Supplementary Material

In vitro anti-trypanosomal potential of kaurane and pimarane semi-synthetic derivatives

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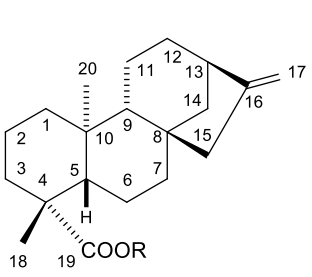
Abstract

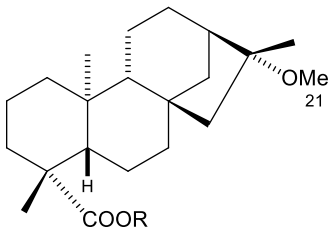
As part of the search for anti-trypanosomal agents, this work presents the production of sixteen derivatives. All of them were obtained from two natural diterpenes, one with kaurane skeleton (*ent*-kaurenoic acid) and other with a pimarane skeleton (*ent*-pimaradienoic acid). Then, the eighteen compounds were assayed against epimastigote form of *Trypanosoma cruzi*, with the derivatives showing increase of activity in relation to their precursors. Moreover, the most active derivative presented an IC_{50} <12,5 μM (estimated 0.8 μM), lower than Benznidazole (IC_{50} = 9.8 μM), used as control. The esterification of acid diterpenes showed to be an interesting way in the search for anti-trypanosomal agents.

Supplementary material contents:

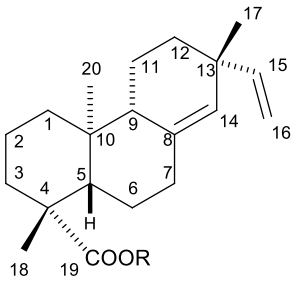
This material contains ^{1}H and ^{13}C {^{1}H} spectra with expansions and complete spectroscopic data for all eighteen substances. (Total of 50 pages)



1: R = H
4: R = CH_3
5: R = $(CH_2)_3CH_3$
6: R = $PhCH_2$
7: R = 4-$BrPhCH_2$
8: R = 4-$ClPhCH_2$



3: R = H
9: R = CH_3
10: R = $(CH_2)_3CH_3$
11: R = $PhCH_2$
12: R = 4-$BrPhCH_2$
13: R = 4-$ClPhCH_2$



2: R = H
14: R = CH_3
15: R = $(CH_2)_3CH_3$
16: R = $PhCH_2$
17: R = 4-$BrPhCH_2$
18: R = 4-$ClPhCH_2$

Fig. S1 Chemical structures of kaurane (**1** and **3**-**13**) and pimarane (**2** and **14**-**18**) diterpenes

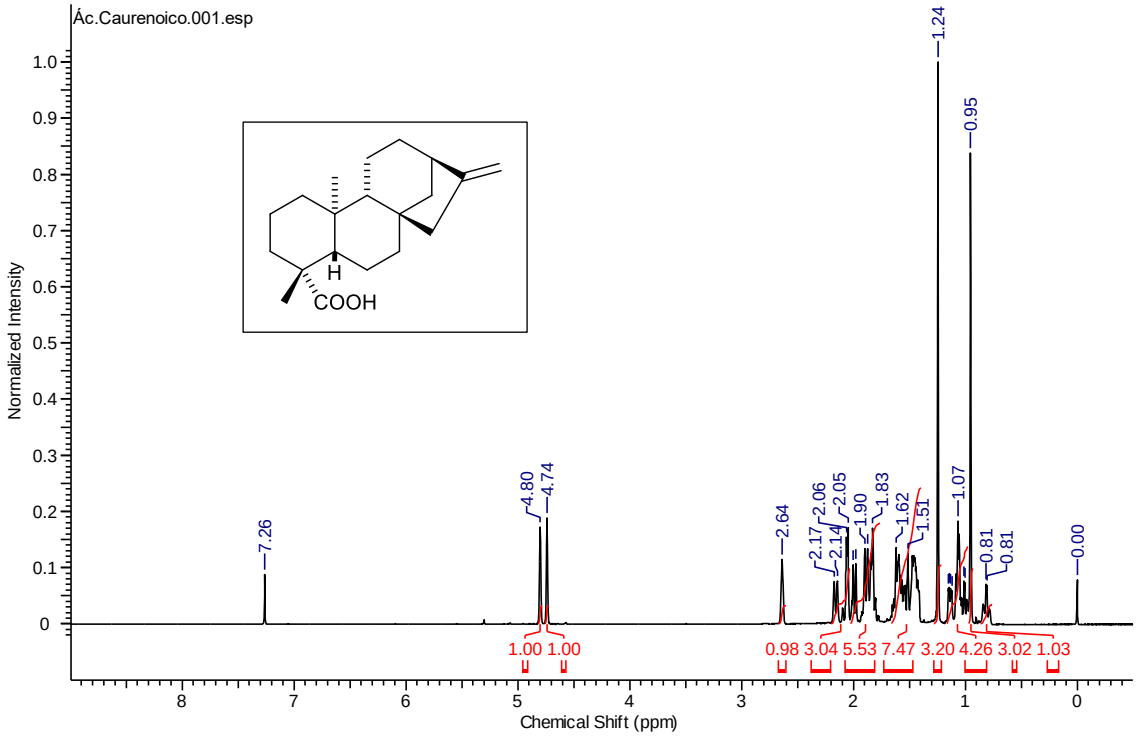


Fig. S2 Compound **1** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

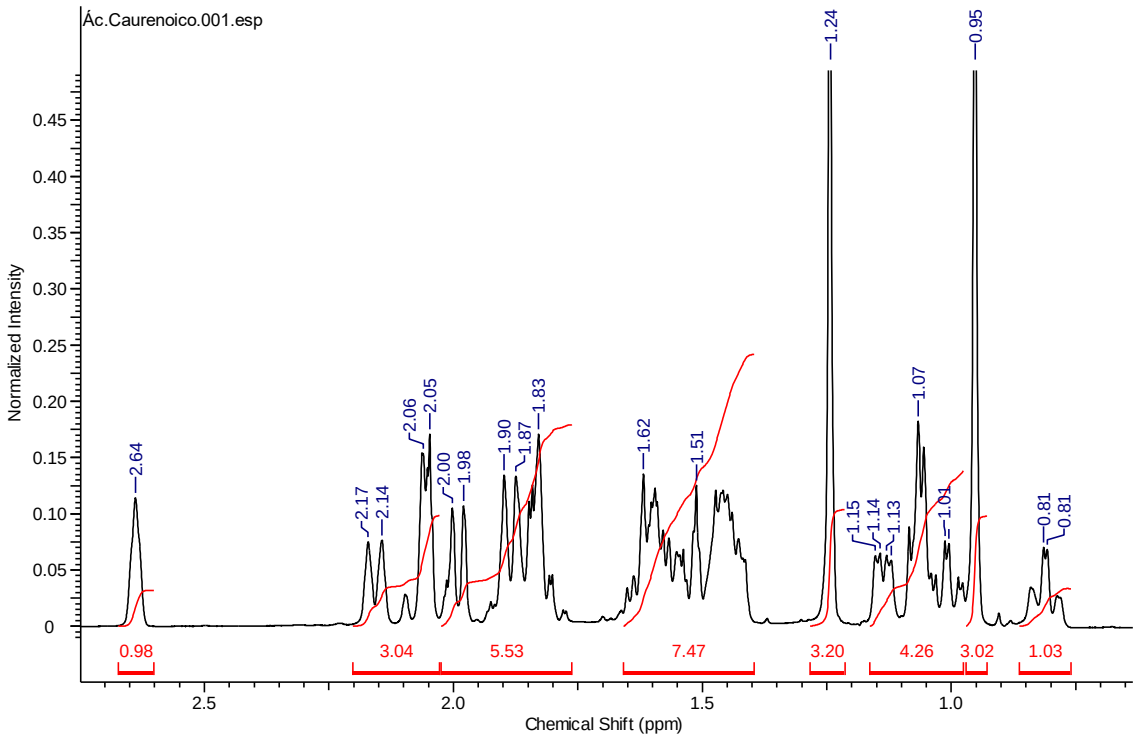


Fig. S3 Compound **1** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

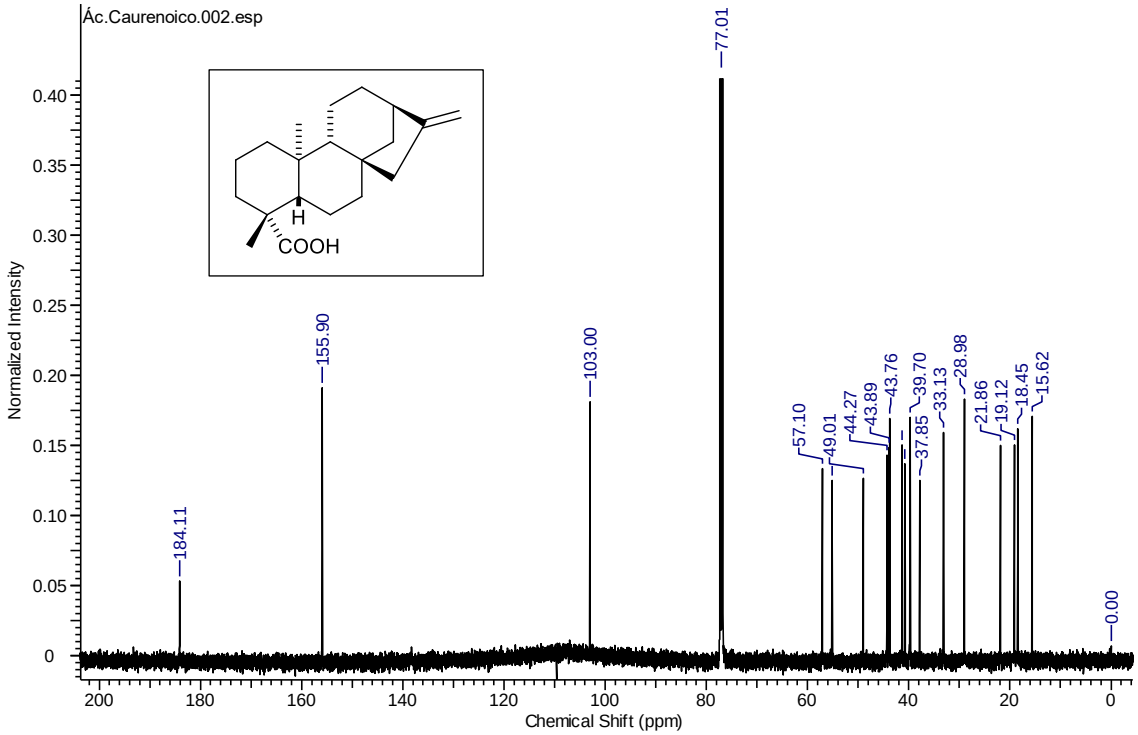


Fig. S4 Compound **1** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

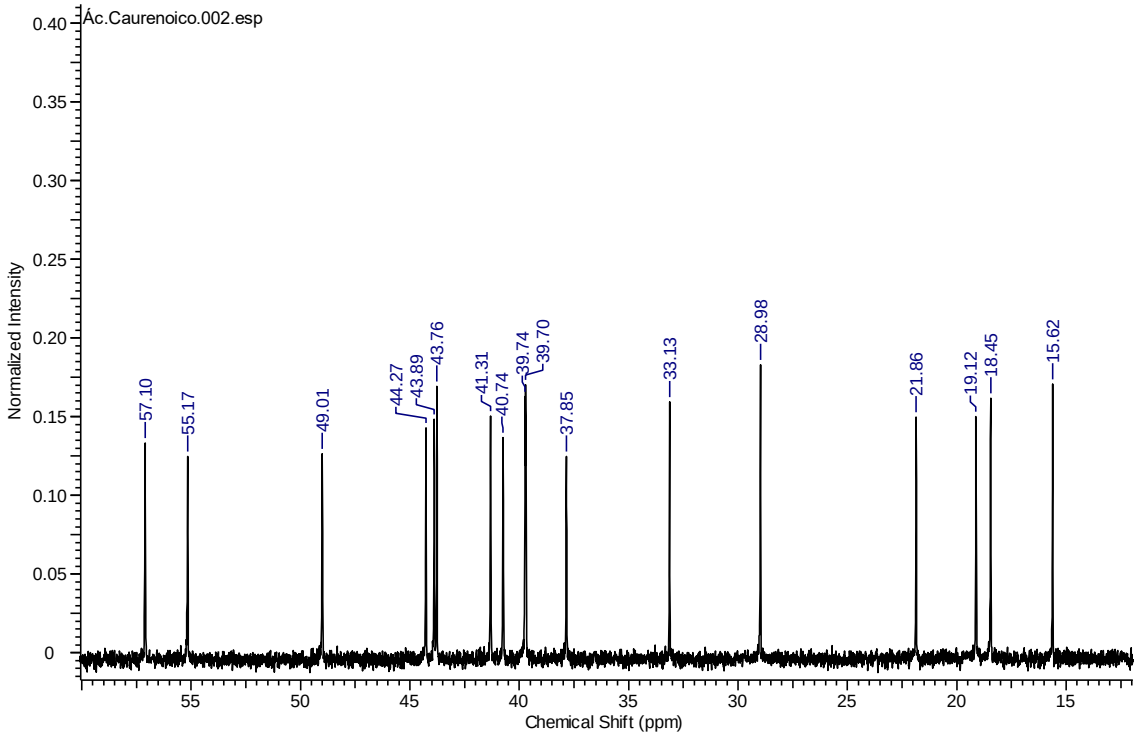


Fig. S5 Compound **1** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ – Expansion

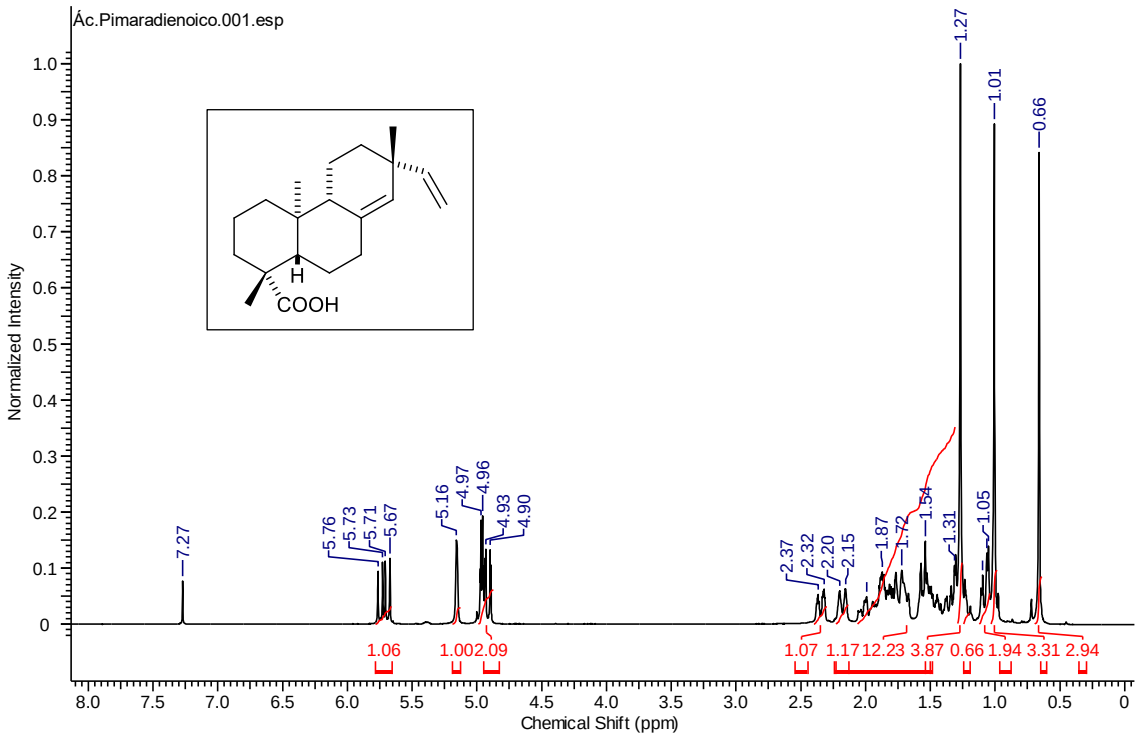


Fig. S6 Compound **2** ^{1}H-NMR spectrum, 300MHz, $CDCl_3$

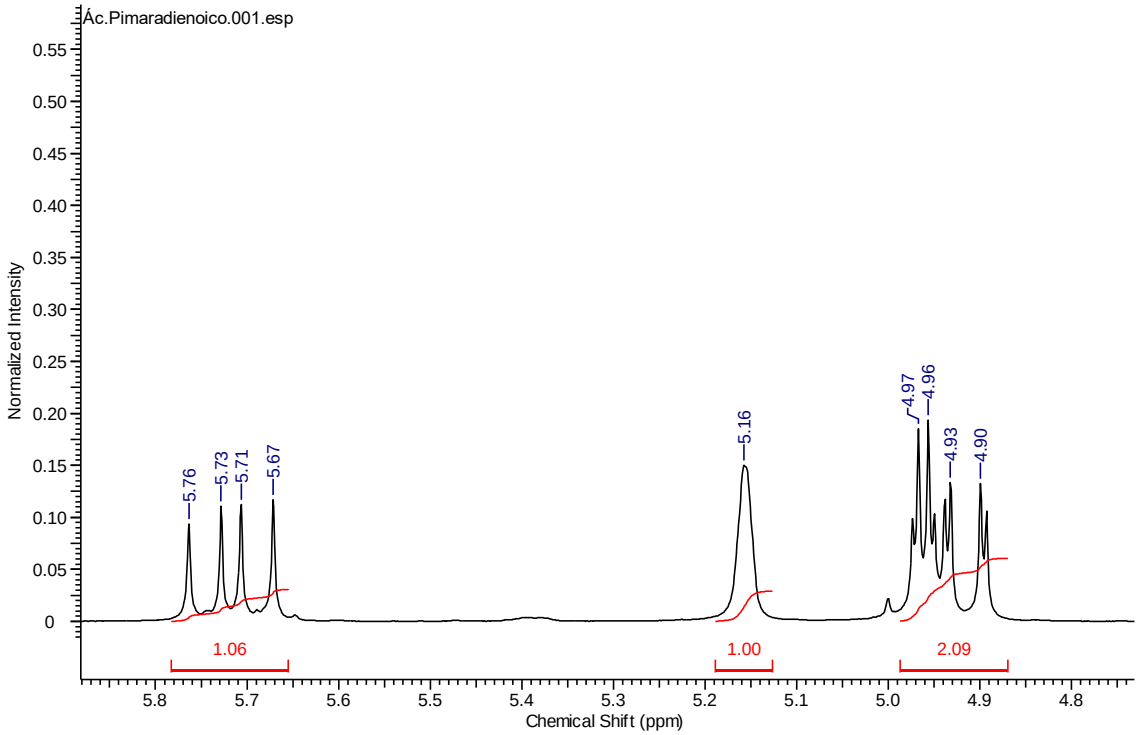


Fig. S7 Compound **2** ^{1}H-NMR spectrum, 300MHz, $CDCl_3$ – Expansion 1

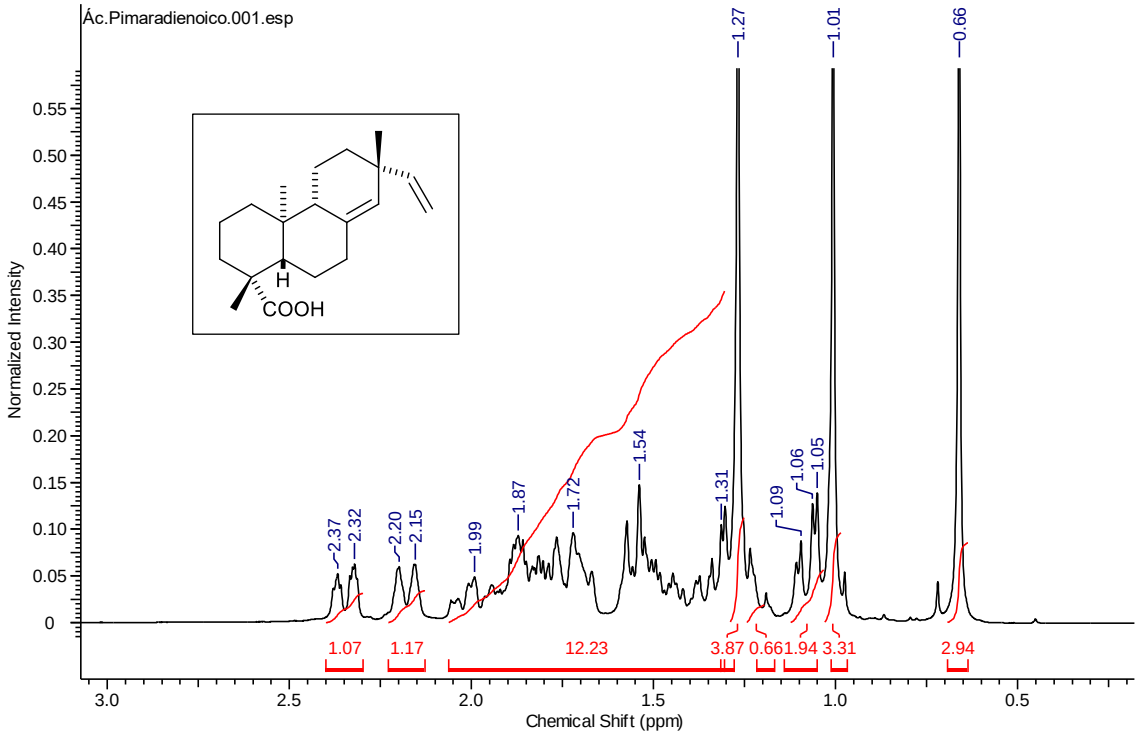


Fig. S8 Compound **2** ^{1}H-NMR spectrum, 300MHz, $CDCl_3$ – Expansion 2

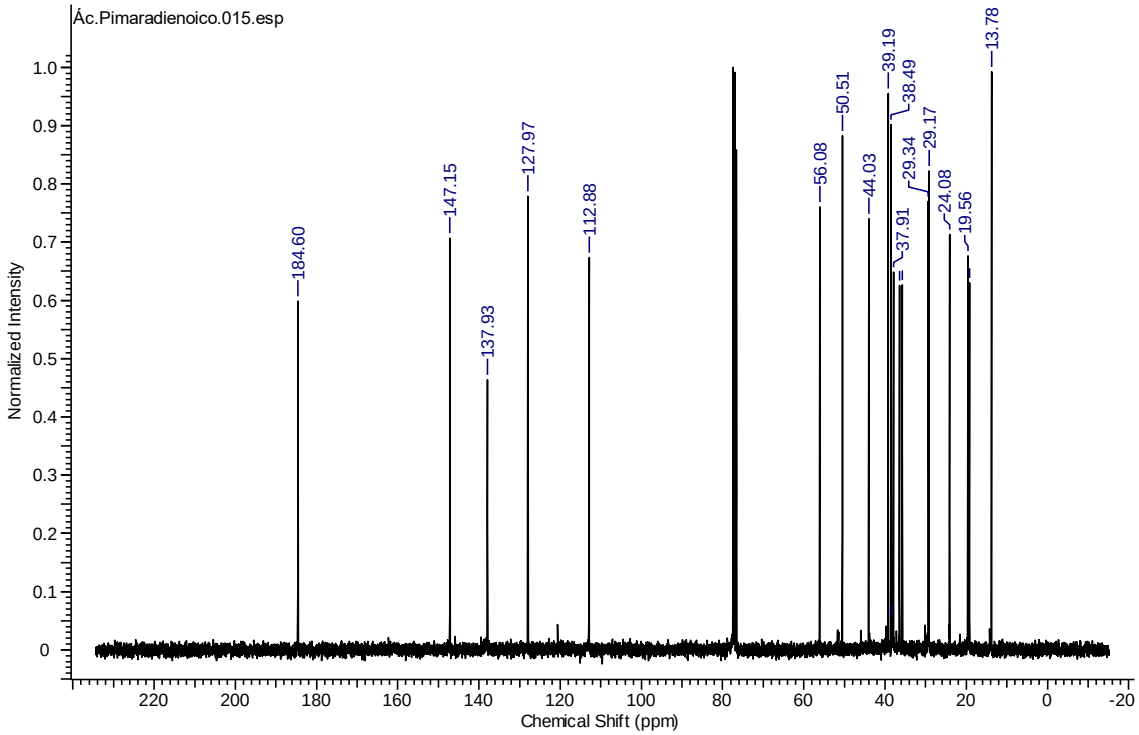


Fig. S9 Compound **2** ^{13}C-NMR spectrum, 75MHz, $CDCl_3$

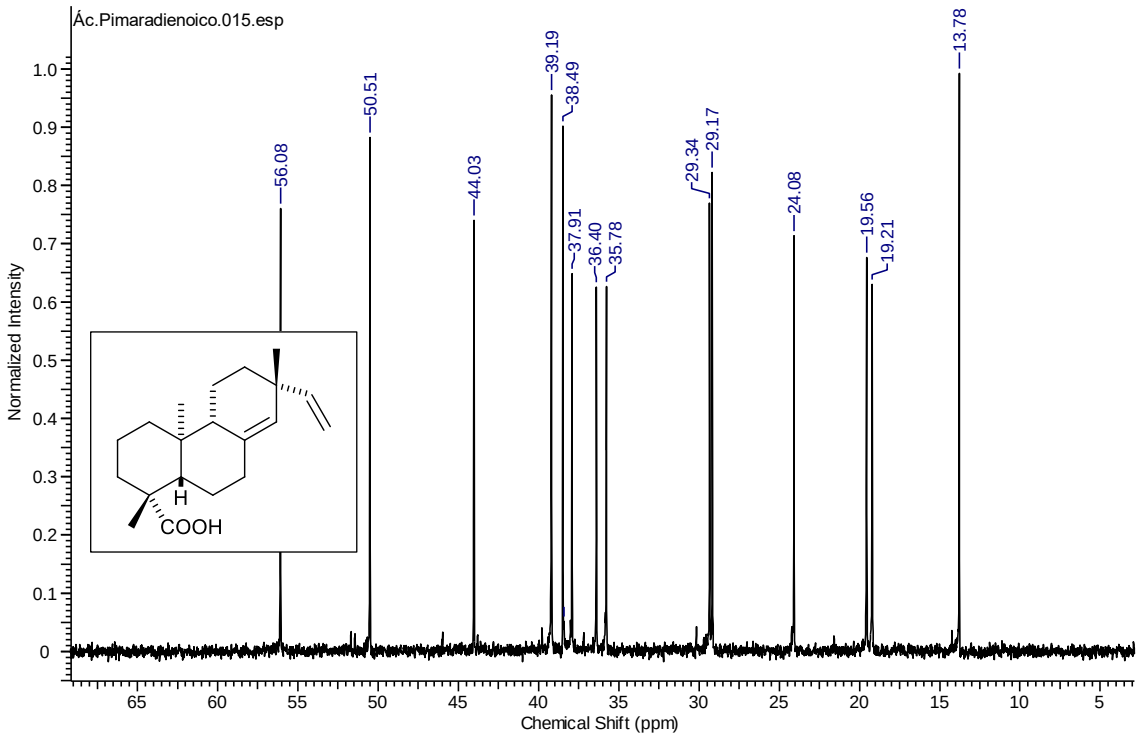


Fig. S10 Compound **2** ^{13}C-NMR spectrum, 75MHz, $CDCl_3$ - Expansion

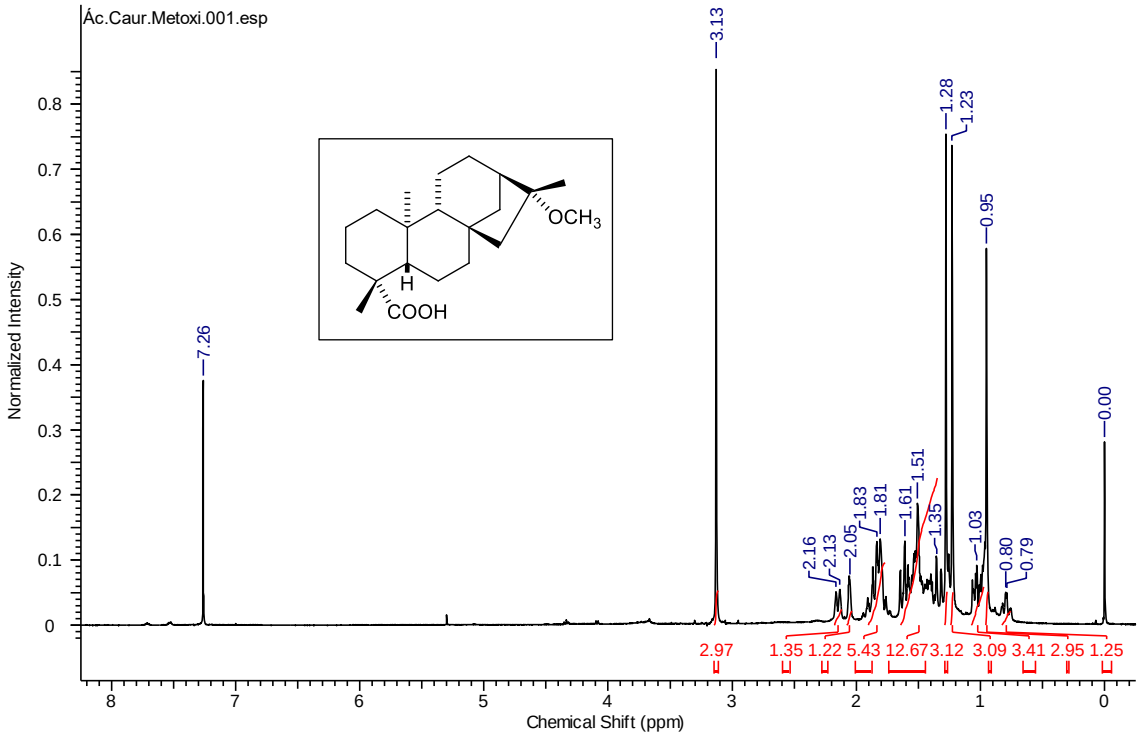


Fig. S11 Compound **3** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

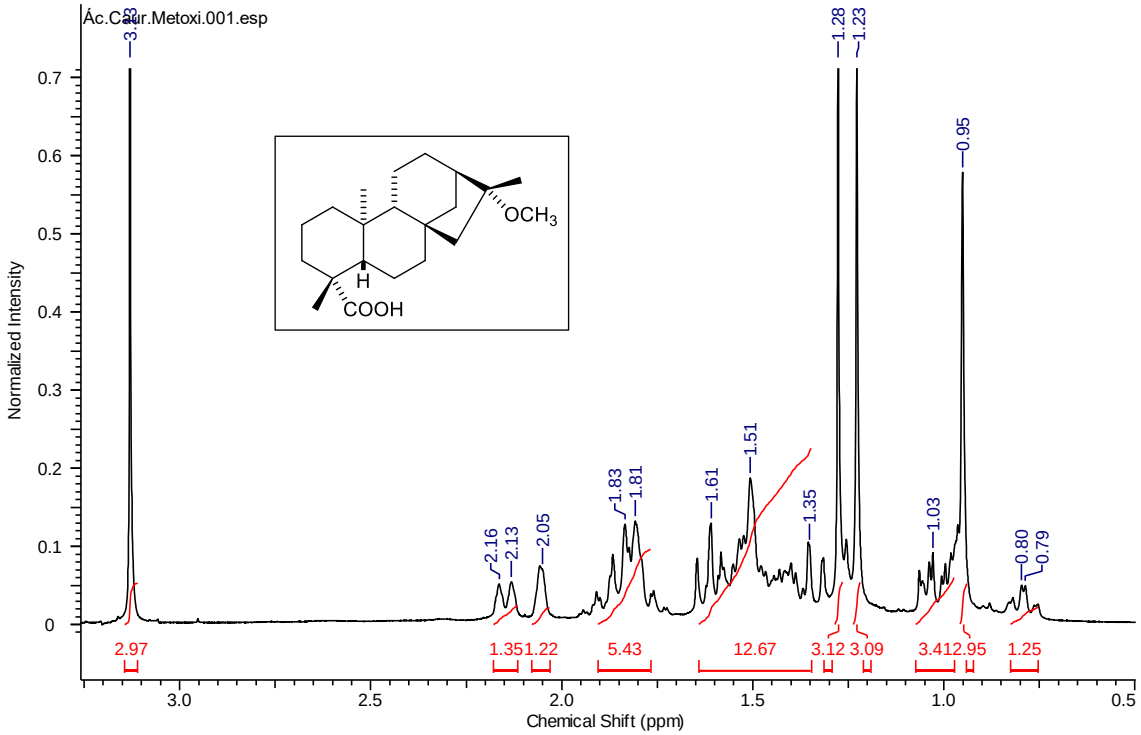


Fig. S12 Compound **3** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ - Expansion

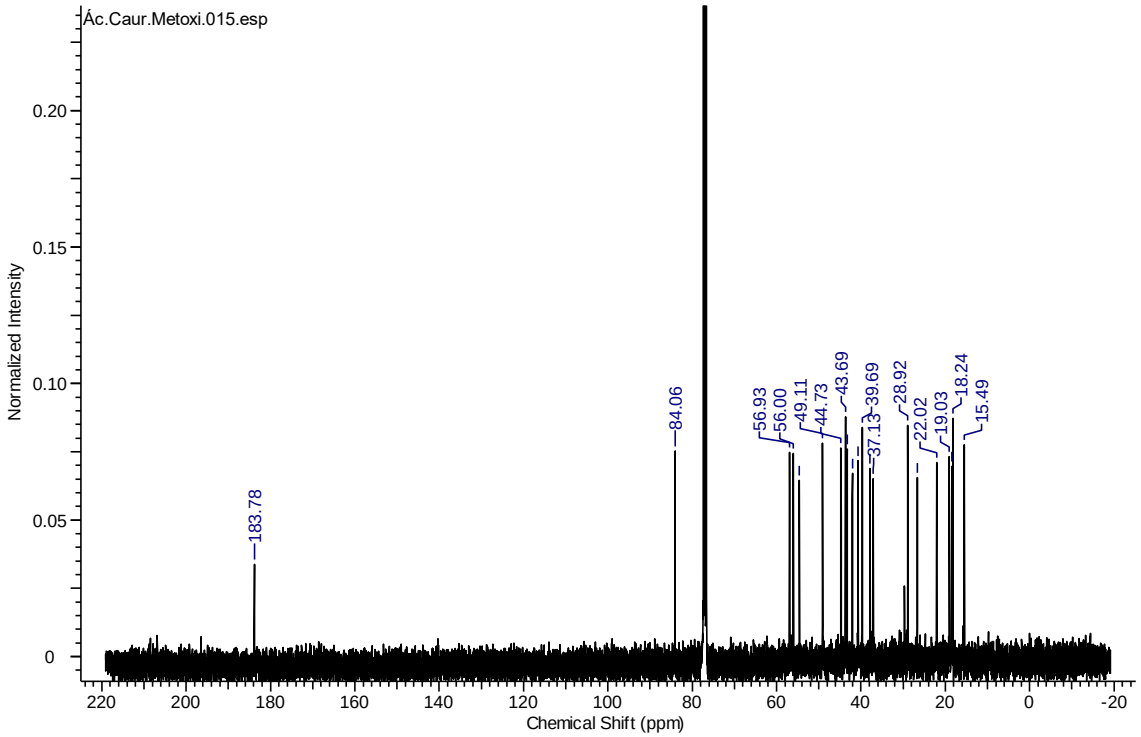


Fig. S13 Compound **3** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

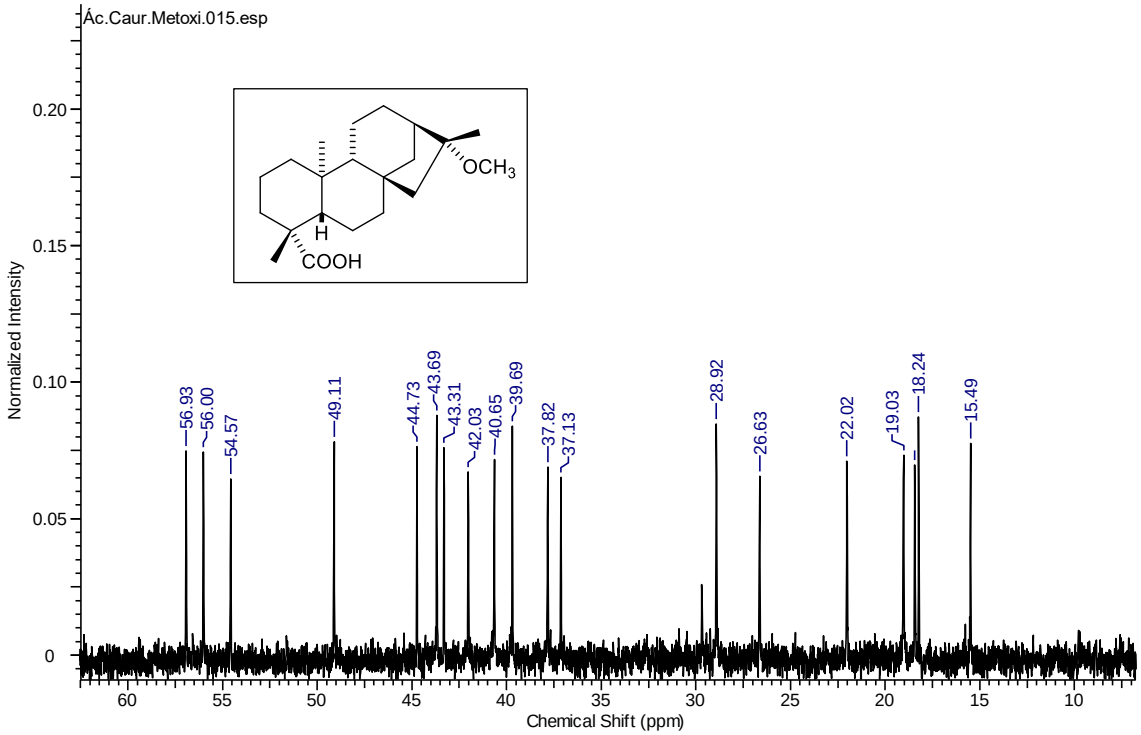


Fig. S14 Compound **3** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ - Expansion

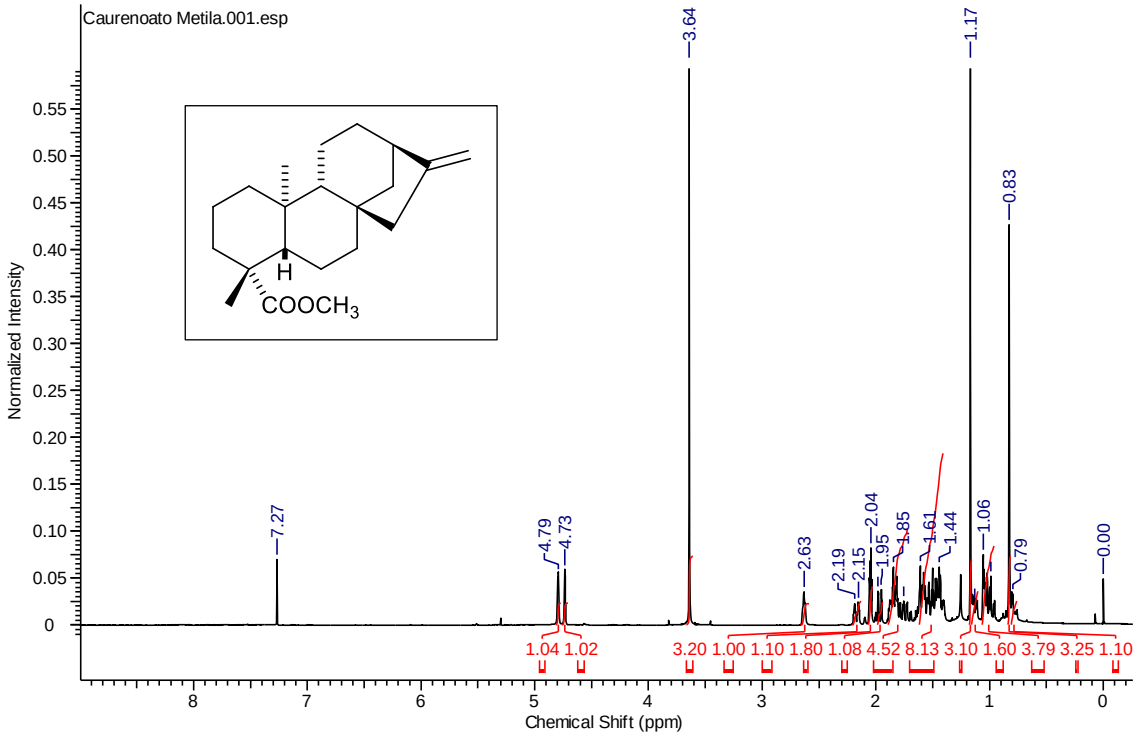


Fig. S15 Compound **4** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

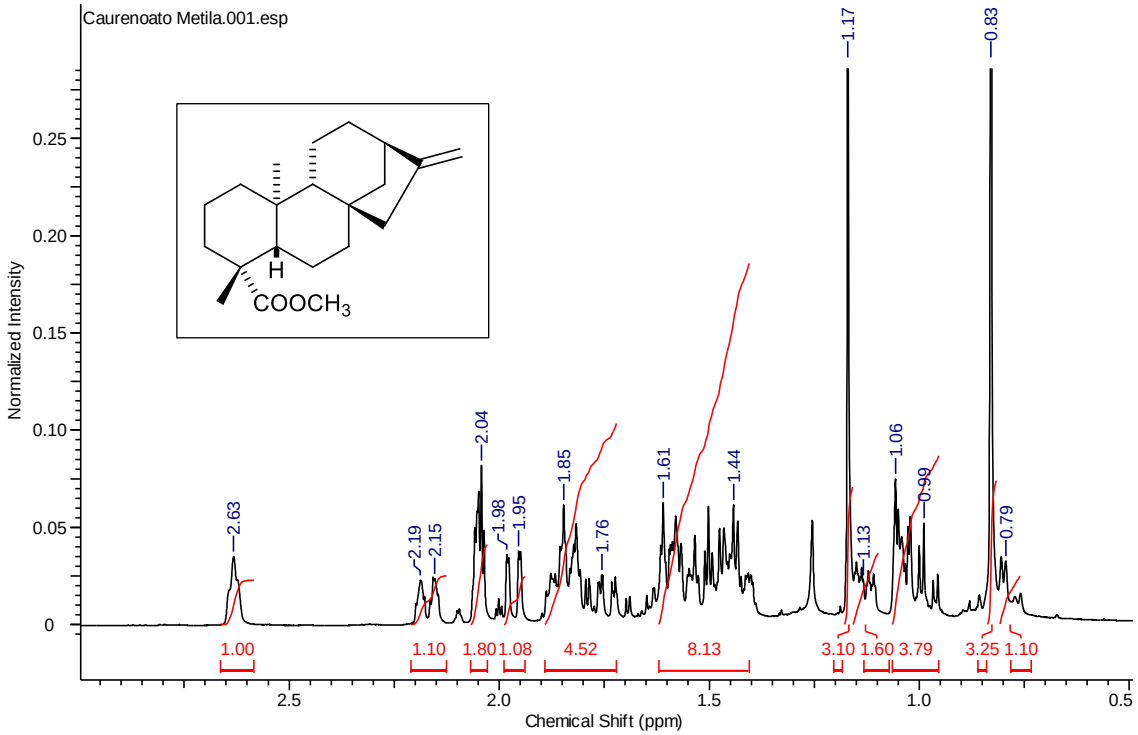


Fig. S16 Compound **4** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion

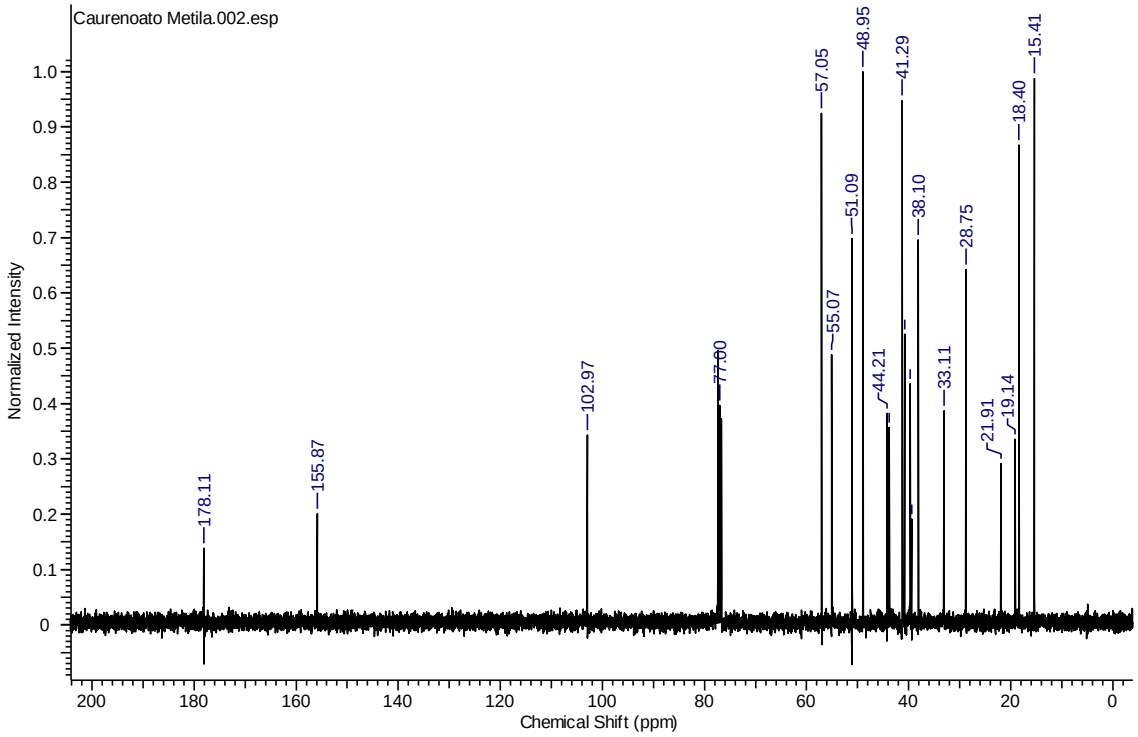


Fig. S17 Compound **4** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

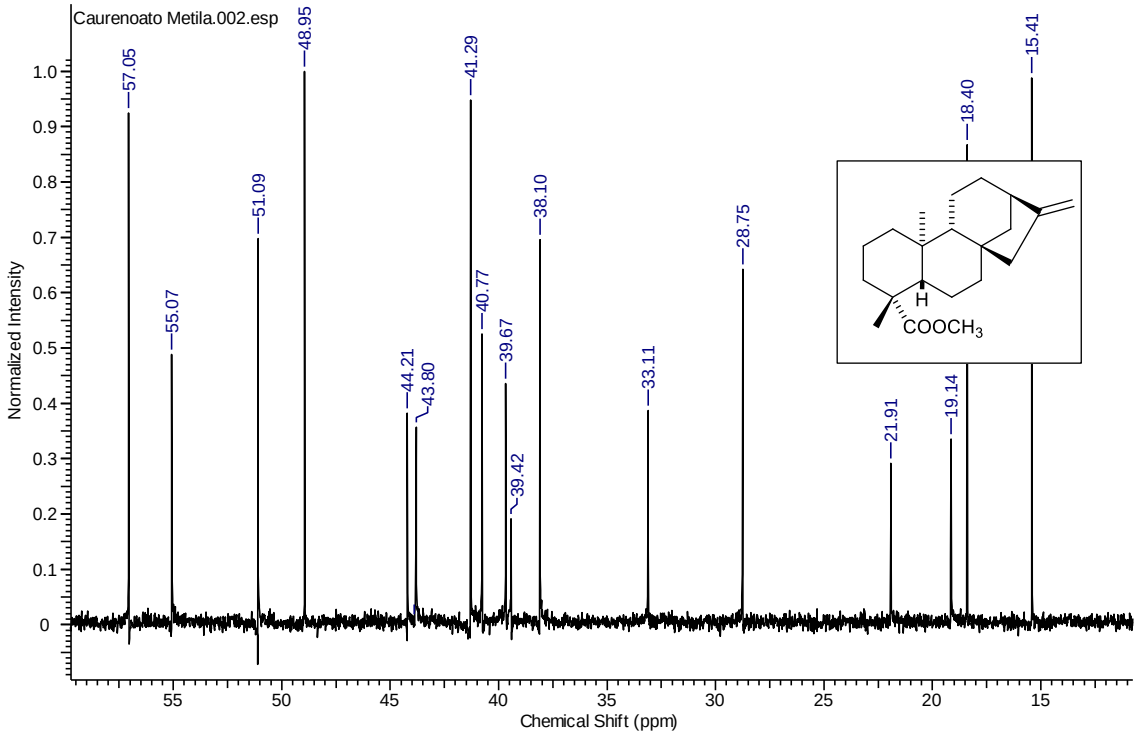


Fig. S18 Compound **4** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ - Expansion

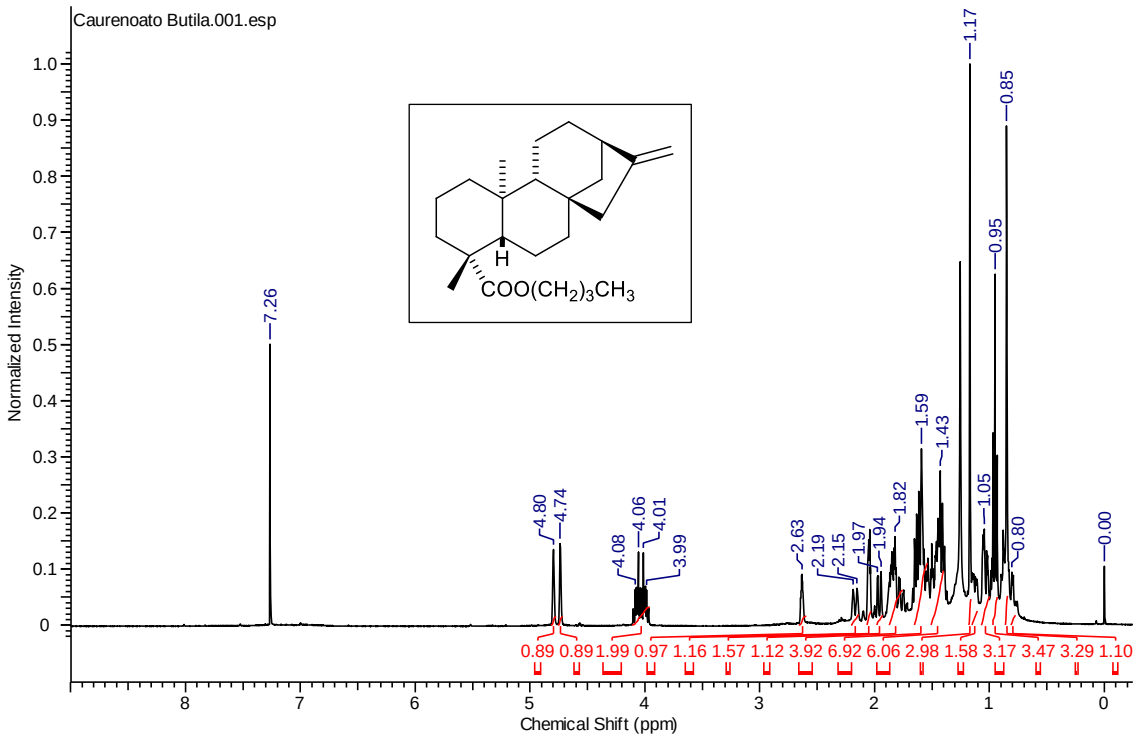


Fig. S19 Compound **5** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

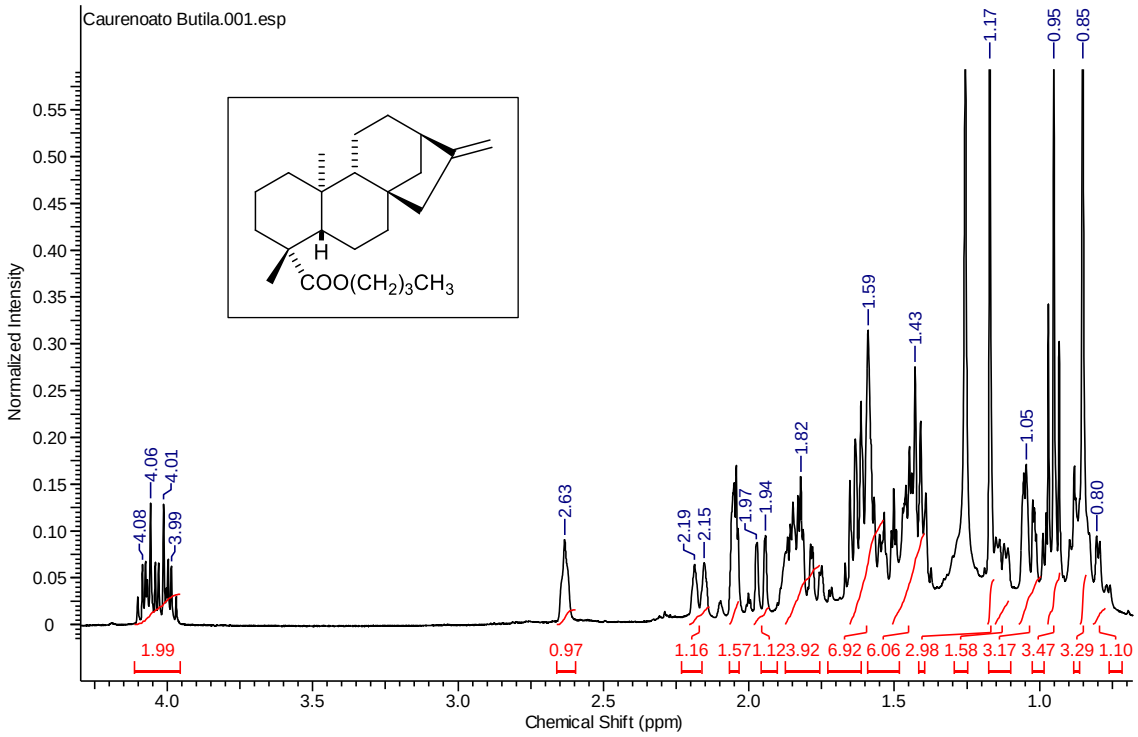


Fig. S20 Compound **5** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion

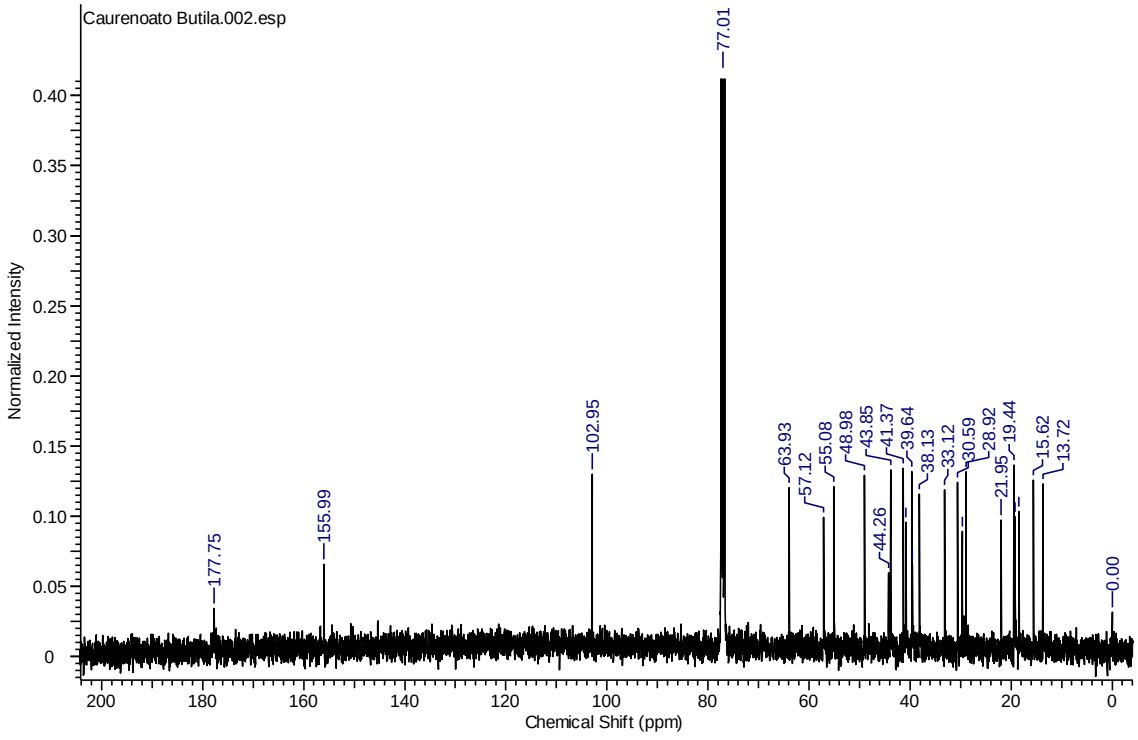


Fig. S21 Compound **5** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

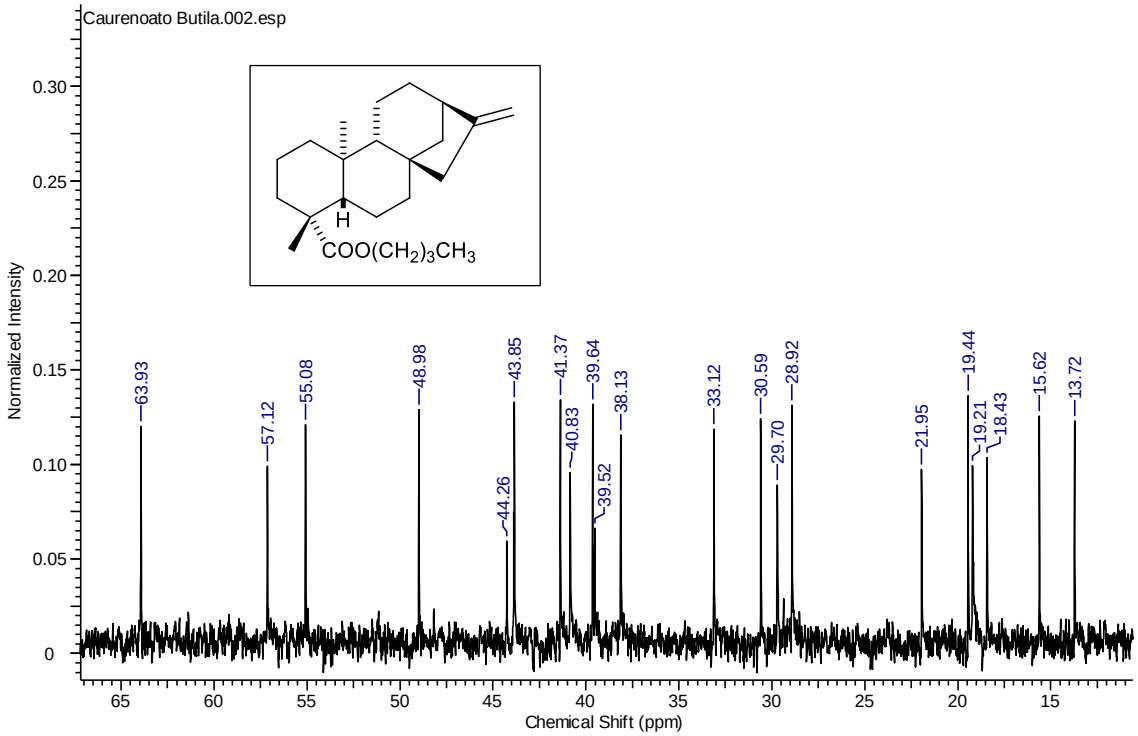


Fig. S22 Compound **5** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ – Expansion

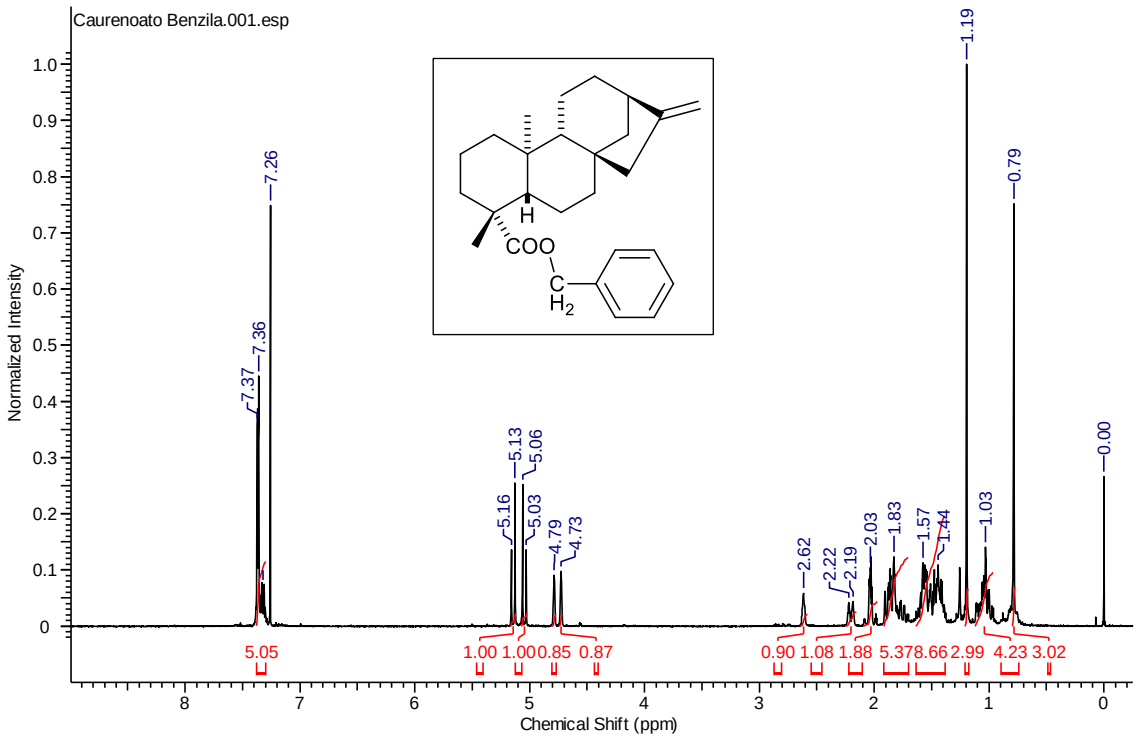


Fig. S23 Compound **6** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

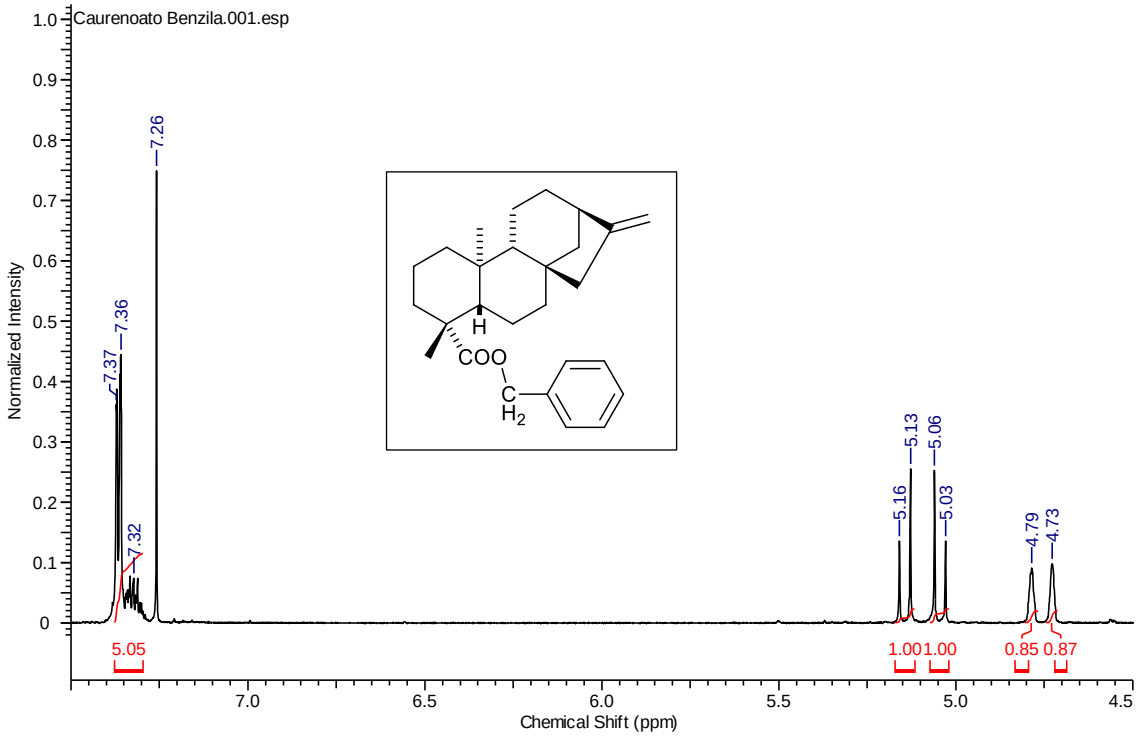


Fig. S24 Compound **6** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

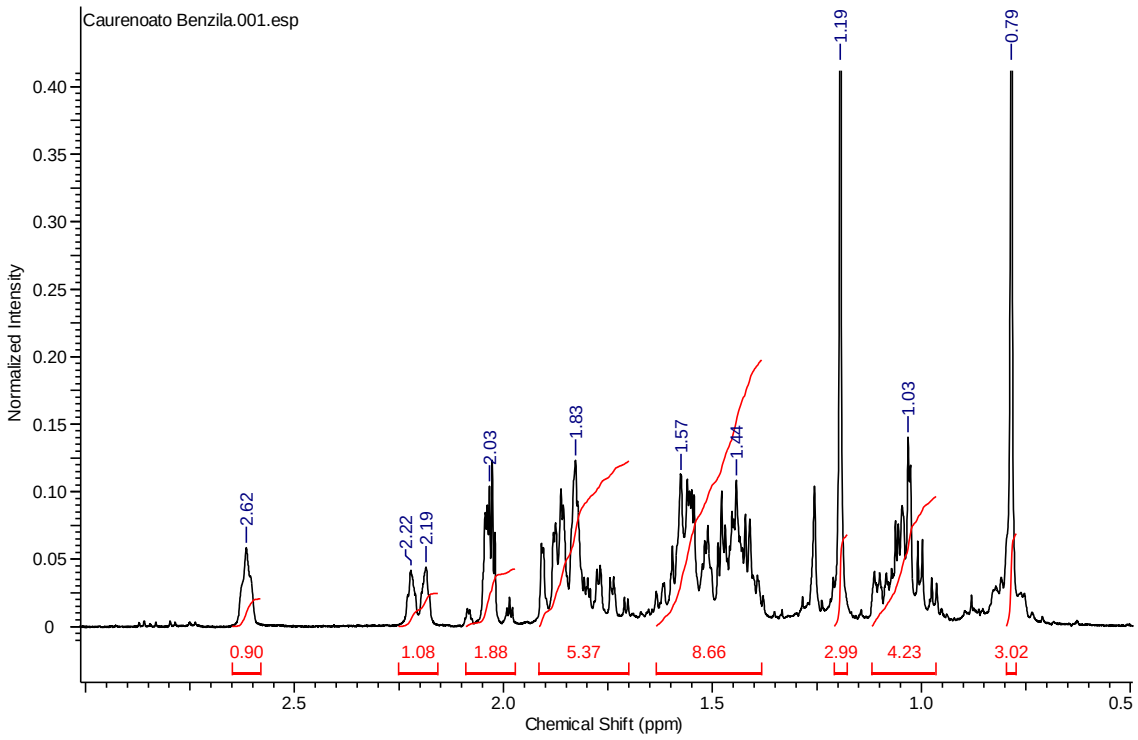


Fig. S25 Compound **6** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 2

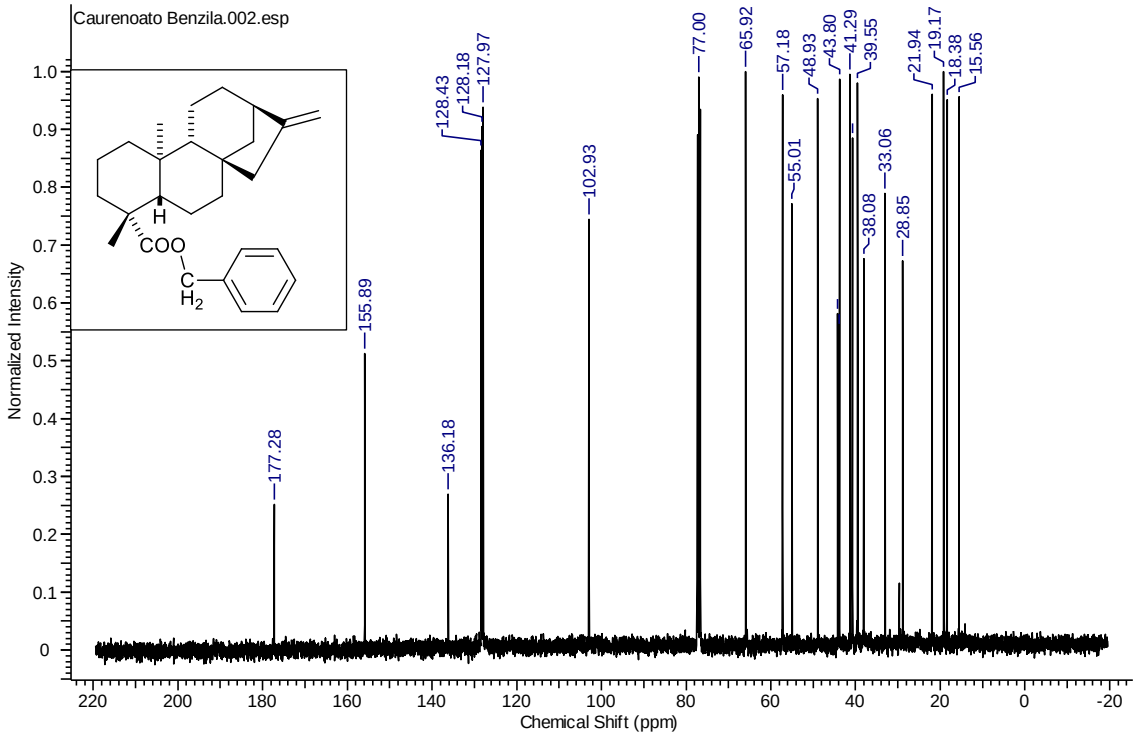


Fig. S26 Compound **6** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

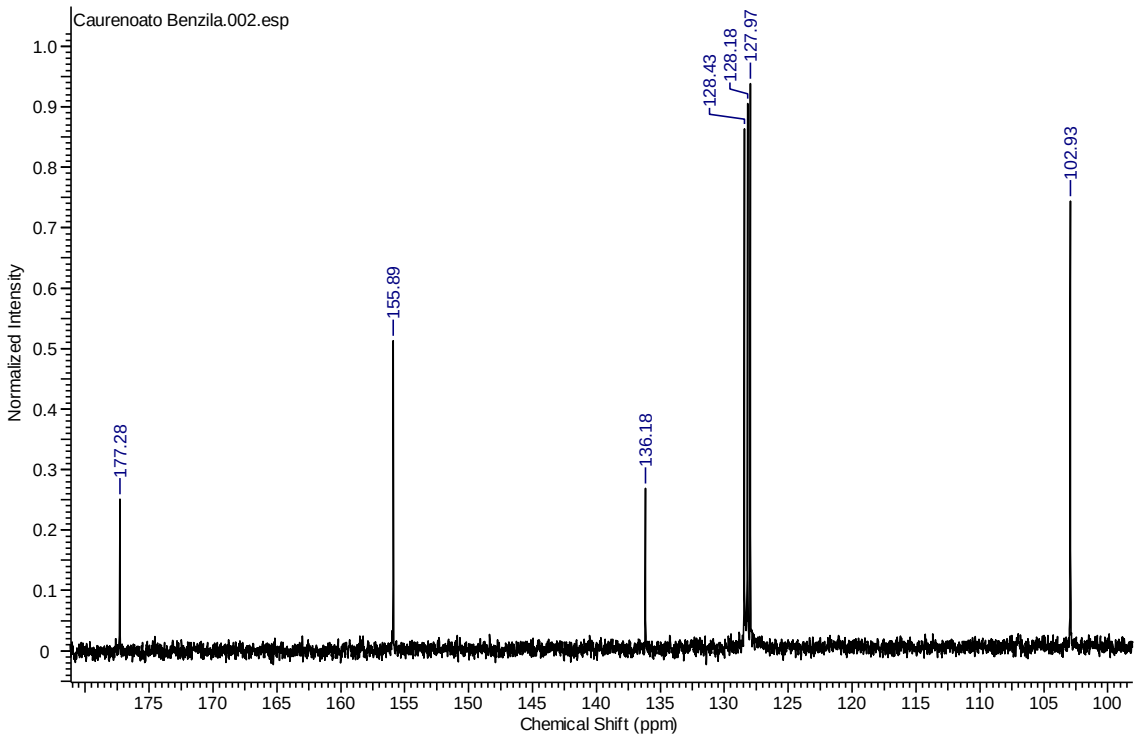


Fig. S27 Compound **6** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ – Expansion 1

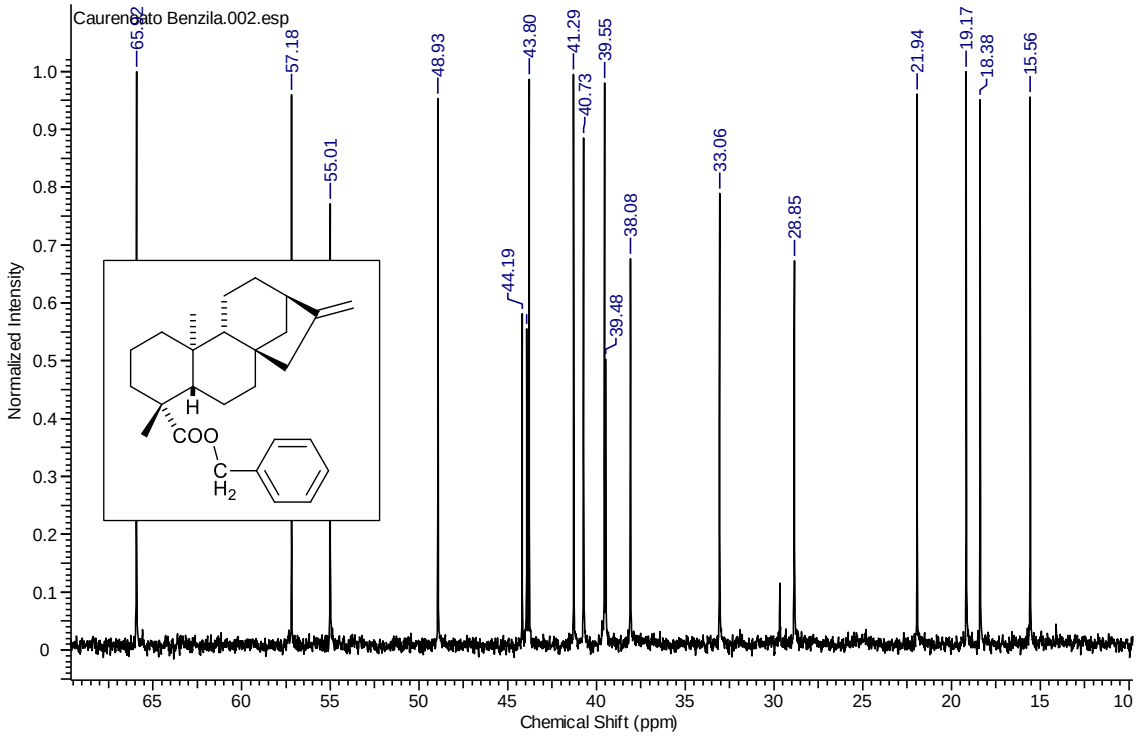


Fig. S28 Compound **6** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ – Expansion 2

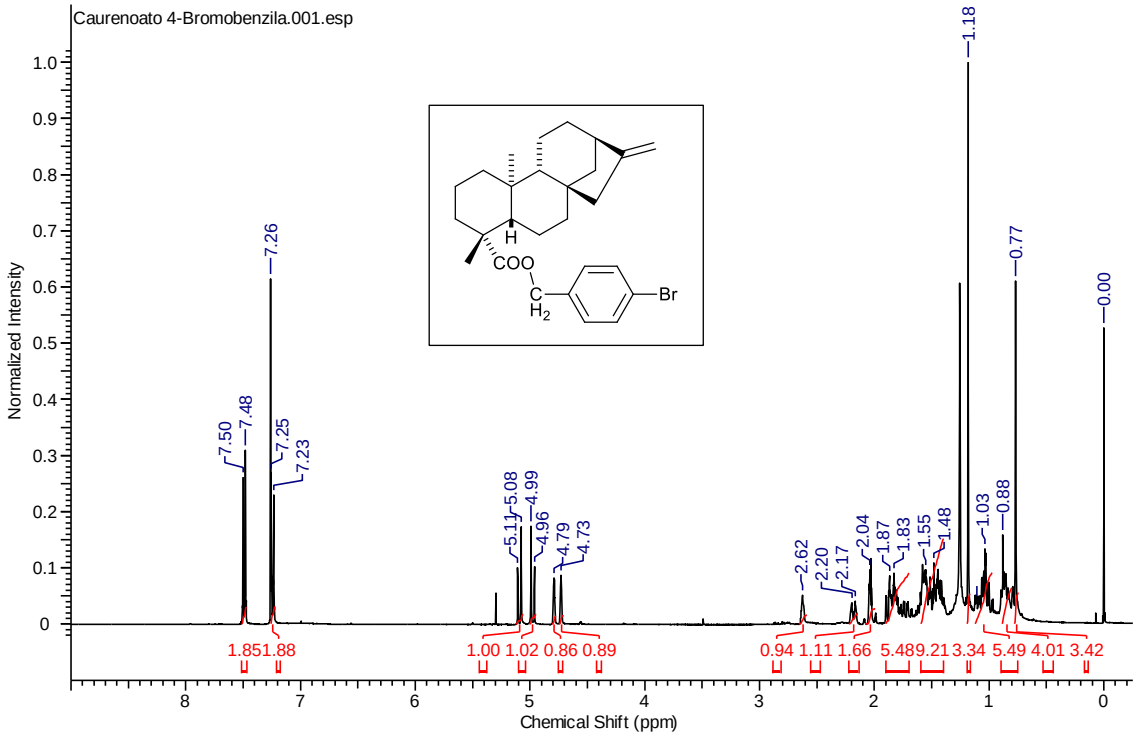


Fig. S29 Compound **7** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$

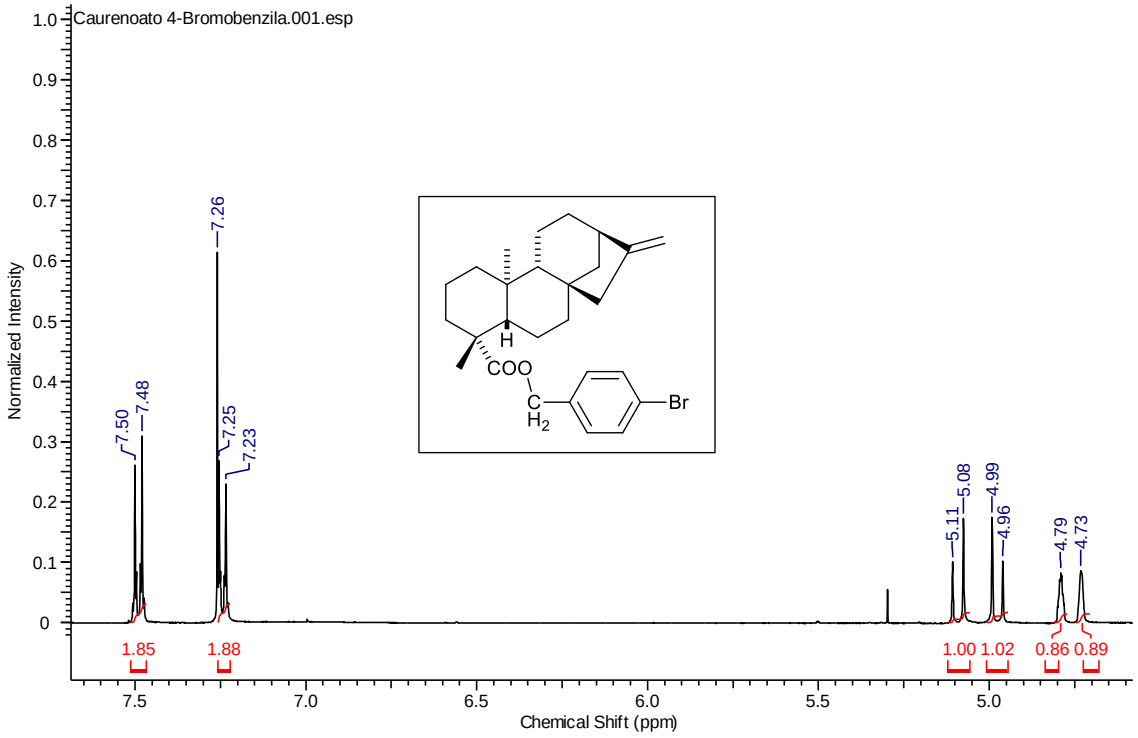


Fig. S30 Compound **7** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 1

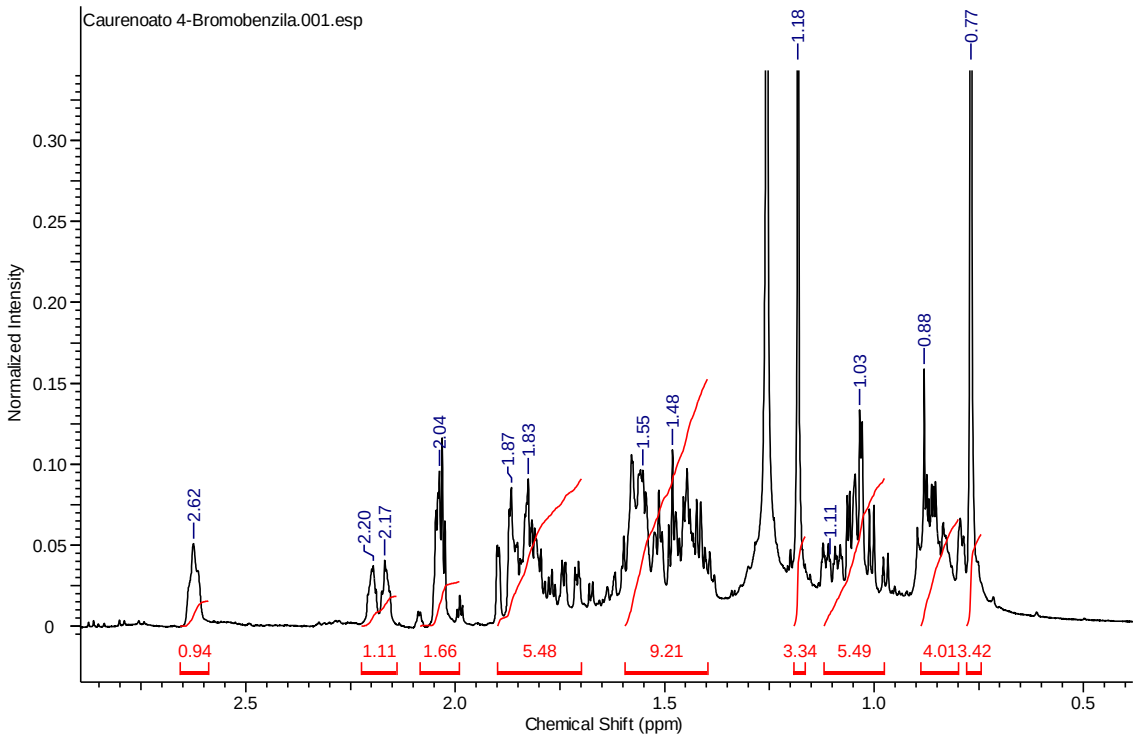


Fig. S31 Compound **7** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 2

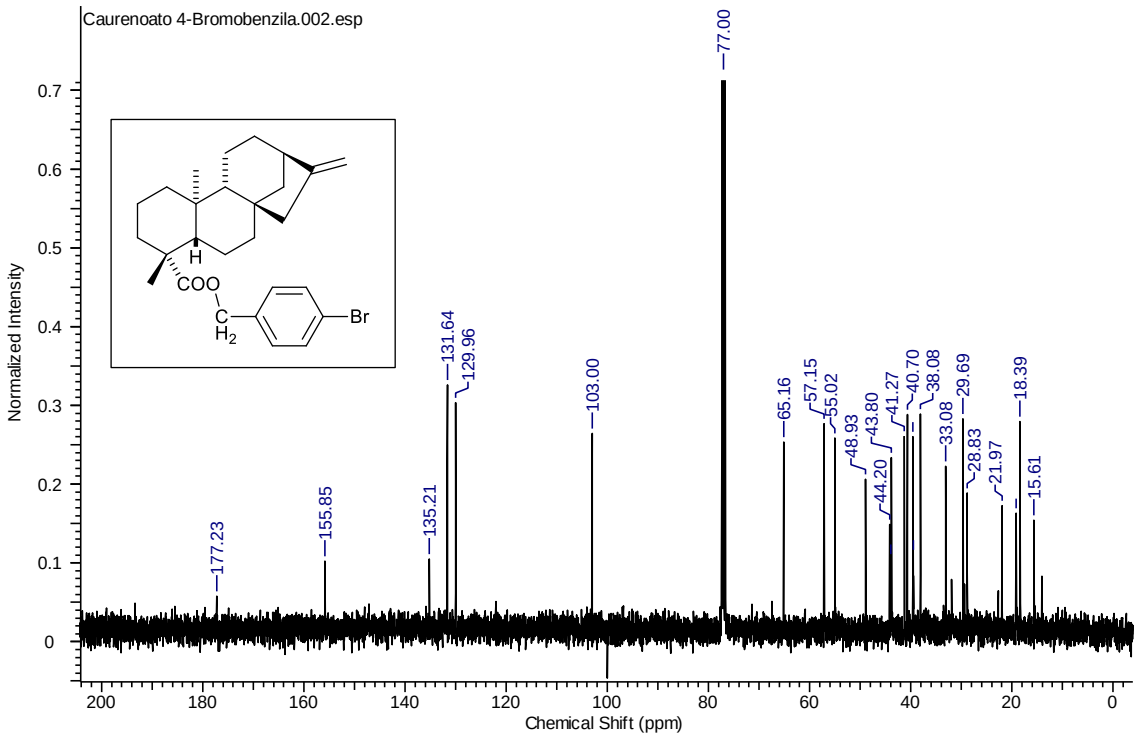


Fig. S32 Compound **7** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$

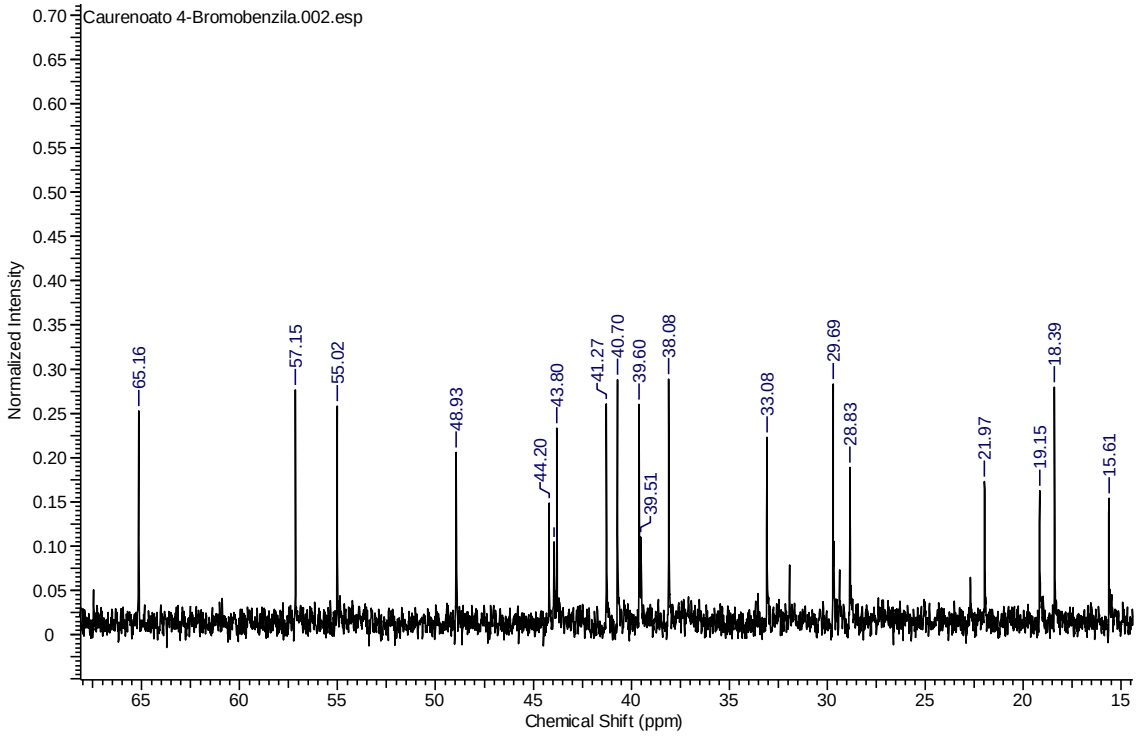


Fig. S33 Compound **7** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$ – Expansion

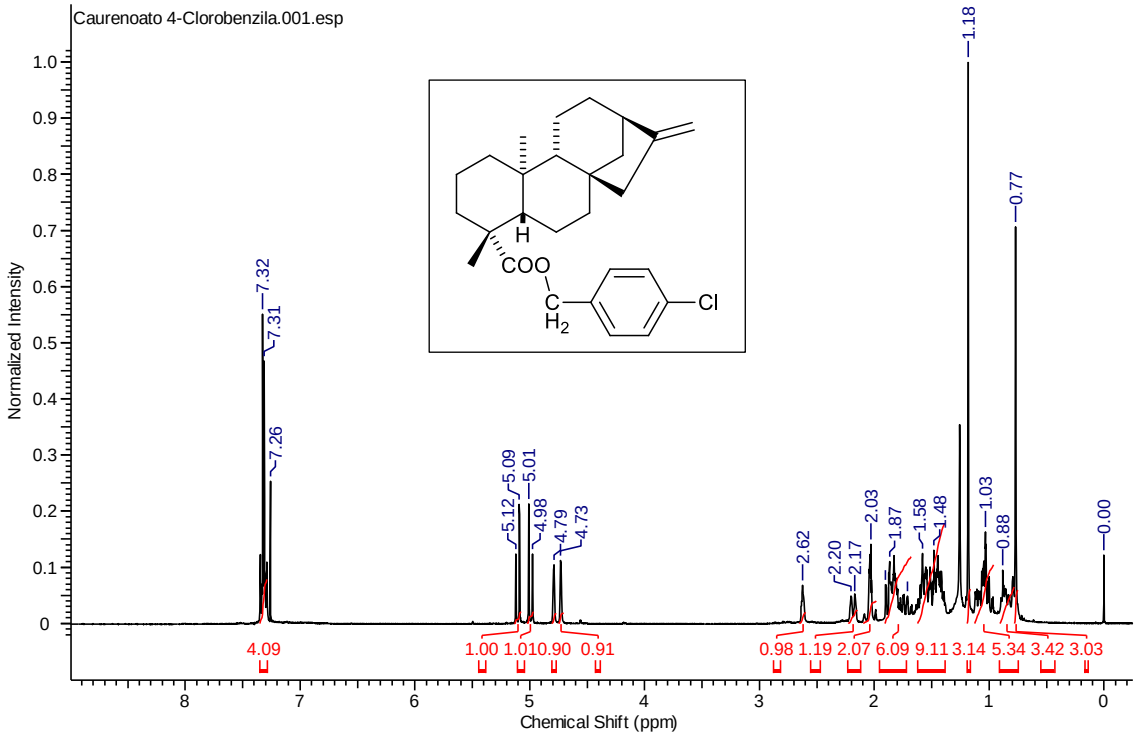


Fig. S34 Compound **8** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

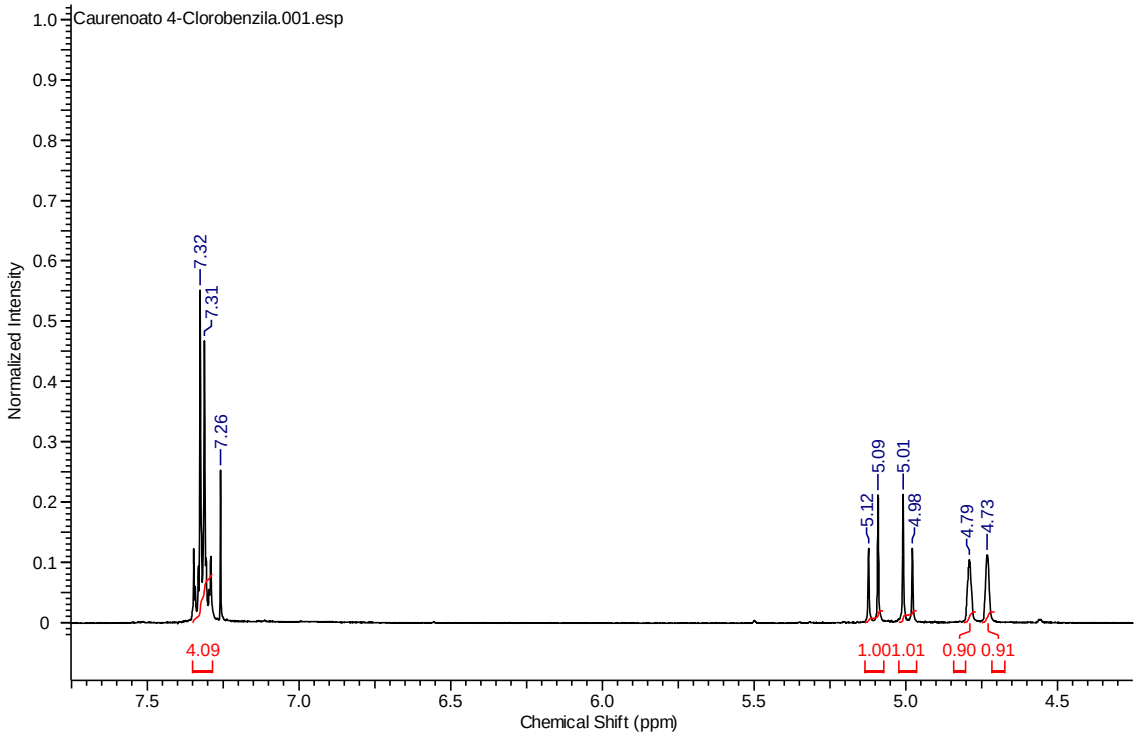


Fig. S35 Compound **8** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

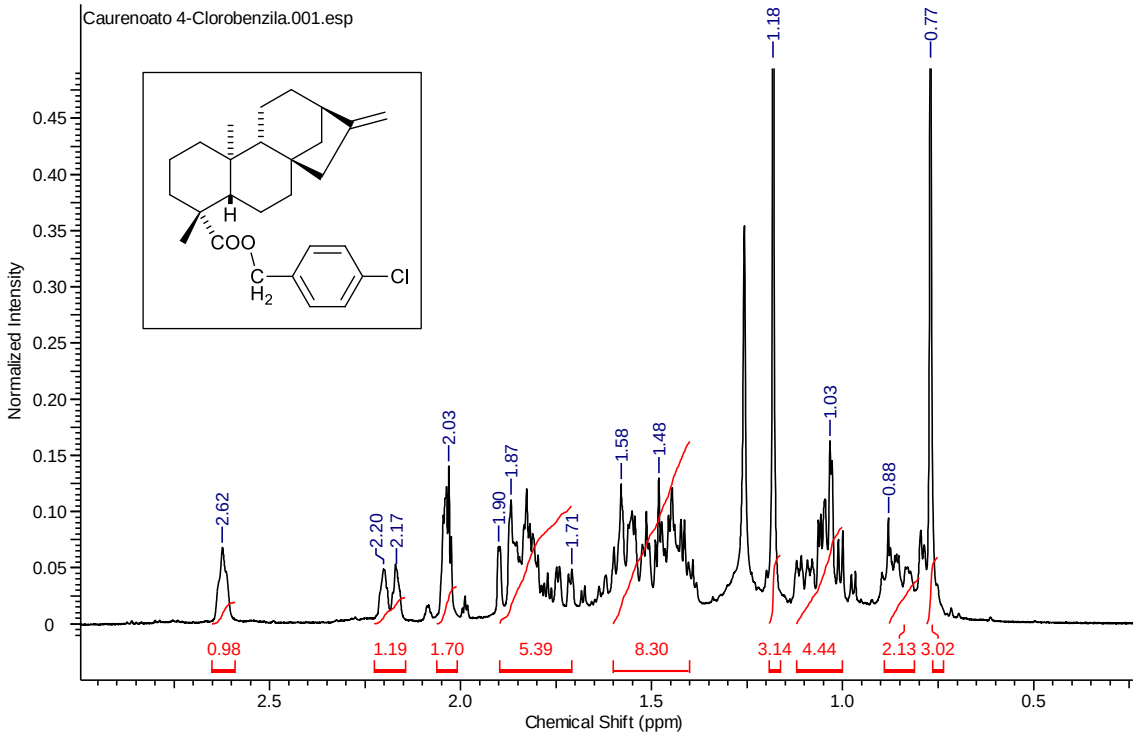


Fig. S36 Compound **8** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 2

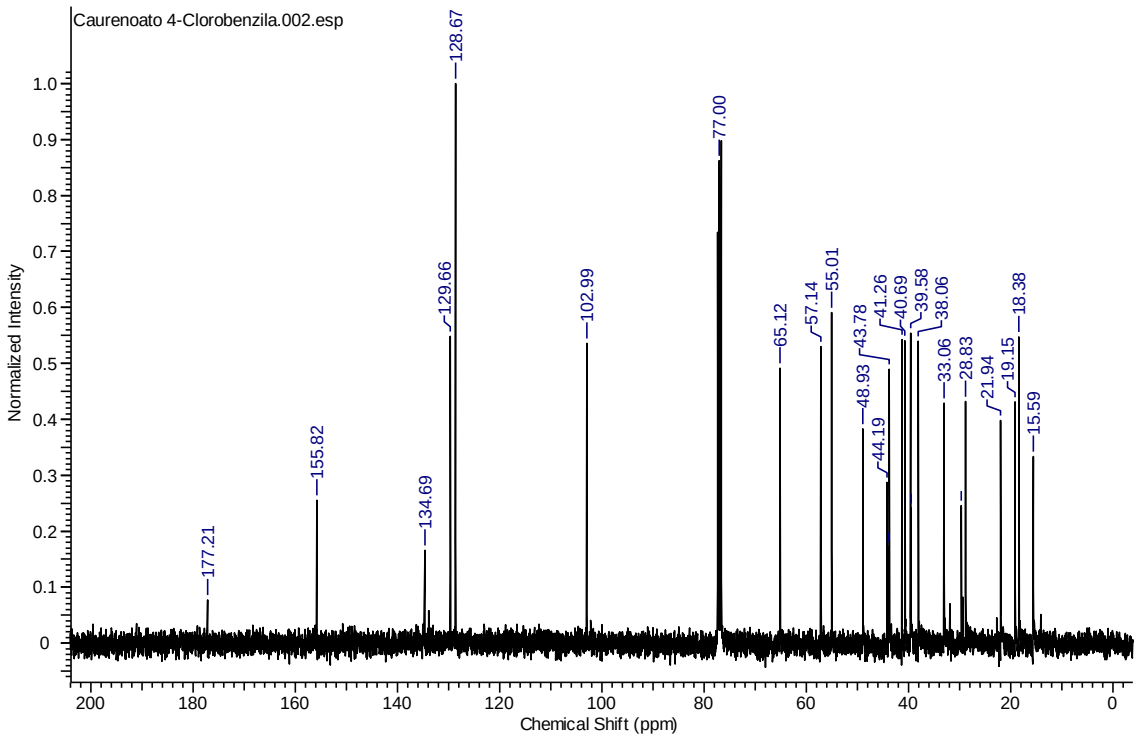


Fig. S37 Compound **8** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

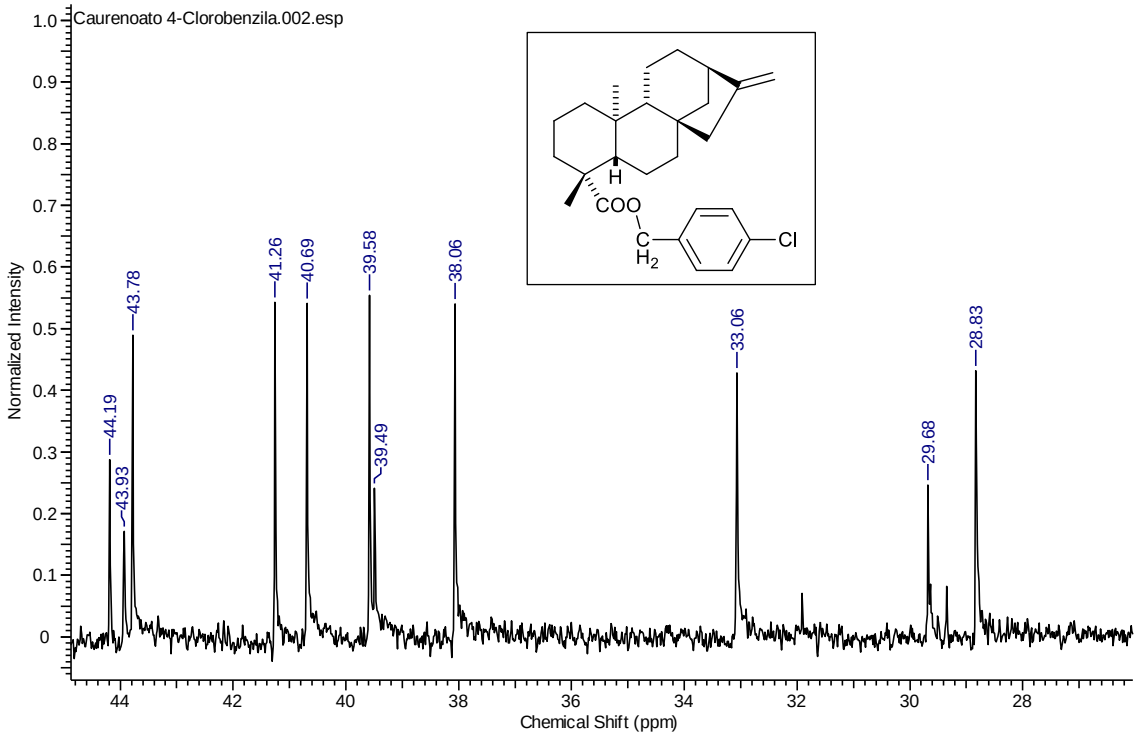


Fig. S38 Compound **8** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ – Expansion 1

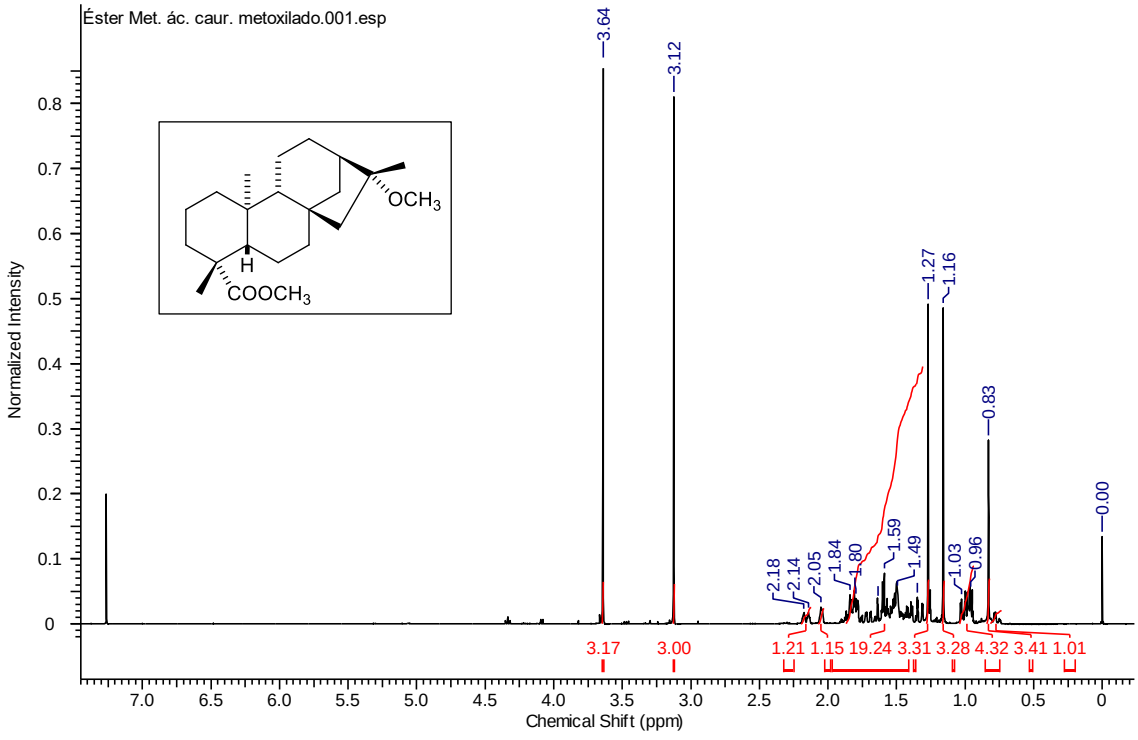


Fig. S39 Compound **9** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

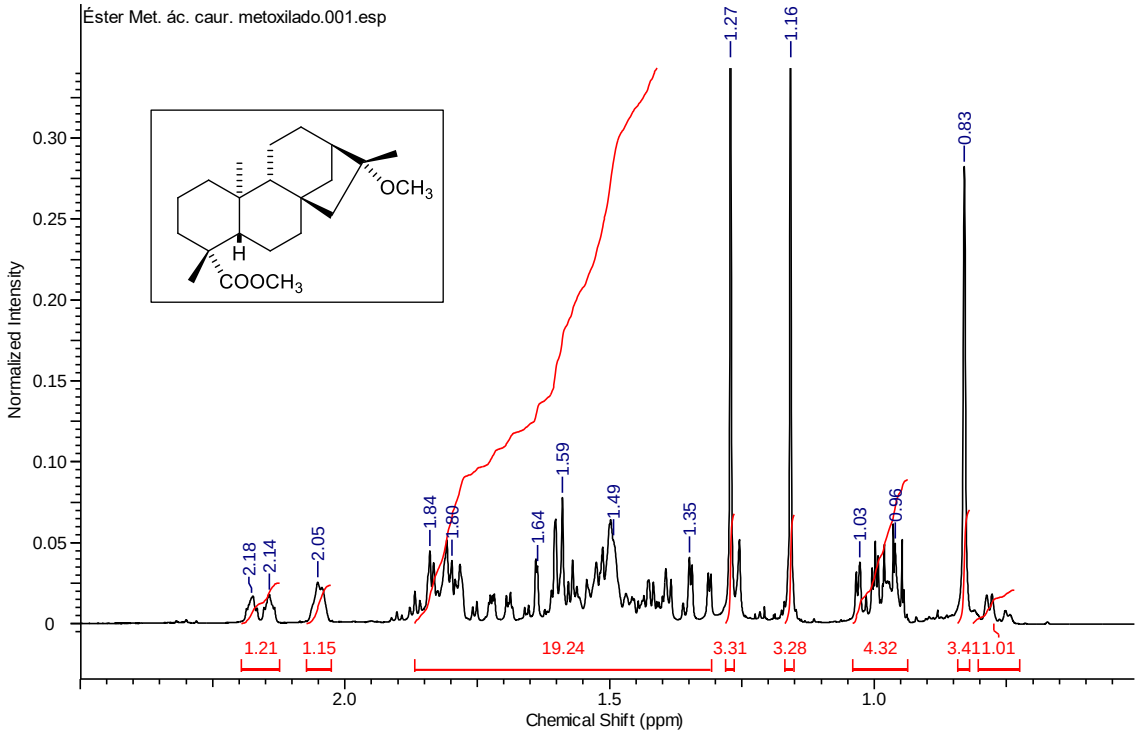


Fig. S40 Compound **9** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

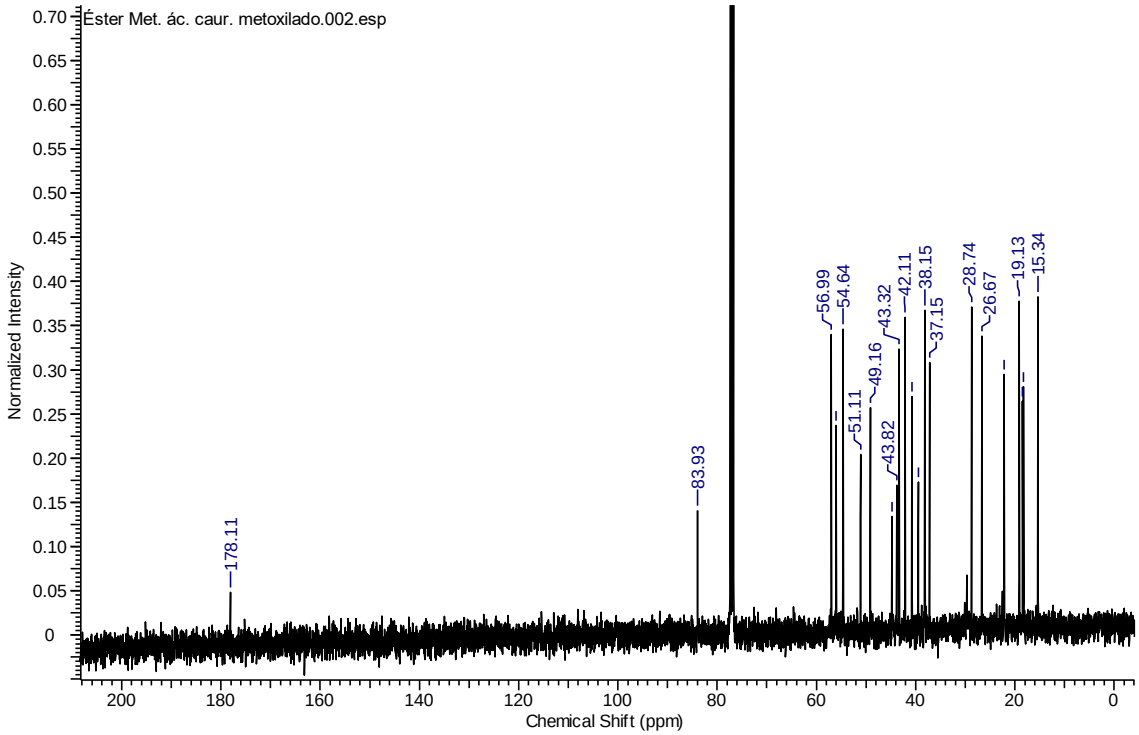


Fig. S41 Compound **9** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

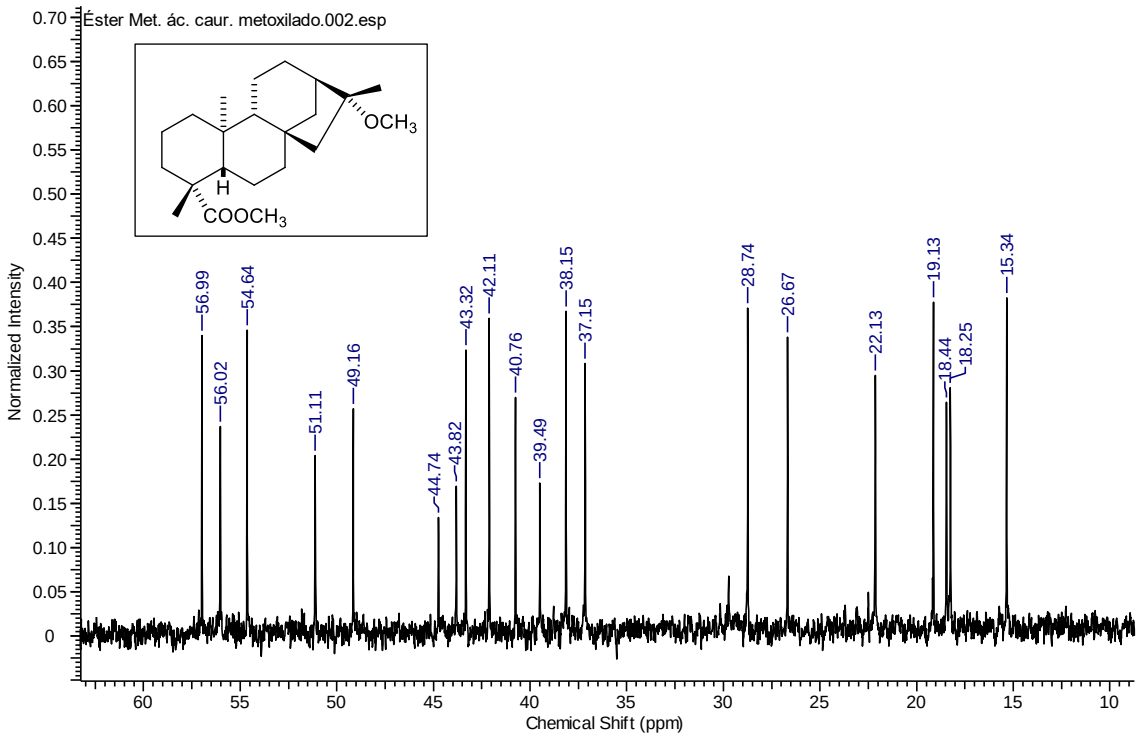


Fig. S42 Compound **9** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ - Expansion

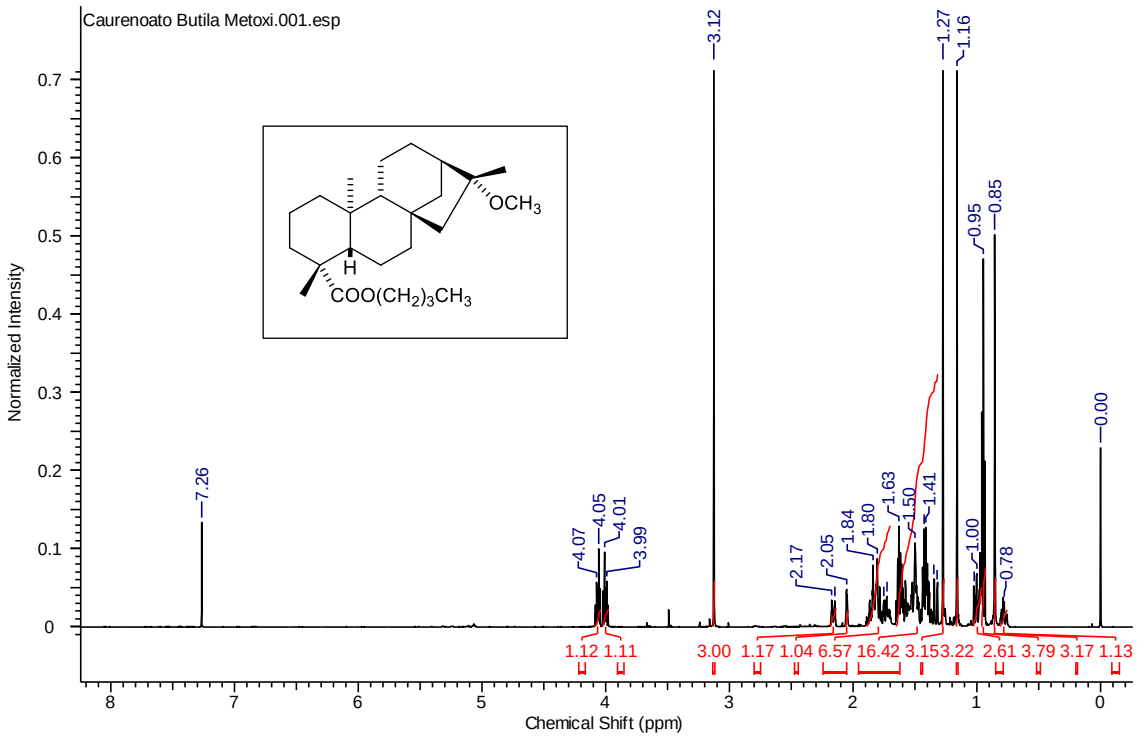


Fig. S43 Compound **10** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

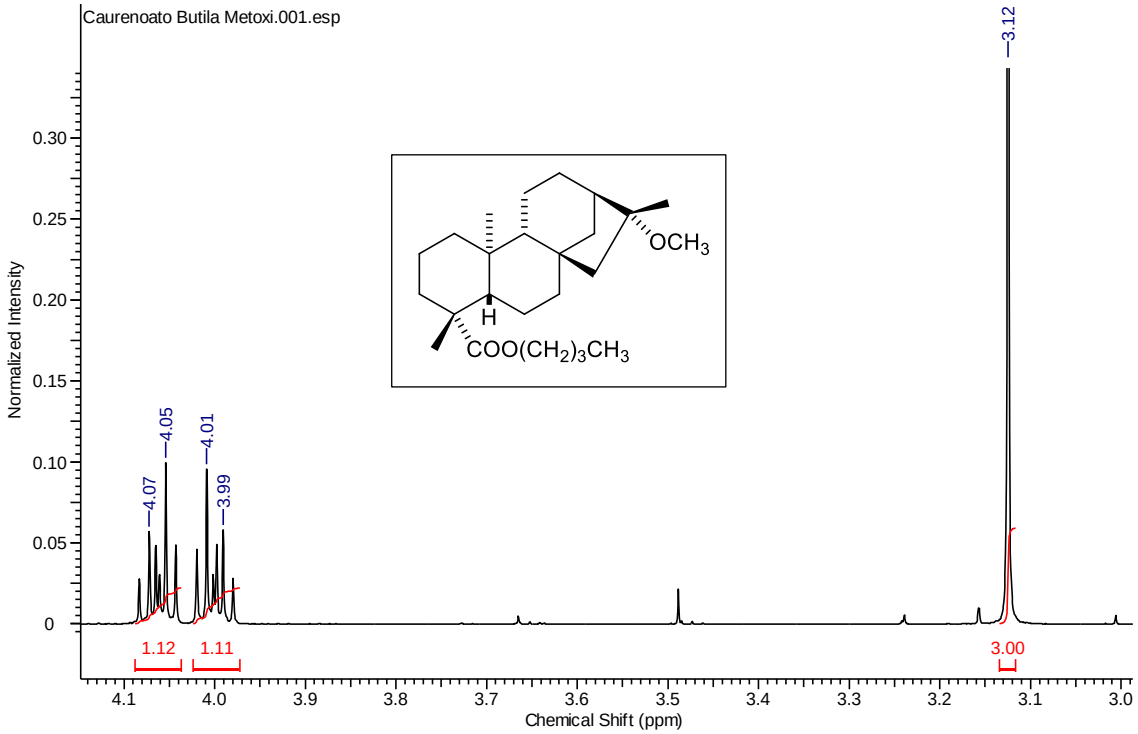


Fig. S44 Compound **10** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

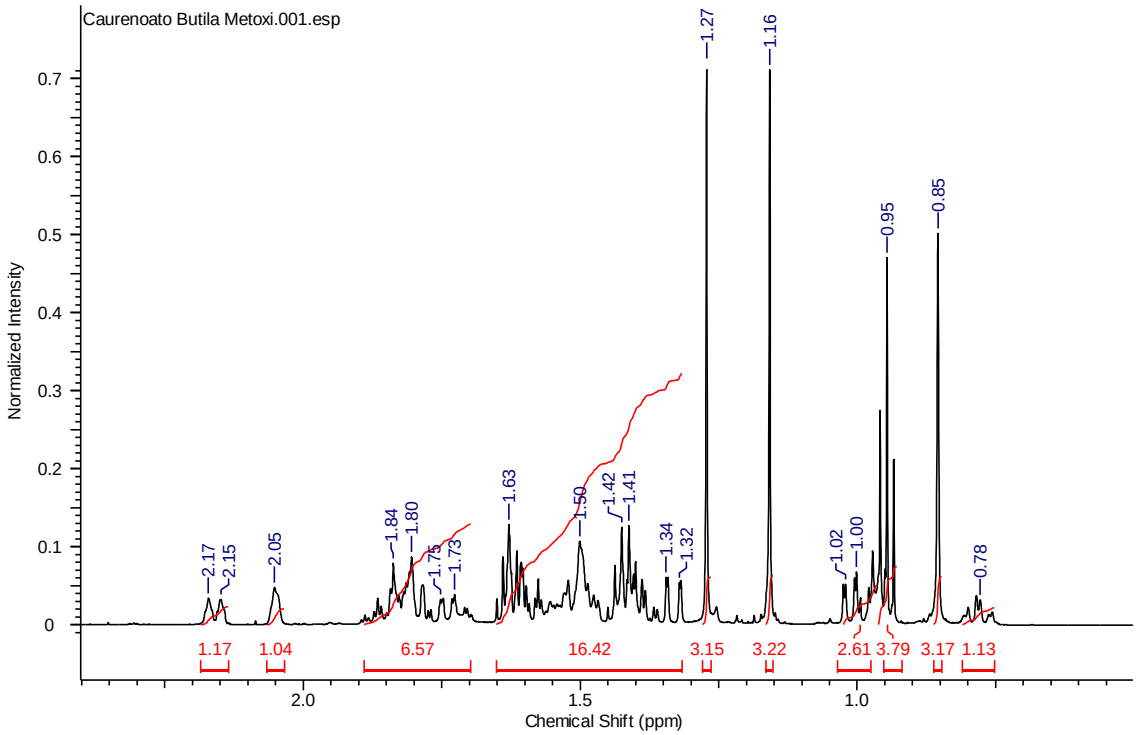


Fig. S45 Compound **10** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 2

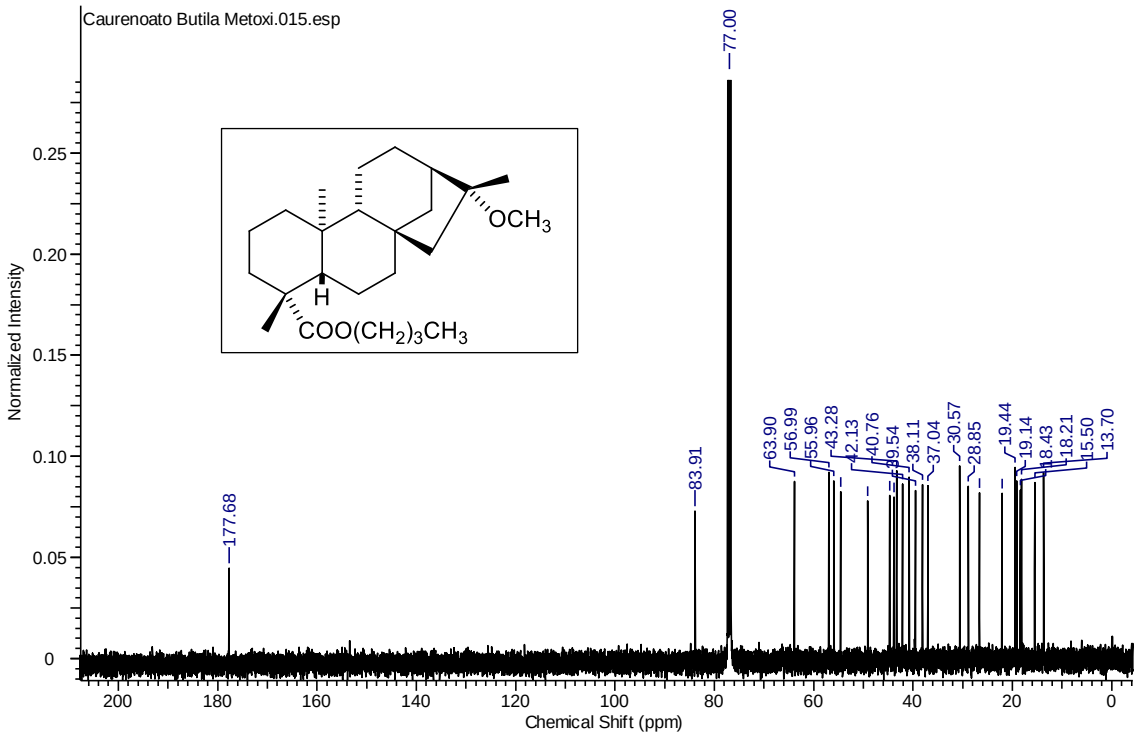


Fig. S46 Compound **10** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

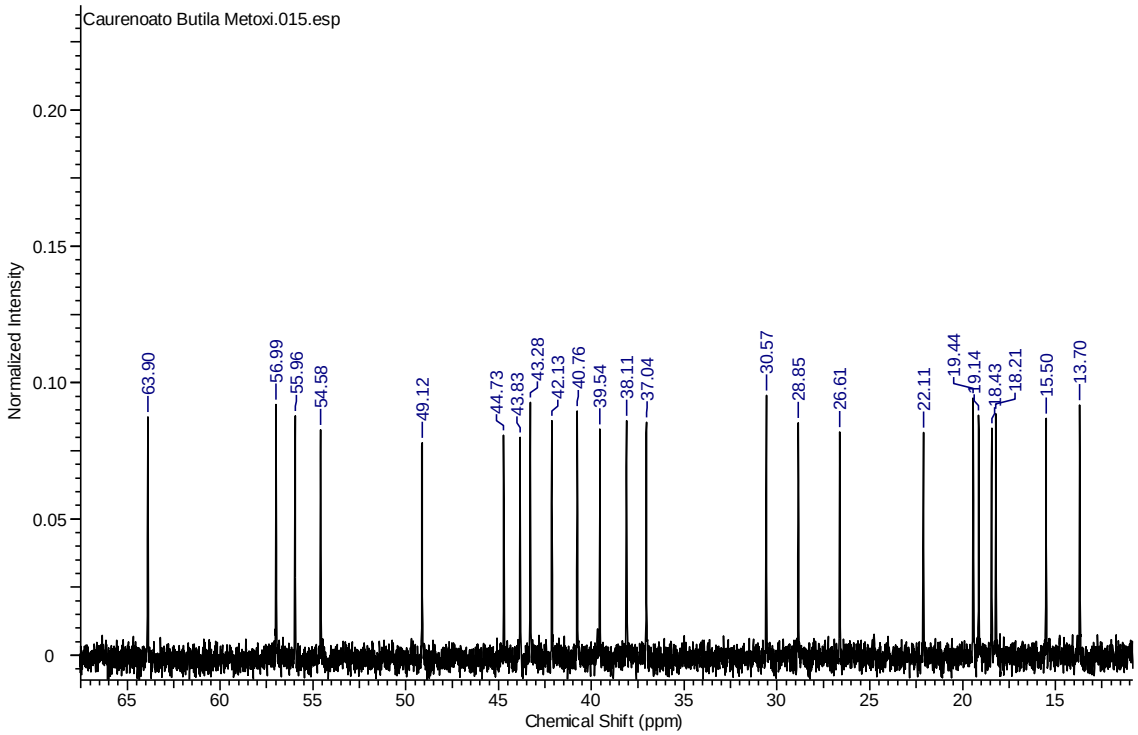


Fig. S47 Compound **10** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ - Expansion

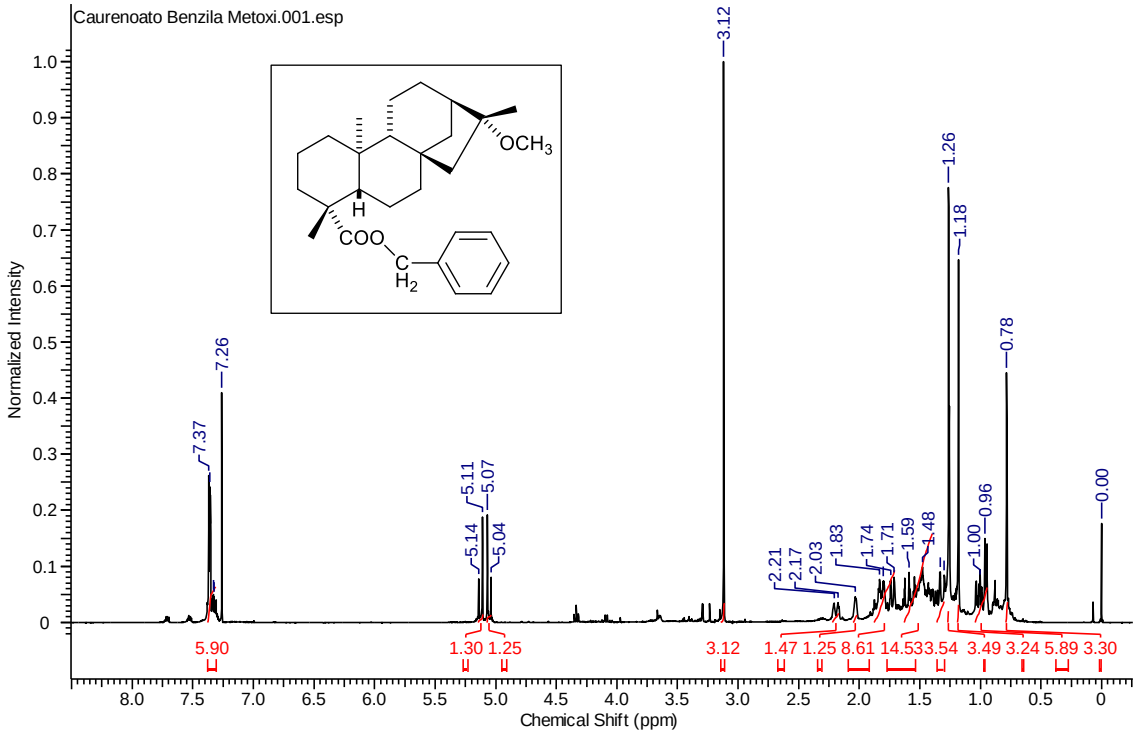


Fig. S48 Compound **11** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

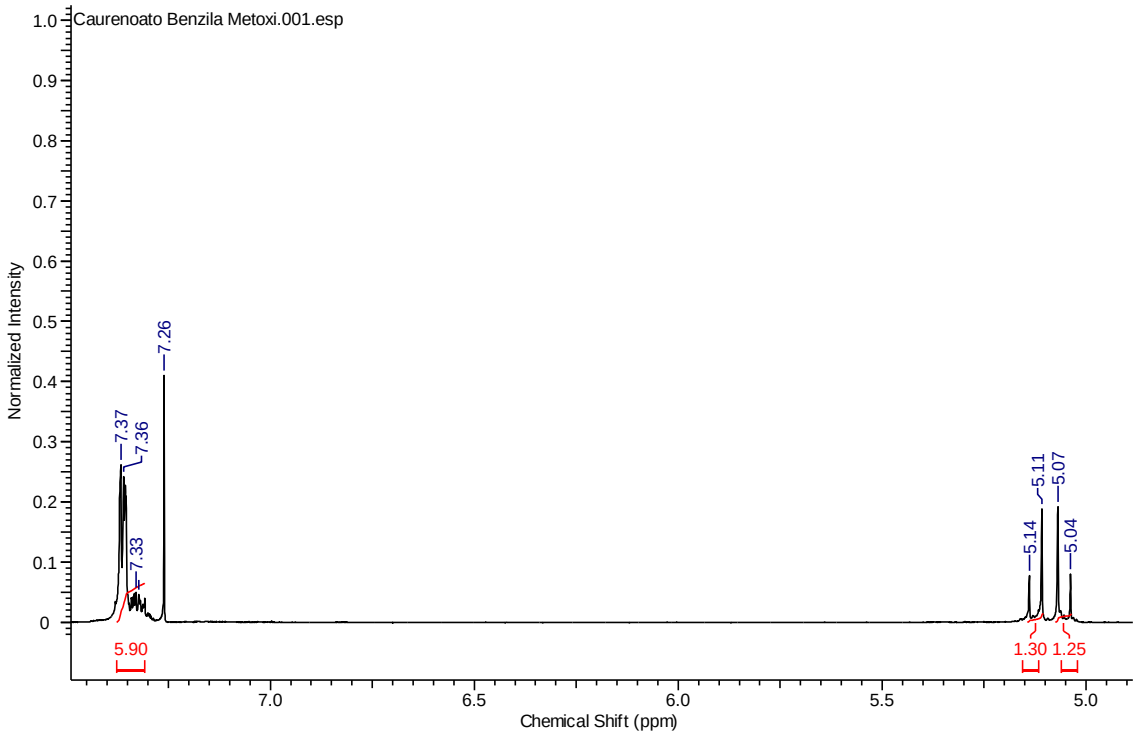


Fig. S49 Compound **11** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

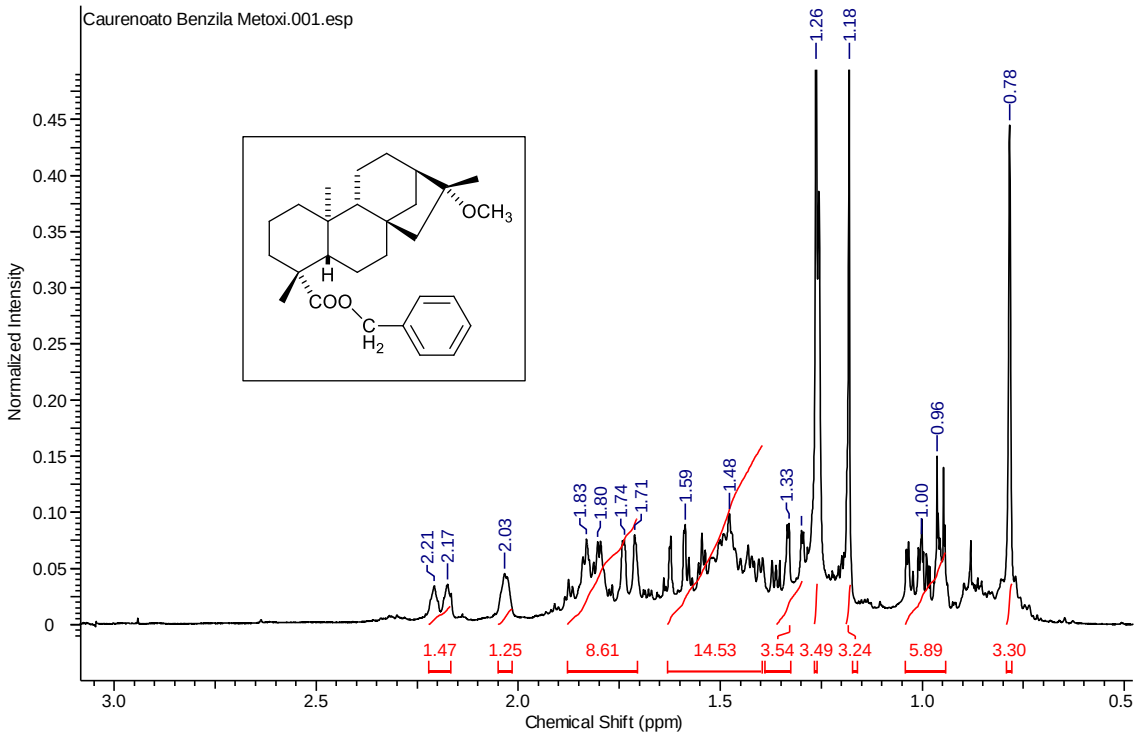


Fig. S50 Compound **11** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 2

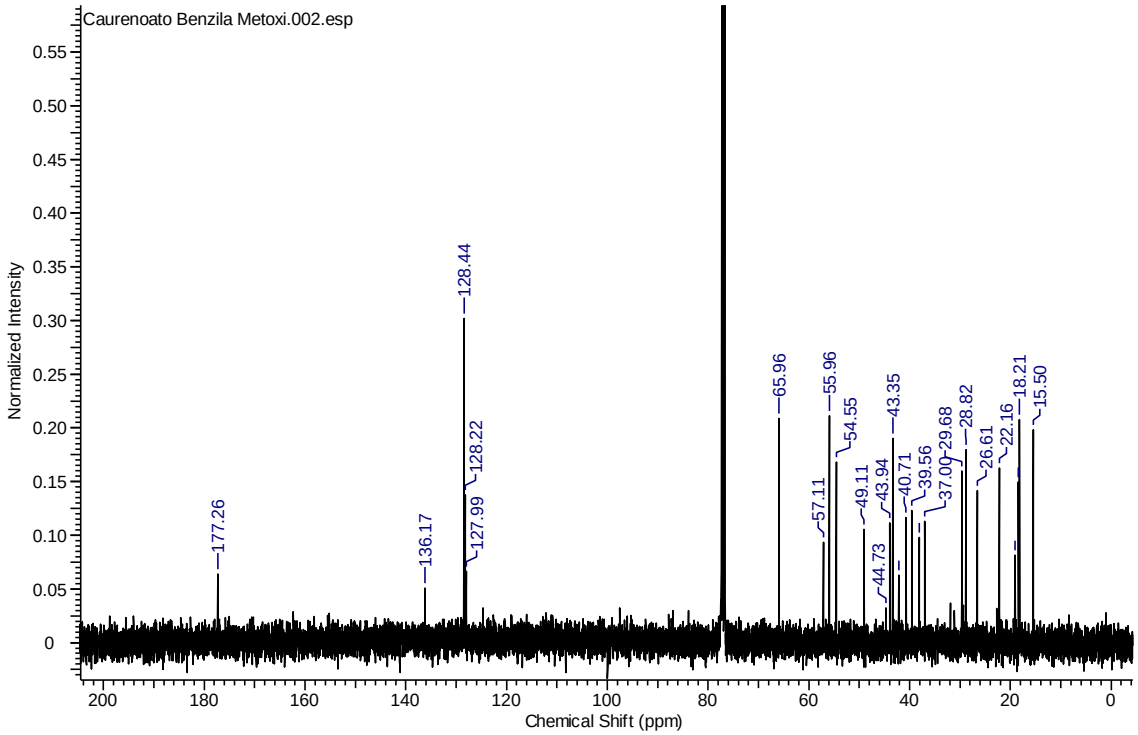


Fig. S51 Compound **11** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

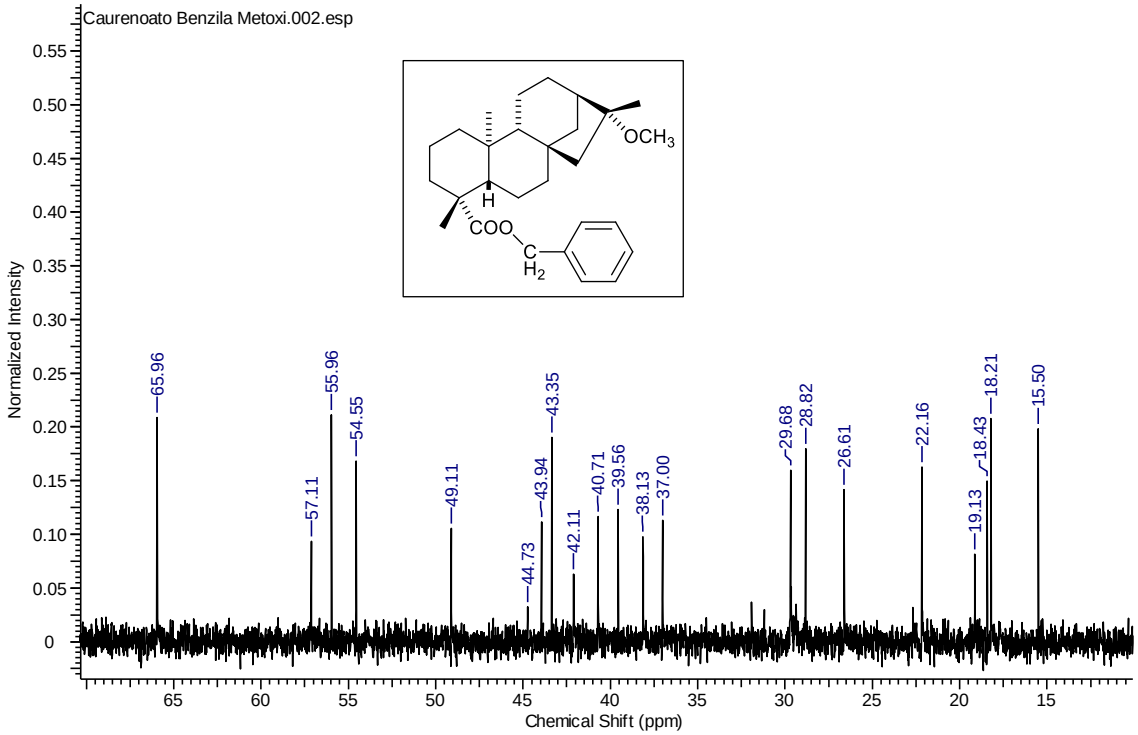


Fig. S52 Compound **11** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ - Expansion

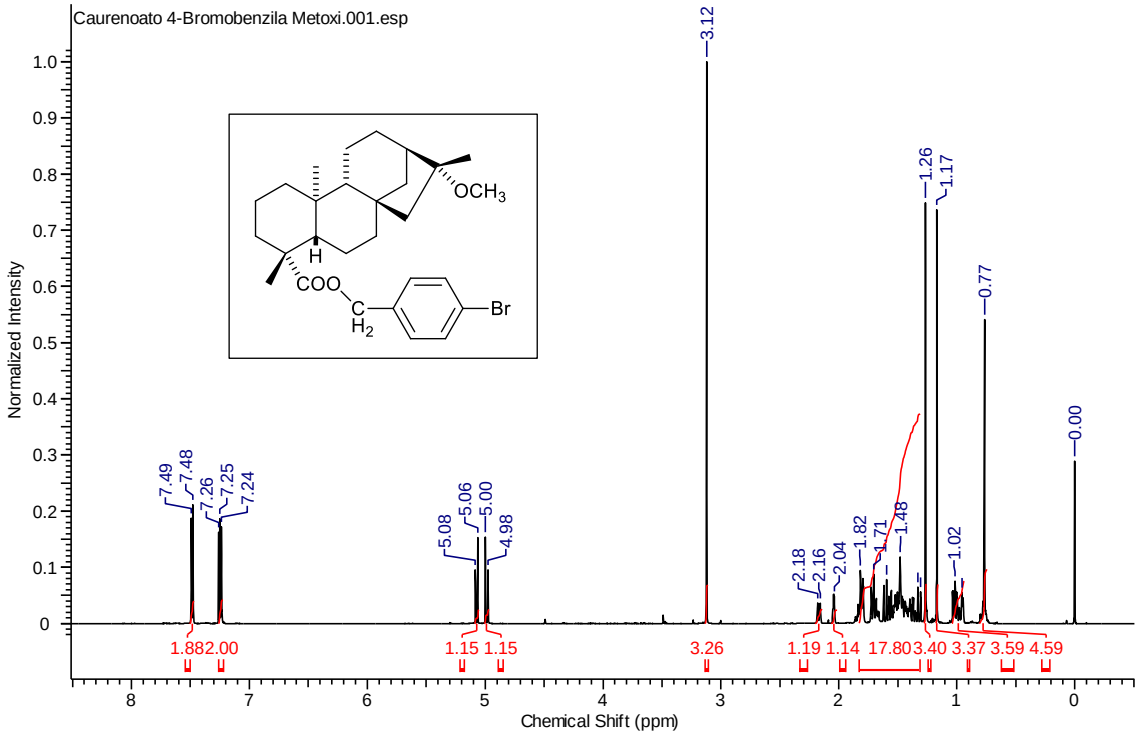


Fig. S53 Compound **12** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

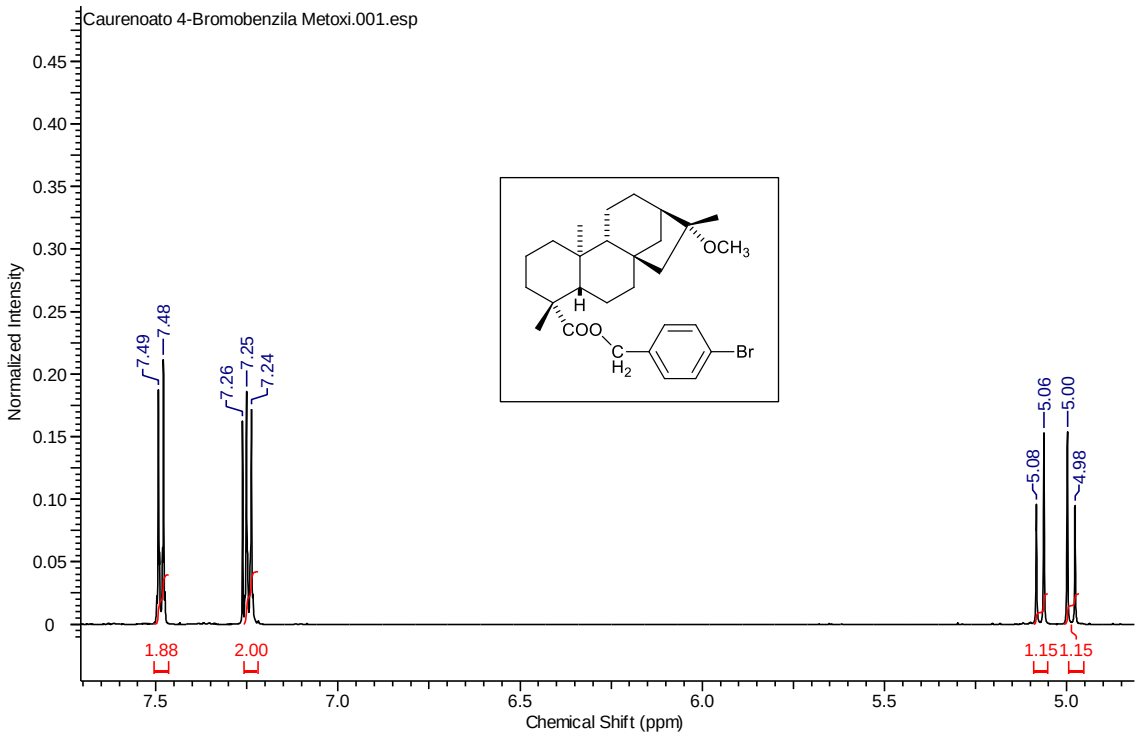


Fig. S54 Compound **12** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

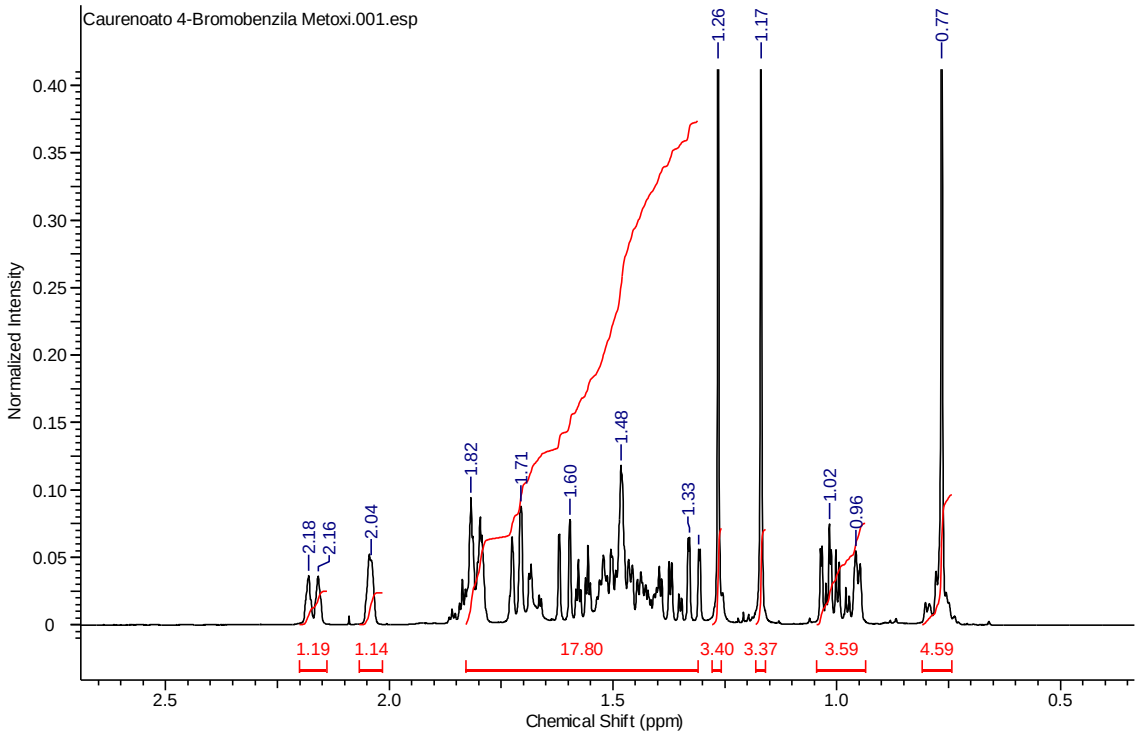


Fig. S55 Compound **12** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 2

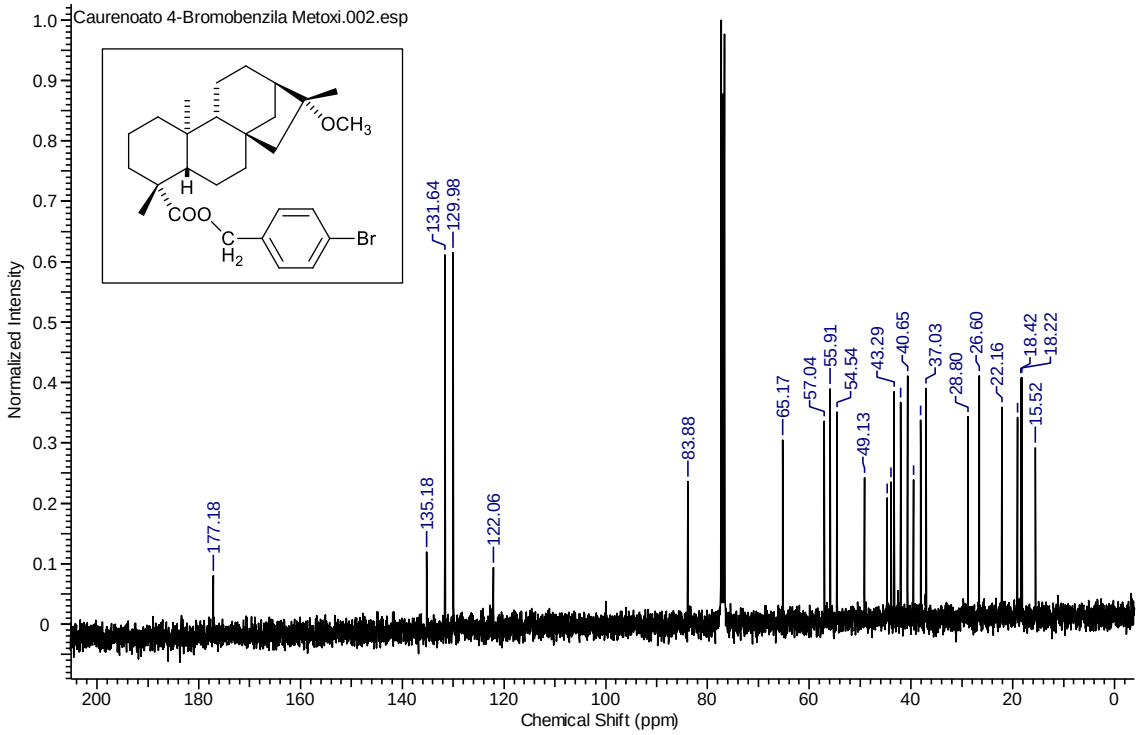


Fig. S56 Compound **12** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

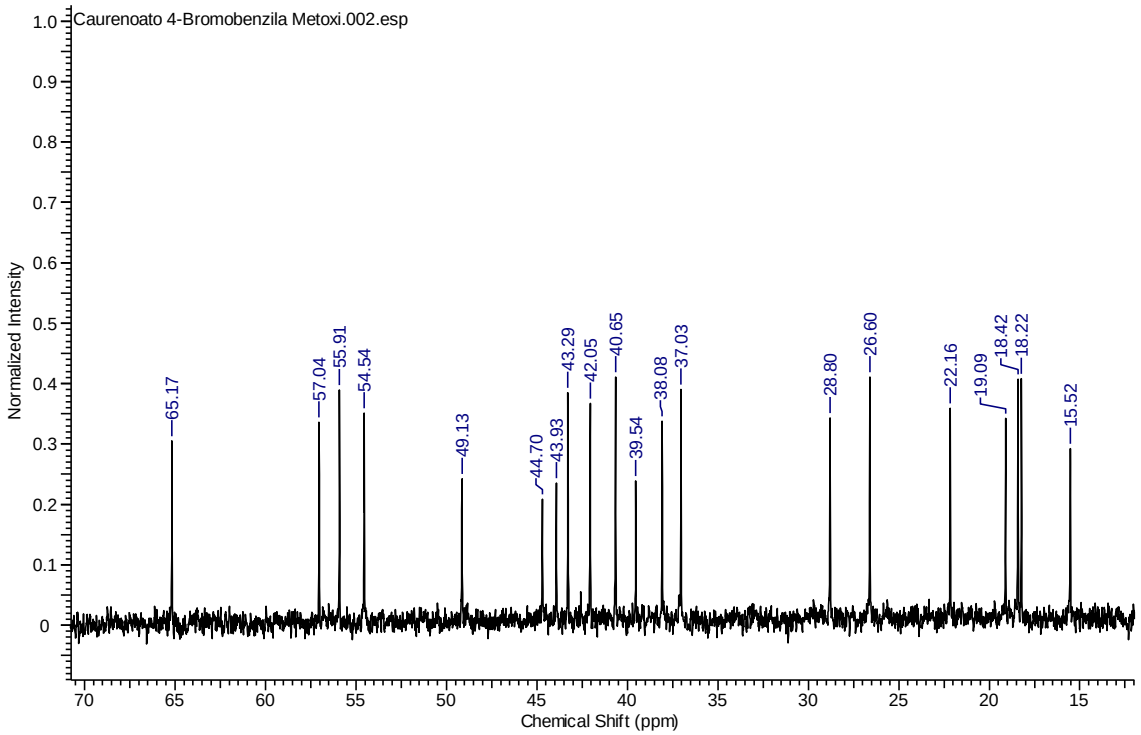


Fig. S57 Compound **12** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ - Expansion

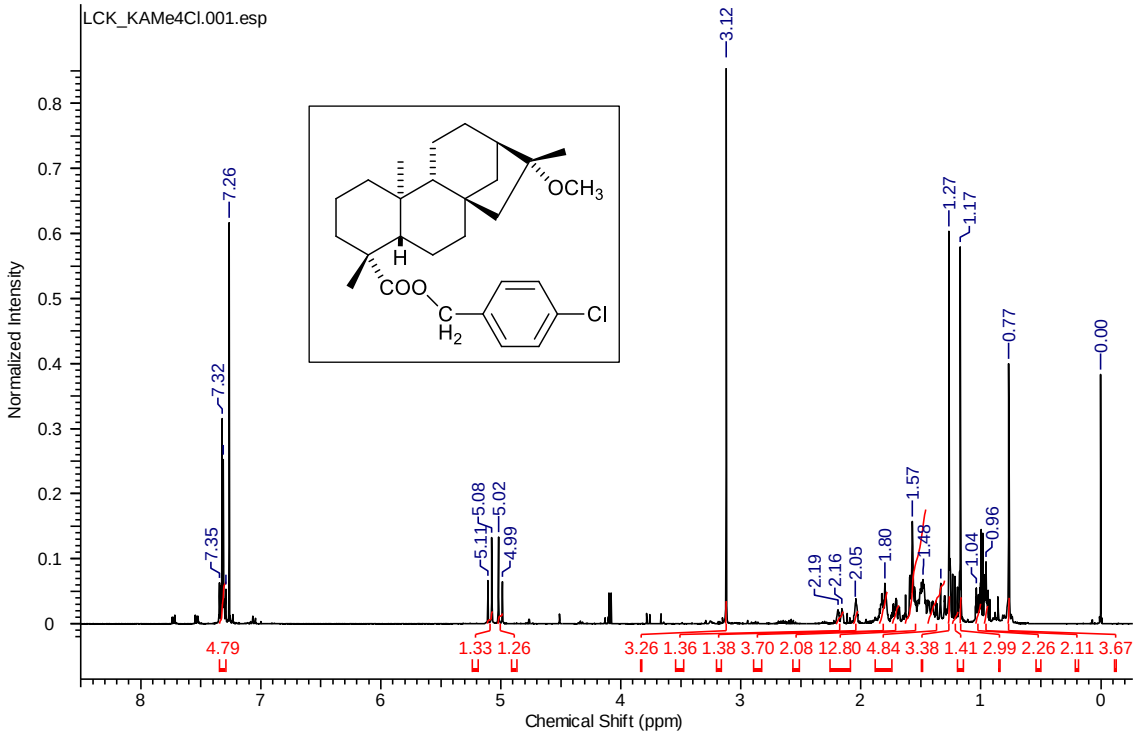


Fig. S58 Compound **13** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$

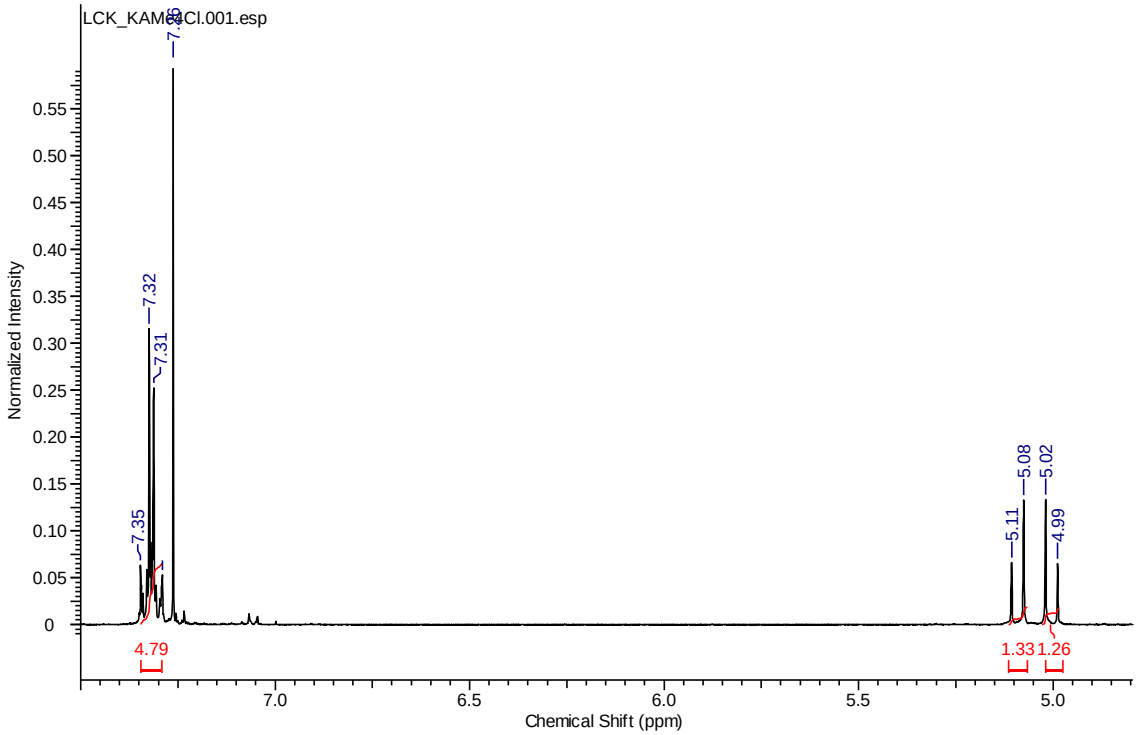


Fig. S59 Compound **13** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 1

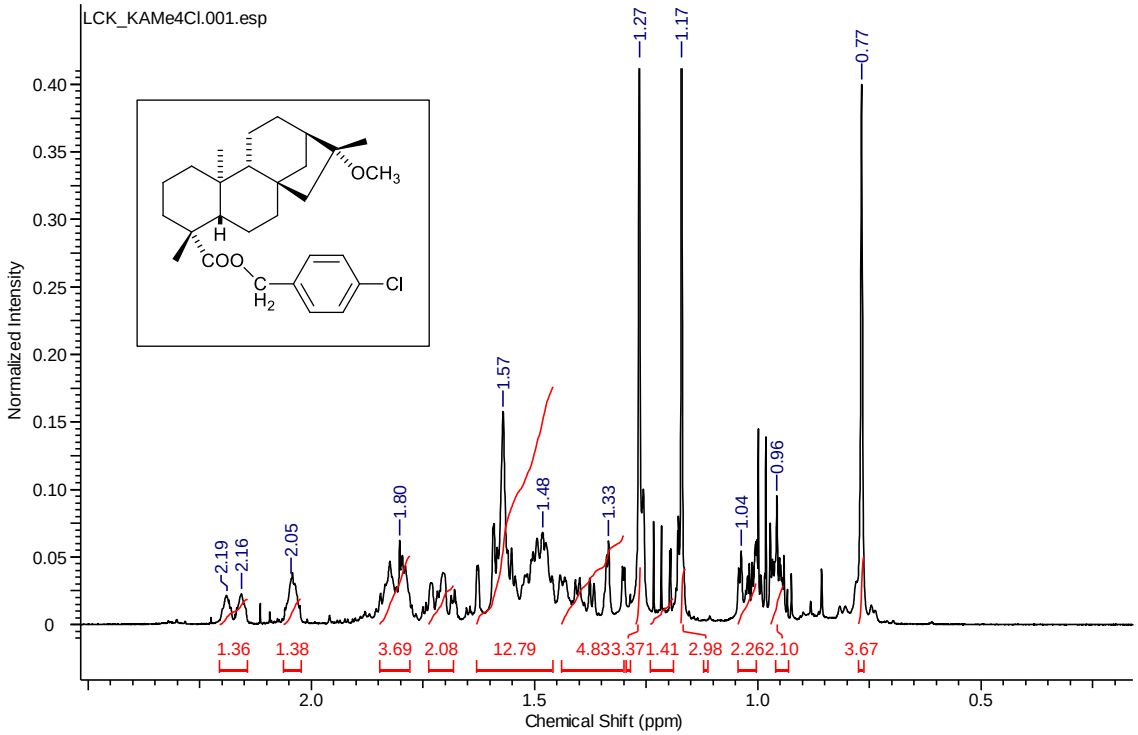


Fig. S60 Compound **13** ^{1}H-NMR spectrum, 500MHz, $CDCl_3$ – Expansion 2

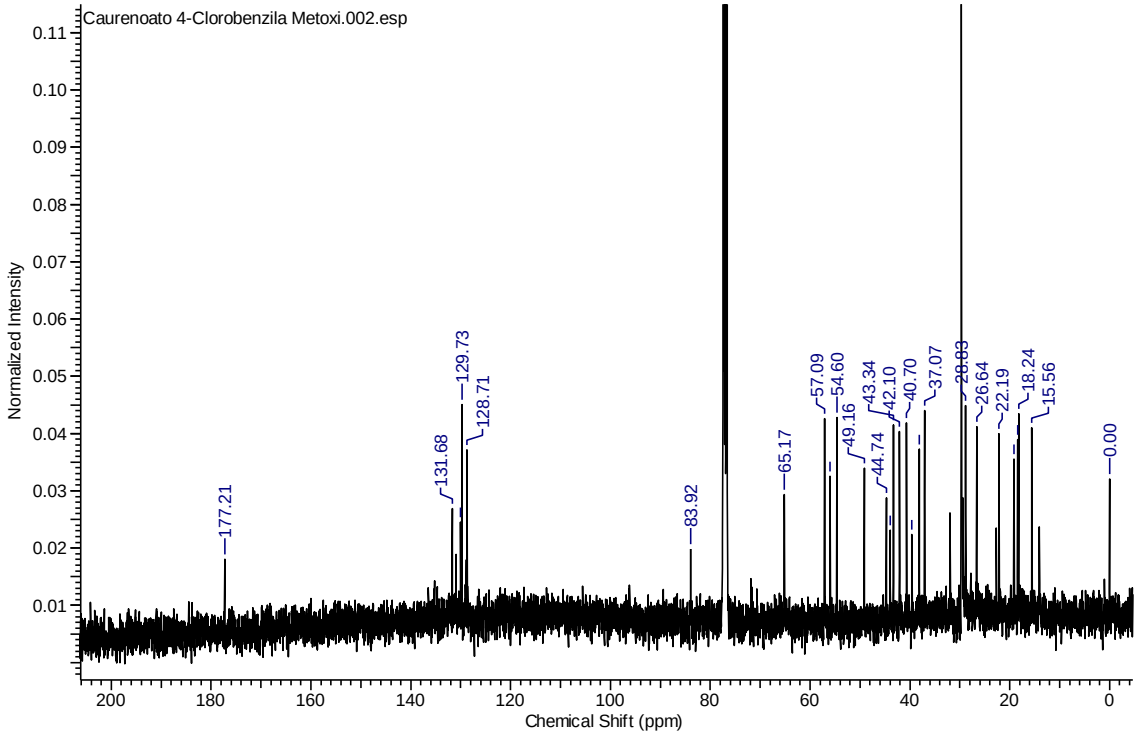


Fig. S61 Compound **13** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$

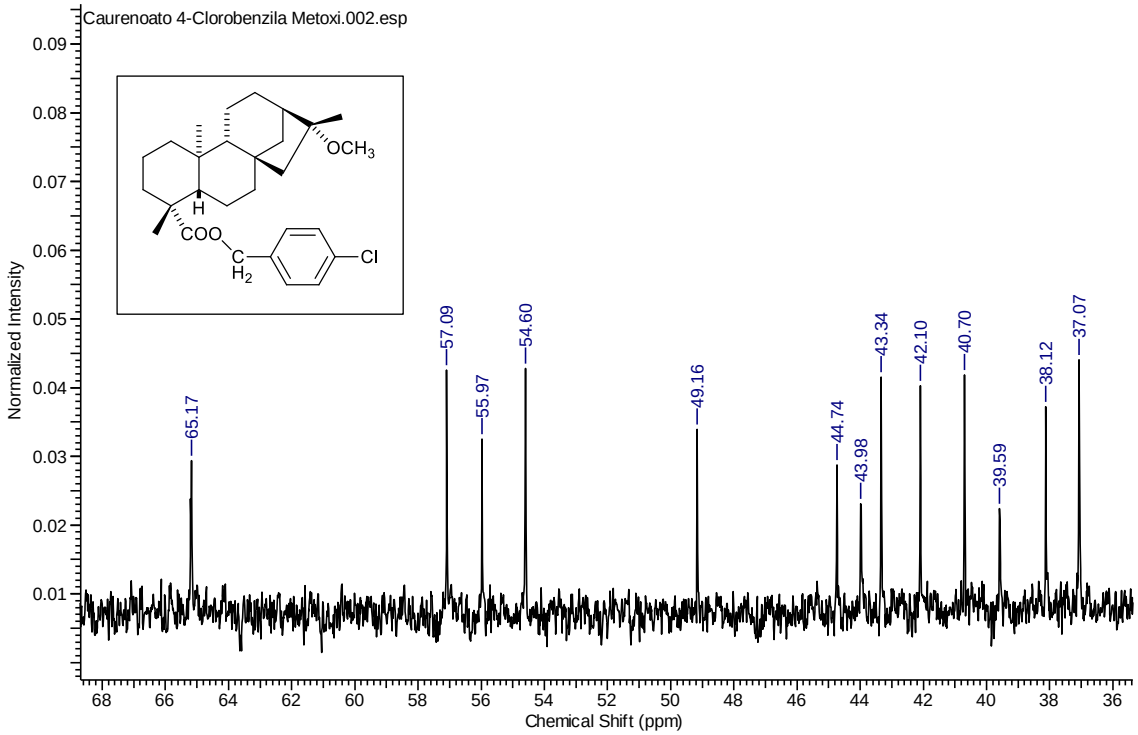


Fig. S62 Compound **13** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ – Expansion 1

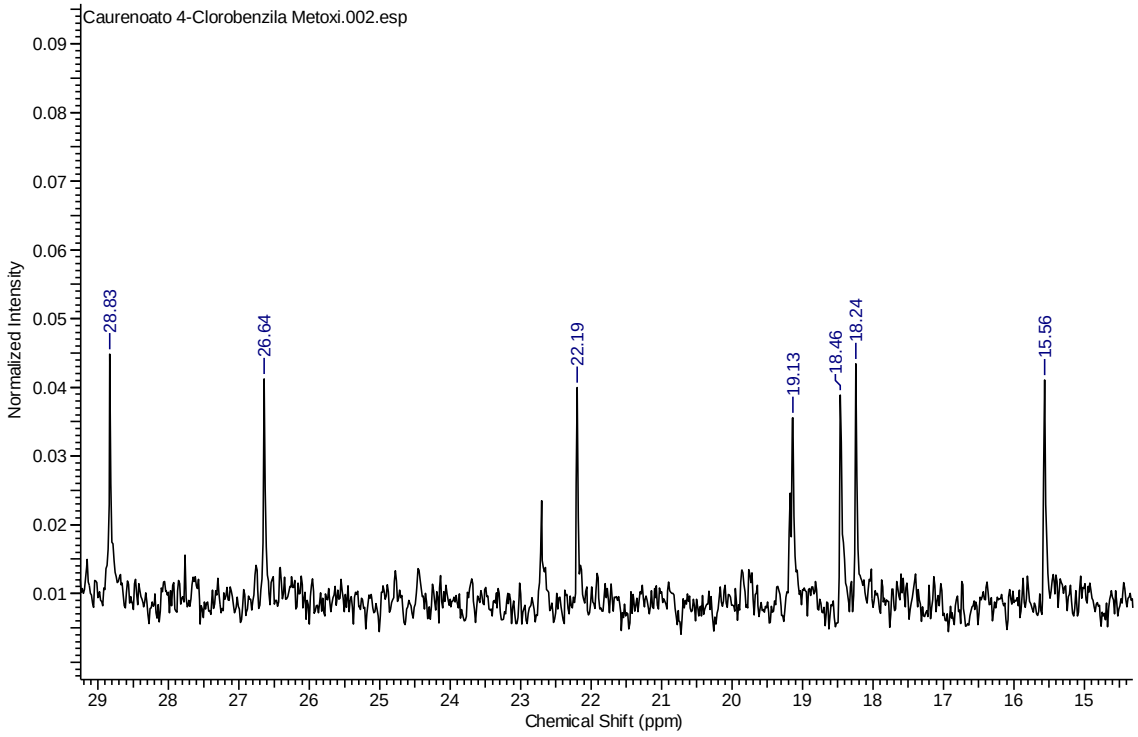


Fig. S63 Compound **13** ^{13}C-NMR spectrum, 125MHz, $CDCl_3$ – Expansion 2

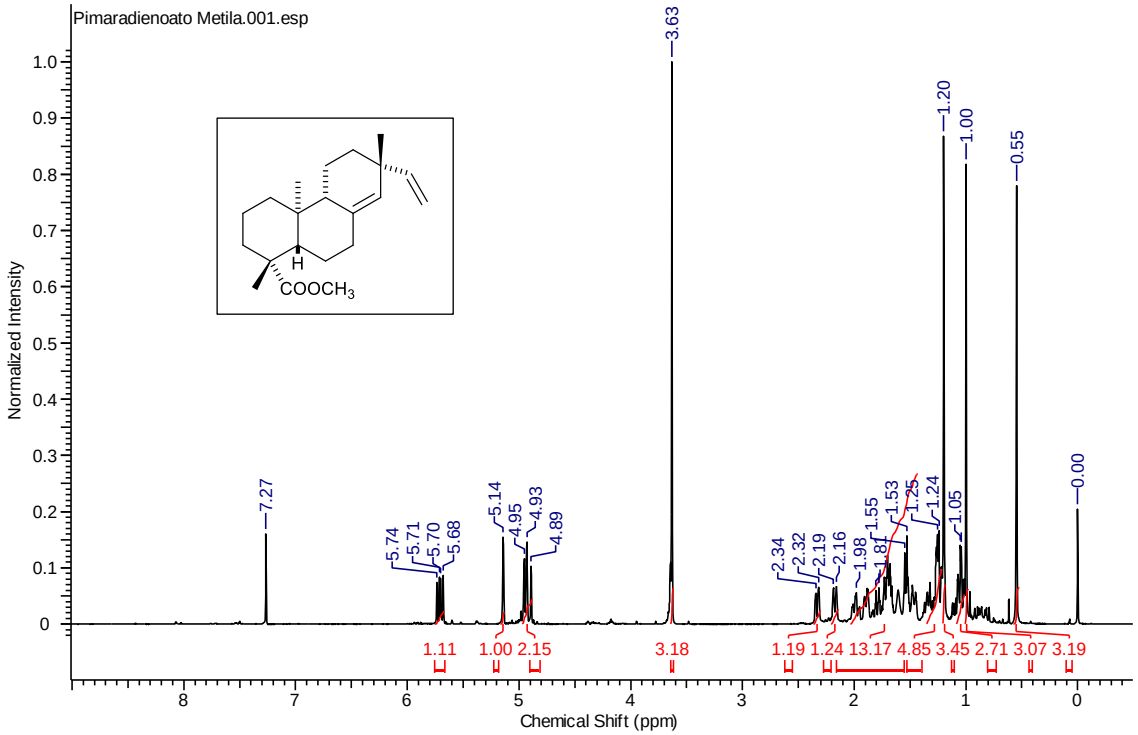


Fig. S64 Compound **14** ^{1}H-NMR spectrum, 300MHz, $CDCl_3$

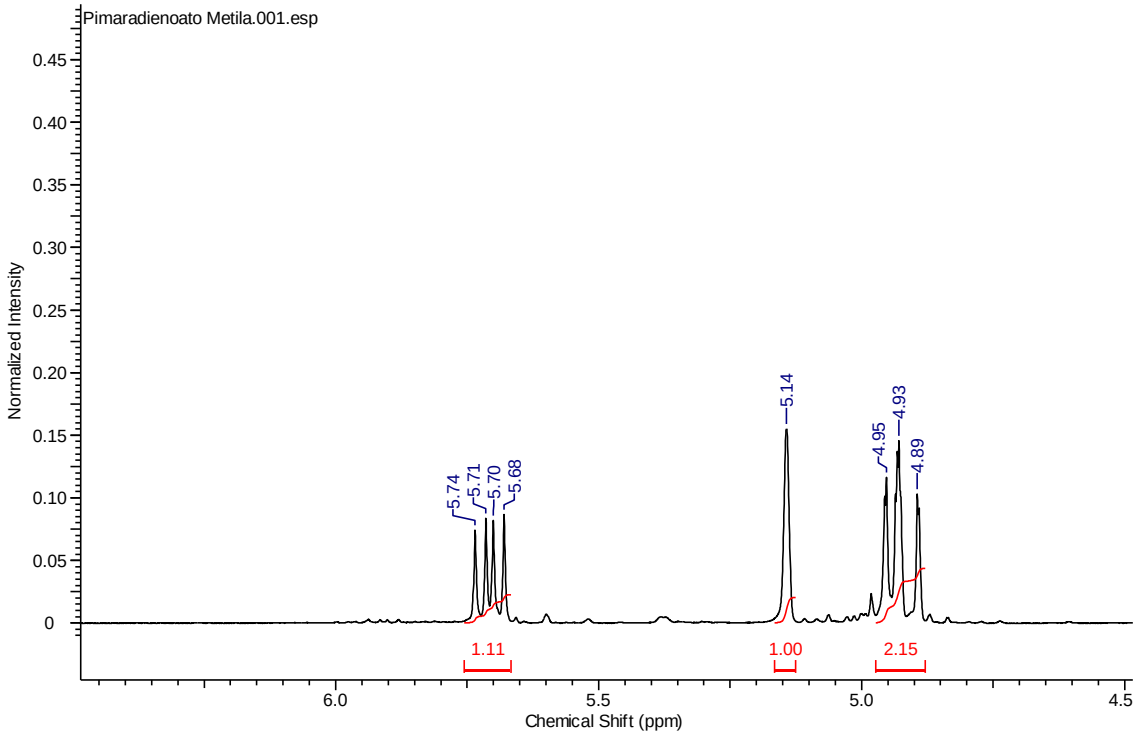


Fig. S65 Compound **14** ^{1}H-NMR spectrum, 300MHz, $CDCl_3$ – Expansion 1

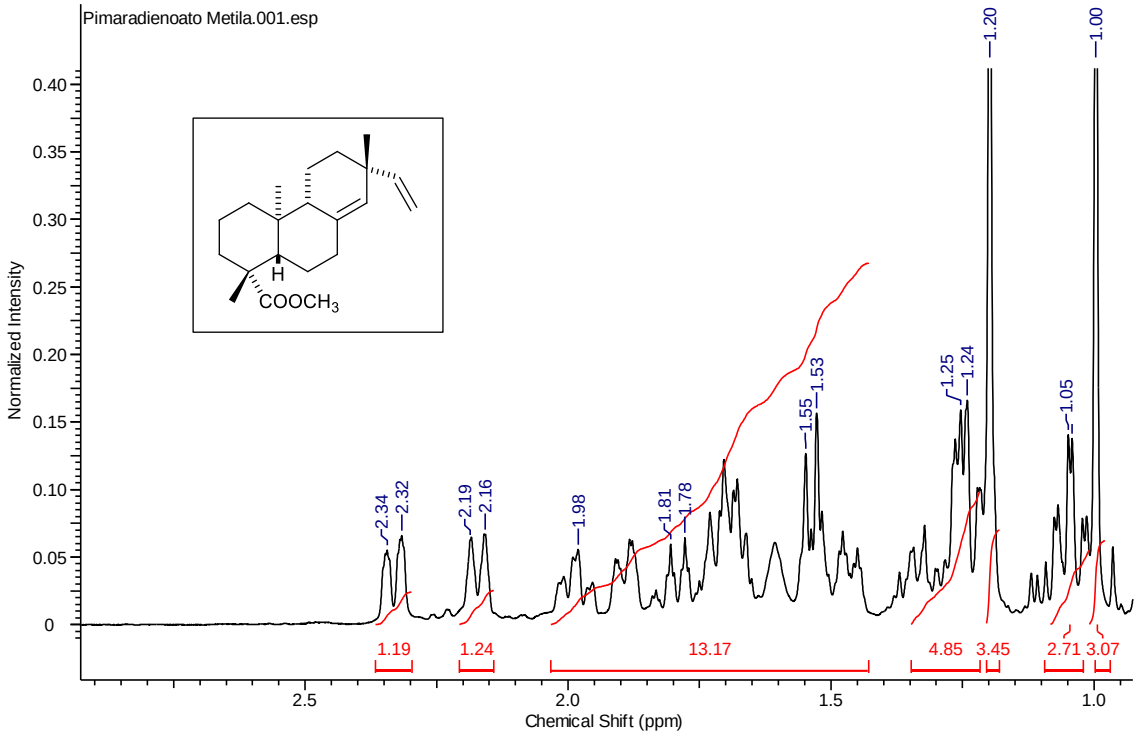


Fig. S66 Compound **14** ^{1}H-NMR spectrum, 300MHz, $CDCl_3$ – Expansion 2

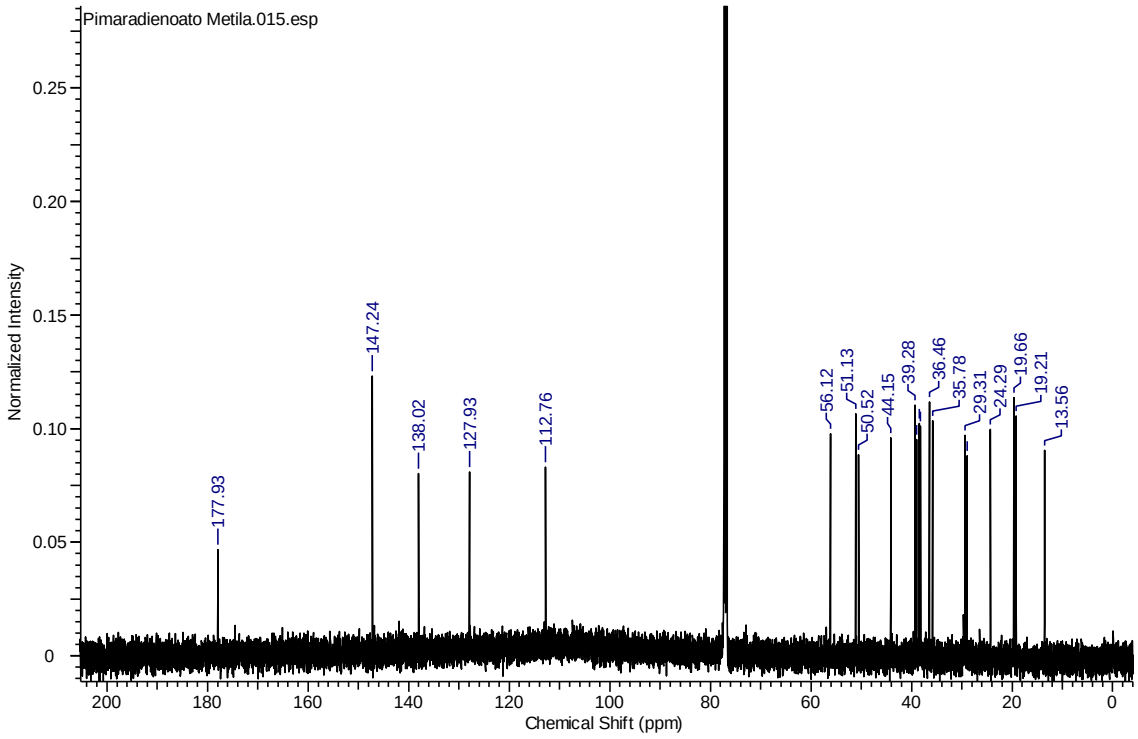


Fig. S67 Compound **14** ^{13}C-NMR spectrum, 75MHz, $CDCl_3$

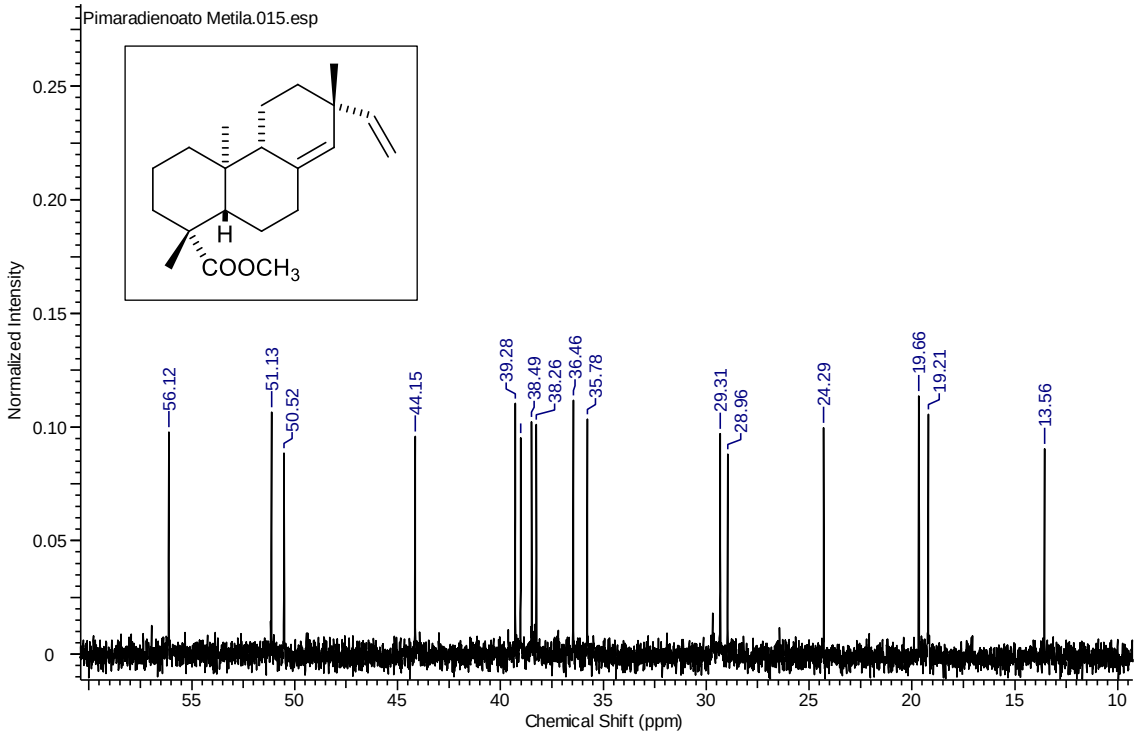


Fig. S68 Compound **14** ^{13}C-NMR spectrum, 75MHz, $CDCl_3$ - Expansion

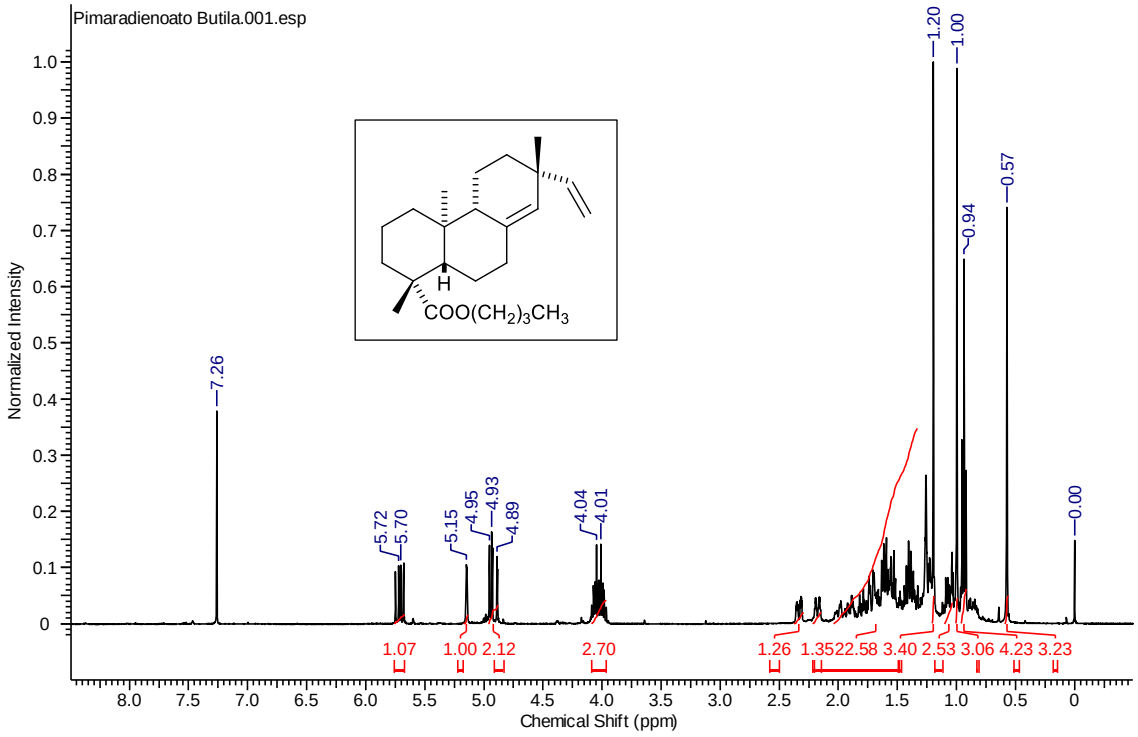


Fig. S69 Compound **15** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$

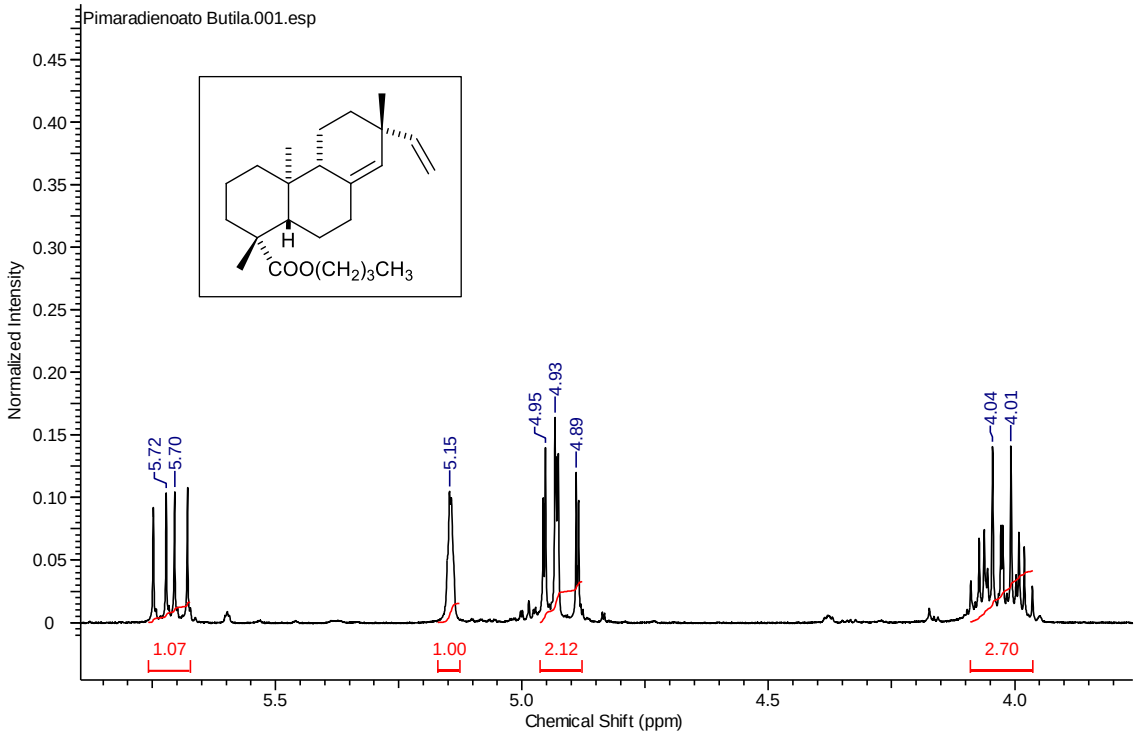


Fig. S70 Compound **15** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 1

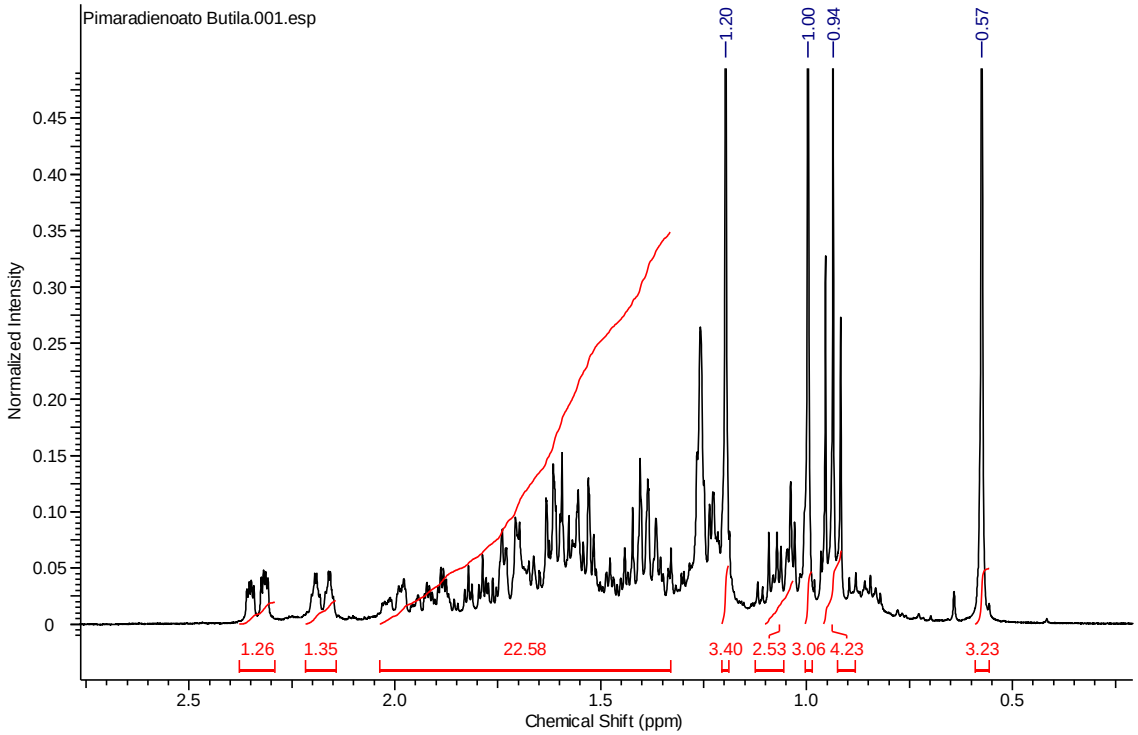


Fig. S71 Compound **15** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 2

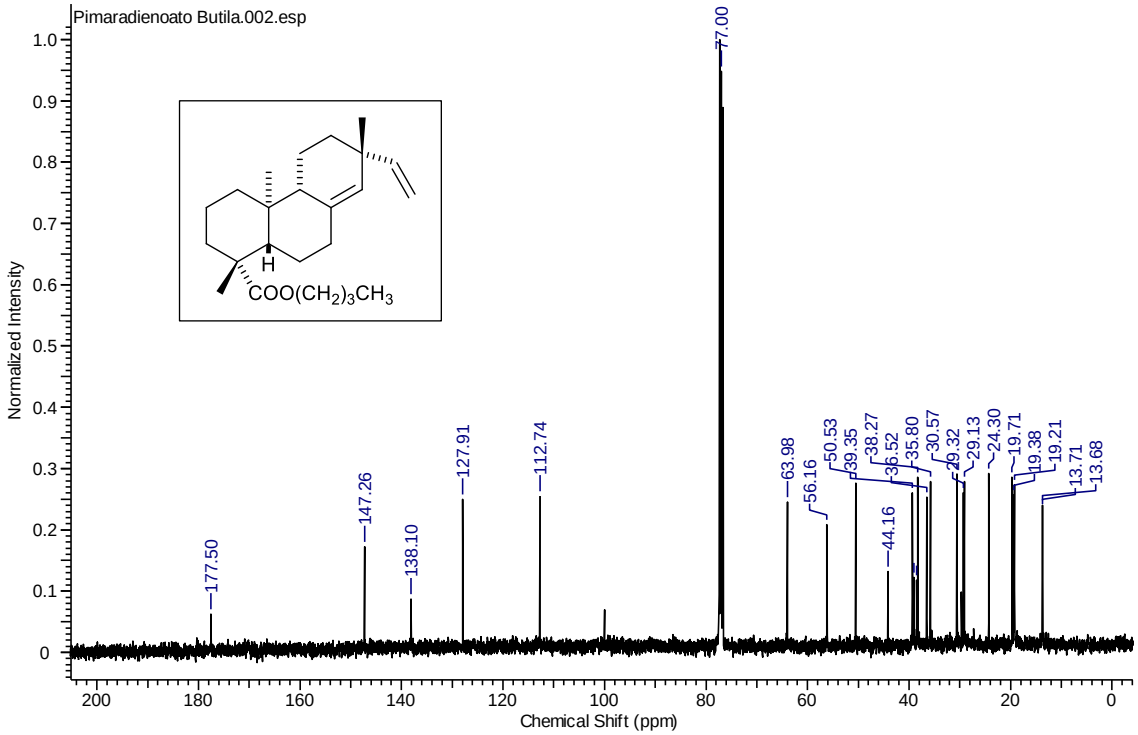


Fig. S72 Compound **15** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$

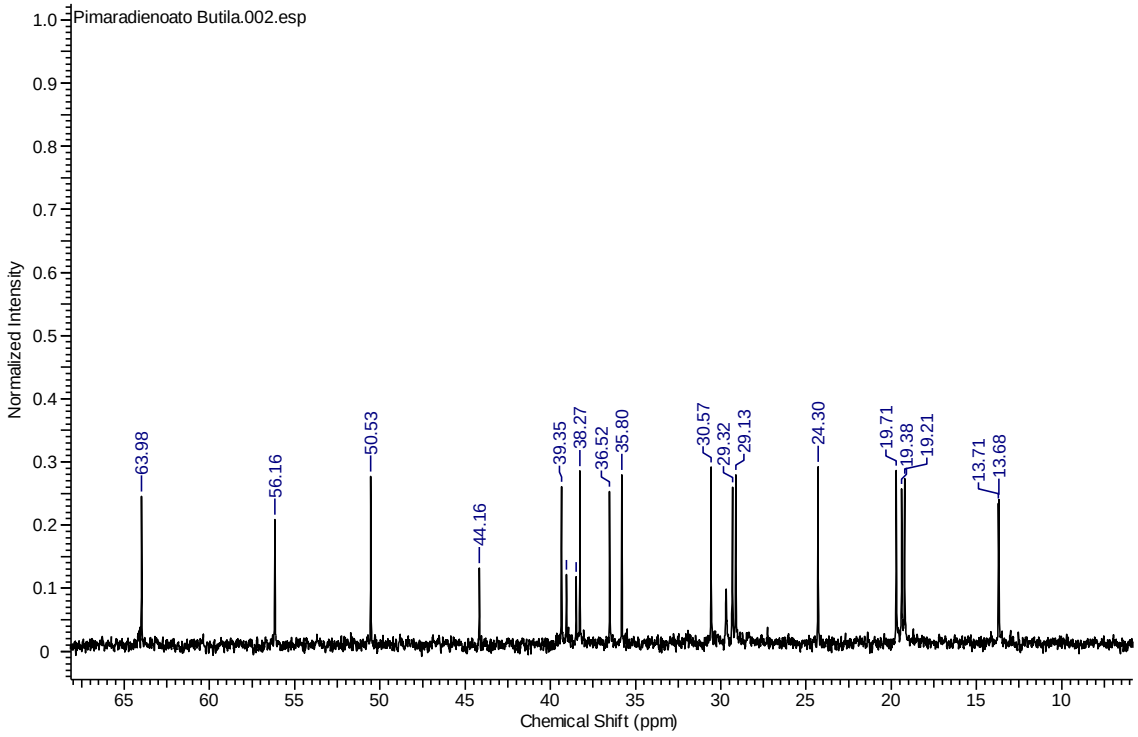


Fig. S73 Compound **15** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$ - Expansion

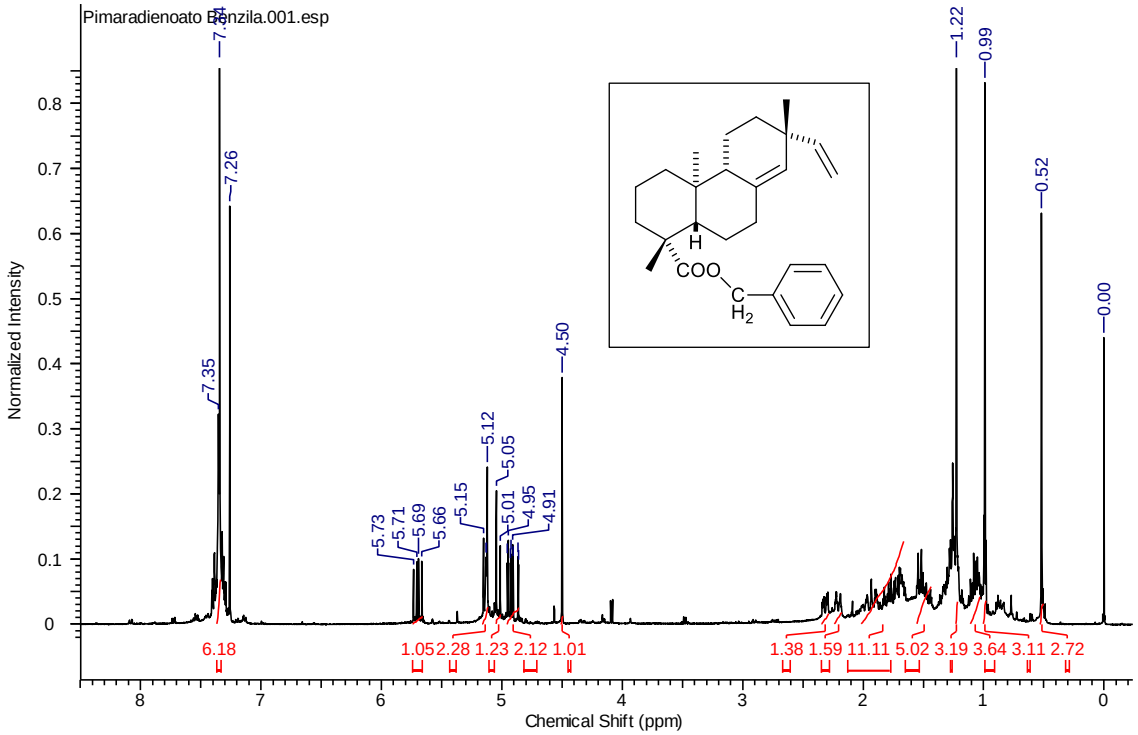


Fig. S74 Compound **16** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$

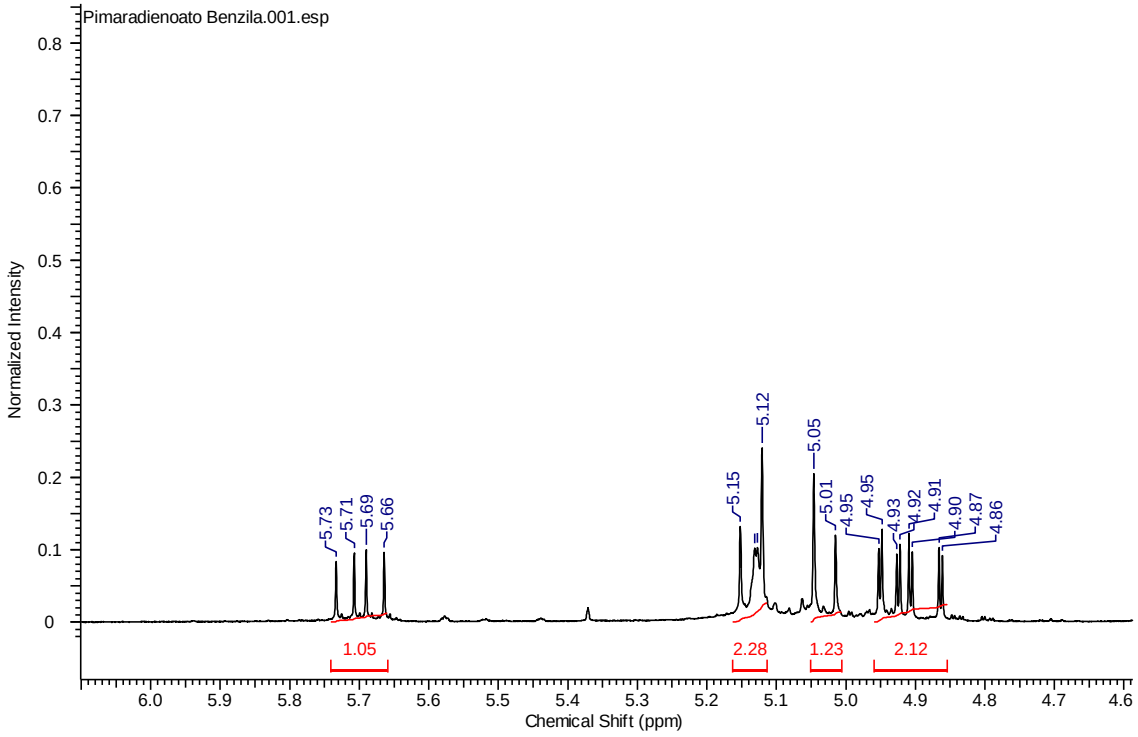


Fig. S75 Compound **16** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 1

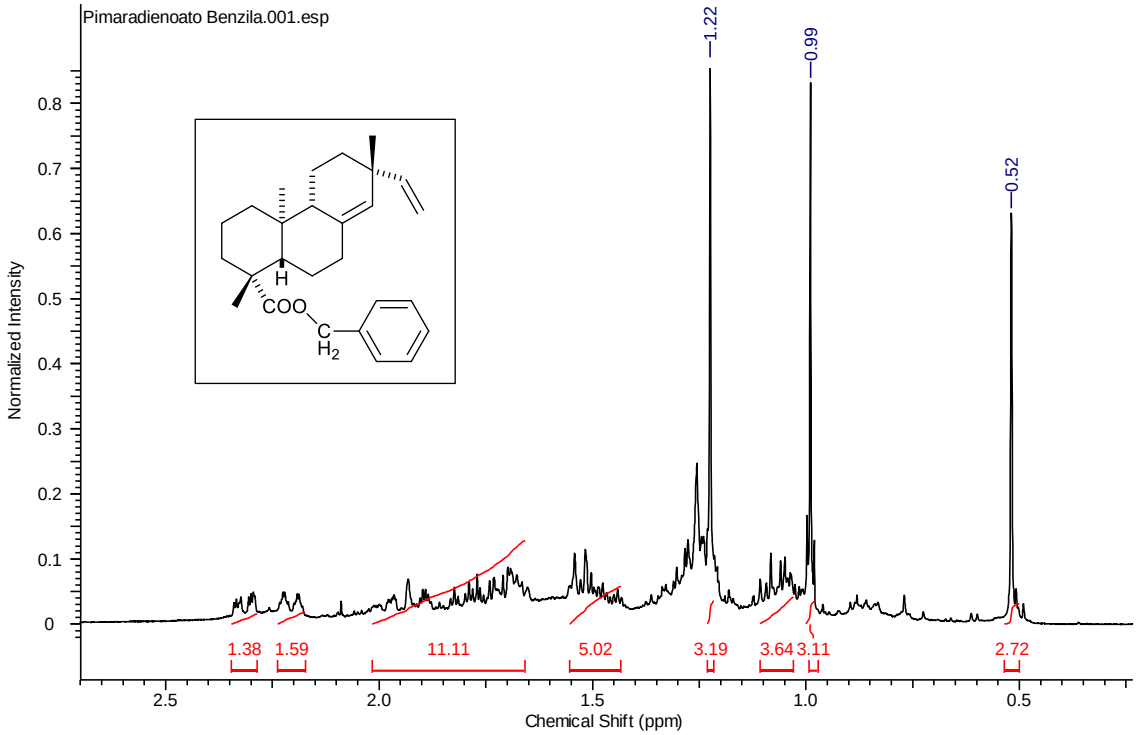


Fig. S76 Compound **16** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 2

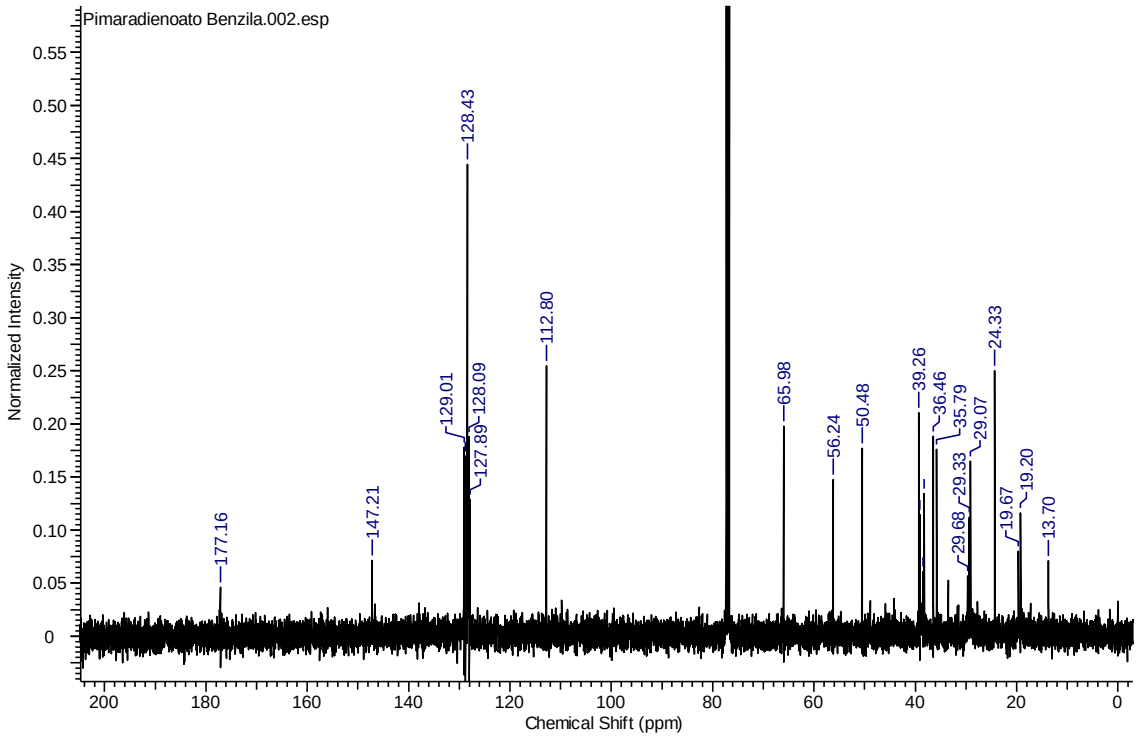


Fig. S77 Compound **16** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$

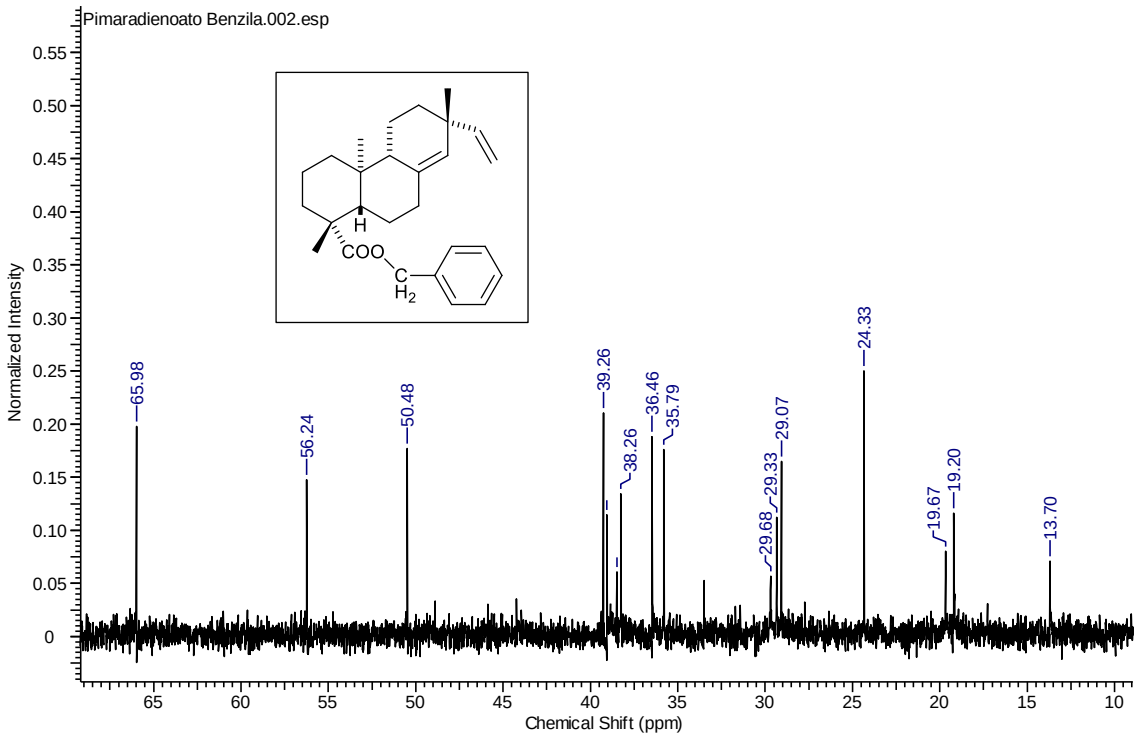


Fig. S78 Compound **16** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$ - Expansion

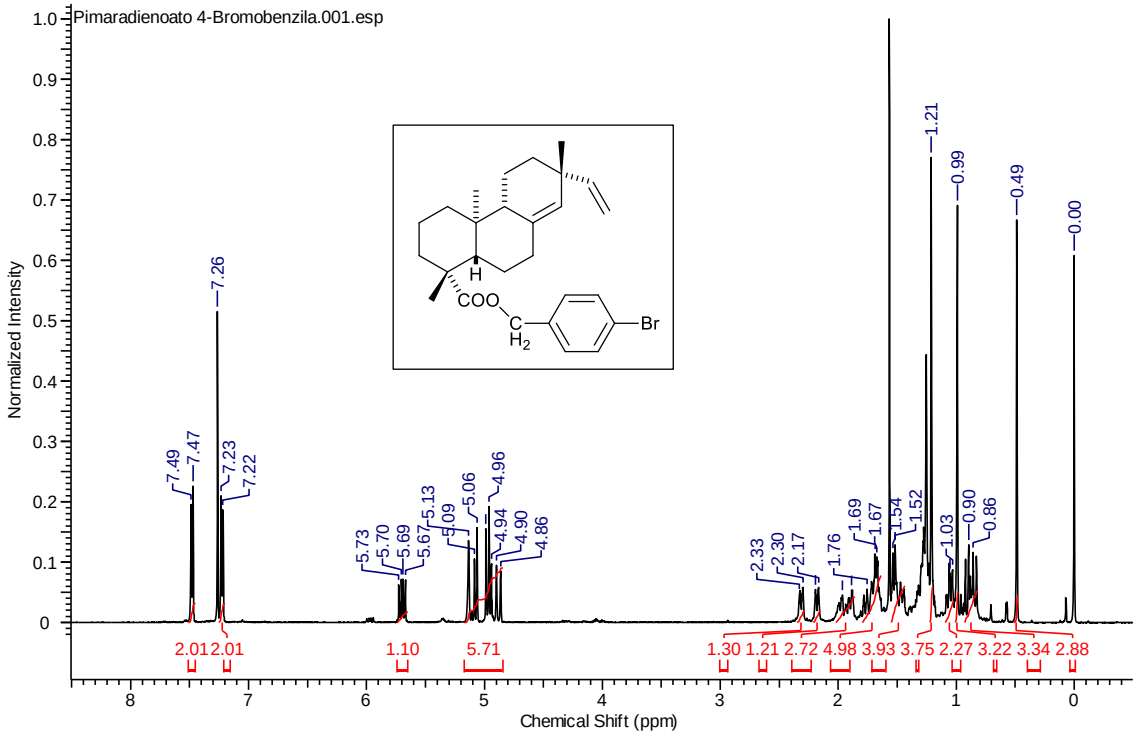


Fig. S79 Compound **17** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$

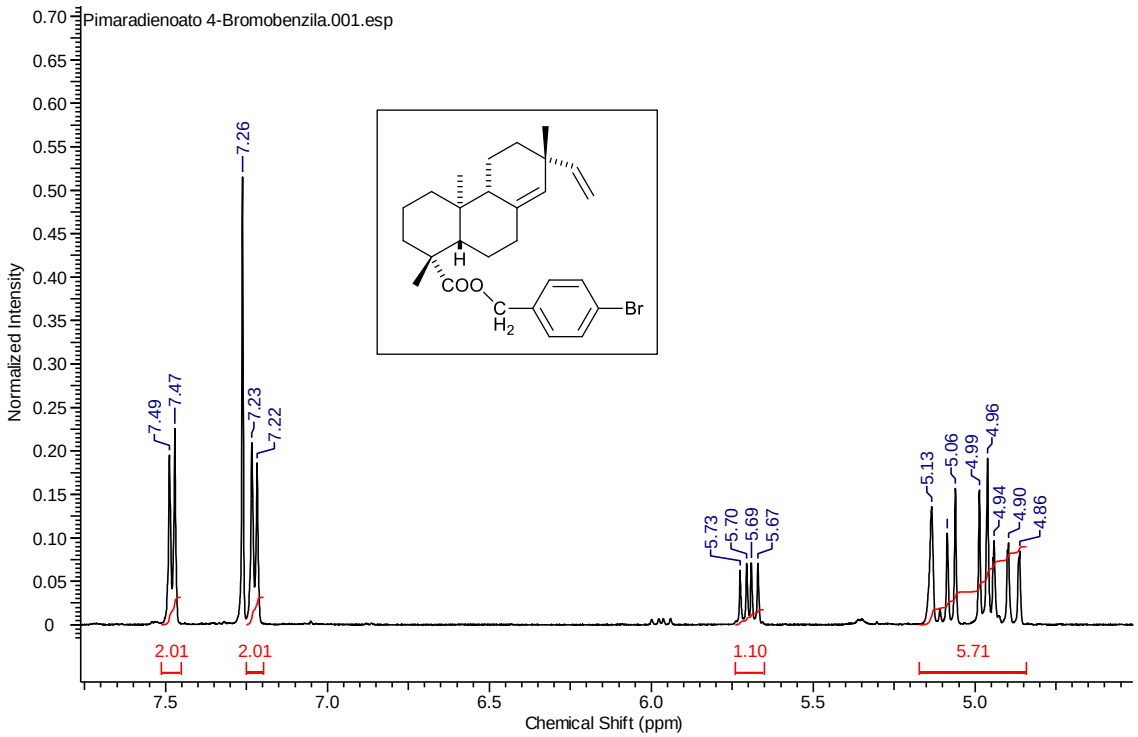


Fig. S80 Compound **17** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 1

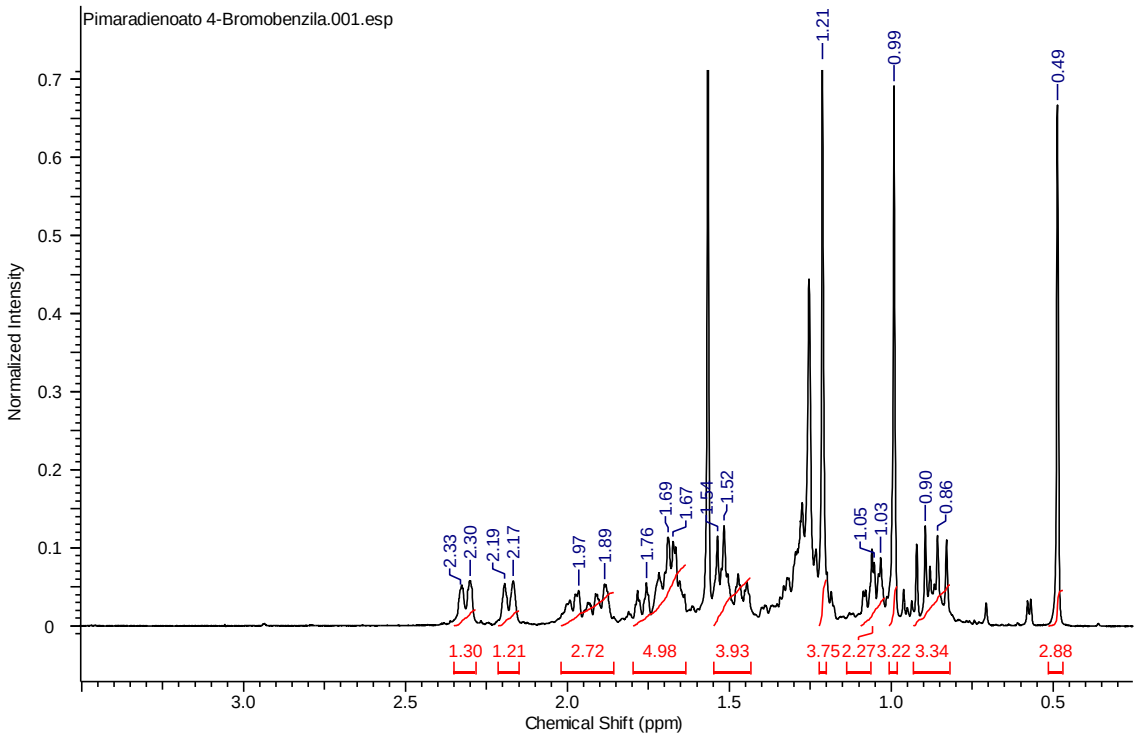


Fig. S81 Compound **17** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 2

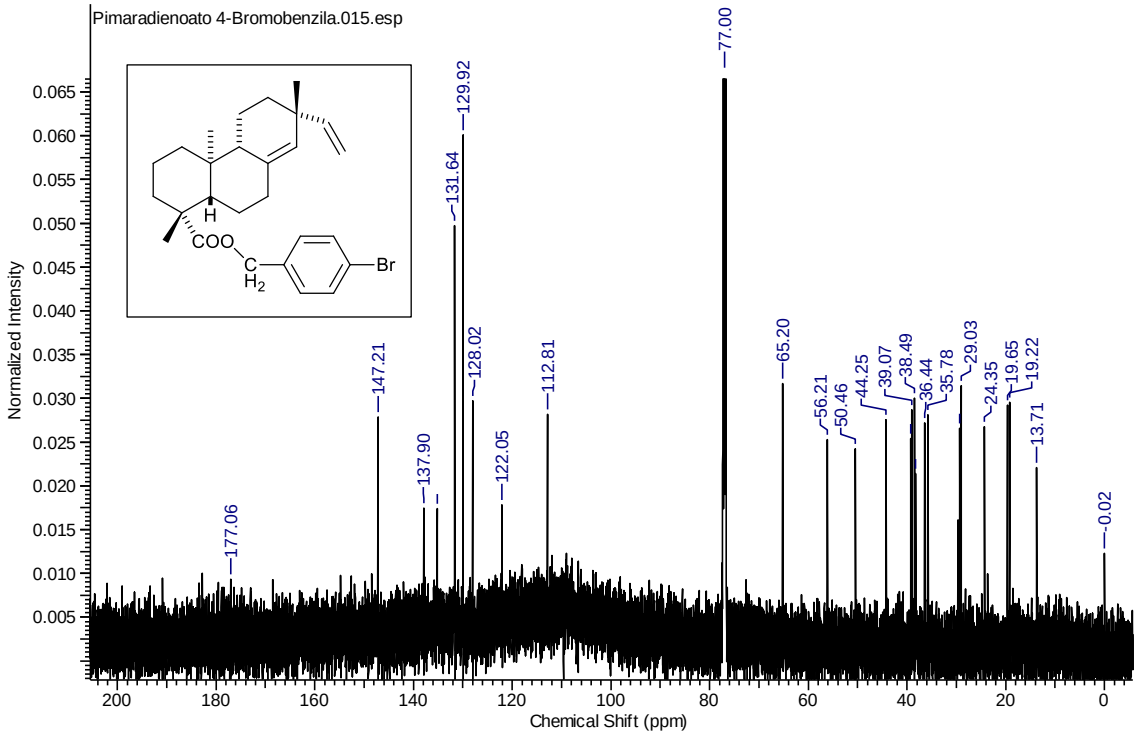


Fig. S82 Compound **17** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$

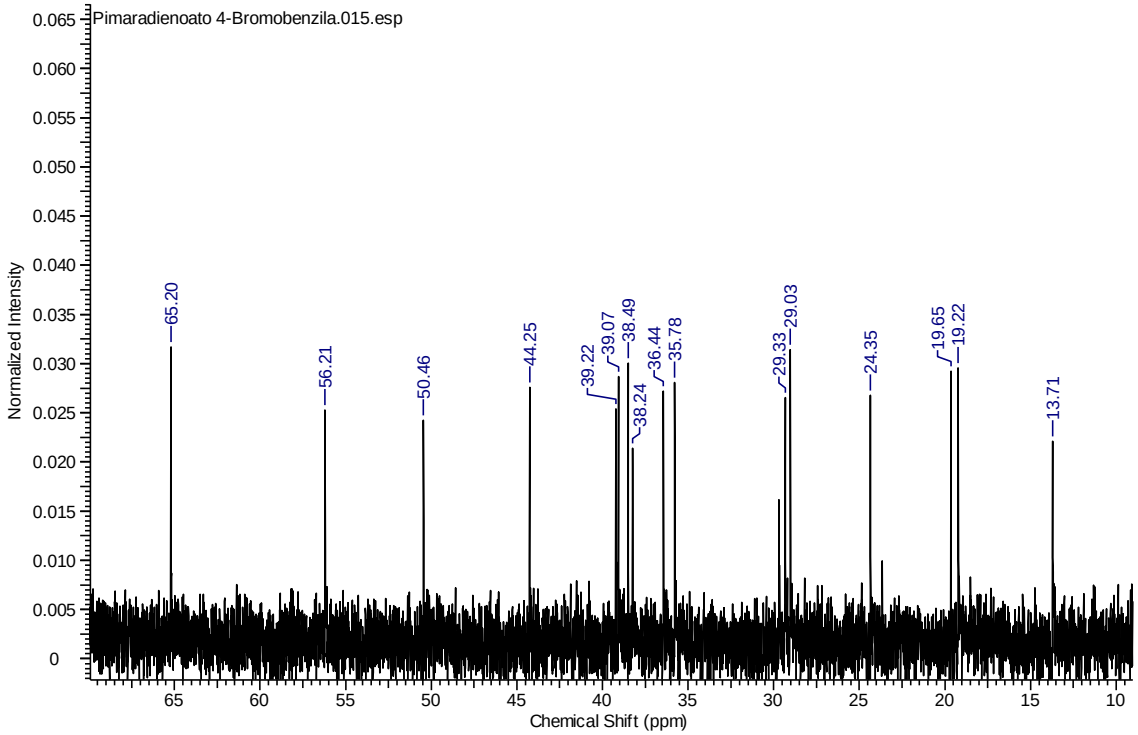


Fig. S83 Compound **17** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$ - Expansion

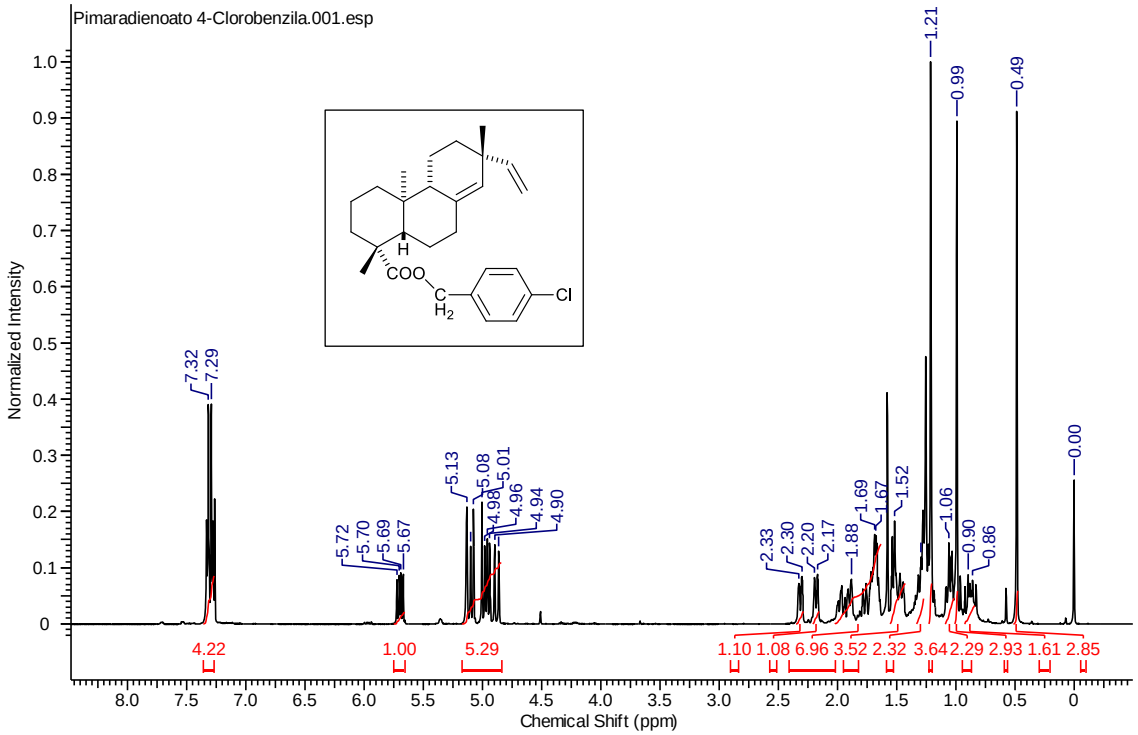


Fig. S84 Compound **18** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$

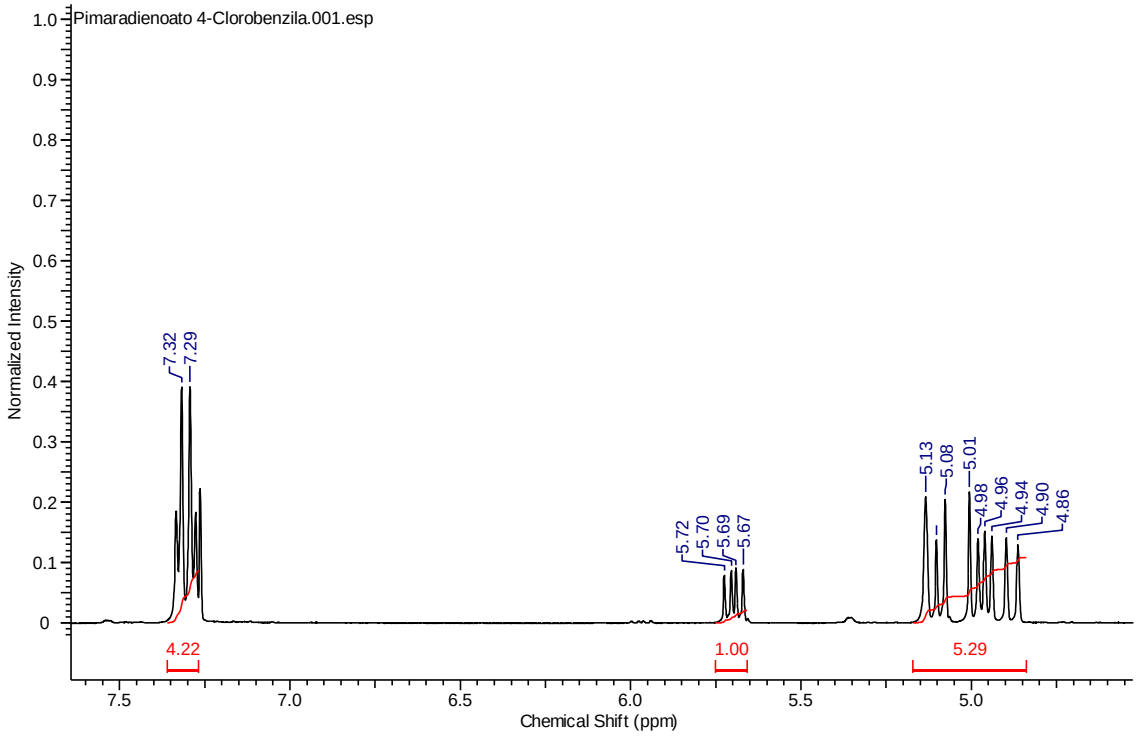


Fig. S85 Compound **18** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 1

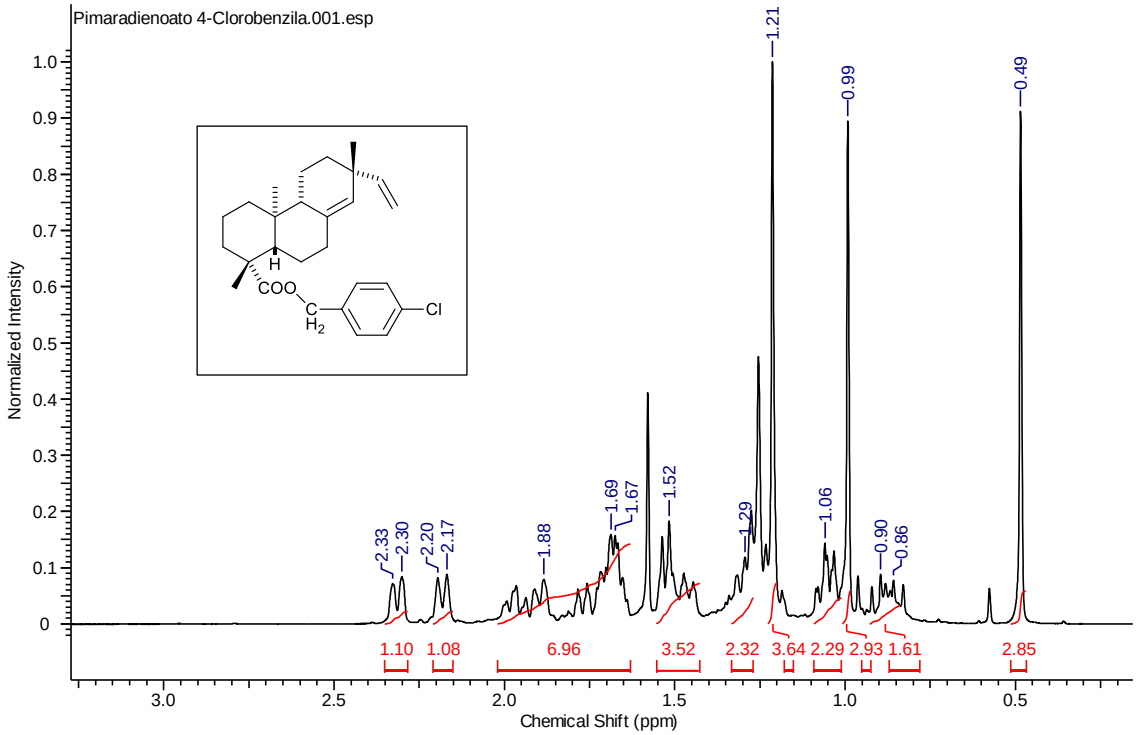


Fig. S86 Compound **18** ^{1}H-NMR spectrum, 400MHz, $CDCl_3$ – Expansion 2

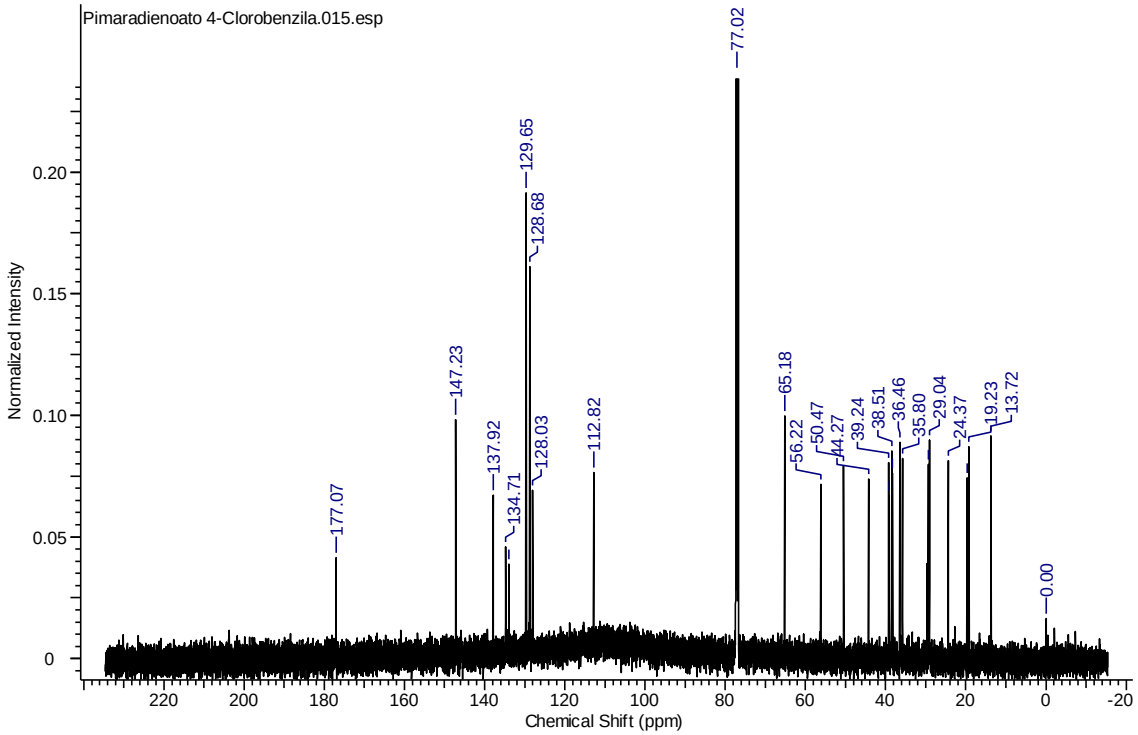


Fig. S87 Compound **18** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$

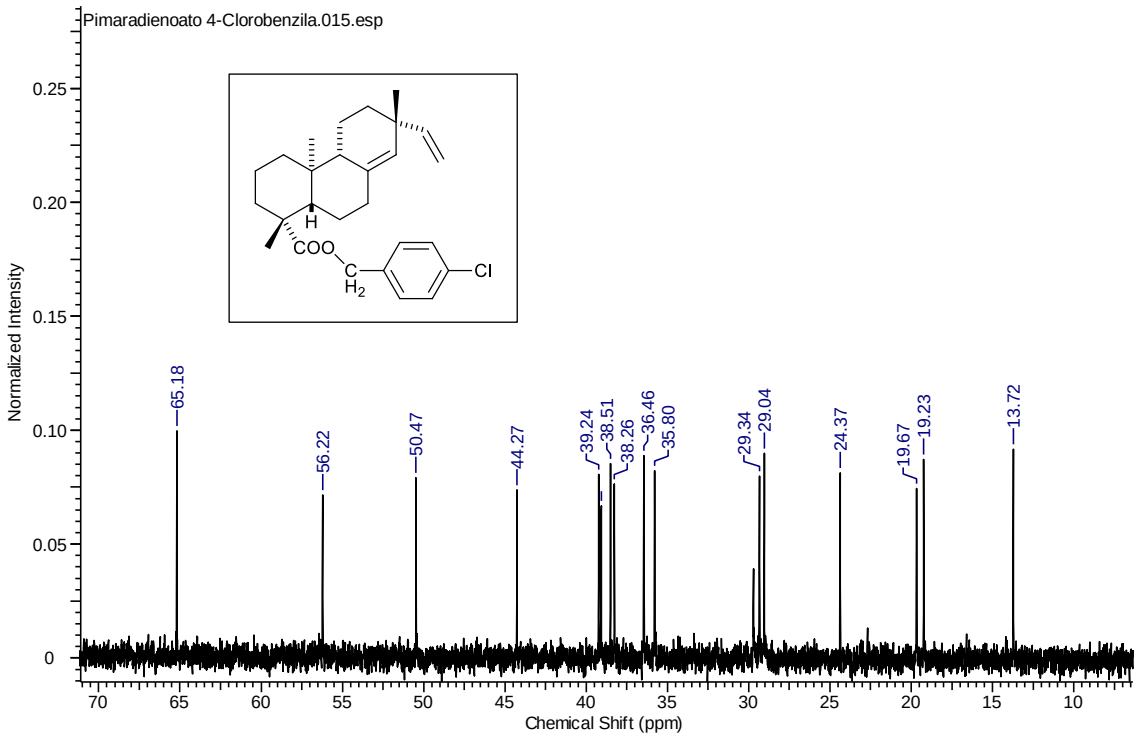


Fig. S88 Compound **18** ^{13}C-NMR spectrum, 100MHz, $CDCl_3$ - Expansion

Compound 1 *(ent-kaur-16-en-19-oic acid)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80 (m, 1H, H-17a), 4.74 (m, 1H, H-17b), 2.64 (m, 1H, H-13), 2.20-1.35 (m, 16H, CH and CH_2 groups), 1.24 (s, 3H, CH_3-18), 1.18-0.97 (m, 4H, CH and CH_2 groups), 0.95 (s, 3H, CH_3-20), 0.85-0.75 (m, 1H, CH and CH_2 groups); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.1, 155.9, 103.0, 57.1, 55.2, 49.0, 44.2, 43.9, 43.8, 41.3, 40.7, 39.7, 39.6, 37.8, 33.1, 29.0, 21.8, 19.1, 18.4, 15.6.

Compound 2 *(ent-pimara-8(14),15-dien-19-oic acid)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (dd, 1H, J_1 = 17.1 Hz, J_2 = 10.4 Hz, H-15), 5.16 (m, 1H, H-14), 4.95 (dd, 1H, J_1 = 10.4 Hz, J_2 = 2.0 Hz, H-16a), 4.92 (dd, 1H, J_1 = 17.1 Hz, J_2 = 2.0 Hz, H-16b), 2.42-1.16 (m, 15H, CH and CH_2 groups), 1.27 (s, 3H, CH_3-18), 1.13-0.98 (m, 2H, CH and CH_2 groups), 1.01 (s, 3H, CH_3-17), 0.66 (s, 3H, CH_3-20); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.6, 147.1, 137.9, 128.0, 112.9, 56.1, 50.5, 44.0, 39.2, 38.5, 38.47, 37.9, 36.4, 35.8, 29.3, 29.2, 24.1, 19.6, 19.2, 13.8.

Compound 3 *(ent-16-methoxykauran-19-oic acid)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.13 (s, 3H, OCH_3), 2.20-1.30 (m, 19H, CH and CH_2 groups), 1.28 (s, 3H, CH_3-17), 1.23 (s, 3H, CH_3-18), 1.07-0.96 (m, 2H, CH and CH_2 groups), 0.95 (s, 3H, CH_3-20), 0.84-0.74 (m, 1H, CH and CH_2 groups); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.8, 84.1, 56.9, 56.0, 54.6, 49.1, 44.7, 43.7, 43.3, 42.0, 40.6, 39.7, 37.8, 37.1, 28.9, 26.6, 22.0, 19.0, 18.4, 18.2, 15.5.

Compound 4 *(ent-16-kauren-19-oic acid methyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.79 (m, 1H, H-17a), 4.73 (m, 1H, H-17b), 3.64 (s, 3H, CH_3-1'), 2.63 (m, 1H, H-13), 2.25-1.35 (m, 15H, CH and CH_2 groups), 1.17 (s, 3H, CH_3-18), 1.16-0.95 (m, 4H, CH and CH_2 groups), 0.83 (s, 3, CH_3-20), 0.78 (m, 1H, CH and CH_2 groups); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 155.9, 103.0, 57.1, 55.1, 51.1, 49.0, 44.2, 43.9, 43.8, 41.3, 40.8, 39.7, 39.4, 38.1, 33.1, 28.8, 21.9, 19.1, 18.4, 15.4.

Compound 5 *(ent-16-kauren-19-oic acid butyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80 (m, 1H, H-17a), 4.74 (m, 1H, H-17b), 4.07 (dt, 1H, J_1 = 10.9 Hz, J_2 = 6.7 Hz, H-1'a), 4.00 (dt, 1H, J_1 = 10.9 Hz, J_2 = 6.7 Hz, H-1'b), 2.63 (m, 1H, H-13), 2.20-1.35 (m, 19H, CH and CH_2 groups), 1.17 (s, 3, CH_3-18), 1.15-0.98 (m, 4H, CH and CH_2 groups), 0.95 (t, 3, J = 7.5 Hz, CH_3-4'), 0.85 (s, 3, CH_3-20), 0,80 (m, 1H, CH and CH_2 groups),; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 156.0, 102.9, 63.9, 57.1, 55.1, 49.0, 44.2, 43.8, 41.4, 40.8, 39.6, 39.5, 38.1, 33.1, 30.6, 29.7, 28.9, 21.9, 19.4, 19.2, 18.4, 15.6, 13.7.

Compound 6 *(ent-16-kauren-19-oic acid benzyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H, H-Ar), 5.14 (d, 1H, J = 12.4 Hz, H-1'a), 5.05 (d, 1H, J = 12.4 Hz, H-1'b), 4.79 (m, 1H, H-17a), 4.73 (m, 1H, H-17b), 2.62 (m, 1H, H-13), 2.25-1.35 (m, 16H, CH and CH_2 groups), 1.19 (s, 3H, CH_3-18), 0.79 (s, 3H, CH_3-20) 1.13-0.92 (m, 4H, CH and CH_2 groups); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 155.9, 136.2, 128.4, 128.2, 128.0, 102.9, 65.9, 57.2, 55.0, 48.9, 44.2, 43.9, 43.8, 41.3, 40.7, 39.6, 39.5, 38.1, 33.1, 28.9, 21.9, 19.2, 18.4, 15.6.

Compound 7 *(ent-16-kauren-19-oic acid p-bromobenzyl ester)* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (m, 2H, H-Ar), 7.25 (m, 2H, H-Ar), 5.09 (d, 1H, *J* = 12.6 Hz, H-1'a), 4.98 (d, 1H, *J* = 12.6 Hz, H-1'b), 4.79 (m, 1H, H-17a), 4.73 (m, 1H, H-17b), 2.63 (m, 1H, H-13), 2.70-1.35 (m, 13H, CH and CH_2 groups), 1.18 (s, 3H, CH_3-18), 1.15-0.78 (m, 7H, CH and CH_2 groups), 0.77 (s, 3H, CH_3-20); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 155.8, 135.2, 131.6, 130.0, 103.0, 65.2, 57.2, 55.0, 48.9, 44.2, 44.0, 43.8, 41.3, 40.7, 39.6, 39.5, 38.1, 33.1, 29.7, 28.8, 22.0, 19.2, 18.4, 15.6.

Compound 8 *(ent-16-kauren-19-oic acid p-chlorobenzyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 4H, H-Ar), 5.11 (d, 1H, *J* = 12.5 Hz, H-1'a), 5.00 (d, 1H, *J* = 12.5 Hz, H-1'b), 4.79 (m, 1H, H-17a), 4.73 (m, 1H, H-17b), 2.62 (m, 1H, H-13), 2.25-1.35 (m, 15H, CH and CH_2 groups), 1.18 (s, 3H, CH_3-18), 1.15-0.79 (m, 5H, CH and CH_2 groups), 0.77 (s, 3H, CH_3-20); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 155.8, 134.7, 129.7, 128.7, 103.0, 65.1, 57.1, 55.0, 48.9, 44.2, 43.9, 43.8, 41.3, 40.7, 39.6, 39.5, 38.1, 33.1, 29.7, 28.8, 21.9, 19.2, 18.4, 15.6.

Compound 9 *(ent-16-methoxykauran-19-oic acid methyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (s, 3H, CH_3-1'), 3.12 (s, 3H, OCH_3), 2.21-1.30 (m, 17H, CH and CH_2 groups), 1.27 (s, 3H, CH_3-17), 1.16 (s, 3H, CH_3-18), 1.04-0.93 (m, 3H, CH and CH_2 groups), 0.83 (s, 3H, CH_3-20), 0.83-0.73 (m, 1H, CH and CH_2 groups); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.1, 83.9, 57.0, 56.0, 54.6, 51.1, 49.1, 44.7, 43.8, 43.3, 42.1, 40.7, 39.5, 38.1, 37.1, 28.7, 26.6, 22.1, 19.1, 18.4, 18.2, 15.3.

Compound 10 *(ent-16-methoxykauran-19-oic acid butyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.06 (dt, 1H, *J* = 11.0 Hz, J_2 = 6.6 Hz, H-1'a), 4.00 (dt, 1H, *J* = 11.0 Hz, J_2 = 6.6 Hz, H-1'b), 3.12 (s, 3H, OCH_3), 2.20-1.30 (m, 22H, CH and CH_2 groups), 1.27 (s, 3H, CH_3-17), 1.16 (s, 3H, CH_3-18), 1.04-0.97 (m, 2H, CH and CH_2 groups), 0.95 (t, 3H, *J* = 7.4 Hz, CH_3-4'), 0.85 (s, 3H, CH_3-20), 0.82-0.74 (m, 1H, CH and CH_2 groups); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 83.9, 63.9, 57.0, 56.0, 54.6, 49.1, 44.7, 43.8, 43.3, 42.1, 40.8, 39.5, 38.1, 37.0, 30.6, 28.8, 26.6, 22.1, 19.4, 19.1, 18.4, 18.2, 15.5, 13.7.

Compound 11 *(ent-16-methoxykauran-19-oic acid benzyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.30 (m, 5H, H-Ar), 5.12 (d, 1H, *J* = 12.5 Hz, H-1'a), 5.06 (d, 1H, *J* = 12.5 Hz, H-1'b), 3.12 (s, 3H, OCH_3), 2.23-1.29 (m, 18H, CH and CH_2 groups), 1.26 (s, 3H, CH_3-17), 1.18 (s, 3H, CH_3-18), 1.05-0.93 (m, 3H, CH and CH_2 groups), 0.78 (s, 3H, CH_3-20); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.3, 136.2, 128.4, 128.2, 128.0, 66.0, 57.1, 56.0, 54.6, 49.1, 44.7, 43.9, 43.4, 42.1, 40.7, 39.6, 38.1, 37.0, 29.7, 28.8, 26.6, 22.2, 19.1, 18.4, 18.2, 15.5.

Compound 12 *(ent-16-methoxykauran-19-oic acid p-bromobenzyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (m, 2H, H-Ar), 7.24 (m, 2H, H-Ar), 5.07 (d, 1H, *J* = 12.6 Hz, H-1'a), 4.99 (d, 1H, *J* = 12.6 Hz, H-1'b), 3.12 (s, 3H, OCH_3), 2.21-1.29 (m, 15H, CH and CH_2 groups), 1.26 (s, 3H, CH_3-17), 1.17 (s, 3H, CH_3-18), 1.05-0.93 (m, 2H, CH and CH_2 groups), 0.82-0.73 (m, 1H, CH and CH_2 groups), 0.77 (s, 3H, CH_3-20); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 135.2, 131.6, 130.0, 122.1, 83.9, 65.2, 57.0, 55.9, 54.5, 49.1, 44.7, 43.9, 43.3, 42.1, 40.6, 39.5, 38.1, 37.0, 28.8, 26.6, 22.2, 19.1, 18.4, 18.2, 15.5.

Compound 13 *(ent-16-methoxykauran-19-oic acid p-chlorobenzyl ester)* ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.28 (m, 4H, H-Ar), 5.09 (d, 1H, *J* = 12.5 Hz, H-1'a), 5.00 (d, 1H, *J* = 12.5 Hz, H-1'b), 3.12 (s, 3H, OCH_3), 2.21-1.18 (m, 19H, CH and CH_2 groups), 1.27 (s, 3H, CH_3-17), 1.17 (s, 3H, CH_3-18), 1.05-0.93 (m, 2H, CH and CH_2 groups), 0.77 (s, 3H, CH_3-20); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.2, 131.7, 130.0, 129.7, 128.7, 83.9, 65.1, 57.1, 55.9, 54.6, 49.1, 44.7, 44.0, 43.3, 42.1, 40.7, 39.6, 38.1, 37.0, 28.8, 26.6, 22.2, 19.1, 18.4, 18.2, 15.5.

Compound 14 *(ent-pimara-8(14),15-dien-19-oic acid methyl ester)* ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.71 (dd, 1H, J_1 = 17.4, J_2 = 10.4 Hz, H-15), 5.14 (m, 1H, H-14), 4.94 (dd, 1H, J_1 = 10.4 Hz, J_2 = 1.8 Hz, H-16a), 4.91 (dd, 1H, J_1 = 17.4 Hz, J_2 = 1.8 Hz, H-16b), 3.63 (s, 3H, OCH_3), 2.40-1.21 (m, 14H, CH and CH_2 groups), 1.20 (s, 3H, CH_3-18), 1.08-1.01 (m, 2H, CH and CH_2 groups), 1.00 (s, 3H, CH_3-17), 0.55 (s, 3H, CH_3-20). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 147.2, 138.0,

127.9, 112.8, 56.1, 51.1, 50.5, 44.2, 39.3, 39.0, 38.5, 38.3, 36.5, 35.8, 29.3, 29.0, 24.3, 19.7, 19.2, 13.6.

Compound 15 *(ent-pimara-8(14),15-dien-19-oic acid butyl ester)* ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (dd, 1H, J_1 = 17.3 Hz, J_2 = 10.4 Hz, H-15), 5.14 (m, 1H, H-14), 4.94 (dd, 1H, J_1 = 10.4 Hz, J_2 = 1.9 Hz, H-16a), 4.91 (dd, 1H, J_1 = 17.3 Hz, J_2 = 1.9 Hz, H-16b), 4.06 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.7 Hz, H-1'a), 4.00 (dt, 1H, J_1 = 10.8 Hz, J_2 = 6.7 Hz, H-1'b), 2.40-1.25 (m, 18H, CH and CH_2 groups), 1.20 (s, 3H, CH_3-18), 1.14-1.02 (m, 2H, CH and CH_2 groups), 1.00 (s, 3H, CH_3-17), 0.94 (t, 3H, J = 7.4 Hz, CH_3-4'), 0.57 (s, 3H, CH_3-20); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 147.3, 138.1, 127.9, 112.7, 64.0, 56.2, 50.5, 44.2, 39.4, 39.1, 38.5, 38.3, 36.5, 35.8, 30.6, 29.3, 29.1, 24.3, 19.7, 19.4, 19.2, 13.71, 13,68.

Compound 16 *(ent-pimara-8(14),15-dien-19-oic acid benzyl ester)* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.26 (m, 5H, H-Ar), 5.70 (dd, 1H, J_1 = 17.3 Hz, J_2 = 10.5 Hz, H-15), 5.14 (d, 1H, J = 12.5 Hz, H-1'a), 5.13 (m, 1H, H-14), 5.03 (d, 1H, J = 12.5 Hz, H-1'b), 4.94 (dd, 1H, J_1 = 10.5 Hz, J_2 = 2.0 Hz, H-16a), 4.89 (dd, 1H, J_1 = 17.3 Hz, J_2 = 2.0 Hz, H-16b), 2.40-1.40 (m, 14H, CH and CH_2 groups), 1.22 (s, 3H, CH_3-18), 1.14-1.02 (m, 2H, CH and CH_2 groups), 0.99 (s, 3H, CH_3-17), 0.52 (s, 3H, CH_3-20). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 147.2, 129.0, 128.84, 128.78 128.4, 128.1, 127.9, 112.8, 66.0, 56.2, 50.5, 39.3, 39.1, 38.5, 38.3, 36.5, 35.8, 29.7, 29.3, 29.1, 24.3, 19.7, 19.2, 13.7.

Compound 17 *(ent-pimara-8(14),15-dien-19-oic acid p-bromobenzyl ester)* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 2H, H-Ar), 7.22 (m, 2H, H-Ar), 5.70 (dd, 1H, J_1 = 17.4 Hz, J_2 = 10.4 Hz, H-15), 5.14 (m, 1H, H-14), 5.07 (d, 1H, J = 12.5 Hz, H-1'a), 4.97 (d, 1H, J = 12.5 Hz, H-1'b), 4.95 (dd, 1H, J_1 = 10.4 Hz, J_2 = 1.6 Hz, H-16a), 4.88 (dd, 1H, J_1 = 17.4, J_2 = 1.6 Hz, H-16b), 2.40-1.40 (m, 11H, CH and CH_2 groups), 1.21 (s, 3H, CH_3-18), 1.10-0.80 (m, 5H, CH and CH_2 groups), 0.99 (s, 3H, CH_3-17), 0.49 (s, 3H, CH_3-20). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 147.2, 137.9,

135.2, 131.6, 129.9, 128.0, 122.1, 112.8, 65.2, 56.2, 50.5, 44.2, 39.2, 39.1, 38.5, 38.2, 36.4, 35.8, 29.3, 29.0, 24.4, 19.6, 19.2, 13.7.

Compound 18 *(ent-pimara-8(14),15-dien-19-oic acid p-chlorobenzyl ester)* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 2H, H-Ar), 7.28 (m, 2H, H-Ar), 5.70 (dd, 1H, J_1 = 17.1 Hz, J_2 = 10.4 Hz, H-15), 5.13 (m, 1H, H-14), 5.09 (d, 1H, *J* = 12.5 Hz, H-1'a), 4.99 (d, 1H, *J* = 12.5 Hz, H-1'b), 4.94 (dd, 1H, J_1 = 10.4 Hz, J_2 = 2.0 Hz, H-16a), 4.88 (dd, 1H, J_1 = 17.1 Hz, J_2 = 2.0 Hz, H-16b), 2.40-1.24 (m, 13H, CH and CH_2 groups), 1.21 (s, 3H, CH_3-18), 1.10-0.80 (m, 3H, CH and CH_2 groups), 0.99 (s, 3H, CH_3-17), 0.49 (s, 3H, CH_3-20). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 147.2, 137.9, 134.7, 133.9, 129.6, 128.7, 128.0, 112.8, 65.2, 56.2, 50.4, 44.2, 39.2, 39.1, 38.5, 38.2, 36.4, 35.8, 29.3, 29.0, 24.4, 19.6, 19.2, 13.7.