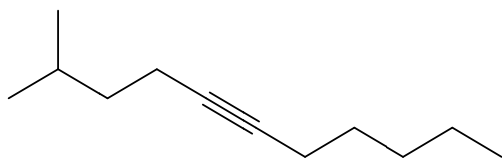


Title	Synthesis of the quorum sensing molecule Diffusible Signal Factor using the alkyne zipper reaction
Authors	Kumar, Vydula P.;Gupta, Manoj K.;Horgan, Conor;O'Sullivan, Timothy P.
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Synthesis of the quorum sensing molecule Diffusible Signal Factor using the alkyne zipper reaction.

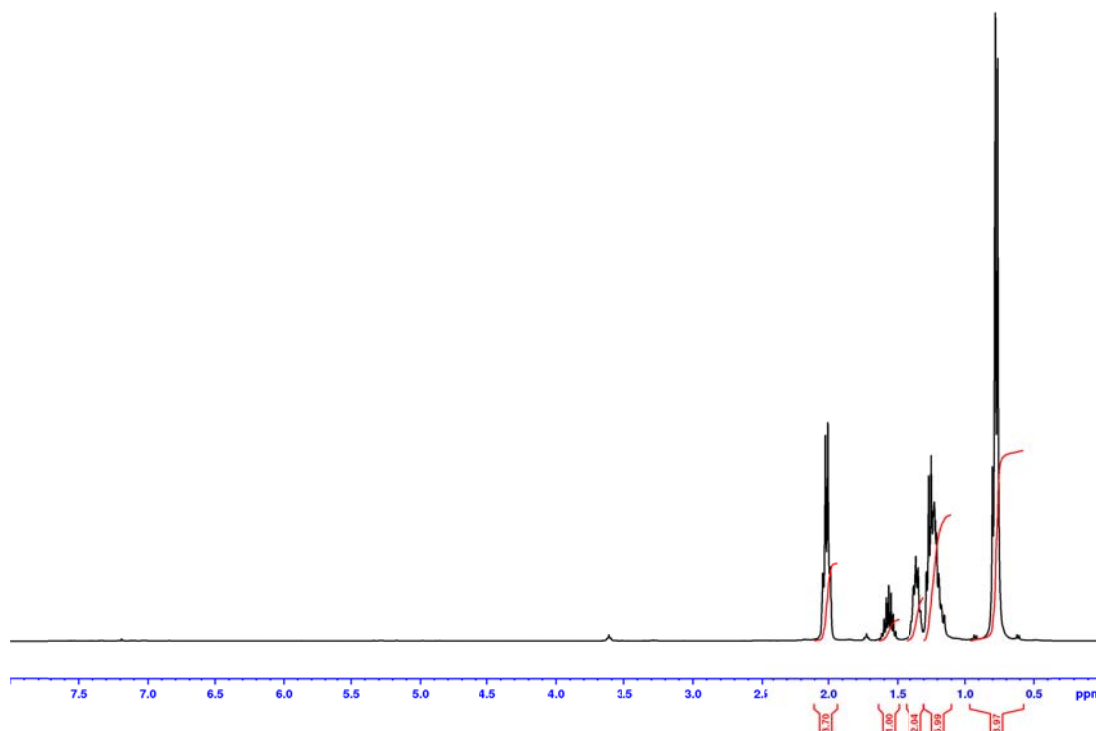
Vydyula P. Kumar^{a,b}, Manoj K. Gupta^{a,b#}, Conor Horgan^{a,b} and Timothy P. O'Sullivan^{a,b,c*}.

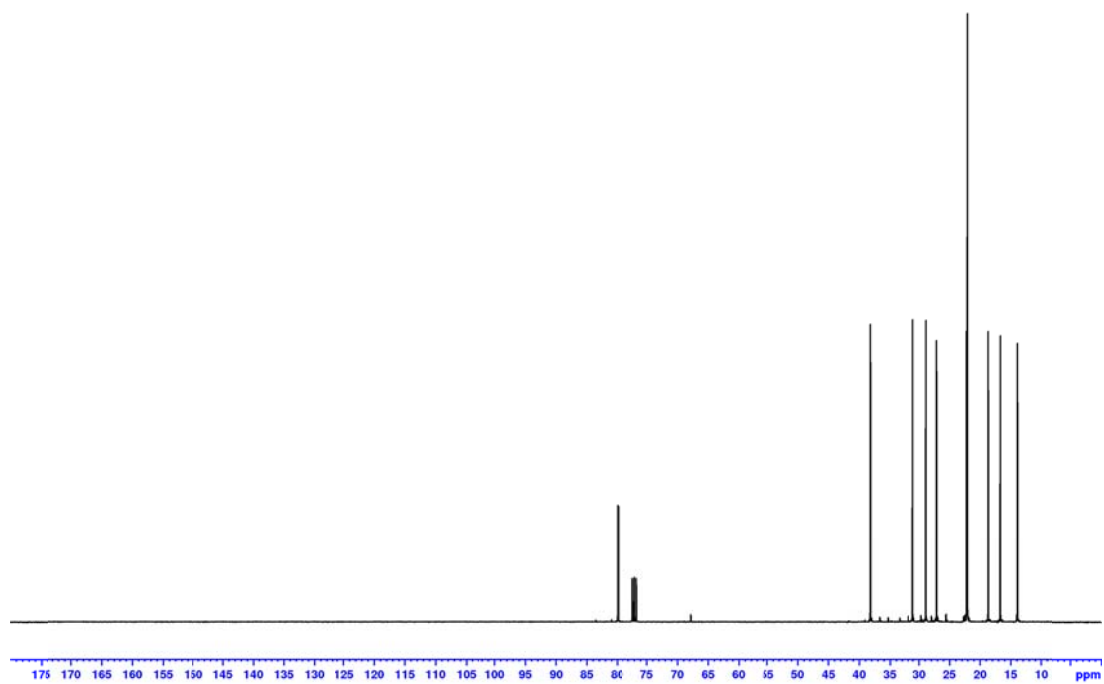
2-Methylundec-5-yne (15)



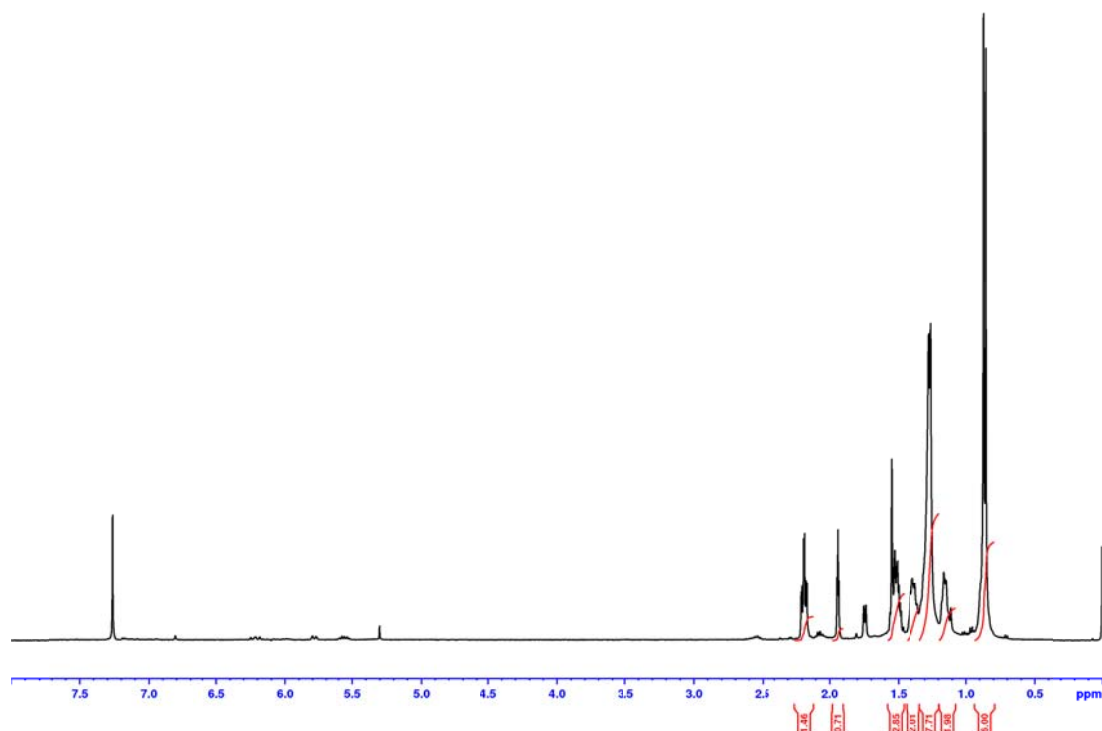
A solution of 1-heptyne (2 g, 20.833 mmol) was cooled to 0°C in THF (20 mL) before *n*-BuLi (2.7 M solution in hexane, 15.4 mL, 41.666 mmol) was added and the resulting solution stirred for 30 mins. Next, *i*-pentyl bromide (6.28 g, 41.666 mmol), sodium iodide (312 mg, 2.083 mmol), and HMPA (4 mL) were added. The resulting mixture was stirred at reflux for 16 hrs before cooling to room temperature. The reaction mixture was poured into water (40 mL) and extracted with diethyl ether (2 x 30 mL). The organic phase was washed with HCl and brine before being dried over Na₂SO₄ concentrated under reduced pressure. The crude mixture purified by column chromatography on silica gel using hexane (100%) to afford a yield of 98% (3.401 g, 20.444 mmol) as a colourless liquid.

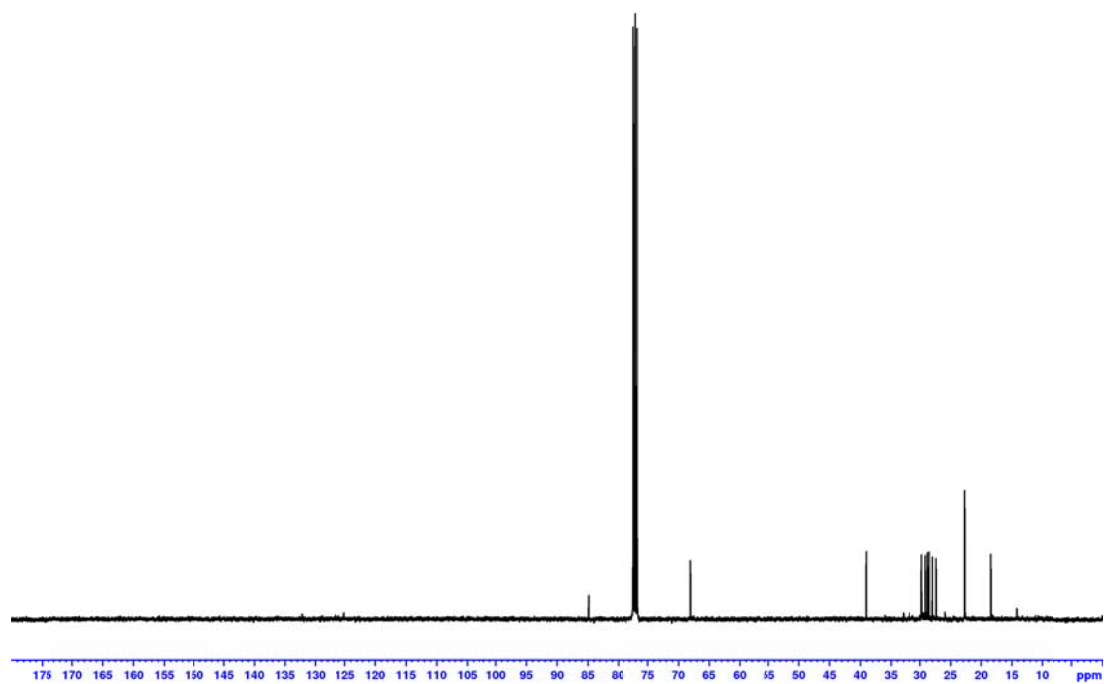
¹H NMR (400 MHz, CDCl₃) δ 0.57-0.96 (m, 9H), 1.10-1.30 (m, 6H), 1.30-1.44 (m, 2H), 1.56 (h, 1H, J=6.71 Hz), 1.93-2.10 (m, 4H); ¹³C NMR (75 MHz) 13.86, 16.67, 18.64, 22.05, 22.19, 27.09, 28.85, 31.03, 38.15, 79.83, 79.92; IR (ATR) ν_{max} cm⁻¹ 2956, 2929, 2870, 1467, 1384, 1367, 1329, 1170, 1112, 733; HRMS (ESI)⁺ calcd for C₁₂H₂₃ (M+H), 167.1794; Found, 167.1799.



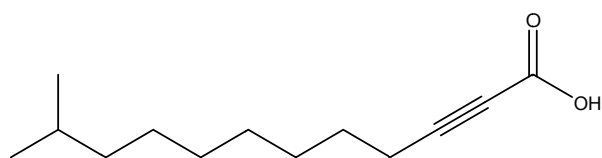


¹H NMR (400 MHz, CDCl₃) δ 0.86 (d, 6H, J=6.61 Hz), 1.07-1.20 (m, 2H), 1.20-1.34 (m, 8H), 1.34-1.44 (m, 2H), 1.46-1.58 (m, 1H), 1.93 (t, 1H, J=2.59 Hz), 2.18 (dt, 2H, J=2.59 Hz, J=7.07 Hz); ¹³C NMR (75 MHz) 18.40, 22.66, 27.34, 27.96, 28.51, 28.77, 29.15, 29.76, 39.01, 68.02, 84.83; IR (ATR) ν_{max} cm⁻¹ 3315, 2954, 2922, 2853, 2121, 1464, 1377, 1239, 867, 629; HRMS (ESI)⁺ calcd for C₁₂H₂₃ (M+H), 167.1794; Found, 167.1798.



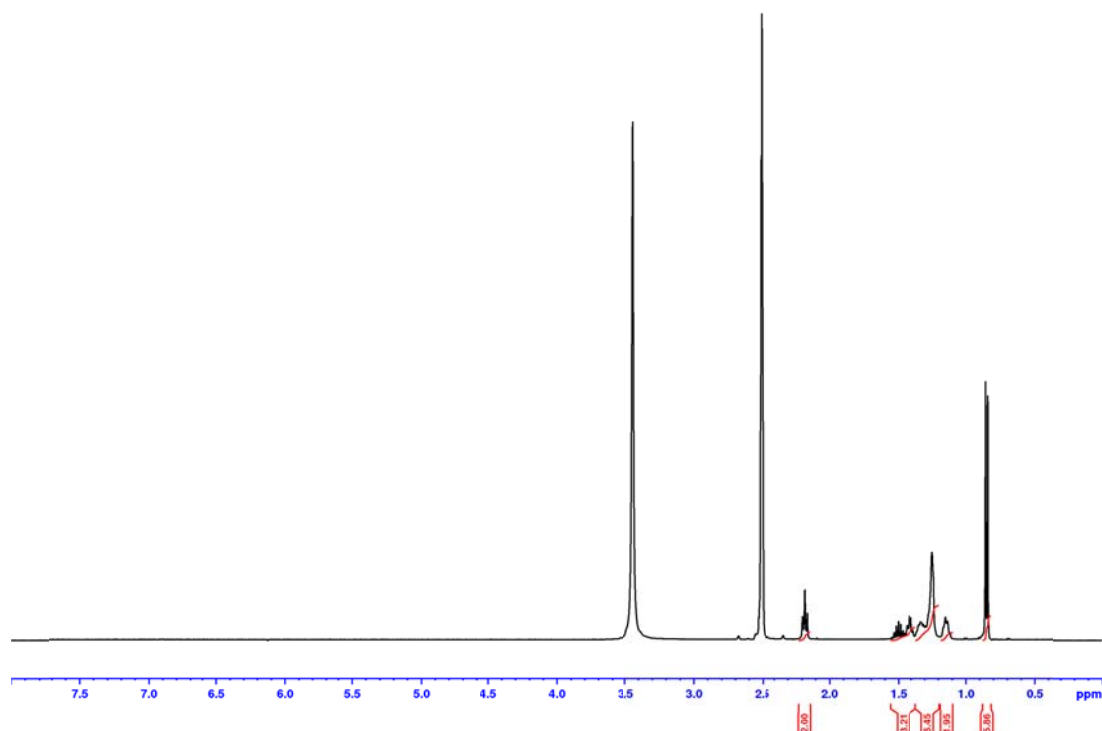


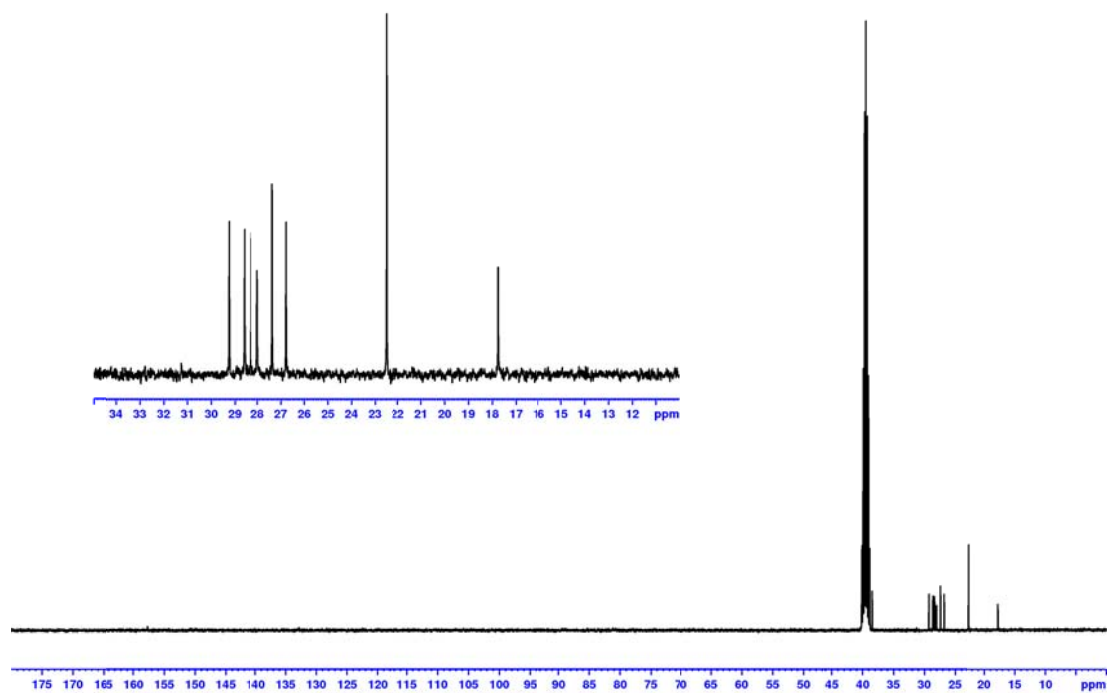
11-Methyldodec-2-ynoic acid (**13**)



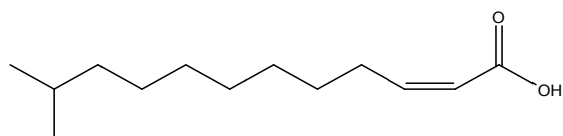
A solution of 10-methylundec-1-yne (**16**) (5.0 g, 30.120 mmol) in 20 mL THF was charged and cooled to -5°C. *n*-BuLi (2.5 M in hexane, 13.25 mL, 33.132 mmol) was added dropwise and stirred for 10 mins. Carbon dioxide gas, generated by adding H₂SO₄ to Na₂CO₃, was passed to the above at 0°C before bringing to room temperature. The reaction mixture was added to 10% aqueous NH₄Cl (25 mL) solution and extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine, dried with MgSO₄, filtered, and evaporated under vacuum. The crude mixture was purified by column chromatography on silica gel using MeOH-DCM (0:100-2:98) to afford a yield of 87% (5.498 g, 26.141 mmol) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 0.85 (d, 6H, J = 6.61 Hz), 1.09-1.19 (m, 2H), 1.19-1.37 (m, 8H), 1.37-1.46 (m, 2H), 1.50 (h, 1H, J = 6.60), 2.17 (t, 2H, J = 6.90 Hz); ¹³C NMR (75 MHz) 17.73, 22.49, 26.76, 27.36, 27.99, 28.30, 28.58, 29.23, 38.42, 157.68; IR (ATR) ν_{max} cm⁻¹ 3437, 2953, 2921, 2850, 2234, 1550, 1504, 1467, 1381, 794, 720, 503, 417; HRMS (ESI)⁺ calcd for C₁₃H₂₃O₂ (M+H), 211.1693; Found, 211.1688.



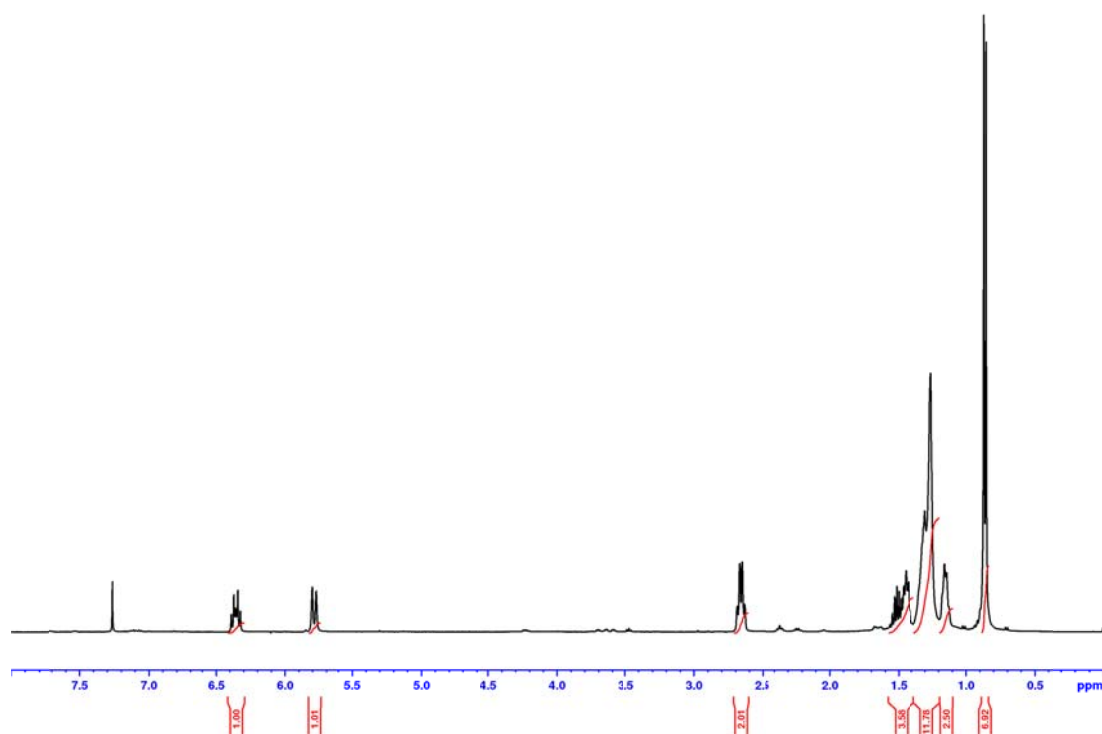


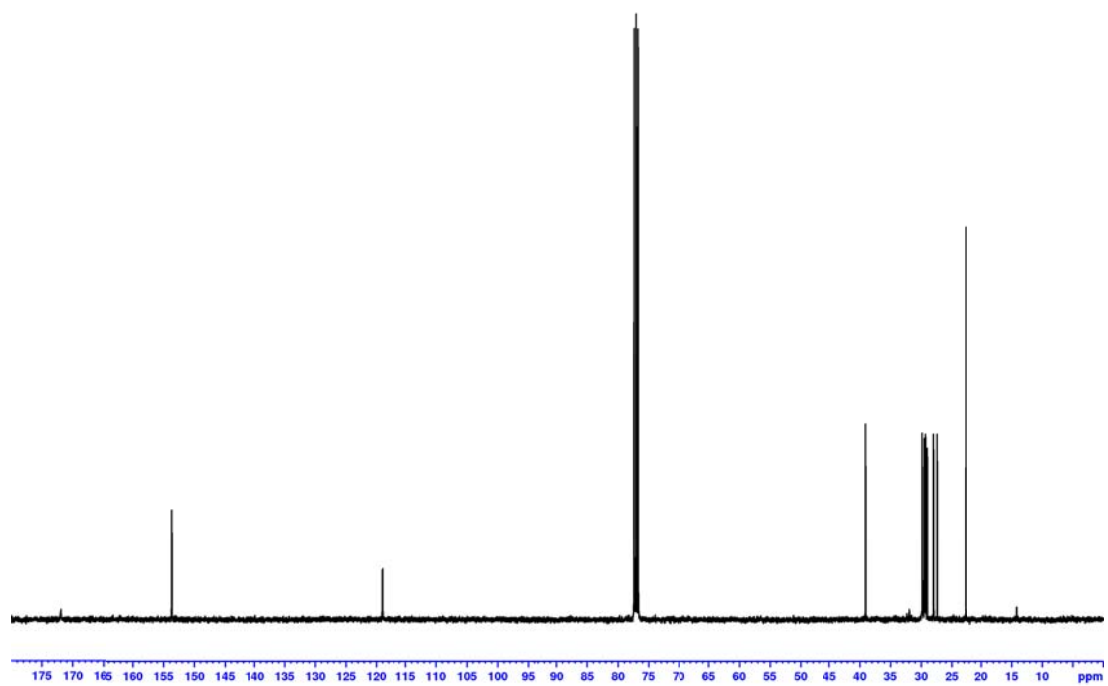
(Z)-11-Methyldodec-2-enoic acid (**1**)



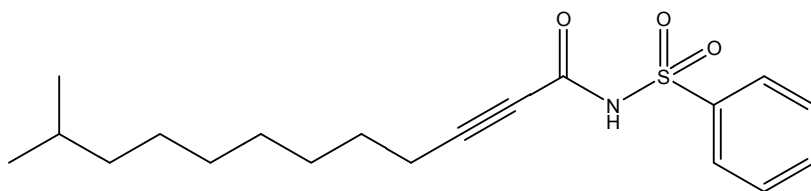
Lindlar's catalyst (400 mg) and (Z)-11-methyldodec-2-ynoic acid (**13**) (450 mg, 2.139 mmol) were added to dichloromethane (15 mL). This solution was shaken vigorously in a 60 PSI hydrogen atmosphere for 24 hrs using a Parr hydrogenator. A further 200 mg of Lindlar's catalyst was added to the mixture and this was shaken for 48 h under the same conditions. The crude mixture was filtered and purified by column chromatography on silica gel using MeOH-DCM (2:98) to afford a yield of 89% (404 mg, 1.902 mmol) as a low melting point, off-white solid.

IR (ATR) ν_{max} cm^{-1} 3044, 2956, 2918, 2849, 2581, 1695, 1636, 1437, 1240, 930, 819, 723, 624, 410; ^1H NMR (400 MHz, CDCl_3) δ 0.86 (d, 6H, $J=6.63$), 1.09-1.18 (m, 2H), 1.19-1.38 (m, 9H), 1.39-1.57 (m, 3H), 2.66 (qd, 2H, $J=1.37$ Hz, $J=7.35$ Hz), 5.78 (d, 1H, $J=11.53$), 6.36 (dt, 1H, $J=7.51$, $J=11.53$); ^{13}C NMR (75 MHz) 22.66, 27.37, 27.96, 28.97, 29.24, 29.29, 29.47, 29.82, 39.02, 118.97, 153.67, 171.90; HRMS (ESI) $^+$ calcd for $\text{C}_{13}\text{H}_{25}\text{O}_2$ (M+H), 213.1849; Found, 213.1854.



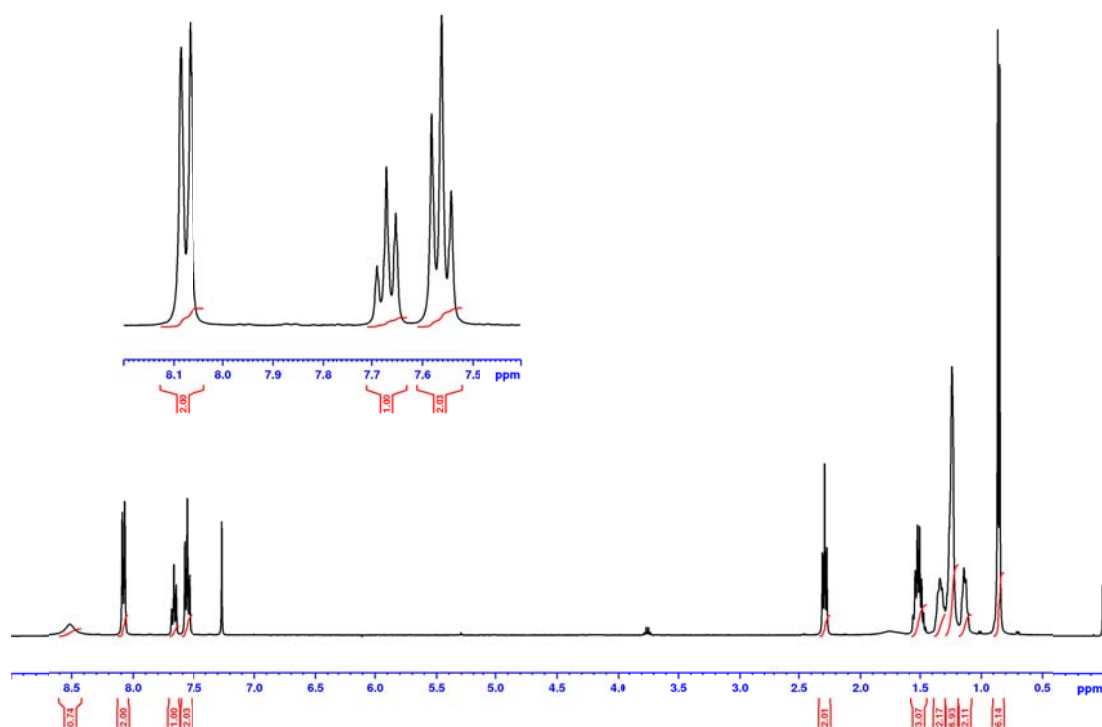


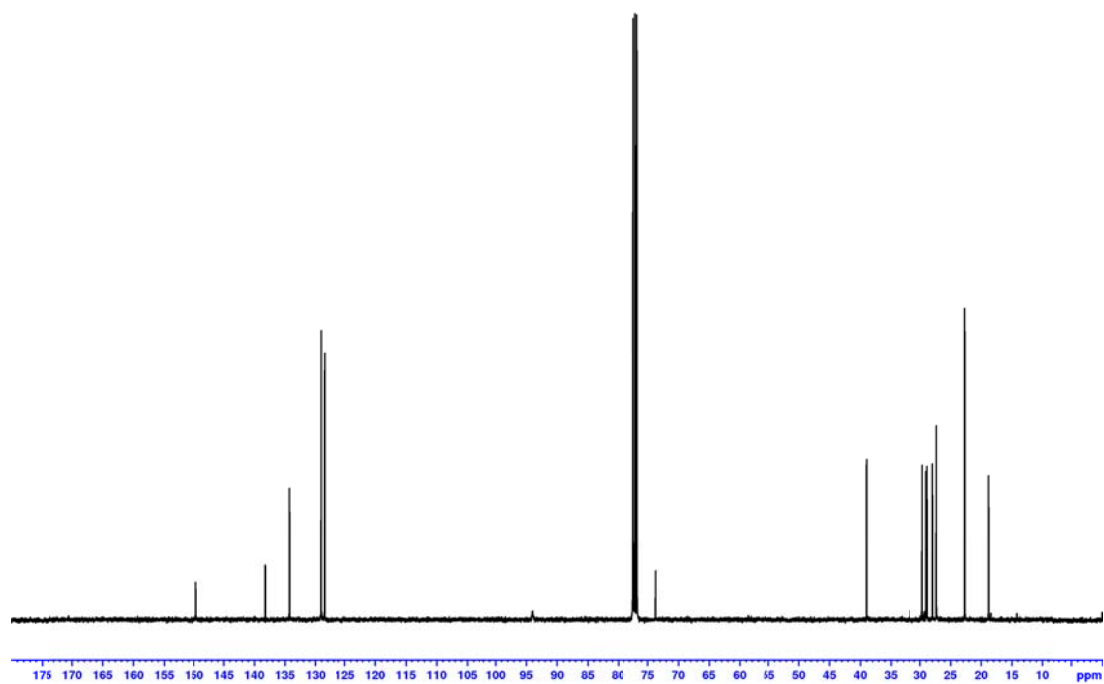
11-Methyl-*N*-(phenylsulfonyl)dodec-2-ynamide (**15**)



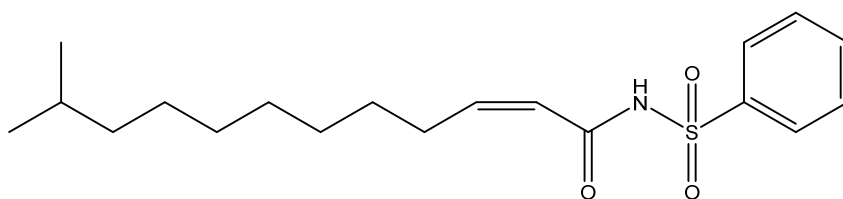
A solution of 11-methyldodec-2-ynoic acid (**13**) (350 mg, 1.664 mmol), DMAP (226 mg, 1.850 mmol), and EDCI (287 mg, 1.850 mmol) in DCM (15 mL) were stirred at 0°C for 15 mins under an atmosphere of N₂. Benzenesulfonamide (277 mg, 1.769 mmol) was added and the mixture stirred for 20 hrs at room temperature. The reaction mixture was poured into 2M aqueous HCl (20 mL) and extracted with DCM (3 x 60 mL). The combined organic extracts were washed with brine, dried with MgSO₄, filtered, and evaporated under vacuum. The crude mixture was purified by column chromatography on silica gel using DCM-MeOH (100:0-98:2) to afford yield of 39% (230 mg, 0.658 mmol) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 0.85 (d, 6H, J=6.63 Hz), 1.08-1.19 (m, 2H), 1.19-1.29, (m, 6H), 1.29-1.39 (m, 2H), 1.45-1.57 (m, 3H), 2.29 (t, 2H, J=7.12 Hz), 7.52-7.61 (m, 2H), 7.67 (t, 1H, J=7.44 Hz), 8.08 (d, 2H, J=7.41 Hz); ¹³C NMR (75 MHz) 18.75, 22.65, 27.37, 27.32, 27.94, 28.83, 29.01, 29.63, 38.95, 73.68, 93.94, 128.48, 129.05, 134.24, 138.21, 149.60; IR (ATR) ν_{max} cm⁻¹ 566, 587, 685, 737, 866, 1057, 1089, 1163, 1218, 1351, 1433, 1450, 1671, 2226, 2855, 2924, 3219; HRMS (ESI)⁺ calcd for C₁₉H₂₈NO₃S (M+H), 350.1784; Found, 350.1783.





(Z)-11-Methyl-N-(phenylsulfonyl)dodec-2-enamide (**14**)



Lindlar's catalyst (100 mg) and 11-methyl-N-(phenylsulfonyl)dodec-2-ynamide (**15**) (160 mg, 0.458 mmol) were added to dichloromethane (6 mL). This solution was shaken vigorously in a 60 PSI hydrogen atmosphere for 6 hrs using a Parr hydrogenator. The crude mixture was filtered and purified by careful column chromatography on silica gel using MeOH-DCM (0:100-1:99) to afford a yield of 64% (103 mg, 0.293 mmol) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 0.86 (d, 6H, $J=6.62$ Hz), 1.08-1.17 (m, 2H), 1.17-1.31 (m, 8H), 1.3-1.43 (m, 2H), 1.50 (h, 1H, $J=6.57$ Hz), 2.49-2.69 (m, 2H), 5.70 (d, 1H, $J=11.39$ Hz), 6.25 (dt, 1H, $J=11.38$ Hz, $J=7.42$ Hz), 7.52-7.61 (m, 2H), 7.65 (t, 1H, $J=7.44$ Hz), 8.09 (d, 2H, $J=7.48$ Hz); ^{13}C NMR (75 MHz) 22.66, 27.35, 27.95, 28.90, 29.25, 29.30, 29.43, 29.78, 39.01, 118.75, 128.30, 129.04, 133.93, 138.73, 154.07, 162.82; IR (ATR) ν_{max} cm^{-1} 563, 595, 684, 718, 756, 847, 864, 1088, 1140, 1187, 1346, 1438, 1453, 1633, 1696, 2851, 2919, 3278; HRMS (ESI) $^+$ calcd for $\text{C}_{19}\text{H}_{30}\text{NO}_3\text{S}$ (M+H), 352.1941; Found, 352.1938.

