Design, synthesis and biological evaluation of novel β-caryophyllene derivatives as potential anti-cancer agents through the ROS-mediated apoptosis pathway

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Table S1. IC_{50} values of **AC-1** - **AC-23** and *β*-caryolanol determined in three human normal cell lines, LO2 normal hepatocytes, MCF-10A mammary epithelial cells, and BEAS-2B bronchial epithelial cells, with *β*-CP, and 5-FU as the positive control. The selectivity index (SI) was calculated as the IC_{50} ratio. IC_{50} values listed as >500/1000 indicate that no 50% inhibition was observed at the 500/1000 μM dose, nor was the maximum inhibition observed.

Cmpd	IC_{50}(μM) LO2	SI=LO2/ HepG2	IC_{50}(μM) MCF-10A	SI=MCF-10A /MCF-7	IC_{50}(μM) BEAS-2B	SI=BEAS-2B/ A549
AC-7	24.65 ± 1.56	1.8	11.71 ± 1.51	/	11.02 ± 0.44	0.7
AC-8	36.30 ± 27.72	2.4	15.88 ± 1.42	/	14.52 ± 1.01	/
AC-9	17.52 ± 0.80	2.9	13.02 ± 1.42	1.4	14.11 ± 0.65	1.4
AC-10	7.01 ± 0.46	/	8.81 ± 0.20	/	46.36 ± 12.42	/
AC-11	17.81 ± 4.68	2.7	14.14 ± 1.21	1.7	10.77 ± 0.33	1.4
AC-12	16.27 ± 0.56	2.9	15.17 ± 1.07	1.6	14.07 ± 1.08	1.4
AC-13	6.64 ± 0.23	2.3	6.27 ± 0.16	1.4	7.44 ± 0.34	1.0
AC-14	3.79 ± 0.11	1.7	3.10 ± 0.03	0.2	3.52 ± 0.19	0.6
AC-15	1.91 ± 0.01	0.9	1.82 ± 0.04	0.4	4.49 ± 0.21	1.0
AC-16	2.90 ± 0.27	0.7	5.63 ± 0.73	1.3	6.12 ± 0.09	0.9
AC-17	13.20 ± 3.26	2.8	6.67 ± 0.18	0.5	15.31 ± 6.20	1.1
AC-18	31.06 ± 0.98	1.8	20.24 ± 0.60	/	28.95 ± 3.16	/
AC-19	25.74 ± 4.47	3.5	15.77 ± 0.97	1.2	12.93 ± 0.61	1.1
AC-20	9.64 ± 1.15	1.8	4.42 ± 0.07	0.6	9.19 ± 0.22	0.7
AC-21	28.03 ± 2.38	3.8	15.77 ± 0.97	1.4	55.763±2.229	/
AC-22	14.04 ± 1.75	1.5	6.24 ± 0.19	0.6	9.00 ± 0.29	/
AC-23	25.41 ± 0.46	/	13.59 ± 0.99	/	18.32 ± 1.20	/
***β*-CP**	400.74 ± 37.07	1.4	> 1000	/	221.90 ± 6.07	1.1

***β*-Caryolanol**	61.45 ± 6.55	0.6	97.37 ± 4.22	1.0	>500	/
5-FU	0.37 ± 0.02	0.3	4.42 ± 0.07	21	3.89 ± 0.28	1.7

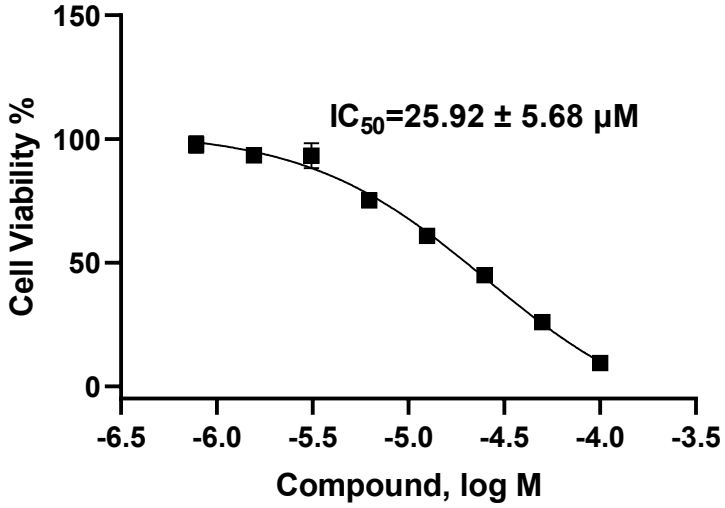
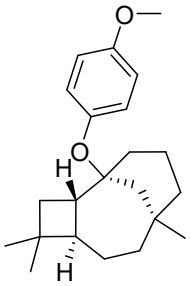


Figure S1. Cell viability of HT-29 after treatment with LY294002.

Characterization data of synthetic compounds

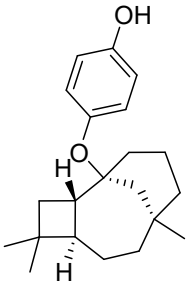
*(1R,2S,5R,8S)-1-(4-methoxyphenoxy)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodecane (**AC -1**).*



According to the genenal procedure, compound ***AC-1*** could be obtained with 70% yield as white solid using β-Caryophyllene and 4-methoxyphenol as substrates;

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.81 (m, 2H), 6.81 – 6.74 (m, 2H), 3.78 (s, 3H), 2.46 – 2.34 (m, 1H), 2.07 – 1.97 (m, 1H), 1.89 – 1.74 (m, 4H), 1.73 – 1.65 (m, 2H), 1.58 (m, 2H), 1.38 (m, 3H), 1.21 – 1.15 (m, 1H),1.13(d, *J* = 9.6 Hz, 1H), 1.05(s, 3H), 1.04 (s, 3H), 1.02 – 0.95 (m, 1H), 0.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.76, 147.91, 122.81, 112.64, 79.20, 54.49, 45.77, 44.20, 39.60, 36.19, 36.11, 35.64, 33.94, 33.76, 33.70, 32.40, 29.38, 21.12, 19.95, 19.86.

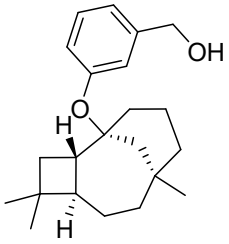
*4-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodecan-1-yl)oxy)phenol (**AC -2**).*



According to the genenal procedure, compound ***AC-2*** could be obtained with 70% yield as white solid using β-Caryophyllene and Hydroquinone as substrates; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 – 6.72 (m, 2H), 6.71 – 6.65 (m, 2H), 2.42 – 2.32 (m, 1H), 2.04 – 1.95 (m, 1H), 1.84-1.76 (m, 2H), 1.72-1.65 (m, 3H), 1.54 – 1.48 (m, 3H), 1.36 – 1.32 (m, 3H), 1.17 – 1.12 (m, 1H), 1.12 – 1.07 (m, 2H), 1.02 (s, 3H), 1.01 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.18 , 148.43 , 124.16 , 115.32 , 80.41 , 46.72 , 45.16 , 40.49 , 37.22, 37.15, 36.58 , 35.00 , 34.76, 34.74, 33.44 , 30.42 , 22.09 , 21.01,

20.91.

*(3-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)phenyl)metha nol (**AC -3**)*.



According to the genenal procedure, compound ***AC-3*** could be obtained with 70% yield as white solid using β-Caryophyllene and 3-Hydroxybenzyl alcohol as substrates; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.9 Hz, 1H), 6.87 (m, 2H), 6.74 – 6.63 (m, 1H), 5.08 (s,1H), 4.44 (d, *J* = 12.1 Hz, 1H), 4.32 (d, *J* = 12.1 Hz, 1H), 2.28 – 2.18 (m, 1H), 1.91 (m, 1H), 1.87 – 1.77 (m, 2H), 1.75 – 1.71 (m, 2H), 1.64 (d, *J* = 9.6 Hz, 1H), 1.52 (ddd, *J* = 10.3, 6.1, 2.5 Hz, 2H), 1.45 – 1.37 (m, 2H), 1.37 – 1.25 (m, 2H), 1.21 (d, *J* = 12.8 Hz, 1H), 1.16 – 1.05 (m, 2H), 1.00 (s, 6H), 0.89 (d, *J* = 2.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.64, 142.21, 129.39, 119.15, 113.93, 113.85, 63.82, 46.93, 46.00, 40.41, 37.75, 37.69, 36.78, 35.28, 34.69, 34.60, 33.92, 30.50, 22.76, 20.95, 20.64

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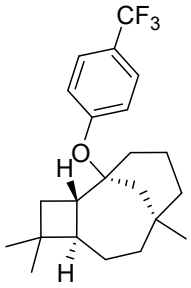
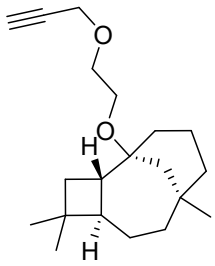
*(1R,2S,5R,8S)-4,4,8-trimethyl-1-(4-(trifluoromethyl)phenoxy)tricyclo[6.3.1.0^{2,5}]dode cane (**AC -4**)*.



According to the genenal procedure, compound ***AC-4*** could be obtained with 91% yield as white solid using β-Caryophyllene and 4-(trifluoromethyl)phenol as substrates; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 4.55 (s, 1H), 2.40 – 2.24 (m, 1H), 1.78 – 1.68 (m, 4H), 1.63 – 1.58 (m, 1H), 1.58 – 1.53 (m, 2H), 1.49-1.40 (m, 2H), 1.38 – 1.26 (m, 4H), 1.18 (d, *J* = 12.8 Hz, 1H), 1.12-1.08(m, 1H), 1.02 (s, 3H), 0.99 (s, 3H), 0.80 (s, 3H)。^{13}C NMR (101 MHz,

$CDCl_3$) δ 158.86, 125.95 (q, *J*=3.7 Hz), 122.82 (t, *J* = 40.5 Hz), 120.11, 81.92, 47.63, 46.15, 42.60, 38.87, 38.32, 36.06, 35.68, 34.67, 34.52, 33.43, 30.21, 23.12, 20.75, 20.69.

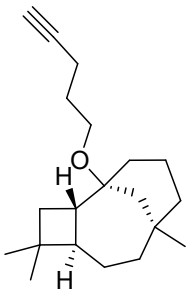
*(1R,2S,5R,8S)-4,4,8-trimethyl-1-(2-(prop-2-yn-1-yloxy)ethoxy)tricyclo[6.3.1.$0^{2,5}$] dodecane (**AC -5**)*.



According to the genenal procedure, compound ***AC-5*** could be obtained with 70% yield as white solid using β-Caryophyllene and Propynol ethoxylate as substrates;

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (d, *J* = 2.4 Hz, 2H), 3.64 (dd, *J* = 8.0, 3.2 Hz, 2H), 3.61 – 3.54 (m, 1H), 3.40 (dt, *J* = 10.2, 5.1 Hz, 1H), 2.41 (t, *J* = 2.4 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.88 – 1.81 (m, 1H), 1.66 – 1.57 (m, 3H), 1.56 – 1.47 (m, 3H), 1.47 – 1.41 (m, 2H), 1.34 – 1.28 (m, 3H), 1.15 – 1.08 (m, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.87 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 80.00 , 76.00 , 74.22 , 69.87 , 61.33 , 58.54 , 46.92 , 45.89 , 40.19 , 37.69 , 36.65 , 35.19 , 34.61 , 34.35 , 33.86 , 30.42 , 22.72 , 20.90 , 20.62 .

*(1R,2S,5R,8S)-4,4,8-trimethyl-1-(pent-4-yn-1-yloxy)tricyclo[6.3.1.$0^{2,5}$]dodecane (**AC -6**)*.

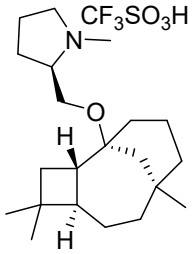


According to the genenal procedure, compound ***AC-6*** could be obtained with 70% yield as white solid using β-Caryophyllene and 4-Pentyn-1-ol as substrates;

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (dt, *J* = 9.0, 6.6 Hz, 1H), 3.22 (dt, *J* = 9.0, 6.4 Hz, 1H), 2.19 (td, *J* = 7.1, 2.6 Hz, 2H), 2.14 – 2.02 (m, 1H), 1.85 (t, *J* = 2.7 Hz, 1H), 1.79

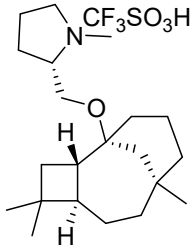
– 1.71 (m, 1H), 1.69 – 1.57 (m, 6H), 1.51 – 1.36 (m, 3H), 1.32 – 1.18 (m, 4H), 1.09 – 0.96 (m, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 84.46 , 75.46 , 68.17 , 60.22 , 46.73 , 45.89 , 40.31 , 37.74 , 36.50 , 35.13 , 34.63 , 34.36 , 33.95 , 30.47 , 29.61 , 22.74 , 20.92 , 20.64 , 15.38 .

*(R)-1-methyl-2-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) methyl)pyrrolidine trifluoromethanesulfonate (**AC-7**).*



According to the genenal procedure, compound ***AC-7*** could be obtained with 70% yield as white solid using β-Caryophyllene and (R)-(1-methylpyrrolidin-2-yl)methanol as substrates; HRMS(ESI): calcd for C21H37NO $[M + H]^+$ *m/z* 320.2948, found 320.2740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (m, 1H), 3.80 (dd, *J* = 10.8, 9.2 Hz, 1H), 3.49 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.40-3.28 (m, 1H), 3.09 (d, *J* = 5.0 Hz, 3H), 3.00 – 2.86 (m, 1H), 2.28 – 2.12 (m, 3H), 2.12 – 2.01 (m, 1H), 1.83 – 1.75 (m, 3H), 1.74 – 1.69 (m, 2H), 1.65 (d, *J* = 9.1 Hz, 1H), 1.63 – 1.59 (m, 1H), 1.53-1.43 (m, 3H), 1.41-1.34 (m, 2H), 1.32 – 1.28 (m, 1H), 1.26 (s, 1H), 1.17 (d, *J* = 12.9 Hz, 1H), 1.10 – 1.03 (m, 1H), 0.99 (s, 6H), 0.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 77.20, 69.90, 61.27, 58.05, 45.93, 45.91, 42.59, 40.06, 37.66, 37.40, 36.53, 35.38, 34.74, 33.80, 33.32, 30.53, 27.01, 22.63, 22.28, 20.80, 20.52.

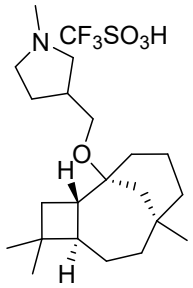
*(S)-1-methyl-2-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) methyl)pyrrolidine trifluoromethanesulfonate (**AC-8**).*



According to the genenal procedure, compound ***AC-8*** could be obtained with 60% yield

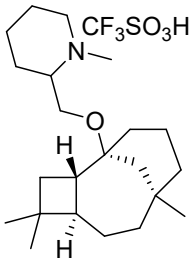
as white solid using β-Caryophyllene and (S)-(1-methylpyrrolidin-2-yl)methanol as substrates; HRMS(ESI): calcd for C21H37NO $[M + H]^+$ *m/z* 320.2948, found 320.2743; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85-3.72 (m, 1H), 3.72 – 3.61 (m, 2H), 3.42 – 3.27 (m, 1H), 3.17 – 2.99 (m, 1H), 2.98 (s, 3H), 2.27 – 2.11 (m, 3H), 2.12 – 1.94 (m, 2H), 1.82 – 1.69 (m, 3H), 1.67 – 1.55 (m, 3H), 1.51–1.43 (m, 3H), 1.43 – 1.28 (m, 4H), 1.18 – 1.10 (m, 2H), 1.09 – 1.02 (m, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 76.92, 60.39, 57.65, 45.85, 44.95, 40.26, 37.56, 37.39, 36.07, 35.23, 34.85, 33.87, 33.22, 30.62, 29.71, 26.91, 22.50, 22.12, 20.82, 20.52.

*1-methyl-3-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) methyl)pyrrolidine trifluoromethanesulfonate (**AC-9**).*



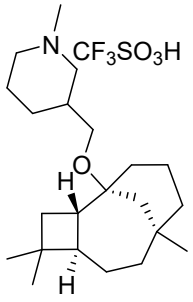
According to the genenal procedure, compound ***AC-9*** could be obtained with 68% yield as white solid using β-Caryophyllene and (1-methylpyrrolidin-3-yl)methanol as substrates; HRMS(ESI): calcd for C21H37NO $[M + H]^+$ *m/z* 320.2953, found 320.2813; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 – 3.21 (m, 4H), 3.06 (brs, 1H), 2.89 (s, 3H), 2.70 – 2.59 (m, 1H), 2.23 – 2.05 (m, 2H), 2.00 – 1.83 (m, 1H), 1.75 – 1.66 (m, 1H), 1.66 – 1.58 (m, 2H), 1.57-1.50 (m, 2H), 1.45 – 1.36 (m, 2H), 1.35 – 1.27 (m, 2H), 1.28 – 1.19 (m, 3H), 1.10 – 0.95 (m, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 75.76 , 75.72 , 62.00 , 61.81 , 58.53 , 58.36 , 56.60 , 56.46 , 45.98 , 45.88 , 41.47, 41.43 , 40.32 , 40.30 , 37.83 , 37.73, 37.65 , 37.60 , 36.39 , 36.35 , 35.22 , 34.73 , 34.71 , 33.95, 33.85 , 30.63 , 30.61 , 29.67 , 27.16 , 27.05 , 22.62 , 20.84 , 20.49.

*1-methyl-2-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) methyl)piperidine trifluoromethanesulfonate (**AC-10**).*



According to the genenal procedure, compound ***AC-10*** could be obtained with 98% yield as white solid using β-Caryophyllene and (1-methylpiperidin-2-yl)methanol as substrates; HRMS(ESI): calcd for C22H39NO $[M+H]^+$ *m/z* 334.3110, found 334.2894; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 – 3.68 (m, 1H), 3.56 (dd, *J* = 10.2, 4.9 Hz, 0.6H), 3.42 (dd, *J* = 10.2, 4.8 Hz, 0.4H), 3.25 (dd, *J* = 10.7, 3.3 Hz, 1H), 2.70 (s, 1.8H), 2.62 (s, 1.2H), 2.59-2.48 (m, 2H), 2.23 – 2.09 (m, 1H), 1.92 – 1.73 (m, 5H), 1.72 – 1.65 (m, 3H), 1.66 – 1.57 (m, 3H), 1.55-1.49 (m, 1H), 1.49 – 1.43 (m, 2H), 1.42 – 1.34 (m, 3H), 1.34 – 1.28 (m, 2H), 1.15-1.07 (m, 2H), 1.07 – 1.01 (m, 1H), 1.00 – 0.95 (m, 6H), 0.89 – 0.87 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 76.49, 76.23, 65.74, 65.29, 63.57, 62.59, 57.06, 46.22, 46.22, 45.94, 45.87, 45.79, 40.34, 40.17, 37.74, 37.57, 36.51, 36.34, 35.25, 35.21, 34.74, 33.95, 33.82, 30.56, 30.53, 29.71, 28.12, 23.95, 23.75, 22.87, 22.70, 22.89, 20.90, 20.86, 20.58.

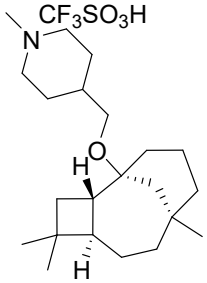
*1-methyl-3-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) methyl)piperidine trifluoromethanesulfonate (**AC-11**)*.



According to the genenal procedure, compound ***AC-11*** could be obtained with 55% yield as white solid using β-Caryophyllene and (1-methylpiperidin-3-yl)methanol as substrates; HRMS(ESI): calcd for C22H39NO $[M + H]^+$ *m/z* 334.3110, found 334.2943; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.44 (s, 1H), 3.43 – 3.33 (m, 2H), 3.29 (dd, *J* = 9.3, 4.8 Hz, 0.5H), 3.21 – 3.13 (m, 1H), 3.08 (dd, *J* = 9.2, 5.8 Hz, 0.5H), 2.77 (dq, *J* = 43.8, 10.7 Hz, 2H), 2.07 (dd, *J* = 19.1, 11.0 Hz, 1H), 2.01 - 1.91

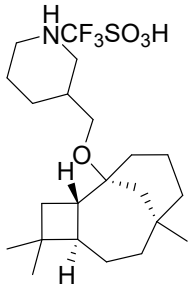
(m, 1H), 1.88 – 1.81 (m, 1H), 1.79 – 1.67 (m, 3H), 1.64 – 1.57 (m, 2H), 1.56 – 1.50 (m, 2H), 1.45 – 1.35 (m, 3H), 1.34 – 1.27 (m, 2H), 1.26 – 1.18 (m, 3H), 1.09 – 0.95 (m, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 75.60 , 75.52 , 63.39 , 63.32 , 58.22 , 47.87 , 47.85 , 45.93 , 45.84 , 45.04 , 40.32 , 40.26 , 37.73 , 37.69 , 37.63 , 36.22 , 36.16 , 35.16 , 34.66 , 34.58 , 34.47 , 33.98 , 33.94 , 33.75 , 30.45 , 30.42 , 25.68 , 22.69 , 22.64 , 21.78 , 21.74 , 20.84 , 20.55 , 18.23.

*1-methyl-4-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) methyl)piperidine trifluoromethanesulfonate (**AC-12**).*



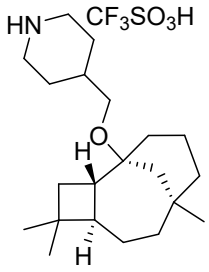
According to the genenal procedure, compound ***AC-12*** could be obtained with 63% yield as white solid using β-Caryophyllene and (1-methylpiperidin-4-yl)methanol as substrates; HRMS(ESI): calcd for C22H39NO $[M + H]^+$ *m/z* 334.3110, found 334.2943; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (d, *J* = 10.1 Hz, 2H), 3.22 – 3.14 (m, 1H), 3.12 - 3.03 (m, 1H), 2.79 (s, 3H), 2.78 – 2.60 (m, 2H), 2.08 (td, *J* = 11.0, 7.9 Hz, 1H), 2.02 – 1.87 (m, 3H), 1.75 – 1.69 (m, 1H), 1.65 – 1.59 (m, 4H), 1.57 – 1.51(m, 3H), 1.45 – 1.36 (m, 3H), 1.26 – 1.23 (m, 2H), 1.08 – 1.03 (m, 1H), 1.02 – 0.96 (m, 2H), 0.91 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.20(q , *J* = 375.2 Hz) , 75.53 , 64.90 , 46.28 , 45.99 , 40.35 , 37.74 , 37.65 , 36.37 , 35.19 , 34.70 , 34.05 , 34.00 , 30.56 , 29.70 , 22.71 , 20.87 , 20.56.

*3-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)methyl)pipe ridine trifluoromethanesulfonate (**AC-13**).*



According to the genenal procedure, compound ***AC-13*** could be obtained with 55% yield as white solid using β-Caryophyllene and piperidin-3-ylmethanol as substrates; HRMS(ESI): calcd for C21H37NO $[M + H]^+$ *m/z* 320.2953, found 320.2793; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.44 (s, 1H), 3.43 – 3.33 (m, 2H), 3.29 (dd, *J* = 9.3, 4.8 Hz, 0.5H), 3.21 – 3.13 (m, 1H), 3.08 (dd, *J* = 9.2, 5.8 Hz, 0.5H), 2.77 (dq, *J* = 43.8, 10.7 Hz, 2H), 2.07 (dd, *J* = 19.1, 11.0 Hz, 1H), 2.01 - 1.91 (m, 1H), 1.88 – 1.81 (m, 1H), 1.79 – 1.67 (m, 3H), 1.64 – 1.57 (m, 2H), 1.56 – 1.50 (m, 2H), 1.45 – 1.35 (m, 3H), 1.34 – 1.27 (m, 2H), 1.26 – 1.18 (m, 3H), 1.09 – 0.95 (m, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 75.60 , 75.52 , 63.39 , 63.32 , 58.22 , 47.87 , 47.85 , 45.93 , 45.84 , 45.04 , 40.32 , 40.26 , 37.73 , 37.69 , 37.63 , 36.22 , 36.16 , 35.16 , 34.66 , 34.58 , 34.47 , 33.98 , 33.94 , 33.75 , 30.45 , 30.42 , 25.68 , 22.69 , 22.64 , 21.78 , 21.74 , 20.84 , 20.55 , 18.23.

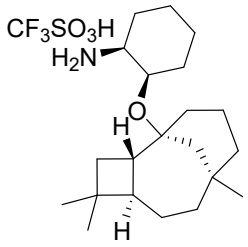
*4-((((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)methyl)pipe ridine trifluoromethanesulfonate (**AC-14**)*.



According to the genenal procedure, compound ***AC-14*** could be obtained with 56% yield as white solid using β-Caryophyllene and piperidin-4-ylmethanol as substrates; HRMS(ESI): calcd for C21H37NO $[M + H]^+$ *m/z* 320.2953, found 320.2796; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 60.0 Hz, 2H), 3.78 (s, 1H), 3.31 (s, 2H), 3.15 (s, 2H), 2.22 - 2.08 (m, 1H), 1.90 (s, 2H), 1.75 – 1.56 (m, 5H), 1.56 – 1.46 (m, 3H), 1.46 – 1.35 (m, 3H), 1.35 – 1.20 (m, 3H), 1.10 – 1.01 (m, 2H), 1.01 – 0.95 (m, 1H), 0.92 (s, 3H),

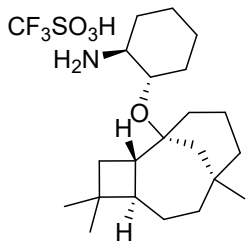
0.91 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.20(q , *J* = 375.2 Hz) , 76.95 , 60.61 , 45.49 , 45.41 , 41.28 , 41. 24, 40.27 , 37.76 , 37.45 , 35.45 , 35.03 , 34.97 , 34.55 , 34.08 , 30.63 , 30.54 , 30.36 , 22.35 , 21.06, 20.65.

*(1S,2R)-2-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)cyclo hexan-1-amine trifluoromethanesulfonate (**AC-15**).*



According to the genenal procedure, compound ***AC-15*** could be obtained with 71% yield as white solid using β-Caryophyllene and (1R,2S)-2-aminocyclohexan-1-ol as substrates; HRMS(ESI): calcd for C21H37NO $[M + H]^+$ *m/z* 320.2953, found 320.2798; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (brs, 3H), 3.85 – 3.75 (m, 1H), 3.30 (td, *J* = 6.8, 3.1 Hz, 1H), 2.19 (dd, *J* = 20.1, 10.6 Hz, 1H), 1.80-1.70 (m, 3H), 1.69-1.58 (m, 4H), 1.54 (d, *J* = 10.1 Hz, 1H), 1.49-1.36 (m, 7H), 1.32 – 1.21 (m, 5H), 1.19 – 1.16 (m, 2H), 1.07 (dd, *J* = 10.0, 7.1 Hz, 1H), 1.04 – 0.97 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ119.67 (q, *J* = 375.2 Hz), 77.27 , 67.10 , 65.17 , 53.59 , 45.29 , 44.63 , 40.52 , 37.68 , 37.41 , 35.29 , 35.12 , 35.05 , 34.59 , 33.71 , 30.88 , 30.44 , 29.71 , 25.96 , 22.21 , 21.27 , 20.64.

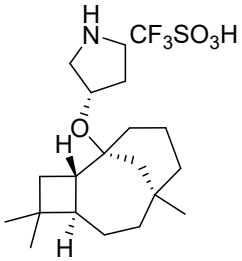
*(1S,2S)-2-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)cyclo hexan-1-amine trifluoromethanesulfonate (**AC-16**).*



According to the genenal procedure, compound ***AC-16*** could be obtained with 67% yield as white solid using β-Caryophyllene and (1S,2S)-2-aminocyclohexan-1-ol as substrates; HRMS(ESI): calcd for C21H37NO $[M + H]^+$ *m/z* 320.2953, found 320.2812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (s, 3H), 3.46 – 3.31 (m, 1H), 2.82 – 2.71 (m, 1H), 2.19 (dd, *J* = 20.1, 10.3 Hz, 1H), 2.06 (d, *J* = 11.2 Hz, 1H), 1.96 (d, *J* = 9.6

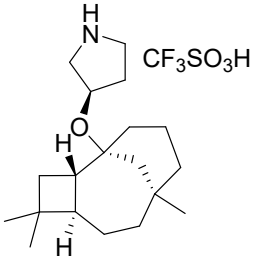
Hz, 1H), 1.78 – 1.59 (m, 5H), 1.56 – 1.46 (m, 4H), 1.45 – 1.33 (m, 3H), 1.31 – 1.20 (m, 7H), 1.03 (d, *J* = 12.2 Hz, 2H), 0.91 (s, 6H), 0.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 119.67 (q, *J* = 375.2 Hz), 70.23 , 67.08 , 56.43 , 45.55 , 44.45 , 39.45 , 37.31 , 36.49 , 35.32 , 34.90 , 34.70 , 34.06 , 33.55 , 33.00 , 30.58 , 29.70 , 28.44 , 23.93 , 23.86 , 21.41 , 20.81.

*(S)-3-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)pyrrolidine trifluoromethanesulfonate (**AC-17**)*.



According to the genenal procedure, compound ***AC-17*** could be obtained with 63% yield as white solid using β-Caryophyllene and (S)-pyrrolidin-3-ol as substrates; HRMS(ESI): calcd for C19H33NO $[M + H]^+$ *m/z* 292.2640, found 292.2494; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 77.1 Hz, 2H), 4.26 – 4.17 (m, 1H), 3.41 – 3.27 (m, 3H), 3.18-3.06 (m, 1H), 2.14 – 1.98 (m, 2H), 1.93 – 1.84 (m, 1H), 1.72 – 1.63 (m, 2H), 1.62 – 1.53 (m, 3H), 1.45 – 1.36 (m, 2H), 1.35 – 1.28 (m, 2H), 1.28 – 1.20 (m, 3H), 1.10 – 1.03 (m, 1H), 1.02 – 0.96 (m, 2H), 0.91 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q, *J* = 318 Hz) , 78.10 , 69.63 , 52.71 , 46.40 , 46.03 , 45.00 , 40.15 , 37.99 , 37.80 , 36.43 , 35.63 , 35.09 , 34.86 , 34.29 , 33.63 , 30.46 , 22.86 , 21.13 , 20.46.

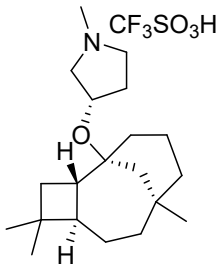
*(R)-3-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)pyrrolidine trifluoromethanesulfonate (**AC-18**)*.



According to the genenal procedure, compound ***AC-18*** could be obtained with 56%

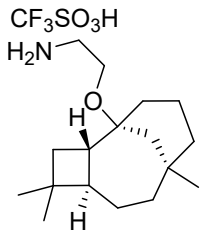
yield as white solid using β-Caryophyllene and (R)-pyrrolidin-3-ol as substrates; HRMS(ESI): calcd for C19H33NO [M + H]$^+$ *m/z* 292.2640, found 292.2497; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 21.7 Hz, 2H), 4.19 (s, 1H), 3.35 (s, 3H), 3.13 (s, 1H), 2.16 - 2.01 (m, 2H), 1.95 (s, 1H), 1.74 – 1.68 (m, 1H), 1.62 – 1.50 (m, 4H), 1.44 – 1.35 (m, 3H), 1.33 – 1.23 (m, 4H), 1.08 – 1.02 (m, 1H), 0.99 (d, *J* = 12.9 Hz, 2H), 0.92 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 77.14 , 68.62 , 52.22 , 45.50 , 44.87 , 43.62 , 39.05 , 36.93 , 36.77 , 35.46 , 34.53 , 34.13 , 33.80 , 33.17 , 31.80 , 29.37 , 28.68 , 21.80 , 20.16 , 19.47.

*(S)-1-methyl-3-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) pyrrolidine trifluoromethanesulfonate (**AC-19**)*.



According to the genenal procedure, compound ***AC-19*** could be obtained with 72% yield as white solid using β-Caryophyllene and (S)-1-methylpyrrolidin-3-ol as substrates; HRMS(ESI): calcd for C20H35NO [M + H]$^+$ *m/z* 306.2797, found 306.2641; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 – 4.23 (m, 1H), 3.74 (dd, *J* = 12.1, 5.3 Hz, 1H), 3.64 (t, *J* = 8.0 Hz, 1H), 3.23 – 3.10 (m, 1H), 2.91 (s, 3H), 2.91 – 2.83(s, 1H), 2.27 – 2.16 (m, 1H), 2.11 (td, *J* = 11.1, 7.8 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.70 – 1.60 (m, 4H), 1.59 – 1.51 (m, 2H), 1.47 – 1.37 (m, 2H), 1.36 – 1.31 (m, 1H), 1.27 – 1.21 (m, 3H), 1.10 – 1.04 (m, 1H), 1.02 – 0.96 (m, 2H), 0.92 (s, 3H), 0.92 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.20(q , *J* = 375.2 Hz) , 78.52 , 69.89 , 63.13 , 55.51 , 46.49 , 46.23 , 42.96 , 40.26 , 38.08 , 37.75 , 36.72 , 35.70 , 35.21 , 34.94 , 34.51 , 34.37 , 30.58 , 22.95 , 21.13 , 20.41.

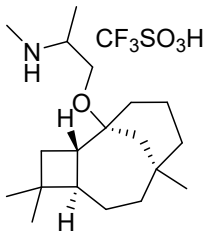
*2-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)ethan-1-amine trifluoromethanesulfonate (**AC-20**)*.



According to the genenal procedure, compound ***AC-20*** could be obtained with 51% yield as white solid using β-Caryophyllene and 2-aminoethan-1-ol as substrates; HRMS(ESI): calcd for C17H31NO $[M + H]^+$ *m/z* 266.2484, found 266.2363;

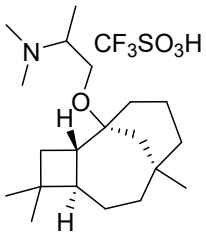
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 3H), 3.54 (dt, *J* = 10.8, 5.4 Hz, 1H), 3.46 – 3.30 (m, 1H), 3.16 – 3.02 (m, 2H), 2.08 (td, *J* = 11.1, 7.9 Hz, 1H), 1.79 – 1.69 (m, 1H), 1.65 – 1.54 (m, 4H), 1.47 – 1.34 (m, 3H), 1.34 – 1.26 (m, 2H), 1.26 – 1.19 (m, 2H), 1.10 – 0.95 (m, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.20(q , *J* = 375.2 Hz) , 76.85 , 56.77 , 45.84 , 45.81 , 41.03 , 40.19 , 37.78 , 37.52 , 36.24 , 35.26 , 34.68 , 33.90 , 33.86 , 30.27 , 22.72 , 20.87 , 20.52.

*N-methyl-1-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy)propan-2-amine trifluoromethanesulfonate (**AC-21**)*.



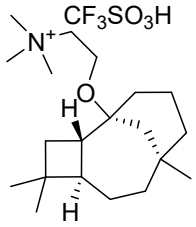
According to the genenal procedure, compound ***AC-21*** could be obtained with 49% yield as white solid using β-Caryophyllene and 2-(methylamino)propan-1-ol as substrates; HRMS(ESI): calcd for C19H35NO $[M + H]^+$ *m/z* 294.2797, found 294.2646; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (brs, 2H), 3.58 – 3.39 (m, 1H), 3.37 – 3.21 (m, 2H), 2.71 (d, *J* = 9.0 Hz, 3H), 2.15 – 2.02 (m, 1H), 1.79 – 1.70 (m, 1H), 1.65 (d, *J* = 7.9 Hz, 1H), 1.59 – 1.52 (m, 2H), 1.46 – 1.36 (m, 3H), 1.34 – 1.19 (m, 7H), 1.10 – 1.02 (m, 2H), 1.02 – 0.95 (m, 1H), 0.92 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) , 76.80 , 76.72 , 61.42 , 60.78 , 56.15 , 45.83 , 45.82 , 45.70 , 45.44 , 40.28 , 40.22 , 37.78 , 37.50 , 36.28 , 36.14 , 35.25 , 35.19 , 34.71 , 34.67 , 33.91 , 33.87 , 33.69 , 33.68 , 31.12 , 31.11 , 30.38 , 30.35 , 22.70 , 20.87 , 22.83 , 20.45 , 13.82 , 13.52.

*N,N-dimethyl-1-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) propan-2-amine trifluoromethanesulfonate (**AC-22**).*



According to the genenal procedure, compound ***AC-22*** could be obtained with 49% yield as white solid using β-Caryophyllene and 2-(dimethylamino)propan-1-ol as substrates; HRMS(ESI): calcd for C20H37NO [M + H]$^+$ *m/z* 308.2953, found 308.2798; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 - 3.63 (m, 0.5H), 3.51 – 3.35 (m, 2.5H), 2.85 (s, 6H), 2.11 (tt, *J* = 11.0, 7.4 Hz, 1H), 1.77 – 1.69 (m, 1H), 1.67 – 1.63 (m, 2H), 1.60 – 1.53 (m, 2H), 1.45 – 1.38 (m, 2H), 1.38 – 1.33 (m, 2H), 1.33 – 1.26 (m, 5H), 1.08 – 1.03 (m, 2H), 1.01 – 0.96 (m, 1H), 0.92 (m, 6H), 0.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 120.31 (q , *J* = 318 Hz) ,, 62.18 , 62.03 , 60.80 , 60.62 , 46.00 , 45.72 , 45.47 , 40.21 , 40.10 , 37.70 , 37.67 , 37.48 , 36.47 , 36.36 , 35.39 , 35.30 , 34.84 , 34.79 , 33.94 , 33.92 , 33.65 , 33.50 , 30.61 , 30.54 , 29.71 , 22.65 , 22.60 , 20.86 , 20.83 , 20.45 , 11.99 , 11.84.

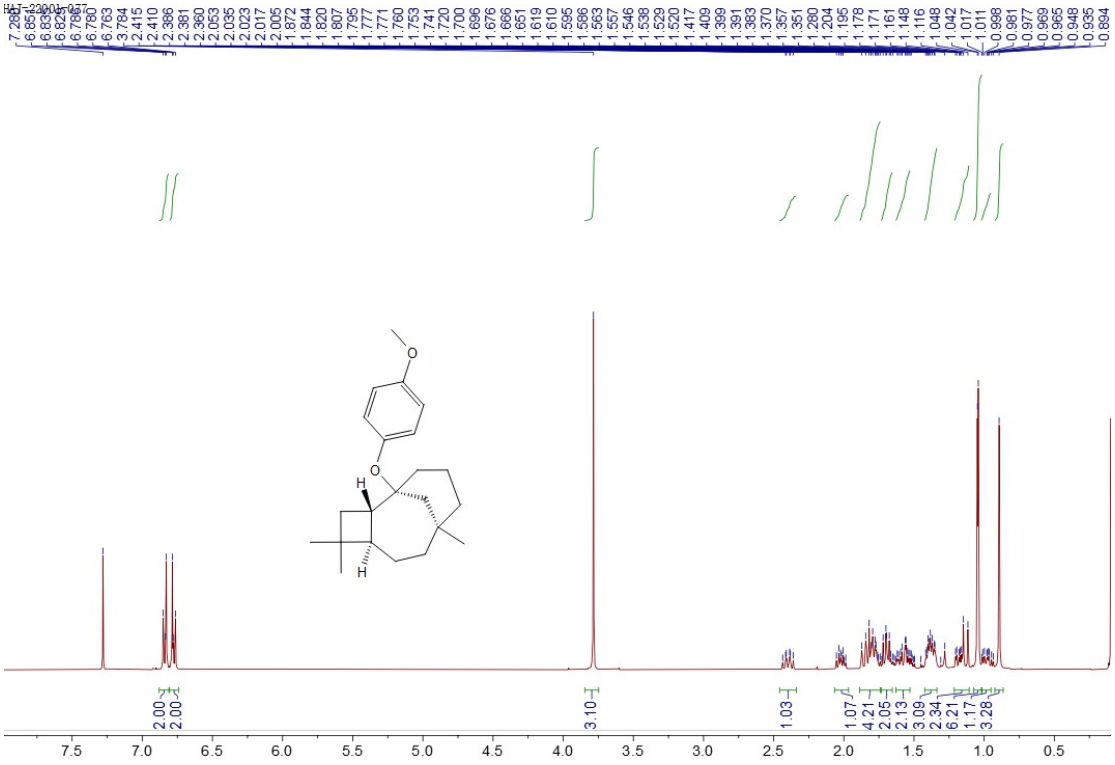
*N,N,N-trimethyl-2-(((1R,2S,5R,8S)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodecan-1-yl)oxy) ethan-1-aminium trifluoromethanesulfonate (**AC-23**).*

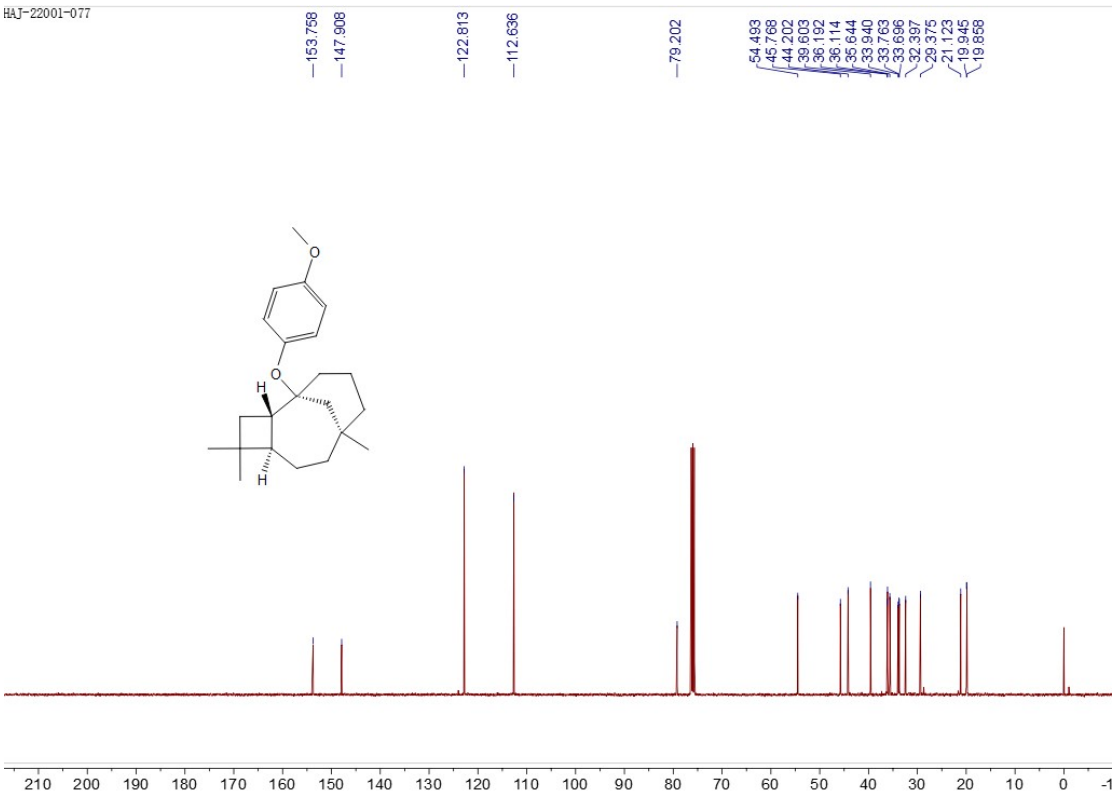


According to the genenal procedure, compound ***AC-23*** could be obtained with 43% yield as white solid using β-Caryophyllene and Choline hydroxide as substrates; HRMS(ESI): calcd for C20H38NO M$^+$ *m/z* 308.2948, found 308.2799; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (d, *J* = 7.1 Hz, 1H), 3.62 – 3.53 (m, 1H), 3.53 - 3.43 (m, 2H), 3.19 (s, 9H), 2.10 (td, *J* = 11.1, 7.9 Hz, 1H), 1.74 – 1.61 (m, 3H), 1.61 – 1.53 (m, 3H), 1.48 – 1.37 (m, 2H), 1.36 – 1.28 (m, 3H), 1.27 – 1.22 (m, 1H), 1.09 – 1.01 (m, 2H), 0.98 (dd, *J* = 8.7, 4.9 Hz, 1H), 0.92(s, 3H), 0.91(s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz,

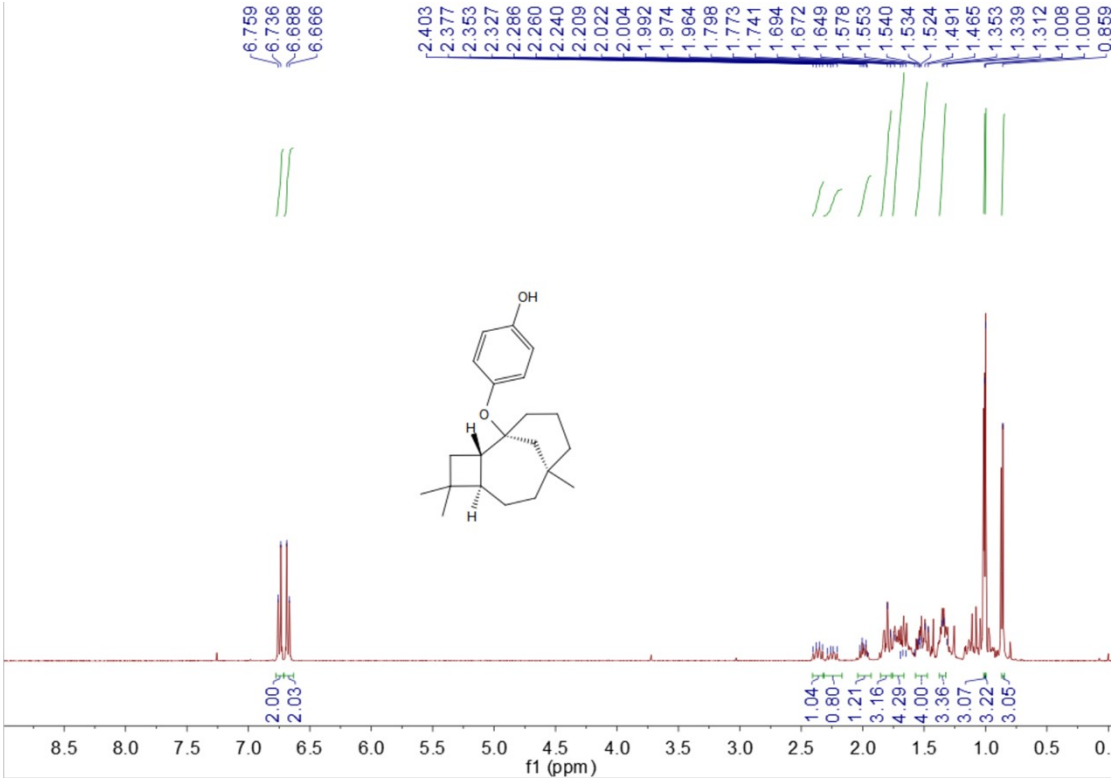
$CDCl_3$) δ 120.60(q , J = 318 Hz) , 77.49 , 66.65 , 56.20 , 54.45 , 54.42 , 54.39 , 45.93 , 45.64 , 39.97 , 37.61 , 37.44 , 36.38 , 35.28 , 34.80 , 33.91 , 33.46 , 30.49 , 22.56 , 20.79 , 20.47.

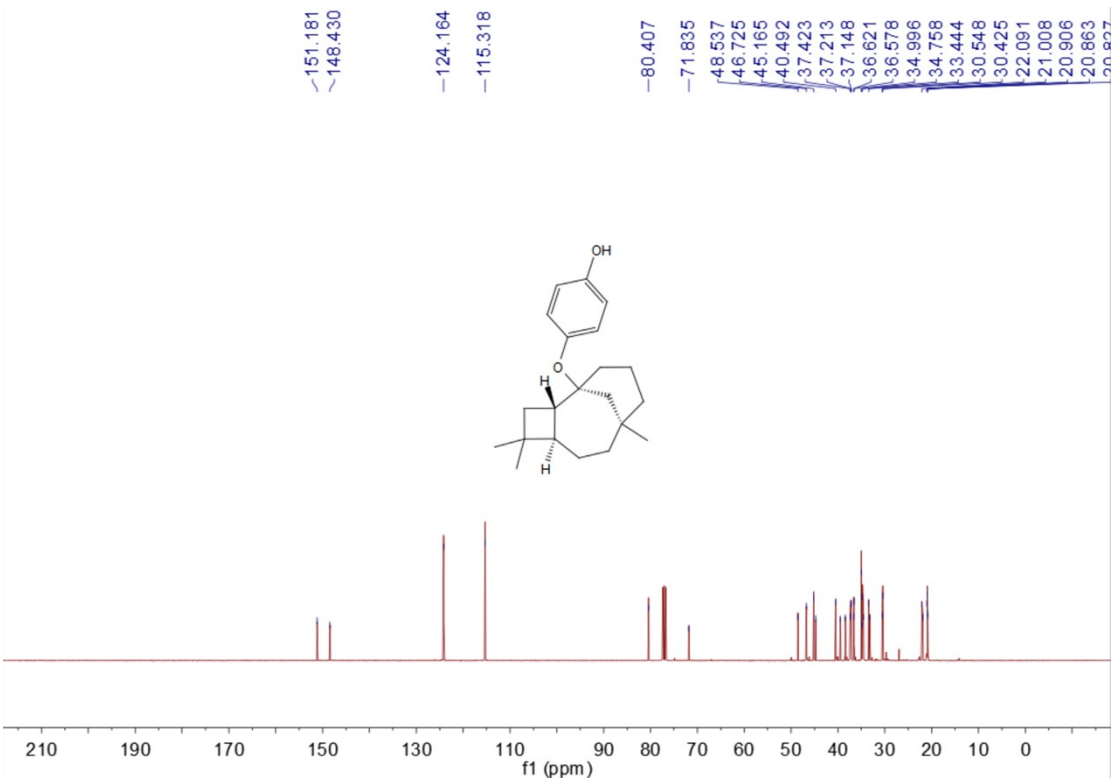
Compound AC-1



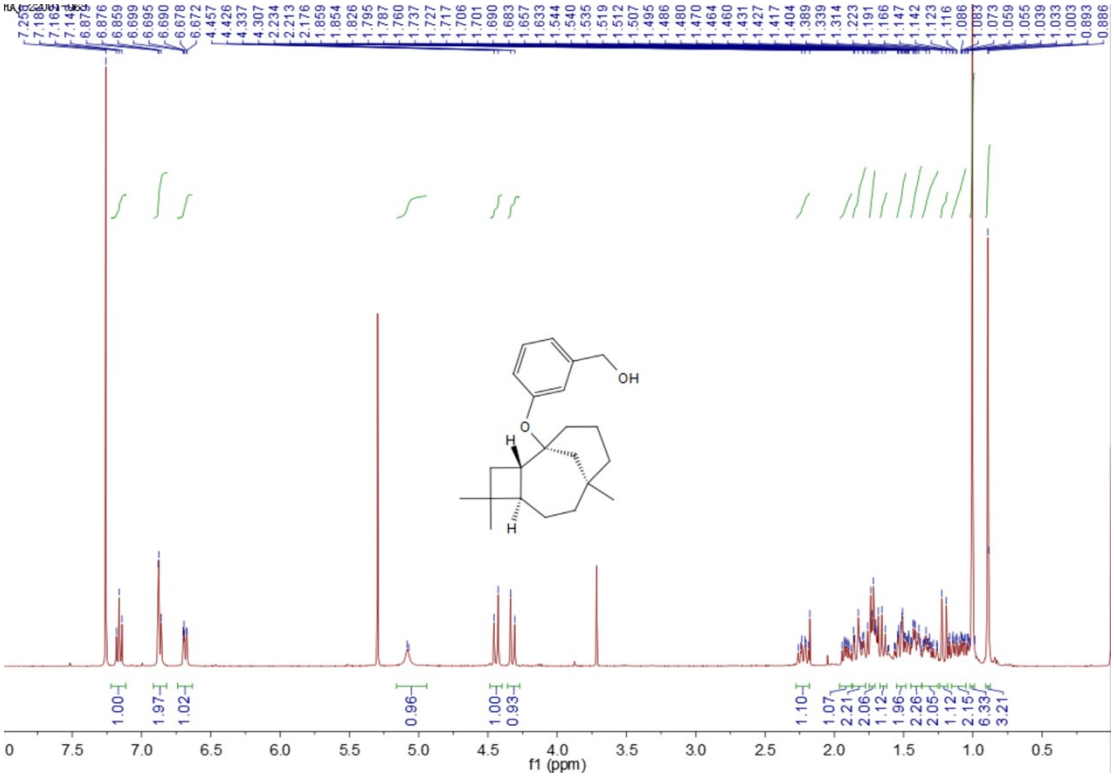


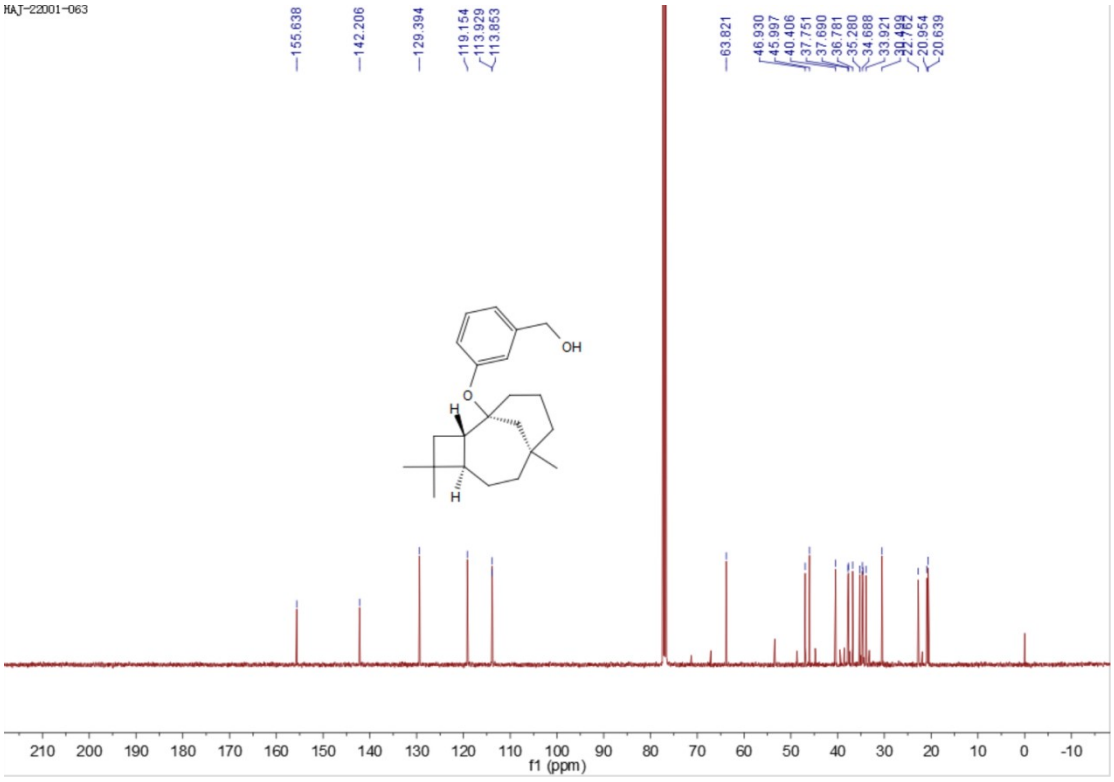
Compound AC-2



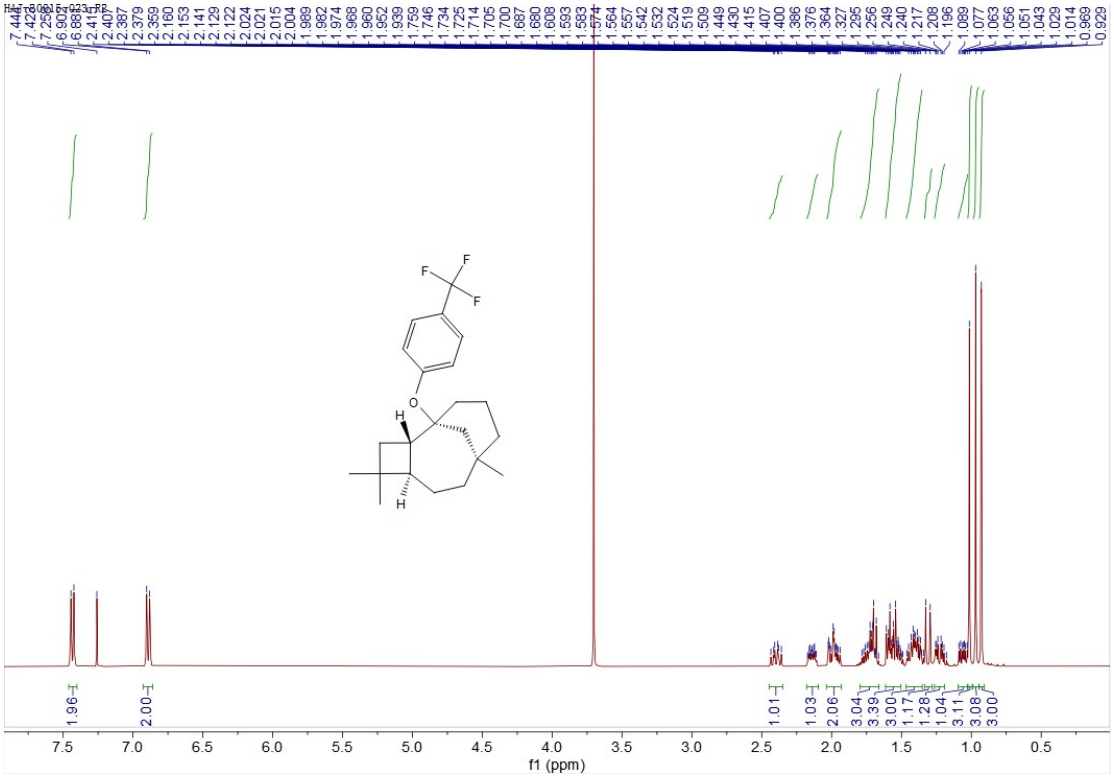


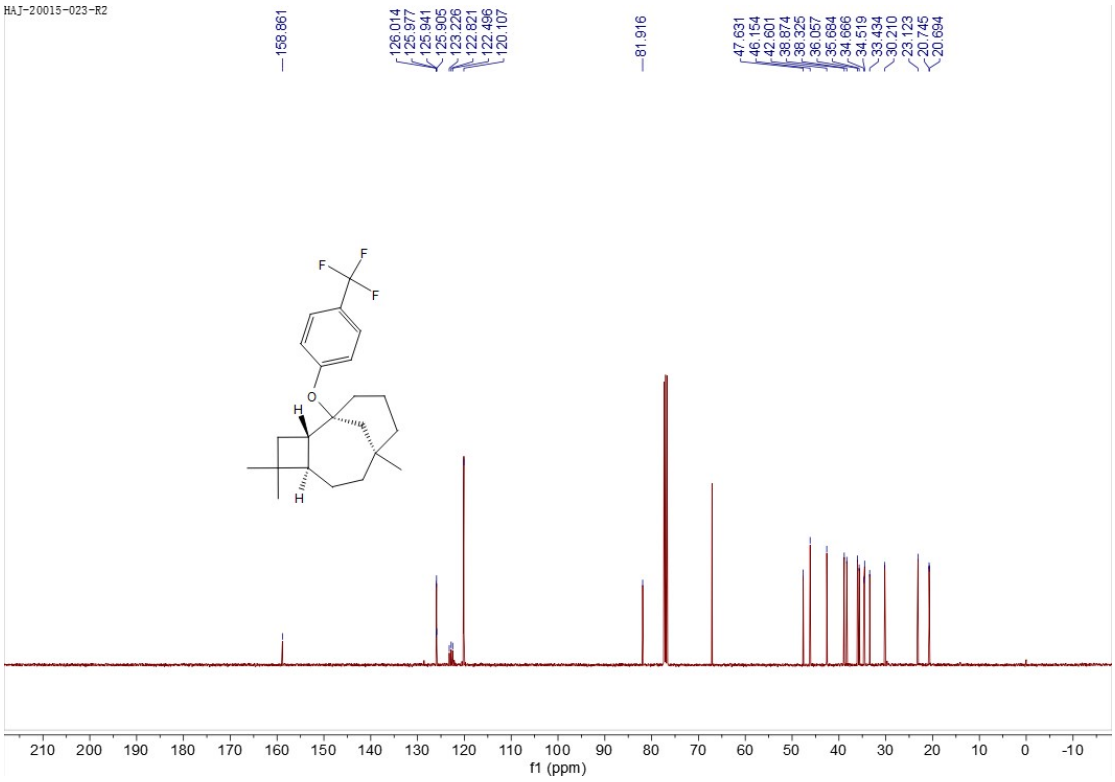
Compound AC-3



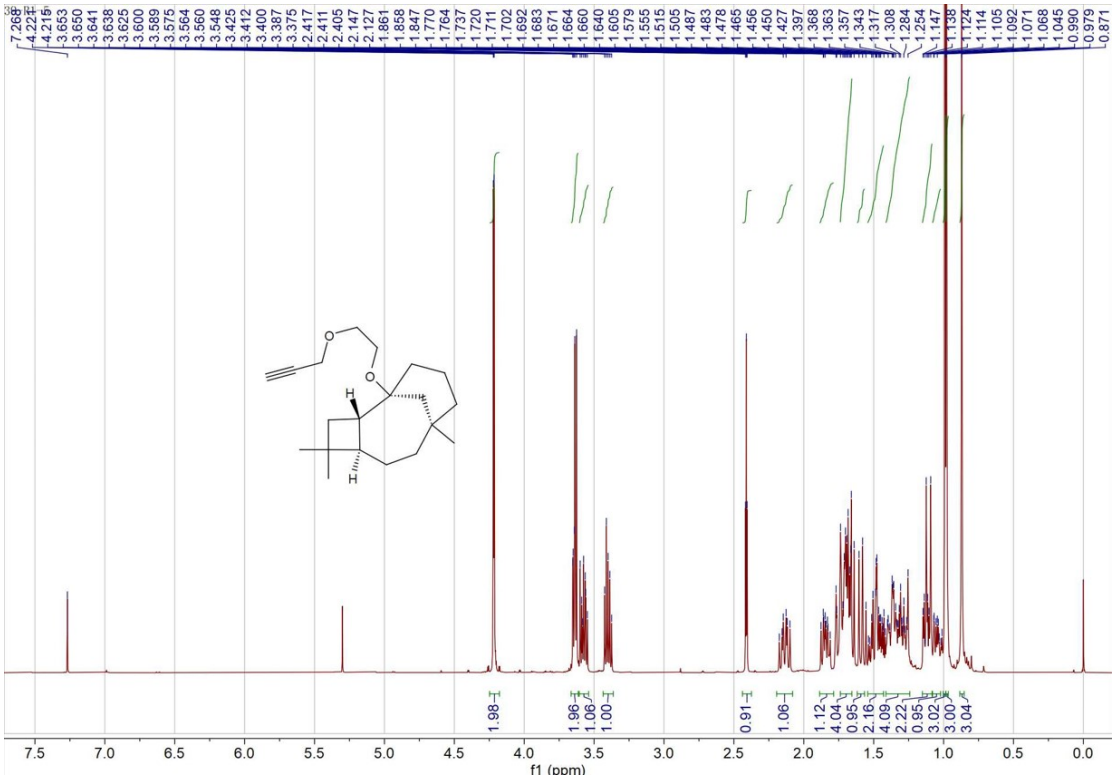


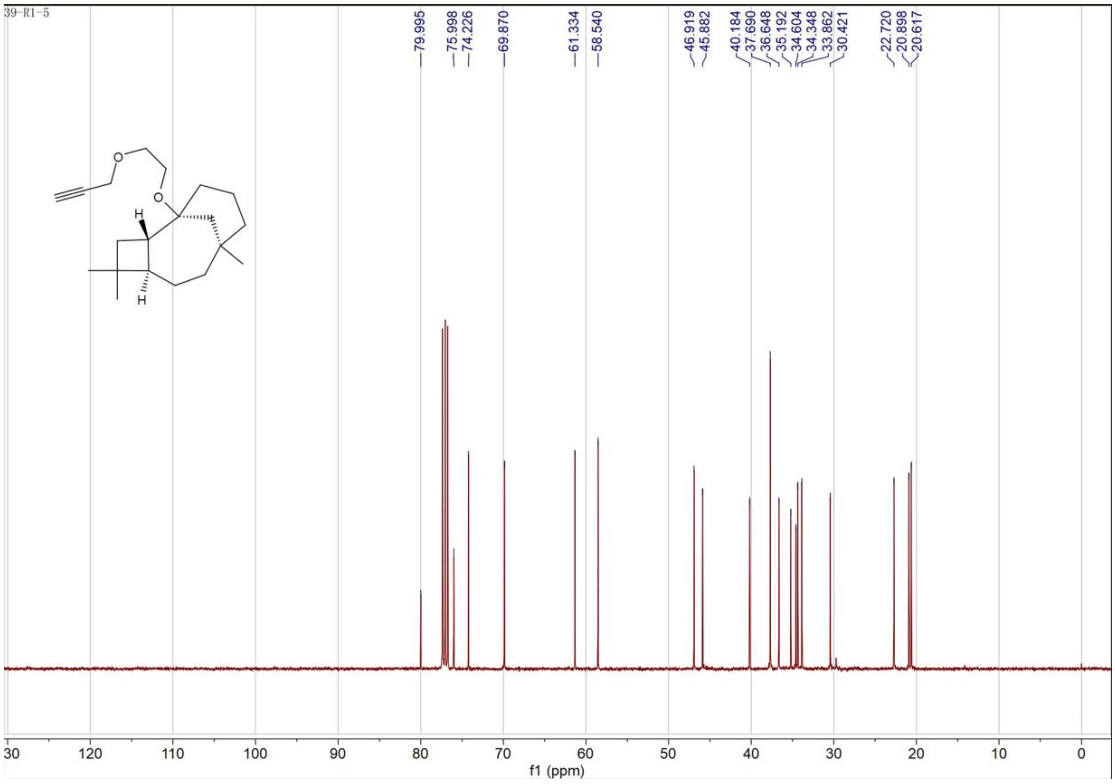
Compound AC-4



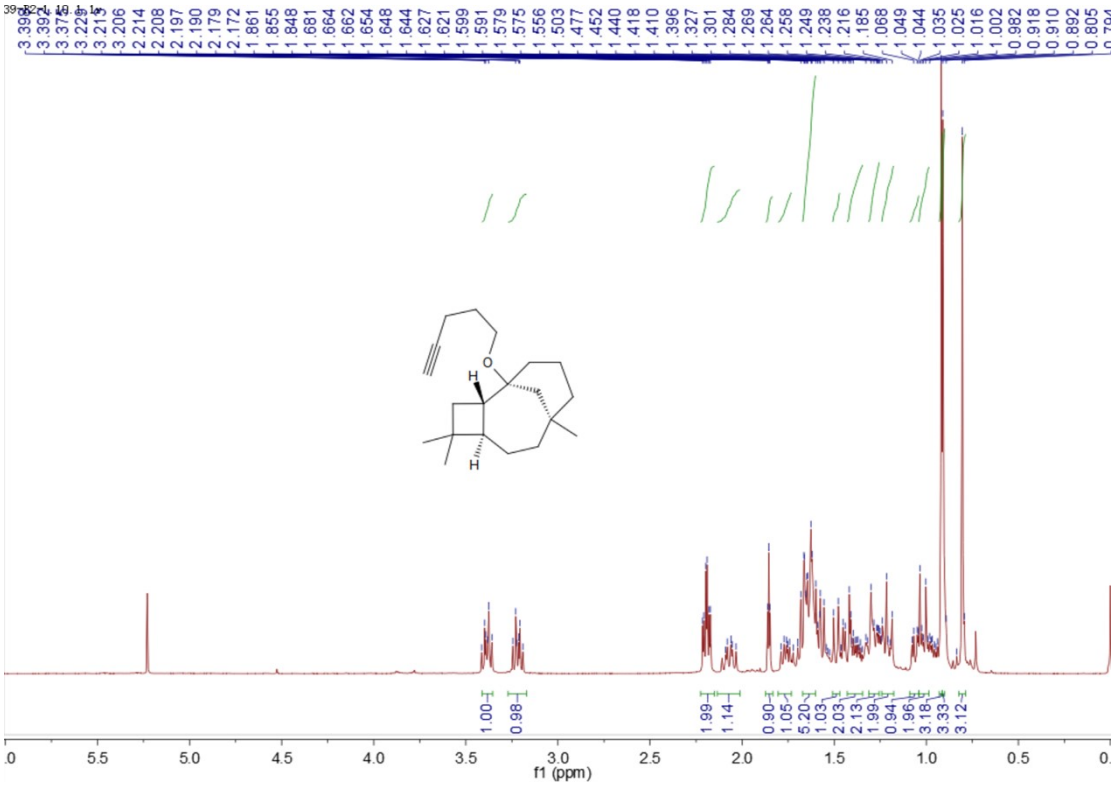


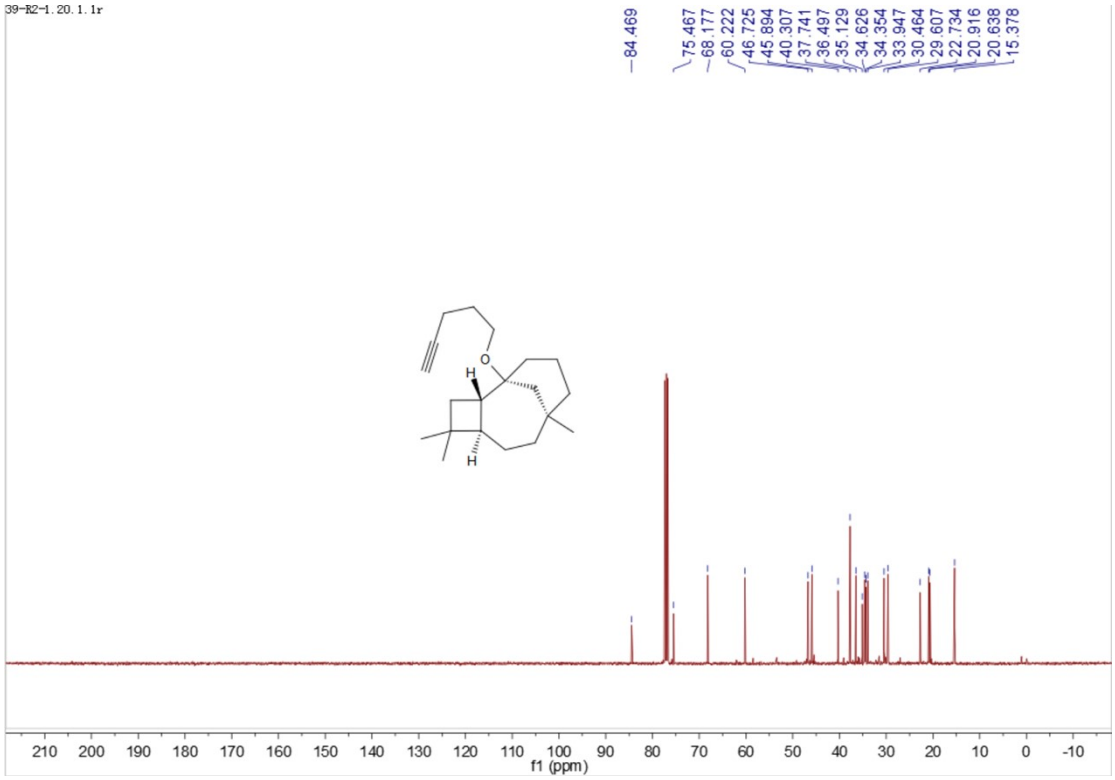
Compound AC-5



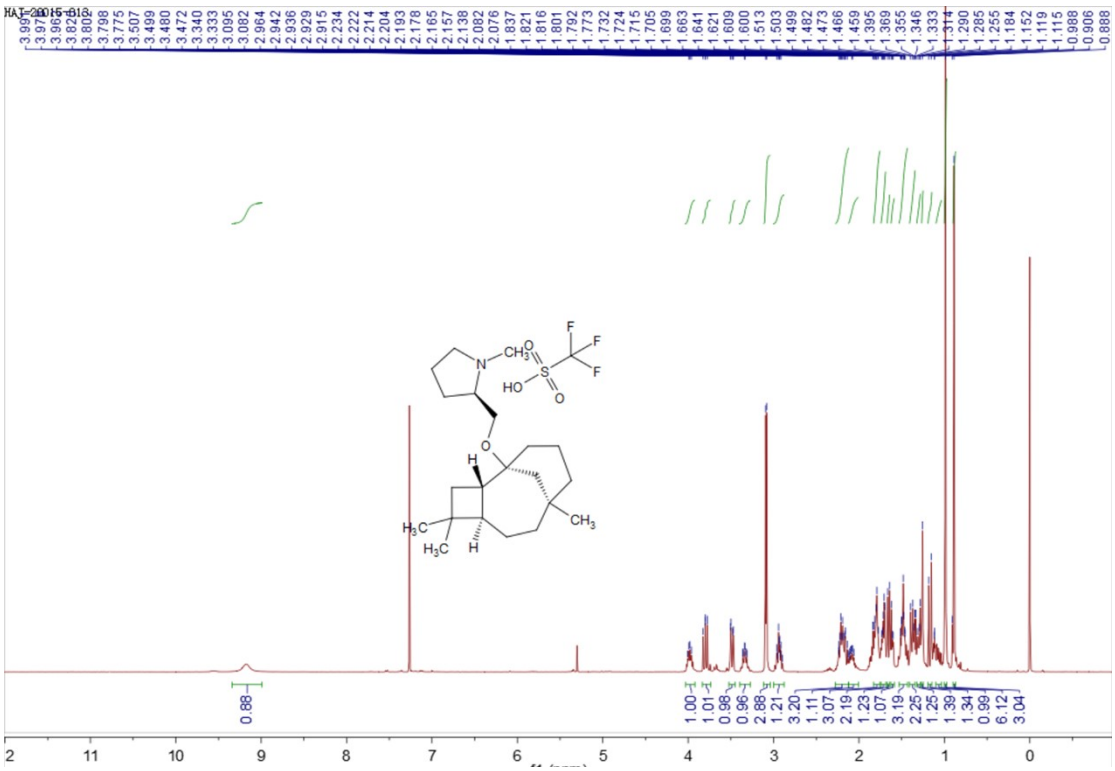


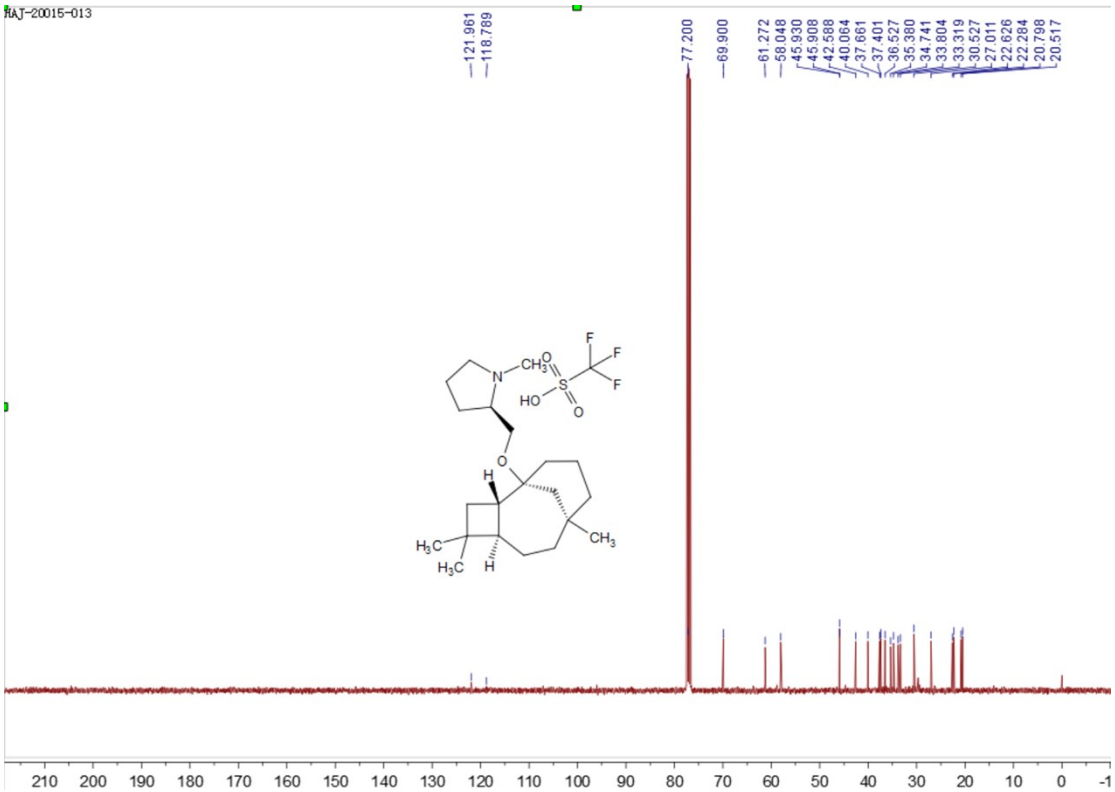
Compound AC-6



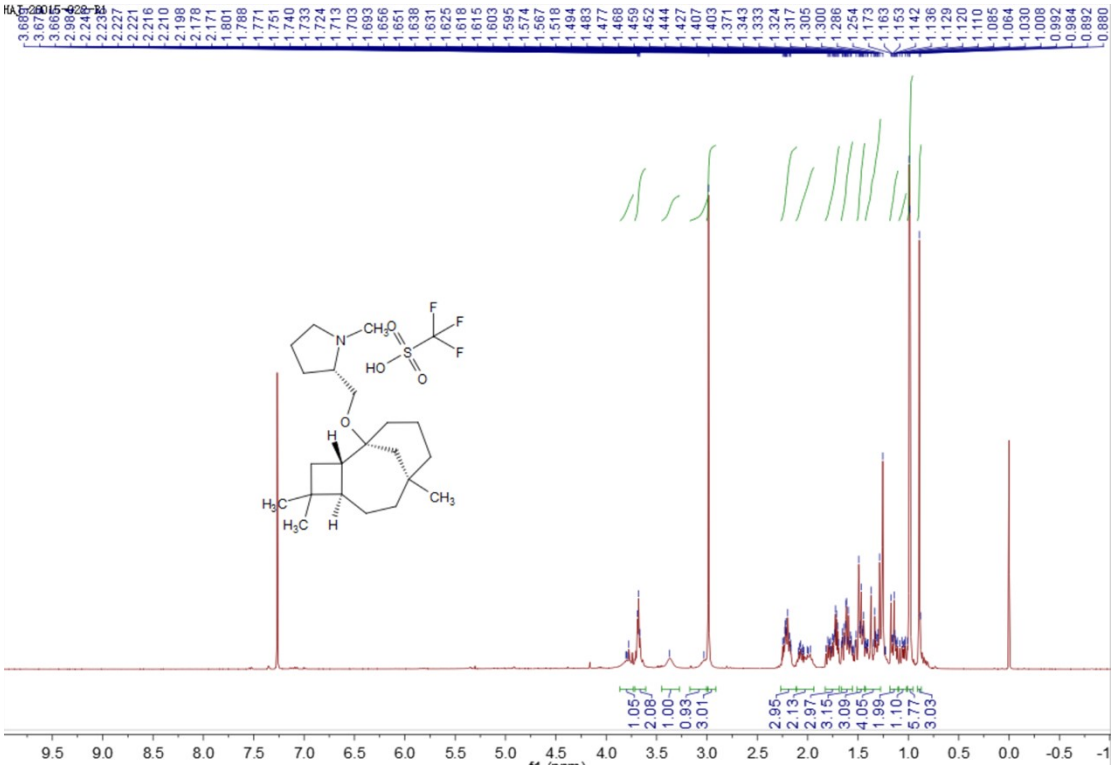


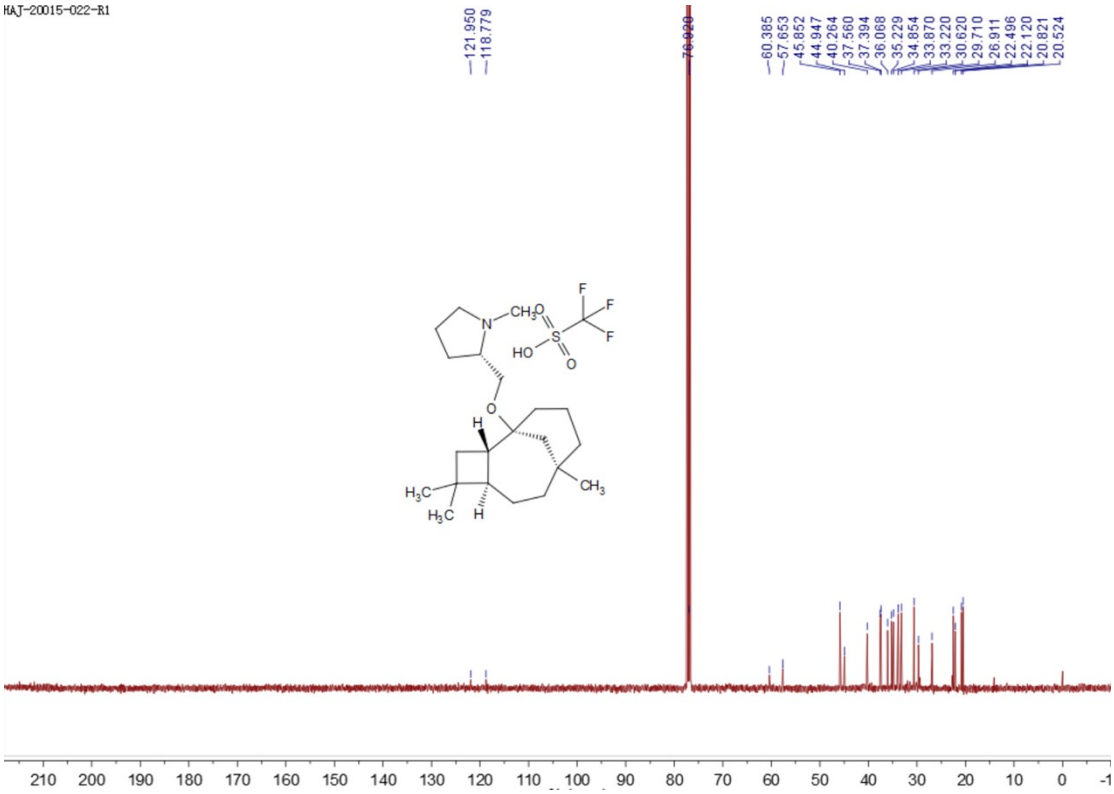
Compound AC-7



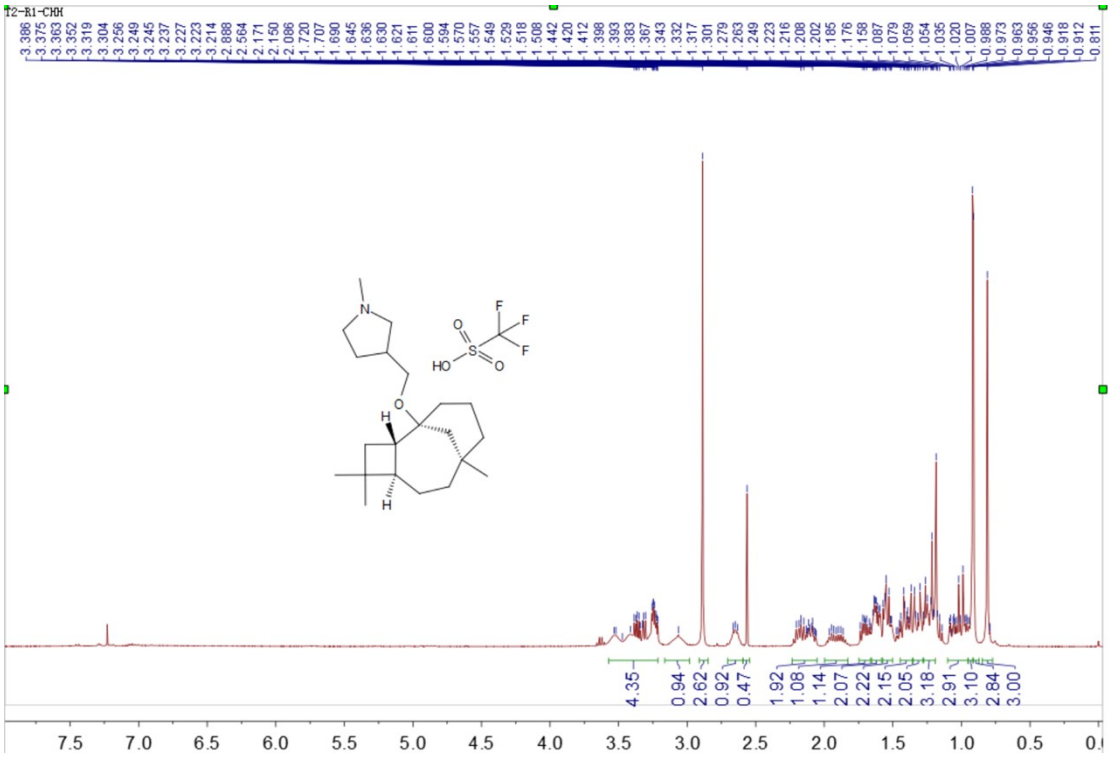


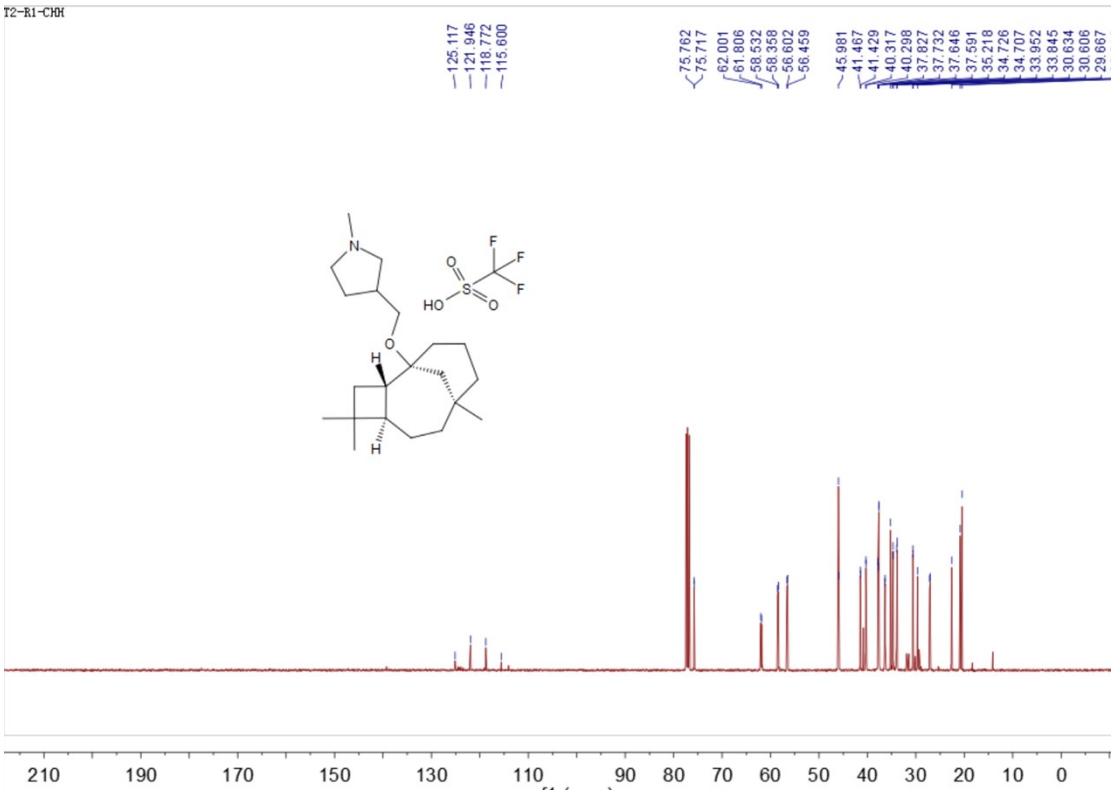
Compound AC-8



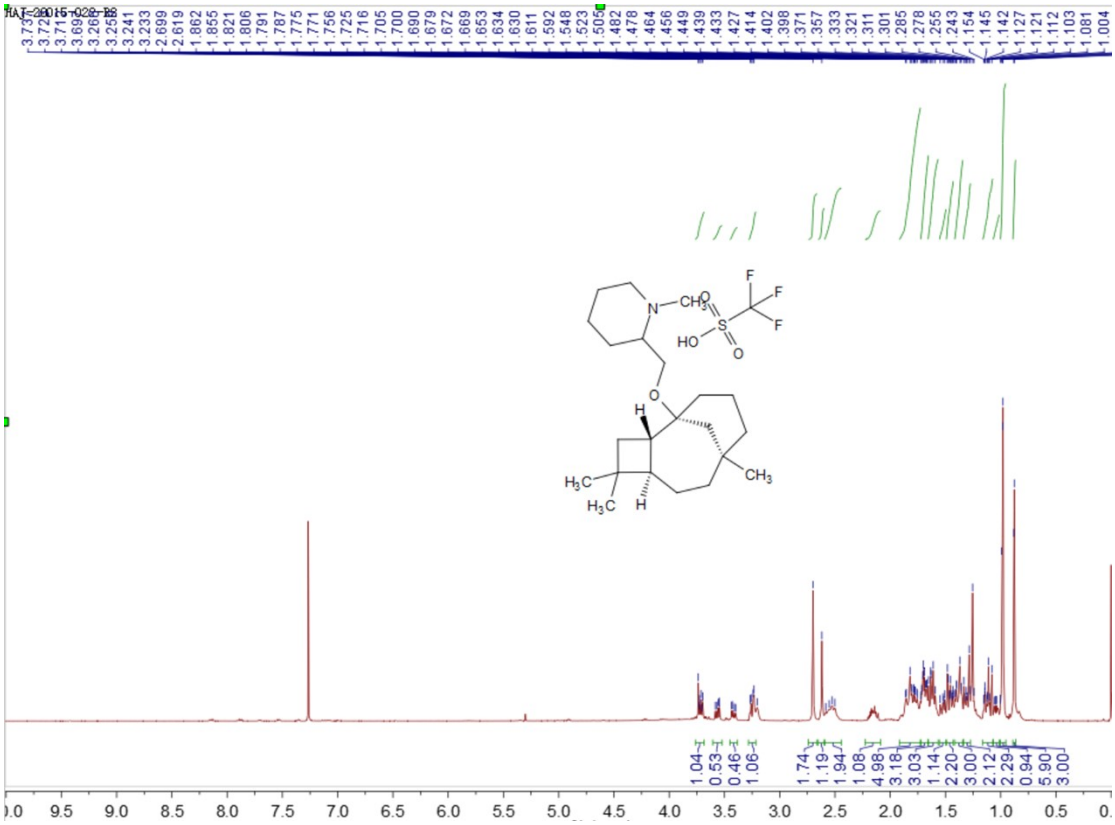


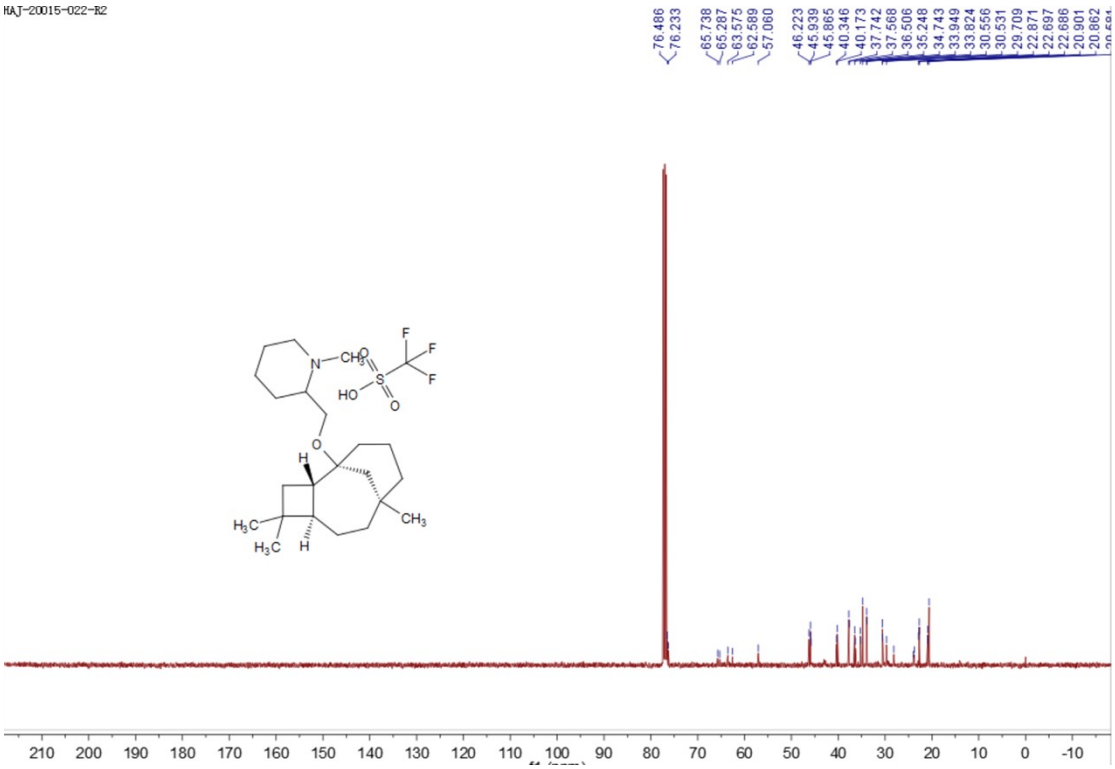
Compound AC-9



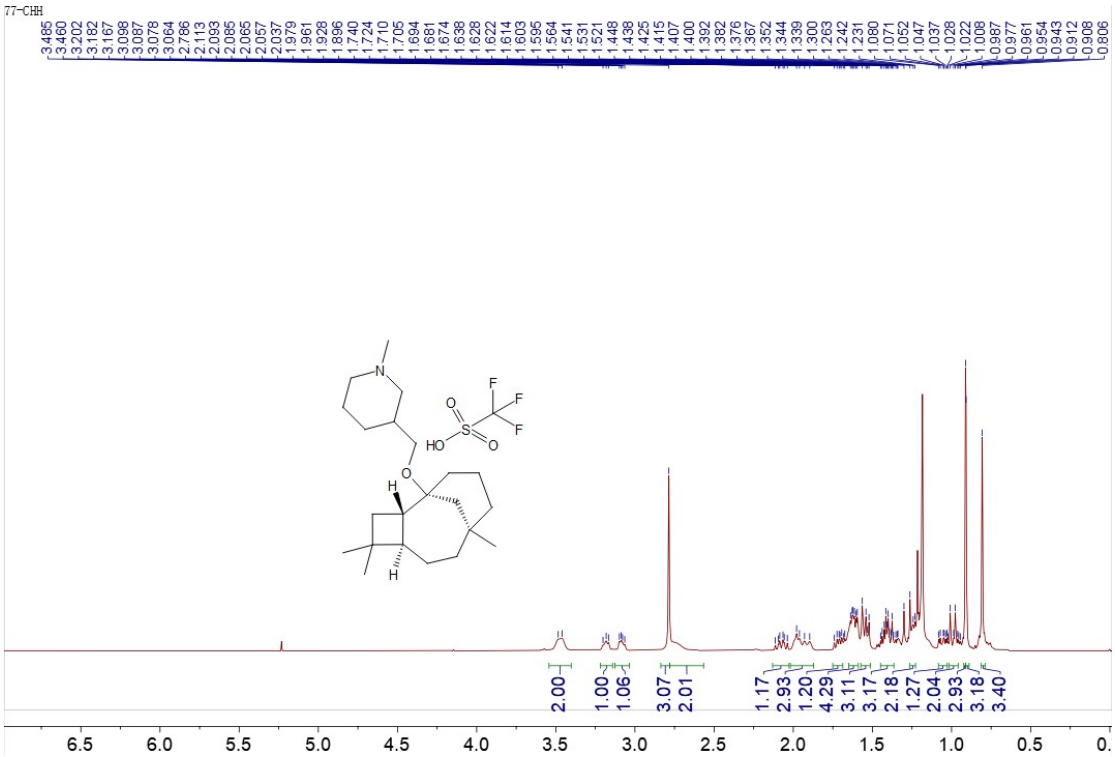


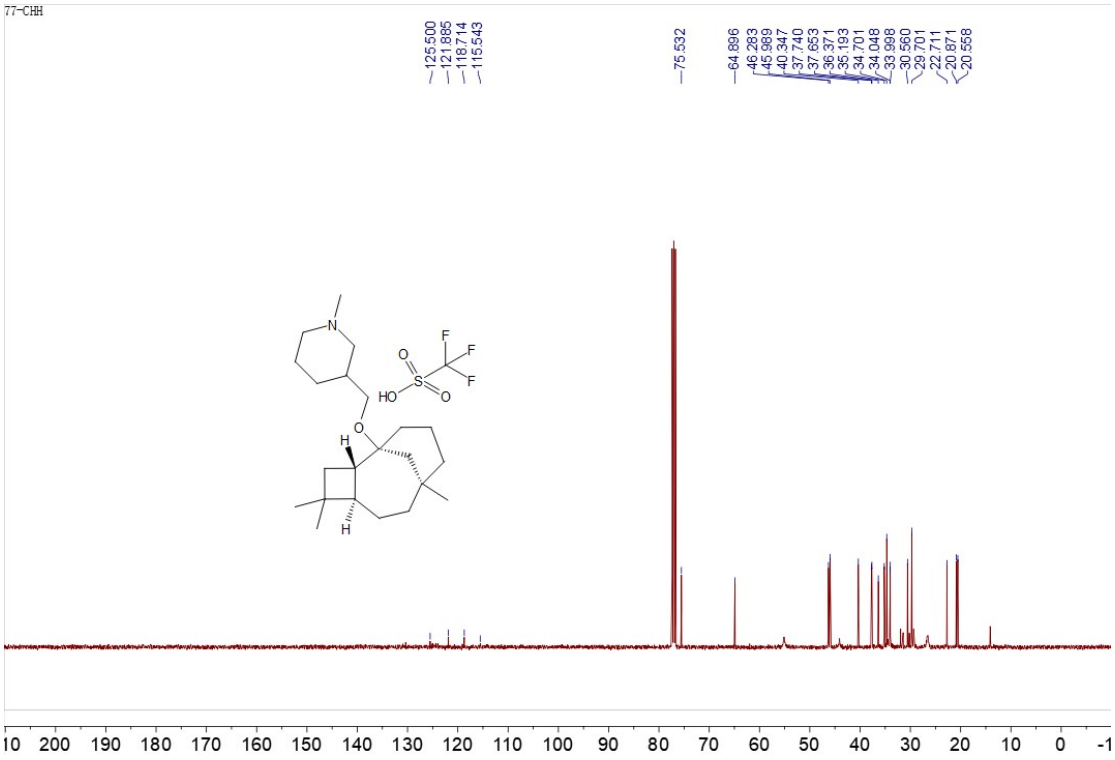
Compound AC-10



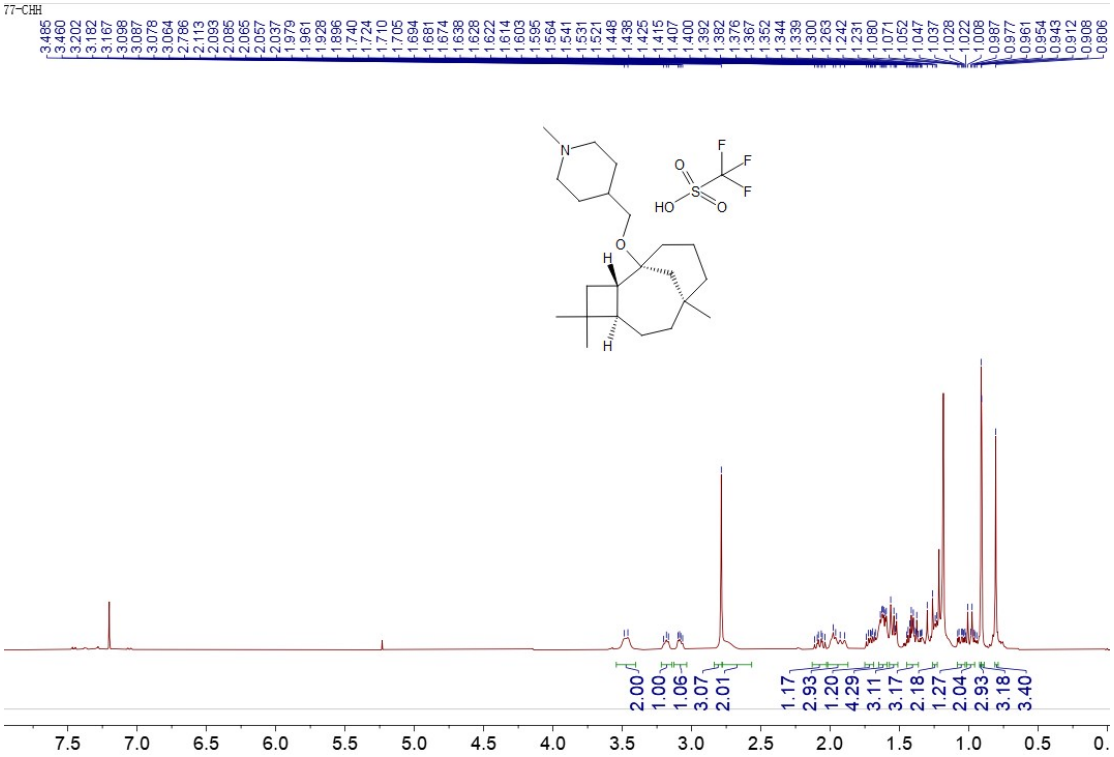


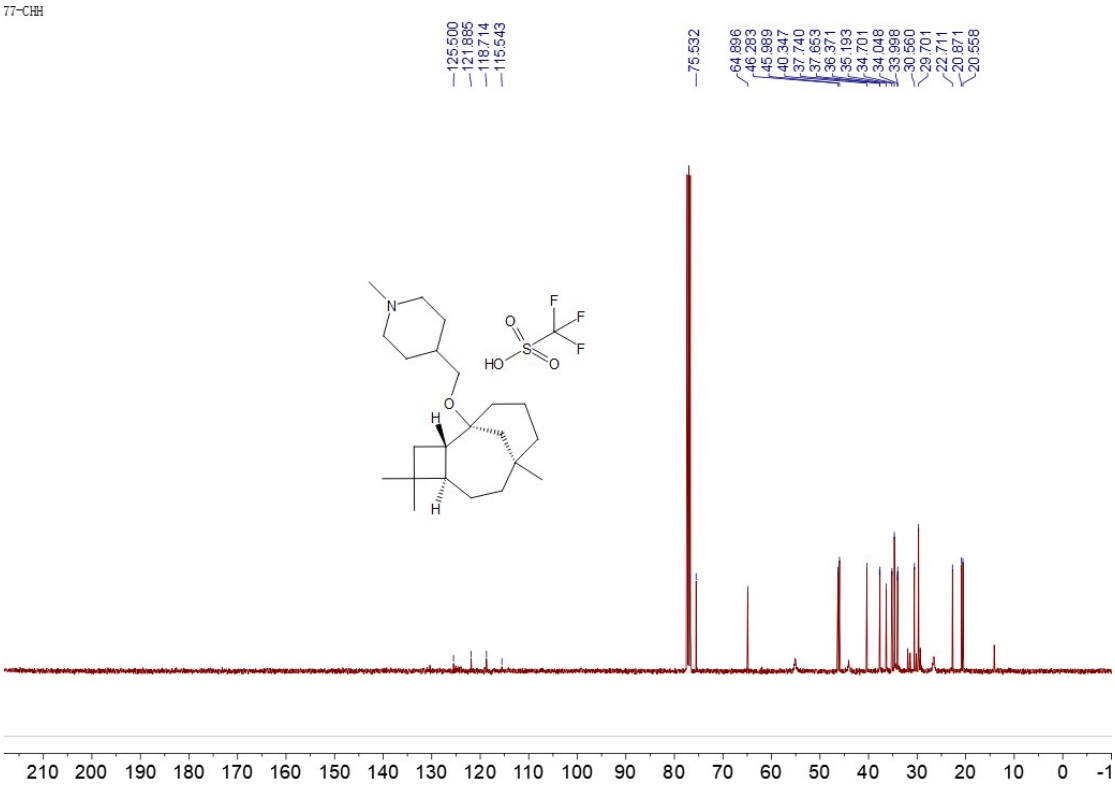
Compound AC-11



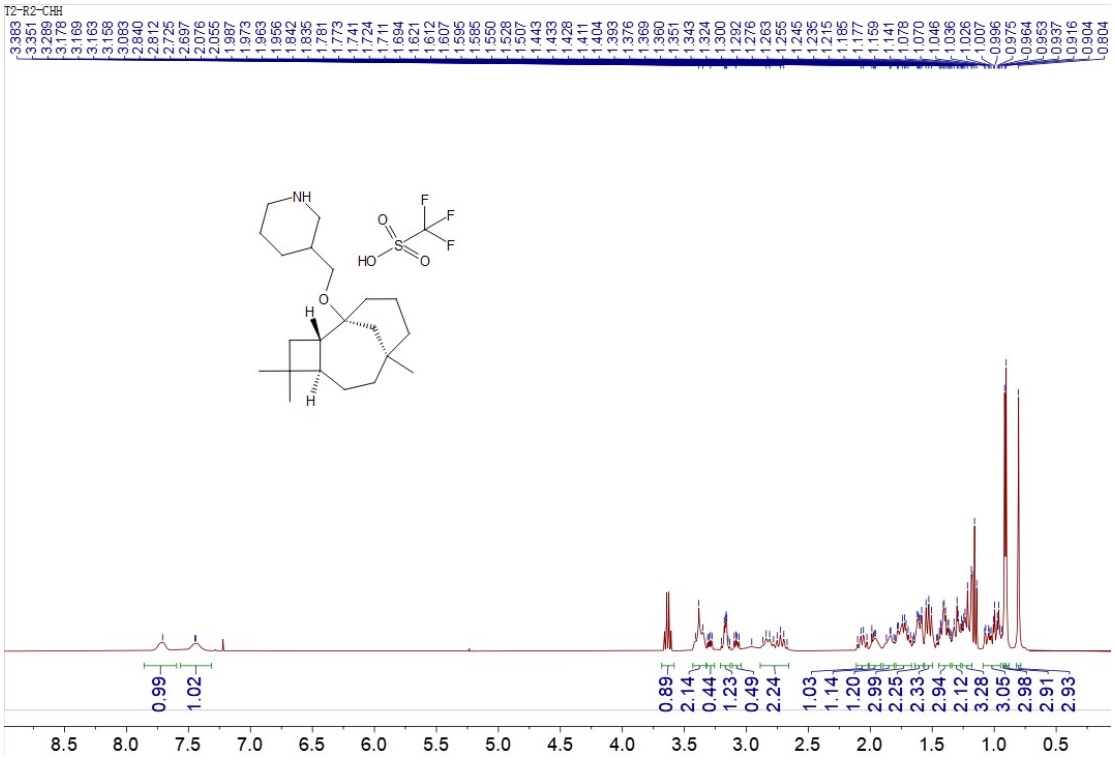


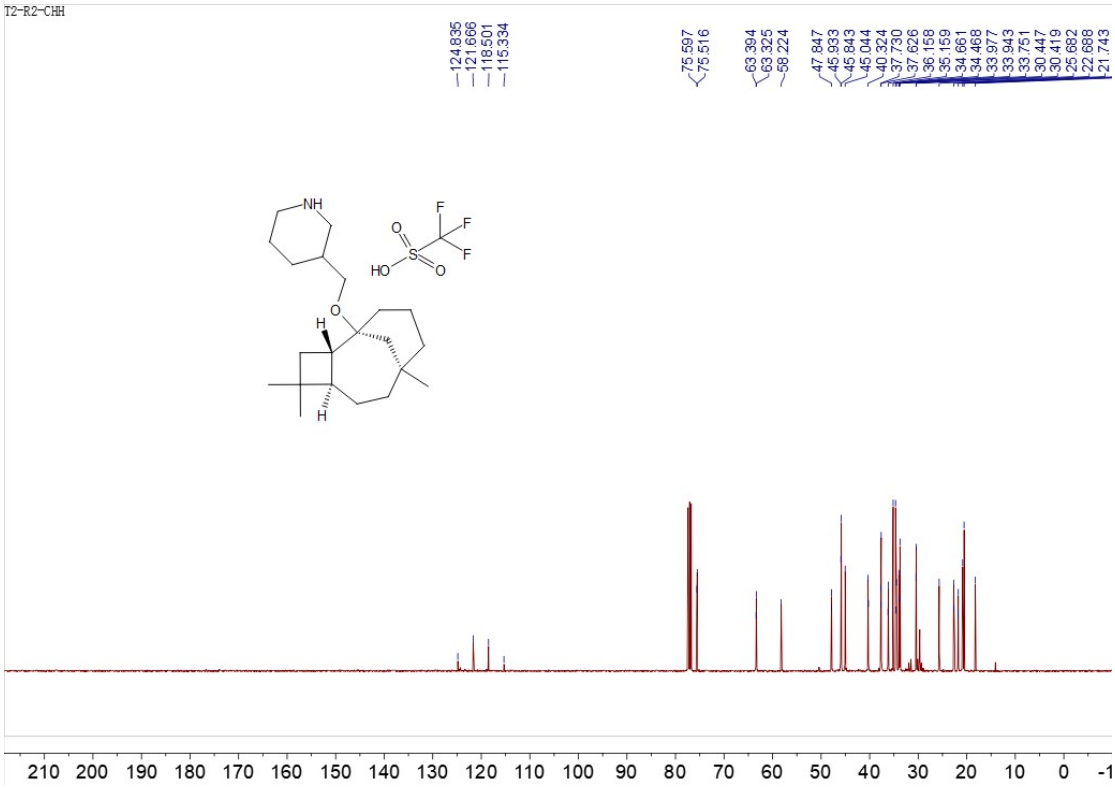
Compound AC-12



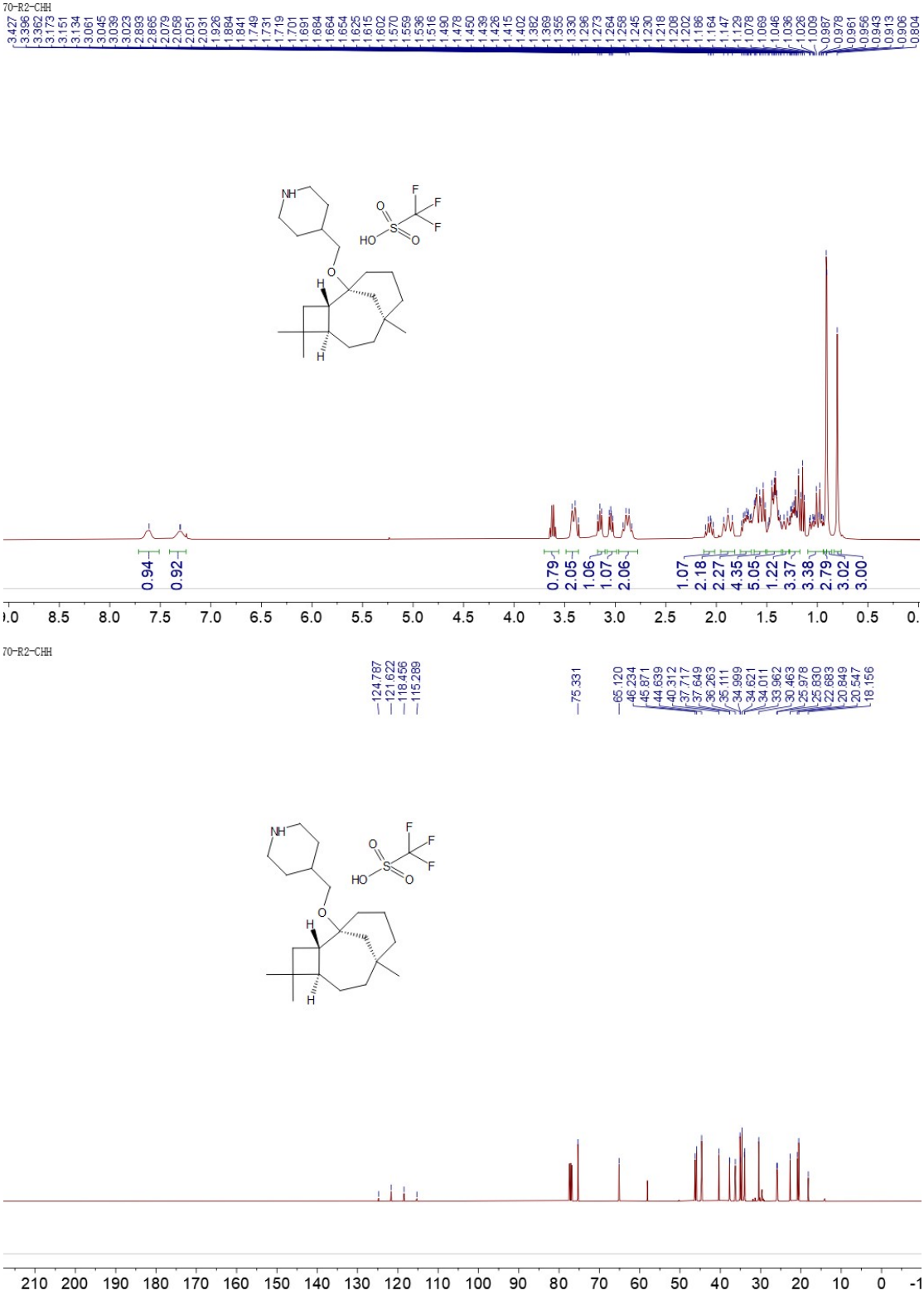


Compound AC-13

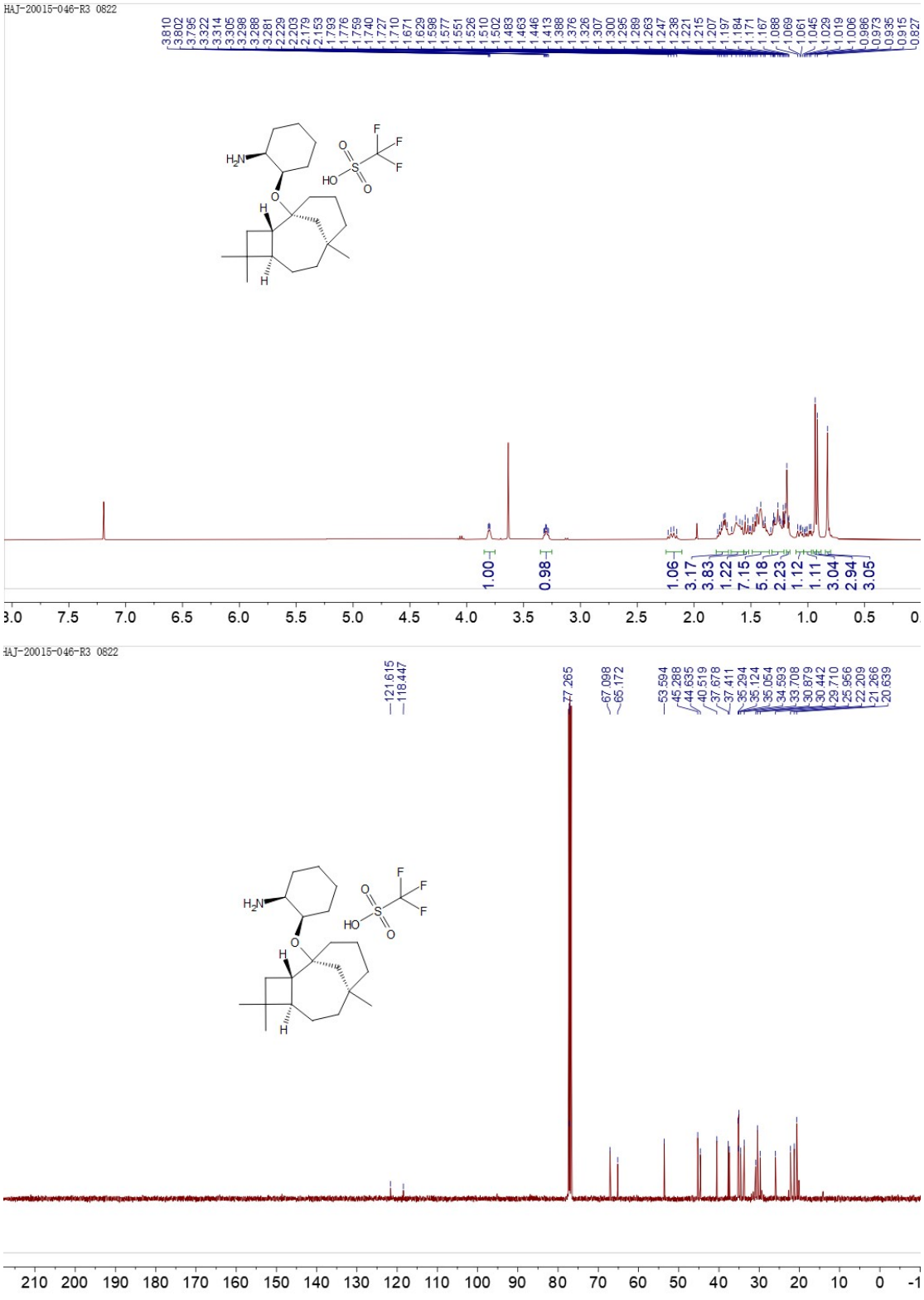




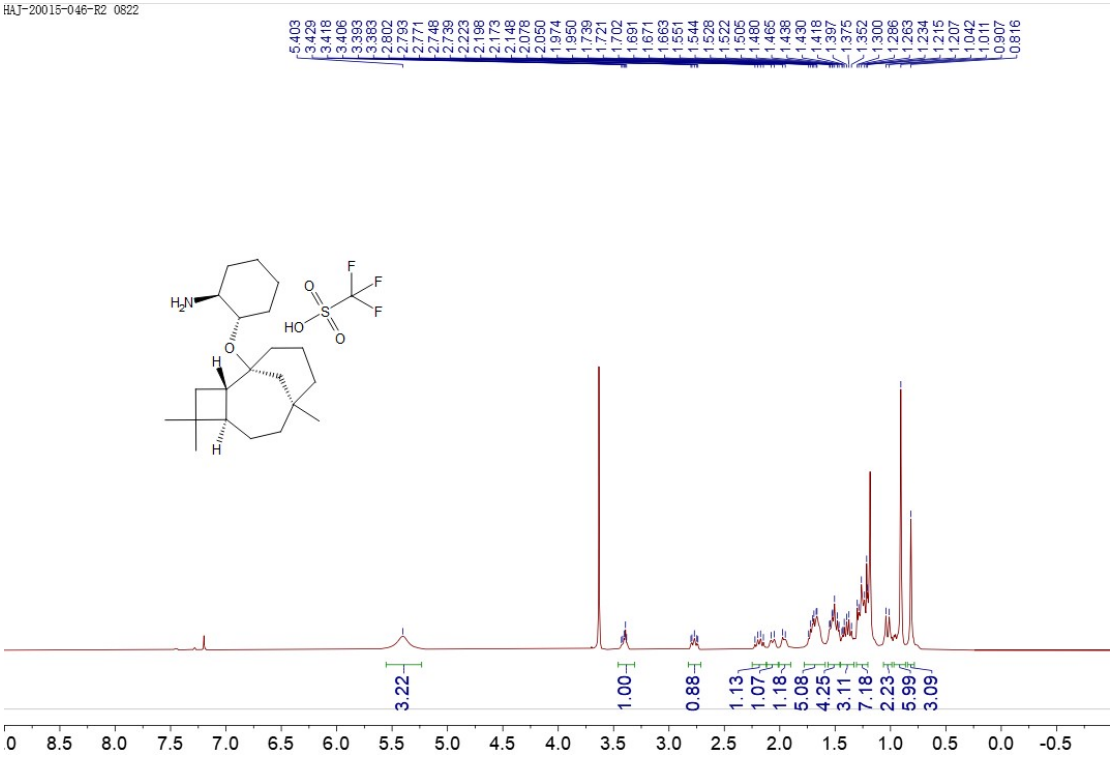
Compound AC-14

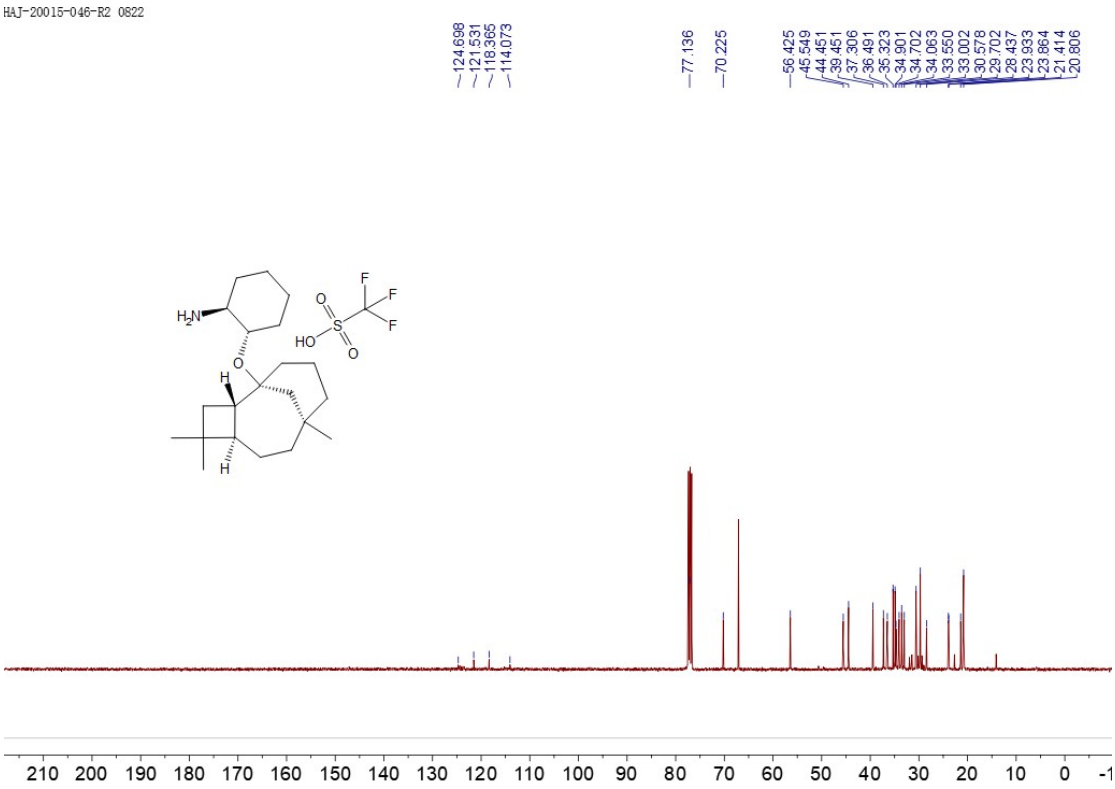


Compound AC-15

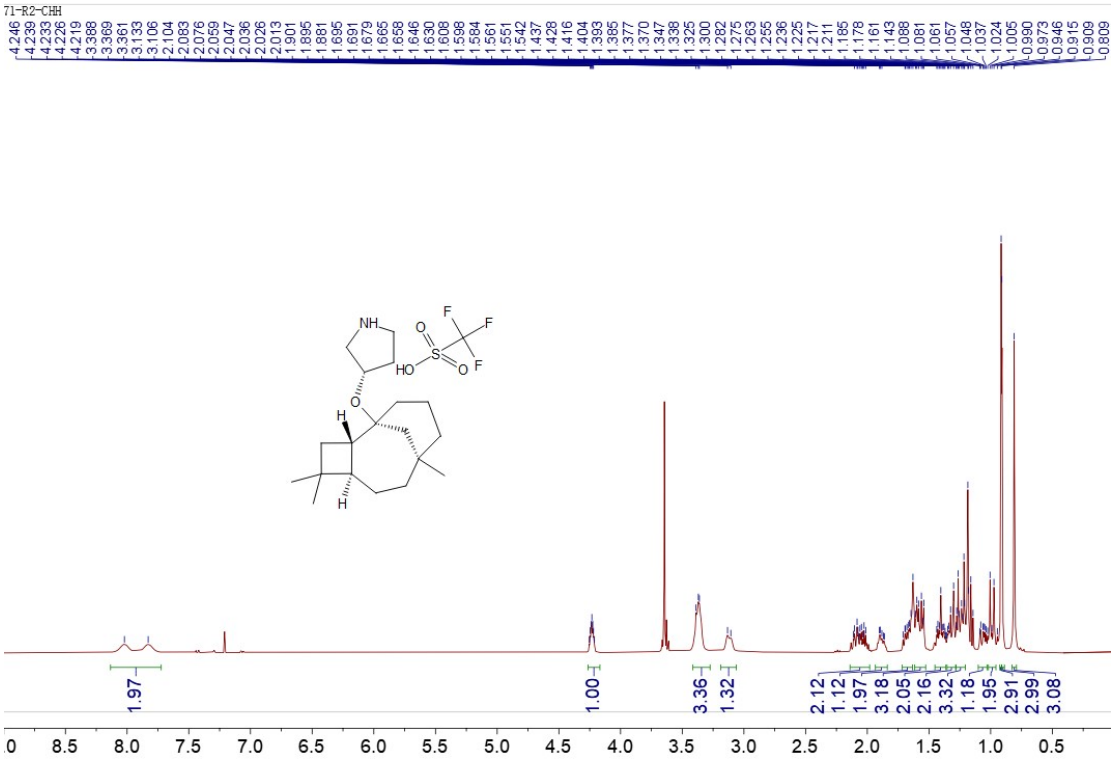


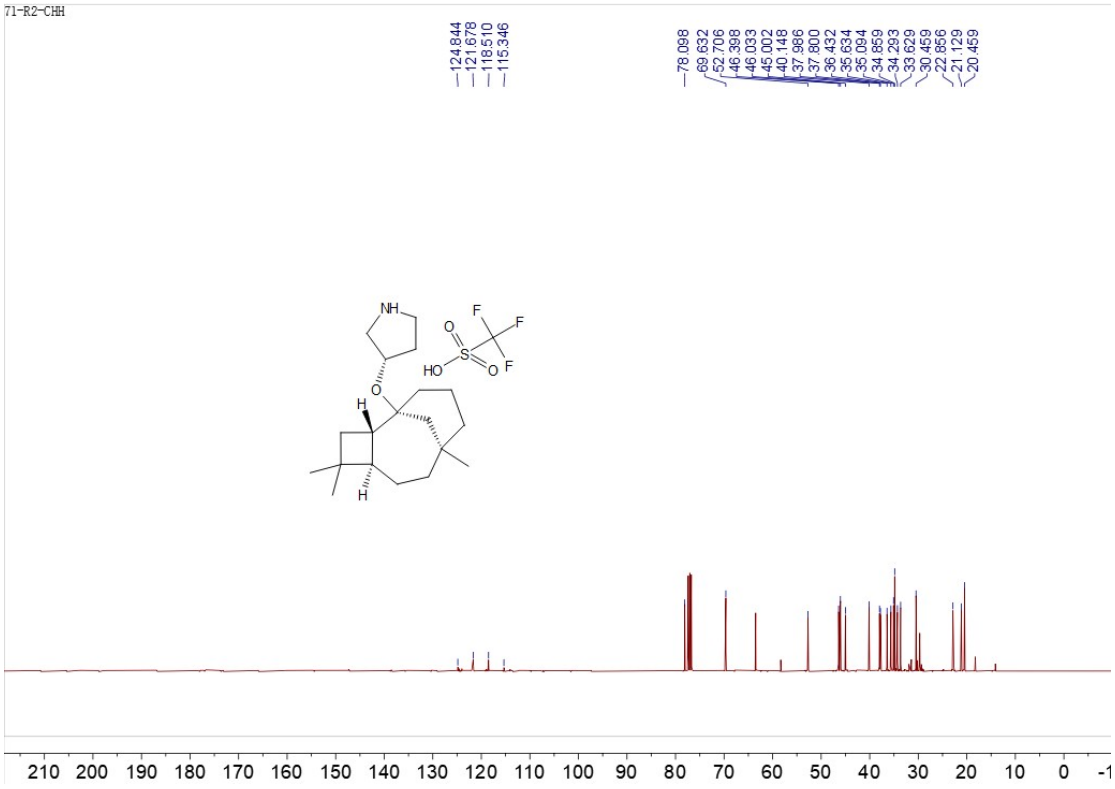
Compound AC-16



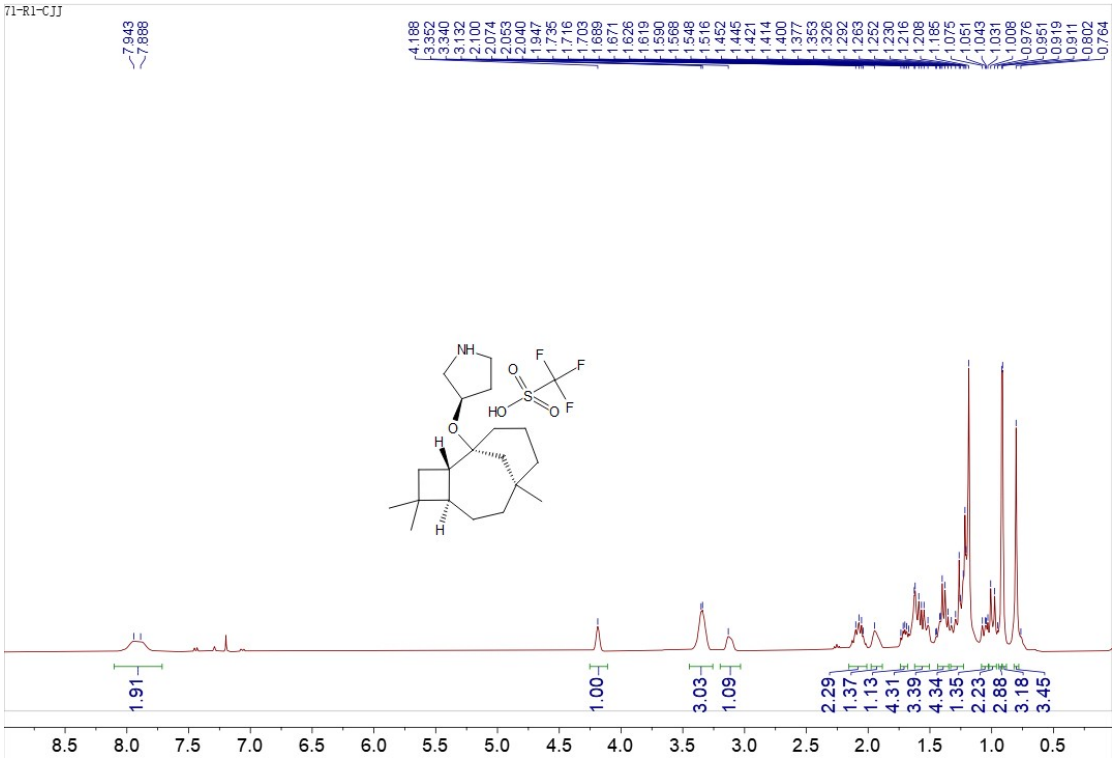


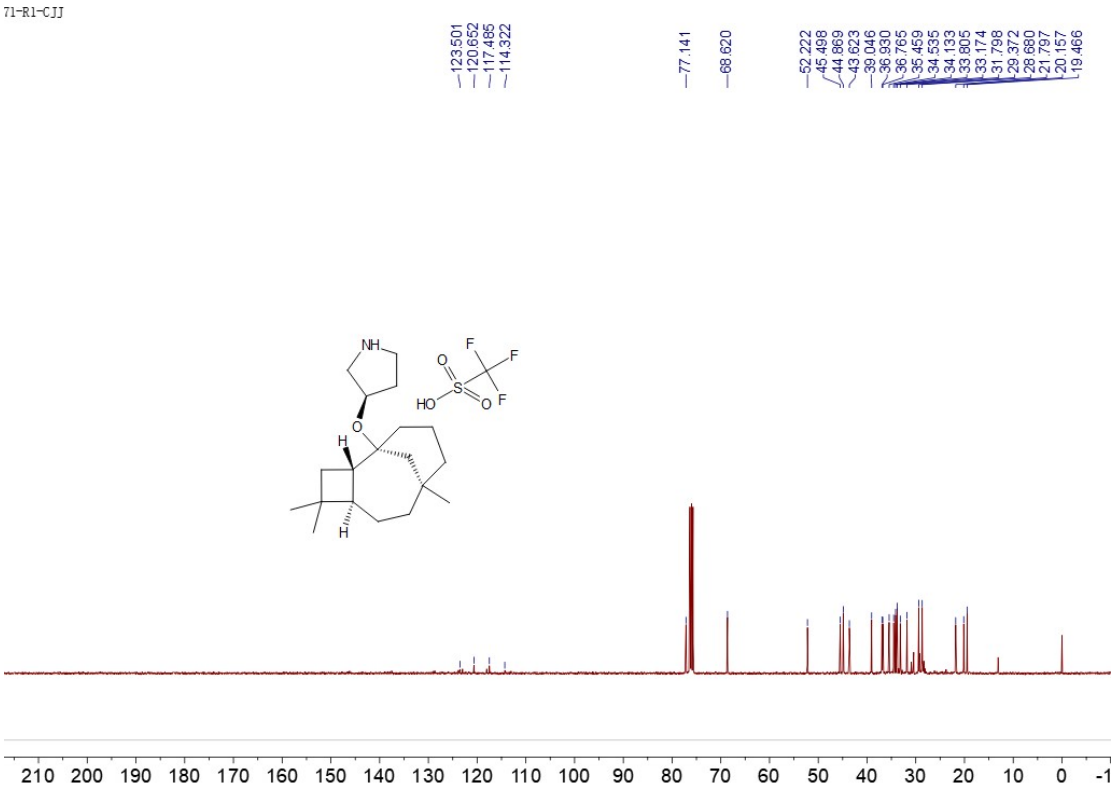
Compound AC-17



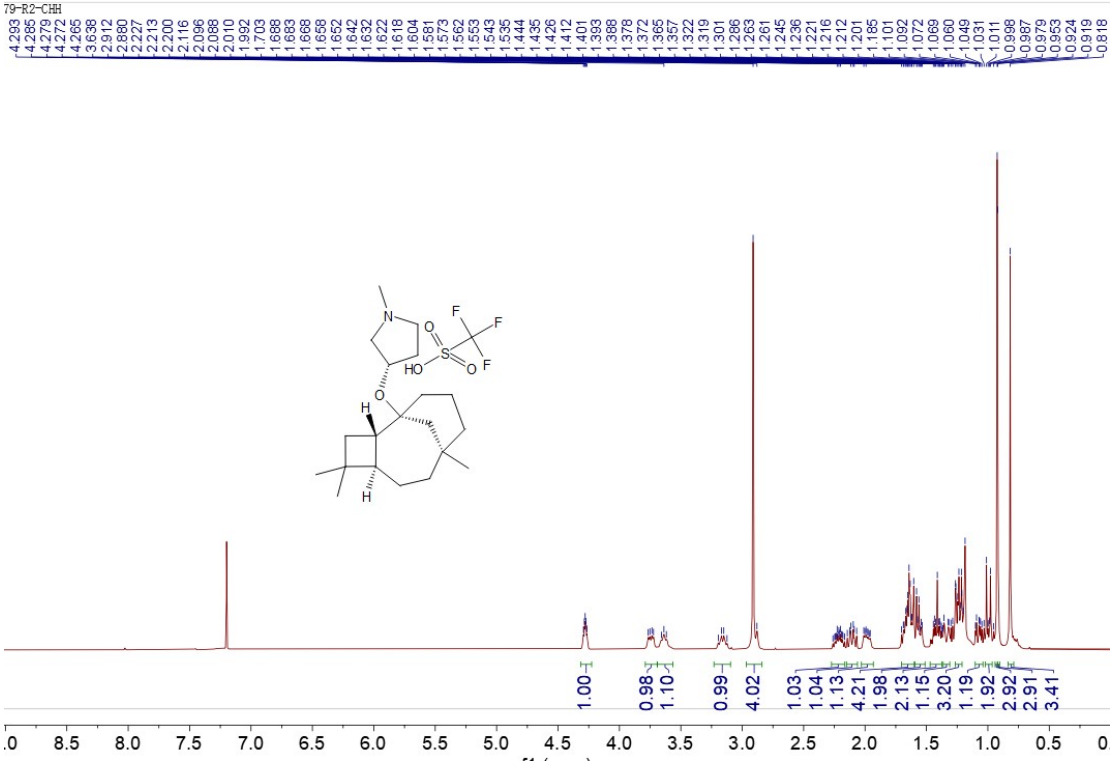


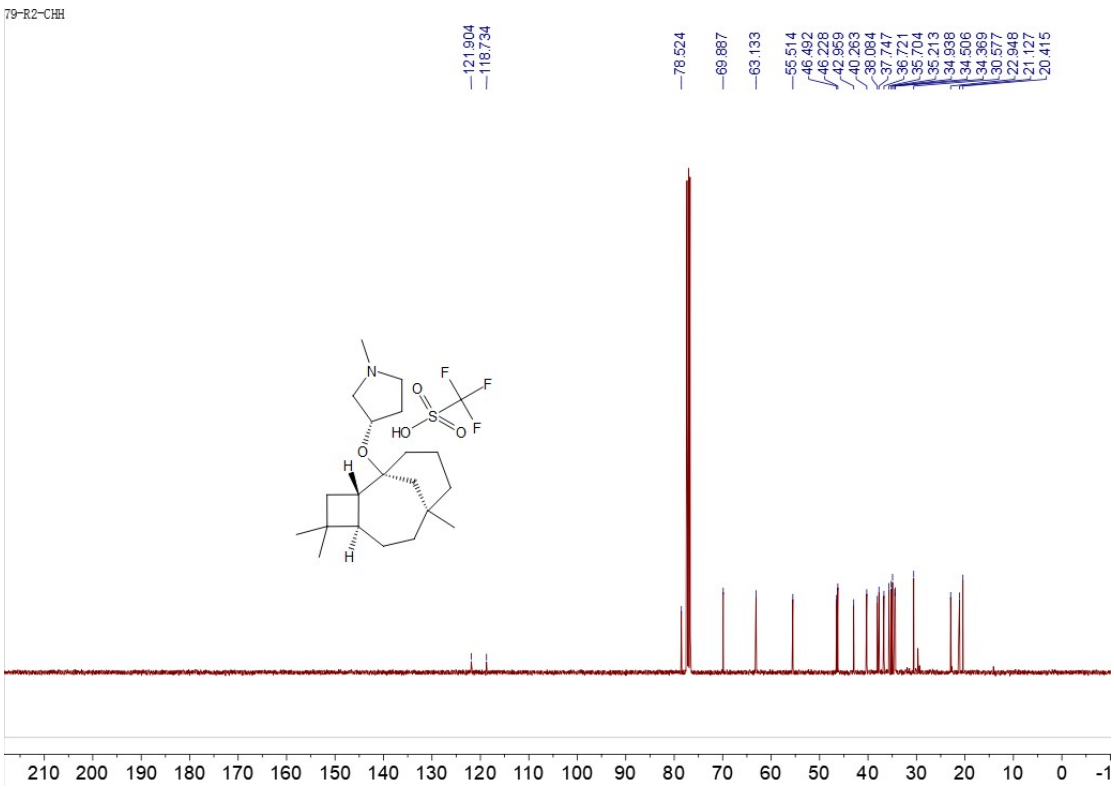
Compound AC-18



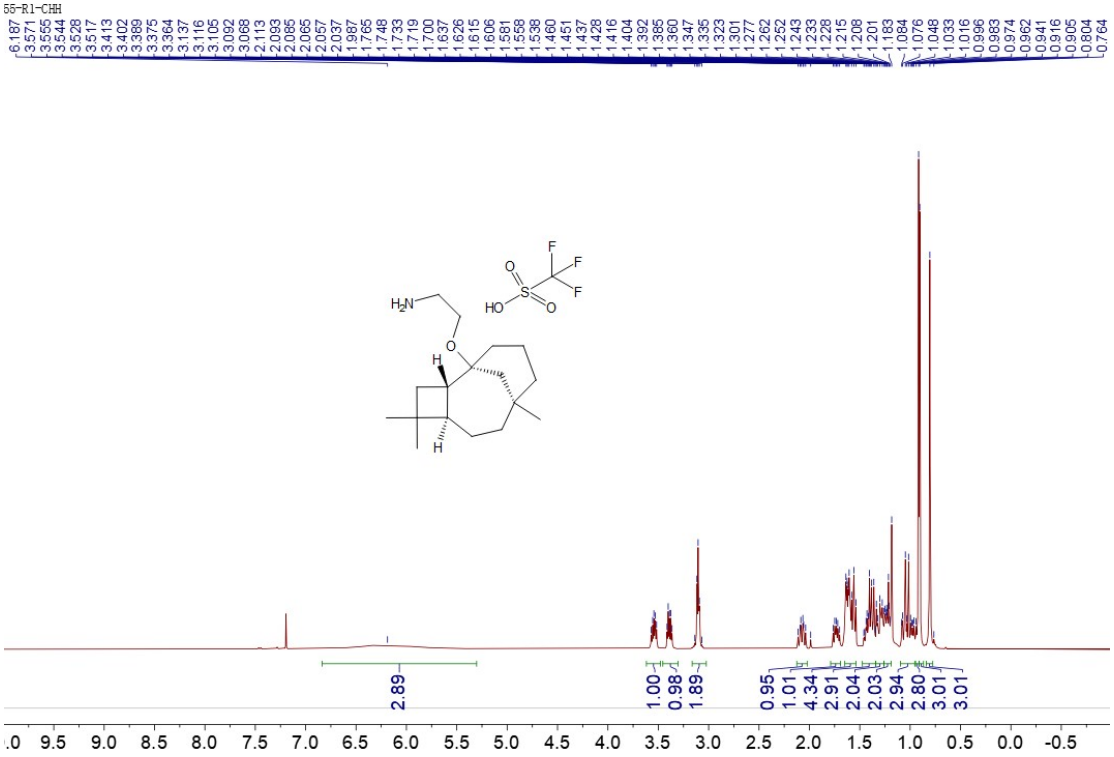


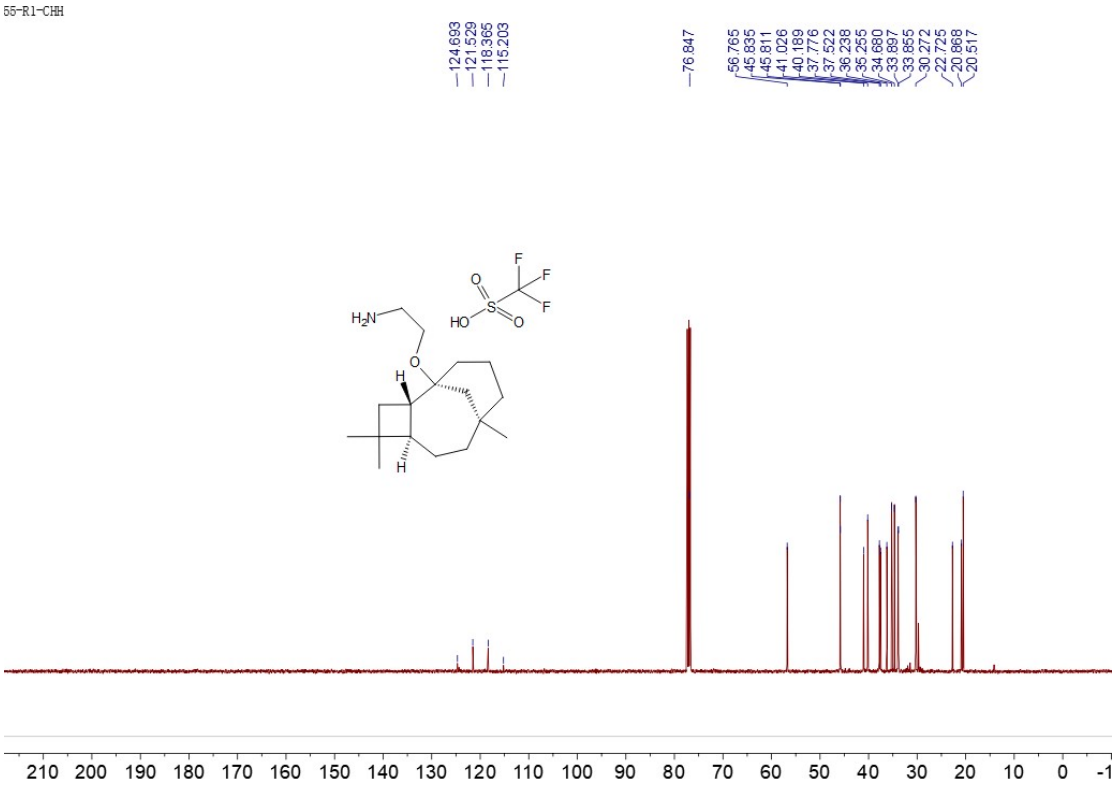
Compound AC-19



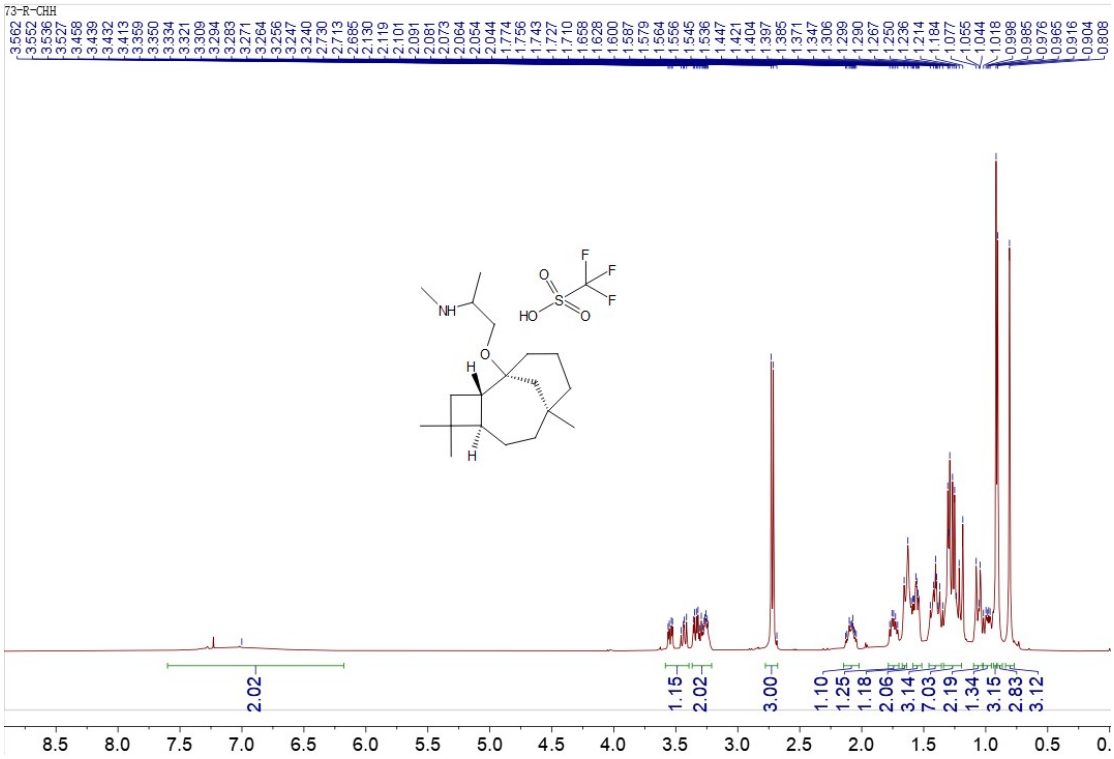


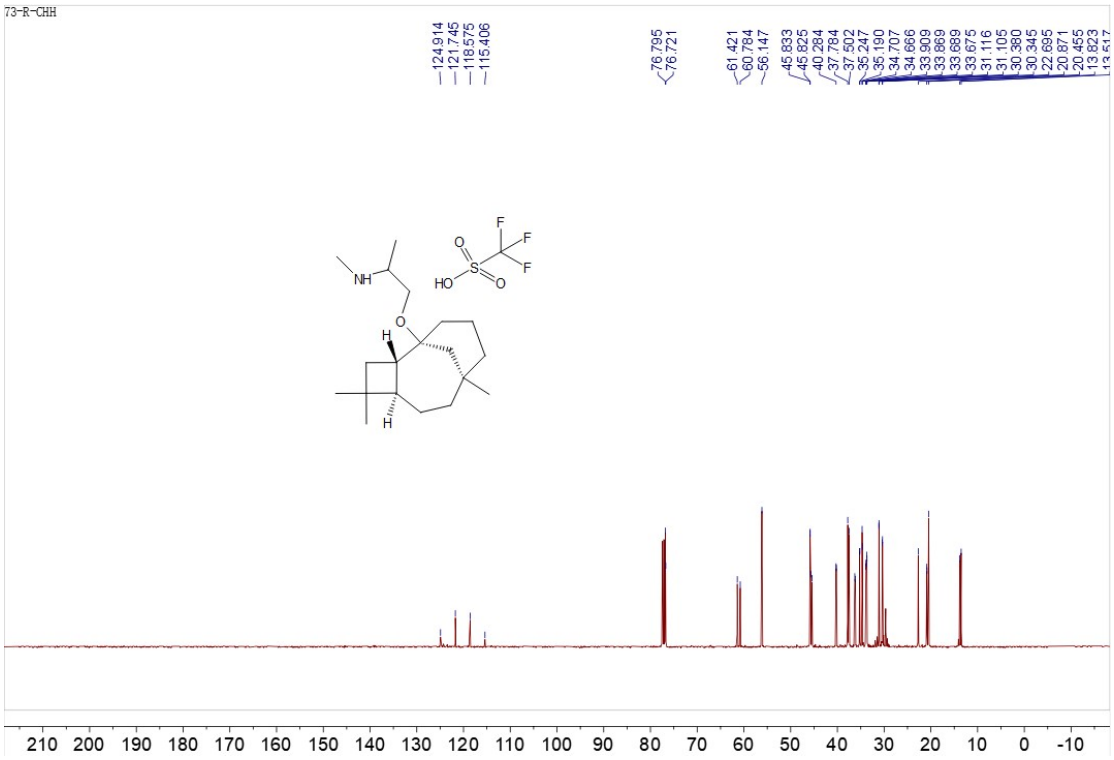
Compound AC-20



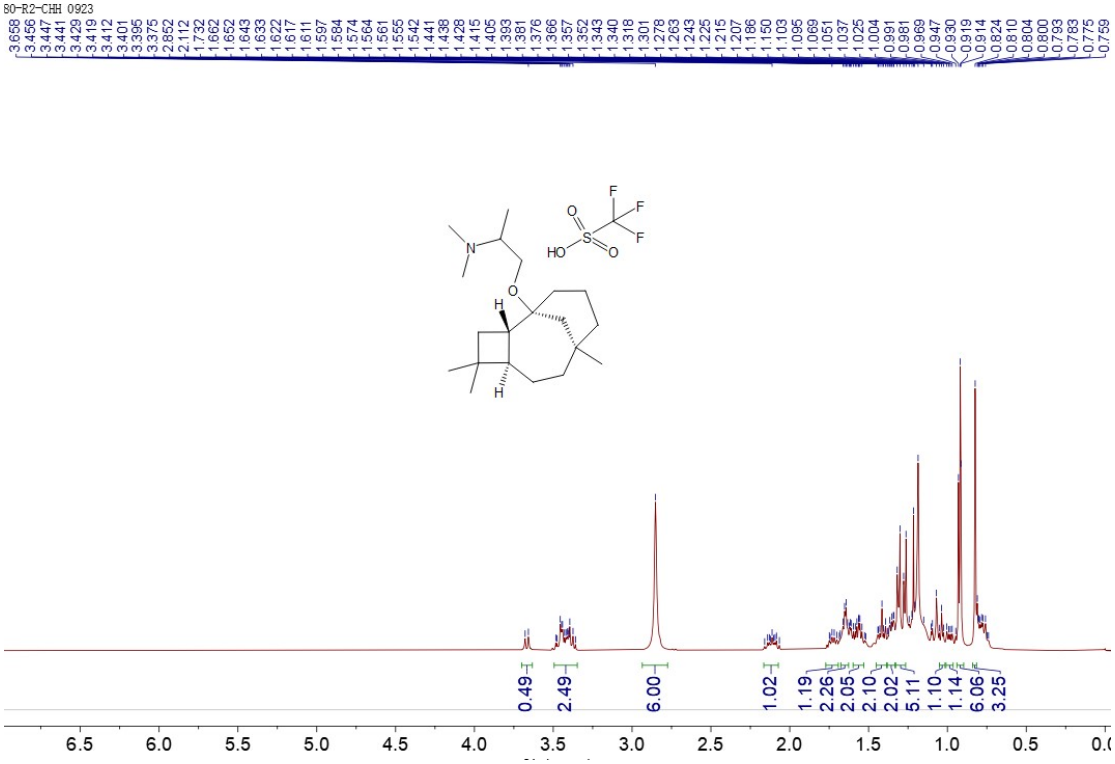


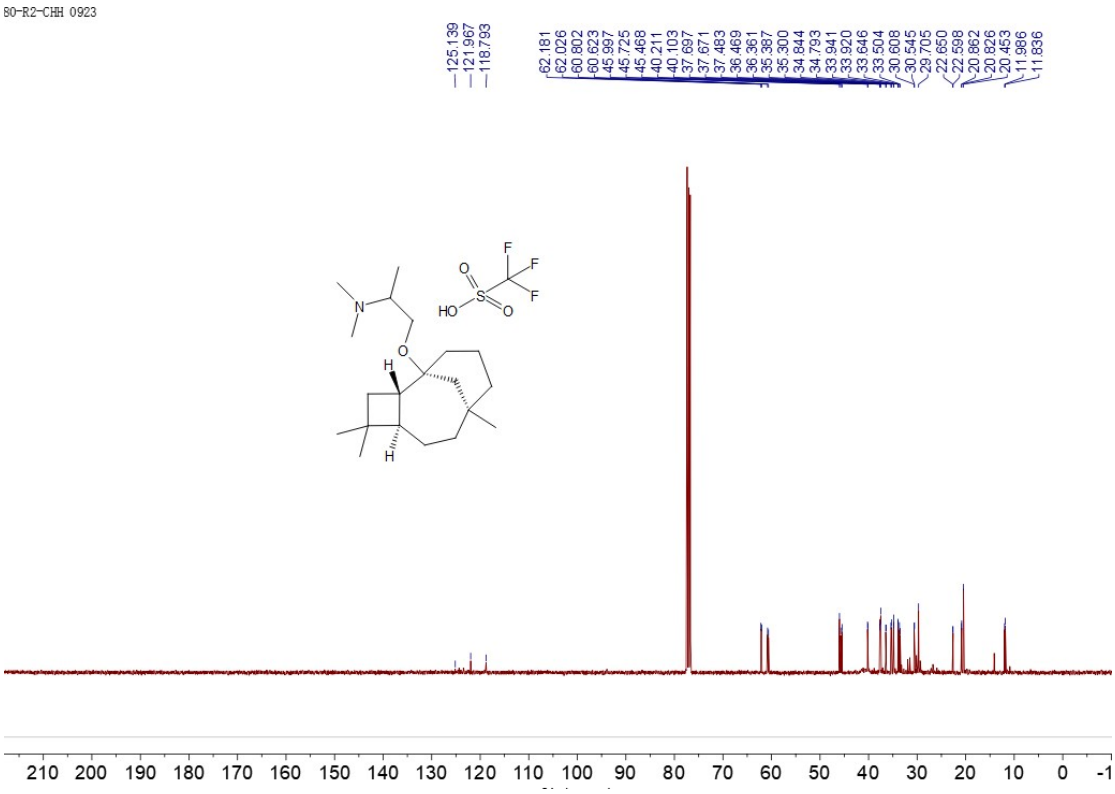
Compound AC-21





Compound AC-22





Compound AC-23

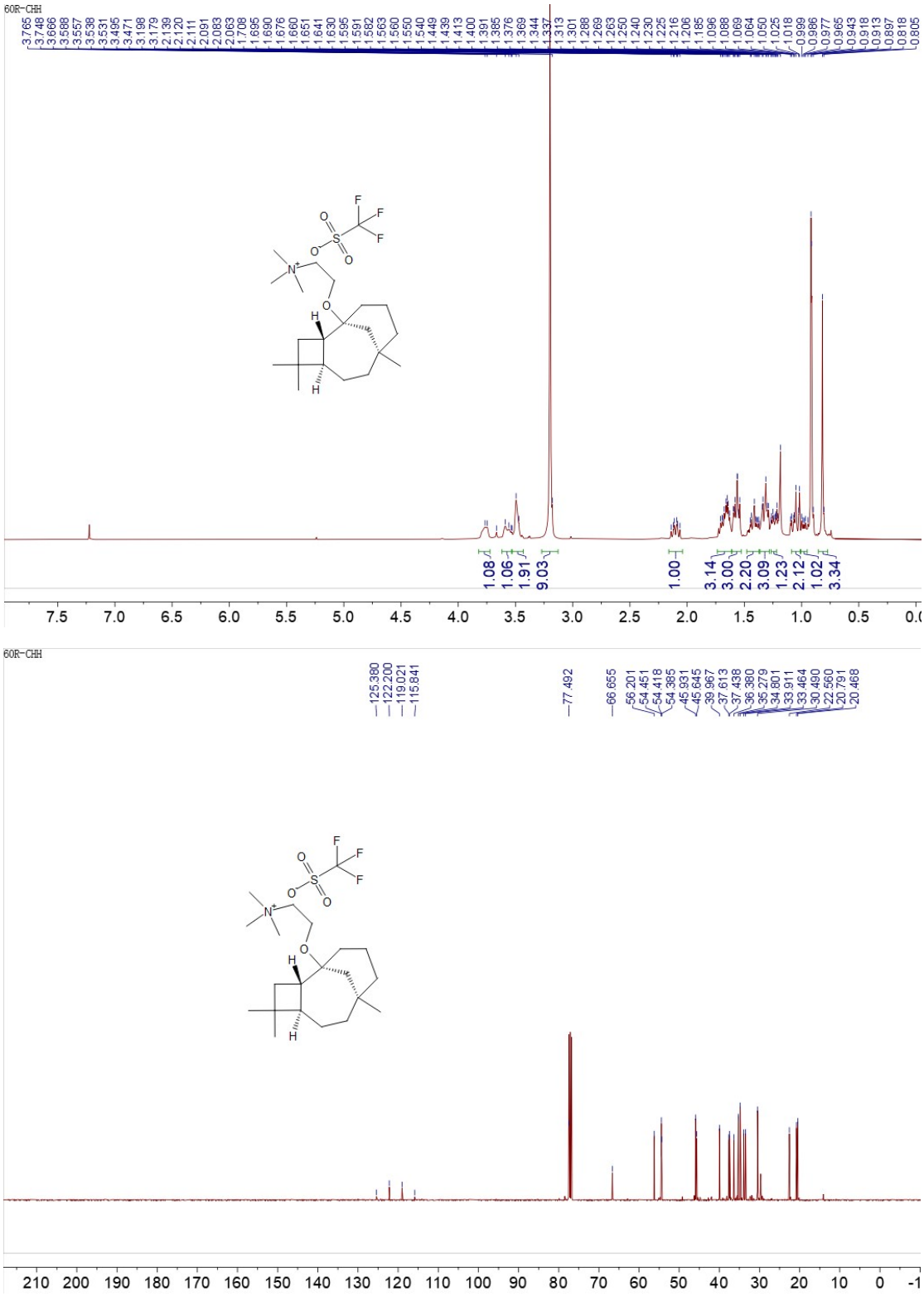
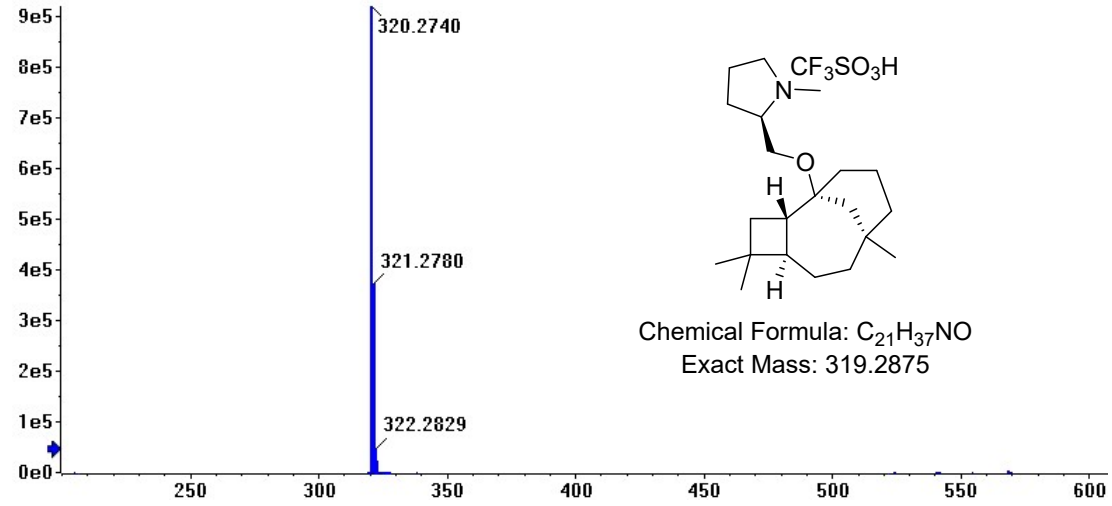
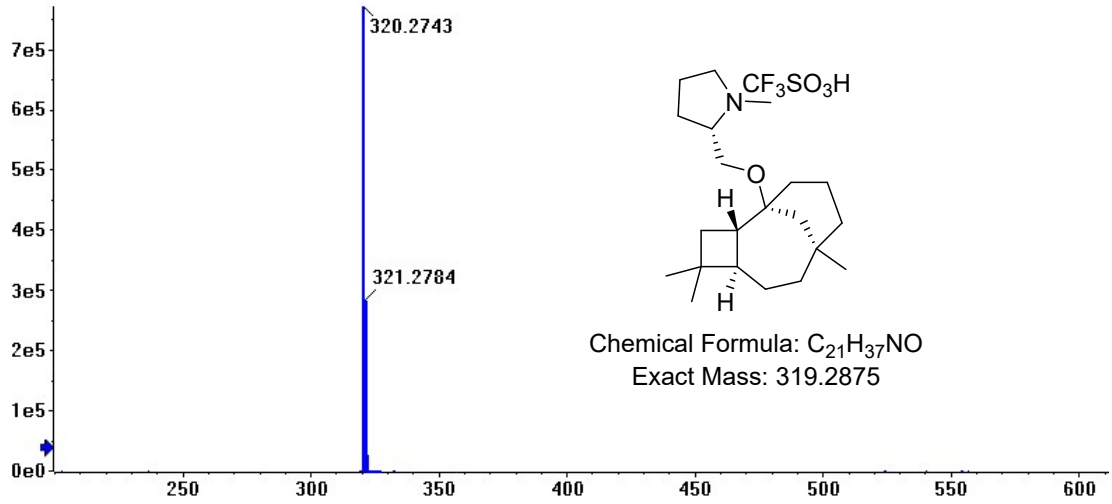


Fig S2. ^{1}H and ^{13}C NMR spectra of AC-1 to AC-23.

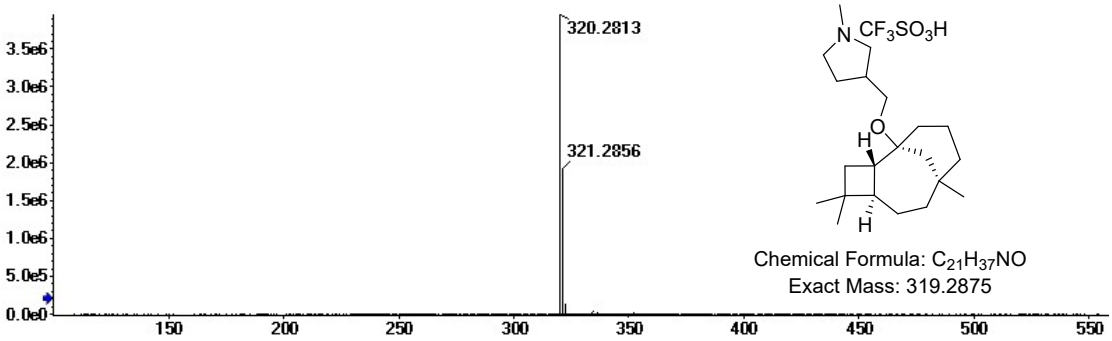
AC-7


320.2740
321.2780
322.2829
CF3SO3H
N
O
H
H
Chemical Formula: C21H37NO
Exact Mass: 319.2875

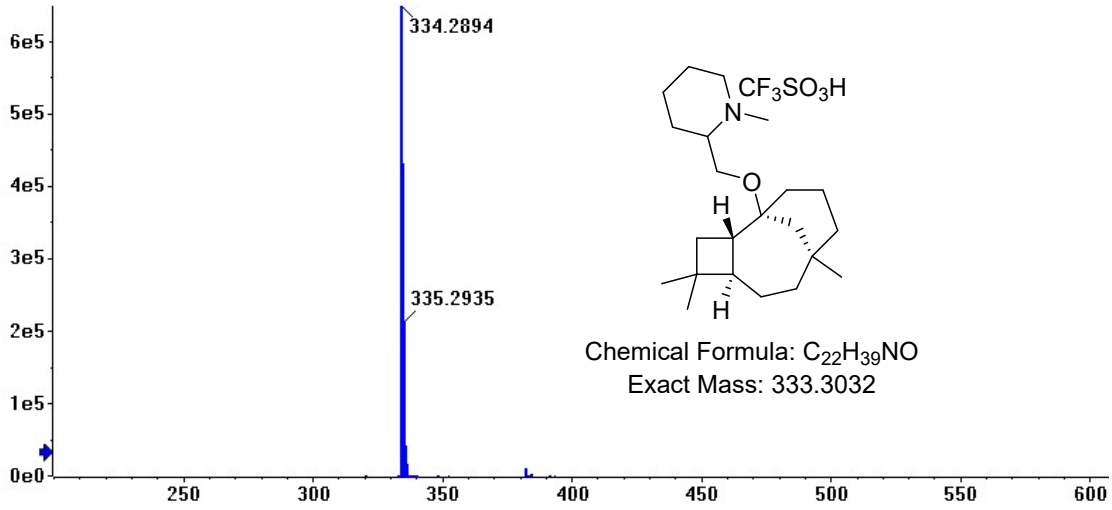
AC-8


320.2743
321.2784
CF3SO3H
N
O
H
H
Chemical Formula: C21H37NO
Exact Mass: 319.2875

AC-9

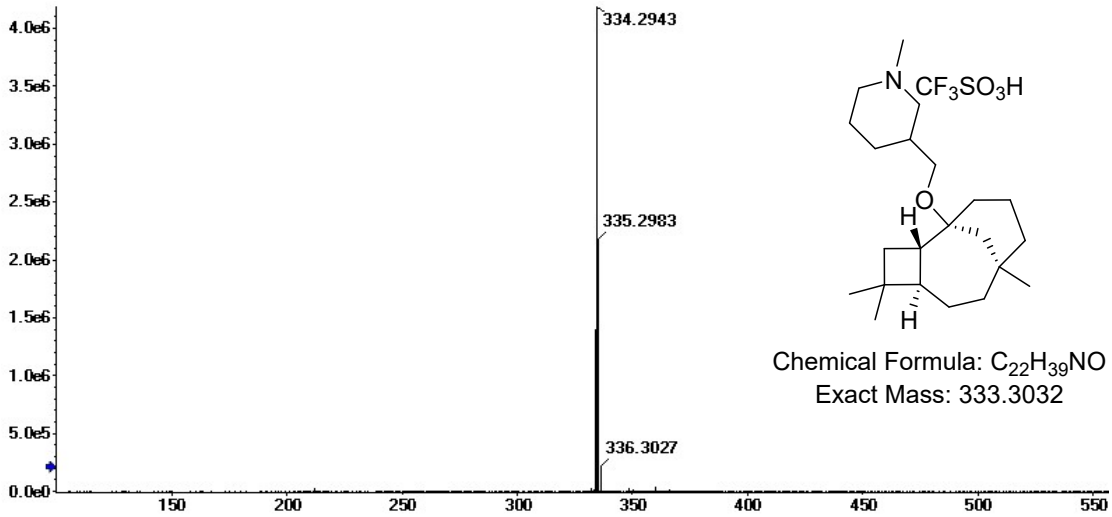

320.2813
321.2856
N
CF3SO3H
O
H
H
Chemical Formula: C21H37NO
Exact Mass: 319.2875

AC-10



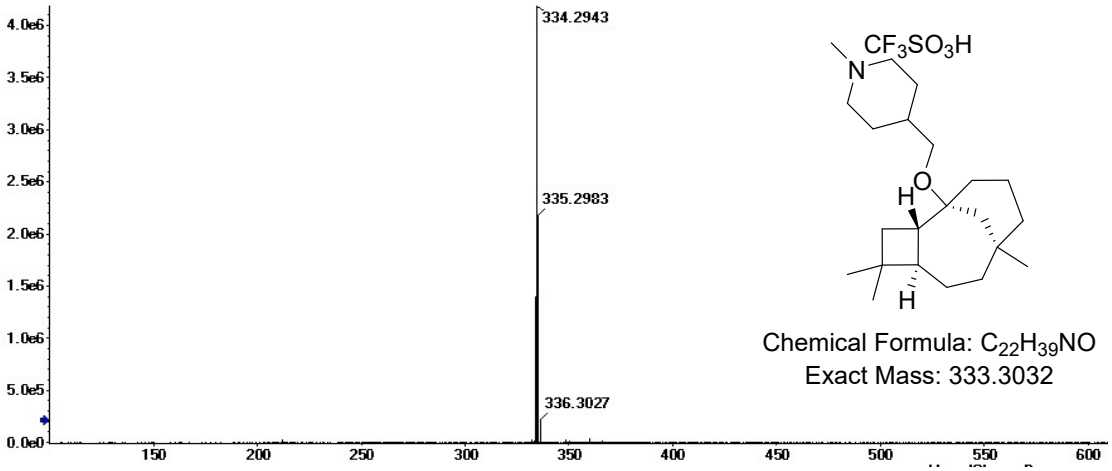
Chemical Formula: $C_{22}H_{39}NO$
Exact Mass: 333.3032

AC-11



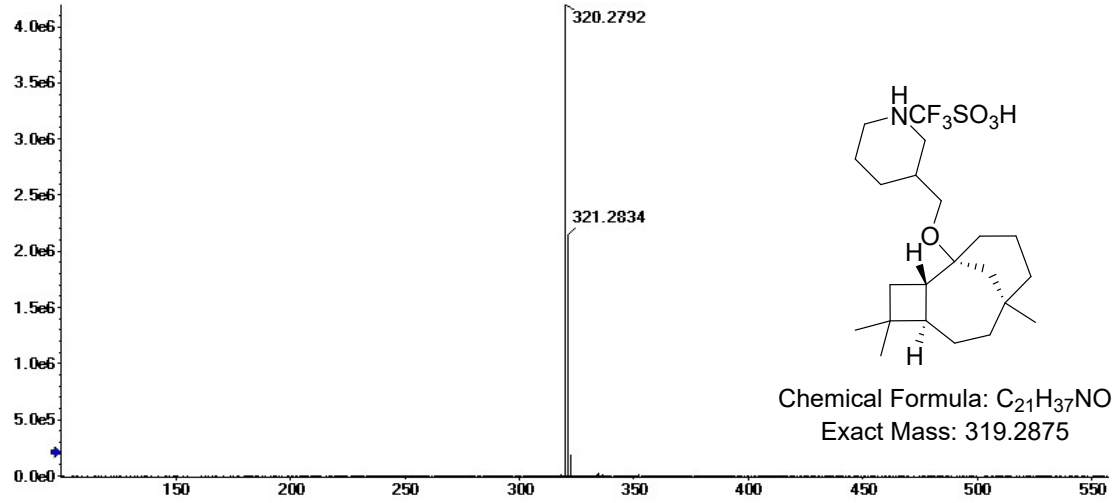
Chemical Formula: $C_{22}H_{39}NO$
Exact Mass: 333.3032

AC-12

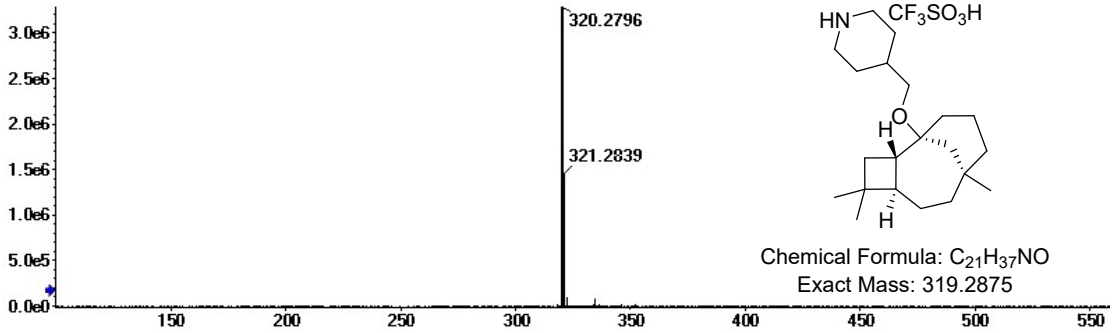


Chemical Formula: $C_{22}H_{39}NO$
Exact Mass: 333.3032

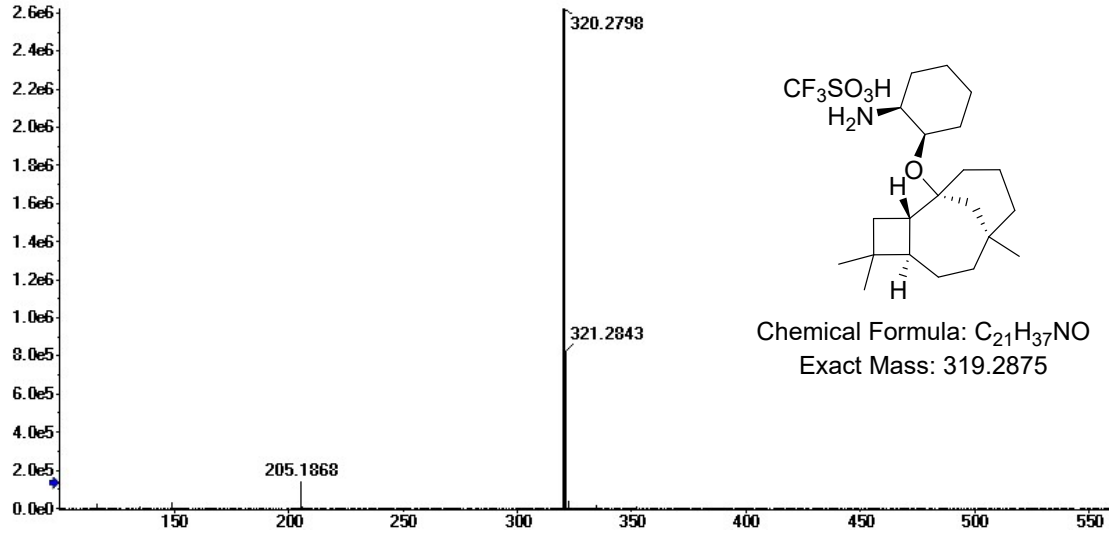
AC-13



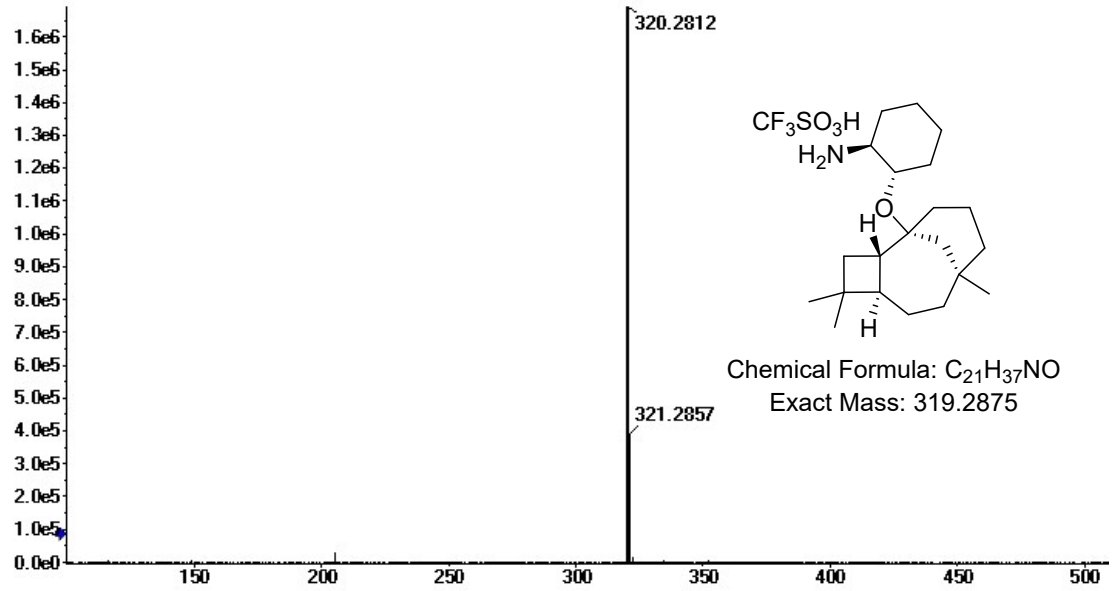
AC-14



AC-15

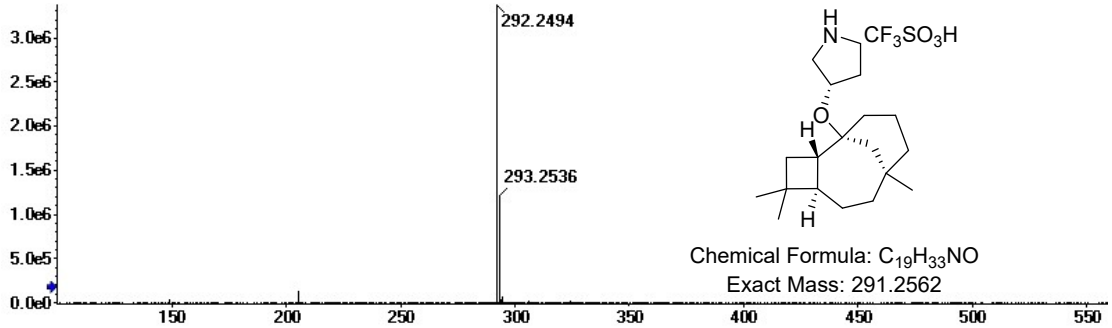


AC-16



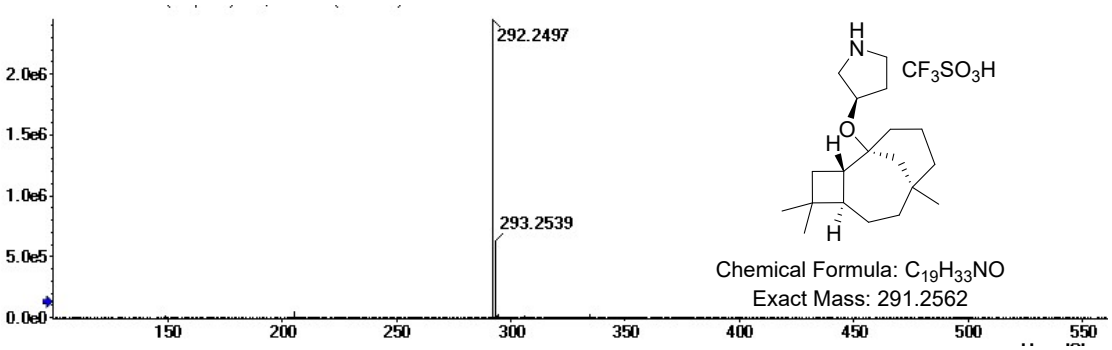
Chemical Formula: $C_{21}H_{37}NO$
Exact Mass: 319.2875

AC-17



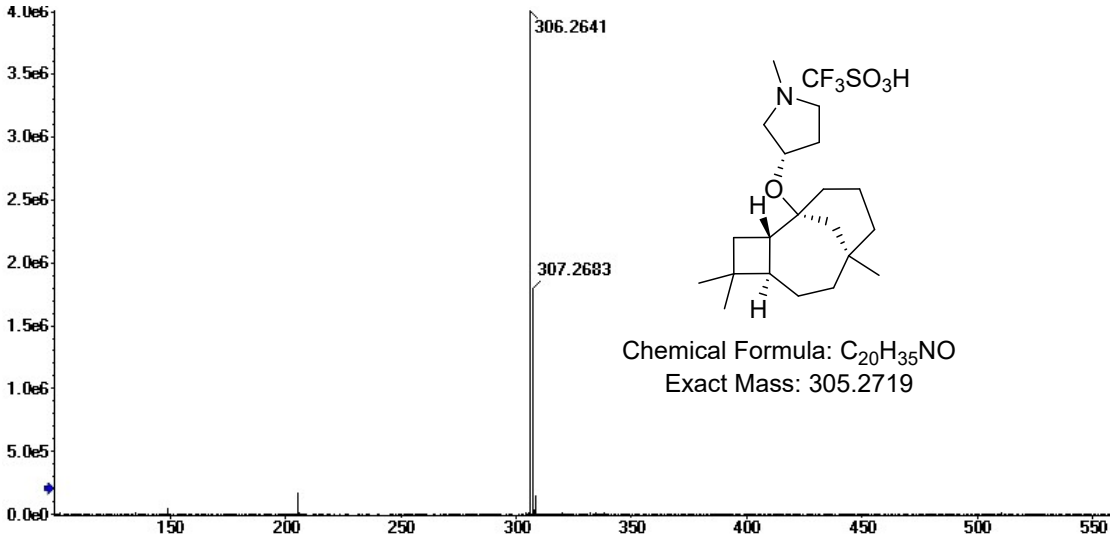
Chemical Formula: $C_{19}H_{33}NO$
Exact Mass: 291.2562

AC-18

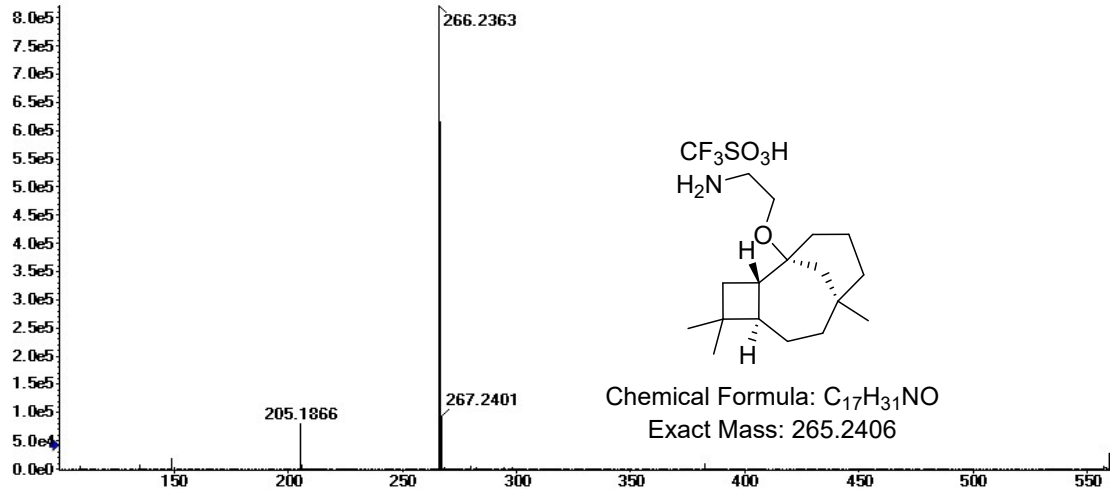


Chemical Formula: $C_{19}H_{33}NO$
Exact Mass: 291.2562

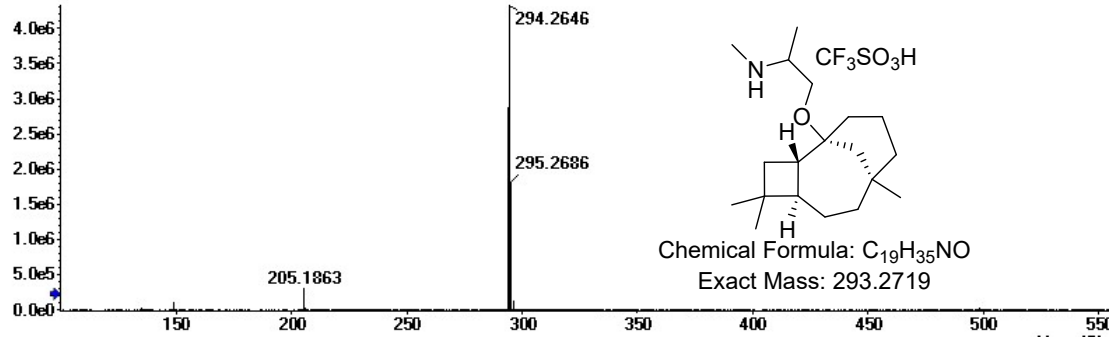
AC-19


306.2641
307.2683
CF3SO3H
N
O
H
H
Chemical Formula: C20H35NO
Exact Mass: 305.2719

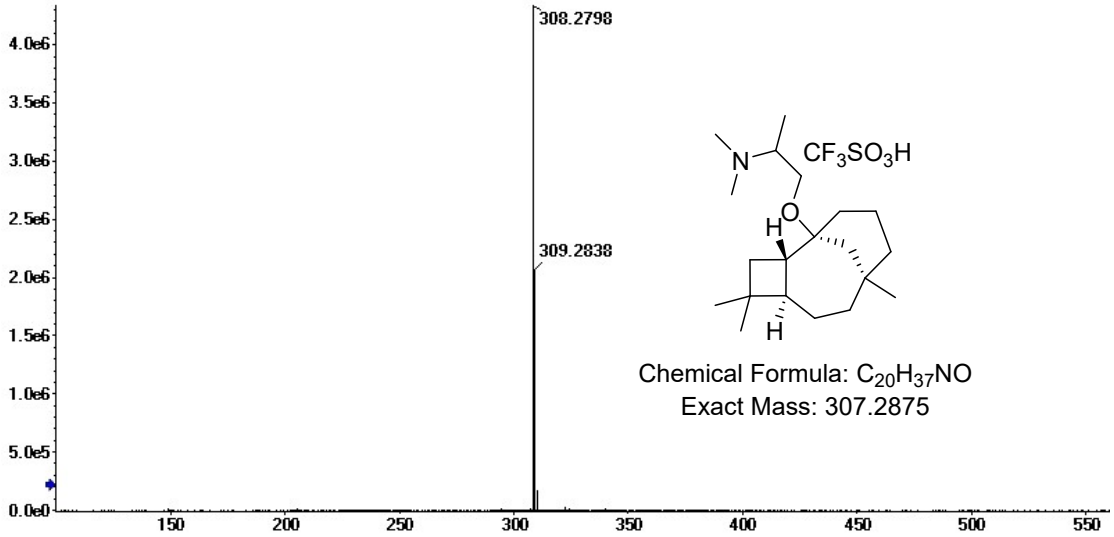
AC-20


266.2363
205.1866
267.2401
CF3SO3H
H2N
O
H
H
Chemical Formula: C17H31NO
Exact Mass: 265.2406

AC-21



AC-22



AC-23

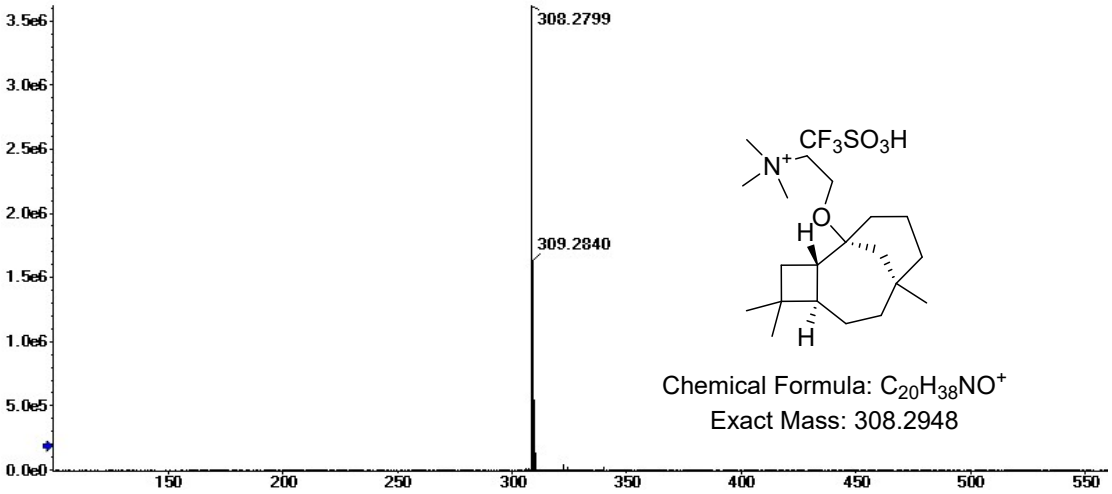


Fig S3. HRMS-ESI spectra of AC-7 to AC-23.