Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supplementary information

Synthesis of Sesquiterpene-Inspired Derivatives Designed for Covalent Binding and their Inhibition of the NF-κB pathway

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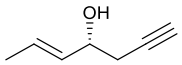
1. General techniques

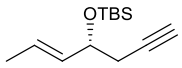
All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Anhydrous solvents were obtained by passing them through commercially available alumina columns (Innovative technology, Inc., MA). Reactions were monitored by LC-MS or thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 10% ethanolic phosphomolybdic acid or vanillin solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. LC-MS were recorded using a Thermo Electron Corporation HPLC with a Thermo Finnigan Surveyor MSQ or LCQ Fleet Mass Spectrometer System. NMR spectra were recorded on Bruker Advance-400 instrument at 400 (^{1}H), 100 (^{13}C) MHz. Chemical shifts are given in parts per million δ and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: b = broad, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dq = doublet of quartets, dqd = double quartet of doublets, m = multiplet, sept = septuplet, q = quartet, t = triplet, s = singlet. CSA = (±)-camphor-10-sulfonic acid, Dibal-H = diisobutylaluminum hydride, DMDO = dimethyldioxirane, DMP = Dess-Martin periodinane, DMSO = dimethylsulfoxide, HMPA = hexamethylphosphoramide, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilane, TBDPS = *tert*-butyldiphenylsilane, Bz = benzoyl, TBTA = tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine, DMAP = 4-dimethylaminopyridine, HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate, DIPEA = diisopropylethylamine, THF = tetrahydrofuran, DMF = dimethylformamide, PTLC = preparative thin layer chromatography

2. Experimental conditions



6

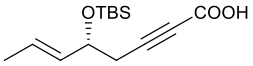
Alcohol 6. A solution containing Mg (2.0 equiv, 500 mg, 21.7 mmol), $HgCl_2$ (0.5 mol%, 14.6 mg, 50 μmol) and I_2 (0.01 equiv, 27 mg, 0.1 mmol) in Et_2O (120 mL) was heated until reflux. Propargyl bromide (1.9 equiv, 3.10 mL, 80% in toluene) was added over a period of 2 hours and the reaction was stirred for 12 hours at 23 ºC. The freshly prepared propargyl magnesium bromide solution was transferred *via* cannula into another flask containing a solution of crotonaldehyde (1.0 equiv, 890 μL, 10.8 mmol) in Et_2O (60 mL) at -78 ^oC and the resulting mixture was stirred for 12 hours at 23 ^oC. The reaction was quenched with sat. aqueous NH_4Cl (120 mL) and extracted with Et_2O (2×100 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to afford the desired alcohol **6** (1.12 g, 94%), which was used in the next step without further purification. R_f = 0.46 (70:30 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal not visible): δ 5.76 (dq, J = 15.2, 6.4 Hz, 1H), 5.56 (ddd, J = 15.2, 6.7, 1.4 Hz, 1H), 4.25-4.21 (m, 1H), 2.45-2.41 (m, 2H), 2.06 (dd, J = 2.6, 2.6 Hz, 1H), 1.71 (d, J = 6.4 Hz, 3H) ppm.



I

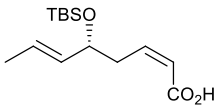
Silyl ether I. A solution containing imidazole (2.0 equiv, 1.48 g, 21.8 mmol), *tert*-butylchlorodimethylsilane (2.0 equiv, 3.80 mL, 21.8 mmol) and the corresponding alcohol **6** (1.0 equiv, 1.20 g, 10.9 mmol) in CH_2Cl_2 (150 mL) was stirred for 10 hours at 23 ºC. The reaction was quenched with water (100 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. After purification by flash chromatography (SiO_2, 95:5 pentane/Et_2O), 2.40 g of silyl ether **I**

were obtained in 98% yield as a colourless oil. R_f = 0.85 (70:30 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 5.65 (dq, J = 15.2, 6.4 Hz, 1H), 5.51 (ddd, J = 15.2, 6.3, 1.1 Hz, 1H), 4.24 (ddd, J = 6.2, 6.2, 6.2 Hz, 1H), 2.42 (ddd, J = 16.5, 6.0, 2.5 Hz, 1H), 2.34 (ddd, J = 16.5, 6.8, 2.5 Hz, 1H), 1.97 (dd, J = 2.5, 2.5 Hz, 1H), 1.69 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 133.1, 126.0, 81.5, 72.1, 69.7, 28.6, 25.8 (×3), 18.2, 17.5, -4.6, -4.8 ppm.



II

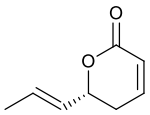
Acid II. *n*-BuLi (1.1 equiv, 7.80 mL, 11.7 mmol, 1.6 M in hexanes) was added to a solution of alkyne **I** (1.0 equiv, 2.40 g, 10.7 mmol) in Et_2O (50 mL) at -78 °C. After stirring for 45 minutes at this temperature, crushed dry ice was added and the reaction was stirred for 1 hour at 23 °C. The reaction was then quenched with sat. aqueous NH_4Cl (50 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 and filtrated. The solvent was evaporated under reduced pressure to afford the desired carboxylic acid **II**, which was used in the next step without further purification. R_f = 0.11 (70:30 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.95 (bs, 1H), 5.64 (dq, J = 15.2, 6.4 Hz, 1H), 5.46 (dd, J = 15.2, 6.4 Hz, 1H), 4.23 (ddd, J = 6.4, 6.4, 6.4 Hz, 1H), 2.49 (dd, J = 16.8, 6.3 Hz, 1H), 2.40 (dd, J = 16.8, 6.4 Hz, 1H), 1.66 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 160.9, 132.8, 126.3, 80.6, 78.8, 71.6, 28.8, 25.8 (×3), 18.2, 17.6, -4.6, -4.7 ppm.



III

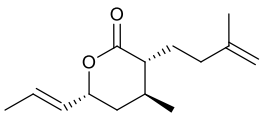
Alkene III. A solution containing carboxylic acid **II** (1.0 equiv, 2.90 g, 10.8 mmol), quinoline (1.0 equiv, 1.30 mL, 10.8 mmol) and Lindlar's catalyst (0.4 equiv, 460 mg, 4.32 mmol) in EtOAc (100 mL) was stirred under hydrogen atmosphere for 8 hours at 23 ºC. The mixture was then filtered through celite and washed with 2.0 M aqueous

HCl, water and brine. The organic layer was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to afford the desired alkene **III**, which was used in the next step without further purification. R_f = 0.56 (70:30 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 10.79 (bs, 1H), 6.43 (ddd, J = 11.6, 7.2, 7.2 Hz, 1H), 5.87 (d, J = 11.6 Hz, 1H), 5.59 (dq, J = 15.2, 6.4 Hz, 1H), 5.43 (ddd, J = 15.2, 6.4, 1.4 Hz, 1H), 4.26 (ddd, J = 6.1, 6.1, 6.1 Hz, 1H), 2.85-2.82 (m, 2H), 1.68 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 171.4, 148.8, 133.7, 125.8, 120.4, 72.5, 37.8, 25.8 (×3), 18.1, 17.5, -4.4, -4.9 ppm.



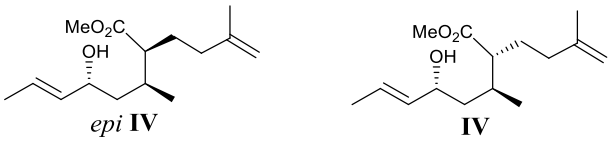
7

Lactone 7. CSA (0.24 equiv, 600 mg, 2.6 mmol) was added to a solution of carboxylic acid **III** (1.0 equiv, 2.90 g, 10.7 mmol) in 4:1 mixture of CH_2Cl_2/MeOH (150 mL) at 23 ºC. The reaction was stirred for 12 hours at this temperature and then quenched with sat. aqueous $NaHCO_3$ (100 mL). The aqueous phase was extracted with Et_2O (2×100 mL). The combined organic extracts were washed with water (200 mL) and brine (200 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, 80:20 petroleum ether/EtOAc), to yield 970 mg of lactone **7** (70%, over 3 steps) as a colourless oil. R_f = 0.34 (70:30 petroleum ether/EtOAc). ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.81 (ddd, J = 8.7, 4.6, 3.7 Hz, 1H), 5.97 (ddd, J = 9.7, 1.5, 1.5 Hz, 1H), 5.79 (dq, J = 15.2, 6.5 Hz, 1H), 5.55 (ddd, J = 15.2, 6.8, 1.5 Hz, 1H), 4.80 (ddd, J = 7.1, 7.1, 7.1 Hz, 1H), 2.37-2.35 (m, 2H), 1.68 (d, J = 7.0 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 164.0, 144.7, 130.5, 128.0, 121.5, 78.2, 29.7, 17.6 ppm. HRMS (ESI$^+$) calcd. for $C_8H_{11}O_2$ $[M + H]^+$ 139.0759; found: 139.0764.



8

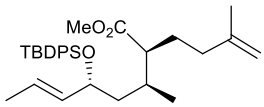
Lactone 8. Methylithium (4.0 equiv, 17.6 mL, 1.6 M in diethyl ether) was added to a suspension of CuI (2.0 equiv, 2.70 g, 14.1 mmol) in Et_2O (70 mL) at 0 °C. After the mixture was stirred for 30 minutes, a solution of lactone **7** (1.0 equiv, 970 mg, 7.0 mmol) in Et_2O (7 mL) was added and the reaction was stirred for 1 hour at 0 °C. Then, 1:1 mixture of THF/HMPA (36 mL) was added followed by a solution of 4-iodoisopentene[1] (8.0 equiv, 8.40 g, 56.2 mmol) in THF (5 mL). The reaction was stirred for 12 hours at 23 °C and quenched with 10% aqueous NH_4OH (70 mL). The aqueous phase was extracted with Et_2O (2×50 mL) and the combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 and filtrated. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, 80:20 pentane/Et_2O), afforded the desired lactone **IV** in 41% yield (0.64 g) as a colourless oil. R_f = 0.68 (70:30 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 5.75 (dq, d, J = 15.3, 6.5 Hz, 1H), 5.47 (ddd, J = 15.3, 6.4, 1.5 Hz, 1H), 4.79-4.75 (m, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 2.21-2.14 (m, 1H), 2.10-2.02 (m, 2H), 1.92-1.80 (m, 3H), 1.77-1.68 (m, 4H), 1.71 (d, J = 6.5 Hz, 3H), 1.63-1.57 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 174.3, 145.0, 129.1, 129.0, 110.3, 76.3, 45.7, 35.9, 35.1, 28.3, 27.1, 22.3, 20.8, 17.5 ppm. HRMS (ESI$^+$) calcd. for $C_{14}H_{23}O_2$ $[M + H]^+$ 223.1698; found: 223.1712.



epi **IV** **IV**

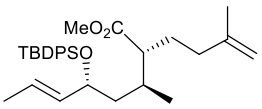
Esters *epi* IV and IV. Sodium methoxide (1.2 equiv, 29 mg, 0.5 mmol) was added to a solution of the lactone **8** (1.0 equiv, 100 mg, 0.4 mmol) in MeOH (1 mL) at 23 ºC. After stirring for 10 hours, the reaction was quenched with sat. aqueous NH_4Cl (1 mL) and extracted with EtOAc (2×2 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 80:20 pentane/Et_2O), to provide a mixture of separable diastereoisomers ester *epi* **IV** (44 mg, 40%) and ester **IV** (46 mg, 40%) as a yellow oils. The identity of each diastereoisomer was established by comparison of the NMR data of subsequent compound to a sample previously obtained without racemization.[2] **Ester *epi* IV**, R_f = 0.5 (50:50 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC) (OH not visible): δ 5.67 (dq, J = 15.2, 6.5 Hz, 1H), 5.42 (ddd, J = 15.2,

7.6, 1.4 Hz, 1H), 4.71 (s, 1H), 4.66 (s, 1H), 4.14 (ddd, J = 6.9, 6.9, 6.9 Hz, 1H), 3.66 (s, 3H), 2.38-2.33 (m, 1H), 1.98-1.93 (m, 2H), 1.86-1.77 (m, 2H), 1.70 (s, 3H), 1.69 (d, J = 6.5 Hz, 3H), 1.61-1.53 (m, 2H), 1.45-1.38 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 175.5, 145.1, 134.0, 127.5, 110.4, 71.6, 51.1, 49.8, 41.8, 35.9, 32.2, 27.4, 22.3, 17.7, 17.0 ppm. **Ester IV**, R_f = 0.4 (50:50 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC) (OH not visible): δ 5.66 (dq, J = 15.2, 6.5 Hz, 1H), 5.41 (ddd, J = 15.2, 7.6, 1.4 Hz, 1H), 4.71 (s, 1H), 4.65 (s, 1H), 4.07 (ddd, J = 7.1, 7.1, 7.1 Hz, 1H), 3.67 (s, 3H), 2.32-2.26 (m, 1H), 2.02-1.88 (m, 2H), 1.86-1.73 (m, 2H), 1.74-1.70 (m, 6H), 1.59-1.54 (m, 2H), 1.48-1.44 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 175.9, 144.9, 133.9, 127.7, 110.4, 71.6, 51.3, 50.3, 41.7, 35.9, 32.0, 29.1, 22.3, 17.7, 17.1 ppm.



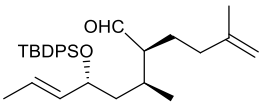
epi **9**

Silyl ether *epi* **9**. A solution containing imidazole (2.0 equiv, 450 mg, 6.6 mmol), *tert*-butylchlorodiphenylsilane (1.1 equiv, 1.01 g, 3.7 mmol) and alcohol *epi* **IV** (1.0 equiv, 850 mg, 3.3 mmol) in CH_2Cl_2 (50 mL) was stirred for 10 hours at 23 ºC. The reaction was quenched with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (150 mL) and dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. After purification by column chromatography (SiO_2, 95:5 pentane/Et_2O), silyl ether *epi* **9** (1.60 g, 95%) was obtained as a colorless oil. R_f = 0.6 (80:20 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 7.65 (dd, J = 6.9, 6.9 Hz, 4H), 7.43-7.33 (m, 6H), 5.34 (dd, J = 15.2, 7.6 Hz, 1H), 5.21 (dq, J = 15.2, 6.3 Hz, 1H), 4.71 (s, 1H), 4.65 (s, 1H), 4.16-4.07 (m, 1H), 3.61 (s, 3H), 2.17-2.12 (m, 1H), 1.96-1.84 (m, 2H), 1.77-1.69 (m, 1H), 1.70 (s, 3H), 1.64-1.58 (m, 2H), 1.54 (d, J = 6.3 Hz, 3H), 1.51-1.45 (m, 1H), 1.33-1.28 (m, 1H), 1.06 (s, 9H), 0.63 (d, J = 6.7 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 175.5, 145.1, 136.0 (×2), 135.9 (×2), 134.5, 134.4, 133.5, 129.5, 129.3, 127.4 (×2), 127.2 (×2), 126.7, 110.2, 73.2, 51.0, 50.5, 42.8, 35.9, 31.8, 27.4, 27.0 (×3), 22.3, 19.2, 17.5, 16.6 ppm.



9

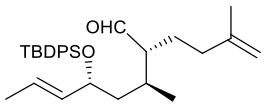
Silyl ether 9. Following the same procedure as for silyl ether *epi* **9**, alcohol **V** (1.0 equiv, 1.10 g, 4.3 mmol) and *tert*-butylchlorodiphenylsilane (1.1 equiv, 1.30 g, 4.8 mmol) gave, after purification by column chromatography (SiO_2, 95:5 pentane/Et_2O), silyl ether **9** (1.90 g, 93%) as a colorless oil. R_f = 0.4 (95:5 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 7.67 (dd, J = 7.7, 7.7 Hz 4H), 7.43-7.33 (m, 6H), 5.33 (ddd, J = 15.3, 7.7, 1.0 Hz, 1H), 5.19 (dq, J = 15.3, 6.3 Hz, 1H), 4.70 (s, 1H), 4.63 (s, 1H), 4.07-4.01 (m, 1H), 3.64 (s, 3H), 2.16 (ddd, J = 10.6, 5.5, 3.8 Hz, 1H), 1.97-1.81 (m, 2H), 1.73-1.64 (m, 2H), 1.68 (s, 3H), 1.54 (d, J = 6.3 Hz, 3H), 1.49-1.33 (m, 3H), 1.05 (s, 9H), 0.63 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 175.7, 145.1, 136.0 (×2), 135.9 (×2), 134.5, 134.4, 133.4, 129.4, 129.3, 127.4 (×2), 127.2 (×2), 126.8, 110.3, 73.3, 51.1, 50.4, 42.5, 35.9, 31.4, 27.0 (×3), 25.8, 22.3, 19.2, 17.5, 16.6 ppm.



epi **V**

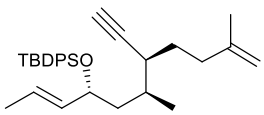
Aldehyde *epi* **V**. Dibal-H (2.0 equiv, 6.91 mL, 1M in toluene) was added to a solution of ester *epi* **9** (1.0 equiv, 1.70 g, 3.4 mmol) in toluene (35 mL) at -78 ºC. After stirring for 2 hours at this temperature, the reaction was quenched with Rochelle's salt (30 mL) and extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2, 90:10 pentane/Et_2O). After evaporation of the solvent, the resulting oil was dissolved in CH_2Cl_2 (33 mL) and the solution cooled to 0 ºC. DMP (2.0 equiv, 2.90 g, 6.90 mmol) was added and the mixture was stirred for 4 hours at 23 ºC. The reaction was quenched with 1:1 mixture of 10% aqueous $Na_2S_2O_3$/$NaHCO_3$ (30 mL) and extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue

was purified by column chromatography (SiO_2, 95:5 pentane/Et_2O), to afford aldehyde *epi* **V** (1.20 g, 80%) as a colorless oil. R_f = 0.5 (95:5 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 9.54 (d, J = 2.8 Hz, 1H), 7.70-7.64 (m, 4H), 7.42-7.33 (m, 6H), 5.33 (ddd, J = 15.3, 7.7, 1.1 Hz, 1H), 5.22 (dq, J = 15.3, 6.1, Hz, 1H), 4.72 (s, 1H), 4.64 (s, 1H), 4.12-4.06 (m, 1H), 2.10-2.05 (m, 1H), 1.99-1.82 (m, 2H), 1.80-1.72 (m, 2H), 1.69 (s, 3H), 1.57-1.50 (m, 1H), 1.55 (dd, J = 6.1, 1.1 Hz, 3H), 1.44-1.34 (m, 2H), 1.05 (s, 9H), 0.68 (d, J = 6.9 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 205.5, 145.0, 136.0 (×2), 135.9 (×2), 134.4, 134.3, 133.3, 129.5, 129.4, 127.5 (×2), 127.3 (×2), 127.1, 110.5, 73.1, 56.4, 42.2, 35.6, 29.8, 27.0 (×3), 23.9, 22.3, 19.2, 17.5, 16.8 ppm.



V

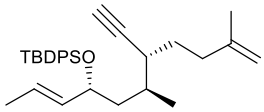
Aldehyde V. Following the same procedure as for aldehyde *epi* **V**, ester **9** (1.0 equiv, 1.80 g, 3.7 mmol) afforded, after purification by column chromatography (SiO_2, 95:5 pentane/Et_2O), aldehyde **V** (1.40 g, quantitative) as a colourless oil. R_f = 0.5 (95:5 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 9.47 (d, J = 2.2 Hz, 1H), 7.68-7.63 (m, 4H), 7.44-7.33 (m, 6H), 5.36 (ddd, J = 15.2, 7.7, 1.2 Hz, 1H), 5.23 (dq, J = 15.2, 6.3, Hz, 1H), 4.70 (s, 1H), 4.61 (s, 1H), 4.09 (ddd, J = 7.4, 7.4, 7.4 Hz, 1H), 2.05-2.01 (m, 1H), 1.98-1.87 (m, 2H), 1.84-1.69 (m, 2H), 1.67 (s, 3H), 1.55 (d, J = 6.3, 1.1 Hz, 3H), 1.49-1.44 (m, 2H), 1.35-1.28 (m, 1H), 1.05 (s, 9H), 0.62 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 205.0, 145.1, 136.0 (×2), 135.9 (×2), 134.4, 134.2, 133.5, 129.6, 129.4, 127.5 (×2), 127.3 (×2), 126.9, 110.5, 73.0, 55.8, 42.5, 35.8, 28.6, 27.0 (×3), 22.2, 21.9, 19.2, 17.5, 16.2 ppm.



epi **10**

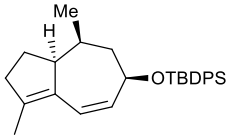
Enyne *epi* **10**. A solution containing tetrabromomethane (4.0 equiv, 2.92 g, 8.8 mmol) and triphenylphosphine (8.0 equiv, 4.62 g, 17.6 mmol) in CH_2Cl_2 (40 mL) was stirred for 10 minutes at 0 ºC. The aldehyde *epi* **V** (1.0 equiv, 1.0 g, 2.2 mmol) was then added

and the resulting mixture was stirred for additional 30 minutes. The reaction was filtered through a pad of silica, the solvent evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, 95:5 pentane/Et_2O). After removal of the solvent, the resulting oil was dissolved in THF (20 mL) and the mixture was cooled to -78 ºC. *n*BuLi (2.2 equiv, 1.94 mL, 4.84 mmol, 2.5 M in hexanes) was then added and the solution was stirred for 30 minutes. The reaction was quenched with sat. aqueous NH_4Cl (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. After purification by column chromatography (SiO_2, 95:5 pentane/Et_2O), enyne *epi* **10** (870 mg, 95%) was obtained as a colourless oil. R_f = 0.8 (95:5 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 7.70-7.64 (m, 4H), 7.41-7.33 (m, 6H), 5.33 (dd, J = 15.3, 7.7 Hz, 1H), 5.18 (dq, J = 15.3, 6.3, Hz, 1H), 4.72 (s, 1H), 4.68 (s, 1H), 4.10 (ddd, J = 6.7, 6.7, 6.7 Hz, 1H), 2.25-2.15 (m, 2H), 2.00-1.93 (m, 1H), 1.98 (d, J = 2.3 Hz, 1H), 1.71 (s, 3H), 1.62-1.47 (m, 4H), 1.51 (d, J = 6.3 Hz, 3H), 1.43-1.35 (m, 1H), 1.05 (s, 9H), 0.75 (d, J = 5.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 145.5, 136.1 (×2), 135.9 (×2), 134.6, 134.5, 133.9, 129.4, 129.3, 127.4 (×2), 127.2 (×2), 126.3, 110.0, 85.5, 73.1, 70.4, 43.7, 36.5, 35.8, 32.2, 30.8, 27.1 (×3), 22.5, 19.3, 17.5, 15.3 ppm.



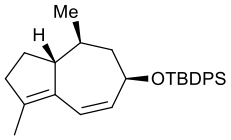
10

Enyne 10. Following the same procedure as for enyne *epi* **10**, aldehyde **V** (1.0 equiv, 3.20 g, 6.9 mmol) afforded, after purification by column chromatography (SiO_2, 95:5 pentane/Et_2O), enyne **10** (2.20 g, 72%) as a colourless oil. R_f = 0.8 (95:5 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 7.67-7.63 (m, 4H), 7.43-7.32 (m, 6H), 5.33 (dbd, J = 15.3, 7.6 Hz,1H), 5.18 (dq, J = 15.3, 6.4 Hz, 1H), 4.70 (s, 1H), 4.66 (s, 1H), 4.07-4.02 (m, 1H), 2.21-2.10 (m, 2H), 2.03-1.95 (m, 1H), 2.00 (s, 1H), 1.69 (s, 3H), 1.64-1.39 (m, 3H), 1.53 (d, J = 6.4 Hz, 3H), 1.32-1.24 (m, 2H), 1.05 (s, 9H), 0.70 (d, J = 6.7 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 145.4, 136.0 (×4), 134.6, 134.5, 133.7, 129.4, 129.3, 127.4 (×2), 127.2 (×2), 126.6, 110.1, 86.4, 73.5, 70.1, 41.1, 37.4, 35.7, 32.4, 29.3, 27.1 (×3), 22.5, 19.2, 17.5 (×2) ppm.



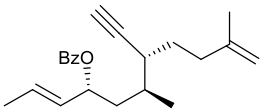
epi **VI**

Hydroazulene *epi* **VI**. A solution containing Grubbs' II catalyst (0.1 equiv, 119 mg, 0.14 mmol) and the corresponding enyne *epi* **10** (1.0 equiv, 660 mg, 1.4 mmol) in toluene (1.4 L) was heated for 12 hours at 120 ^{o}C. The reaction was quenched by the addition of DMSO and was stirred for additional 12 hours. The solvent was evaporated under reduced pressure. After purification by flash chromatography (SiO_2, pentane), hydroazulene *epi* **VI** (250 mg, 42%) was obtained as a colourless oil. R_f = 0.2 (pentane); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 7.68-7.65 (m, 4H), 7.43-7.35 (m, 6H), 6.08 (d, J = 12.2 Hz, 1H), 5.65 (d, J = 12.2 Hz, 1H), 4.80 (d, J = 10.0 Hz, 1H), 2.87 (bs, 1H), 2.30-2.10 (m, 2H), 2.00-1.94 (m, 1H), 1.83-1.74 (m, 2H), 1.70 (s, 3H), 1.63-1.42 (m, 2H), 1.07 (s, 9H), 0.77 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 138.1, 136.1, 135.9 (×2), 135.8 (×2), 134.5, 134.4, 134.2, 129.5 (×2), 127.5 (×4), 123.0, 70.7, 49.9, 45.8, 37.8, 33.0, 27.0 (×3), 26.9, 19.2, 16.1, 14.2 ppm.



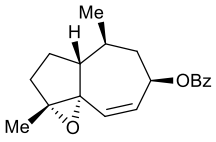
VI

Hydroazulene VI. Following the same procedure as for hydroazulene *epi* **VI**, enyne **10** (1.0 equiv, 470 mg, 1.0 mmol) provided, after purification by column chromatography (SiO_2, pentane), hydroazulene **VI** (428 mg, 100%) as a colourless oil. R_f = 0.73 (75:15 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.78-7.73 (m, 4H), 7.48-7.40 (m, 6H), 6.17 (d, J = 12.4 Hz, 1H), 5.78 (d, J = 12.4 Hz, 1H), 4.35 (d, J = 9.6 Hz, 1H), 2.30-2.15 (m, 3H), 2.08-2.01 (m, 1H), 1.80-1.73 (m, 1H), 1.77 (s, 3H), 1.67-1.57 (m, 2H), 1.25-1.16 (m, 1H), 1.17 (s, 9H), 0.86 (d, J = 6.4 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 140.56, 135.9 (×4), 135.3, 134.5, 134.3 (×2), 129.5 (×2), 127.5 (×4), 121.0, 73.40, 55.3, 46.1, 36.5, 35.6, 30.2, 27.0 (×3), 22.0, 19.2, 14.7 ppm. HRMS (ESI$^+$) calcd. for $C_{28}H_{36}OSi$ $[M]^+$ 416.2535; found: 416.2460.



VIII

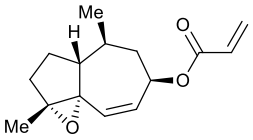
Ester VIII. Pyridine (4.0 equiv, 333 μL, 4.1 mmol) and BzCl (4.0 equiv, 478 μL, 4.1 mmol) were added sequentially to a solution of unprotected **VII**[2] (1.0 equiv, 227 mg, 1.0 mmol) in CH_2Cl_2 (13 mL) at 23 ºC. The resulting mixture was stirred 12 hours at 23°C. The reaction was then quenched with sat. aqueous NH_4Cl (10 mL), extracted with EtOAc (2×10 mL), water (20 mL) and brine (20 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, petroleum ether to 10:1 petroleum ether/EtOAc) yielded the Bz-protected alcohol **VIII** (320 mg, 96%). R_f = 0.64 (4:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.06-8.03 (m, 2H), 7.57-7.52 (m, 1H), 7.45-7.41 (m, 2H), 5.91-5.82 (m, 1H), 5.53-5.45 (m, 2H), 4.73 (s, 1H), 4.70 (s, 1H), 2.33-2.21 (m, 2H), 2.12-2.05 (m, 1H), 2.07 (d, J = 2.4 Hz, 1H), 1.92-1.87 (m, 1H), 1.83-1.54 (m, 7H), 1.73 (s, 3H), 1.07 (d, J = 6.0 Hz, 3H) ppm.



15

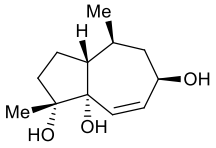
Epoxide 15. Grubbs' II catalyst (7.5 mol%, 65 mg, 75 μmol) was added to a solution of alkene **VIII** (1.0 equiv, 320 mg, 1.0 mmol) in toluene (350 mL) at 100 ºC. The mixture was stirred 1 hour at 100 °C. The reaction was then quenched by addition of DMSO (275 μL) and stirred for another 12 hours. Evaporation of the solvents under reduced pressure followed by a simple filtration afforded hydroazulene **14** which was used in the next step without further purification. R_f = 0.62 (4:1 petroleum ether/EtOAc). *m*CPBA (1.0 equiv, 236 mg, 1.0 mmol) was added to a solution of compound **14** (1.0 equiv, 291 mg, 1.0 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The mixture was stirred 1 hour at 0 °C. The reaction was quenched with sat. aqueous $NaHCO_3$ (20 mL), extracted with EtOAc (2×20 mL), water (40 mL) and brine (40 mL), and dried over Na_2SO_4. Evaporation of the

solvents under reduced pressure followed by flash chromatography (SiO_2, petroleum ether to 5:1 petroleum ether/EtOAc) yielded epoxide **15** in 18% yield over 2 steps (55 mg). R_f = 0.52 4:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.06 (d, J = 8.0 Hz, 2H), 7.58-7.54 (m, 1H), 7.45 (t, J = 7.6 Hz, 2H), 6.23-6.20 (m, 1H), 5.89-5.84 (m, 1H), 5.62 (dd, J = 12.0, 2.4 Hz, 1H), 2.07-1.98 (m, 2H), 1.92 (dd, J = 13.2, 8.0 Hz, 1H), 1.81-1.65 (m, 3H), 1.62-1.51 (m, 1H), 1.39 (s, 3H), 1.17-1.07 (m, 1H), 1.00 (d, J = 6.4 Hz, 3H) ppm. The stereochemistry of the epoxide was assigned based on X-ray crystallographic information obtained for derivative **18**.



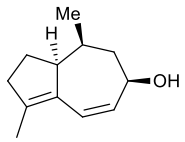
17

Epoxide 17. Sodium hydroxide (1.2 equiv, 0.5 mg, 0.01 mmol) was added by portions to a solution of epoxide **15** (1.0 equiv, 6.0 mg, 20 μmol) in methanol (1.0 mL). The reaction mixture was stirred at 23 °C. The reaction was then quenched with sat. aqueous NH_4Cl (1 mL), extracted with EtOAc (2×1 mL), water (2 mL) and brine (2 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the alcohol **16** (3.0 mg) as a colourless oil. This crude material (1.0 equiv, 3.0 mg, 15 μmol) was treated with triethylamine (8.0 equiv, 16.2 μL, 120 μmol) and acryloyl chloride (4.0 equiv, 6.0 μL, 60 μmol) gave, after purification by flash chromatography (SiO_2, 80:20 petroleum ether/Et_2O), 3.0 mg of compound **17** as a colourless oil in 58% yield over 2 steps. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.44 (d, J = 17.0 Hz, 1H), 6.14 (dd, J = 17.0, 10.2 Hz, 1H), 6.13-6.09 (m, 1H), 5.85 (d, J = 10.2 Hz, 1H), 5.74-5.67 (m, 1H), 5.60 (dd, J = 11.8, 2.5 Hz, 1H), 2.04-1.95 (m, 2H), 1.92 (dd, J = 13.4, 8.2 Hz, 1H), 1.76-1.62 (m, 3H), 1.55-1.51 (m, 1H), 1.39 (s, 3H), 1.18-1.05 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H) ppm.



18

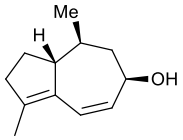
Triol 18. Trifluoroacetic acid (1.0 equiv, 13 µL, 180 µmol) was added to a solution of epoxide **15** (1.0 equiv, 55 mg, 180 µmol) in CH_2Cl_2 (9 mL) at 23 °C. The mixture was stirred 1 hour at 23 °C. The reaction was then quenched with sat. aqueous $NaHCO_3$ (10 mL), extracted with EtOAc (2×10 mL), water (20 mL) and brine (20 mL), and dried over Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (SiO_2, petroleum ether to 20:1 petroleum ether/EtOAc) yielded tertiary alcohol **IX** which was used in the next step without further purification. R_f = 0.31 (4:1 petroleum ether/EtOAc). A 1% solution of NaOH in MeOH (4.9 mL) was added to alcohol **IX** (1.0 equiv, 71 mg, 180 µmol) at 23 °C. The mixture was stirred 6 hours at 23 °C. The reaction was then quenched with sat. aqueous NH_4Cl (5 mL), extracted with EtOAc (2×5 mL), water (10 mL) and brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure followed by flash chromatography (SiO_2, petroleum ether to 50:1 petroleum ether/EtOAc) afforded triol **18** in 60% yield over 2 steps (23 mg). R_f = 0.11 (1:2 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, acetone-d_6, 25 °C): δ 5.87 (dd, J = 12.0, 1.2 Hz, 1H), 5.78 (dd, J = 12.0, 2.4 Hz, 1H), 4.69-4.65 (m, 1H), 3.70 (d, J = 4.8 Hz, 1H), 3.63 (s, 1H), 3.23 (s, 1H), 2.14-2.07 (m, 1H), 1.84-1.76 (m, 2H), 1.71-1.63 (m, 1H), 1.55-1.47 (m, 2H), 1.45-1.41 (m, 1H), 1.36 (q, J = 11.6 Hz, 1H), 1.18 (s, 3H), 0.88 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, acetone-d_6, 25 °C): δ 143.79, 129.33, 81.75, 80.86, 69.95, 50.22, 48.07, 36.94, 33.71, 26.13, 25.11, 21.78 ppm.



epi **11**

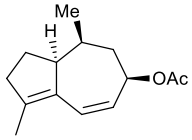
Alcohol *epi* **11**. TBAF (3.0 equiv, 0.51 mL, 510 µmol, 1M in toluene) was added to a solution of silyl ether *epi* **VI** (1.0 equiv, 70 mg, 170 µmol) in THF (2.0 mL) at 23 ºC. After stirring for 14 hours, the reaction was quenched with sat. aqueous NH_4Cl (2 mL) and extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. After purification by column chromatography (SiO_2, 85:15 pentane/Et_2O), alcohol *epi* **11** (30 mg, 99%) was obtained as a colourless oil. R_f = 0.3 (80:20 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 6.20 (d, J = 11.5 Hz, 1H), 5.61 (d,

J = 11.5 Hz, 1H), 4.72 (d, *J* = 9.6 Hz, 1H), 3.01 (bs, 1H), 2.35-2.18 (m, 2H), 2.07-2.02 (m, 2H), 1.94-1.84 (m, 1H), 1.74 (s, 3H), 1.63-1.48 (m, 3H), 0.84 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 139.1 134.3, 134.0, 124.0, 69.5, 50.3, 45.4, 37.8, 33.1, 26.9, 16.1, 14.2 ppm.



11

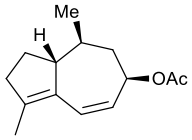
Alcohol 11. Following the same procedure as for alcohol *epi* **11**, silyl ether **VI** (1.0 equiv, 14 mg, 30 μmol) gave after purification by column chromatography (SiO_2, 85:15 pentane/Et_2O), alcohol **11** (5.0 mg, 70%) as a colourless oil. R_f = 0.3 (80:20 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC) (OH not visible): δ 6.21 (d, *J* = 12.5 Hz, 1H), 5.61 (d, *J* = 12.5 Hz, 1H), 4.25 (d, *J* = 11.1 Hz, 1H), 2.28-2.16 (m, 3H), 2.09-2.02 (m, 1H), 1.93-1.89 (m, 1H), 1.76 (s, 3H), 1.59-1.48 (m, 1H), 1.38-1.25 (m, 2H), 0.99 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 139.1 134.3, 134.0, 124.0, 69.5, 50.3, 45.4, 37.8, 33.1, 26.9, 16.1, 14.2 ppm.



epi **X**

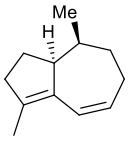
Acetate *epi* **X**. A solution containing acetic anhydride (1.5 equiv, 31 μL, 0.33 mmol) and alcohol *epi* **2** (1.0 equiv, 40 mg, 0.22 mmol) in pyridine (3.0 mL) was stirred for 14 hours at 23 ºC. The reaction was diluted with water (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. After purification by column chromatography (SiO_2, 90:10 pentane/Et_2O), acetate *epi* **X** (48 mg, 99%) was obtained as a colourless oil. R_f = 0.8 (80:20 pentane/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 6.27 (d, *J* = 11.6 Hz, 1H), 5.75 (d, *J* = 9.0 Hz, 1H), 5.47 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.11 (bs, 1H), 2.36-2.18 (m, 2H), 2.11-2.02 (m, 2H), 2.03 (s,

3H), 1.95-1.86 (m, 1H), 1.74 (s, 3H), 1.68-1.53 (m, 2H), 0.84 (d, J = 6.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 170.3, 140.0, 133.6, 129.5, 125.3, 72.2, 50.5, 41.7, 37.9, 32.9, 26.9, 21.4, 15.6, 14.3 ppm.



X

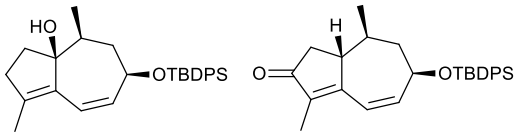
Acetate X. Following the same procedure as for acetate *epi* **X**, alcohol **2** (1.0 equiv, 5.0 mg, 20 μmol) yielded, after purification by column chromatography (SiO_2, 90:10 pentane/Et_2O) acetate **X** (6.0 mg, 100%) as a colourless oil (R_f = 0.8, 80:20 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 6.27 (d, J = 12.4 Hz, 1H), 5.44 (d, J = 12.4 Hz, 1H), 5.36 (d, J = 11.1 Hz, 1H), 2.31-2.22 (m, 3H), 2.07 (s, 3H), 2.04-2.02 (m, 2H), 1.90-1.85 (m, 1H), 1.76 (s, 3H), 1.33-1.28 (m, 2H), 0.99 (d, J = 6.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 170.3, 142.0, 134.8, 128.2, 123.2, 73.9, 55.5, 42.1, 36.6, 35.3, 30.2, 22.0, 21.4, 14.8 ppm.



clavukerin A

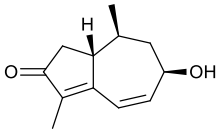
Clavukerin A. $Pd(PPh_3)_4$ (1.0 equiv, 35 mg, 30 μmol) was added to a solution of acetate *epi* **X** (1.0 equiv, 7.0 mg, 30 μmol) in THF (0.06 mL) at 23 ºC. After stirring for 15 minutes, $LiAlH_4$ (2.0 equiv, 2.4 mg, 6 μmol) was added at 0 ºC and the mixture was stirred for 1 hour at 23 ºC. The reaction was diluted with Et_2O (2 mL), filtrated through a pad of silica and the solvent removed under 300 mbar at 20°C. After purification by column chromatography (SiO_2, pentane), clavukerin A (3.0 mg, 62%) was obtained as a colourless oil. R_f = 1.0 (pentane); The compound was found to have identical spectral properties as previously reported by P.Metz *et al*, *Eur. J. Org. Chem.* **2010**, 6145–6148; ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ºC): δ 6.21 (d, J = 12.2 Hz, 1H), 5.56-5.53 (m, 1H), 2.92-2.89 (m, 1H), 2.30-2.24 (m, 4H), 1.94-1.88 (m, 2H), 1.73 (s, 3H), 1.72-1.67 (m,

1H), 1.66-1.51 (m, 1H), 1.52-1.62 (m, 1H), 0.75 (d, J = 6.9 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 ºC): δ 138.8, 134.9, 128.8, 123.8, 54.5, 37.8, 34.4, 34.2, 27.2, 26.7, 14.5, 11.4 ppm.



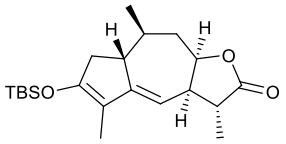
XI **XII**

Compounds XI and XII. A solution containing hydroazulene **VI** (1.0 equiv, 390 mg, 940 µmol), acetic acid (1.8 mL), acetic anhydride (2.6 mL), NaOAc (8.0 equiv, 620 mg, 7.5 mmol) and Na_2CrO_4 (5.7 equiv, 860 mg, 5.3 mmol) in benzene (20 mL) was heated for 12 hours at 70 °C. The reaction was quenched with sat. aqueous $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (2×20 mL). The combined organic extracts were washed with water (60 mL) and brine (60 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, 70:30 petroleum ether/EtOAc), to provide compound **XI** in 20% yield (77 mg) and compound **XII** in 19% yield (77 mg) as yellow oils. Compound **XI**: R_f = 0.39 (75:25 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.69-7.65 (m, 4H), 7.46-7.37 (m, 6H), 6.30 (d, J = 12.0 Hz, 1H), 6.19 (d, J = 12.0 Hz, 1H), 4.39-4.34 (m, 1H), 2.55 (dd, J = 18.0, 6.4 Hz, 1H), 2.50-2.42 (m, 1H), 2.01 (dd, J = 18.0, 3.6 Hz, 1H), 1.79-1.75 (m, 2H), 1.67 (bs, 3H), 1.40-1.22 (m, 1H), 1.09 (m, 9H), 0.89 (d, J = 6.4 Hz, 3H) ppm. Compound **XII**: R_f = 0.35 (75:25 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 7.74-7.62 (m, 4H), 7.47-7.38 (m, 6H), 6.24 (dd, J = 12.8, 2.0 Hz, 1H), 5.75 (dd, J = 12.8, 2.0 Hz, 1H), 4.24-4.32 (m, 1H), 2.36-2.27 (m, 2H), 2.18-2.12 (m,1H), 2.07 (s, 3H), 1.82-1.63 (m, 2H), 1.54-1.21 (m, 2H), 1.06 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H) ppm.



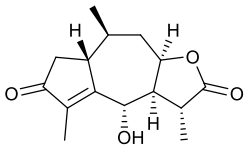
1

Alcohol 1. Following the same procedure as for alcohol *epi* **11**, hydroazulenone **XII** (1.0 equiv, 76.9 mg, 0.2 mmol) yielded, after purification by flash chromatography (SiO_2, 80:20 petroleum ether/EtOAc) 25.9 mg (75%) of alcohol **1** as a colourless oil. R_f = 0.22 (50:50 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH not visible): δ 6.40 (d, J = 12.5 Hz, 1H), 6.15 (d, J = 12.4 Hz, 1H), 4.42 (d, J = 10.4 Hz, 1H), 2.64 (dd, J = 18.4, 6.4 Hz, 1H), 2.48-2.56 (m, 1H), 2.14 (dd, J = 18.4, 3.6 Hz, 1H), 2.05-1.99 (m, 1H), 1.80-1.76 (m, 1H), 1.74 (d, J = 2.0 Hz, 3H), 1.71-1.63 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 207.4, 165.6, 143.1, 138.2, 122.4, 71.3, 48.1, 46.4, 41.5, 35.6, 22.9, 8.2 ppm. HRMS (ESI$^+$) calcd. for $C_{12}H_{17}O_2$ $[M + H]^+$ 193.1229; found: 193.1222.



XIII

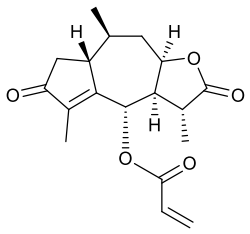
Silyl enol ether XIII. A solution containing alcohol **XII** (1.0 equiv, 2.0 mg, 10 μmol), *tert*-butyldimethylsilyl ketene acetal[2] (4.0 equiv, 8.4 mg, 40 μmol) and $LiClO_4$ (0.1 equiv, 0.11 mg, 1 μmol) in CH_2Cl_2 (0.5 mL) was stirred for 5 hours at 23 °C. The reaction was quenched with sat. aqueous $NaHCO_3$ (0.5 mL) and was extracted with 1:1 mixture of Et_2O/pentane (3×0.5 mL), washed with brine (1 mL), dried over Na_2SO_4 and filtered. Evaporation of the solvents under reduced pressure yielded enol ether **XIII**, which was used in the next step without further purification.



(±)-**geigerin**

(±)-geigerin. A freshly prepared solution of DMDO (1.5 equiv, 450 μL, 15 μmol, 0.05 M in acetone) was added to a mixture of enol ether **XIII** (1.0 equiv, 3.8 mg, 10 μmol) in acetone (0.5 mL) at -90 °C. The reaction was stirred for 10 minutes at this temperature and then quenched with water (0.5 mL). The aqueous phase was extracted with 70:30

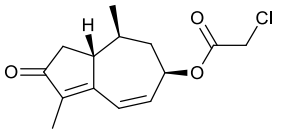
EtOAc/pentane (2×1 mL), washed with brine (2 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (0.5 mL). SiO_2 was added and the mixture was stirred for 12 hours at 23 °C. The solution was filtered and the solvent was removed under reduced pressure. The residue was purified by PTLC (50:50 petroleum ether/EtOAc), to afford 2.4 mg of **(±)-**geigerin (90% yield, over 2 steps) as a colourless oil. R_f = 0.19 (95:5 CH_2Cl_2/acetone); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal not visible): δ 4.63 (d, J = 9.3 Hz, 1H), 4.40 (ddd, J = 11.3, 8.6, 2.6 Hz, 1H), 2.72-2.60 (m, 3H), 2.42-2.35 (m, 1H), 2.13 (d, J = 18. Hz, 1H), 1.95 (bs, 3H), 1.92-1.76 (m, 2H), 1.48 (d, J = 6.4 Hz, 3H), 1.31-1.19 (m, 1H), 1.12 (d, J = 6.4 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 208.1, 178.3, 171.3, 138.3, 78.5, 75.3, 49.3, 48.4, 42.0, 40.6, 40.1, 38.0, 22.6, 16.5, 9.1 ppm. HRMS (ESI$^+$) calcd. for $C_{15}H_{21}O_3$ $[M+Na]^+$ 287.1259; found: 287.1292.



13

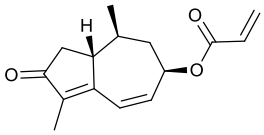
Compound 13. Triethylamine (8.0 equiv, 13.5 µL, 100 µmol) and acryloyl chloride (4.0 equiv, 4.5 mg, 50 µmol) were sequentially added to a solution of geigerin (1.0 equiv, 3.5 mg, 10 µmol) in Et_2O (0.30 mL) at 0 °C. The resulting mixture was stirred for 16 hours at 23 °C. The reaction was quenched with sat. aqueous $NaHCO_3$ (0.30 mL) and extracted with Et_2O (2×1 mL). The combined organic extracts were washed with brine (2 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. After purification by PTLC (SiO_2, 60:40 petroleum ether/EtOAc), 4.1 mg (98%) of compound **13** was obtained as a colourless oil. R_f = 0.5 (50:50 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.50 (d, J = 17.2 Hz, 1H), 6.17 (dd, J = 17.2, 10.5 Hz, 1H), 5.99 (d, J = 10.5 Hz, 1H), 5.50 (d, J = 10.8 Hz, 1H), 4.48-4.42 (m, 1H), 2.85 (ddd, J = 10.5, 10.5, 10.5 Hz, 1H), 2.69 (dd, J = 18.4, 6.3 Hz, 1H), 2.64-2.58 (m, 2H), 2.13 (d, J = 18.4 Hz, 1H), 1.94-1.90 (m, 2H), 1.79 (s, 3H), 1.40 (d, J = 7.1 Hz, 3H), 1.37-1.23 (m, 1H), 1.16 (d, J = 7.0 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 207.3, 177.3, 167.4, 164.6, 137.6, 132.9, 126.9, 78.2, 76.0, 47.9, 46.7, 42.1, 39.5,

37.8, 22.7, 22.5, 16.0, 8.8 ppm. HRMS (ESI^+) calcd. for $C_{18}H_{23}O_5$ $[M + H]^+$ 319.1545; found: 319.1575.



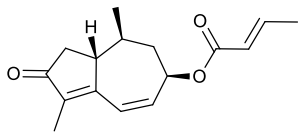
12a

Compound 12a. Following the same procedure as for compound **13**, compound **XII** (1.0 equiv, 3.0 mg, 10 μmol) and 2-chloroacetyl chloride (4.0 equiv, 5.0 μL, 60 μmol) gave, after purification by flash chromatography (SiO_2, 80:20 petroleum ether/Et_2O), 4.0 mg (91%) of compound **12a** as a colourless oil. R_f = 0.32 (50:50 petroleum ether/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 6.53 (d, J = 12.4 Hz, 1H), 6.00 (d, J = 12.4 Hz, 1H), 5.54 (d, J = 10.2 Hz, 1H), 4.09 (s, 2H), 2.65 (dd, J = 18.2, 6.2 Hz, 1H), 2.59-2.54 (m, 1H), 2.27-2.01 (m, 2H), 1.90-1.78 (m, 1H), 1.73 (s, 3H), 1.33-1.22 (m, 1H), 1.12 (d, J = 6.5 Hz, 3H) ppm.



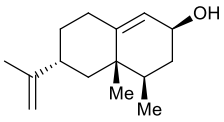
12b

Compound 12b. Following the same procedure as for compound **13**, compound **XII** (1.0 equiv, 3.0 mg, 10 μmol) and acryloyl chloride (4.0 equiv, 6.0 μL, 60 μmol) gave, after purification by flash chromatography (SiO_2, 80:20 petroleum ether/Et_2O), 4.0 mg (95%) of compound **12b** as a colourless oil. R_f = 0.39 (50:50 petroleum ether/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 6.50 (dd, J = 12.4, 2.1 Hz, 1H), 6.46 (dd, J = 17.3, 1.4 Hz, 1H), 6.15 (dd, J = 17.3, 10.4 Hz, 1H), 6.04 (ddd, J = 12.4, 2.0, 2.0 Hz, 1H), 5.89 (dd, J = 10.4, 1.4 Hz, 1H), 5.57-5.52 (m, 1H), 2.65 (ddd, J = 18.2, 7.1, 0.7 Hz, 1H), 2.58-2.55 (m, 1H), 2.16 (dd, J = 18.2, 3.6 Hz, 1H), 2.05-2.01 (m, 1H), 1.89-1.78 (m, 1H), 1.75 (d, J = 2.0 Hz, 3H), 1.34-1.23 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H) ppm.



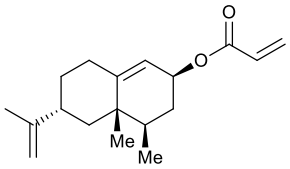
12c

Compound 12c. Following the same procedure as for compound **13**, compound **XII** (1.0 equiv, 3.0 mg, 10 μmol) and (*E*)-but-2-enoyl chloride (4.0 equiv, 7.0 μL, 60 μmol) gave, after purification by flash chromatography (SiO_2, 80:20 petroleum ether/Et_2O), 4.0 mg (98%) of compound **12c** as a colourless oil. R_f = 0.39 (50:50 petroleum ether/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 ^{o}C): δ 6.49 (d, J = 12.5 Hz, 1H), 6.00 (d, J = 12.5 Hz, 1H), 5.97-5.88 (m, 1H), 5.50-5.43 (m, 1H), 5.23-5.18 (m, 1H), 2.65 (dd, J = 18.2, 6.3 Hz, 1H), 2.58-2.51 (m, 1H), 2.15 (dd, J = 18.2, 3.8 Hz, 1H), 2.01-1.96 (m, 1H), 1.82-1.73 (m, 1H), 1.75 (d, J = 2.0 Hz, 3H), 1.60-1.52 (m, 3H), 1.34-1.23 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H) ppm.



3

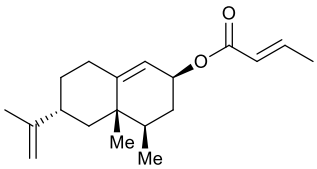
Alcohol 3. Sodium borohydride (1.0 equiv, 1.5 mg, 40 μmol) was added to a solution of (+)-nootkatone (1.0 equiv, 10 mg, 40 μmol) and cerium(III) chloride heptahydrate (1.0 equiv, 15 mg, 40 μmol) in methanol (0.5 mL) at 23 ºC. After stirring for 10 minutes, the reaction was quenched with water (1 mL) and extracted with Et_2O (3×2 mL). The combined organic layers were washed with brine (6 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 85:15 petroleum ether/EtOAc) to afford alcohol **3** (8.0 mg, 91%) as colourless oil. R_f = 0.25 (85:15 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 5.31 (bs, 1H), 4.67 (bs, 2H), 4.23 (m, 1H), 2.23 (dddd, J = 12.4, 12.4, 2.6, 2.6 Hz, 1H), 2.10 (ddd, J = 14.0, 3.8, 2.7 Hz, 1H), 1.84 (ddd, J = 12.7, 2.2, 2.2 Hz, 1H), 1.86-1.73 (m, 3H), 1.69 (s, 3H), 1.52-1.46 (m, 1H), 1.40-1.31 (m, 1H), 1.24-1.43 (m, 1H), 0.98 (s, 3H), 0.94-0.90 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 150.2, 145.9, 124.2, 108.5, 67.9, 44.5, 40.7, 39.2, 38.1, 37.1, 32.8, 32.3, 20.8, 18.1, 15.3 ppm.



20a

General procedure for the acylation of alcohol **3**:

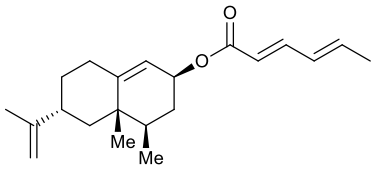
Ester 20a. Triethylamine (1.2 equiv, 8.1 μL, 60 μmol) and acryloyl chloride (1.1 equiv, 8 μL, 55 μmol) were sequentially added to a solution of the alcohol **3** (1.0 equiv, 10 mg, 50 μmol) in THF (0.50 mL) at 0 °C. The resulting mixture was stirred for 16 hours at 23 °C. The reaction was quenched with sat. aqueous $NaHCO_3$ (0.50 mL) and extracted with EtOAc (3×0.50 mL). The combined organic extracts were washed with brine (2 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, 95:5 petroleum ether/EtOAc), yielding ester **20a** in 83% yield (10 mg) as colourless oil. R_f = 0.50 (petroleum ether); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.40 (dd, J = 17.3, 1.4 Hz, 1H), 6.11 (dd, J = 17.3, 10.4 Hz, 1H), 5.80 (dd, J = 10.4, 1.4 Hz, 1H), 5.43-5.39 (m, 1H), 5.30 (bs, 1H), 4.68 (bs, 2H), 2.38-2.29 (m, 1H), 2.25 (dddd, J = 12.4, 12.4, 2.9, 2.9 Hz, 1H), 2.16 (ddd, J = 14.1, 3.9, 2.7 Hz, 1H), 1.90-1.78 (m, 3H), 1.71 (s, 3H), 1.64-1.48 (m, 2H), 1.29-1.20 (m, 1H), 1.02 (s, 3H), 0.98-0.92 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 168.1, 150.1, 148.1, 130.4, 128.9, 119.9, 108.6, 71.1, 44.4, 40.7, 39.6, 38.1, 32.7, 32.5, 32.4, 20.8, 18.1, 15.3 ppm.



20b

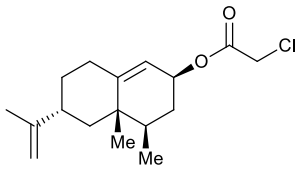
Ester 20b. Following the general procedure, the crude compound was purified by flash chromatography (SiO_2, 95:5 petroleum ether/EtOAc), yielding ester **20b** in 67% yield (8 mg) as colourless oil. R_f = 0.50 (petroleum ether); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.97 (dqd, J = 15.4, 6.9 Hz, 1H), 5.83 (dd, J = 15.4, 1.6 Hz, 1H), 5.41-5.36 (m, 1H),

5.29 (bs, 1H), 4.69 (bs, 2H), 2.37-2.29 (m, 1H), 2.25 (dddd, J = 12.4, 12.4, 2.8, 2.8 Hz, 1H), 2.15-2.11 (m, 1H), 1.87-1.85 (m, 3H), 1.86 (dd, J = 6.9, 1.6 Hz, 3H), 1.71 (s, 3H), 1.64-1.46 (m, 2H), 1.28-1.97 (m, 1H), 1.01 (s, 3H), 0.98-0.92 (m, 1H), 0.90 (d, J = 6.7 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 166.4, 150.1, 147.8, 144.4, 123.1, 120.1, 108.6, 70.6, 44.4, 40.7, 39.1, 38.1, 32.7, 32.6, 32.4, 20.8, 18.1, 17.9, 15.3 ppm.



20c

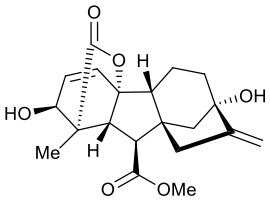
Ester 20c. Following the general procedure, the crude compound was purified by flash chromatography (SiO_2, 95:5 petroleum ether/EtOAc), yielding ester **20c** in 89% yield (25 mg) as colourless oil. R_f = 0.50 (petroleum ether); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.25 (dd, J = 15.4, 9.9 Hz, 1H), 6.21-6.09 (m, 2H), 5.76 (d, J = 15.4 Hz, 1H), 5.42-5.38 (m, 1H), 5.30 (bs, 1H), 4.68 (bs, 2H), 2.38-2.29 (m, 1H), 2.25 (dddd, J = 12.4, 12.4, 2.6, 2.6 Hz, 1H), 2.14 (ddd, J = 14.1, 3.9, 2.5 Hz, 1H), 1.89-1.79 (m, 3H), 1.84 (d, J = 5.8 Hz, 3H), 1.71 (s, 3H), 1.63-1.46 (m, 2H), 1.28-1.16 (m, 1H), 1.01 (s, 3H), 0.98-0.95 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 167.2, 150.1, 147.7, 144.9, 139.1, 129.8, 120.2, 119.3, 108.6, 70.7, 44.5, 40.7, 39.1, 38.1, 32.7, 32.6, 32.4, 20.8, 18.6, 18.1, 15.3 ppm.



20d

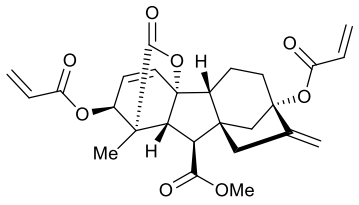
Ester 20d. Following the general procedure, the crude compound was purified by flash chromatography (SiO_2, 95:5 petroleum ether/EtOAc), yielding ester **20d** in 92% yield (24 mg) as colourless oil. R_f = 0.50 (petroleum ether); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 5.44-5.40 (m, 1H), 5.27 (bs, 1H), 4.69 (bs, 1H), 4.68 (bs, 1H), 4.04 (s, 2H), 2.37-2.29 (m, 1H), 2.28 (dddd, J = 12.4, 12.4, 2.8, 2.8 Hz, 1H), 2.17 (ddd, J = 14.1, 3.9, 2.6 Hz, 1H), 1.91-1.83 (m, 3H), 1.74 (s, 3H), 1.65-1.50 (m, 2H), 1.30-1.19 (m, 1H), 1.04 (s,

3H), 1.00-0.97 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 167.2, 149.9, 148.8, 119.0, 108.7, 73.2, 44.4, 41.2, 40.6, 39.0, 38.1, 32.6, 32.3 (×2), 20.8, 18.1, 15.2 ppm.



2

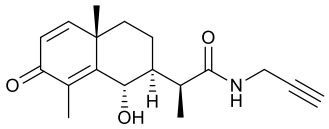
Ester 2. A solution containing gibberellic acid (1.0 equiv, 100 mg, 0.29 mmol), potassium carbonate (1.5 equiv, 60 mg, 0.43 mmol) and iodomethane (1.1 equiv, 20 μL, 0.31 mmol) in acetone (30 mL) was stirred at 23 ºC for 13 hours. The reaction was quenched with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give 20 mg (20%) of ester **2** as a white solid, which was used in the next step without further purification. R_f = 0.30 (50:50 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (2×OH signals not visible): δ 6.39 (d, J = 9.3 Hz, 1H), 5.90 (dd, J = 9.2, 3.2 Hz, 1H), 5.24 (s, 1H), 4.97 (s, 1H), 4.13 (ddd, J = 7.1, 7.1, 7.1 Hz, 1H), 4.01 (d, J = 3.2 Hz, 1H), 3.76 (s, 3H), 3.28 (d, J = 10.7 Hz, 1H), 2.76 (d, J = 10.7 Hz, 1H), 2.22 (ddd, J = 14.6, 14.6, 14.6 Hz, 2H), 2.05-1.71 (m, 5H), 2.04 (s, 2H), 1.19 (s, 3H) ppm.



19

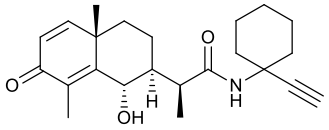
Ester 19. Acryloyl chloride (2.1 equiv, 6.0 μL, 0.07 mmol) was added to a solution containing ester **2** (1.0 equiv, 12 mg, 0.03 mmol) and triethylamine (2.2 equiv, 10 μL, 0.07 mmol) in THF (0.5 mL) at 0 ºC. After stirring for 1 hour at 23 ºC, the reaction was quenched with water (1 mL) and extracted with Et_2O (3×2 mL). The combined organic

layers were washed with brine (6 mL), dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 80:20 petroleum ether/EtOAc) to afford 8 mg (53%) of ester **19** as foam. R_f = 0.32 (80:20 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.99 (d, J = 17.3 Hz, 1H), 6.40 (d, J = 10.5 Hz, 1H), 6.37 (d, J = 17.0 Hz, 1H), 6.16 (dd, J = 17.3, 10.5 Hz, 1H), 6.09 (dd, J = 17.3, 10.5 Hz, 1H), 5.94-5.90 (m, 2H), 5.80 (d, J = 10.4 Hz, 1H), 5.42 (d, J = 3.7 Hz, 1H), 5.19 (bs, 1H), 5.02 (bs, 1H), 3.75 (s, 3H), 3.39 (d, J = 11 Hz, 1H), 2.80 (d, J = 11 Hz, 1H), 2.44 (dd, J = 12.0, 7.8 Hz, 1H), 2.36 (s, 2H), 2.28-2.18 (m, 2H), 2.10-1.94 (m, 2H), 1.88-1.86 (m, 1H), 1.76-1.70 (m, 1H), 1.16 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 176.9, 172.2, 165.0, 164.9, 153.2, 134.4, 132.2, 130.5, 129.3, 129.1, 127.6, 108.4, 90.0, 84.3, 70.3, 53.5, 52.3, 51.1, 50.9, 50.3, 42.6, 39.7, 36.3, 16.8, 14.3 ppm.



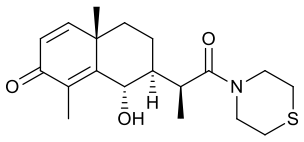
XIV

Alcohol XIV. A solution of propargylamine (2.5 equiv, 196 µL, 3.05 mmol) in 1,2-dichloroethane (0.36 mL) was added to a suspension of $AlCl_3$ (205 mg, 1.52 mmol, 1.25 equiv) in 1,2-dichloroethane (0.63 mL) with agitation at 0 °C. Then, α-santonin (1.0 equiv, 300 mg, 1.22 mmol) was added in 1,2-dichloroethane (0.8 mL) and the mixture was stirred 12 hours at 23 °C. The next day, the reaction was quenched with a mixture of ice and water (2 mL) and stirred an additional 30 minutes. Then, the aqueous phase was extracted with 1,2-dichloroethane (3×1 mL).The combined organic phases were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4. The solvent was removed under vacuum. The crude compound was purified by flash chromatography (SiO_2, 1:1 to 1:2 petroleum ether/EtOAc) to afford **XIV** (124 mg, 34%) as a white solid. R_f = 0.28 (1:2 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 6.67 (d, J = 9.7 Hz, 1H), 6.24 (d, J = 9.7 Hz, 1H), 5.88 (bs, 1H), 4.55 (dd, J = 10.9, 5.5 Hz, 1H), 4.12 - 4.06 (m, 2H), 2.88 (d, J = 5.7 Hz, 1H), 2.72 – 2.62 (m, 1H), 2.25 (s, 3H), 2.01 (tt app, J = 12.0, 3.9 Hz, 1H), 1.84-1.56 (m, 4H), 1.28 (d, J = 7.2 Hz, 3H), 1.25 (s, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{18}H_{24}NO_3^+$: 302.18; found: 302.22.



XV

Alcohol XV. A solution of 1-ethynylcyclohexylamine (2.5 equiv, 781 mg, 6.1 mmol) in 1,2-dichloroethane (0.72 mL) was added to a suspension of $AlCl_3$ (405 mg, 3.04 mmol, 1.25 equiv) in 1,2-dichloroethane (1.3 mL) with agitation at 0 °C. Then, α-santonin (1.0 equiv, 600 mg, 2.44 mmol) was added in 1,2-dichloroethane (1.6 mL) and the mixture was stirred 12 hours at 23 °C. The next day, the reaction was quenched with 2M aqueous NaOH (4 mL) and stirred an additional 30 minutes. Then, the aqueous phase was extracted with 1,2-dichloroethane (3 × 2 mL).The combined organic phases were washed with water (4 mL) and brine (4 mL), dried over Na_2SO_4. The solvent was removed under vacuum. The crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **XV** (541 mg, 60%) as a white solid. R_f = 0.31 (1:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ (OH signal is not visible) δ 6.65 (d, J = 10.1 Hz, 1H), 6.21 (d, J = 10.1 Hz, 1H), 5.81 (s, 1H), 4.54 (d, J = 11.2 Hz, 1H), 2.59 (dq, J = 7.0, 3.7 Hz, 1H), 2.38 (s, 1H), 2.32 (s, 4H), 2.23 (s, 3H), 2.13 (t, J = 12.2 Hz, 1H), 1.93 (tt app, J = 11.6, 3.9 Hz, 1H), 1.71 (m, 9H), 1.24 (s, 3H), 1.23 (d, J = 7.3 Hz, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C23H32NO3^+$: 370.24; found: 370.17.

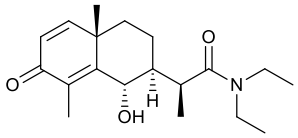


XVI

General Procedure for ring-opening of α-santonin with a secondary amine:

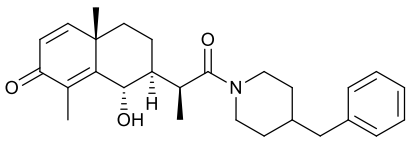
Alcohol XVI. A solution of thiomorpholine (20.0 equiv, 4.3 mL, 6.1 mmol) was added to a suspension of $AlCl_3$ (5.0 equiv, 1.35 g, 3.04 mmol) in 1,2-dichloroethane (50 mL) with agitation at 0 °C. Then, α-santonin (1.0 equiv, 500 mg, 2.44 mmol) was added in one portion and the mixture was stirred 12 hours at 23 °C. The next day, the reaction was quenched with 2M aqueous NaOH (50 mL) and stirred an additional 30 minutes. Then, the aqueous phase was extracted with 1,2-dichloroethane (3×25 mL).The combined organic phases were washed with water (25 mL) and brine (25 mL), dried

over Na_2SO_4. The solvent was removed under vacuum. The crude compound was purified by flash chromatography (SiO_2, EtOAc) to afford **XVI** (965 mg, quantitative) as a white solid. R_f = 0.48 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 6.66 (d, J = 9.3 Hz, 1H), 6.19 (d, J = 9.3 Hz, 1H), 4.47 (d, J = 10.4 Hz, 1H), 3.85 (bs, 4H), 3.21 (t, J = 5.8 Hz, 1H), 3.10 (t, J = 4.5 Hz, 1H), 2.58 (bs, 4H), 2.18 (s, 3H), 1.92 (m, 1H), 1.77 (d, J = 13.0 Hz, 1H), 1.62 (m, 2H), 1.21 (s, 3H), 1.13 (d, J = 6.9 Hz, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{19}H_{28}NO_3S^+$: 350.18; found: 350.06.



XVII

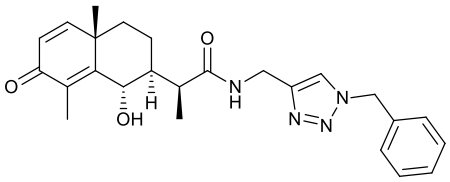
Alcohol XVII. Following general procedure for ring-opening of α-santonin with a secondary amine, the crude compound was purified by flash chromatography (SiO_2, EtOAc) to afford **XVII** (531 mg, 85%) as a white solid. R_f = 0.54 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 6.66 (d, J = 9.8 Hz, 1H), 6.21 (d, J = 9.8 Hz, 1H), 4.49 (dd, J = 10.8, 6.9 Hz, 1H), 3.49 (sept app, J = 14.3, 7.4 Hz, 2H), 3.31 (sept app, J = 14.8, 7.4 Hz, 2H), 2.98 (bs, 1H), 2.22 (s, 3H), 2.06-1.93 (m, 1H), 1.78 (dd, J = 10.9, 3.2 Hz, 2H), 1.57 (dq, J = 12.9, 3.9 Hz, 1H), 1.32-1.19 (m, 10H), 1.14 (t, J = 6.4 Hz, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{19}H_{30}NO_3^+$: 320.22; found: 319.87.



XVIII

Alcohol XVIII. Following general procedure for ring-opening of α-santonin with a secondary amine, the crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **XVIII** (584 mg, 69%) as a white solid. R_f = 0.28 (1:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 7.39-7.31 (m, 3H), 7.20 (d, J = 7.1 Hz, 2H), 6.74 (t, J = 9.9 Hz, 1H), 6.31 (d, J = 9.9 Hz, 0.5H), 6.27 (d, J = 9.9 Hz, 0.5H), 4.69 (d, J = 13.2 Hz, 1H), 4.55 (dd, J = 11.2, 6.7 Hz, 1H), 4.10 (d, J = 13.2 Hz, 1H), 3.53 (t, J = 6.6 Hz, 1H), 3.32 (t, J = 4.9 Hz, 0.5H),

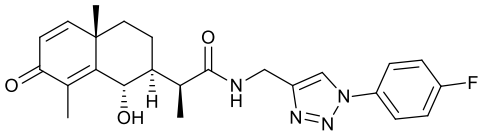
3.25 (t, J = 4.9 Hz, 0.5H), 3.04 (t, J = 12.6 Hz, 1H), 2.69-2.49 (m, 4H), 2.31 (s, 1.5H), 2.28 (s, 1.5H), 2.09-1.94 (m, 2H), 1.90-1.59 (m, 6H), 1.31 (s, 1.5 H), 1.28 (s, 1.5H), 1.25 (d, J = 6.9 Hz, 1.5H), 1.22 (d, J = 6.9 Hz, 1.5H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{27}H_{36}NO_3^+$: 422.27; found: 421.83.



XIX

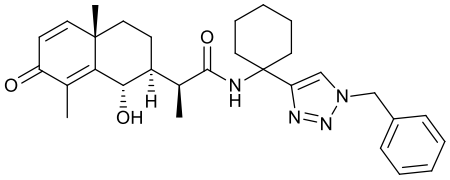
General Procedure for Huisgen 1,3-dipolar cycloaddition with different azides:

Alcohol XIX. Alkyne **XIV** (1.0 equiv, 55 mg, 0.18 mmol) was added in one portion to a solution of benzyl azide (1.0 equiv, 24 mg, 0.18 mmol) in DMF (0.92 mL). Then, a solution of $CuSO_4$ (0.033 equiv, 1 mg, 0.006 mmol) and L-Ascorbate (1.0 equiv, 36 mg, 0.066 mmol) in water (0.23 mL) was added to the previous mixture. Then, TBTA (0.067 equiv, 6.5 mg, 0.012 mmol) was added and the reaction mixture was stirred 16 hours at 23 °C. The next day, the reaction mixture was quenched by addition of sat. aqueous $NaHCO_3$ (2 mL) and then extracted with dichloromethane (3×2 mL). The combined organic phases were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, and evaporated. The compound was then purified by flash chromatography (SiO_2, EtOAc) to afford **XIX** (44 mg, 56%) as a white solid. R_f = 0.31 (EtOAc); ^{1}H-NMR (400 MHz, CD_3OD, 25 °C) (OH and NH signals are not visible): δ 7.82 (s, 1H), 7.40-7.28 (m, 5H), 6.89 (d, 1H), 6.21 (d, 1H), 5.57 (s, 2H), 4.52 (d, J = 10.4 Hz, 1H), 4.49 (dd, J = 15.2 Hz, J = 3.8 Hz, 1H), 4.37 (dd, J = 15.2, 3.8 Hz, 1H), 3.03-2.87 (m, 1H), 2.23 (s, 3H), 1.94 (tt app, J = 11.9 Hz, J = 4.3 Hz, 1H), 1.80 (d, J = 13.3 Hz, 1H), 1.65 (dq, J = 13.5 Hz, J = 4.1 Hz, 1H), 1.51 (d, J = 12.7 Hz, 1H), 1.33-1.27 (m, 1H), 1.26 (s, 3H), 1.14 (d, J = 6.8 Hz, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{25}H_{31}N_4O_3^+$: 435.24; found: 435.17.



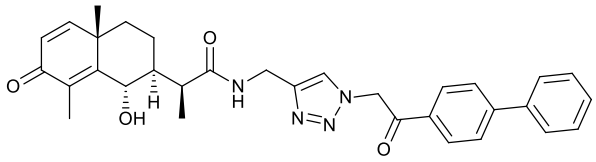
XX

Alcohol XX. Following the general procedure for Huisgen 1,3-dipolar cycloaddition, the crude compound was purified by flash chromatography (SiO_2, EtOAc) to afford **XX** (47 mg, 59%) as a white solid. R_f = 0.28 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 8.02 (s, 1H), 7.67 (dd, J = 8.7, 4.6 Hz, 2H), 7.22 (t, J = 8.3 Hz, 3H), 7.16 (t, J = 5.7 Hz, 1H), 6.4 (d, J = 9.9 Hz, 1H), 6.2 (d, J = 9.9 Hz, 1H), 4.61 (dq, J = 14.9 Hz, J = 5.7 Hz, 2H), 4.47 (d, J = 11.0 Hz, 1H), 2.78 (dq, J = 11.4, 4.2 Hz, 1H), 2.15 (s, 3H), 2.03 (dq, J = 11.3, 5.2 Hz, 1H), 1.77-1.58 (m, 3H), 1.28 (d, J = 6.8 Hz, 3H), 1.16 (s, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{24}H_{28}FN_4O_3^+$: 439.21; found: 439.25.



XXI

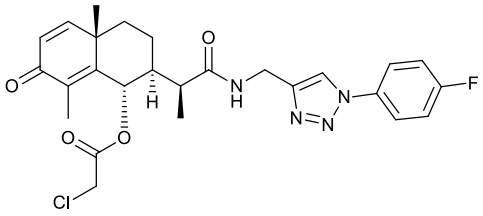
Alcohol XXI. Following the general procedure for Huisgen 1,3-dipolar cycloaddition, the crude compound was purified by flash chromatography (SiO_2, EtOAc) to afford **XXI** (345 mg, 33%) as white solid. R_f = 0.41 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 7.48 (s, 1H), 7.36-7.29 (m, 3H), 7.20 (d, J = 6.9 Hz, 2H), 6.62 (d, J = 9.7 Hz, 1H), 6.22 (s, 1H), 6.19 (d, J = 9.7 Hz, 1H), 5.48 (d, J = 15.1 Hz, 1H), 5.43 (d, J = 15.1 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 2.63-2.55 (m, 1H), 2.40 (t app, J = 12.2 Hz, 2H), 2.22 (s, 3H), 1.94-1.78 (m, 4H), 1.68 (d, J = 11.5 Hz, 2H), 1.63-1.48 (m, 5H), 1.42-1.25 (m, 2H), 1.20 (d, J = 7.1 Hz, 3H), 1.11 (s, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{30}H_{39}N_4O_3^+$: 503.30; found: 502.96.



XXII

Alcohol XXII. Following the general procedure for Huisgen 1,3-dipolar cycloaddition, the crude compound was purified by flash chromatography (SiO_2, EtOAc) to afford **XXII** (74 mg, 38%) as a white solid. R_f = 0.21 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 7.99 (d, J = 8.3 Hz, 2H), 7.77 (s, 1H), 7.70 (d, J =

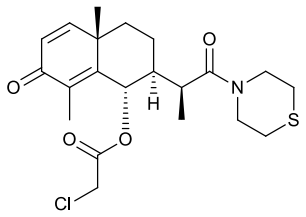
8.3 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 2H), 7.50-7.38 (m, 4H), 6.62 (d, *J* = 9.8 Hz, 1H), 6.16 (d, *J* = 9.8 Hz, 1H), 5.87 (d, *J* = 17.9 Hz, 1H), 5.82 (d, *J* = 17.9 Hz, 1H), 4.55 (d, *J* = 5.3 Hz, 2H), 4.48 (dd, *J* = 10.2, 6.8 Hz, 1H), 4.07 (t, *J* = 6.5 Hz, 1H), 2.84 (dq, *J* = 11.1, 4.5 Hz, 1H), 2.18 (s, 3H), 1.76-1.60 (m, 3H), 1.29-1.21 (m, 5H), 1.16 (s, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{32}H_{35}N_4O_4^+$: 539.27; found: 538.94.



27g

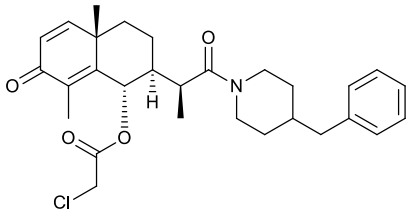
General Procedure for reaction with chloroacetic anhydride:

Compound 27g. Ketone **XX** (1.0 equiv, 16 mg, 0.037 mmol) was dissolved in DMF (0.50 mL) and Hunig's base (1.0 equiv, 7.0 µL, 0.037 mmol) was added. Then, chloroacetic anhydride (1.5 equiv, 10 mg, 0.055 mmol) was added in one portion. The reaction mixture was stirred 12 hours at 23 °C. The next day, the solvent was removed and the residue was diluted in EtOAc (1 mL). The organic solution was washed with water (1 mL) and brine (1 mL), dried over Na_2SO_4 and evaporated. The compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **27g** (18 mg, 96%) as yellow oil. R_f = 0.43 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.98 (s, 1H), 7.71 (dd, *J* = 9.1 Hz, *J* = 4.6 Hz, 2H), 7.23 (t, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 9.8 Hz, 1H), 6.47 (bs, 1H), 6.23 (d, *J* = 9.8 Hz, 1H), 5.58 (d, *J* = 11.9 Hz, 1H), 4.69-4.54 (m, 2H), 4.13 (dd, *J* = 14.3, 7.1 Hz, 2H), 2.65 (dq app, *J* = 11.6, 4.3 Hz, 1H), 2.43-2.31 (m, 1H), 1.97 (s, 3H), 1.89-1.71 (m, 4H), 1.33 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.3, 174.6, 166.3, 163.8, 161.3, 155.6, 154.1, 133.1, 133.0, 128.7, 125.8, 122.5, 122.4, 116.9, 116.7, 75.7, 46.2, 42.4, 40.8, 40.7, 38.2, 34.8, 22.4, 22.3, 12.3, 11.0 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{26}H_{29}ClFN_4O_4^+$: 515.19; found: 514.83.



25e

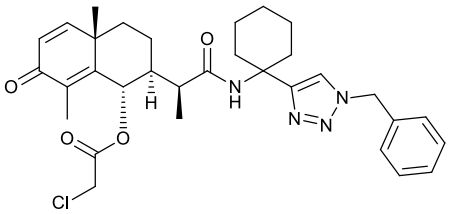
Compound 25e. Following the general procedure for reaction with chloroacetic anhydride, the crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **25e** (48 mg, 84%) as a yellow oil. R_f = 0.32 (1:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.71 (d, J = 9.8 Hz, 1H), 6.26 (d, J = 9.8 Hz, 1H), 5.64 (d, J = 9.9 Hz, 1H), 4.19 (m, 1H), 4.15 (s, 2H), 3.95 (d, J = 12.6 Hz, 1H), 3.71 (t, J = 8.9 Hz, 1H), 3.58 (t, J = 8.9 Hz, 1H), 3.11 (t, J = 3.8 Hz, 1H), 2.69 Hz (t, J = 9.2 Hz, 2H), 2.55 (m, 2H), 2.16 (t, J = 12.3 Hz, 1H), 2.00 (s, 3H), 1.83 (m, 3H), 1.37 (s, 3H), 1.31 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.3, 173.2, 166.0, 155.8, 154.2, 128.9, 125.9, 75.5, 48.4, 45.7, 44.8, 42.6, 40.9, 38.4, 34.7, 30.4, 28.3, 22.6, 21.2, 11.6, 11.2 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{21}H_{29}ClNO_4S^+$: 426.15; found 426.17.



25h

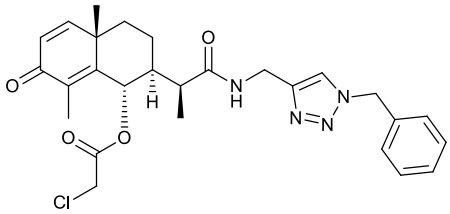
Compound 25h. Following the general procedure for reaction with chloroacetic anhydride, the crude compound was purified by flash chromatography (SiO_2, 60:40 petroleum ether/EtOAc) to afford **25h** (71 mg, 79%) as a yellow oil. R_f = 0.40 (60:40 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.34 (d, J = 6.7 Hz, 3H), 7.18 (m, 2H), 6.77 (t, J = 9.8 Hz, 1H), 6.33 (d, J = 9.8 Hz, 0.4H), 6.29 (d, J = 9.8 Hz, 0.6H), 5.68 (d, J = 11.4 Hz, 1H), 4.76 (d, J = 10.5 Hz, 1H), 4.22 (d, J = 10.5 Hz, 1H), 4.17 (s, 2H), 3.24-2.98 (m, 3H), 2.60 (bs, 4H), 2.35-2.14 (m, 2H), 2.06 (s, 1.2H), 2.02 (s, 1.8H), 1.98-1.70 (m, 7H), 1.43 (s, 1.2H), 1.41 (s, 1.8H), 1.16 (d, J = 6.4 Hz, 1.7H), 1.11 (d, J = 6.4 Hz, 1.3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.5, 173.1, 172.9, 166.1, 156.0, 155.9, 154.5, 154.4, 139.9, 139.8, 129.2, 128.4, 126.2, 125.9, 125.8, 76.3, 75.9, 75.6, 75.2, 62.2, 61.6, 61.5, 60.5, 46.1, 45.9, 45.7, 45.5, 45.2, 44.3, 43.5, 42.7, 42.6, 42.3, 40.9, 40.3, 38.6, 38.2, 35.1, 34.8, 33.1, 32.8, 32.1, 31.9,

22.6, 21.5, 21.2, 12.5, 12.0, 11.3, 11.2 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{29}H_{37}ClNO_4^+$: 498.24; found 497.88.



27f

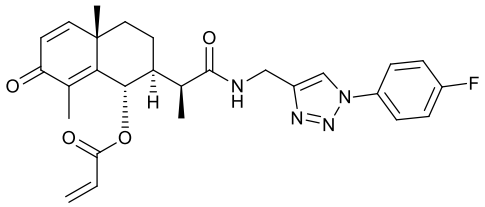
Compound 25f. Following the general procedure for reaction with chloroacetic anhydride, the crude compound was purified by flash chromatography (SiO_2, 1:2 petroleum ether/EtOAc) to afford **25f** (42 mg, 51%) as a yellow oil. R_f = 0.32 (1:2 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.50 (s, 1H), 7.33 (s, 3H), 7.23 (bs, 2H), 6.66 (d, J = 9.9 Hz, 1H), 6.01 (s, 3H), 5.49 (d, J = 12.9 Hz, 1H), 5.47 (s, 2H), 4.11 (d, J = 15.4 Hz, 1H), 4.00 (d, J = 15.4 Hz, 1H), 2.62 (sext app, J = 6.2 hz, J=3.7 hz, 1H), 2.38 (t, J = 13 Hz, 1H), 2.26 (t, J = 11.8 Hz, 1H), 1.98 (m, 2H), 1.92 (s, 3H), 1.74 (d, J = 13.4 Hz, 1H), 1.55 (m, 7H), 1.30 (s, 3H), 1.24 (t, J = 7.0 Hz, 1H), 1.18 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.3, 173.5, 166.4, 155.8, 154.5, 134.9, 129.1 (×2), 128.7, 128.6, 127.9 (×2), 125.7, 121.9, 75.4, 54.1, 53.5, 46.4, 42.5, 40.8, 40.6, 40.4, 38.2, 35.2, 35.1, 25.5, 22.0 (×2), 21.5, 14.3, 11.2, 11.1 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{32}H_{40}ClN_4O_4^+$: 579.27; found 578.95.



27h

Compound 27h. Following the general procedure for reaction with chloroacetic anhydride, the crude compound was purified by flash chromatography (SiO_2, 1:2 petroleum ether/EtOAc) to afford **27h** (24 mg, 51%) as a yellow oil. R_f = 0.11 (1:2 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.48 (s, 1H), 7.37 (s, 3H), 7.29 (s, 2H), 6.69 (d, J = 9.6 Hz, 1H), 6.24 (d, J = 9.6 Hz,1H), 5.55 (d, J = 11.9 Hz, 1H), 5.50 (s, 3H), 4.49 (s, 2H), 4.21 (d, J = 15.5 Hz, 1H), 4.03 (d, J = 15.5 Hz, 1H), 2.61 (dq, J = 11.8, 5.9 Hz, 1H), 2.38-2.21 (m, 2H), 1.96 (s, 3H), 1.85-1.65 (m, 3H), 1.34

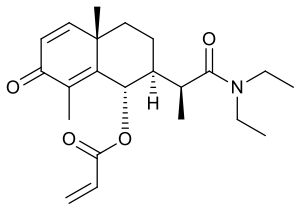
(s, 3H), 1.12 (d, J = 7.2 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.4, 174.6, 166.5, 155.7, 154.3, 144.7, 131.1, 129.3 (×2), 129.1, 128.3 (×2), 125.9, 122.4, 75.8, 61.9, 54.5, 46.3, 42.6, 40.8, 38.4, 34.9, 29.8, 22.6, 22.3, 12.3, 11.2 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{27}H_{32}ClN_4O_4^+$: 511.2; found: 510.86.



27a

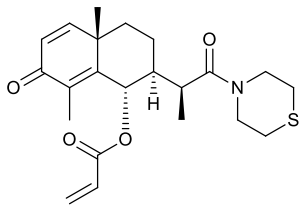
General procedure for acylation reaction:

Compound 27a. Alcohol **XX** (1.0 equiv, 16 mg, 0.0365 mmol) was dissolved in THF (1.0 mL) and Et_3N (3.0 equiv, 8 µL, 0.11 mmol) was added. Then, acryloyl chloride (1.5 equiv, 5 µL, 0.055 mmol) was added dropwised at 0 °C. The reaction mixture was stirred 12 hours at 23 °C. The next day, the reaction mixture was quenched by addition of sat. aqueous $NaHCO_3$ (2 mL) and then extracted with EtOAc (3×1 mL). The combined organic phases were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, and evaporated. The compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **27a** (16 mg, 90%) as a white solid. R_f = 0.41 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.96 (s, 1H), 7.71 (dd, J = 9.1, 4.6 Hz, 3H), 7.24 (t, J = 7.9 Hz, 2H), 6.70 (d, J = 9.8 Hz, 1H), 6.48 (dd, J = 17.3, 1.2 Hz, 1H), 6.34 (bs, 1H), 6.23 (d, J = 9.8 Hz, 1H), 6.14 (dd, J = 17.3, 10.6 Hz, 1H), 5.94 (dd, J = 10.6, 1.2 Hz, 1H), 5.65 (d, J = 11.9 Hz, 1H), 4.57 (dd, J = 15.2, 5.9 Hz, 1H), 4.51 (dd, J = 15.2, 5.9 Hz, 1H), 2.63 (dq, J = 11.6, 4.6 Hz, 1H), 2.46-2.35 (m, 1H), 1.96 (s, 3H), 1.91-1.71 (m, 3H), 1.38 (s, 3H), 1.14 (d, J = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.5, 174.7, 165.0, 163.8, 155.6, 154.8, 132.6, 130.92, 130.89, 128.9, 127.6, 125.8, 122.5, 122.4, 120.7, 116.9, 116.7, 73.6, 46.0, 42.4, 40.7, 38.2, 34.9, 22.5, 21.8, 11.8, 11.1 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{27}H_{30}FN_4O_4^+$: 493.23; found 492.62.



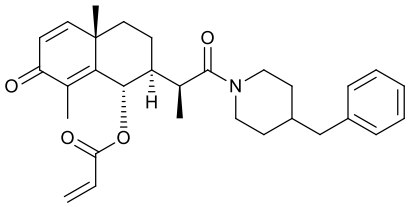
25a

Compound 25a. Following the general procedure for acylation reaction, the crude compound was purified by flash chromatography (SiO_2, 1:2 petroleum ether/EtOAc) to afford **25a** (15 mg, 43%) as a white solid. R_f = 0.40 (1:2 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.72 (d, J = 10 Hz, 1H), 6.49 (d, J = 17.5 Hz, 1H), 6.24 (d, J = 10 Hz, 1H), 6.19 (dd, J = 17.5, 10.4 Hz, 1H), 6.00 (d, J = 10.3 Hz, 1H), 5.64 (d, J = 11.6 Hz, 1H), 3.32 (m, 4H), 2.89 (sext app, J = 11.1, 6.3 Hz, 1H), 2.25 (m, 1H), 1.97 (s, 3H), 1.91 (m, 2H), 1.76 (dq, J = 12.9, 3.9 Hz, 1H), 1.41 (s, 3H), 1.14 (m, 10H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.7, 174.2, 165.0, 155.9, 155.4, 132.5, 128.9, 128.0, 125.9, 74.5, 45.8, 42.7, 41.9, 40.5, 38.7, 35.6, 22.7, 21.8, 14.9, 13.3, 12.6, 11.4 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{22}H_{32}NO_4^+$: 374.23; found 373.85.



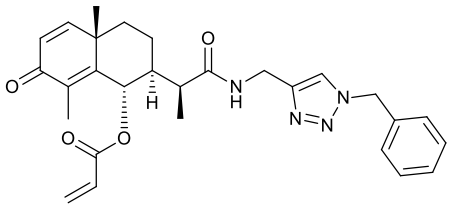
25c

Compound 25c. Following the general procedure for acylation reaction, the crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **25c** (50 mg, 90%) as a white solid. R_f = 0.29 (1:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 6.70 (d, J = 9.8 Hz, 1H), 6.46 (d, J = 17.9 Hz, 1H), 6.22 (d, J = 9.9 Hz, 1H), 6.17 (dd, J = 17.9 ppm, J = 9.9 Hz, 1H), 5.98 (d, J = 9.8 Hz, 1H), 5.65 (d, J = 10.8 Hz, 1H), 4.18 (d, J = 11.2 Hz, 1H), 3.88 (d, J = 11.3 Hz, 1H), 3.60 (t, J = 8.7 Hz, 1H), 3.52 (t, J = 8.7 Hz, 1H), 2.91 (t, J = 6.2 Hz, 1H), 2.66 (t, J = 12 Hz, 2H), 2.54 (bs, 2H), 2.27 (bs, 1H), 1.95 (s, 3H), 1.85 (m, 2H), 1.70 (dq, J = 13.8, 4.3 Hz, 1H), 1.38 (s, 3H), 1.32 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.5, 173.6, 164.9, 155.8, 154.9, 132.7, 128.9, 127.9, 125.9, 74.5, 48.2, 45.5, 44.6, 42.5, 38.5, 35.7, 28.1, 27.6, 22.7, 22.0, 12.9, 11.4 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{22}H_{30}NO_4S^+$: 404.19; found 404.18.



25f

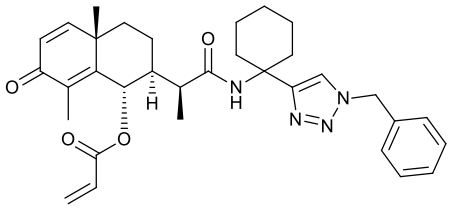
Compound 25f. Following the general procedure for acylation reaction, the crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **25f** (65 mg, 77%) as a white solid. R_f = 0.49 (1:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.33 (d, J = 7.1 Hz, 3H), 7.18 (m, 2H), 6.76 (t, J = 10.4 Hz, 1H), 6.50 (dd, J = 17.1, 11.3 Hz, 1H), 6.33-6.14 (m, 2H), 5.99 (d, J = 9.9 Hz, 1H), 5.69 (t, J = 10.4 Hz, 1H), 4.68 (d, J = 13.2 Hz, 0.6H), 4.62 (d, J = 13.2 Hz, 0.4H), 3.94 (d, J = 13.1 Hz, 1H), 3.13-2.88 (m, 3H), 2.69-2.52 (m, 3H), 2.39-2.15 (m, 3H), 2.02 (s, 1.3H), 1.93 (s, 1.7H), 1.94-1.66 (m, 6H), 1.45 (s, 1.2H), 1.43 (s, 1.8H), 1.14 (d, J = 6.8 Hz, 1.8H), 1.10 (d, J = 6.8 Hz, 1.2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.6, 173.3, 173.1, 164.9, 155.9, 155.8, 155.4, 155.2, 139.9, 139.8, 132.6, 132.4, 129.2, 128.9, 128.4 (×2), 128.0, 127.9, 126.2, 125.9, 74.7, 74.1, 46.0, 45.7, 45.3, 43.1, 42.8, 42.6, 42.5, 42.2, 38.7, 38.6, 35.6, 35.2, 32.9, 32.7, 32.1, 31.8, 22.7, 22.6, 22.0, 21.4, 12.9, 11.6, 11.3, 11.2 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{30}H_{38}NO_4^+$: 476.28; found 476.22.



27b

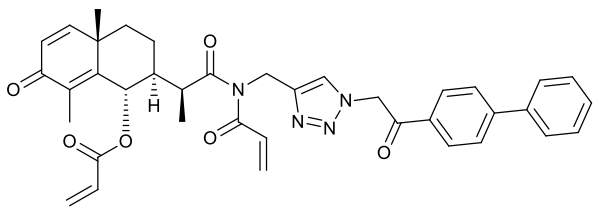
Compound 27b. Following the general procedure for acylation reaction, the crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **27b** (11 mg, 93%) as a white solid. R_f = 0.30 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.48 (s, 1H), 7.40-7.38 (m, 3H), 7.33-7.27 (m, 2H), 6.70 (d, J = 9.8 Hz, 1H), 6.47 (dd, J = 17.2, 1.1 Hz, 1H), 6.42 (t, J = 5.9 Hz, 1H), 6.25 (d, J = 9.8 Hz, 1H), 6.13 (dd, J = 17.2, 10.7 Hz, 1H), 5.92 (dd, J = 10.7, 1.1 Hz, 1H), 5.63 (d, J = 11.9 Hz, 1H), 5.52 (s, 2H), 4.54 (dd, J = 15.4, 5.9 Hz, 1H), 4.42 (dd, J = 15.4, 5.9 Hz, 1H), 2.62 (dq, J = 11.9, 5 Hz, 1H), 2.43-2.33 (m, 1H), 1.96 (s, 3H), 1.92-1.79 (m, 2H), 1.72

(dq app, J = 6.5, 2.0 Hz, 2H), 1.39 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 185.6, 173.8, 164.2, 154.8, 154.0, 133.4, 131.7, 128.3 (×2), 128.1, 127.9, 127.3 (×2), 126.8, 124.9, 72.7, 53.7, 45.0, 41.5, 39.7, 37.3, 34.0, 30.1, 28.8, 21.7, 20.7, 10.7, 10.2 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{28}H_{33}N_4O_4^+$: 489.25; found 488.83.



27c

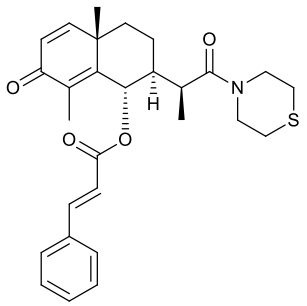
Compound 27c. Following the general procedure for acylation reaction, the crude compound was purified by flash chromatography (SiO_2, 1:2 petroleum ether/EtOAc) to afford **27c** (49 mg, 61%) as a white solid. R_f = 0.27 (1:2 petroleum ether/EtOAc E); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.5 (s, 1H), 7.33 (s, 3H), 7.22 (s, 2H), 6.66 (d, J = 9.7 Hz, 1H), 6.44 (d, J = 17.1 Hz, 1H), 6.21 (d, J = 9.7 Hz, 1H), 6.11 (dd, J = 17.1, 10.4 Hz, 2H), 6.02 (s, 1H), 5.89 (d, J = 10.4 Hz, 1H), 5.56 (d, J = 11.8 Hz, 1H), 5.47 (s, 2H), 2.67 (sext app, J = 6.5, 3.5 Hz, 1H), 2.40 (d, J = 12.9 Hz, 2H), 2.30 (tr app, J = 12.4 Hz, 1H), 1.98 (m, 2H), 1.91 (s, 3H), 1.73 (d, J = 13.4 Hz, 1H), 1.64 (d, J = 13.2 Hz, 1H), 1.50 (bs, 5H), 1.34 (s, 3H), 1.22 (m, 2H), 1.01 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.6, 173.8, 165.1, 155.9, 155.2, 134.9, 132.5, 129.1 (×2), 128.8, 128.7, 127.9 (×2), 127.8, 125.8, 121.8, 73.2, 54.1, 53.5, 46.2, 42.5, 40.2, 38.2, 35.3, 35.1, 25.5, 22.6, 22.0, 21.1, 20.9, 14.3, 11.0, 10.2 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{33}H_{41}N_4O_4^+$: 557.31; found 556.97.



27d

Compound 27d. Alcohol **XXII** (1.0 equiv, 17 mg, 0.0316 mmol) was dissolved in THF (1.0 mL) and Et_3N (3.0 equiv, 13 µL, 0.095 mmol) was added. Then, acryloyl chloride (1.5 equiv, 4 µL, 0.047 mmol) was added dropwised at 0 °C. The reaction mixture was stirred 12 hours at 23 °C. The next day, the reaction was not completed. 1.5 equiv of

acryloyl chloride and 3.0 equiv of Et_3N were added. The day after, the reaction was quenched by addition of sat. aqueous $NaHCO_3$ (2 mL) and then extracted with EtOAc (3×1 mL). The combined organic phases were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, and evaporated. The crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **27d** (10 mg, 48%) as a yellow solid. R_f = 0.24 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.94 (s, 1H), 7.67 (d, J = 9.5 Hz, 2H), 7.60 (bs, 3H), 7.56-7.31 (m, 4H), 6.72 (d, J = 11.2 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 6.53-6.38 (m, 2H), 6.29-6.11 (m, 4H), 5.95 (d, J = 9.6 Hz, 1H), 5.65 (d, J = 12.1 Hz, 1H), 4.61 (dd, J = 15.1, 5.7 Hz, 1H), 4.46 (dd, J = 15.1, 4.8 Hz, 1H), 2.61 (dq, J = 5.7, 11.9 Hz, 1H), 2.48-2.31 (m, 1H), 1.97 (s, 3H), 1.94-1.67 (m, 5H), 1.39 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.6, 174.8, 165.2, 162.8, 155.8, 154.9, 144.6, 143.0, 140.3, 140.1, 135.2, 132.7, 131.1, 129.3, 129.2, 129.1, 128.1, 128.0, 127.9, 127.8, 126.7, 125.9, 125.6, 121.6, 113.09, 73.8, 46.1, 42.6, 42.1, 40.8, 38.4, 35.0, 29.8, 22.7, 21.8, 17.1, 11.7, 11.4 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{38}H_{39}N_4O_6^+$: 647.29; found 647.06.

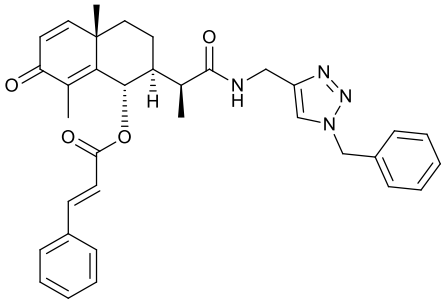


25d

General procedure for modified Yamaguchi esterification:

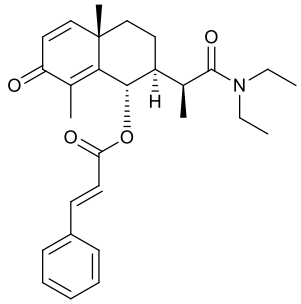
Compound 25d. Carboxylic acid (1.0 equiv, 4.3 mg, 0.029 mmol), 2,4,6-Trichlorobenzoyl chloride (1.0 equiv, 4.5 µL, 0.029 mmol) and **XVI (**1.0 equiv, 10 mg, 0.029 mmol) were dissolved in CH_2Cl_2 (0.50 mL). Then, Et_3N (2.0 equiv, 7.9 µL, 0.057 mmol) was added, followed by DMAP (0.25 equiv, 1 mg, 0.007 mmol). The reaction mixture was stirred 12 hours at 23 °C. The next day, the reaction mixture was quenched with 10% aqueous HCl (1 mL) and then extracted with EtOAc (3×1 mL). The combined organic phases were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, and evaporated. The compound was purified by flash chromatography (SiO_2, 1:1

petroleum ether/EtOAc) to afford **25d** (4 mg, 29%) as a white solid. R_f = 0.17 (1:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.75 (d, J = 15.6 Hz, 1H), 7.56 (bs, 2H), 7.44 (bs, 3H), 6.73 (d, J = 15.6 Hz, 1H), 6.46 (d, J = 15.6 Hz, 1H), 6.25 (d, J = 9.9 Hz, 1H), 5.73 (d, J = 11.8 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 3.93 (d, J = 11.7 Hz, 1H), 3.65 (t, J = 8.8 Hz, 1H), 3.50 (t, J = 8.8 Hz, 1H), 2.97 (t, J = 7.2 Hz, 1H), 2.60 (m, 2H), 2.33 (m, 1H), 2.03 (s, 3H), 1.89 (t, J = 13.3 Hz, 2H), 1.74 (m, 2H), 1.42 (s, 3H), 1.35 (m, 2H), 1.13 (d, 3H) ; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.6, 173.8, 165.9, 155.8, 155.2, 146.9, 134.0, 131.1, 129.3, 129.1, 129.1, 128.4, 126.0, 117.0, 74.5, 48.4, 45.6, 44.8, 42.6, 38.5, 36.0, 28.2, 27.6, 24.0, 22.8, 22.1, 13.1, 11.5 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{28}H_{34}NO_4S^+$: 480.22; found 479.88.



27e

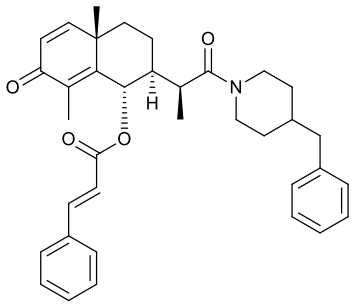
Compound 27e. Following the general procedure for modified Yamaguchi esterification, the crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **27e** (23 mg, 24%) as a yellow solid. R_f = 0.39 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.73 (d, J = 15.7 Hz, 1H), 7.55 (bs, 2H), 7.42 (s, 1H), 7.40 (s, 2H), 7.35 (m, 4H), 7.23 (dd, J = 7.4, 3.7 Hz, 2H), 6.69 (d, J = 9.7 Hz, 1H), 6.46 (d, J = 15.7 Hz, 1H), 6.29 (t, J = 4.8 Hz, 1H), 6.23 (d, J = 9.7 Hz, 1H), 5.69 (d, J = 11.4 Hz, 1H), 5.47 (s, 3H), 4.52 (dd, J = 15.1, 5.6 Hz, 1H), 4.36 (dd, J = 15.1, 5.6 Hz, 1H), 2.63 (dq, J = 12.4, 4.9 Hz, 1H), 2.45-2.33 (m, 1H), 2.00 (s, 3H), 1.82 (m, J = 12.9 Hz, 1H), 1.76-1.70 (m, 2H), 1.40 (s, 3H), 1.11 (d, J = 7.0 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.6, 174.9, 166.0, 155.8, 155.2, 146.6, 144.8, 134.5, 134.1, 130.9, 129.3, 129.1 (×2), 128.9, 128.5 (×2), 128.2 (×2), 125.9, 121.9, 117.1, 73.7, 54.3, 46.1, 42.5, 40.9, 38.4, 35.2, 29.8, 22.8, 22.7, 21.8, 11.8, 11.3 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{34}H_{36}N_4O_4^+$: 564.27; found 564.76.



25b

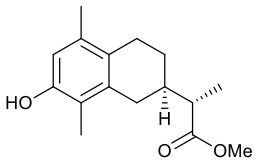
General procedure for esterification by BuLi deprotonation of the secondary alcohol:

Compound 25b. Alcohol **XVII** (1.0 equiv, 75 mg, 0.23 mmol) was dissolved in THF (1.6 mL), *n*BuLi (1.1 equiv, 104 µL, 2.5 M in hexanes, 0.26 mmol) was added at -78 °C, and the resulting mixture was stirred at 0 °C for 1 hour. Then, acyl fluoride[3] (1.5 equiv, 53 mg, 0.35 mmol) was dissolved in THF (0.81 mL) and added to the reaction mixture at 0 °C. The reaction mixture was stirred 12 hours at 23 °C. The next day, the reaction mixture was quenched with sat. aqueous NH_4Cl (1 mL) and then extracted with EtOAc (3×1 mL). The combined organic phases were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, and evaporated. The compound was purified by flash chromatography (SiO_2, 2:1 petroleum ether/EtOAc) to afford **25b** (50 mg, 48%) as a white solid. R_f = 0.20 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.74 (d, J = 15.8 Hz, 1H), 7.55 (t, J = 3.7 Hz, 2H), 7.43 (bs, 3H), 6.72 (d, J = 9.9 Hz, 1H), 6.47 (d, J = 15.8 Hz, 1H), 6.24 (d, J = 9.9 Hz, 1H), 5.69 (d, J = 11.5 Hz, 1H), 3.43 (m, 2H), 3.26 (sextuplet app, J = 13.4, 6.7 Hz, 2H), 2.90 (triplet, J = 6.4 Hz, 1H), 2.30 (m, 1H), 2.01 (s, 3H), 1.93 (m, 2H), 1.75 (dq, J = 13.1 Hz, J = 3.5 Hz, 1H), 1.43 (s, 3H), 1.32 (dt app, J = 13.8, 4.1 Hz, 2H), 1.13 (m, 10H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.7, 174.4, 165.9, 155.9, 155.6, 146.5, 134.1, 130.9, 129.2 (×2), 128.9, 128.3 (×2), 125.9, 117.2, 74.6, 45.8, 42.6, 41.9, 40.6, 38.7, 35.9, 22.7, 22.0, 14.9, 13.3, 12.9, 11.4 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{28}H_{36}NO_4^+$: 450.26; found 449.86.



25g

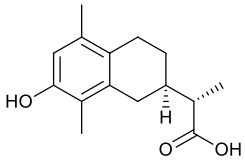
Compound 25g. Following the general procedure for esterification by *n*BuLi deprotonation of the secondary alcohol, the crude compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **25g** (21 mg, 20%) as a white solid. R_f = 0.24 (1:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.76 (d, J = 15.7 Hz, 0.4H), 7.70 (d, J = 15.7 Hz, 0.6H), 7.60-7.52 (m, 2H), 7.44 (bs, 3H), 7.25-7.13 (m, 3H), 7.10 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.72 (t, J = 10.1 Hz, 1H), 6.49 (d, J = 15.7 Hz, 0.4H), 6.44 (d, J = 15.7 Hz, 0.6H), 6.26 (d, J = 10.1 Hz, 0.4H), 6.23 (d, J = 10.1 Hz, 0.6H), 5.71 (t, J = 9.3 Hz, 1H), 4.65 (d, J = 13.2 Hz, 0.6H), 4.57 (d, J = 13.2 Hz, 0.4H), 3.94 (d, J = 13.2 Hz, 1H), 3.06-2.85 (m, 3H), 2.63-2.22 (m, 4H), 2.04 (s, 1.4H), 1.99 (s, 1.6H), 1.95-1.82 (m, 2H), 1.79-1.59 (m, 6H), 1.43 (s, 1.4H), 1.41 (s, 1.6H), 1.11 (d, J = 6.7 Hz, 1.6H), 1.08 (d, J = 6.7 Hz, 1.4 H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 186.7, 186.6, 173.3, 171.2, 165.8, 155.8, 155.7, 155.2, 146.6, 146.4, 139.9, 134.0, 130.9, 130.8, 129.1, 129.0, 128.4, 128.3, 126.1, 126.0, 125.9, 125.8, 117.2, 117.0, 74.5, 74.4, 60.4, 53.5, 45.9, 45.6, 45.5, 45.3, 43.0, 42.6, 42.5, 42.4, 42.0, 41.4, 41.1, 38.7, 38.4, 38.2, 35.6, 32.9, 32.7, 32.1, 31.6, 29.7, 22.7, 22.6, 22.0, 21.9, 21.1, 14.2, 12.9, 12.6, 12.2, 11.3 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{36}H_{42}NO_4^+$: 552.31; found 551.54.



XXIV

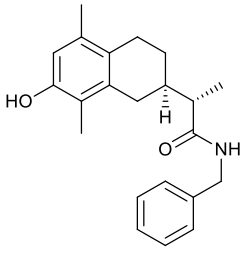
Compound XXIV. A solution of **XXIII**[4, 5] (771 mg, 2.94 mmol) in formic acid (98%, 8 mL) was heated under reflux for 12 hours. The next day, water (10 mL) was added. The reaction mixture was extracted with EtOAc (3×5 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and evaporated.

The crude product was purified by flash chromatography (SiO_2, 2:1 petroleum ether/ Et_2O) to afford **XXIV** (412 mg, 54%) as yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 6.52 (s, 1H), 4.70 (bs, 1H), 3.73 (s, 3H), 2.71 (ddd, J = 13.8, 4.6 Hz, 2H), 2.51 (m, 2H), 2.35 (dd, J = 16.7 ppm, J = 11.3 Hz, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.05-1.92 (m, 2H), 1.38 ppm (dd, J = 11.6, 5.5 Hz, 1H), 1.26 (d, J = 7.2 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 176.8, 150.9, 135.8, 134.3, 127.1, 119.2, 114.3, 51.5, 44.4, 37.2, 32.1, 26.6, 25.7, 19.4, 14.1, 10.7 ppm.



4

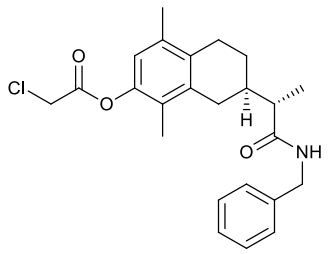
Compound 4. Ester **XXIV** (35 mg, 0.134 mmol) was dissolved in EtOH (1 mL) and 2M aqueous KOH (1.7 mL). The reaction mixture was stirred 12 hours at 23 °C. The next day, the reaction mixture was acidified by addition of 1M aqueous HCl in order to reach pH = 2. Then, the aqueous solution was extracted with EtOAc (3×2 mL). The combined organic layers were washed with water (3 mL) and brine (3 mL), dried over Na_2SO_4, and evaporated. The product **4** (27 mg, 81%), a white solid, was used without purification for the next step. ^{1}H-NMR (400 MHz, CD_3OD, 25 °C) (OH signal is not visible): δ 6.65 (s, 1H), 2.89 (ddd, J = 15.9, 4.4 Hz, 2H), 2.71-2.44 (m, 3H), 2.28 (s, 3H), 2.20 (s, 3H,), 2.11-2.05 (m, 2H), 1.53 (dd, J = 12.1, 5.7 Hz , 1H), 1.42 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 178.9, 151.8, 134.9, 133.2, 125.4, 119.0, 113.7, 44.3, 37.2, 31.9, 26.1, 25.5, 18.1, 13.2, 9.5 ppm.



22

Compound 22. Carboxylic acid **4** (1.0 equiv, 120 mg, 0.483 mmol) was dissolved in DMF (5 mL), HATU (1.2 equiv, 216 mg, 0.58 mmol) and DIPEA (1.2 equiv, 108 µL,

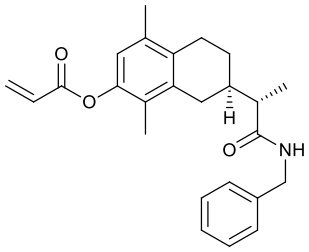
0.58 mmol) were added at 23 °C. Then, after 5 minutes, benzylamine (1.1 equiv, 60 µL, 0.53 µL) was added. The reaction mixture was stirred at 23 °C for 12 hours. The next day, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, and evaporated. The product was purified by flash chromatography (SiO_2, 60:40 petroleum ether/EtOAc) to afford **22** (115 mg, 71%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C) (OH signal is not visible): δ 7.39-7.29 (m, 5H), 6.50 (s, 1H), 5.73 (s, 1H), 4.58 (dd, J = 14.8, 5.8 Hz, 1H), 4.41 (dd, J = 14.8, 5.8 Hz, 1H), 2.72 (ddd, J = 16.5, 4.9 Hz, 2H), 2.52 (m, 1H), 2.33 (dd, J = 16.8Hz, J = 9.7 Hz, 1H), 2.15 (s, 3H), 2.11 (q, J = 6.8 Hz, 1H), 2.05 (m, 2H), 2.00 (s, 3H), 1.42 (m, 1H), 1.28 (d, J = 6.8 Hz, 3H) ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{22}H_{28}NO_2^+$: 338.21; found 337.96.



23f

Compound 23f. Phenol **22** (1.0 equiv, 15 mg, 0.044 mmol) was dissolved in DMF (0.50 mL) and Hunig's base (2.0 equiv, 18 µL, 0.088 mmol) was added. Then, chloroacetic anhydride (3.0 equiv, 24 mg, 0.13 mmol) was added in one portion. The reaction mixture was stirred 12 hours at 23 °C. The next day, the solvent was removed and the residue was diluted in EtOAc (1 mL). The organic solution was washed with water (1 mL) and brine (1 mL), dried over Na_2SO_4 and evaporated. The compound was purified by flash chromatography (SiO_2, 1:1 petroleum ether/EtOAc) to afford **23f** (4.6 mg, 26%) as yellow solid. R_f = 0.37 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.38-7.28 (m, 5H), 6.71 (s, 1H), 5.75 (t, J = 5.4 Hz, 1H), 4.58 (dd, J = 14.8, 5.4 Hz, 1H), 4.39 (dd, J = 14.8, 5.4 Hz, 1H), 4.32 (s, 2H), 2.73 (ddd, J = 16.8, 4.3 Hz, 2H), 2.62-2.51 (m, 1H), 2.35 (dd, J = 16.4, 9.7 Hz, 1H), 2.19 (s, 3H), 2.11 (q, J = 6.8 Hz, 1H), 2.09-1.99 (m, 2H), 1.91 (s, 3H), 1.50-1.39 (m, 1H), 1.28 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 175.6, 166.1, 146.2, 138.5, 136.1, 134.8, 133.3, 128.8 (×2), 127.8 (×2), 127.5, 125.2, 119.7, 46.1, 43.5, 40.7, 36.8, 32.3,

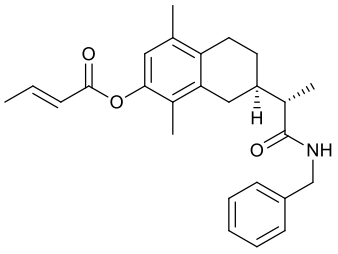
26.4, 25.3, 19.4, 15.3, 11.6 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{24}H_{29}ClNO_3^+$: 414.18; found 414.16.



23a

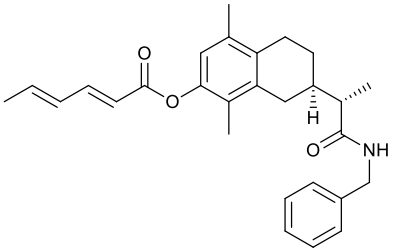
General Procedure for acylation of phenol:

Compound 23a. Phenol **22** (1.0 equiv, 16 mg, 0.046 mmol) was dissolved in dichloromethane (1.0 mL) and Et_3N (2.4 equiv, 16 µL, 0.11 mmol) was added. Then, acyl chloride (1.2 equiv, 5 µL, 0.056 mmol) was added dropwised at 0 °C. The reaction mixture was stirred 12 hours at 23 °C. The next day, the reaction mixture was quenched by addition of sat. aqueous $NaHCO_3$ (1 mL) and then extracted with dichloromethane (3×1 mL). The combined organic phases were washed with water (1 mL) and brine (1 mL), dried over Na_2SO_4, and evaporated. The compound was purified by flash chromatography (SiO_2, 2:1 petroleum ether/EtOAc) afforded **23a** (15.9 mg, 92%) as a white solid. R_f = 0.42 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25°C): δ 7.37-7.28 (m, 5H), 6.72 (s, 1H), 6.62 (d, J = 17.2 Hz, 1H), 6.36 (dd, J = 17.2, 9.9 Hz, 1H), 6.02 (d, J = 9.9 Hz, 1H), 5.79 (t, J = 5.7 Hz, 1H), 4.58 (dd, J = 5.7, 14.8 Hz, 1H), 4.39 (dd, J = 14.8, 5.7 Hz, 1H), 2.74 (ddd, J = 17.8, 4.5 Hz, 2H), 2.62-2.49 (m, 1H), 2.35 (dd, J = 16.7, 9.5 Hz, 1H), 2.19 (s, 3H), 2.13 (q, J = 7.2 Hz, 1H), 2.10-2.00 (m, 2H), 1.90 (s, 3H), 1.50-1.38 (m, 1H), 1.28 (d, J = 7.2 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 175.7, 164.8, 146.4, 138.5, 134.6, 132.8, 132.3, 128.8 (×3), 127.9, 127.8 (×2), 127.5, 125.5, 120.2, 46.1, 43.4, 36.8, 32.3, 26.3, 25.4, 19.4, 15.3, 11.7 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{25}H_{30}NO_3^+$: 392.22; found 392.14.



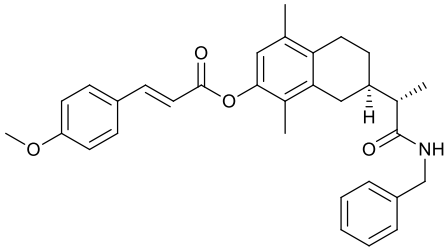
23b

Compound 23b. Following general procedure for acylation of phenol, the compound was purified by flash chromatography (SiO_2, 2:1 petroleum ether/EtOAc) afforded **23b** (9 mg, 51%) as a white solid. R_f = 0.45 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.37-7.28 (m, 5H), 6.67 (s, 1H), 6.07 (ddt app, J = 17.2, 6.9 Hz, 1H), 5.77 (t, J = 5.4 Hz, 1H), 5.31 (dd, J = 17.2, 1.4 Hz, 1H), 4.57 (dd, J = 14.6, 6.3 Hz, 1H), 4.39 (dd, J = 14.6, 6.3 Hz, 1H), 2.72 (ddd, J = 15.2, 5.1 Hz, 2H), 2.61-2.50 (m, 1H), 2.34 (dd, J = 16.8, 9.5 Hz, 1H), 2.17 (s, 3H), 2.11 (q, J = 6.8 Hz, 1H), 2.10-1.99 (m, 2H), 1.89 (s, 3H), 1.50-1.38 (m, 1H), 1.28 (t, J = 2.2 Hz, 3H), 1.26 (d, J = 5.3 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 175.7, 165.7, 146.5, 138.5, 135.9, 134.6, 132.8, 129.9, 128.7 (×2), 127.8 (×2), 127.5, 125.5, 120.2, 119.1, 46.1, 43.4, 39.1, 36.8, 32.3, 26.3, 25.4, 19.4, 15.3, 11.7 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{26}H_{32}NO_3^+$: 406.24; found 406.23.



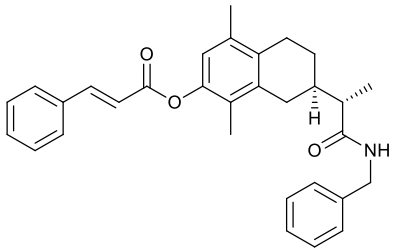
23c

Compound 23c. Following general procedure for acylation of phenol, the compound was purified by flash chromatography (SiO_2, 2:1 petroleum ether/EtOAc) afforded **23c** (12.6 mg, 67%) as a white solid. R_f = 0.47 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.45 (dd, J = 15.4, 10.2 Hz, 1H), 7.38-7.29 (m, 5H), 6.71 (s, 1H), 6.27 (m, 2H), 6.00 (d, J = 15.2 Hz, 1H), 5.78 (t, J = 5.8 Hz, 1H), 4.58 (dd, J = 14.7, 5.8 Hz, 1H), 4.39 (dd, J =14.7, 5.8 Hz, 1H), 2.74 (ddd, J = 17, 3.1 Hz, 2H), 2.57 (m, 1H), 2.36 (dd, J = 16.9, 9.5 Hz, 1H), 2.20 (s, 3H), 2.13 (q, J = 7.4 Hz, 1H), 2.1-1.99 (m, 2H), 1.92 (s, 3H), 1.91 (q, J = 8.4 Hz, 3H), 1.52-1.39 (m, 1H), 1.30 (d, J = 7.4 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 175.7, 166.0, 146.7 (×2), 140.5, 138.6, 135.9, 134.6, 132.7, 129.8, 128.8 (×2), 127.9 (×2), 127.6, 125.7, 120.4, 118.15, 46.2, 43.5, 36.9, 32.4, 26.4, 25.5, 19.5, 18.8, 15.4, 11.8 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{28}H_{34}NO_3^+$: 432.25; found 432.16.



23d

Compound 23d. Following general procedure for acylation of phenol, the compound was purified by flash chromatography (SiO_2, 2:1 petroleum ether/EtOAc) afforded **23d** (16 mg, 74%) as a white solid. R_f = 0.22 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.86 (d, J = 15.9 Hz, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.37-7.28 (m, 5H), 6.98 (d, J = 8.3 Hz, 2H), 6.77 (s, 1H), 6.54 (d, J = 15.9 Hz, 1H), 5.88 (t, J = 5.3 Hz, 1H), 4.61 (dd, J = 15.2, 5.3 Hz, 1H), 4.40 (dd, J = 15.2, 5.3 Hz, 1H), 3.91 (s, 3H), 2.78 (ddd, J = 15.9, 4.1 Hz, 2H), 2.66-2.51 (m, 1H), 2.38 (dd, J = 16.1, 9.5 Hz, 1H), 2.23 (s, 3H), 2.14 (q, J = 6.7 Hz, 1H), 2.11-2.00 (m, 2H), 1.96 (s, 3H), 1.53-1.38 (m, 1H), 1.31 (d, J = 6.7 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 175.8, 166.4, 161.8, 146.7, 146.0, 138.9, 136.2, 134.9, 133.1, 130.0 (×2), 128.8 (×2), 127.9 (×2), 127.5, 127.2, 125.9, 120.4, 114.8, 114.5 (×2), 55.5, 46.2, 43.5, 36.9, 32.4, 26.9, 25.5, 19.5, 15.4, 12.0 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{32}H_{36}NO_4^+$: 498.26; found 498.23.



23e

Compound 23e. Following general procedure for acylation of phenol, the compound was purified by flash chromatography (SiO_2, 2:1 petroleum ether/EtOAc) afforded **23e** (7.5 mg, 37%) as a white solid. **23e**: R_f = 0.40 (2:1 petroleum ether/EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.90 (d, J = 15.9 Hz, 1H), 7.64-7.59 (m, 2H), 7.47-7.42 (m, 3H), 7.37-7.28 (m, 5H), 6.76 (s, 1H), 6.68 (d, J = 15.9 Hz, 1H), 5.80 (t, J = 5.4 Hz, 1H), 4.59 (dd, J = 14.5, 5.4 Hz, 1H), 4.39 (dd, J = 14.5, 5.4 Hz, 1H), 2.80 (ddd, J = 16.4, 3.6 Hz, 2H), 2.63-2.52 (m, 1H), 2.37 (dd, J = 16.4, 9.5 Hz, 1H), 2.20 (s, 3H), 2.13 (q, J = 6.8 Hz, 1H), 2.10-1.98 (m, 2H), 1.94 (s, 3H), 1.52-1.39 (m, 1H), 1.29 (d, J = 6.8 Hz, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C): δ 175.7, 165.8, 146.6, 146.3, 138.6,

135.9, 134.3, 132.8, 130.7, 129.0 (×3), 128.8 (×3), 128.3 (×3), 127.9, 127.5, 125.7, 120.4, 117.4, 46.2, 43.5, 36.9, 32.4, 26.4, 25.5, 15.4, 11.8 ppm; LC-MS (ESI) m/z: $[M+H]^+$: calcd. for $C_{31}H_{34}NO_3^+$: 468.25; found 468.18.

3. Biological assays

Test compounds were diluted into buffer from a 10 mM stock solution in DMSO.

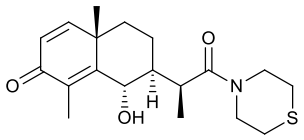
Determination of $TNF\alpha$-induced NF-κB activity in 293 cells.

293 cells stably transfected with NF-κB-luciferase plasmid (Panomics, Fremont, CA) were treated with test compounds and the determination of luciferase activity was performed as described previously (Kang *et al*., 2009). In brief, transfected cells were incubated for 24 hours in 96-well plates. After 24 hours incubation with TNFα (20 ng/ml) and test compounds, cells were analyzed for luciferase activity. Cells were washed with PBS, lysed using 50 µl 1X Reporter Lysis Buffer (Promega, Madison, WI) for 10 minutes, and the luciferase determination was performed according to the manufacturer's protocol. Results were expressed as a percentage, relative to control (TNFα-treated) samples, and dose-response curves were constructed for the determination of IC_{50} values. IC_{50} values were generated from the results of five serial dilutions of test compounds and were the mean of three different experiments. In parallel, the cell viability was determined at 20 µg/ml.

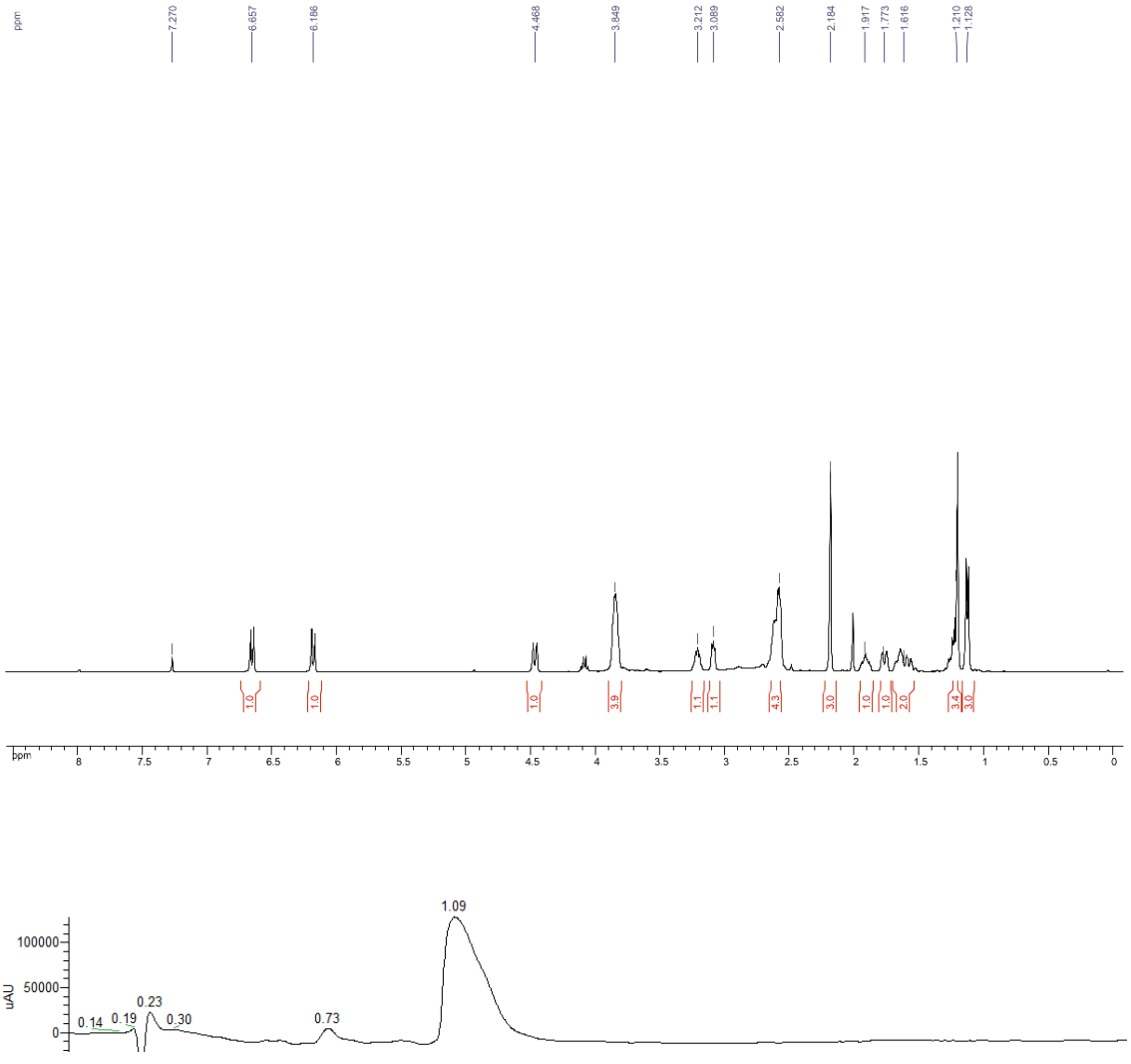
Nitric oxide production in LPS-induced RAW 264.7 cells

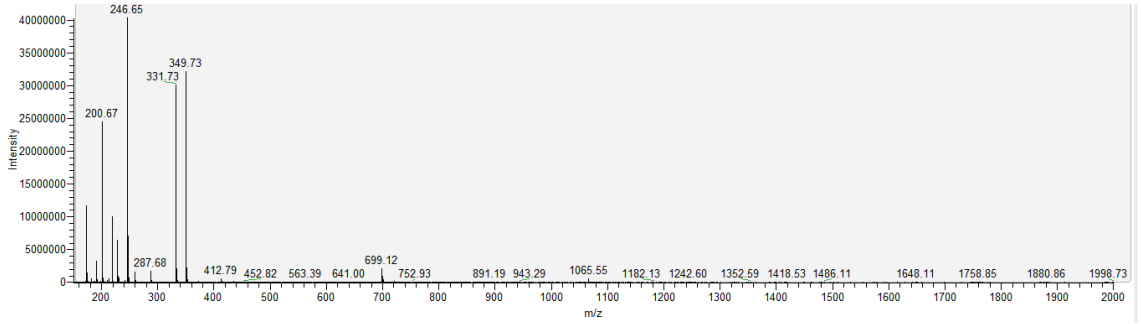
RAW 264.7 cells (ATCC) were incubated for 24 hours in 96-well plates. The cells were treated with test compounds for 30 minutes, followed by induction with lipopolysaccharide (LPS, 1 µg/ml) for an additional 20 hours. Resveratrol was used as positive control. An equal volume of media containing the released nitrite and Griess reagent were mixed and the absorbance was measured at 540 nm. Results were expressed as a percentage relative to control (LPS-induced) samples, and dose-response curves were constructed for the determination of IC_{50} values. IC_{50} values were generated from the results of five serial dilutions of test compounds and were the mean of three different experiments. In parallel, the cell viability was determined at 20 µg/ml.

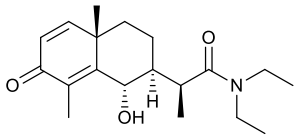
4. ^{1}H-NMR and ^{13}C-NMR Spectra



XVII







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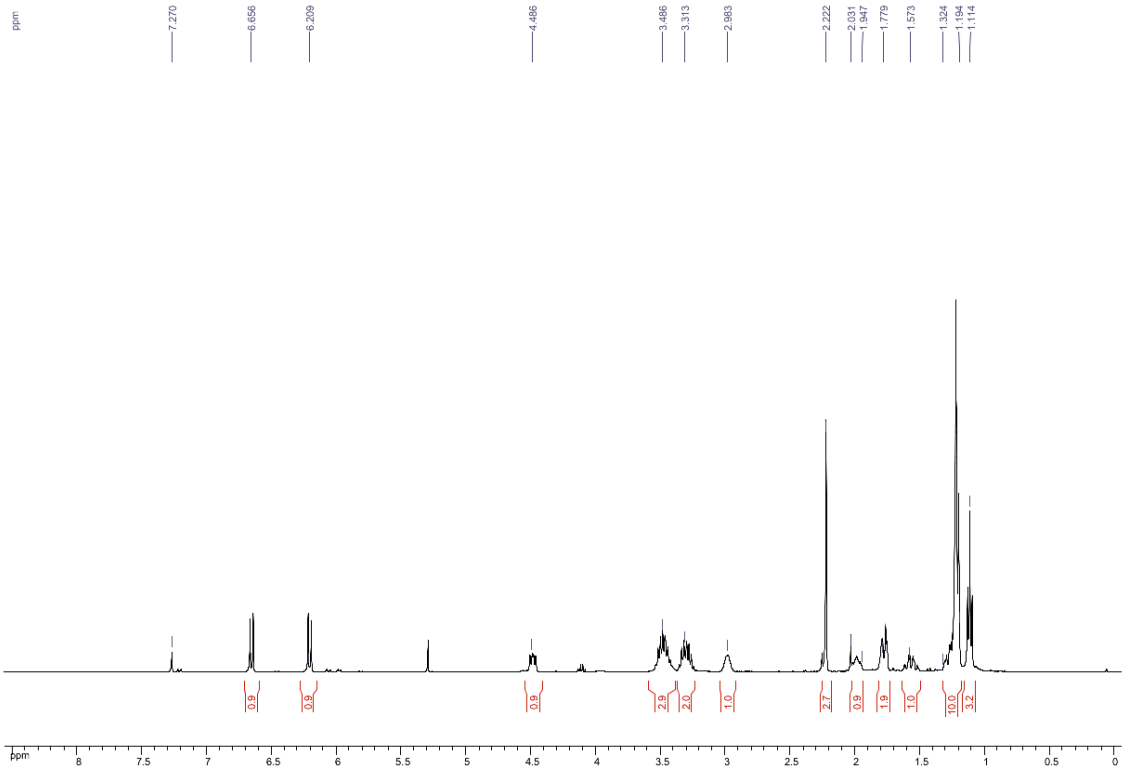
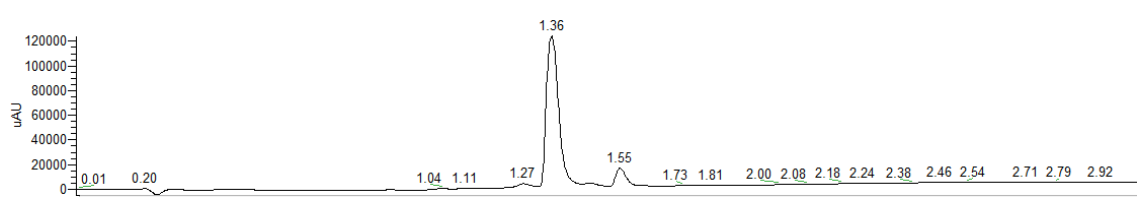
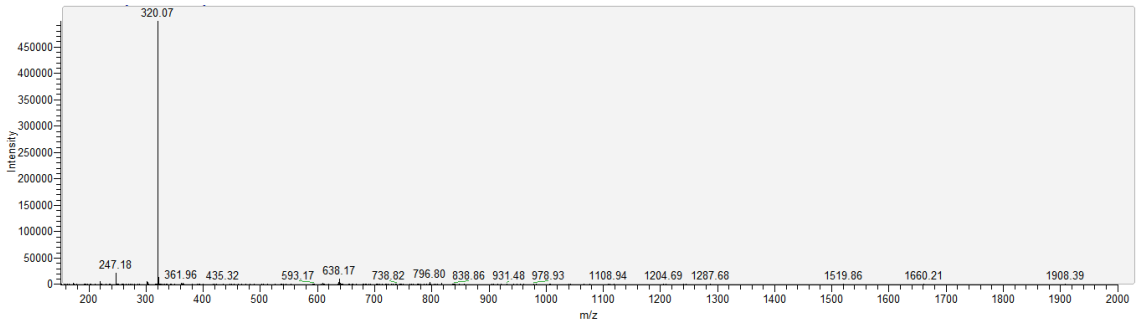
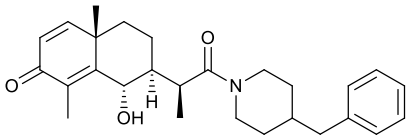
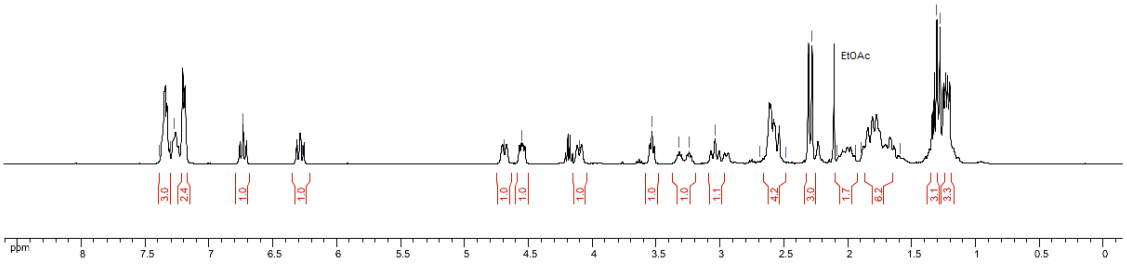


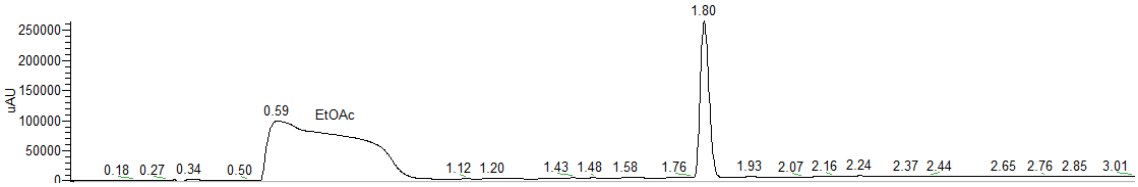


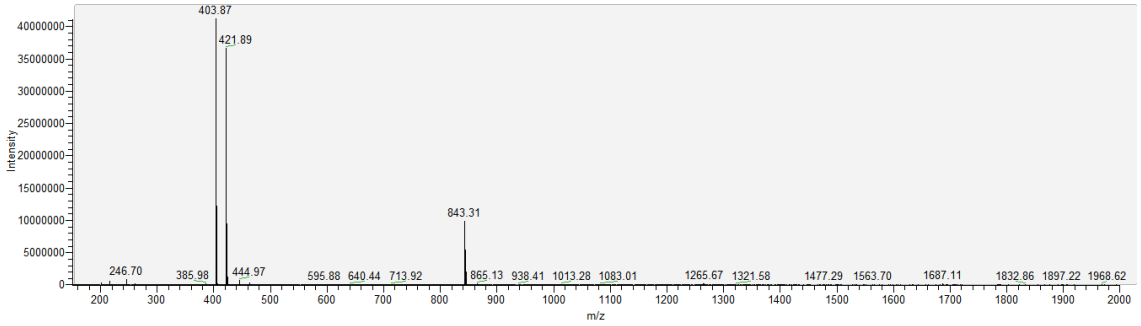


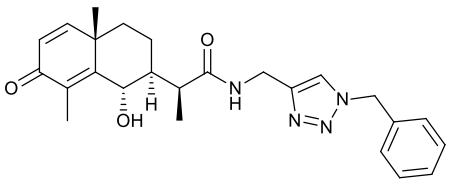


XIX









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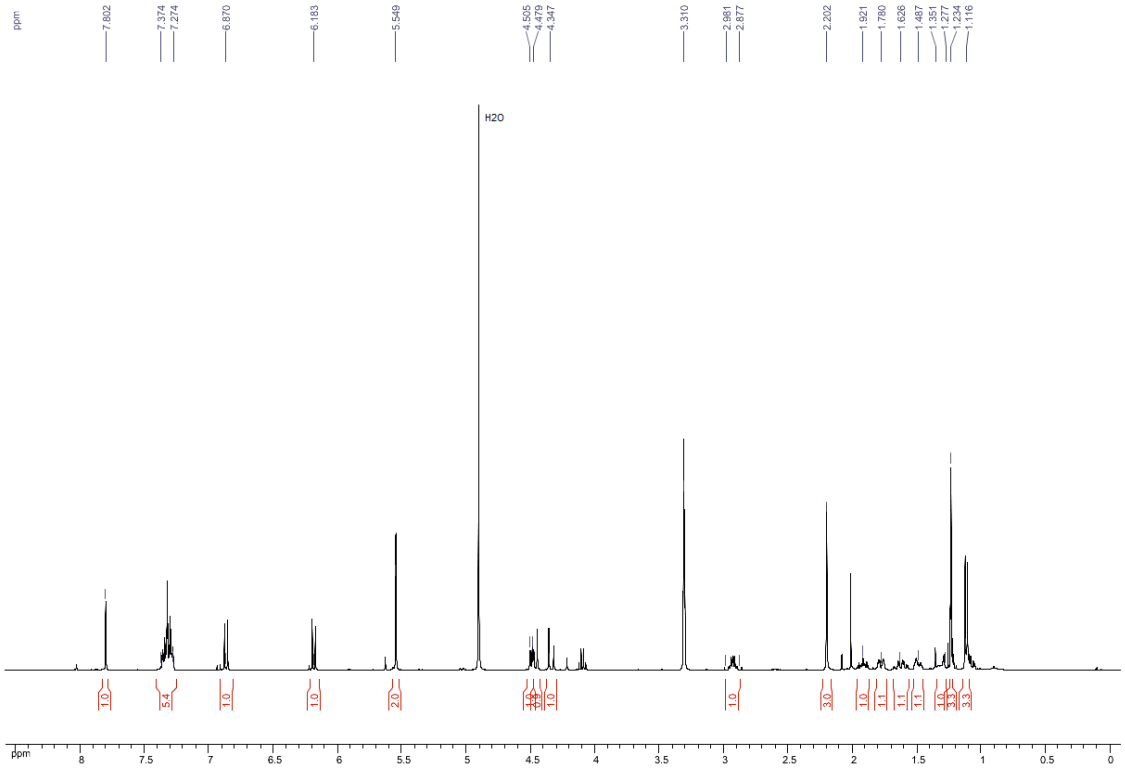

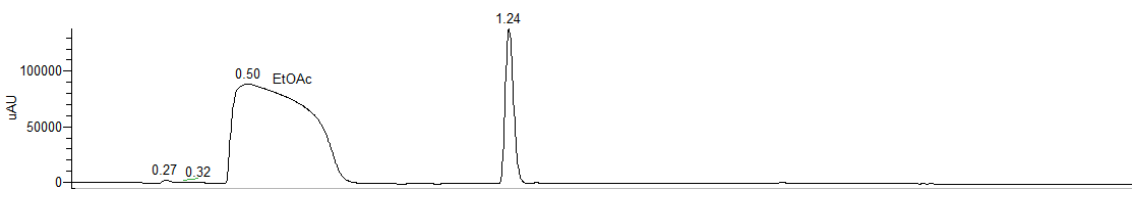

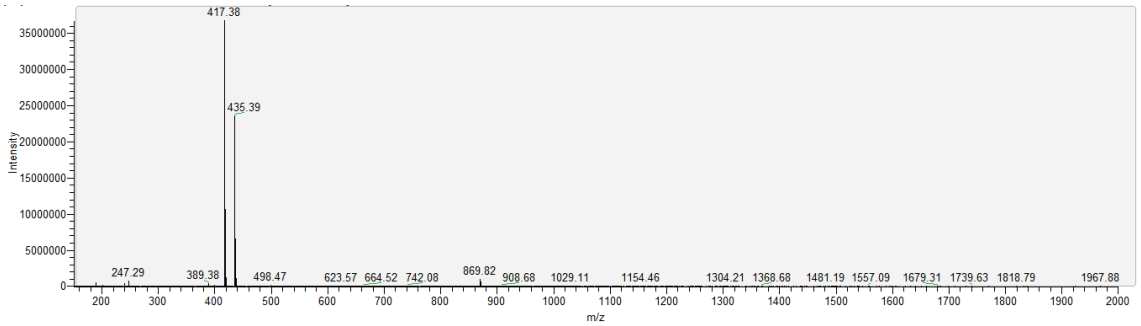

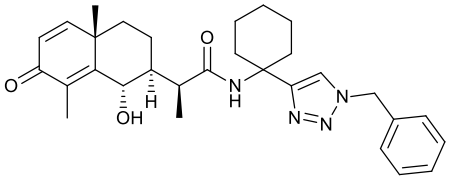

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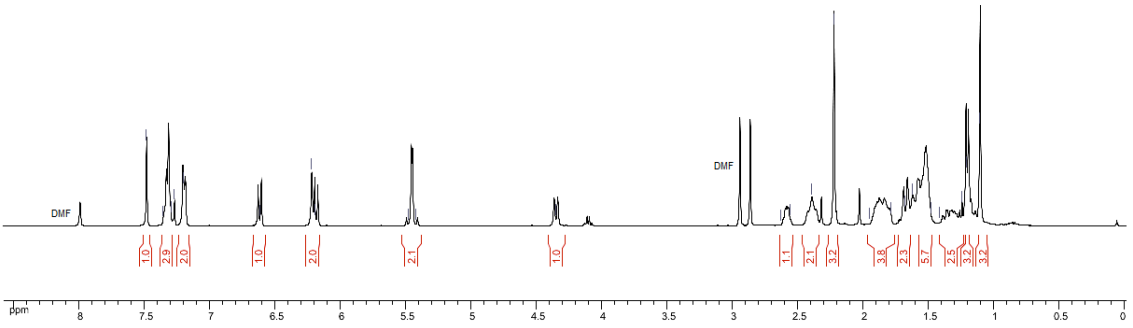

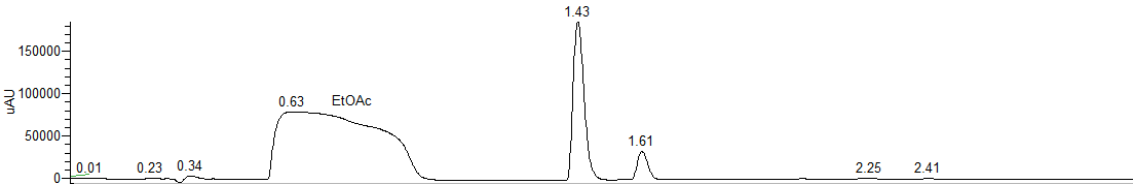

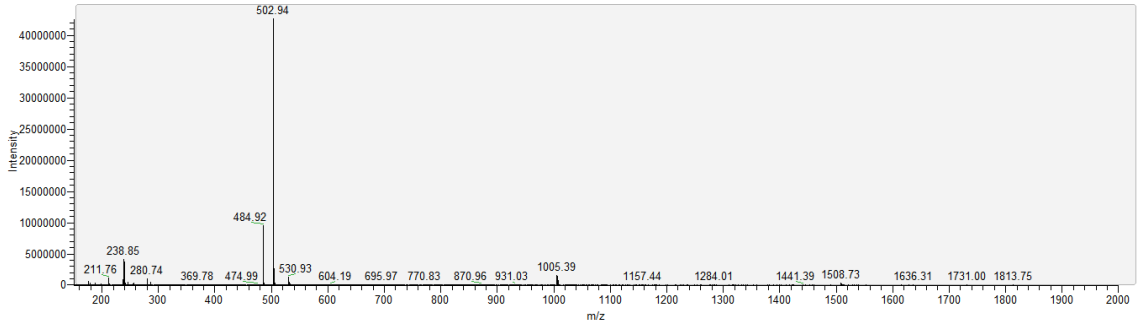

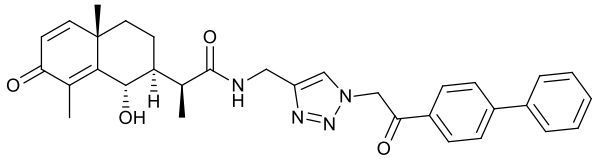

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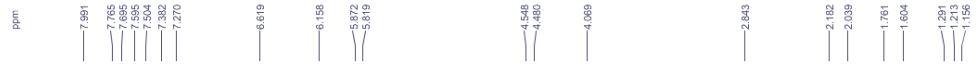

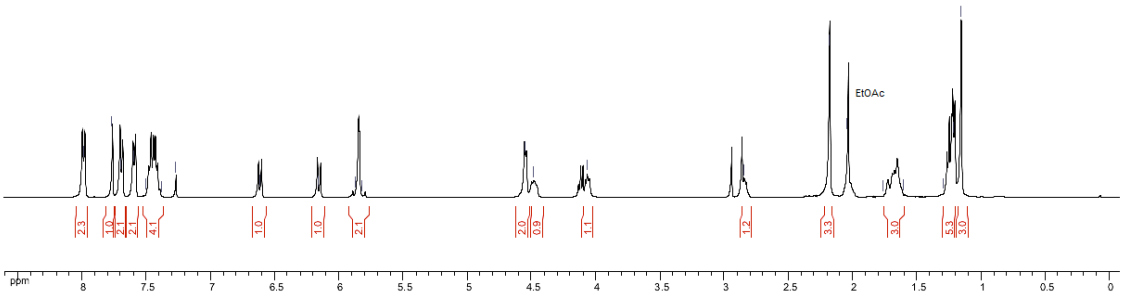

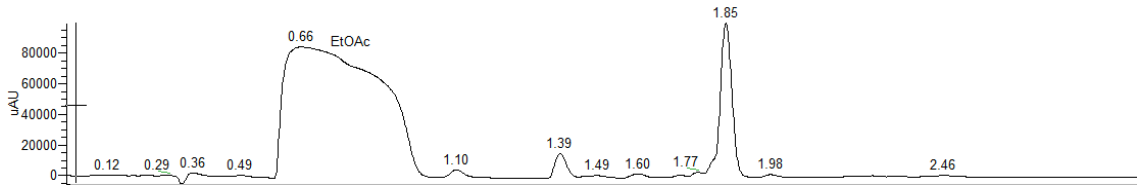

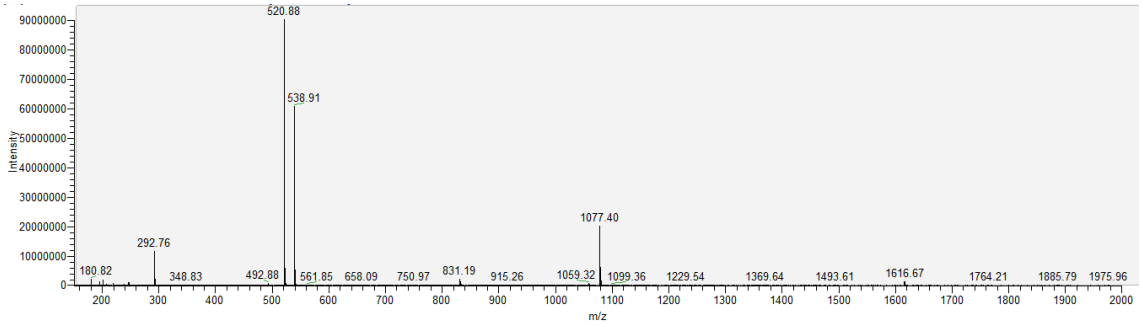

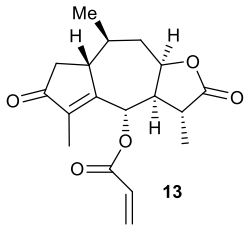

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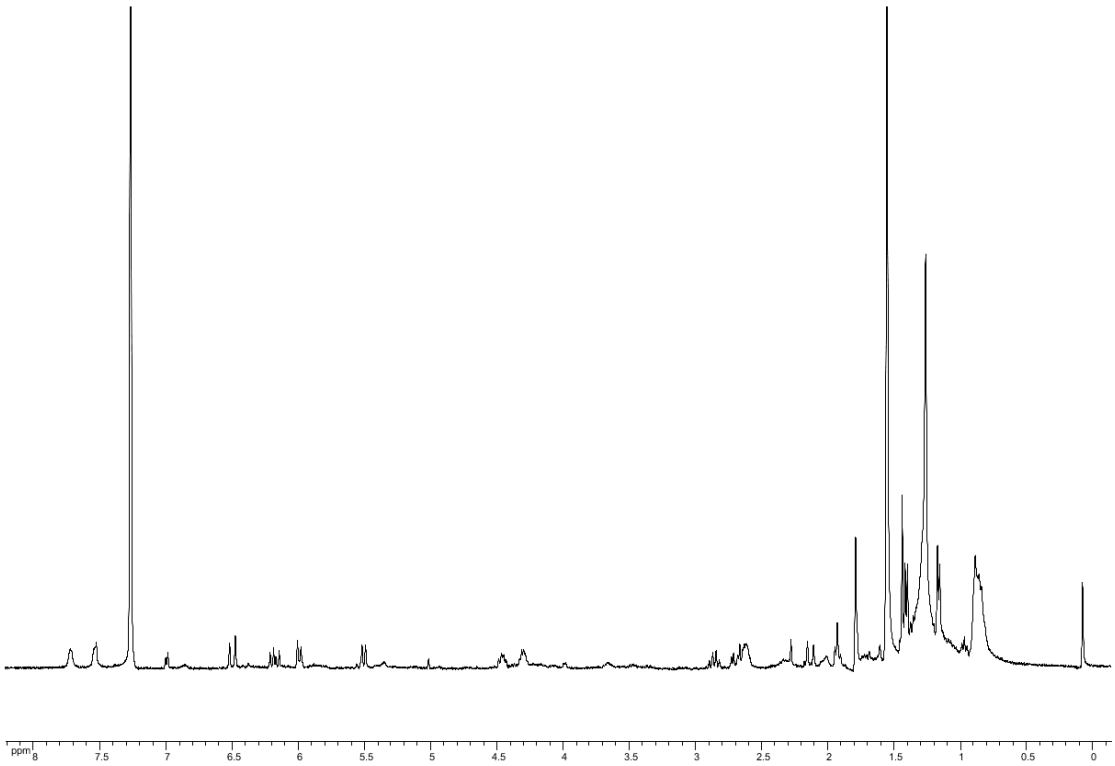

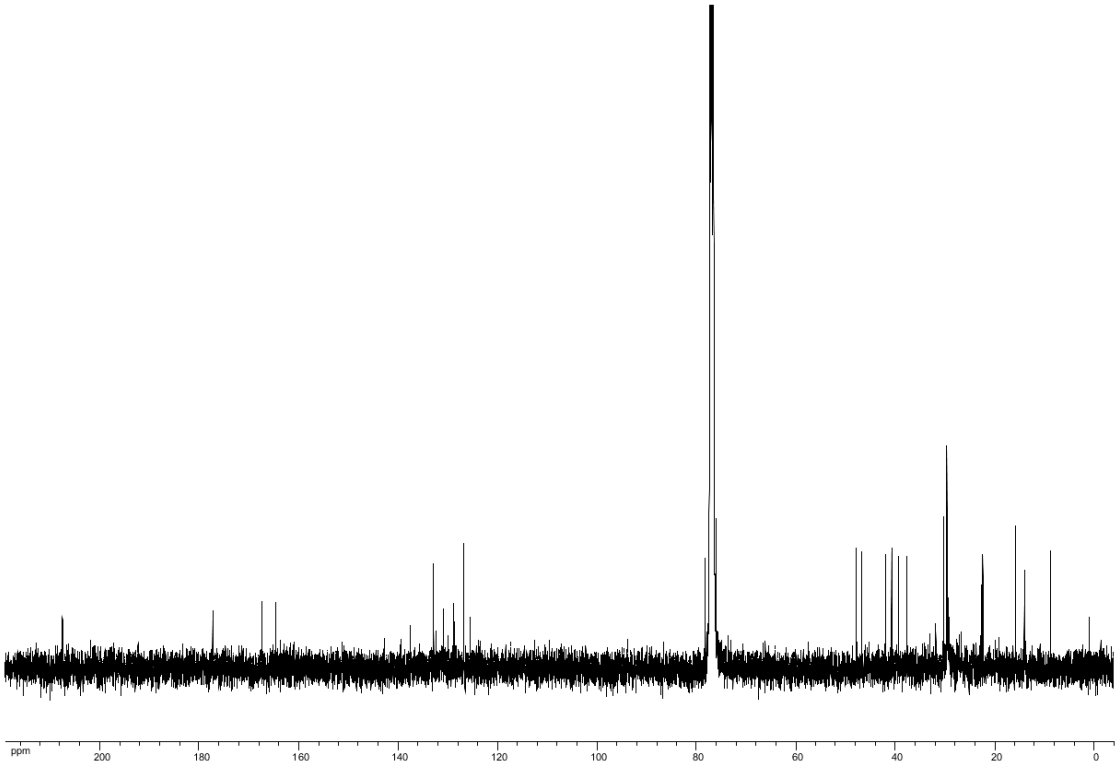

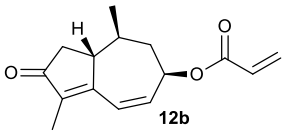

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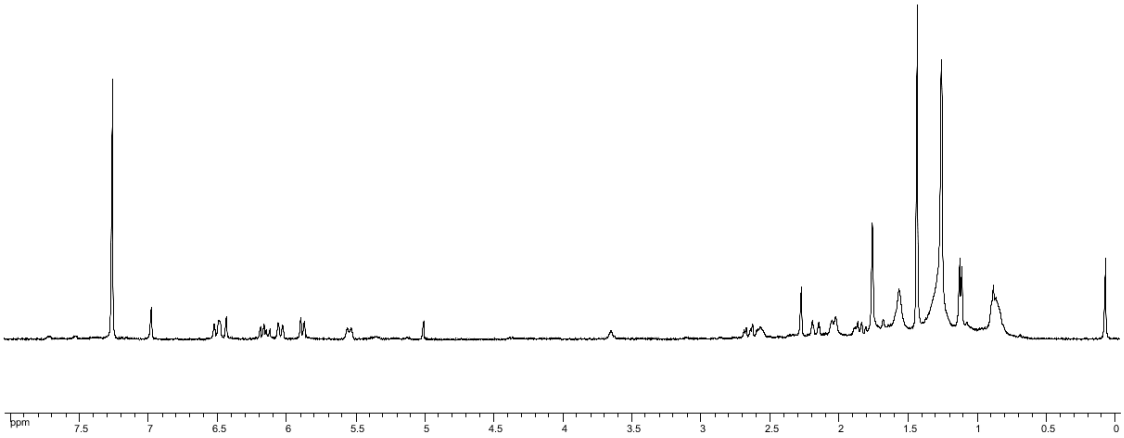

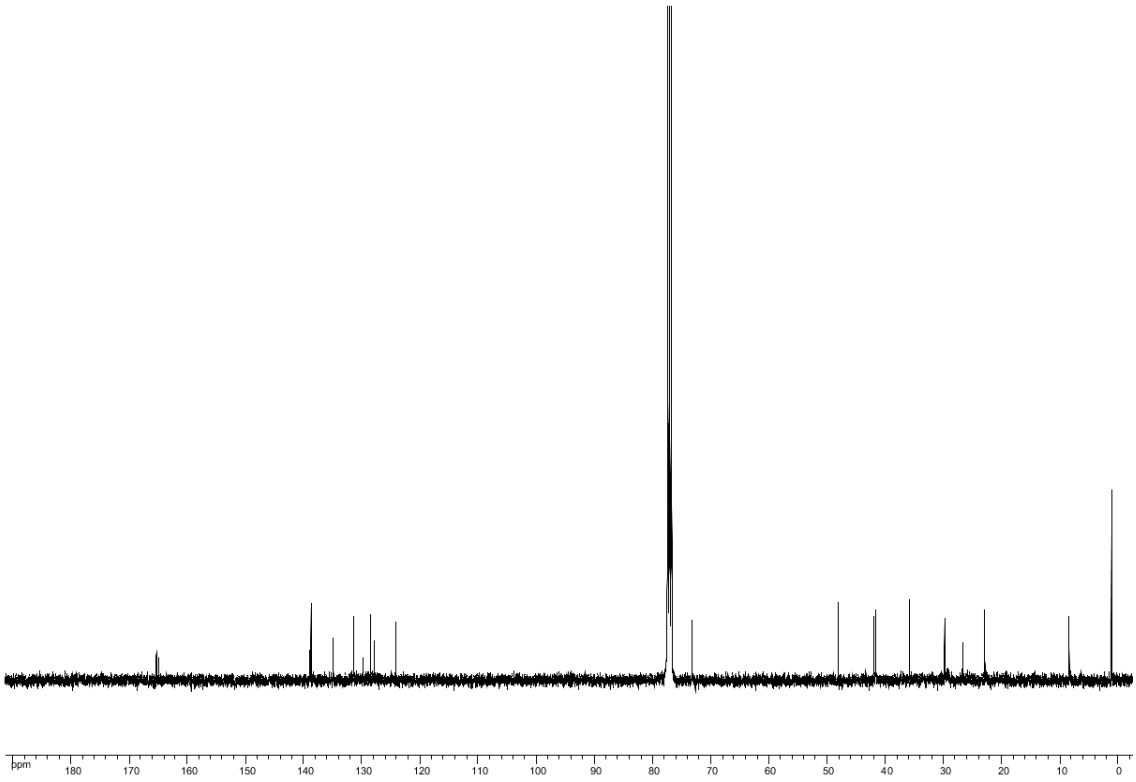

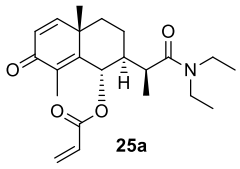

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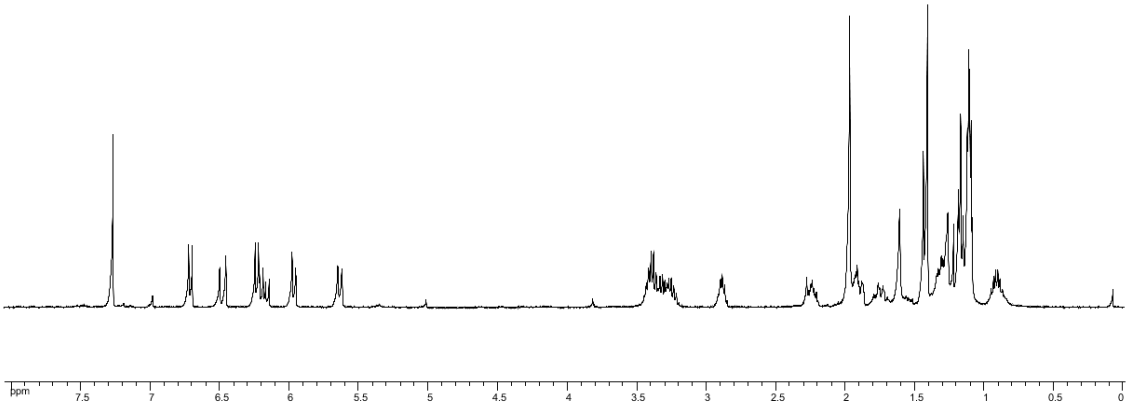

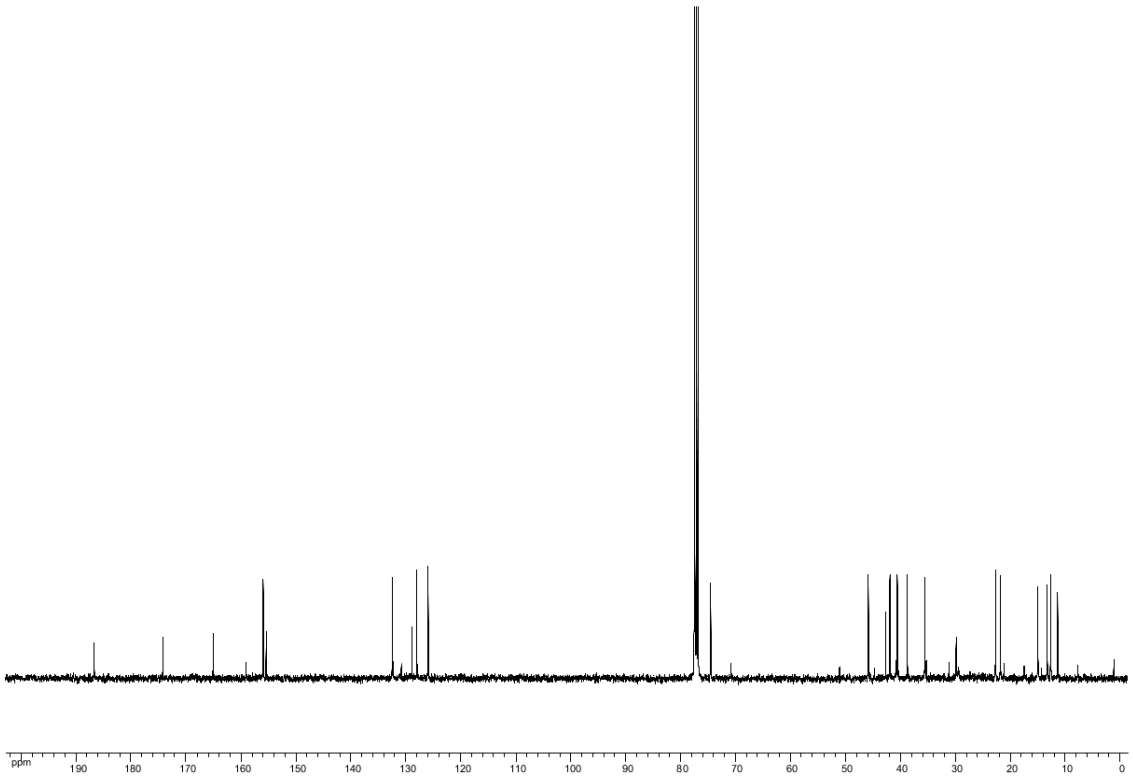

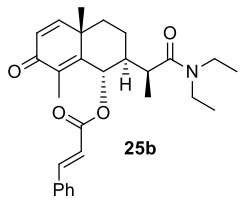

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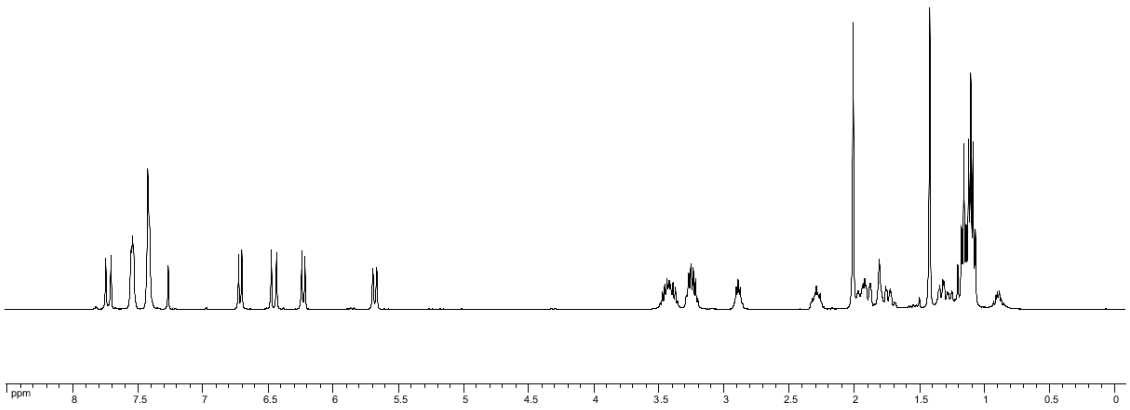

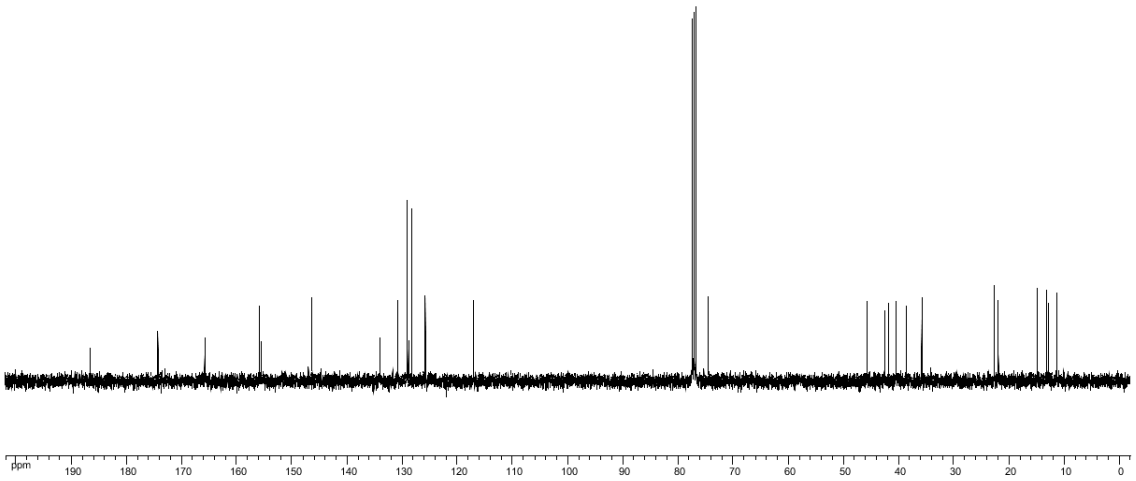

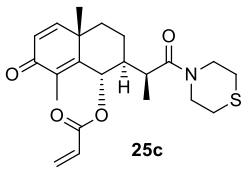

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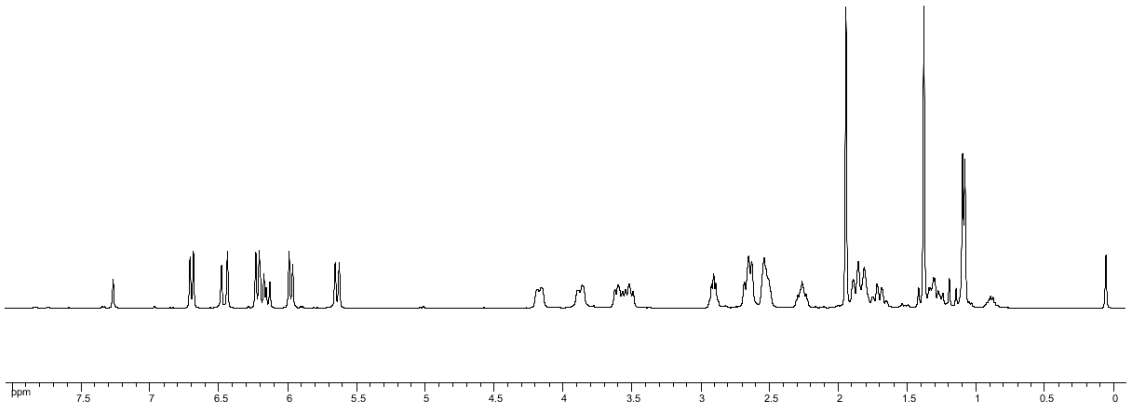

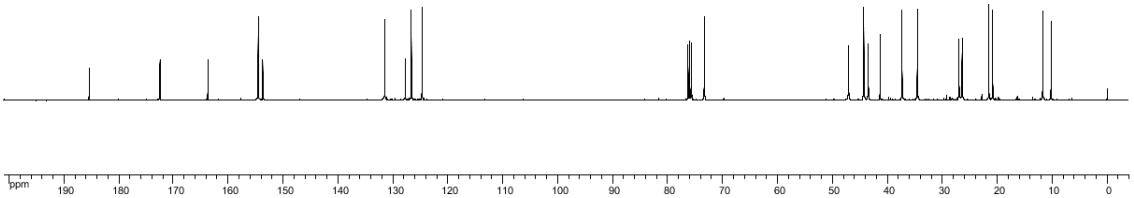

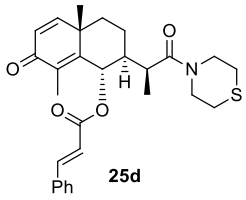

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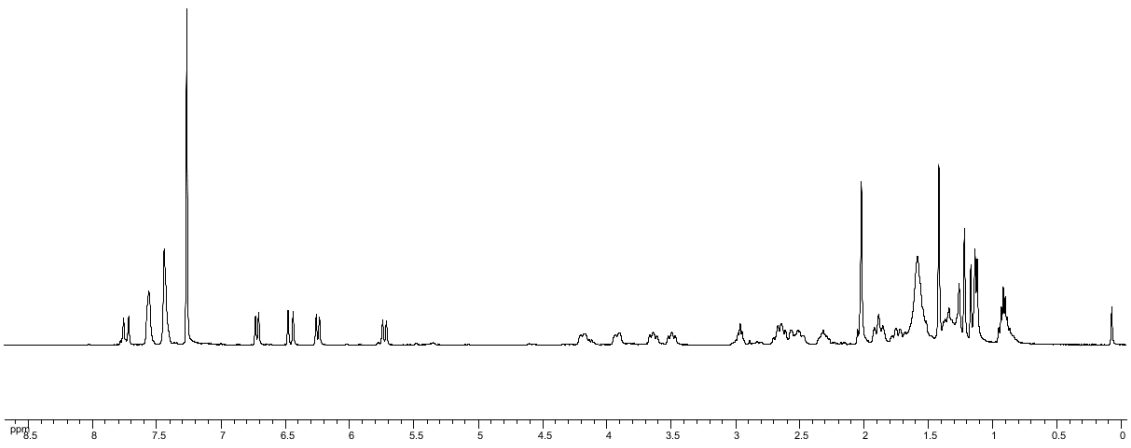

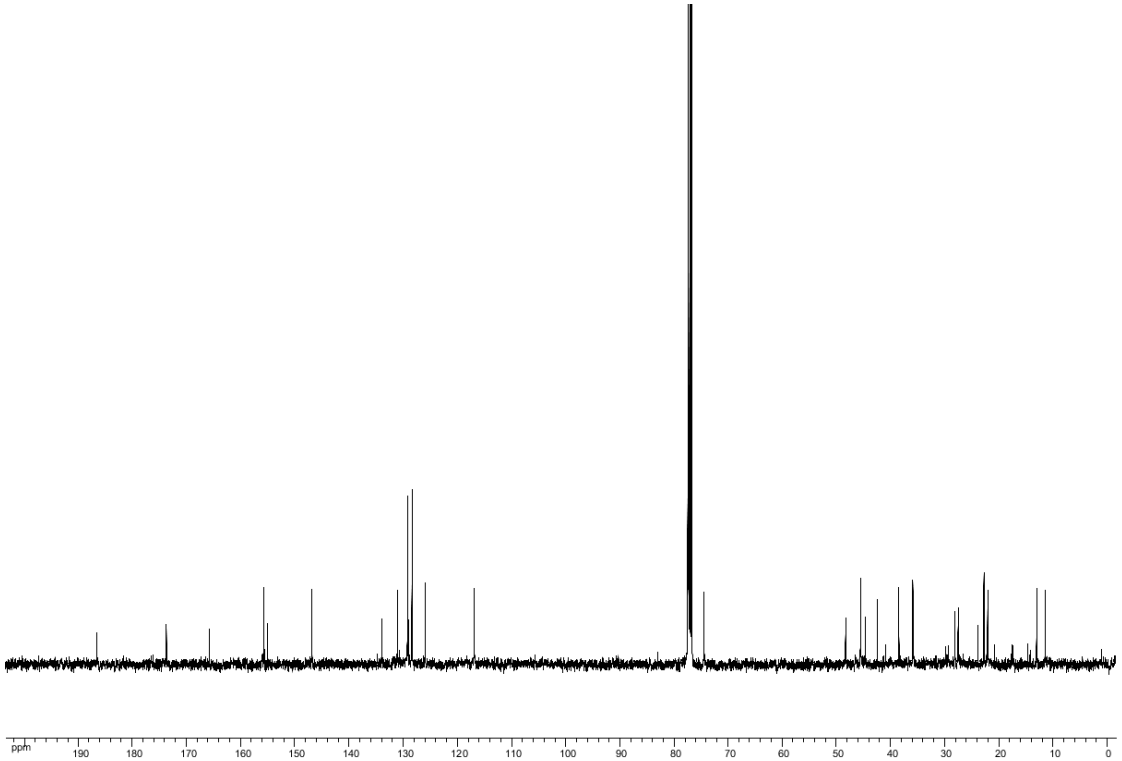

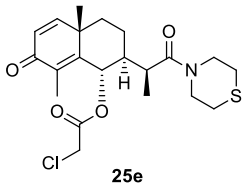

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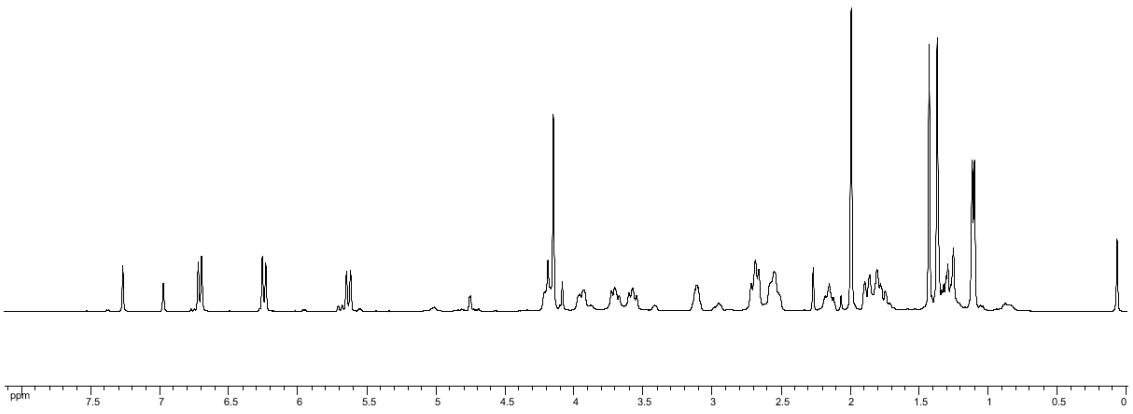

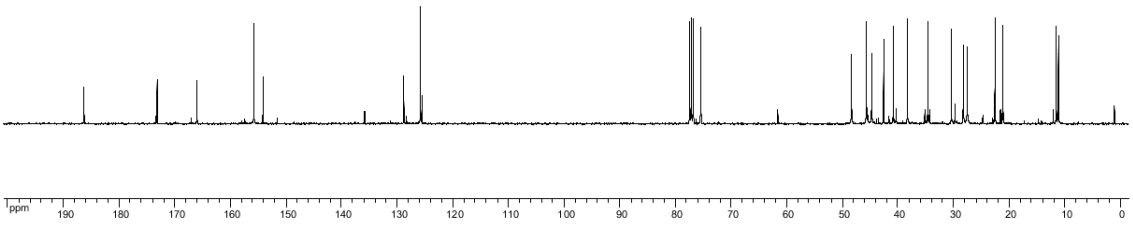

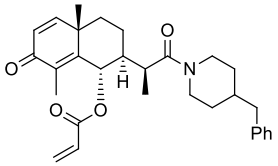

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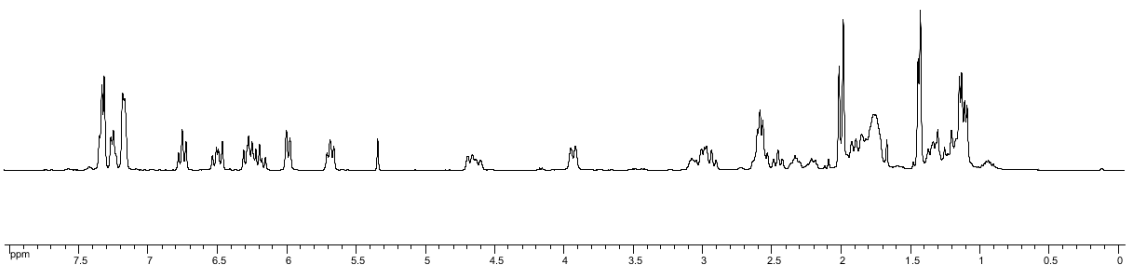

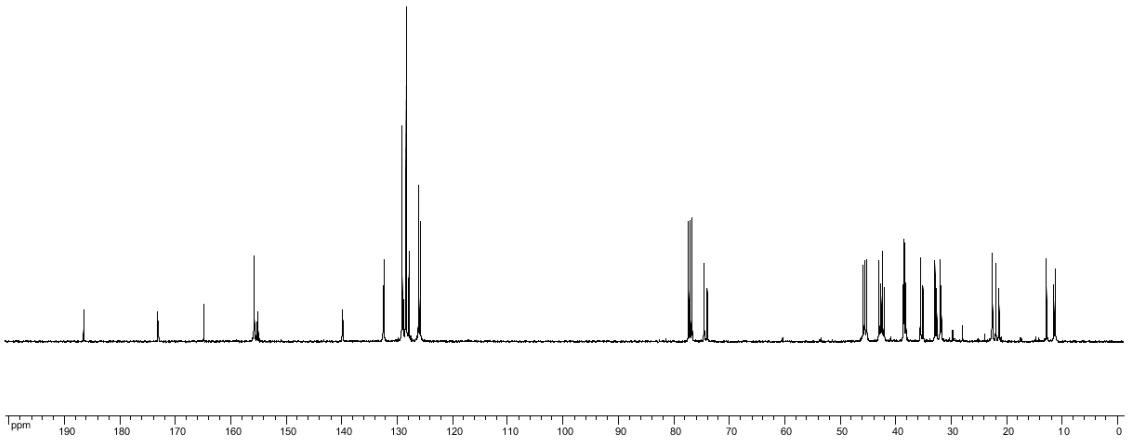

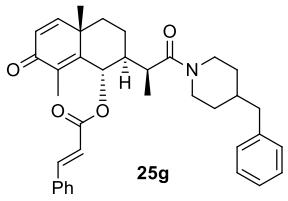

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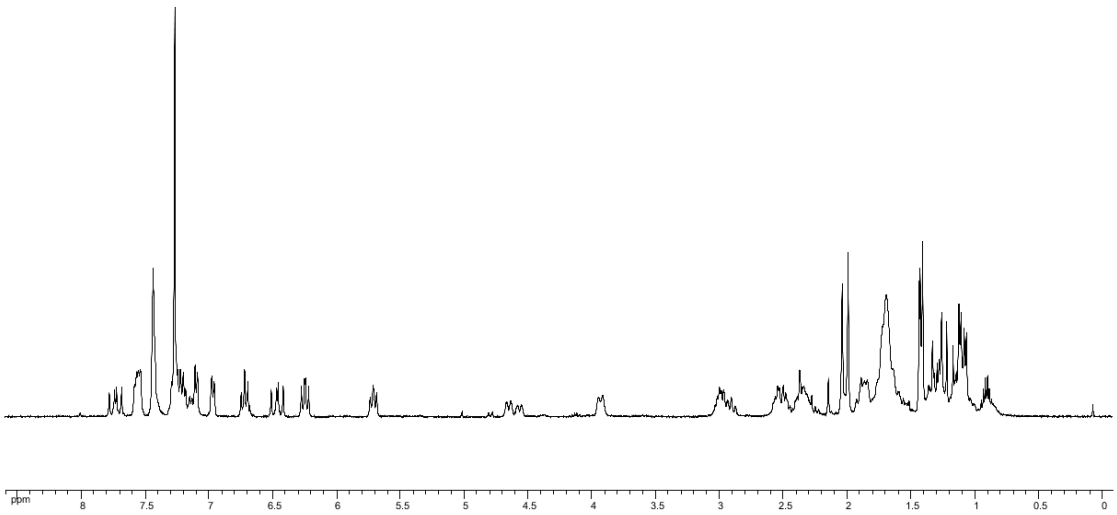

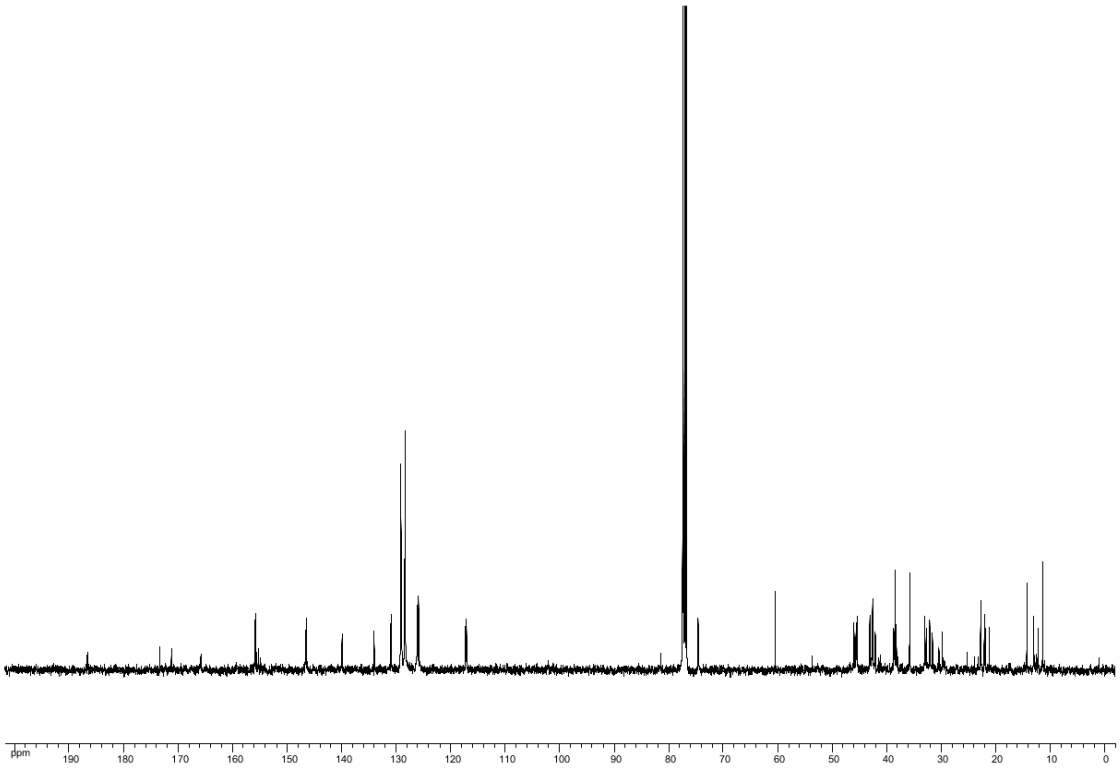

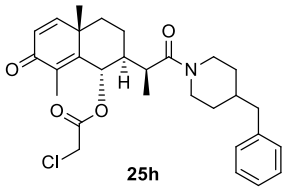

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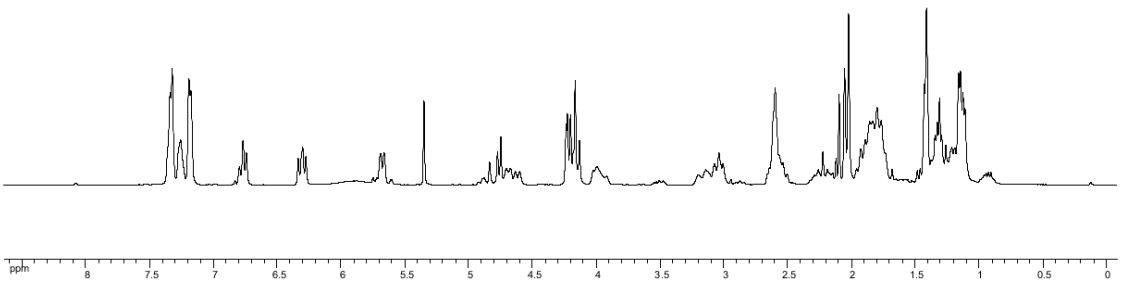

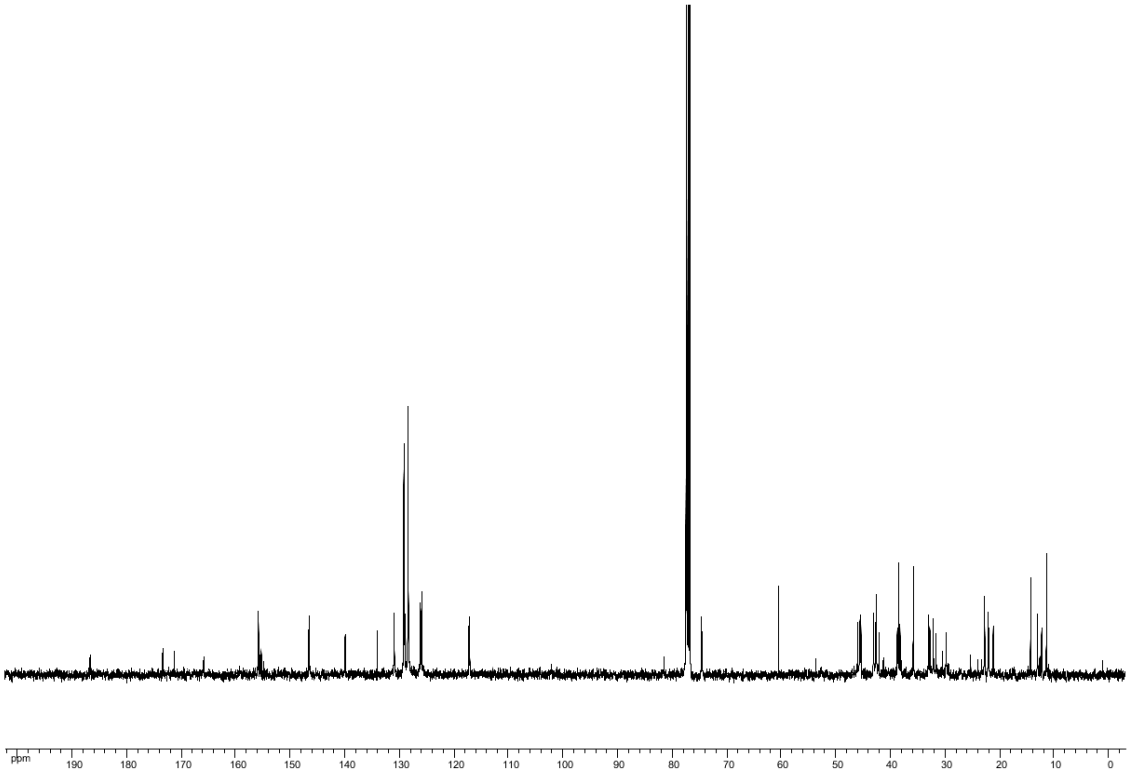

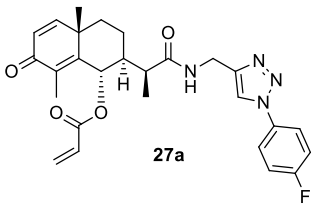

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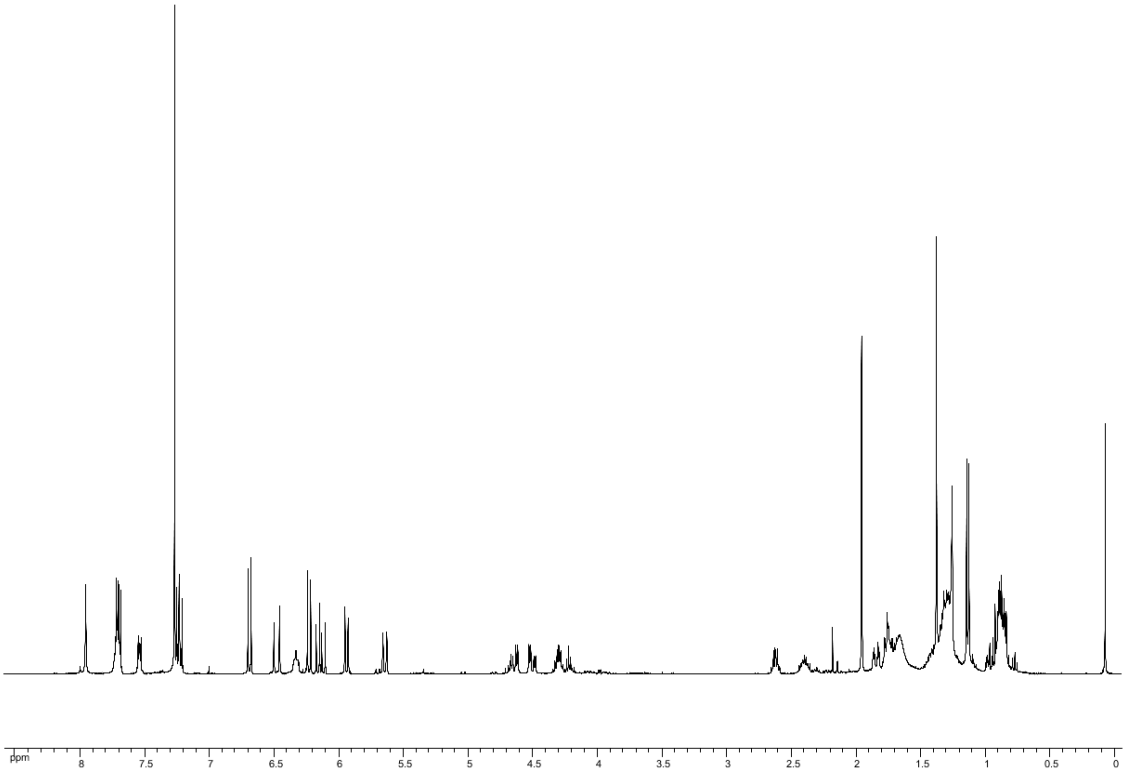

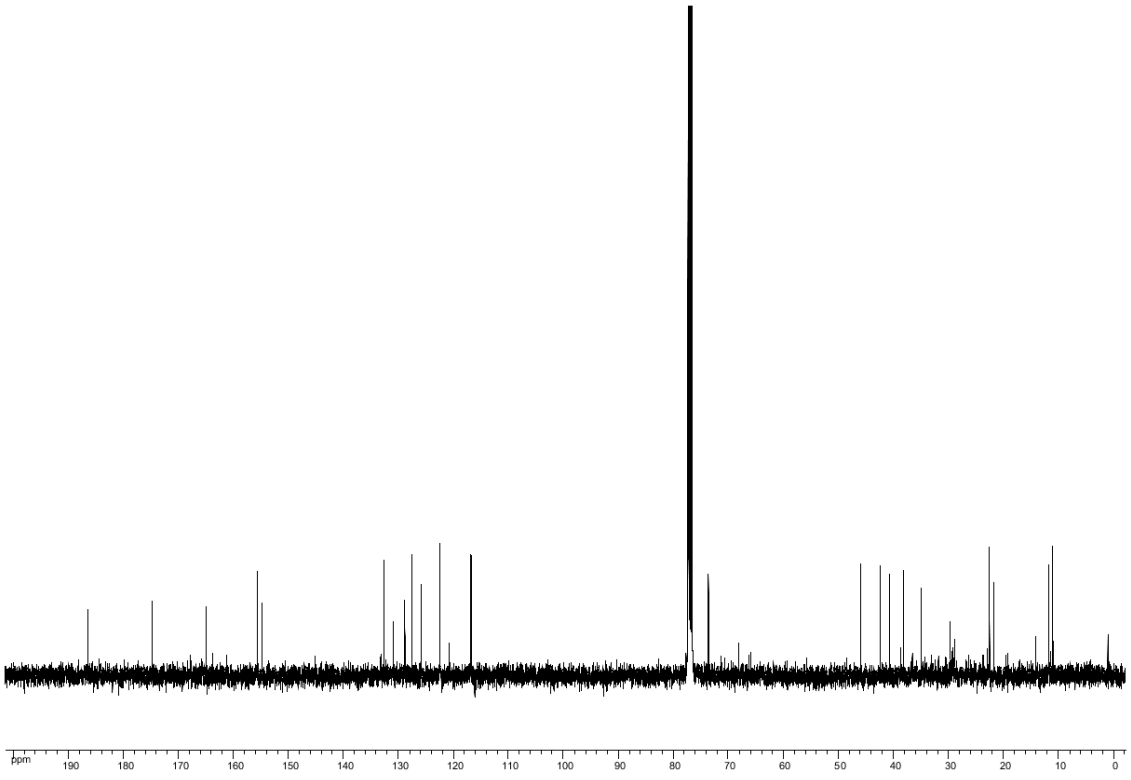

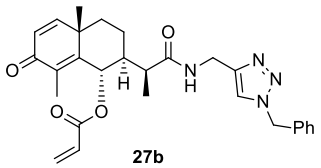

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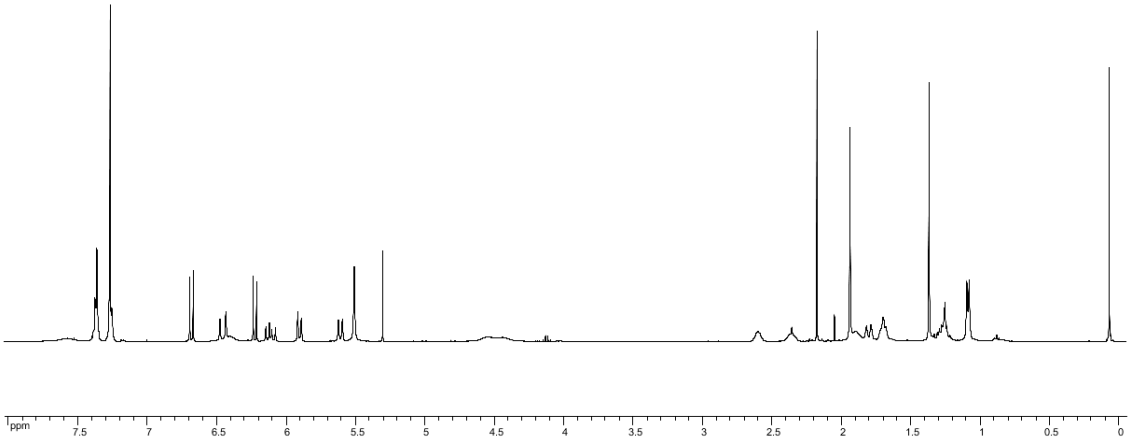

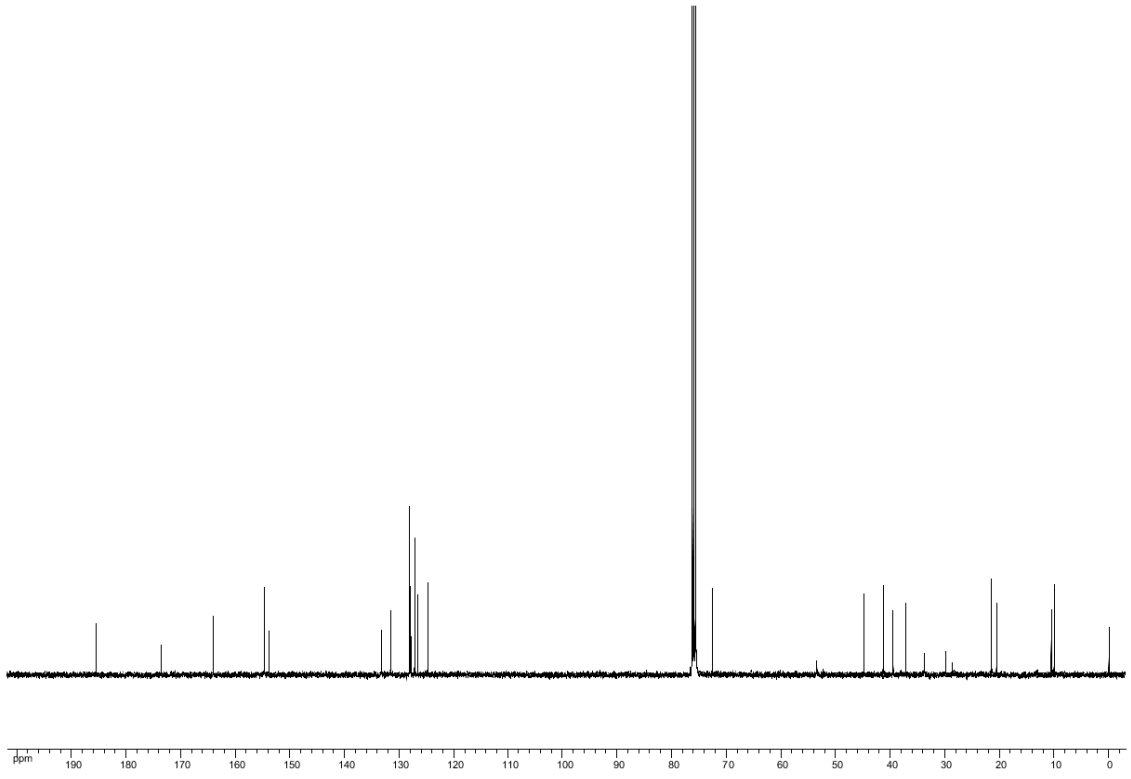

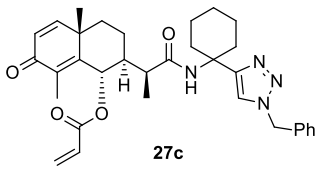

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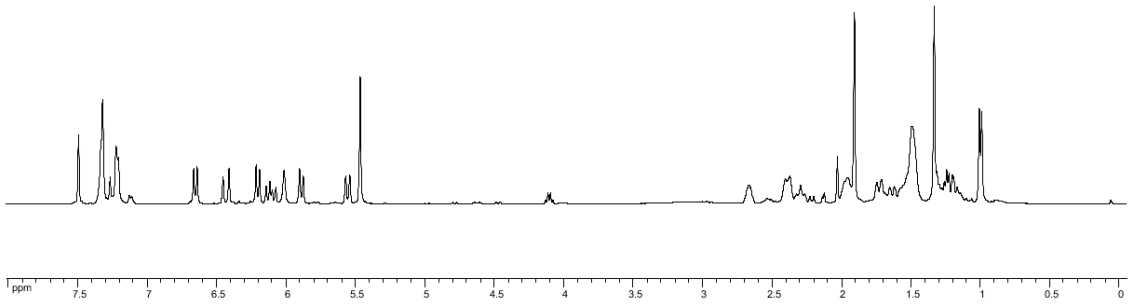

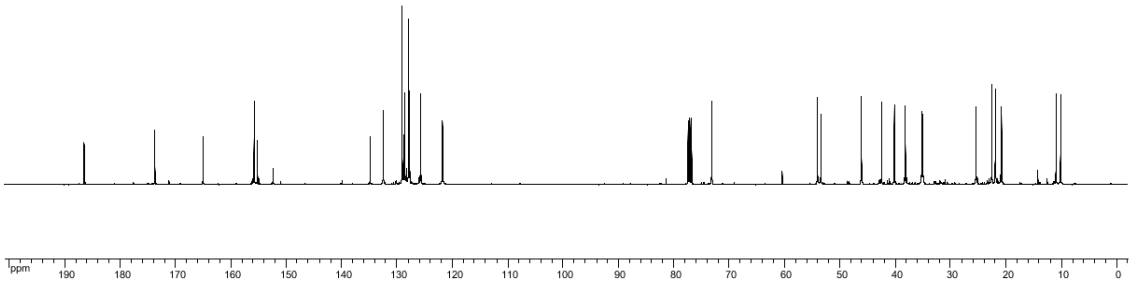

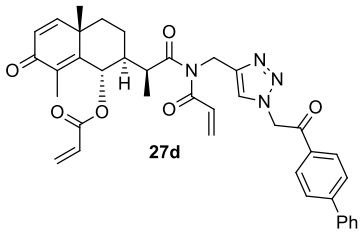

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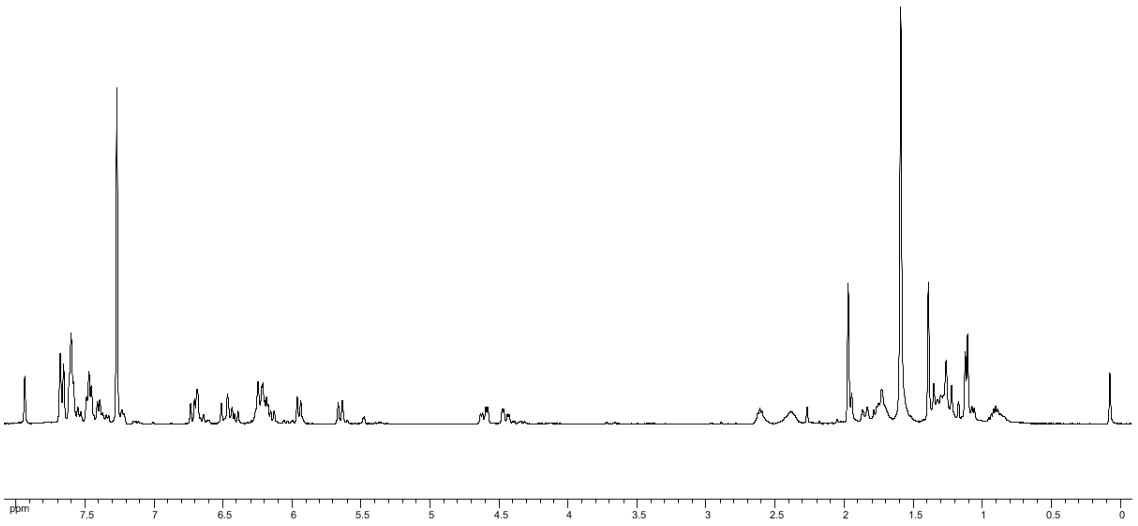

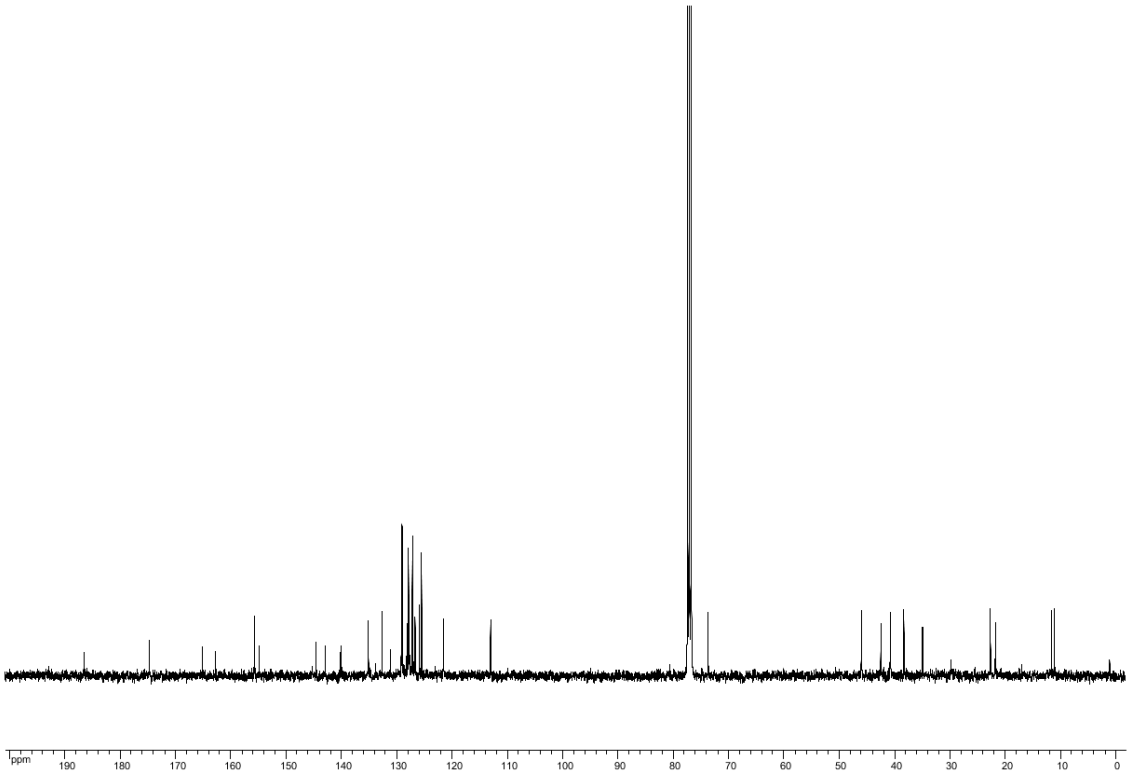

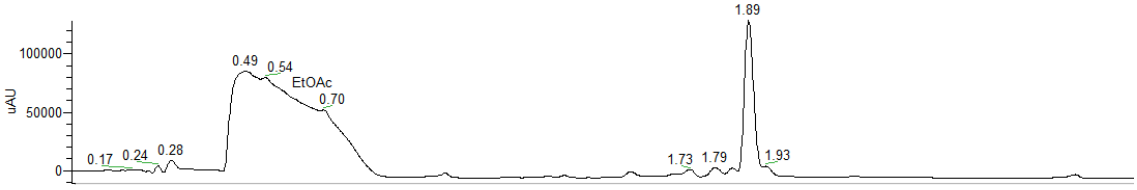

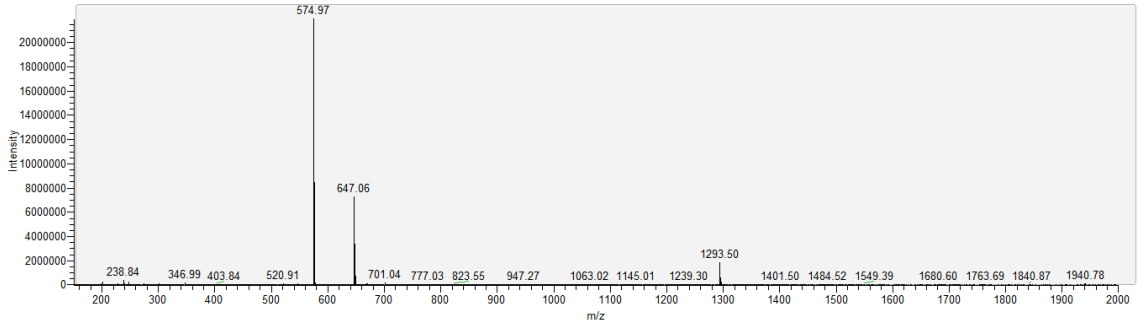

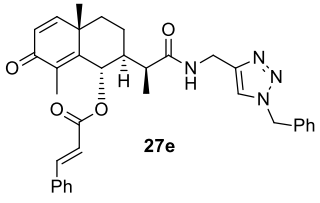

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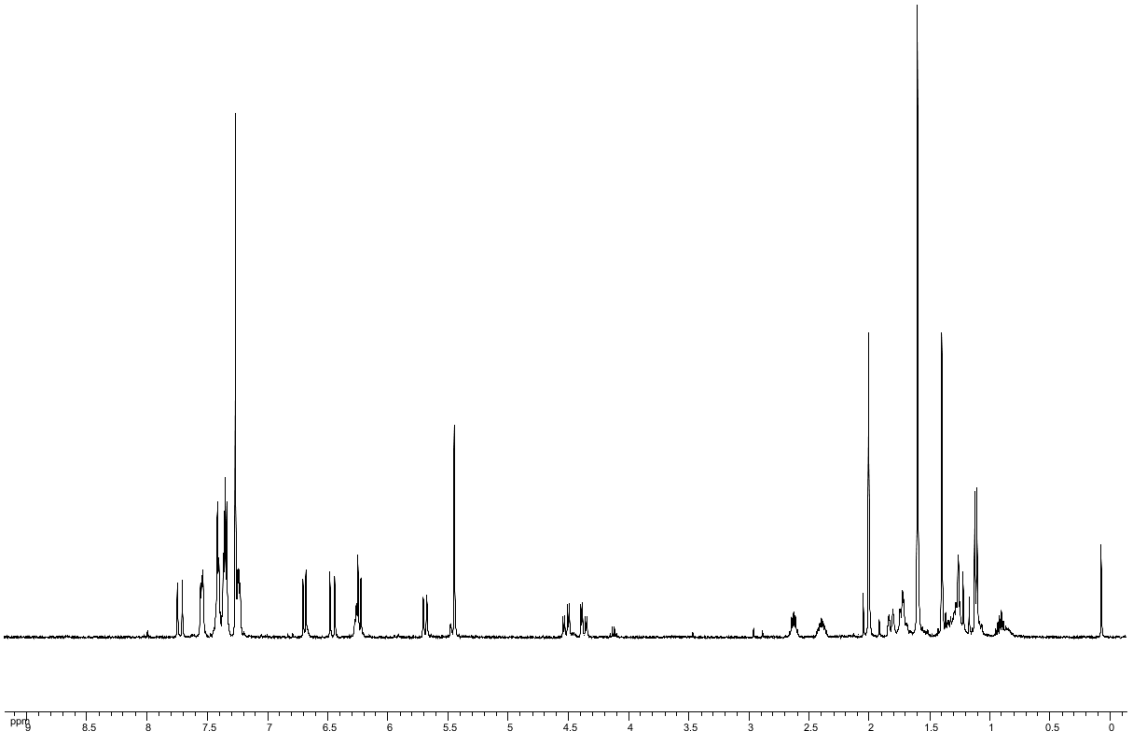

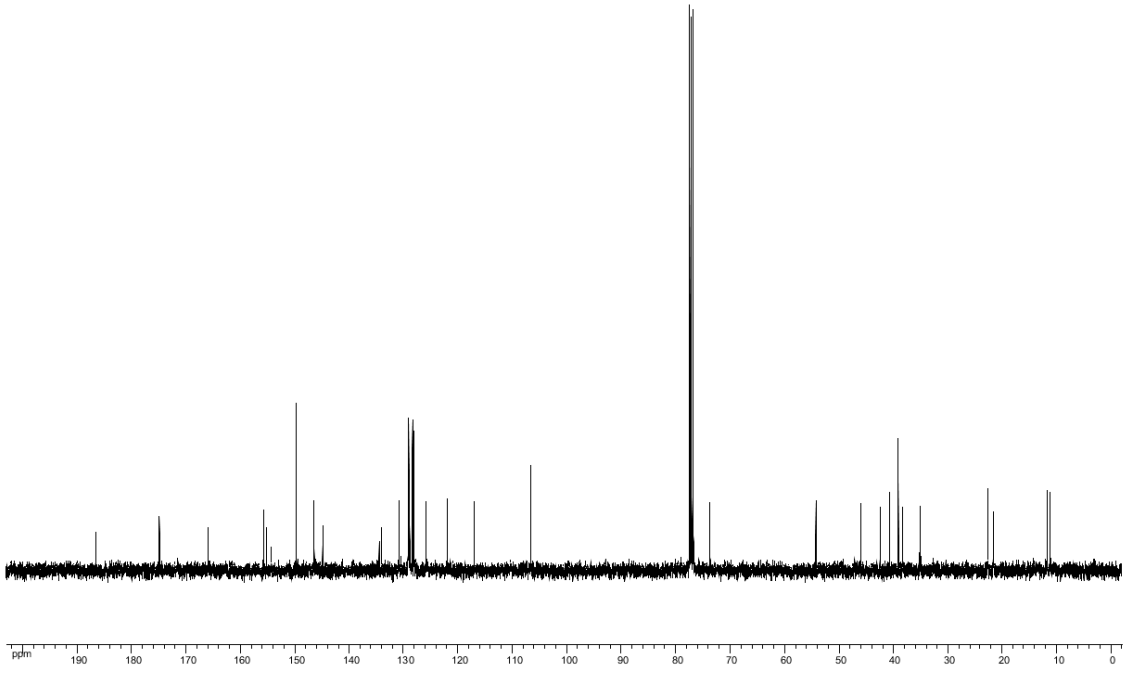

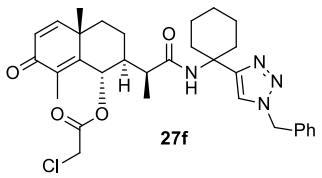

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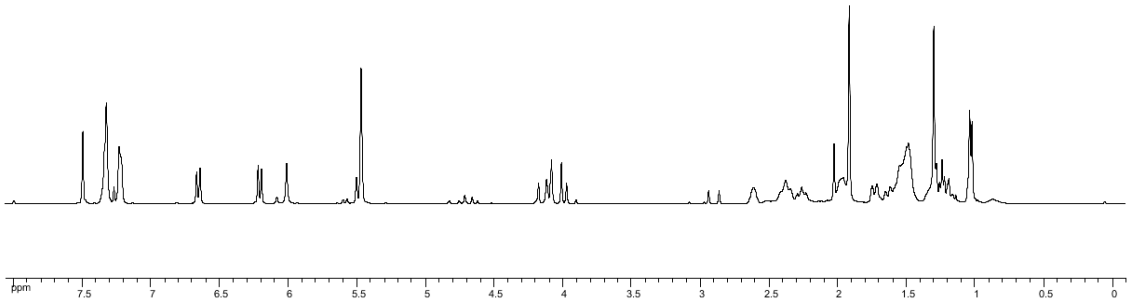

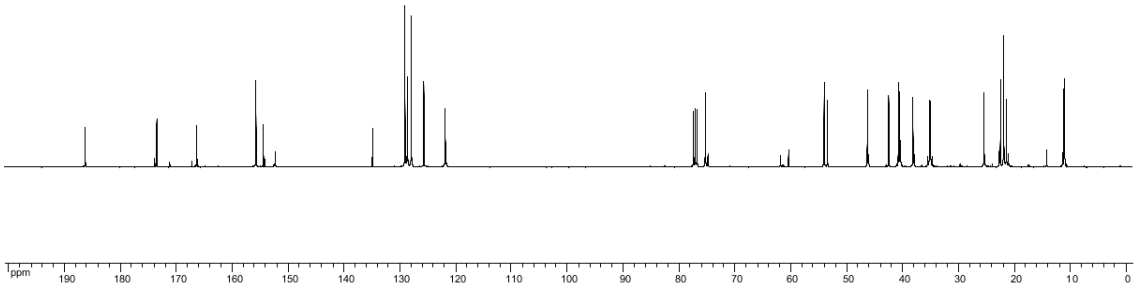

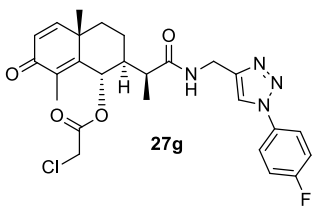

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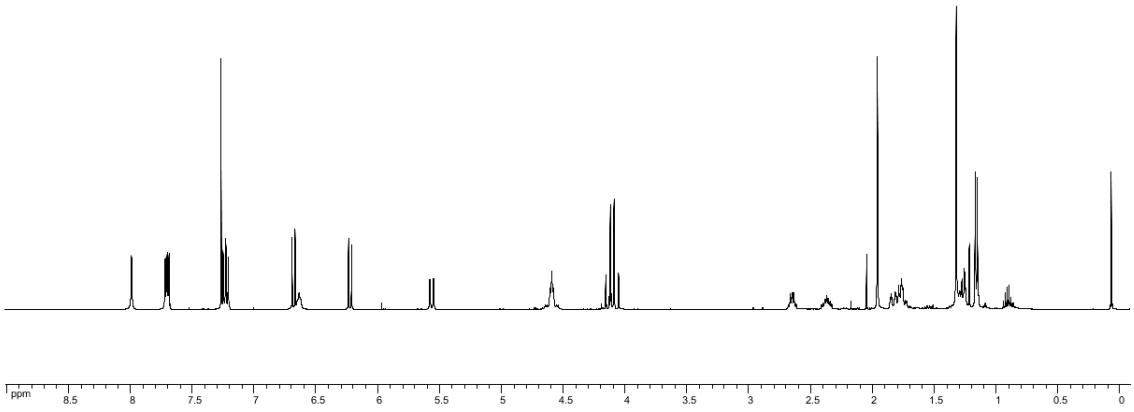

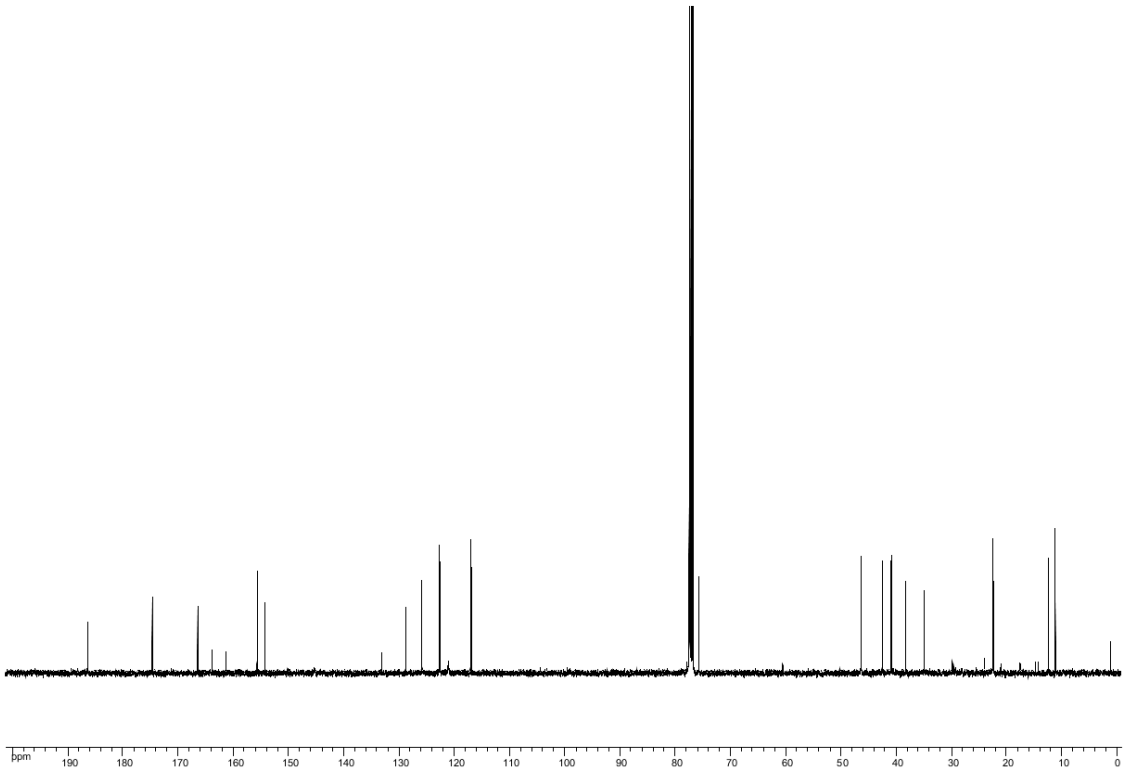

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