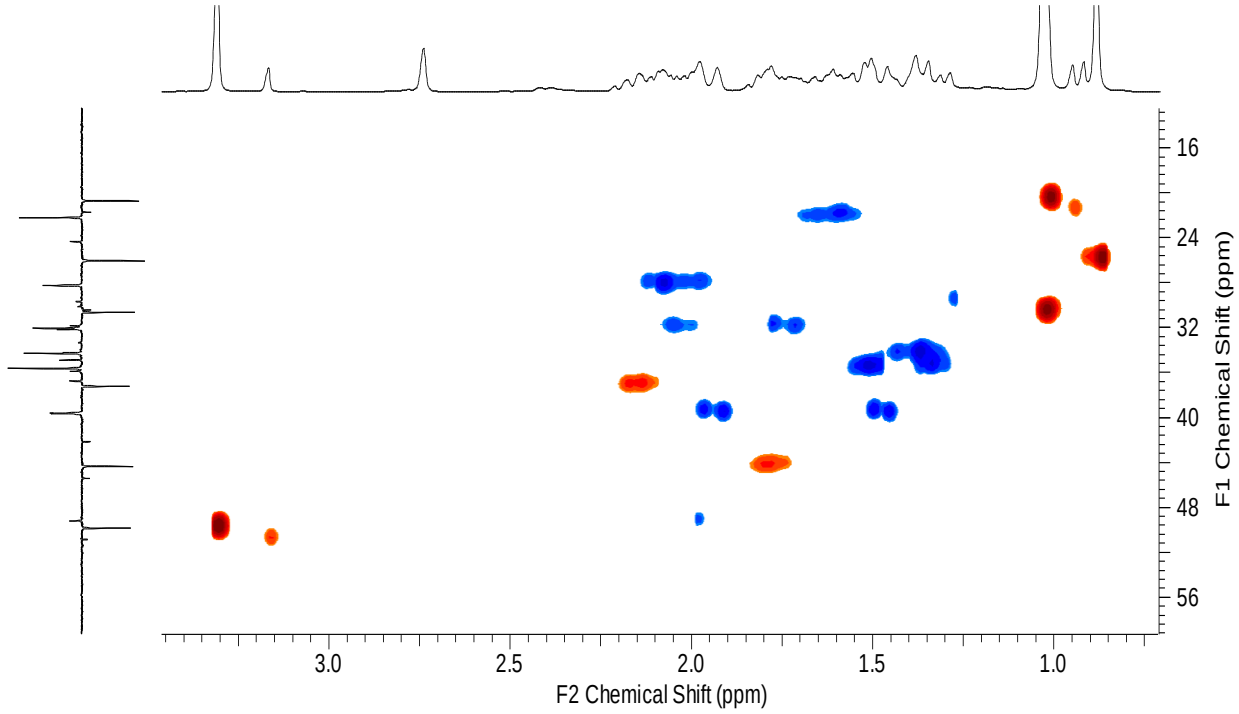


Figure S50. HSQC NMR spectra of **20a** in $CDCl_3$

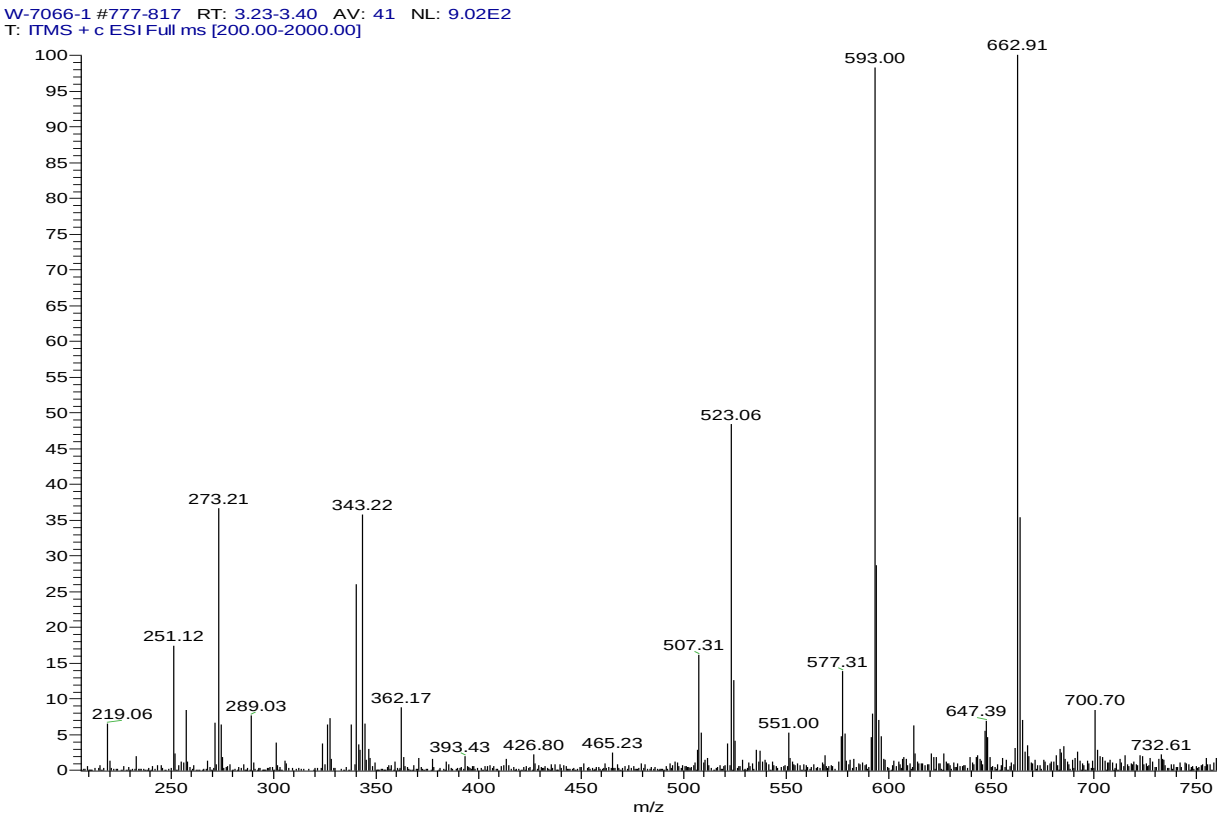


Figure S51. IR spectra of **20a**

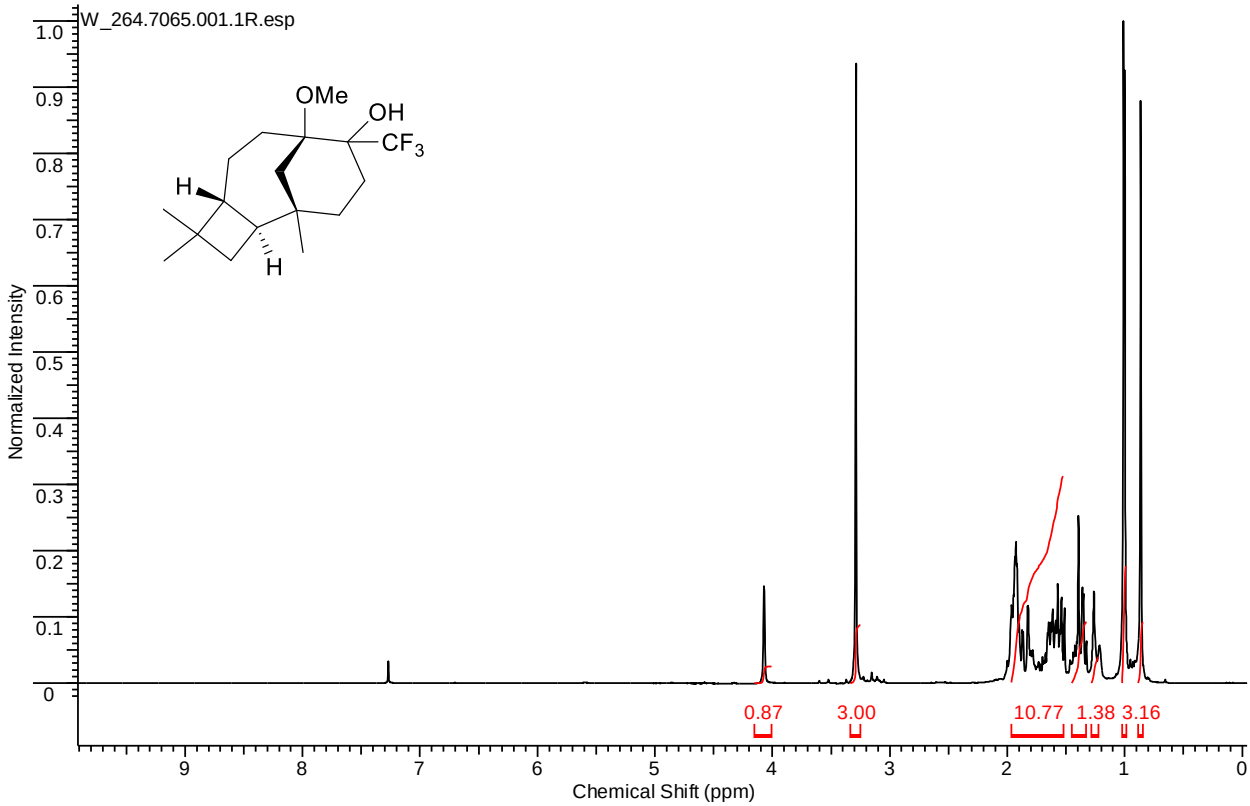


Figure S52. ^{1}H NMR spectra (300 MHz) of **20b** in $CDCl_3$

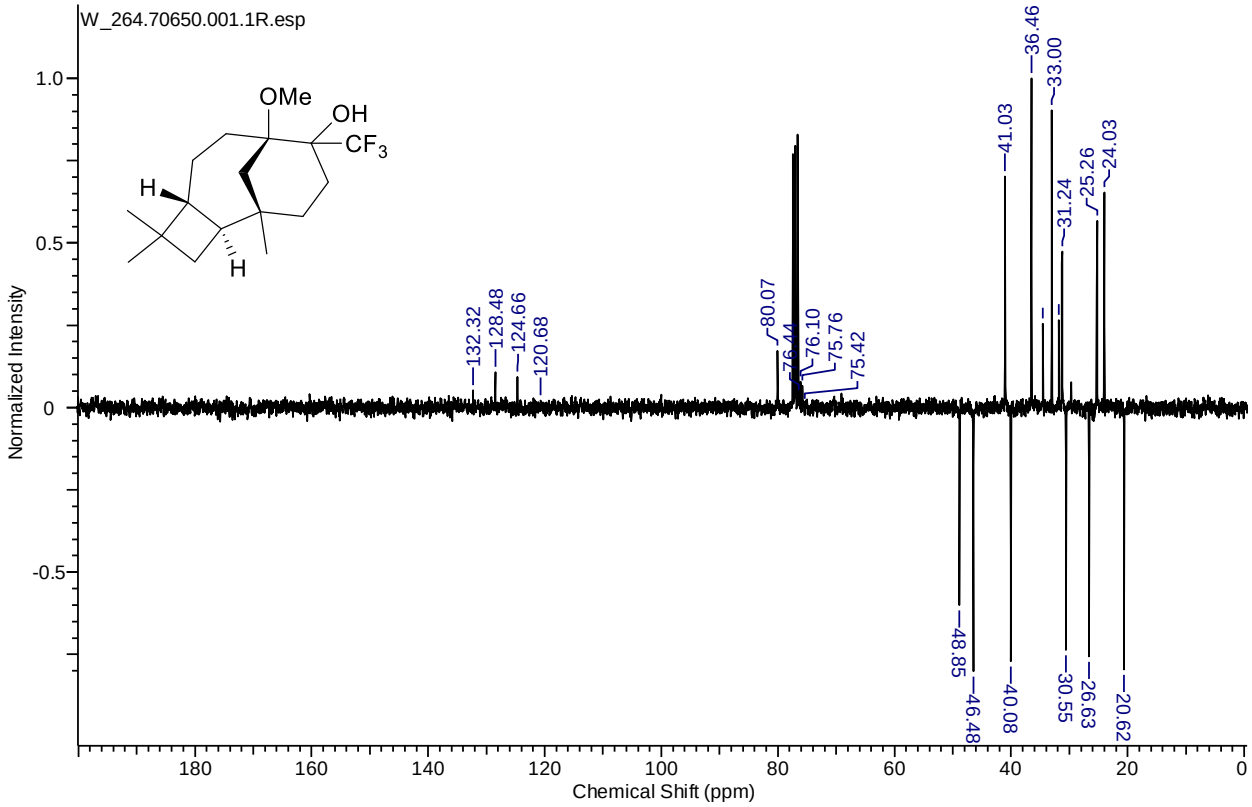


Figure S53. ^{13}C NMR spectra (75 MHz) of **20b** in $CDCl_3$

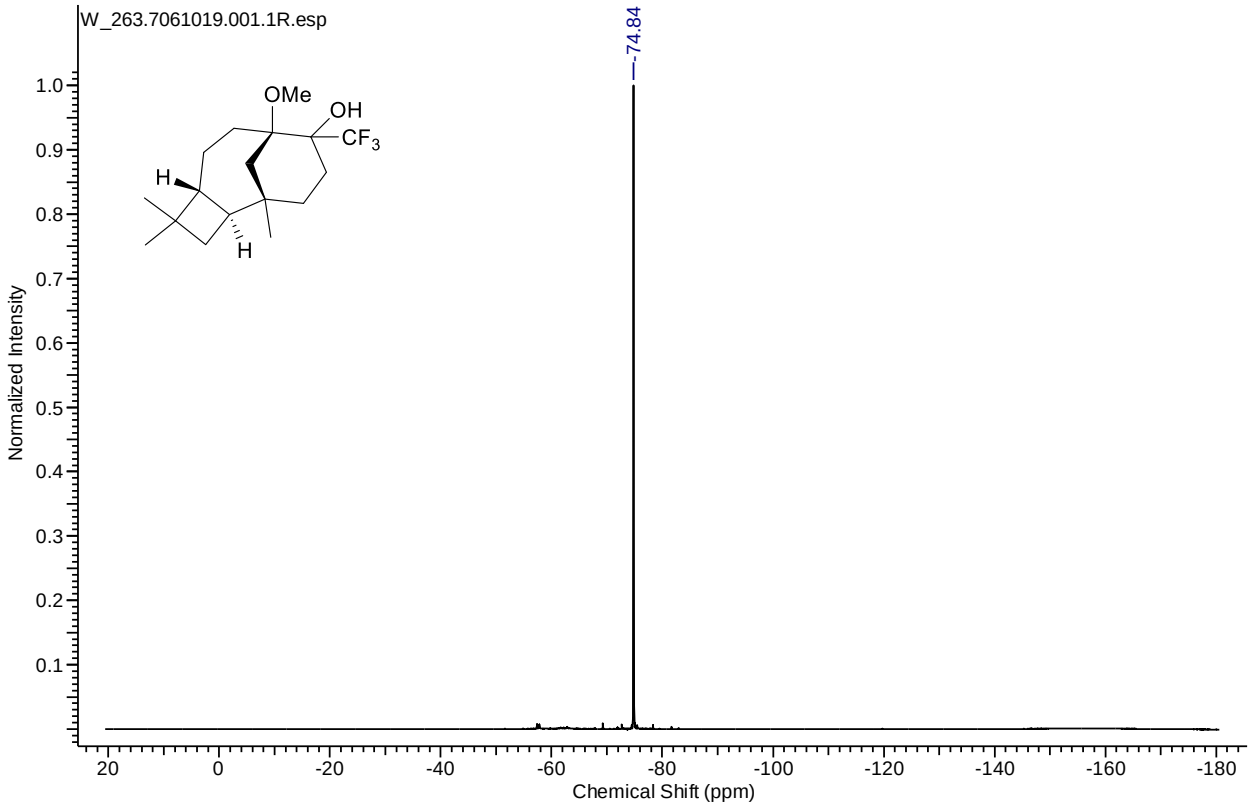


Figure S54. ^{19}F NMR spectra (282 MHz) of **20b** in $CDCl_3$

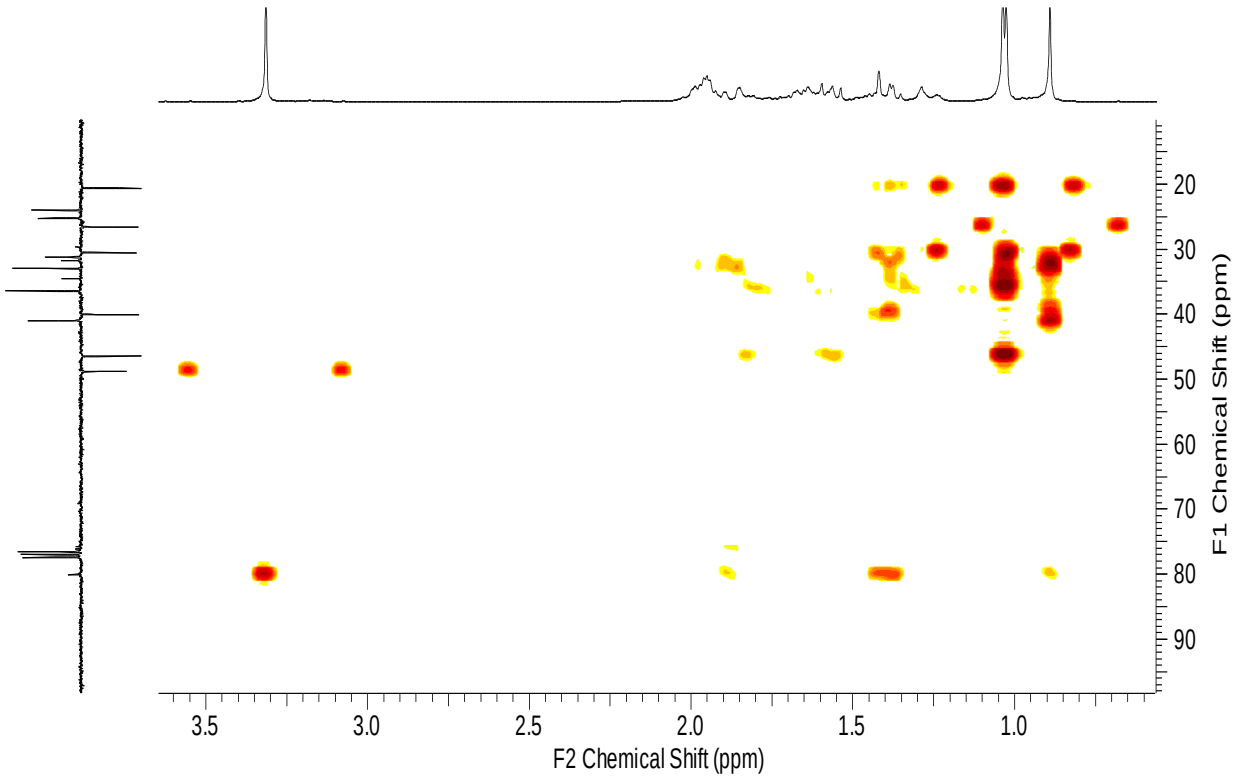


Figure S55. HMBC NMR spectra of **20b** in $CDCl_3$

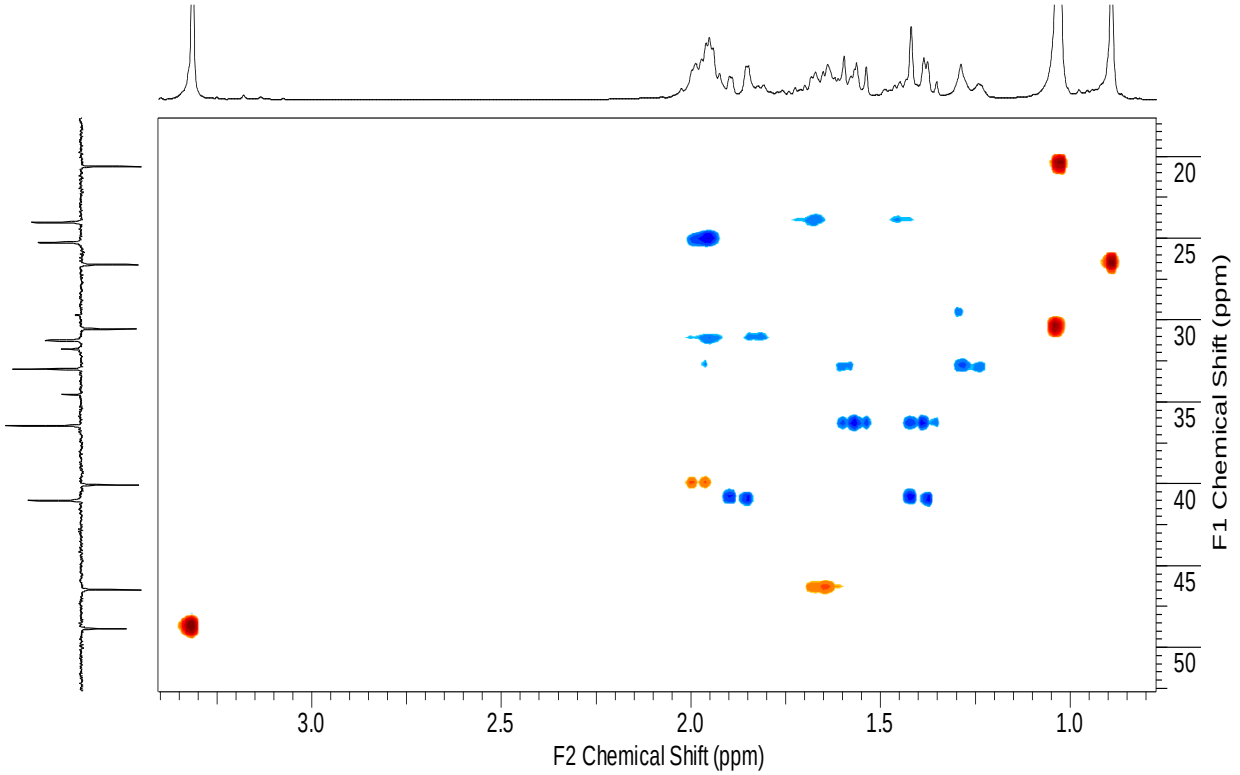


Figure S56. HSQC NMR spectra of **20b** in $CDCl_3$

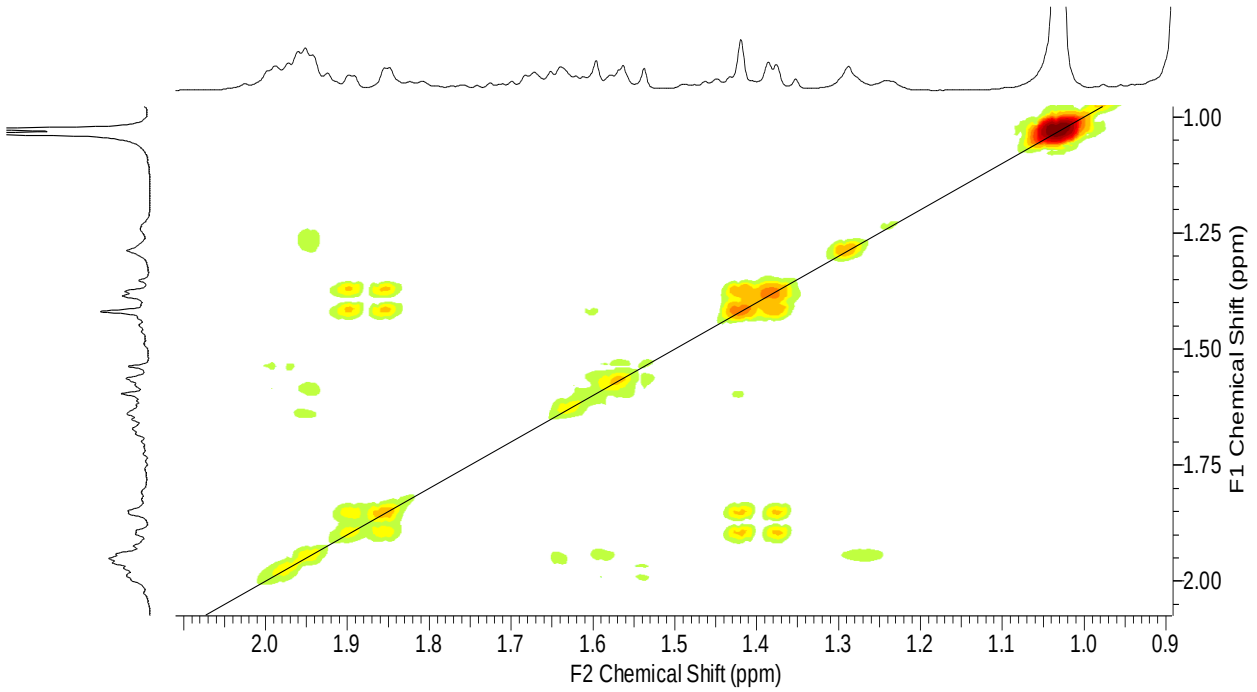


Figure S57. COSY NMR spectra (fragment) of **20b** in $CDCl_3$

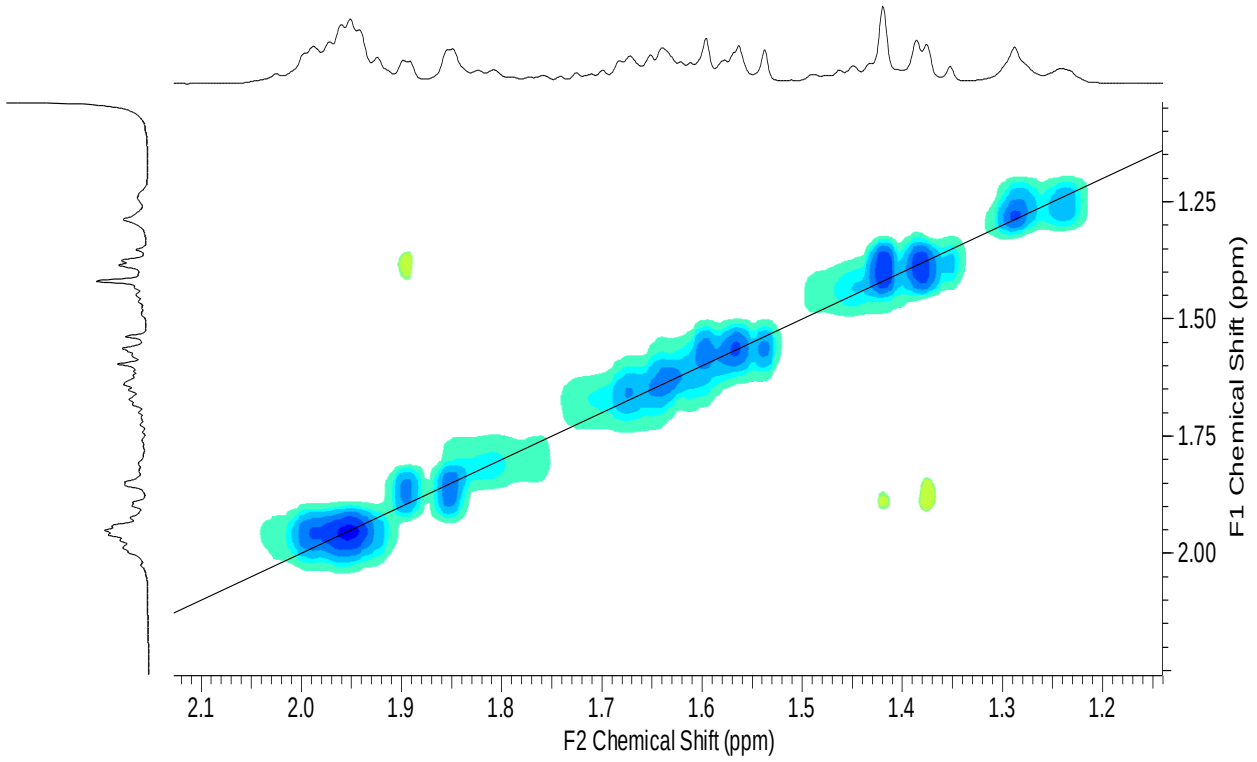


Figure S58. NOESY NMR spectra of **20b** in $CDCl_3$

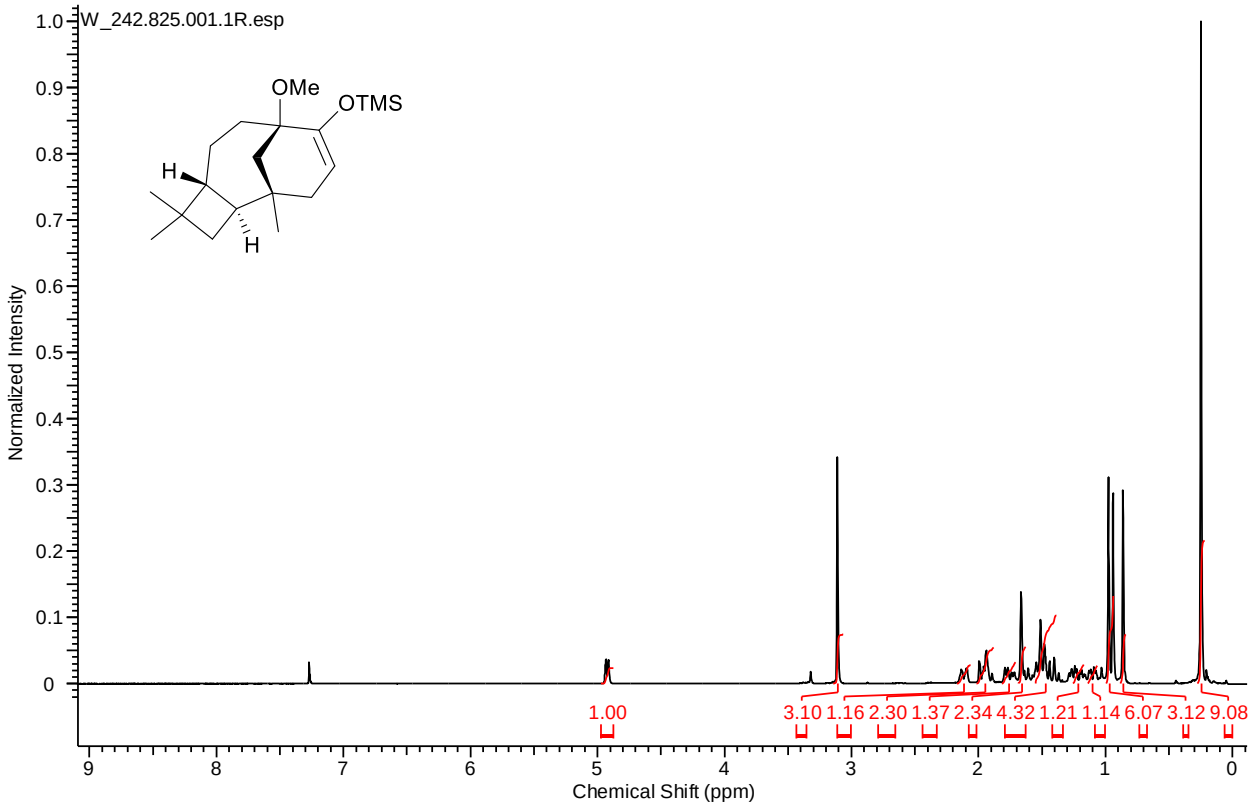


Figure S59. ^{1}H NMR spectra (300 MHz) of **22** in $CDCl_3$

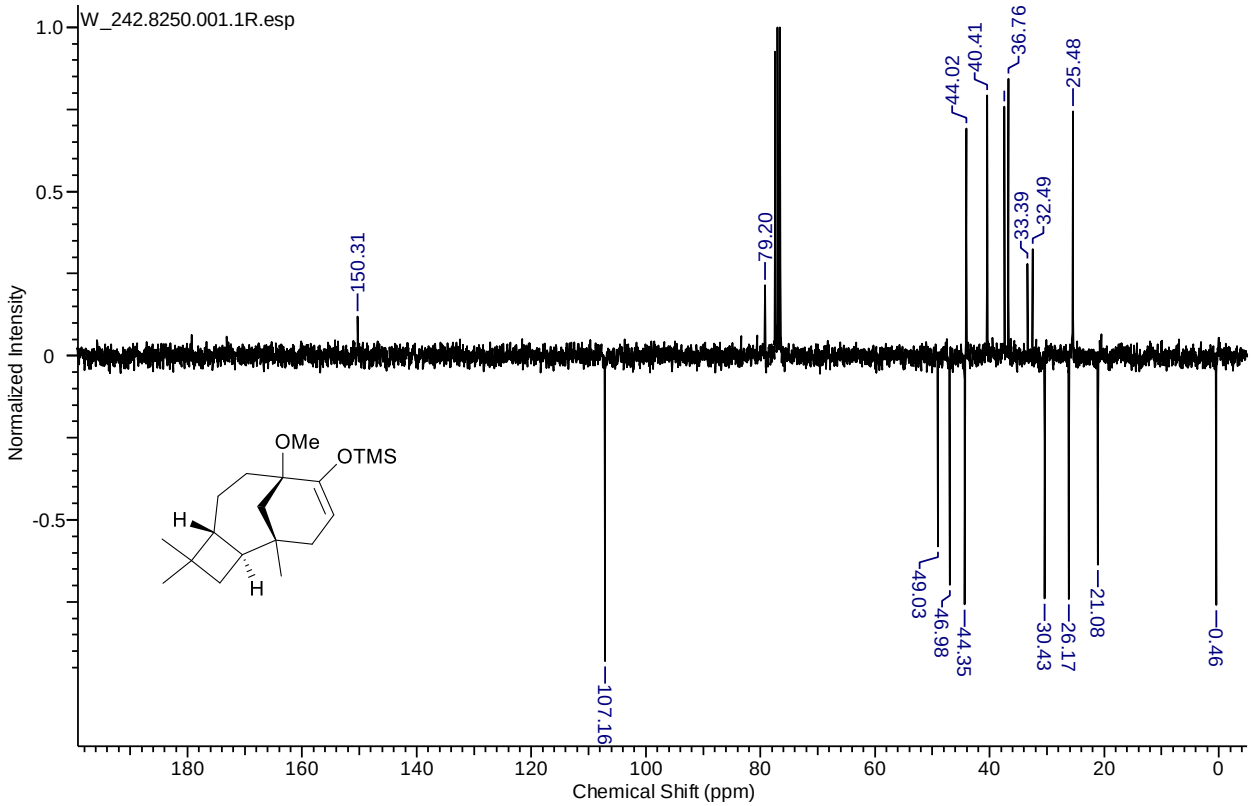


Figure S60. ^{13}C NMR spectra (75 MHz) of **22** in $CDCl_3$

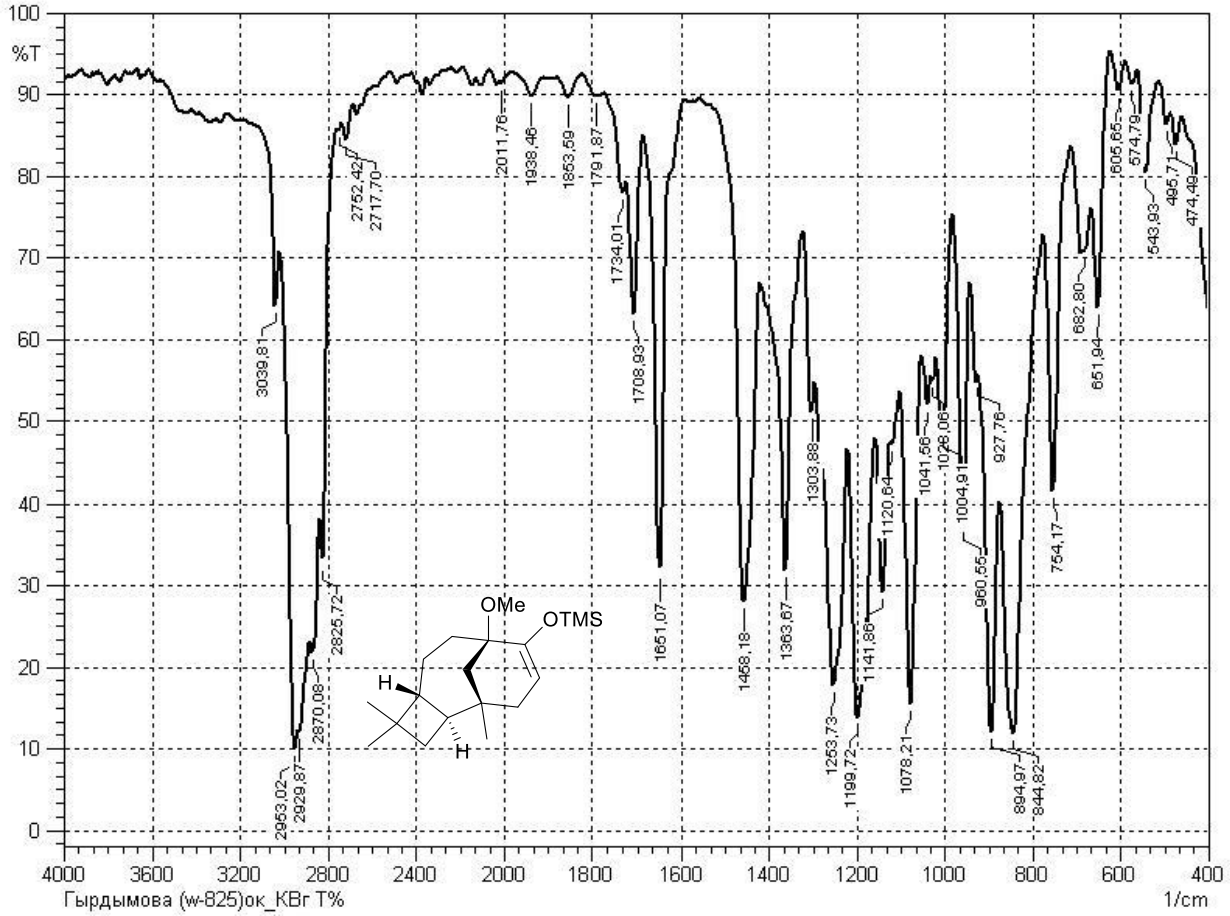


Figure S61. IR spectra of **22**

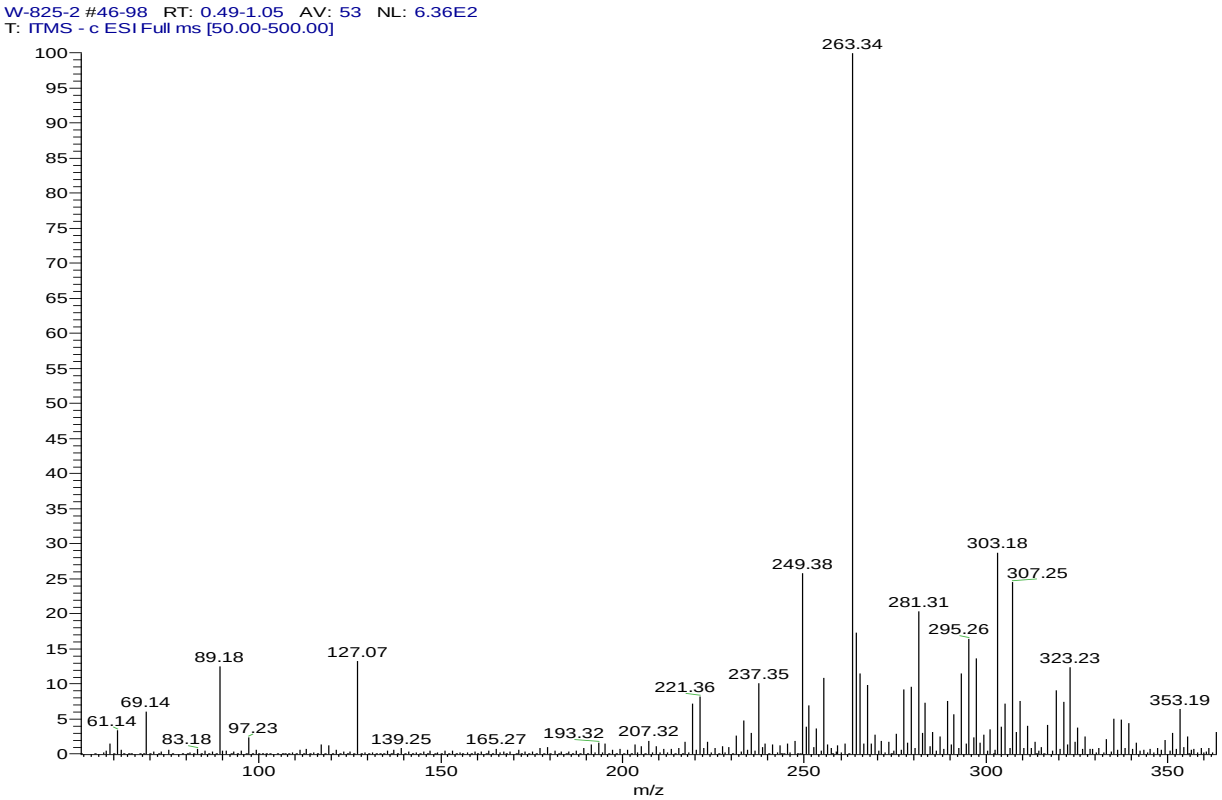


Figure S62. ESI-MS spectra of **22**

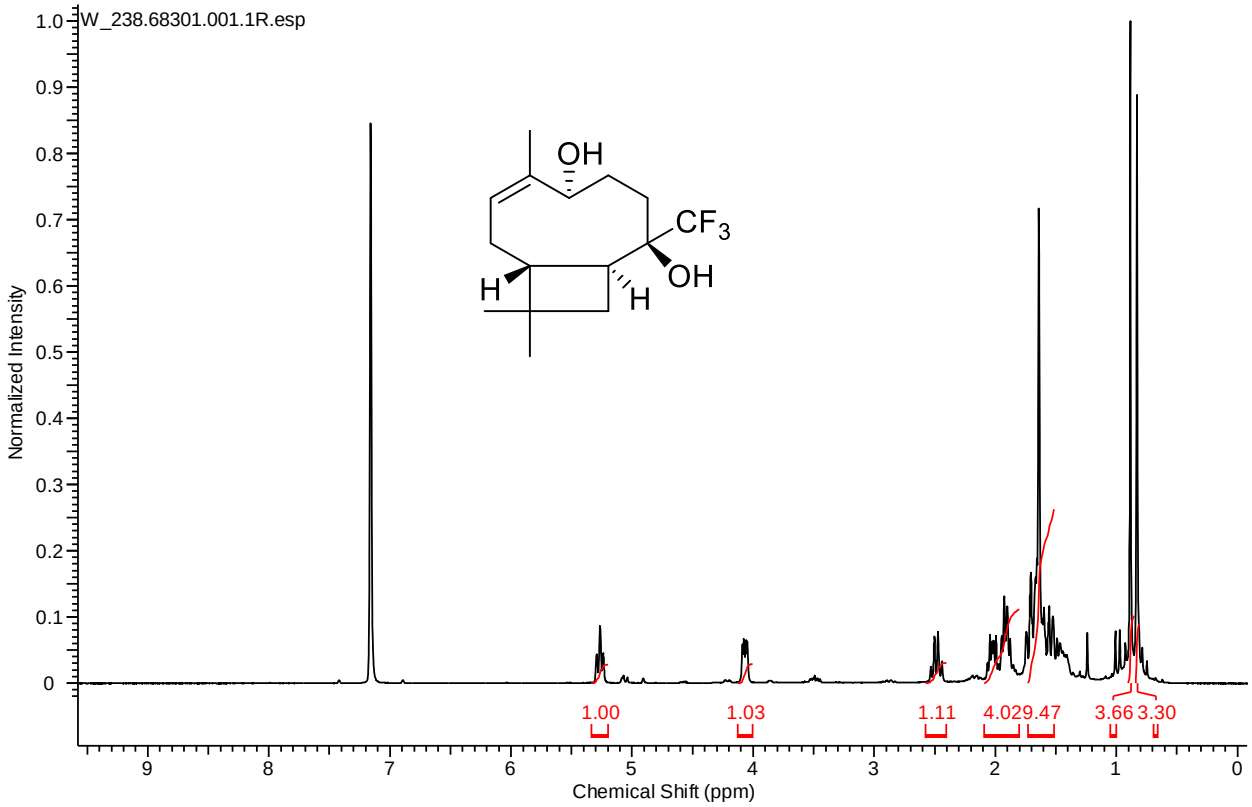


Figure S63. ^{1}H NMR spectra (300 MHz) of **23** in C_6D_6

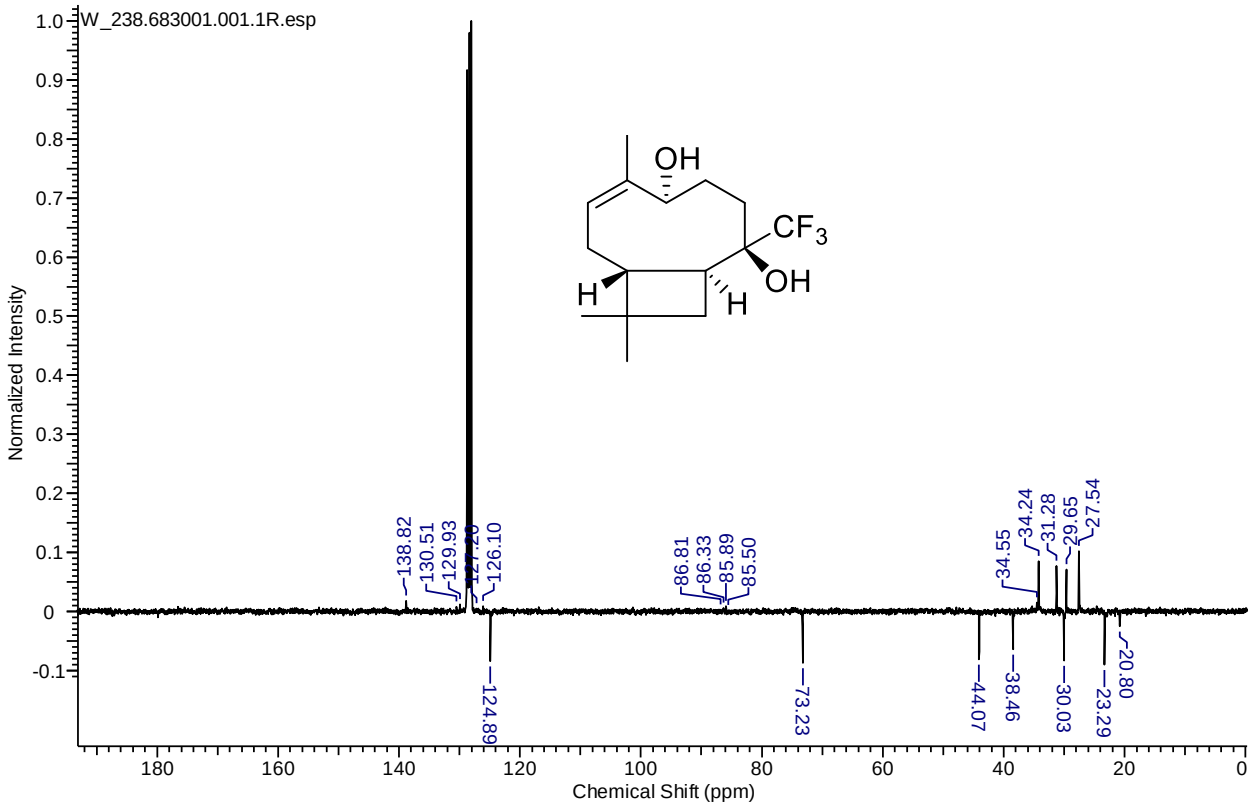


Figure S64. ^{13}C NMR spectra (75 MHz) of **23** in C_6D_6

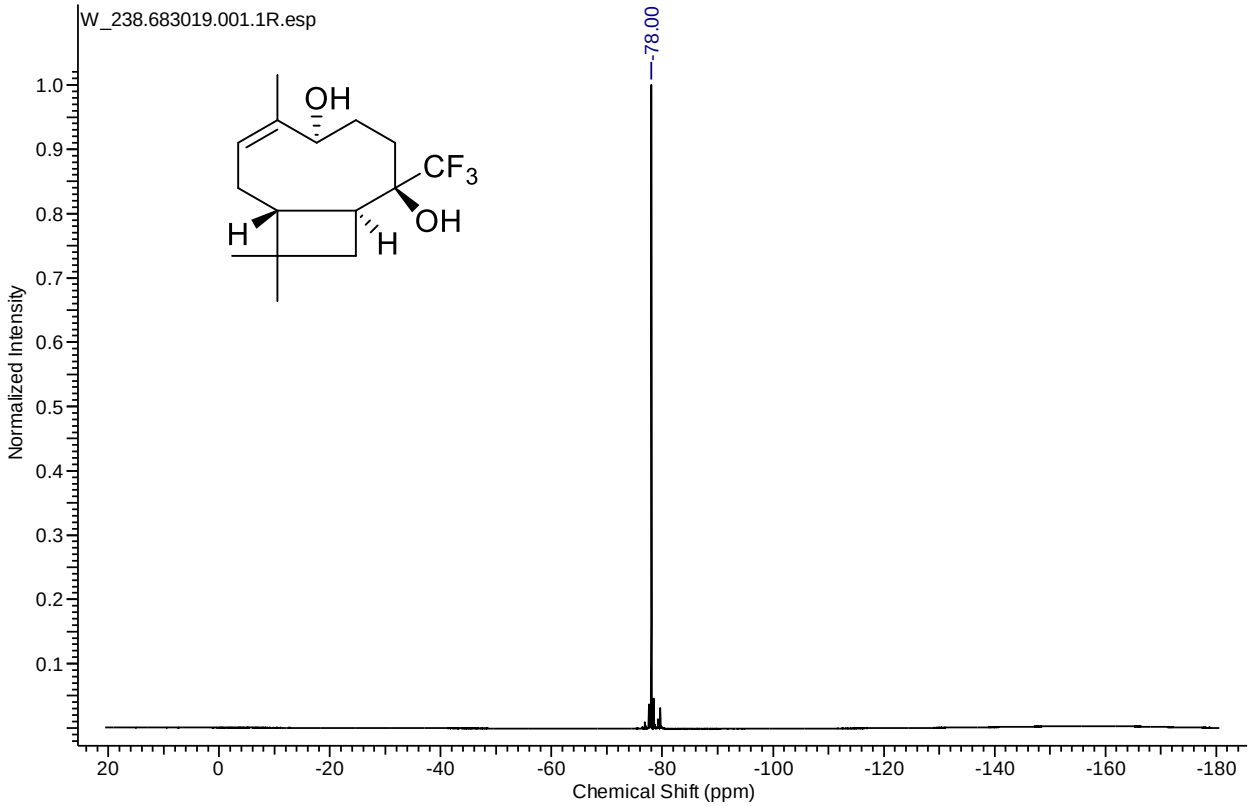


Figure S65. ^{19}F NMR spectra (282 MHz) of **23** in C_6D_6

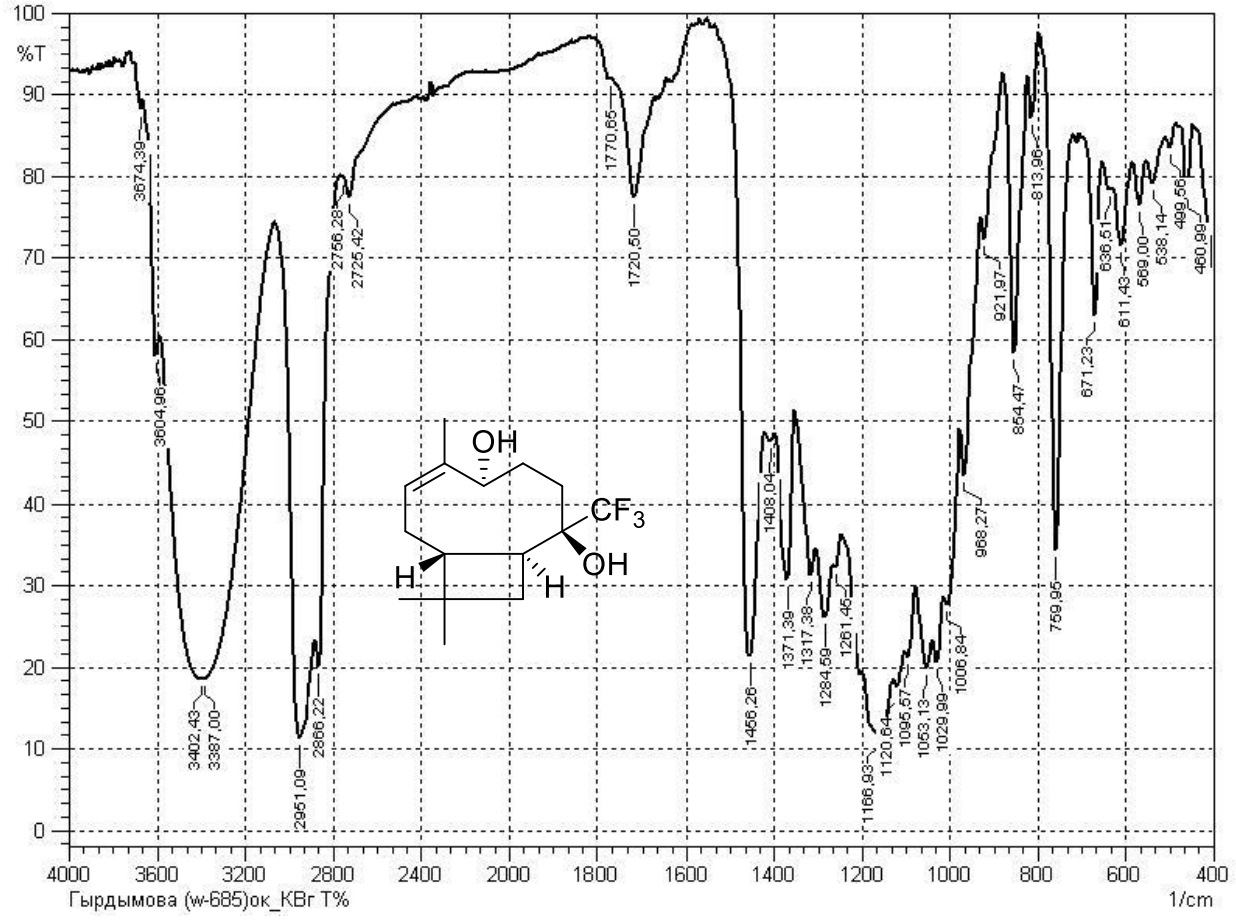


Figure S66. IR spectra of **23**

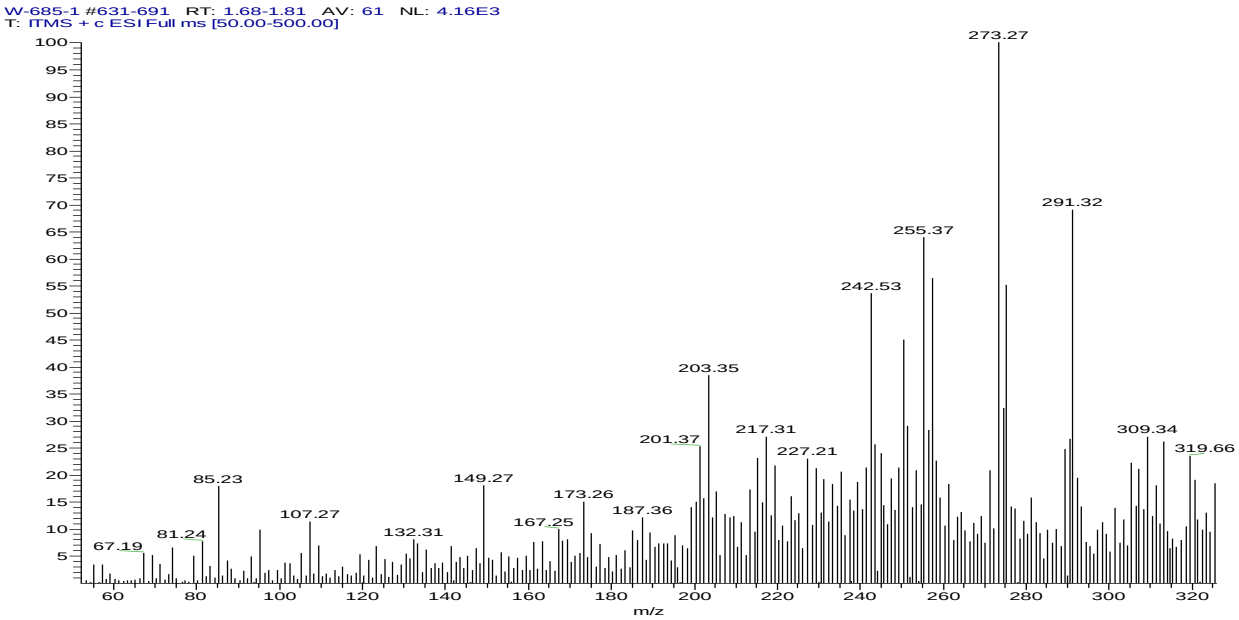


Figure S67. ESI-MS spectra of **23**

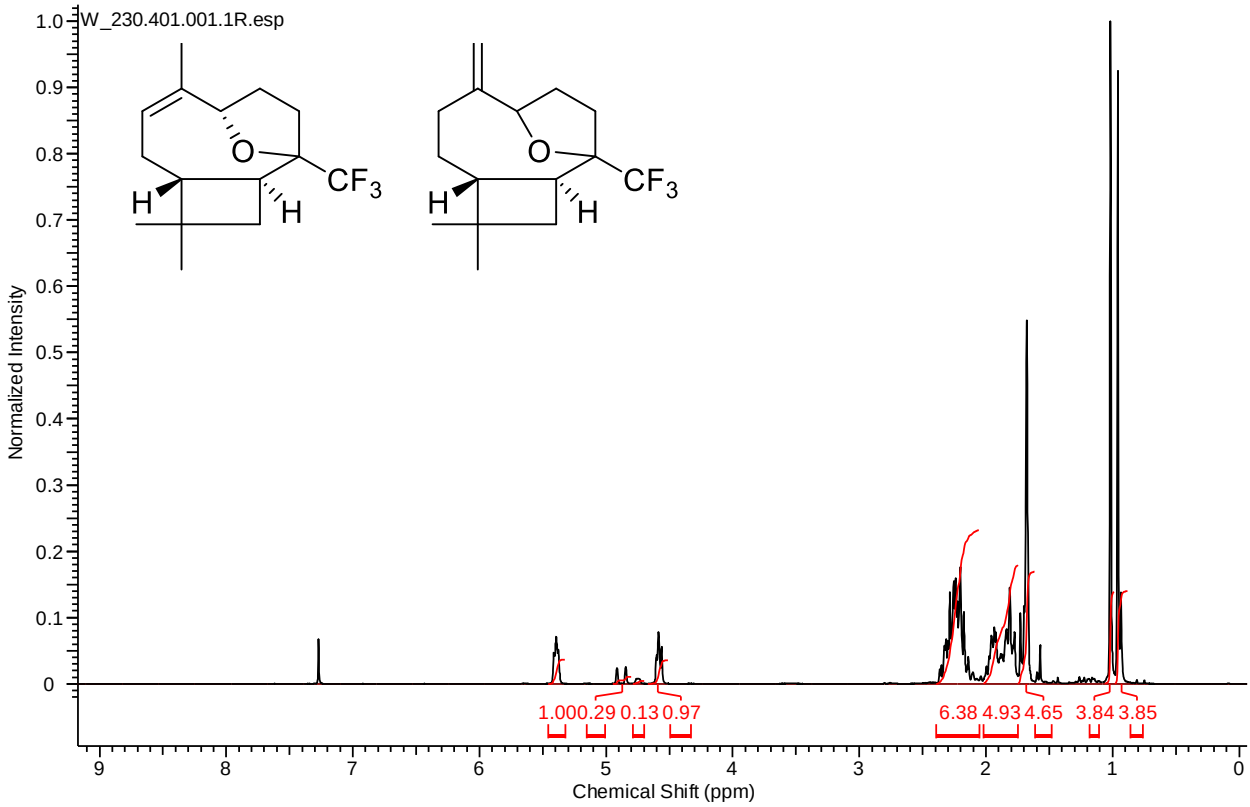


Figure S68. ^{1}H NMR spectra (300 MHz) of mixture **25 + 26** in $CDCl_3$

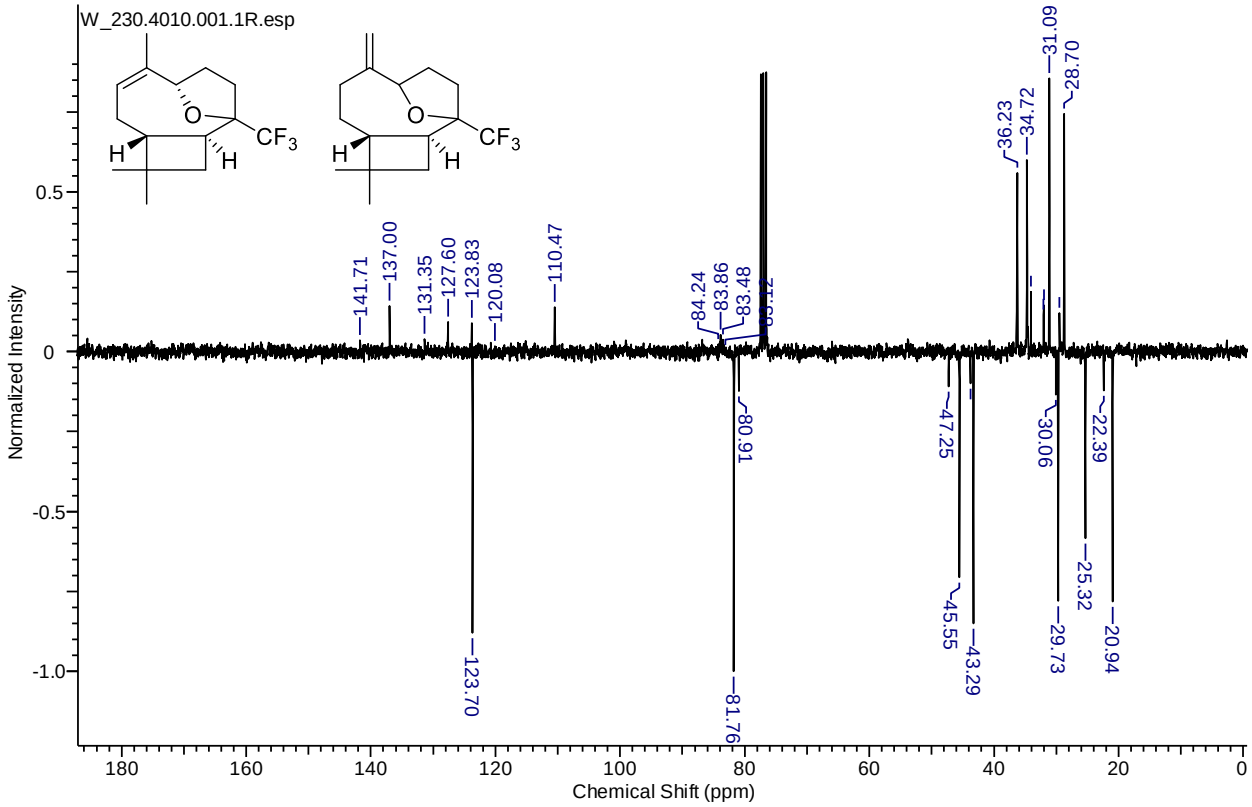


Figure S69. ^{13}C NMR spectra (75 MHz) of mixture **25 + 26** in $CDCl_3$

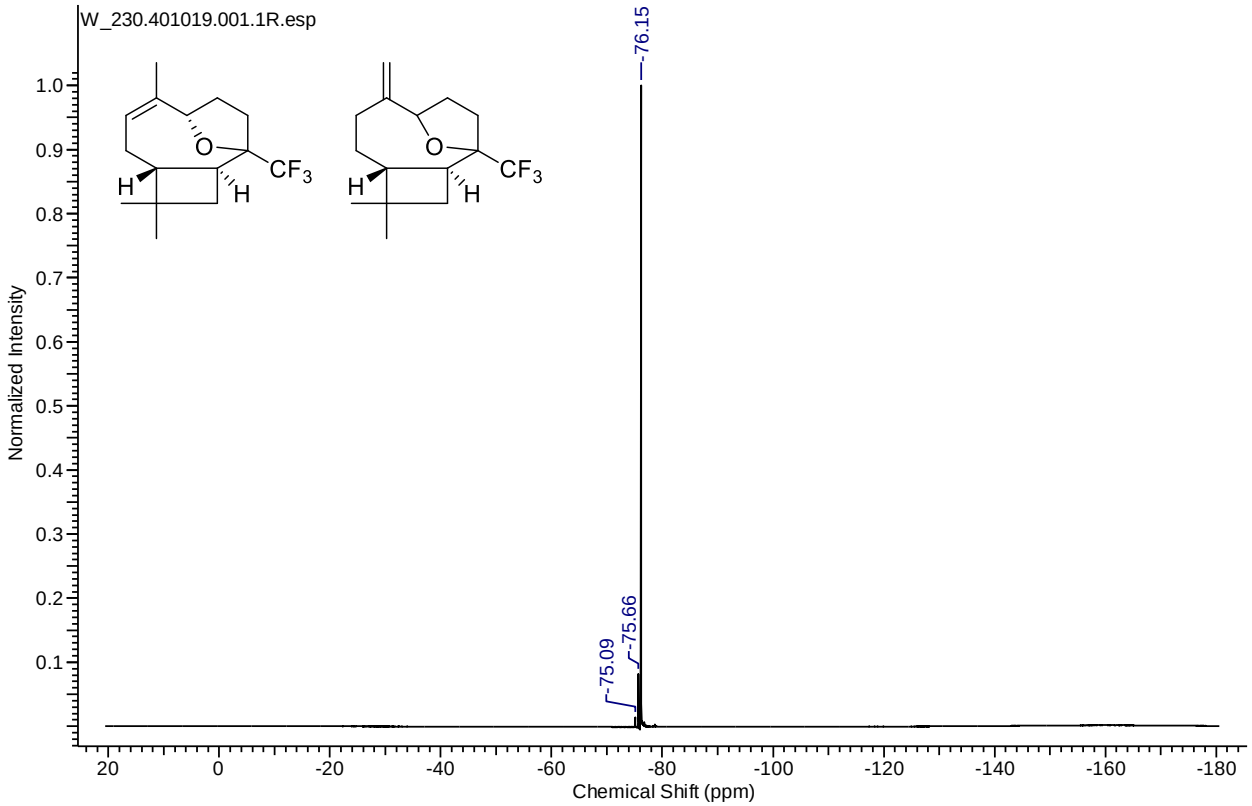


Figure S70. ^{19}F NMR spectra (282 MHz) of mixture **25 + 26** in $CDCl_3$

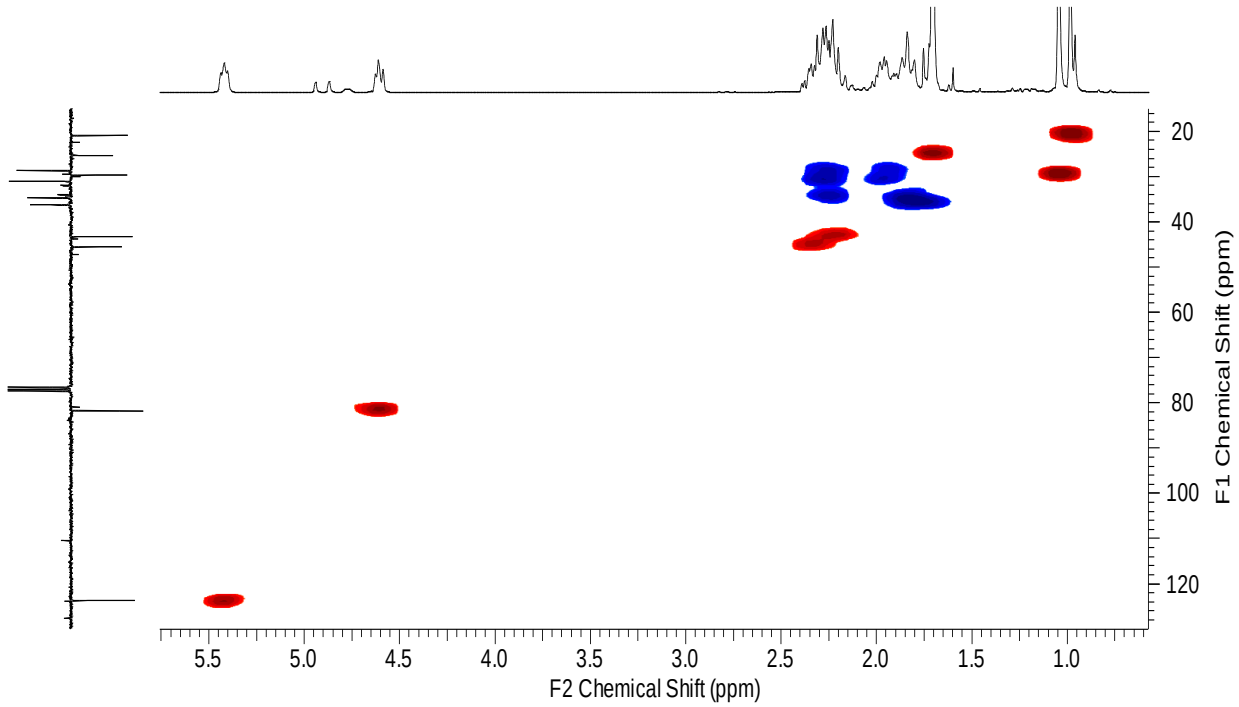


Figure S71. HSQC NMR spectra of mixture **25 + 26** in $CDCl_3$

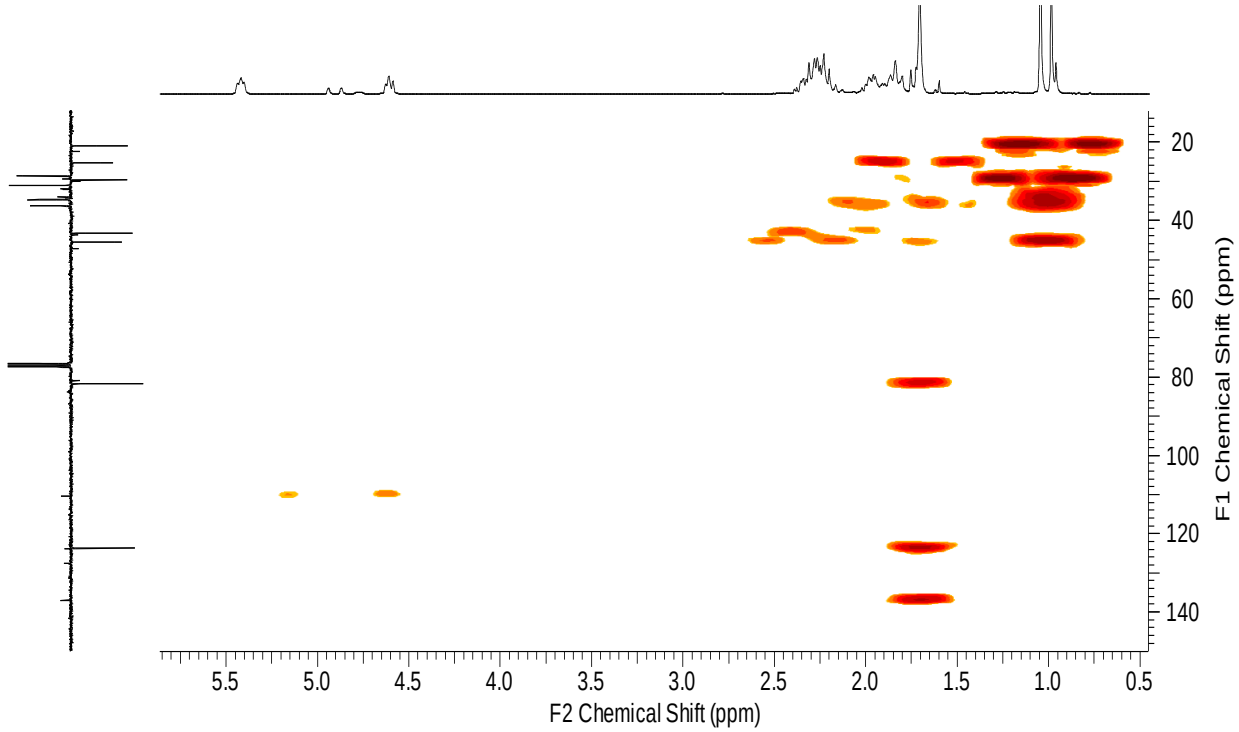


Figure S72. HMBC NMR spectra of mixture **25 + 26** in $CDCl_3$

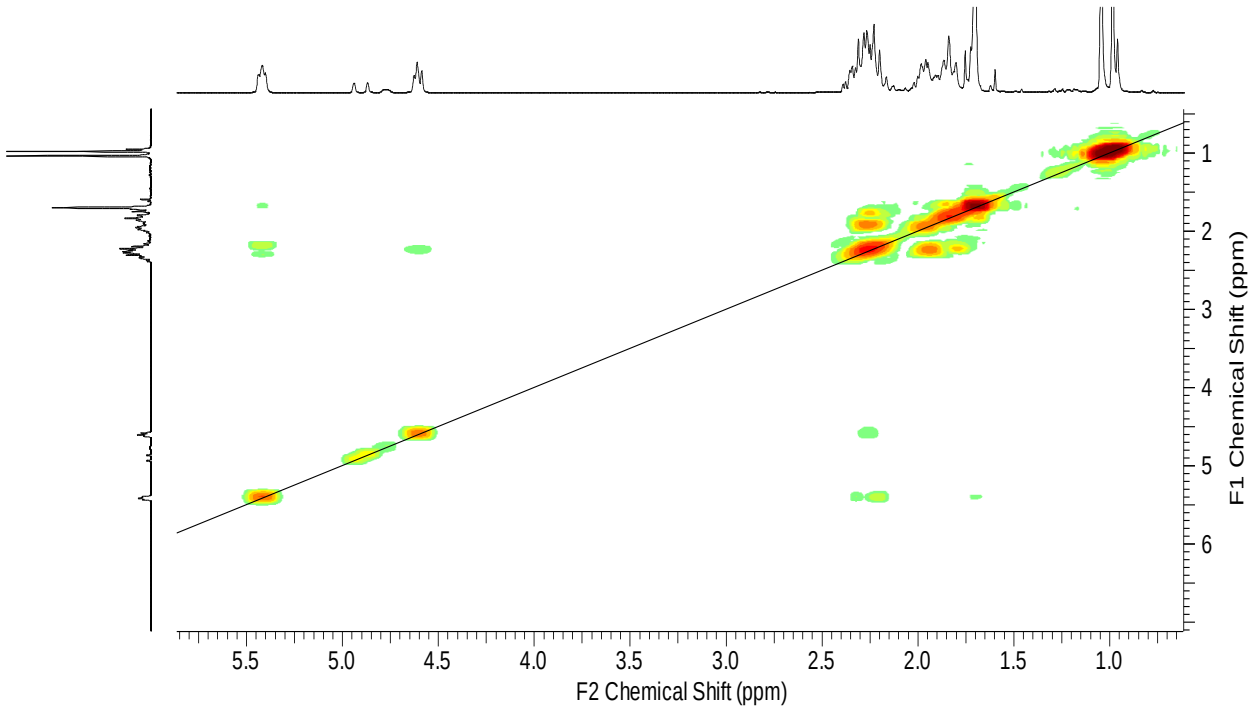


Figure S73. COSY NMR spectra of mixture **25 + 26** in $CDCl_3$

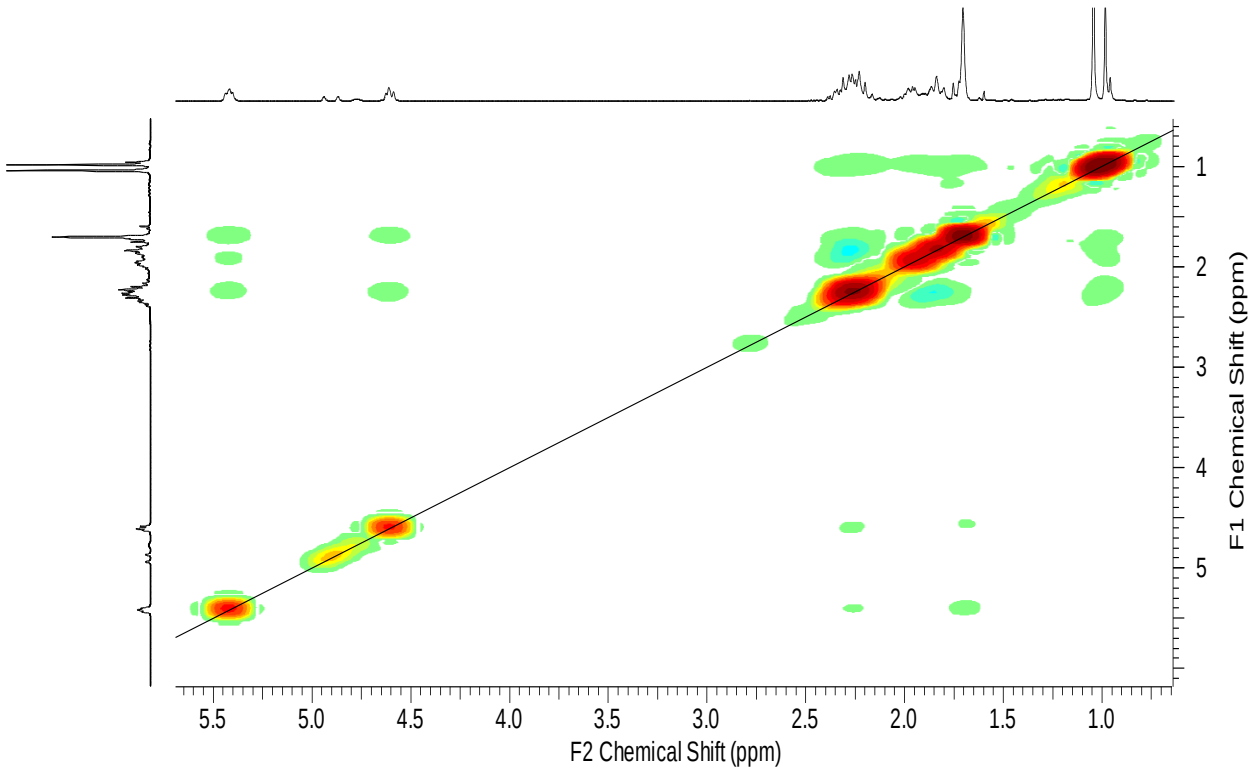


Figure S74. NOESY NMR spectra of mixture **25 + 26** in $CDCl_3$

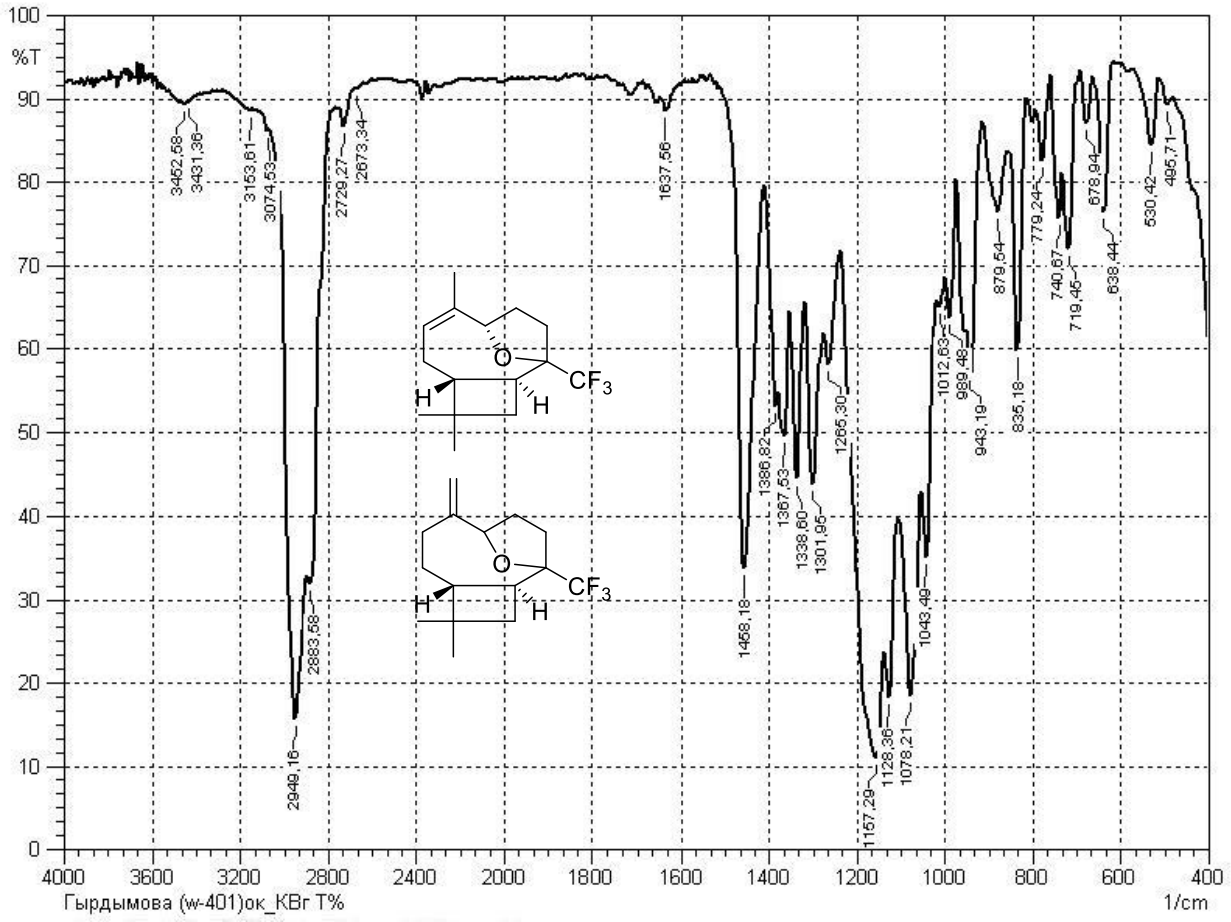


Figure S75. IR spectra of mixture **25 + 26**

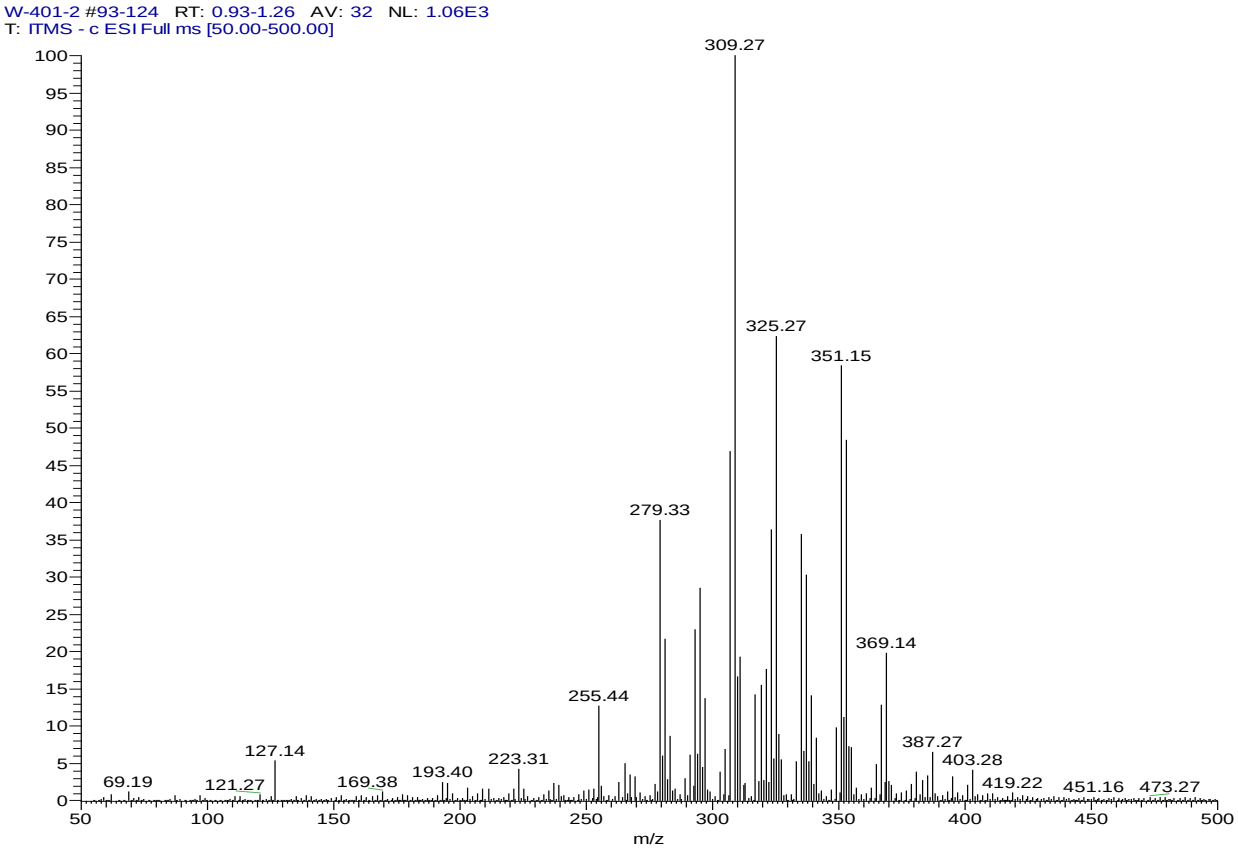


Figure S76. ESI-MS spectra of **25 + 26**

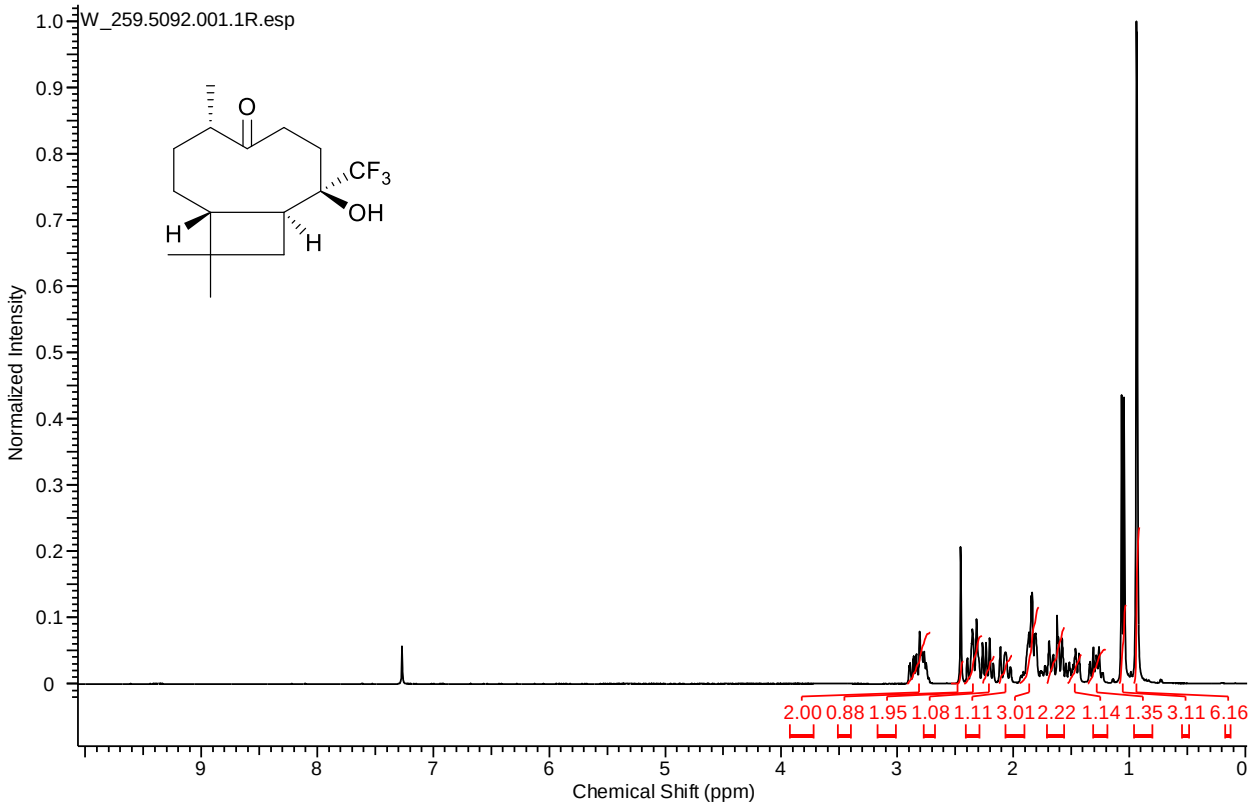


Figure S77. ^{1}H NMR spectra (300 MHz) of **27** in $CDCl_3$

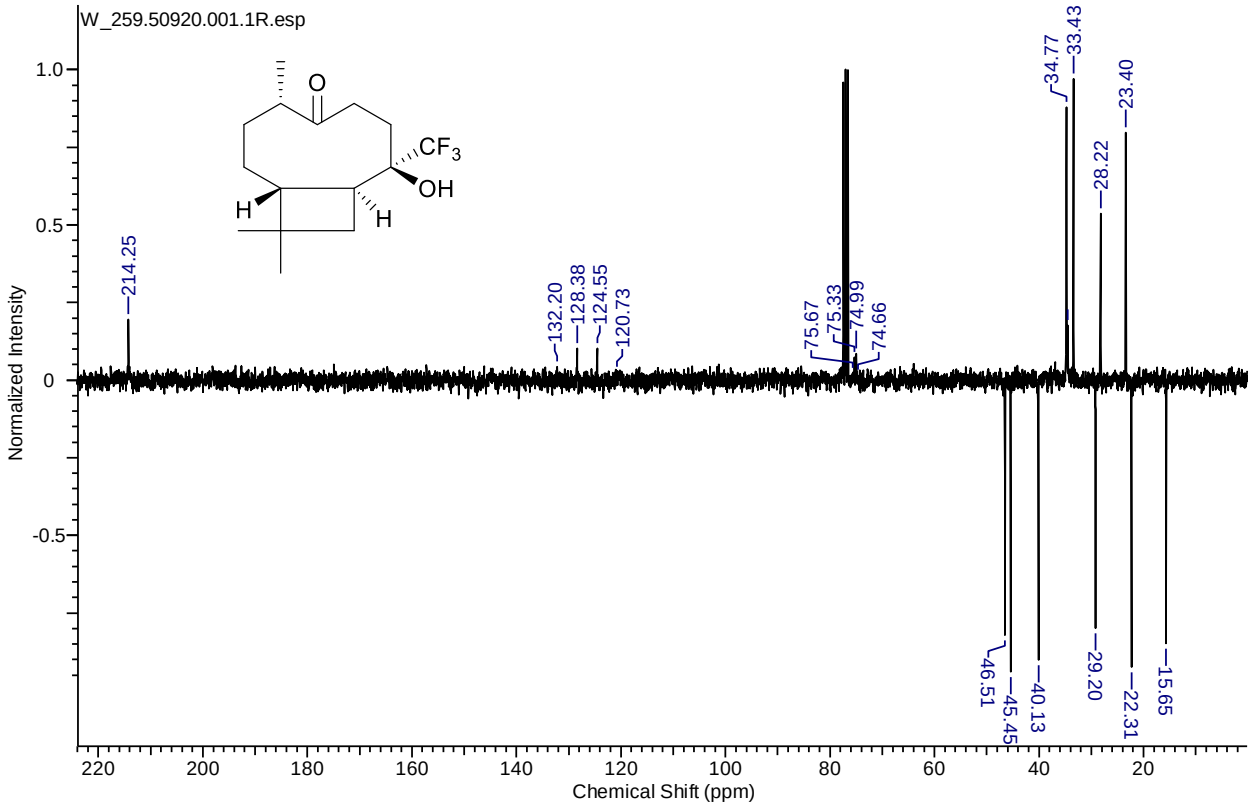


Figure S78. ^{13}C NMR spectra (75 MHz) of **27** in $CDCl_3$

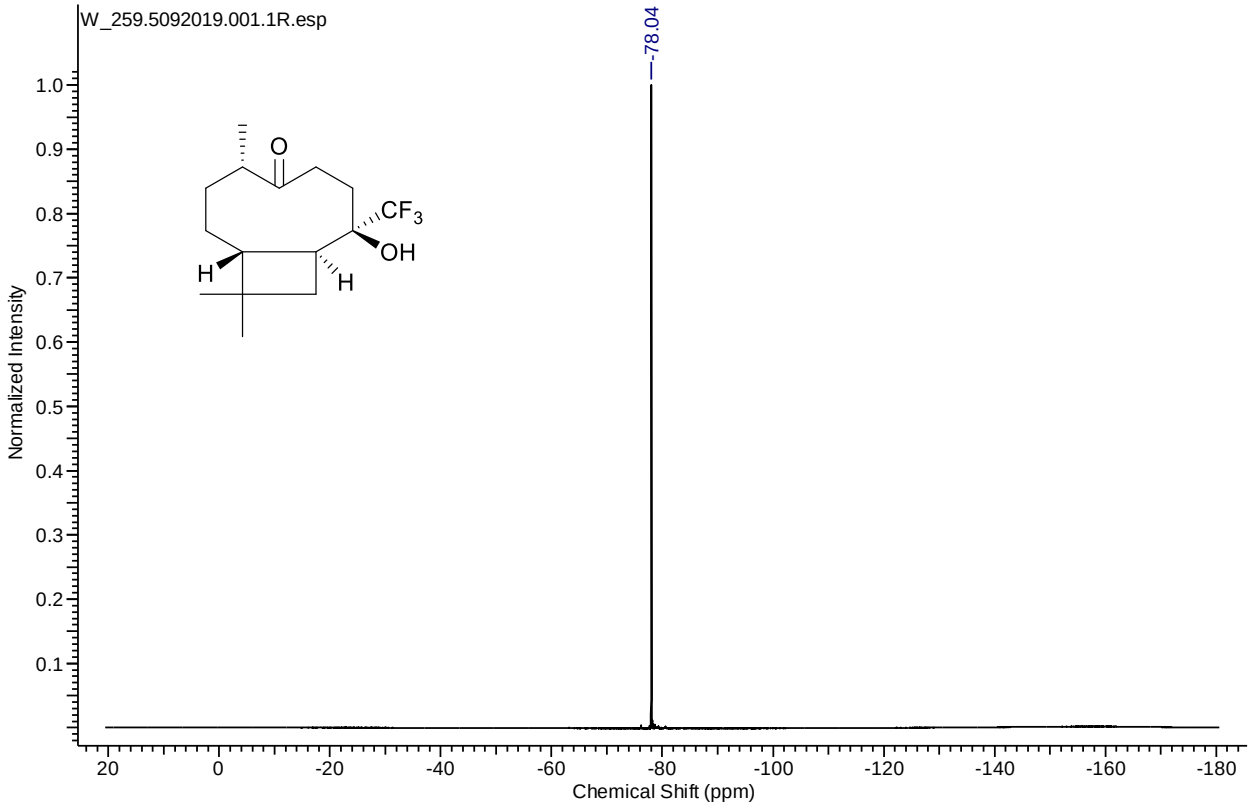


Figure S79. ^{19}F NMR spectra of **27** in $CDCl_3$

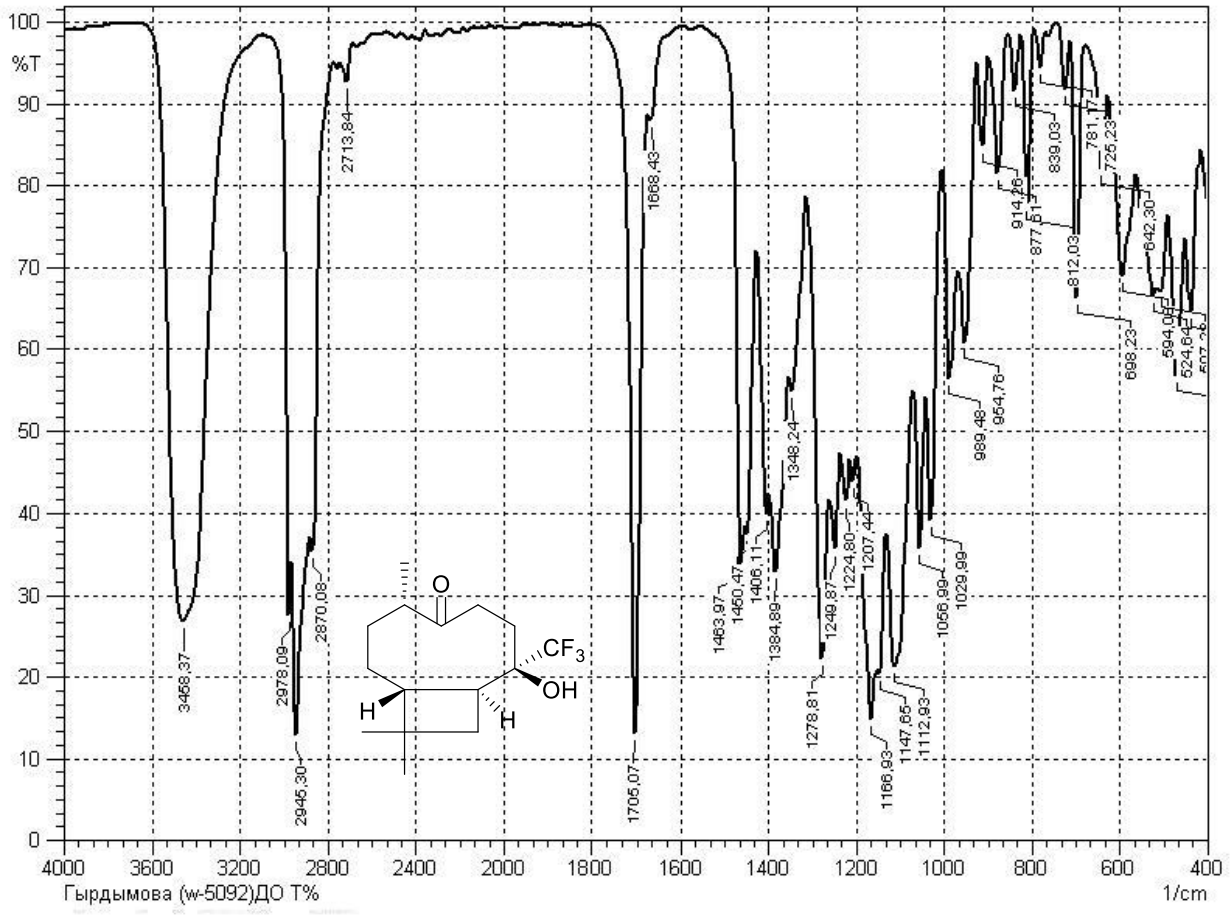


Figure S80. IR spectra of **27**

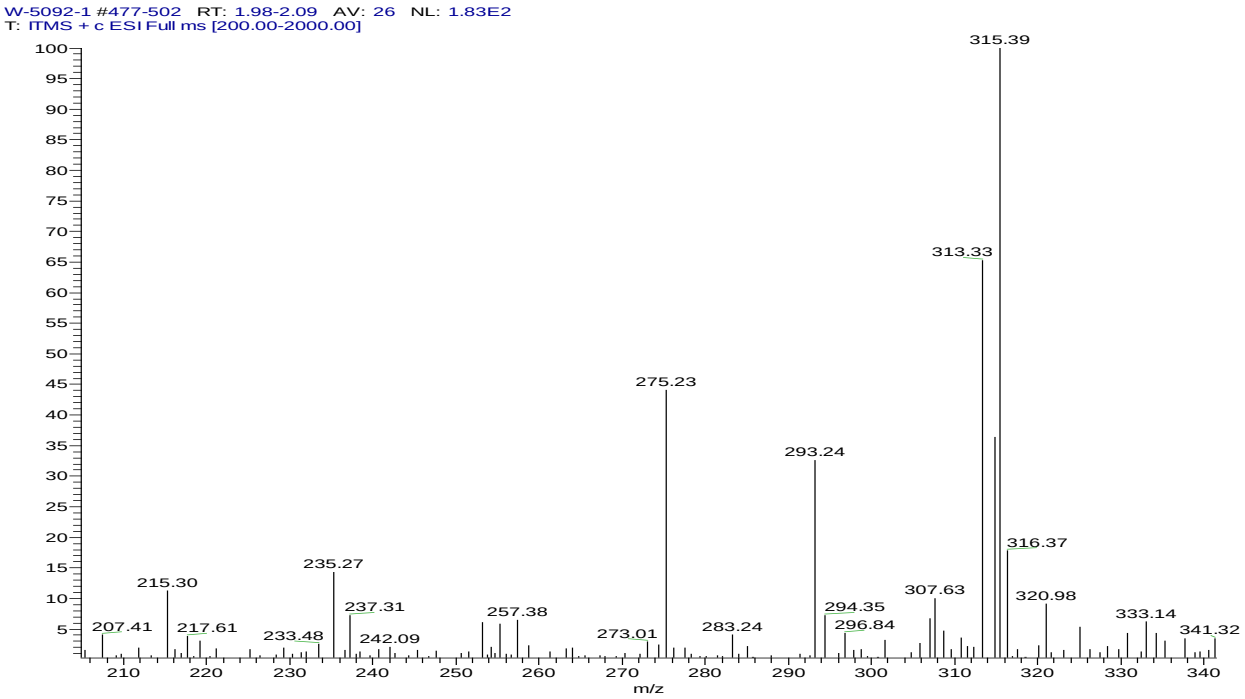


Figure S81. ESI-MS spectra of **27**

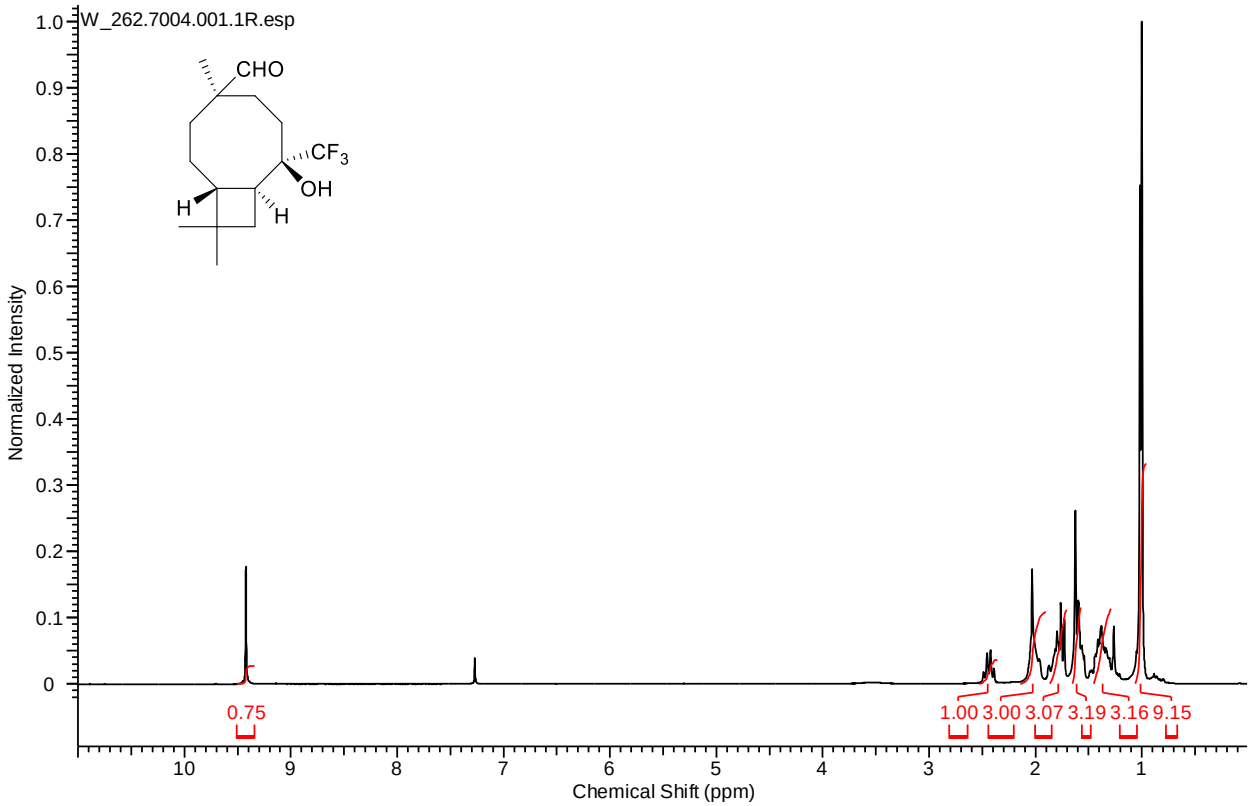


Figure S82. ^{1}H NMR spectra (300 MHz) of **28** in $CDCl_3$

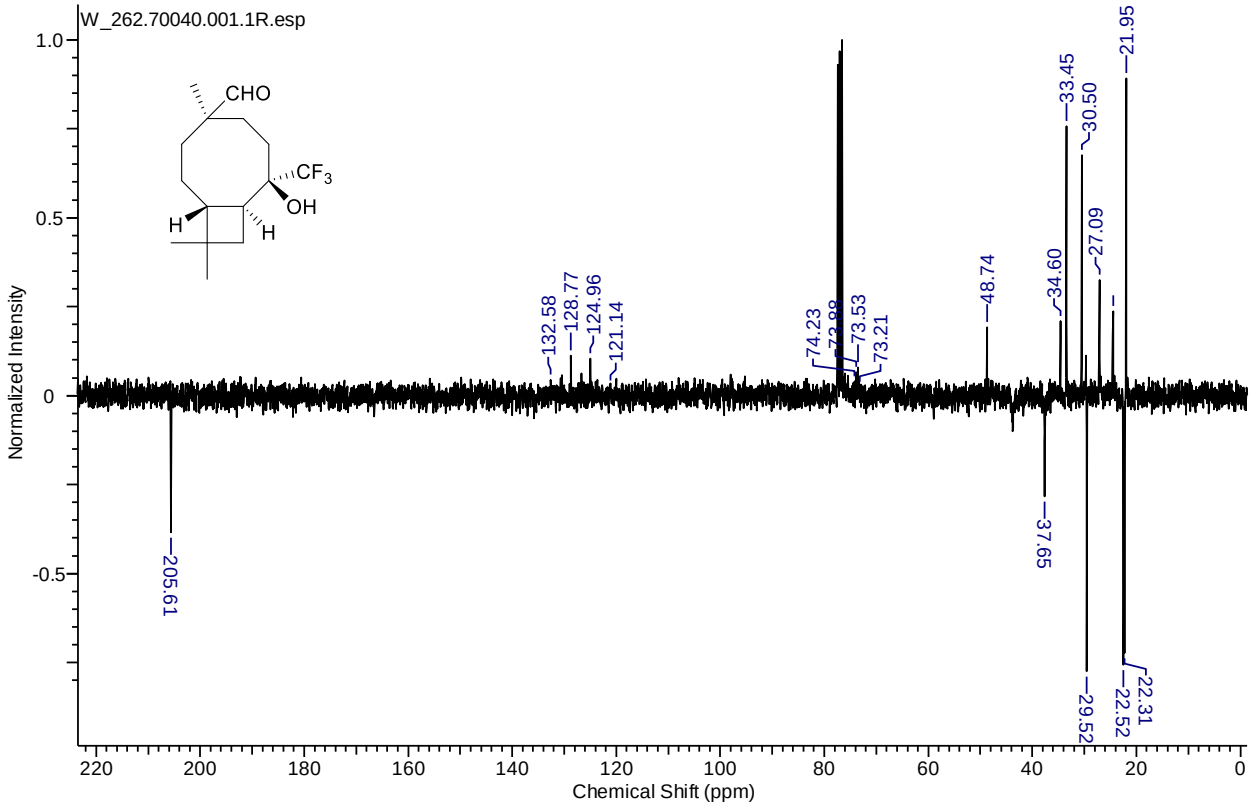


Figure S83. ^{13}C NMR spectra (75 MHz) of **28** in $CDCl_3$

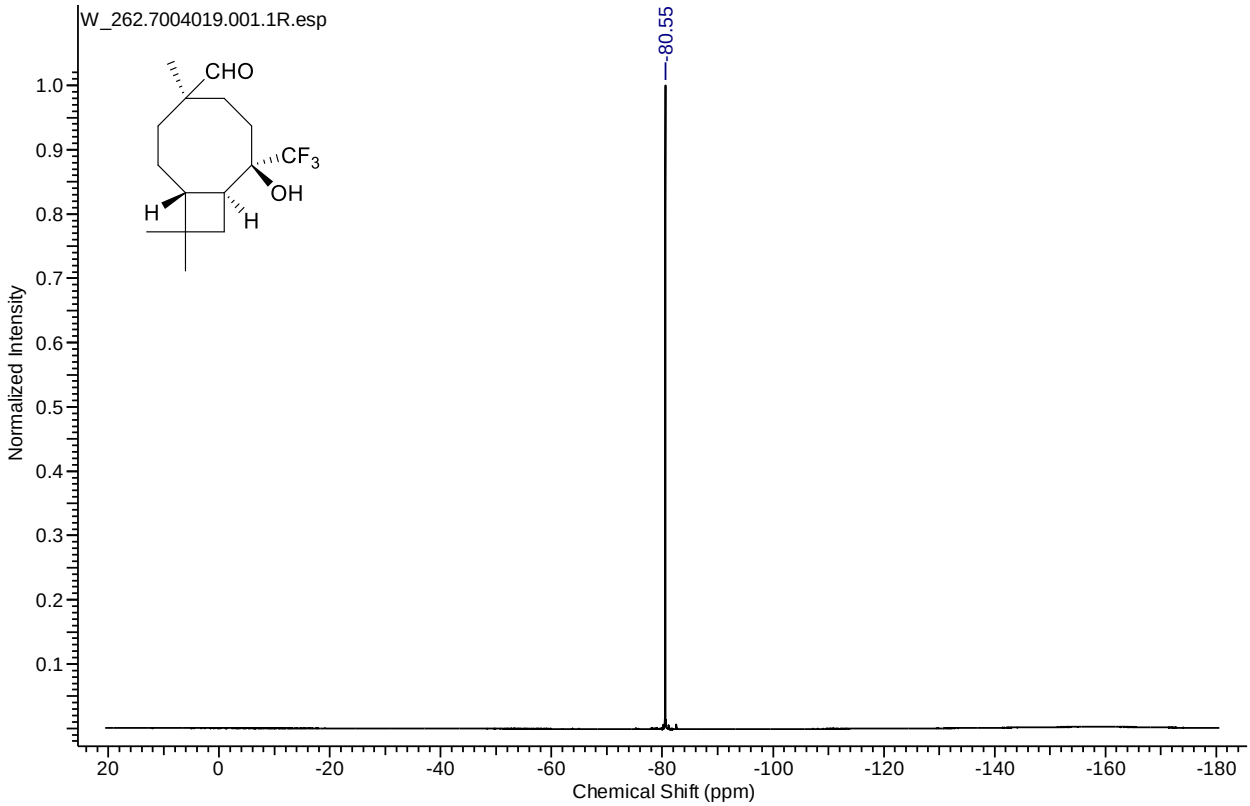


Figure S84. ^{19}F NMR spectra (282 MHz) of **28** in $CDCl_3$

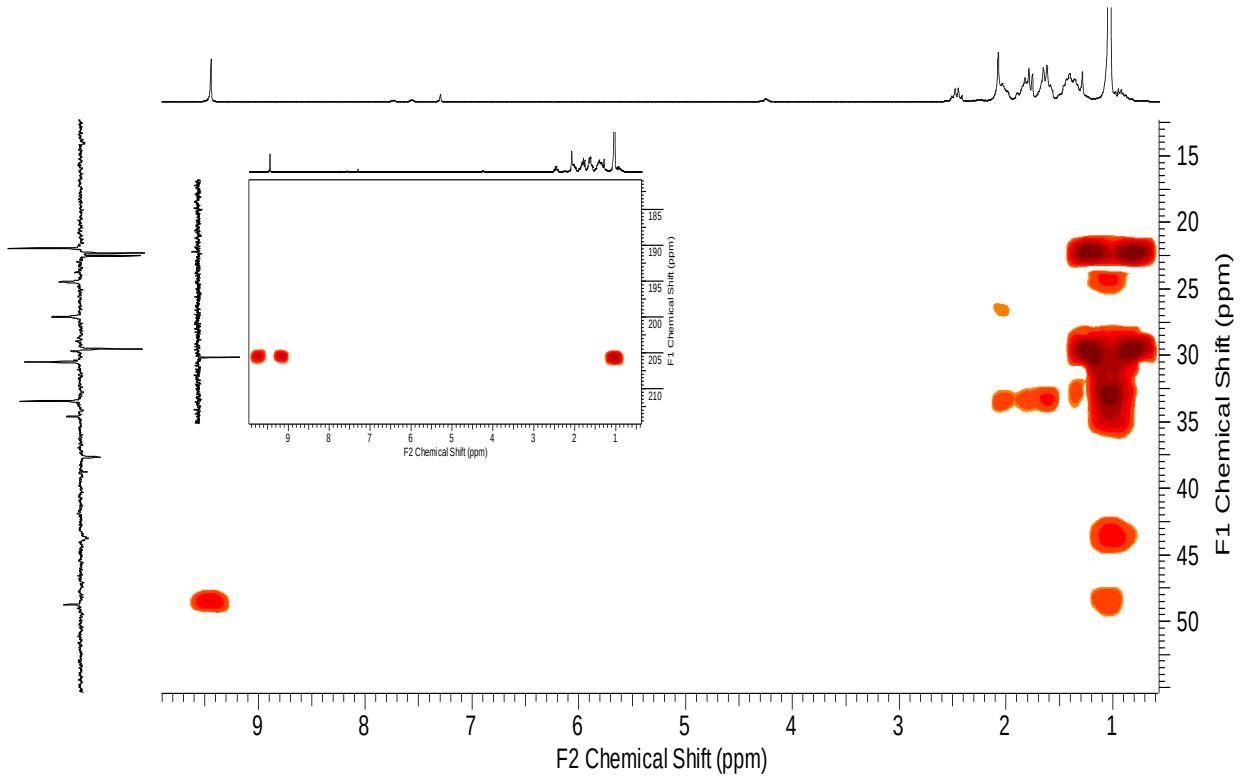


Figure S85. HMBC NMR spectra of **28** in $CDCl_3$

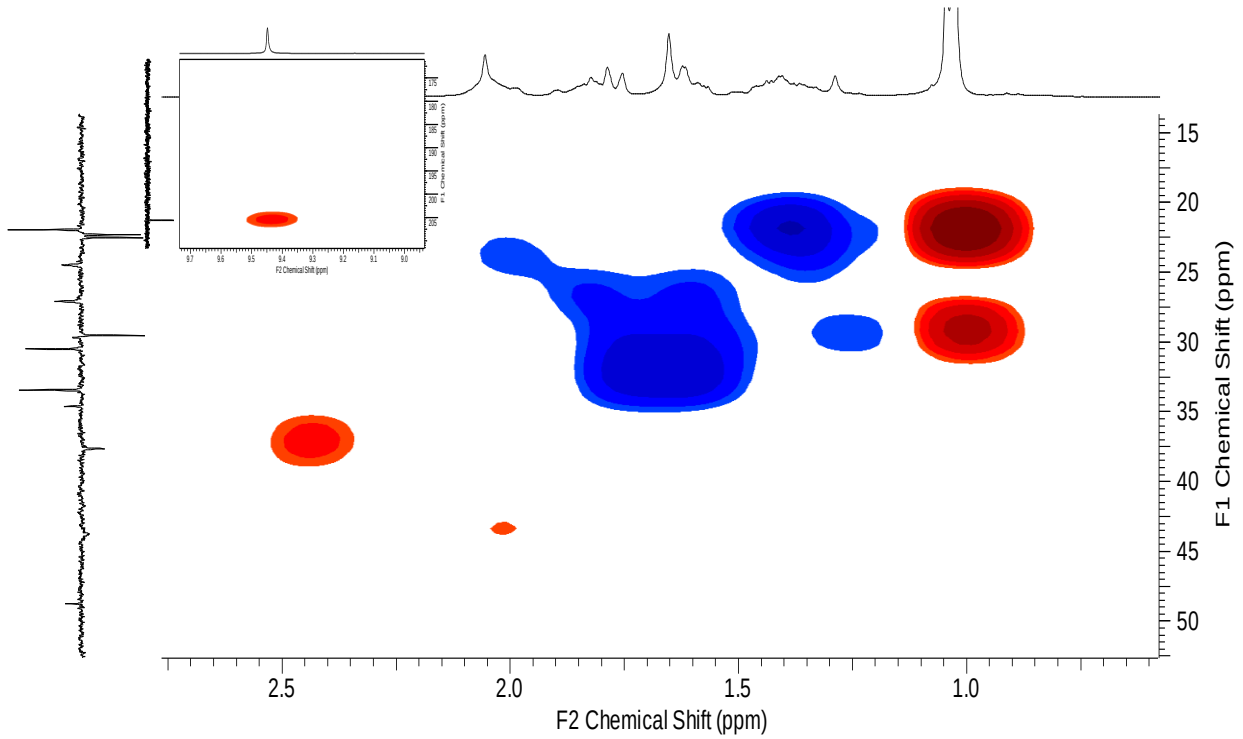


Figure S86. HSQC NMR spectra of **28** in $CDCl_3$

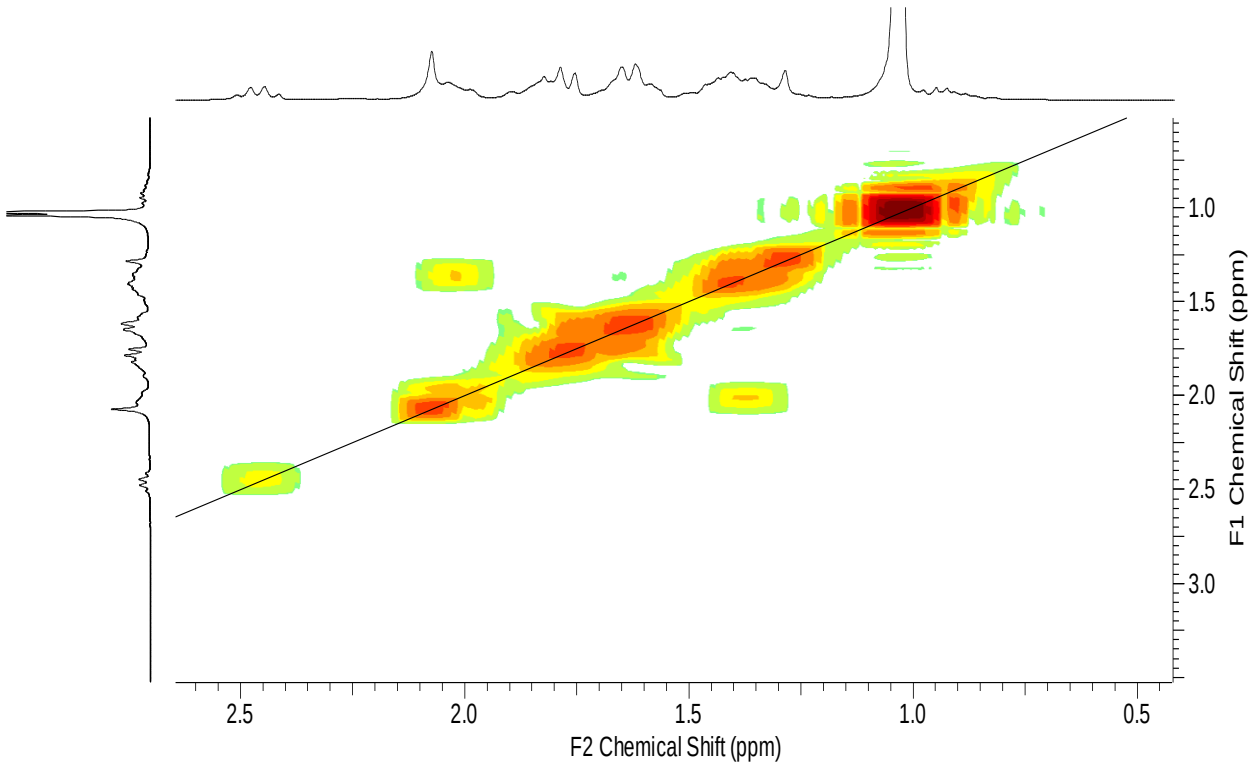


Figure S87. COSY NMR spectra of **28** in $CDCl_3$

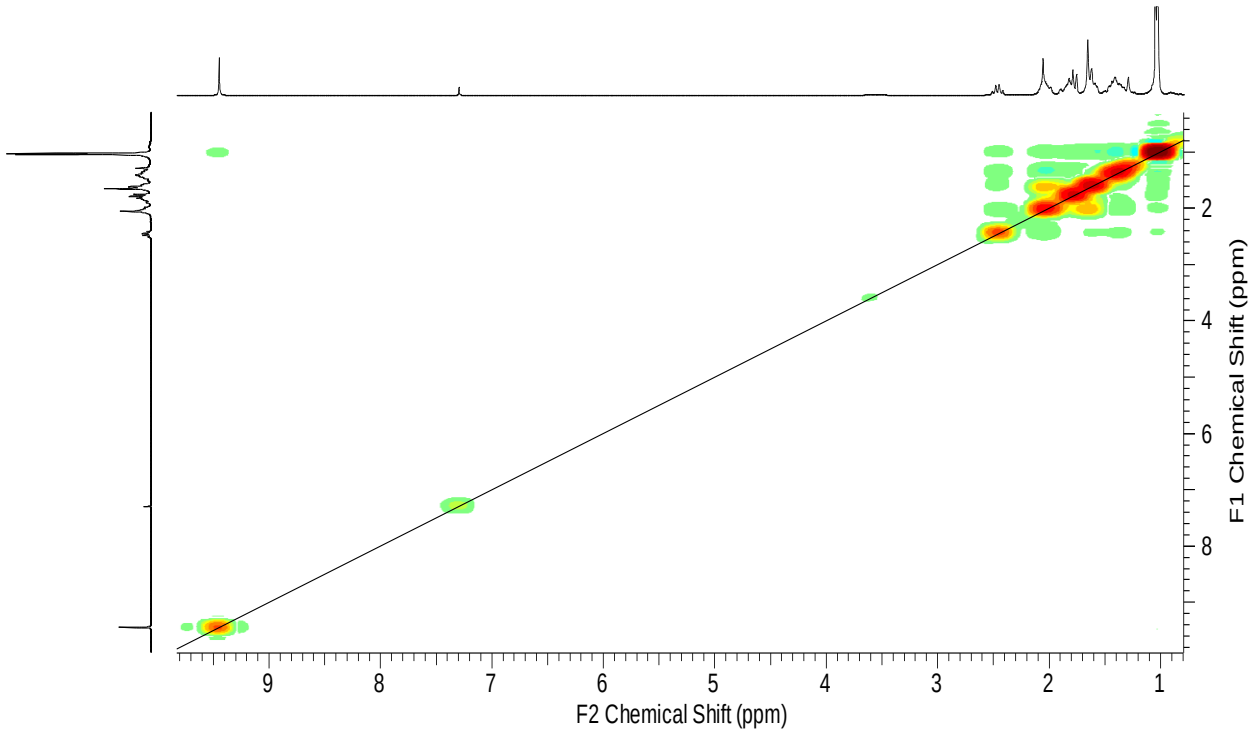


Figure S88. NOESY NMR spectra of **28** in $CDCl_3$

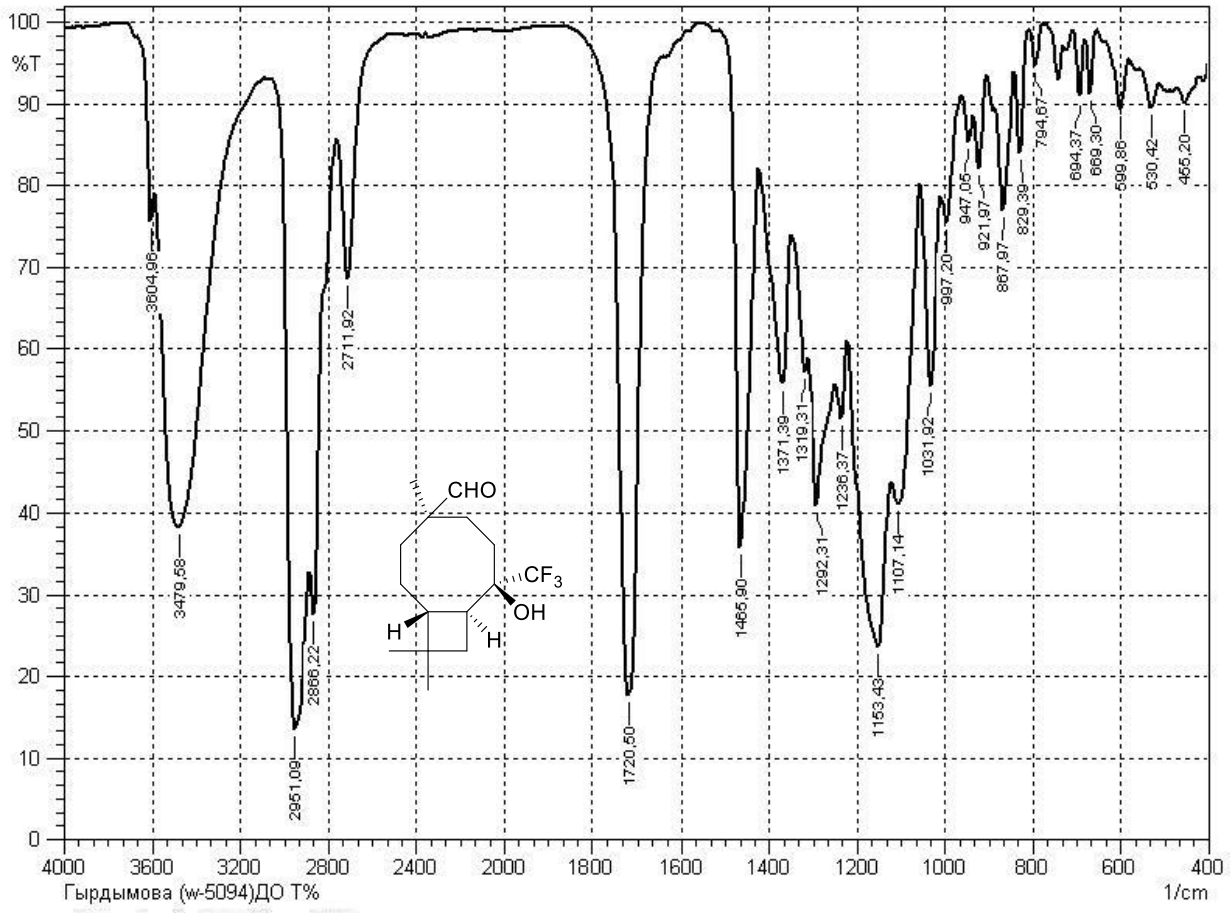


Figure S89. IR spectra of **28**

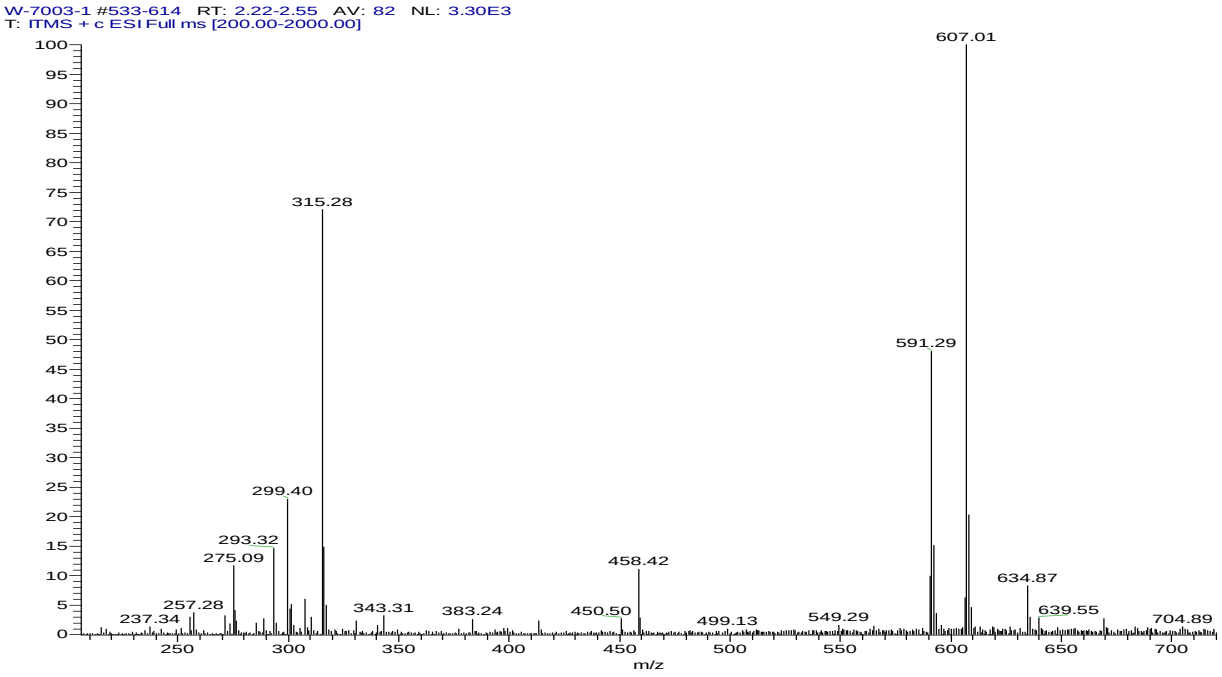


Figure S90. ESI-MS spectra of **28**

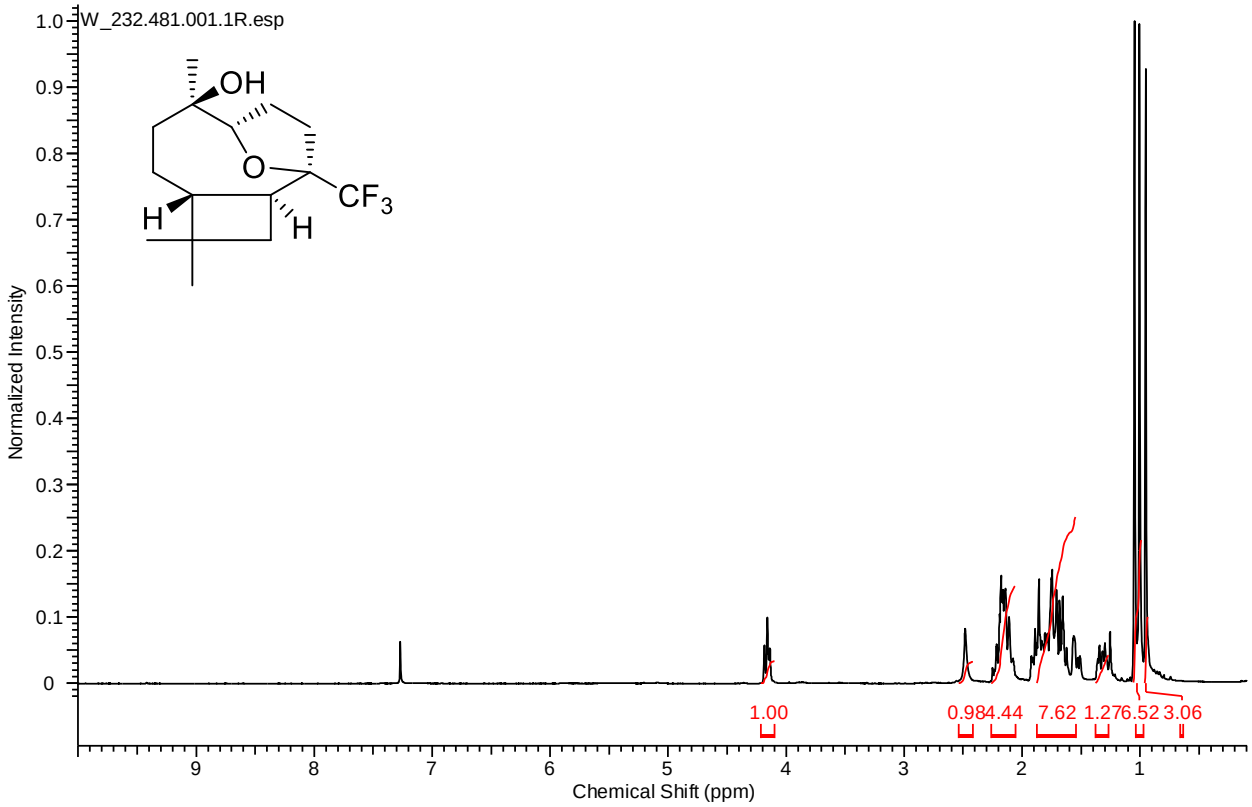


Figure S91. ^{1}H NMR spectra (300 MHz) of **29** in $CDCl_3$

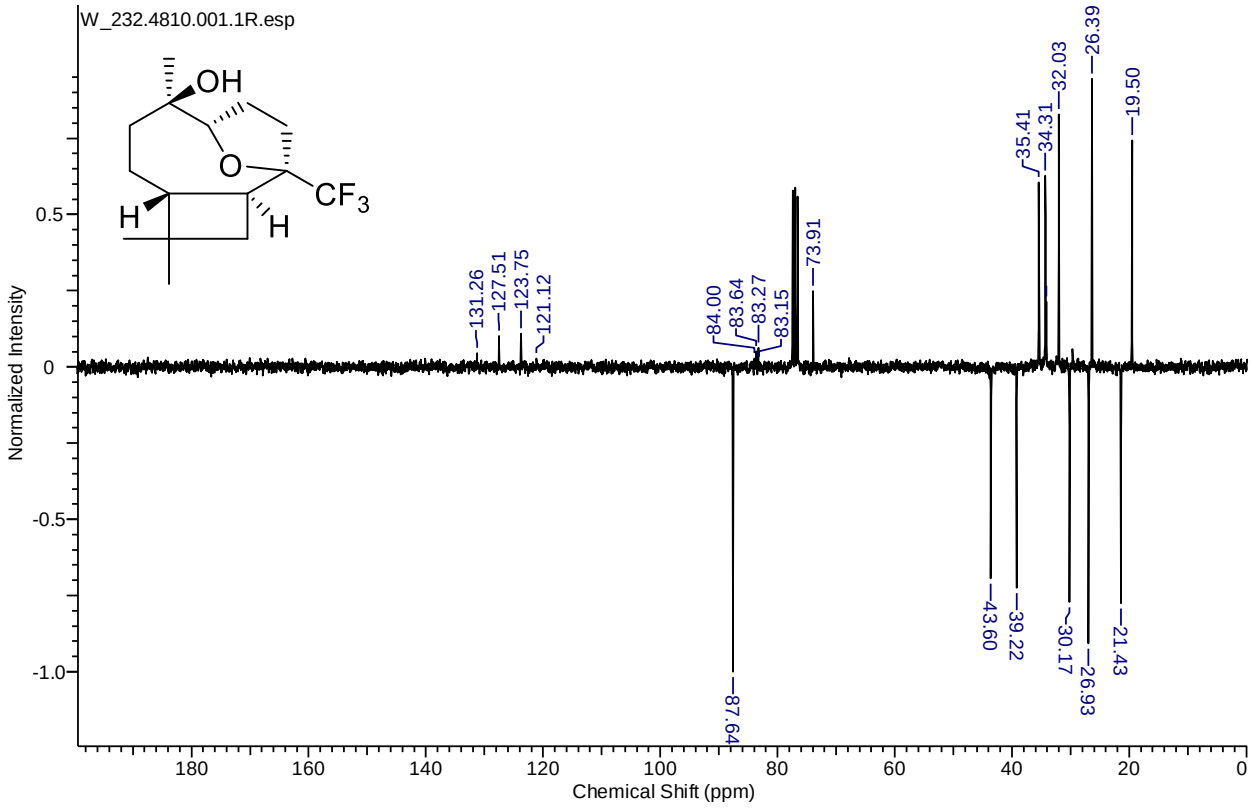


Figure S92. ^{13}C NMR spectra (75 MHz) of **29** in $CDCl_3$

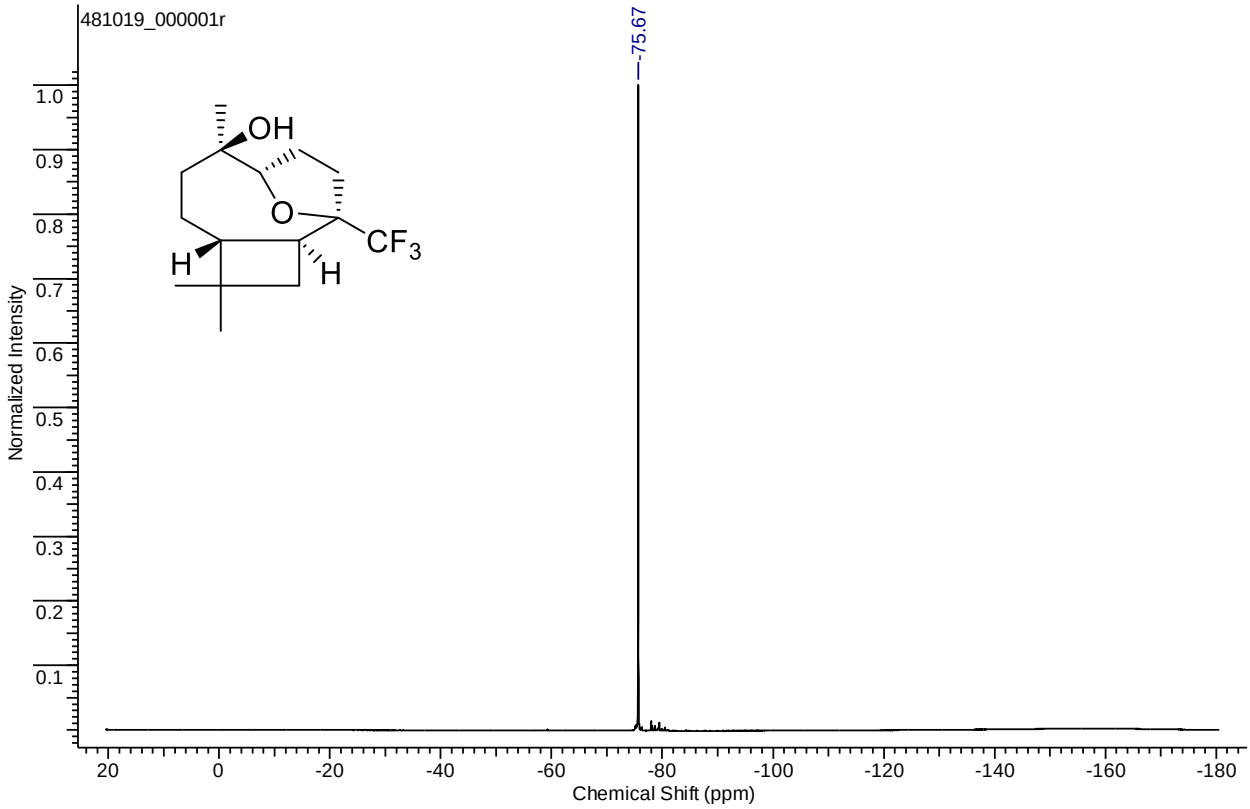


Figure S93. ^{19}F NMR spectra (282 MHz) of **29** in $CDCl_3$

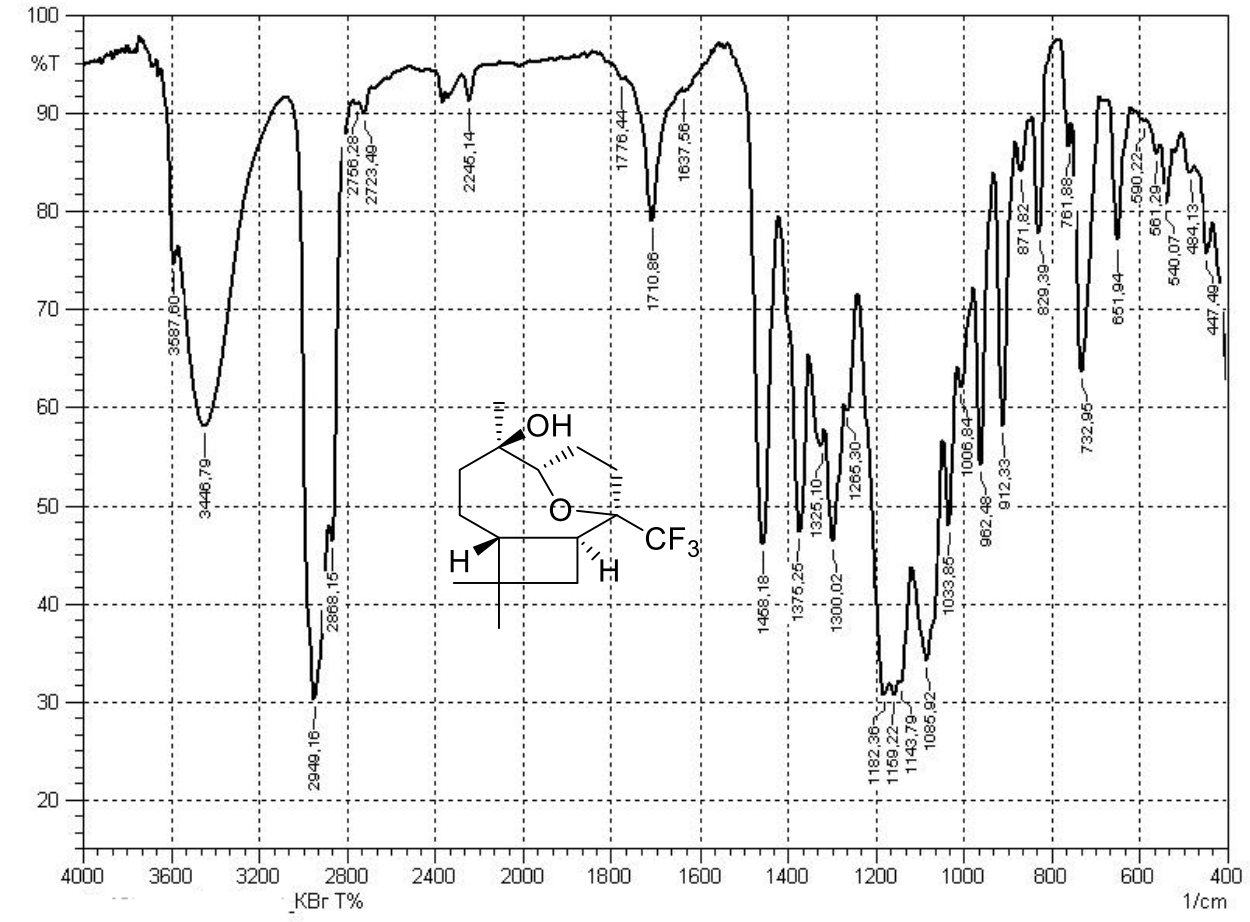


Figure S94. IR spectra of **29**

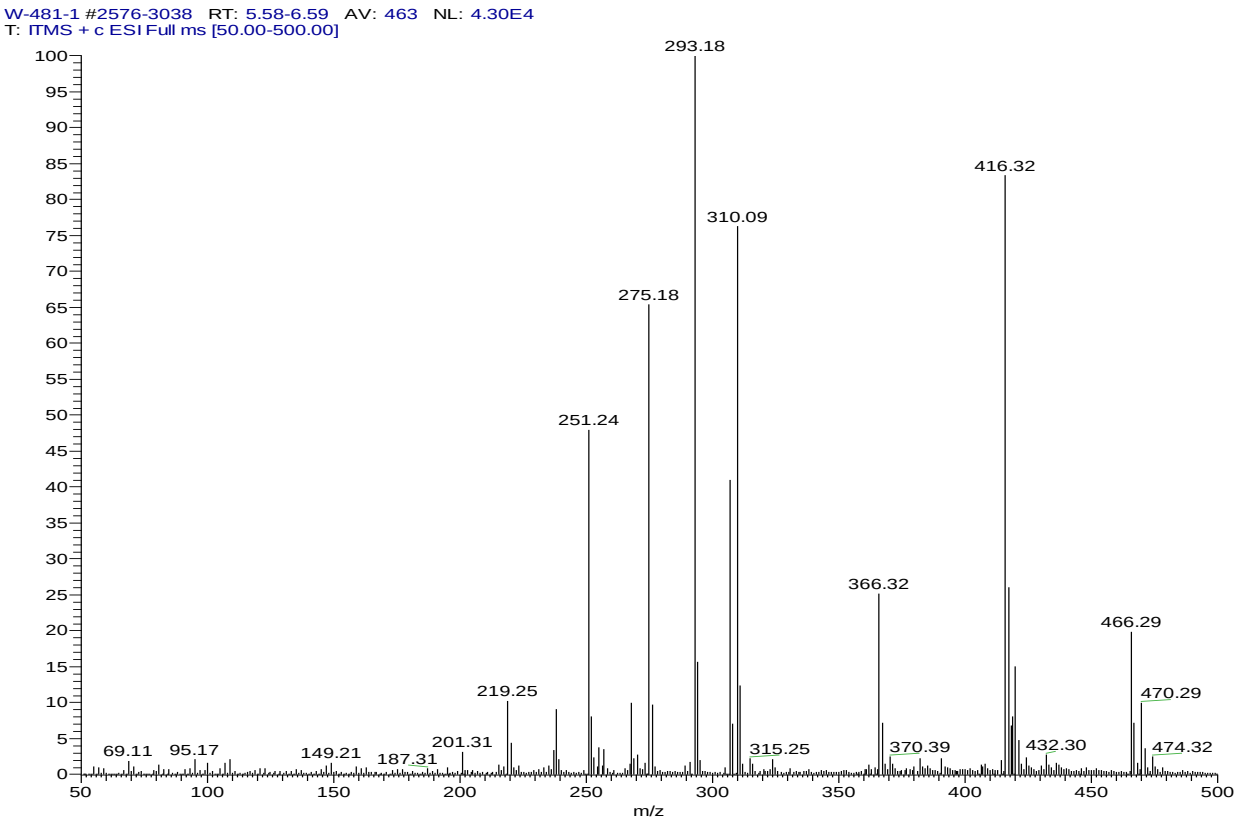


Figure S95. ESI-MS spectra of **29**

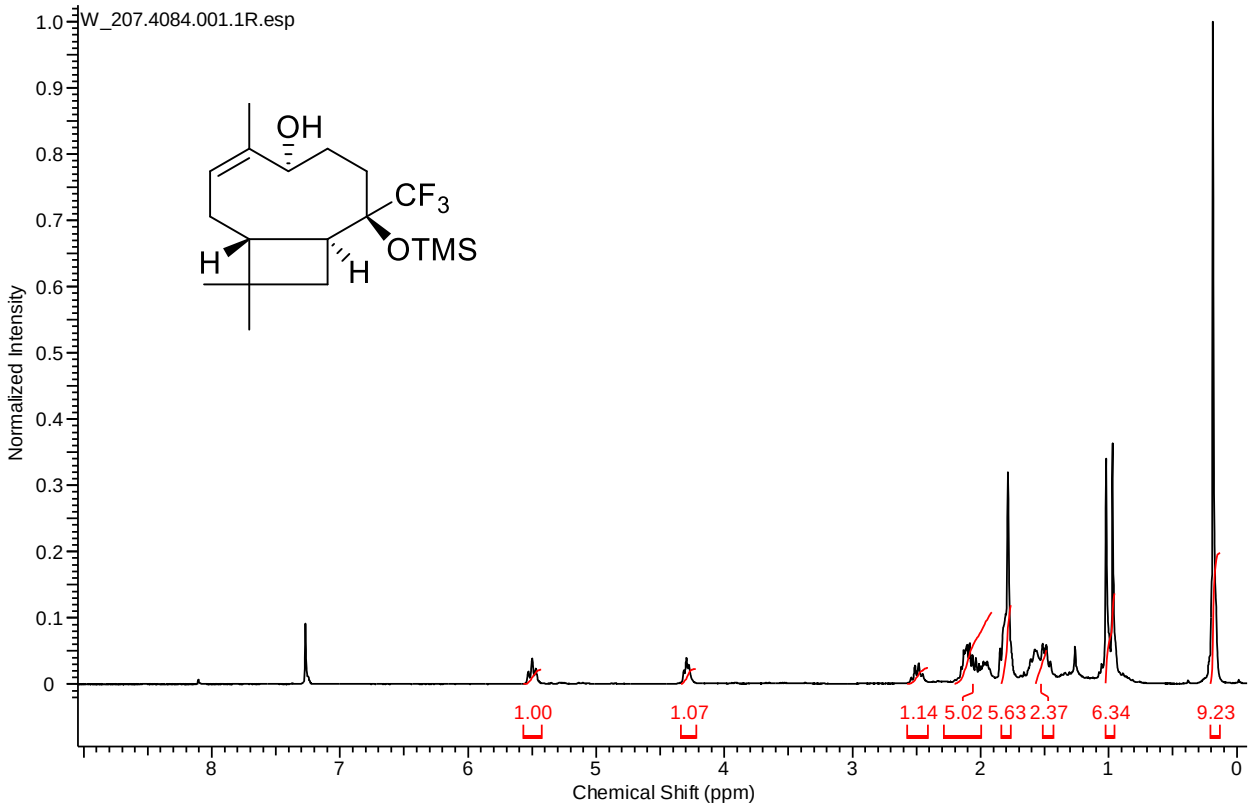


Figure S96. ^{1}H NMR spectra (300 MHz) of **30** in $CDCl_3$

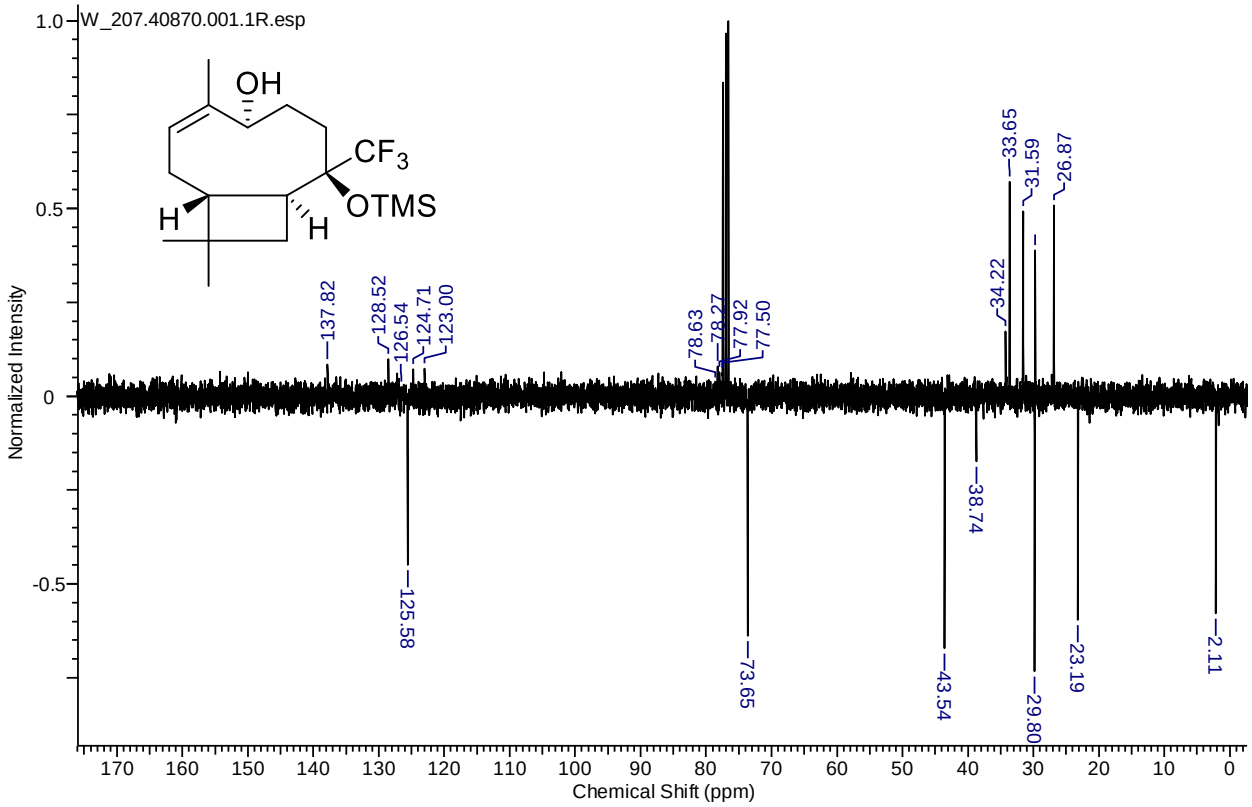


Figure S97. ^{13}C NMR spectra (75 MHz) of **30** in $CDCl_3$

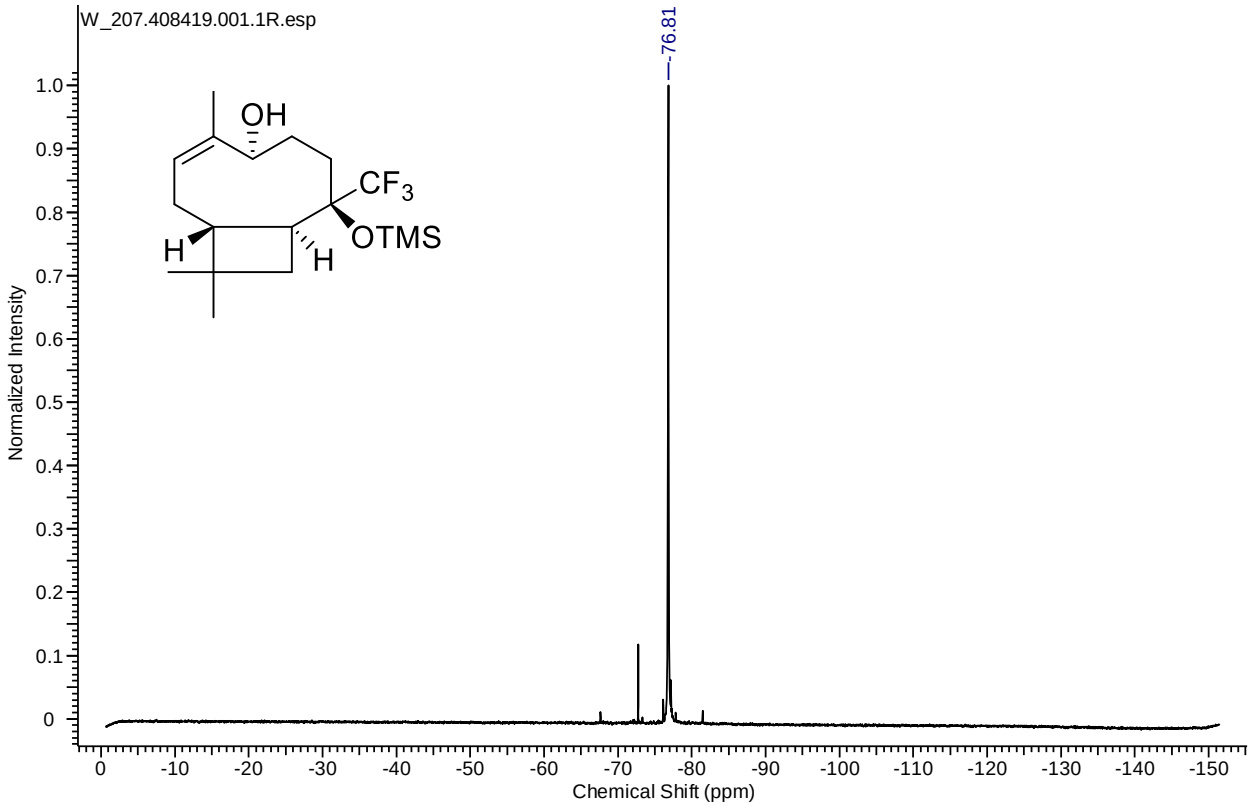


Figure S98. ^{19}F NMR spectra (282 MHz) of **30** in $CDCl_3$

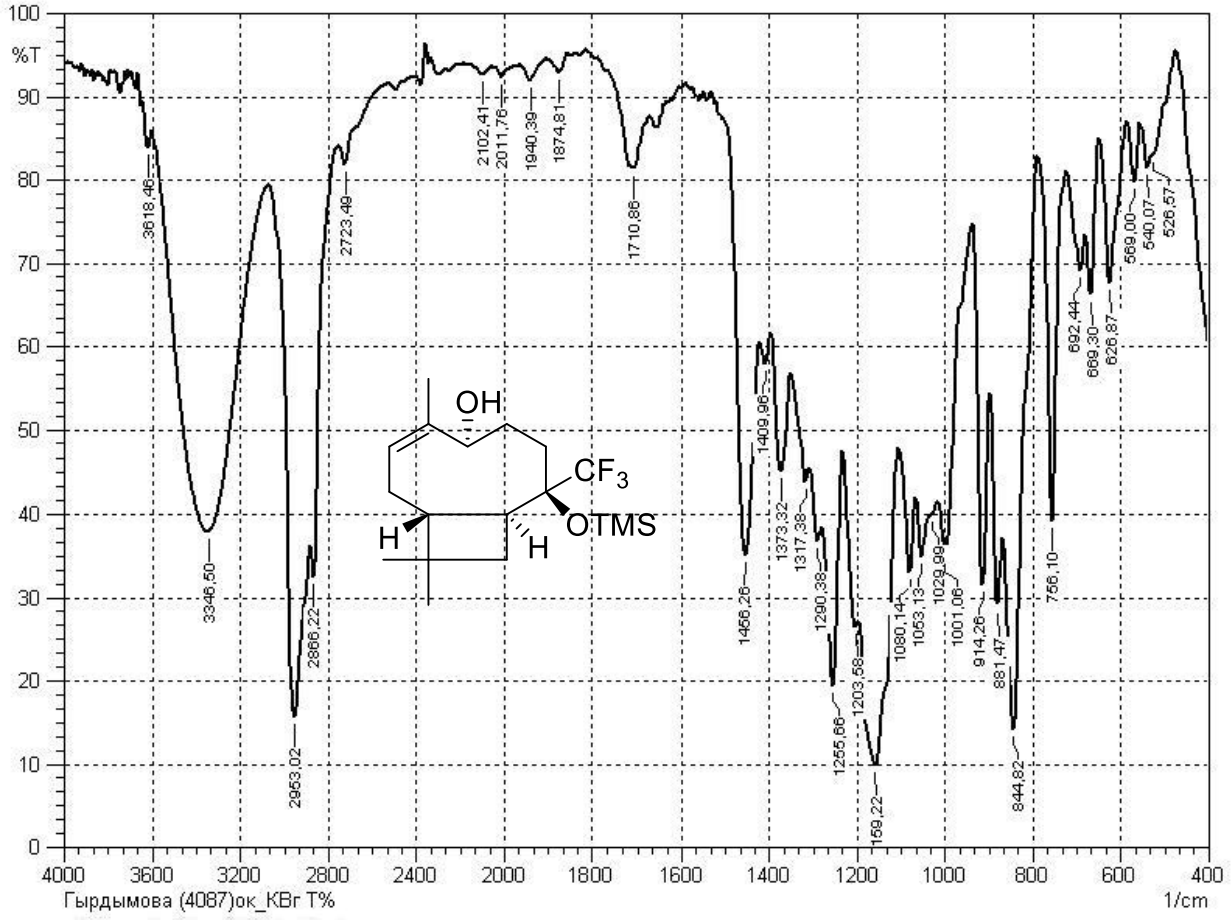


Figure S99. IR spectra of **30**

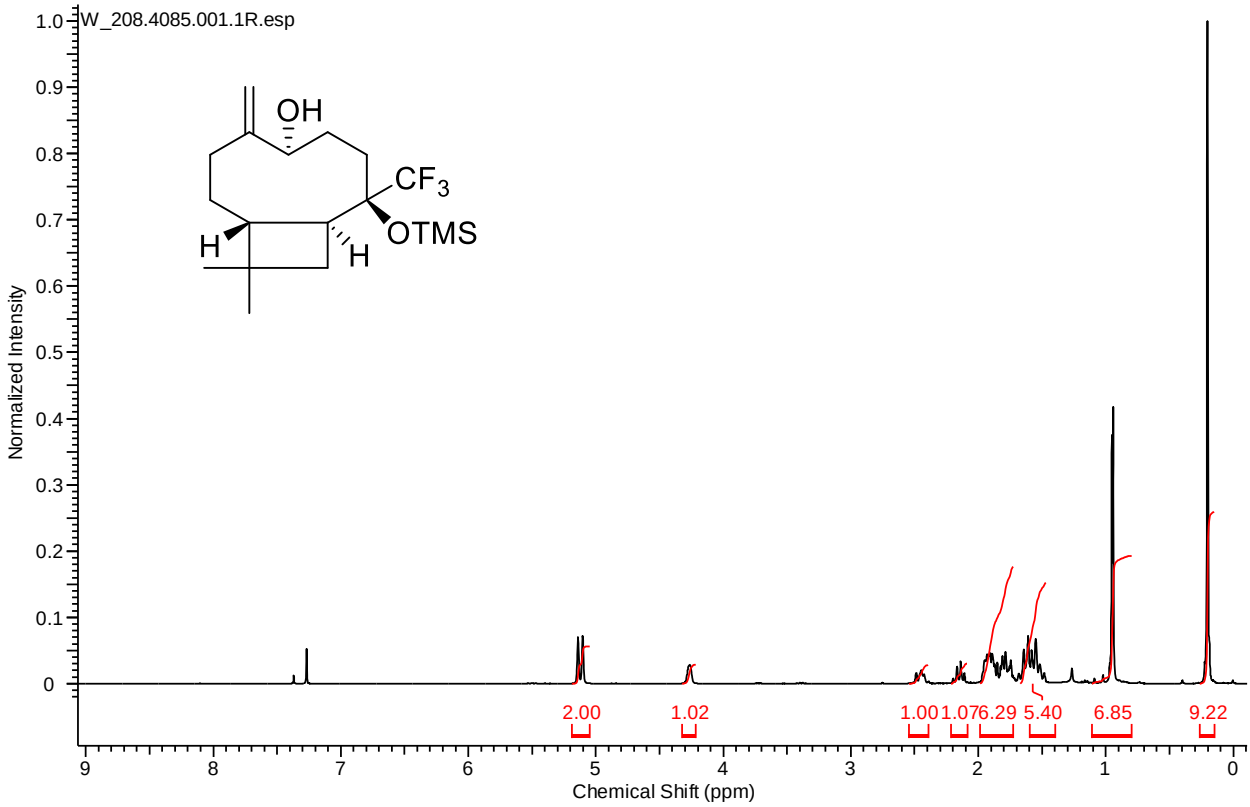


Figure S100. ^{1}H NMR spectra (300 MHz) of **31** in $CDCl_3$

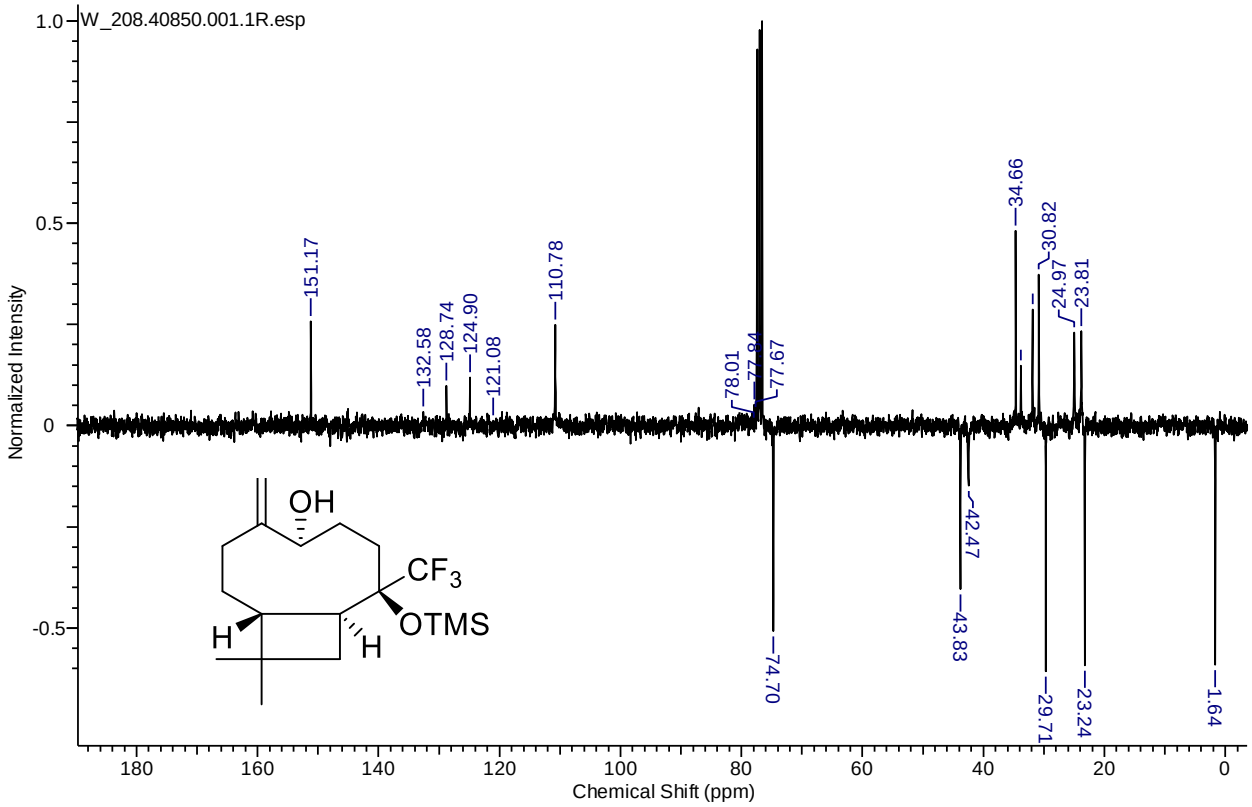


Figure S101. ^{13}C NMR spectra (75 MHz) of **31** in $CDCl_3$

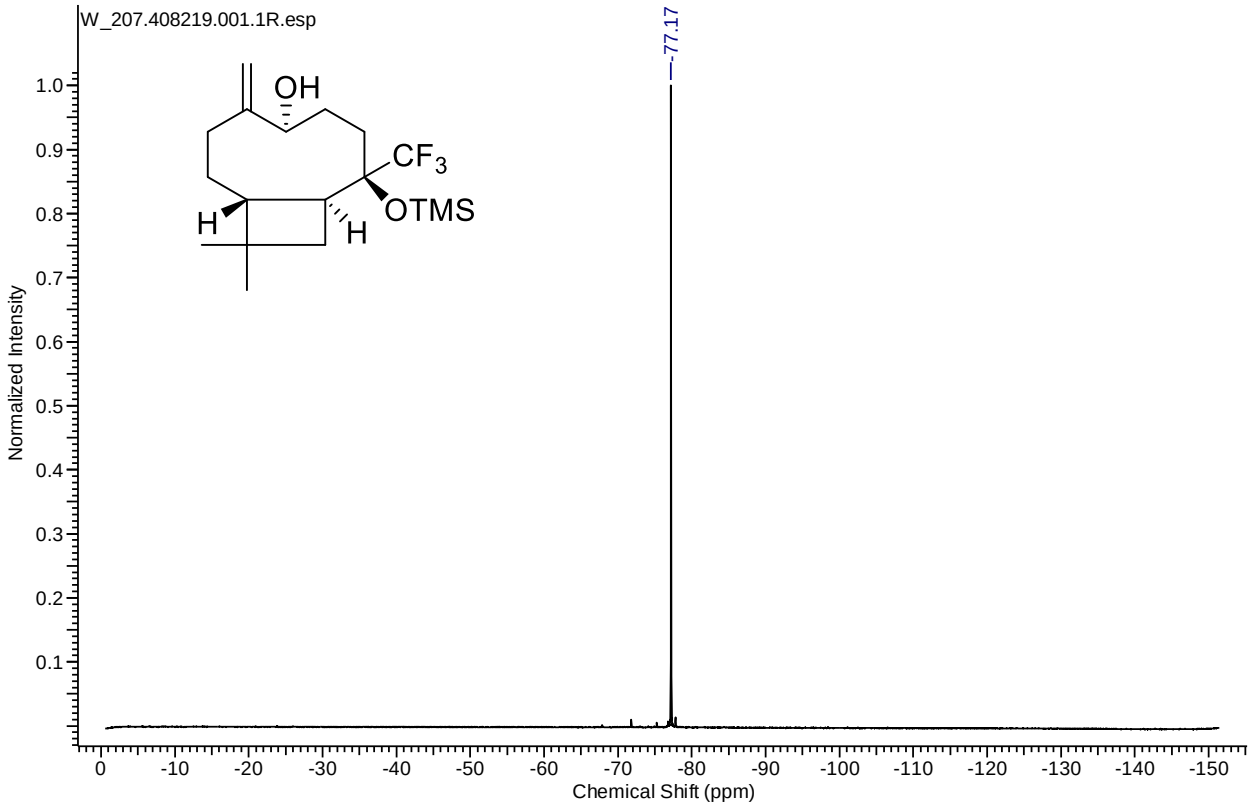


Figure S102. ^{19}F NMR spectra (282 MHz) of **31** in $CDCl_3$

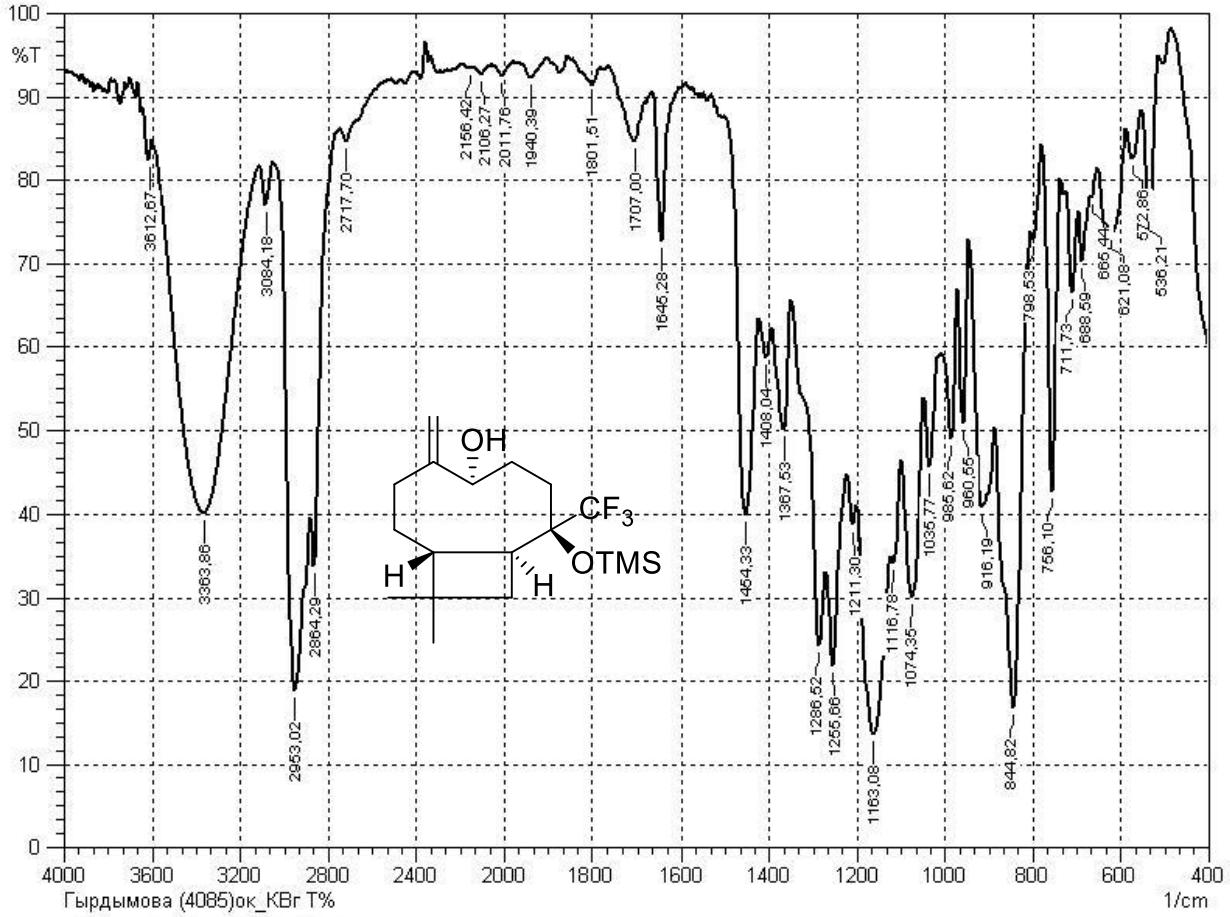


Figure S103. IR spectra of **31**

5. X-ray data of crystalline compounds

Table S2. Crystallographic data and structure refinement details for compounds **15**, **18**, **27** and **29**.

Compound	**15**	**18**	**27**	**29**
Empirical formula	$C_{15}H_{23}F_3O_2$	$C_{17}H_{27}F_3O_2$	$C_{15}H_{23}F_3O_2$	$C_{15}H_{23}F_3O_2$
Formula weight	292.33	320.38	292.33	292.33
Temperature [K]	295(2)	298(2)	298(2)	298(2)
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	*P2₁*	*C2*	*P2₁2₁2₁*	*C2*
Unit cell dimensions				
a [Å]	6.1970(11)	22.1155(11)	9.4232(3)	28.9014(11)
b [Å]	9.8989(13)	8.7469(4)	10.9758(4)	6.6072(3)
c [Å]	12.9485(19)	8.9710(4)	15.1715(6)	20.4393(8)
□ [°]	102.482(19)	102.7503(15)	90	129.2716(11)
V [Å^3]	775.5(2)	1692.58(14)	1569.14(10)	3021.5(2)
Z	2	4	4	8
d_{calc} [g cm^{-3}]	1.252	1.257	1.237	1.285
μ [mm^{-1}]	0.105	0.102	0.104	0.108
F_{000}	312	688	624	1248
Crystal dimensions [mm^3]	0.46 x 0.29 x 0.18	0.61 x 0.15 x 0.11	0.76 x 0.30 x 0.20	0.56 x 0.17 x 0.09
θ range for data collection [°]	3.820–31.050	2.513–26.350	3.150–28.696	2.574–25.023
Reflections collected	5101	12825	13401	17371
Independent reflections (R_{int})	3828 (R_{int} = 0.0406)	3463 (R_{int} = 0.0255)	4055 (R_{int} = 0.0329)	5290 (R_{int} = 0.0244)
Completeness to θ [%]	99.1	99.8	99.8	99.6
Data/restraints/parameters	3828 / 1 / 200	3463 / 1 / 207	4055 / 73 / 211	5290 / 10 / 381
Final *R* indices [*I*>2□(*I*)]	R_1 = 0.0717 wR_2 = 0.1655	R_1 = 0.0353 wR_2 = 0.0817	R_1 = 0.0553 wR_2 = 0.1382	R_1 = 0.0396 wR_2 = 0.0911
Final *R* indices (all data)	R_1 = 0.01290 wR_2 = 0.2341	R_1 = 0.0469 wR_2 = 0.0873	R_1 = 0.0874 wR_2 = 0.1584	R_1 = 0.0549 wR_2 = 0.0988
$S(F^2)$	1.0004	1.031	1.020	1.025
Absolute structure parameter	0.1(15)	-0.08(19)	0.3(4)	0.1(2)

Largest diff. peak and hole [e Å^{-3}]	0.193 / -0.219	0.199 / -0.137	0.245 / -0.227	0.226 / -0.197
CCDC code	2167152	2169284	2169285	2169286

Table 3S. Selected Bond Lengths (Å) in compounds **15**, **18**, **27** and **29**

Bond Lengths	**15**	**18**	**27**	**29**	
				A	**B**
O(1)-C(8)	1.408(5)	–	–	–	–
O(1)-C(2)	–	1.429(3)	–	–	–
O(1)-C(5)	–	–	1.206(4)	–	–
O(1)-C(4)	–	–	–	1.427(4)	1.437(5)
O(1)-C(16)	–	1.426(3)	–	–	–
O(1)-H(1)	0.97(6)	–	–	0.79(5)	0.76(4)
O(2)-C(4)	1.453(5)	–	–	–	–
O(2)-C(5)	1.442(6)	–	–	1.437(4)	1.436(4)
O(2)-C(9)	–	1.417(3)	–	–	–
O(2)-C(8)	–	–	1.411(4)	1.433(3)	1.428(4)
O(2)-H(1)	–	0.79(3)	0.91(4)	–	–
C-F	1.325(7)	1.332(3)	1.331(6)	1.331(4)	1.337(6)
	–	–	–	–	–
	1.344(7)	1.339(3)	1.390(6)	1.335(4)	1.338(5)
C(1)-C(2)	1.525(5)	1.549(3)	1.520(4)	1.560(4)	1.537(4)
C(1)-C(12)	–	1.530(3)	–	–	–
C(1)-C(9)	1.564(5)	–	1.561(4)	1.530(5)	1.525(4)
C(1)-C(11)	1.565(5)	1.528(3)	1.556(4)	1.556(5)	1.570(4)
C(1)-C(5)	–	1.568(3)	–	–	–
C(2)-C(3)	1.525(6)	1.515(3)	1.518(5)	1.514(5)	1.515(5)
C(3)-C(4)	1.506(7)	1.533(4)	1.536(5)	1.529(4)	1.541(4)
C(4)-C(14)	1.504(8)	1.531(4)	1.520(7)	1.511(6)	1.525(6)
C(4)-C(13)	–	1.532(4)	–	–	–
C(4)-C(5)	1.455(7)	1.554(4)	1.496(6)	1.531(4)	1.526(5)
C(5)-C(6)	1.505(8)	1.526(4)	1.502(5)	1.535(5)	1.525(5)
C(6)-C(7)	1.525(7)	1.522(4)	1.486(6)	1.523(5)	1.518(6)
C(7)-C(8)	1.551(6)	1.560(3)	1.540(6)	1.519(4)	1.512(5)
C(8)-C(15)	1.524(6)	1.530(3)	1.542(6)	1.504(4)	1.511(6)
C(8)-C(12)	–	1.536(3)	–	–	–
C(8)-C(9)	1.547(5)	1.575(3)	1.555(4)	1.528(4)	1.516(4)
C(9)-C(10)	1.539(6)	1.526(3)	1.534(5)	1.541(5)	1.543(4)
C(9)-C(17)	–	1.537(3)	–	–	–
C(10)-C(11)	1.526(6)	1.529(4)	1.530(5)	1.544(5)	1.536(5)
C(11)-C(12)	1.518(6)	–	1.516(5)	1.511(6)	1.510(7)
C(11)-C(13)	1.515(6)	–	1.524(5)	1.508(6)	1.512(6)

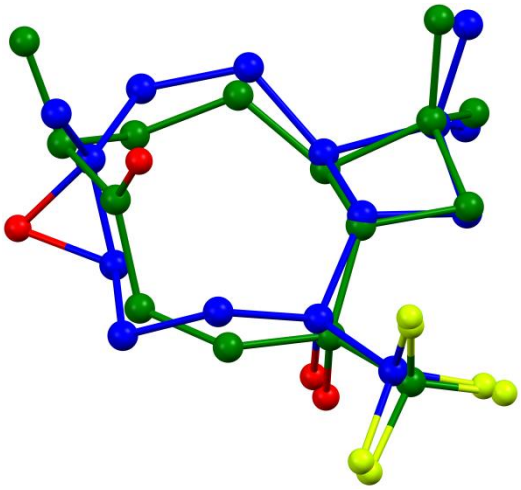


Figure S104. Overlay of molecule **15** and **27**. Carbon atoms are shown in blue (**15**) and green (**27**). The hydrogen atoms are omitted for clarity.

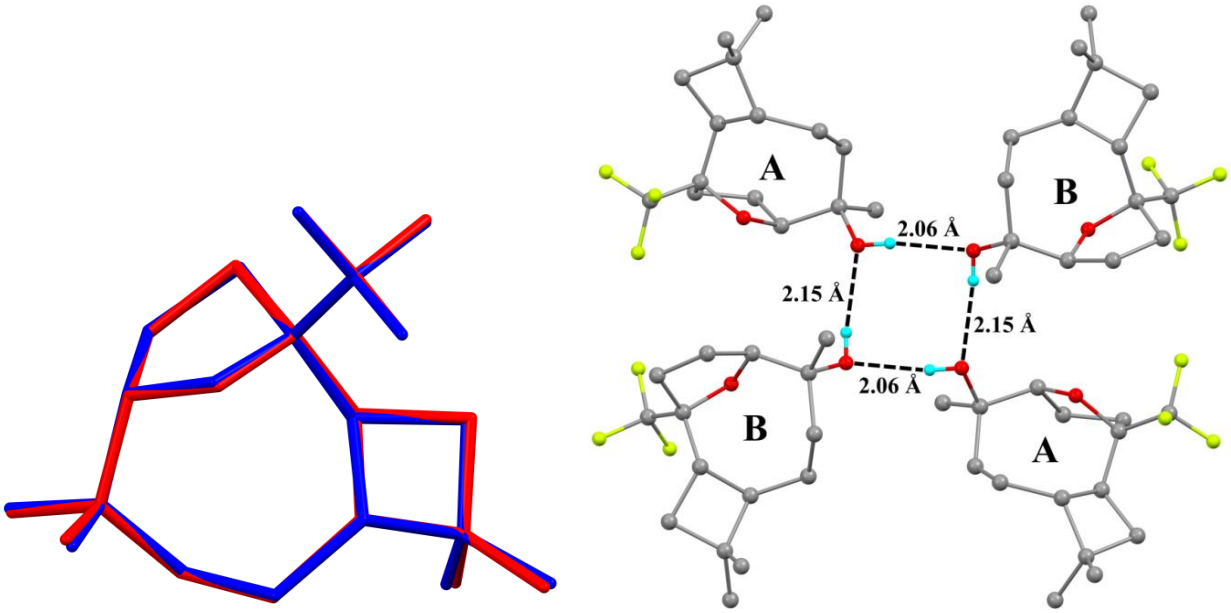


Figure S105. Tetrameric motif showing O-H...O contacts between A...B...A....B molecules of **29** in the solid state.

6. Antimicrobial properties

Table S3. *In vitro* antibacterial activity (MIC, μg/mL, medians) of fluorine-containing compounds and reference antimicrobials

	S. aureus ATCC 29213(MSSA)	*S. aureus MRSA* clinical isolate	*P. aeruginosa ATCC 27853*
15	1024	>1024	>1024
16	512	256	512
17	128	128	526
18	64	64	>1024
27	>1024	>1024	>1024
28	128	128	1024
29	256	256	>1024
Ampicillin	**2**	**512**	**512**

Table S4. Ames test for 2*β*-methoxyclovan-9*β*-ol **18**

TA 98	***TA 100***	***TA 102***	**Mutagenicity**
			Not found

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