Supplementary Material (ESI) for Chemical Communications

Intramolecular Prins Cyclizations for the Synthesis of Bicyclic Tetrahydropyrans

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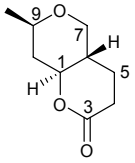
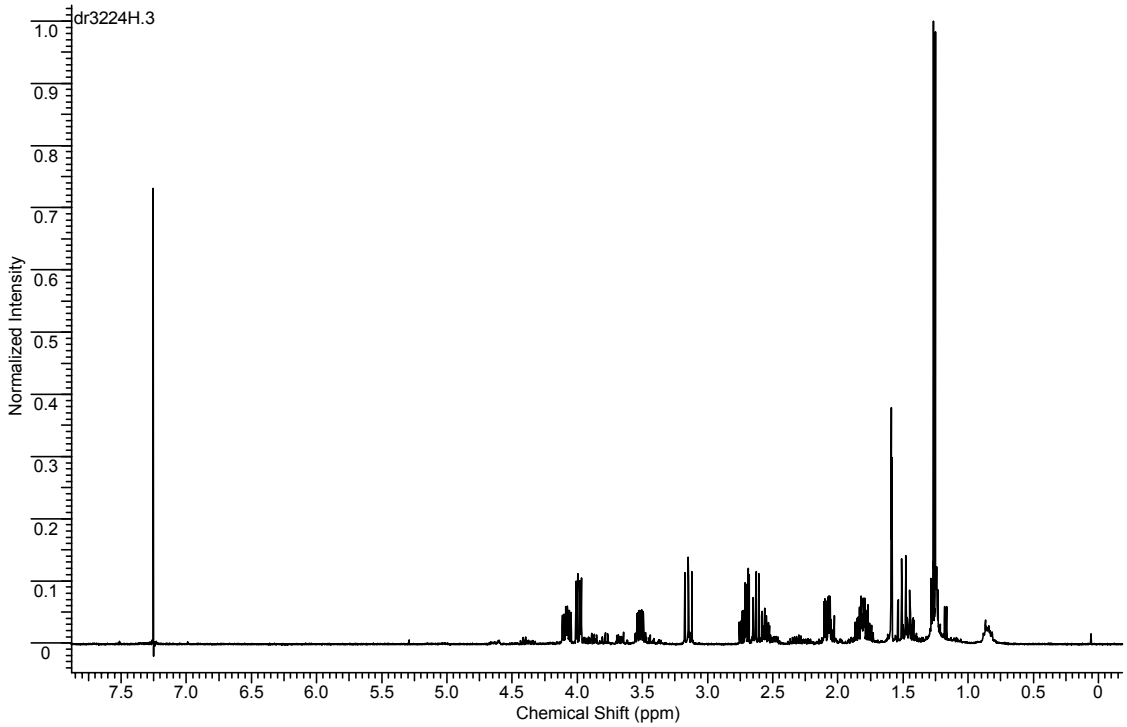
Supporting Information

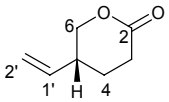
General Procedure for the Prins Cyclisation of 1. Acid (0.1 eq, 0.1 mmol) was added dropwise to a stirred solution of acetal **1** (1.0 mmol) in dry DCM (25) at RT under a nitrogen atmosphere. The solution was stirred for 1-4 h and quenched with the addition of saturated aqueous $NaHCO_3$ (20 ml). The layers were separated and the aqueous fraction extracted with DCM (3 x 25 ml). The combined organic fractions were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was purified by flash column chromatography on silica gel, eluting with 35-50% EtOAc in Petrol to give tetrahydropyran **2** or lactone **3**.



2

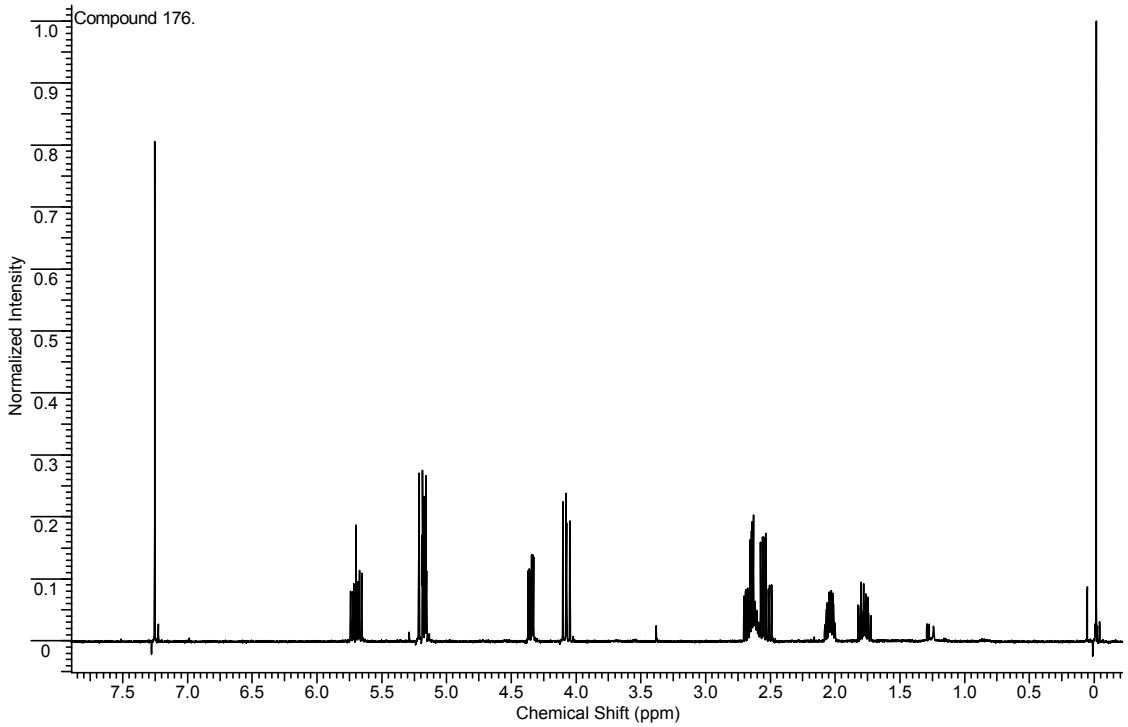
2. Colourless oil: silica gel TLC 0.08 (20% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.1, 9-CH_3), 1.42-1.54 (2H, m, 10-H_{ax} and 5-*H*H), 1.74-1.87 (2H, m, 6-H and 5-H*H*), 2.09 (1H, ddd, *J* 12.7, 4.4, 2.2, 10-H_{eq}), 2.62 (1H, m, 4-H_{ax}), 2.73 (1H, ddd, *J* 18.3, 8.3, 3.7, 4-H_{eq}), 3.15 (1H, t, *J* 11.7, 7-H_{ax}), 3.53 (1H, m, 9-H), 4.0 (1H, dd, *J* 11.7, 4.4, 7-H_{eq}), 4.10 (1H, dt, *J* 10.3, 4.4, 1-H); δ_c (100 MHz, $CDCl_3$) 21.0 (C-5), 21.4 (9-CH_3), 29.2 (C-4), 37.9 (C-6), 39.2 (C-10), 69.6 (C-7), 72.2 (C-9), 80.0 (C-1), 170.8 (C-3); *m/z* (CI) 171 ($[MH]^+$, 31%; found: 171.1020, $C_9H_{15}O_3$ requires: 171.1021) 153 (33), 127 (100), 83 (64).



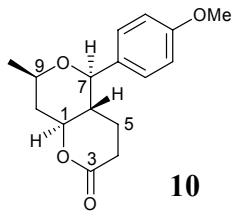


3

3. Colourless oil: silica gel TLC *Rf* 0.41 (50% EtOAc/petrol); $[\alpha]_D^{22}$ –8.0 (*c* 0.13, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2954 (CH), 1729 (C=O), 1642 (C=C), 1240 and 1049 (C-O); δ_H (400 MHz, $CDCl_3$) 1.79 (1H, dtd, *J* 13.6, 9.6, 7.0, 4-H_{ax}), 2.05 (1H, ddtd, *J* 13.6, 7.0, 4.8, 2.0, 4-H_{eq}), 2.55 (1H, ddd, *J* 18.0, 9.6, 7.0, 3-*H*H), 2.64 (1H, m, 5-H), 2.68 (1H, ddd, *J* 18.0, 7.0, 4.8, 3-H*H*), 4.09 (1H, dd, *J* 11.2, 9.8, 6-H_{ax}), 4.36 (1H, ddd, *J* 11.2, 4.8, 2.0, 6-H_{eq}), 5.19 (1H, dt, *J* 10.4, 1.2, 2'-H_{cis}), 5.21 (1H, dt, *J* 17.2, 1.2, 2'-H_{trans}), 5.71 (1H, ddd, *J* 17.2, 10.4, 6.7, 1'-H); δ_C (100 MHz, $CDCl_3$) 25.2 (C-4), 28.8 (C-3), 36.8 (C-5), 72.5 (C-6), 117.3 (C-2'), 135.8 (C-1'), 170.7 (C-2); Found (CI): 127.0763 $[MH]^+$, ($C_7H_{11}O_2$ requires 127.0759); *m/z* (CI) 127 ($[MH]^+$, 100%), 107 (75), 81 (60).

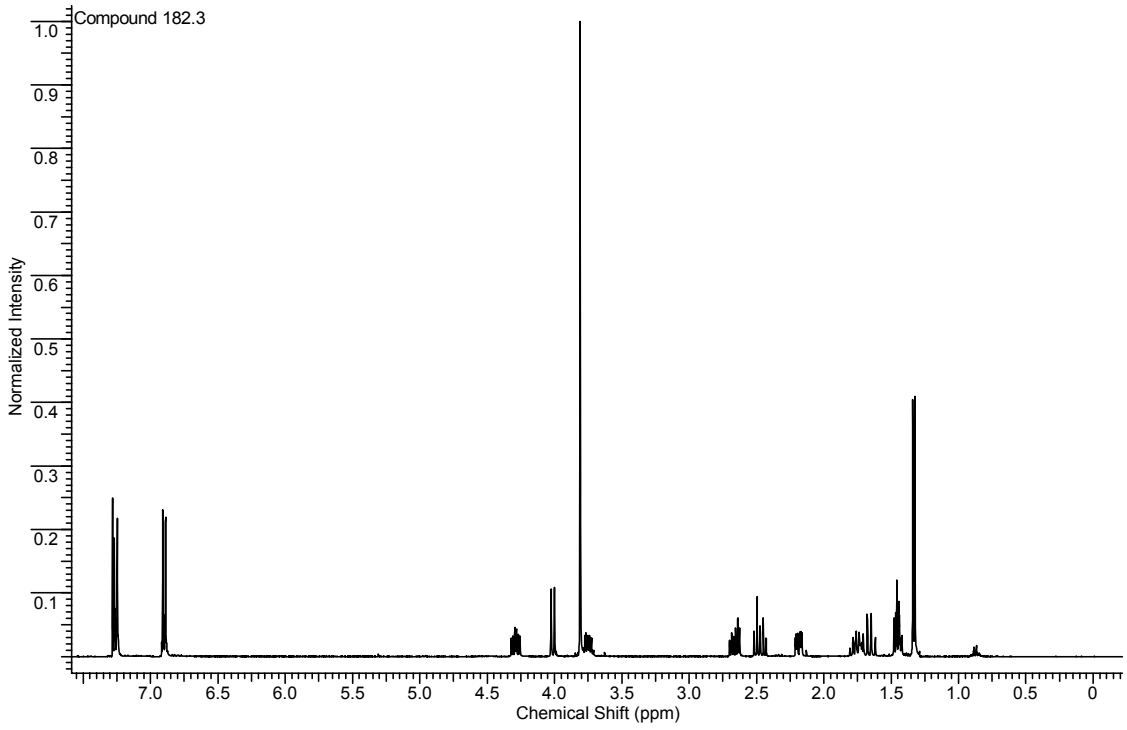


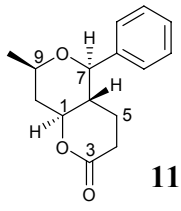
General Procedure for the Prins Cyclisation of 9. TMS triflate (1.0 eq, 1.5 mmol) was added to a stirred solution of homoallylic alcohol (1.5 mmol) and aldehyde (1.1 eq, 1.65 mmol) in dry DCM (25 ml) at -10 ºC under a nitrogen atmosphere. The solution was stirred at -10 ºC for 15 mins and quenched with the addition of saturated aqueous $NaHCO_3$ (30 ml) and DCM (10 ml). The layers were separated and the aqueous layer extracted with DCM (2 x 50 ml). The combined organic fractions were washed with water (100 ml) and brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant yellow oil was purified by column chromatography on silica gel, eluting with 35% EtOAc in Petrol to give the tetrahydropyran product **10-16**.



10

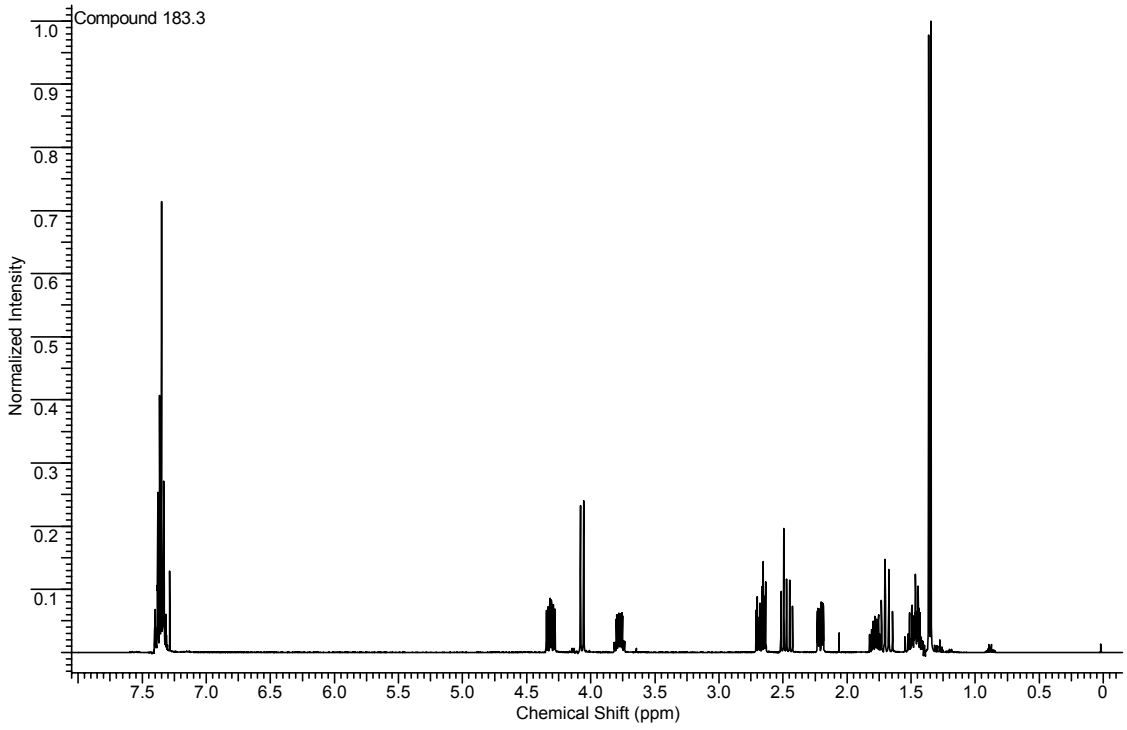
10. Colourless crystalline solid (recrystallised from EtOAc/petrol): silica gel TLC *Rf* 0.25 (40% EtOAc/petrol); mp 98-100 ºC; $[\alpha]_D^{23}$ –27.7 (*c* 2.70, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2932 and 2839 (CH), 1732 (C=O), 1612 (C=C), 1243 and 1031 (C-O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.1, 9-CH_3), 1.41-1.47 (2H, m, 5-H_2), 1.65 (1H, dt, *J* 12.5, 11.5, 10-H_{ax}), 1.75 (1H, m, 6-H), 2.18 (1H, ddd, *J* 12.5, 4.6, 2.0, 10-H_{eq}), 2.46 (1H, dt, *J* 18.0, 8.4, 4-*H*H), 2.65 (1H, dt, *J* 18.0, 6.2, 4-H*H*), 3.74 (1H, m, 9-H), 3.80 (3H, s, OCH_3), 4.00 (1H, d, *J* 9.8, 7-H), 4.28 (1H, ddt, *J* 11.5, 10.5, 4.6, 1-H), 6.87 (2H, d, *J* 8.7, Ar-H), 7.24 (2H, d, *J* 8.7, Ar-H); δ_C (100 MHz, $CDCl_3$) 21.5 (C-5), 21.6 (9-CH_3), 29.2 (C-4), 39.4 (C-10), 43.5 (C-6), 55.3 (OCH_3), 71.9 (C-9), 80.1 (C-1), 82.0 (C-7), 114.0 and 128.3 (C-Ar), 130.9 and 159.6 (C-Ar_{ipso}), 170.8 (C-3); Found (CI): 277.1429 $[MH]^+$, ($C_{16}H_{21}O_4$ requires 277.1439); *m/z* (CI) 277 ($[MH]^+$, 35%), 169 (21), 137 (100), 123 (15), 79 (22).

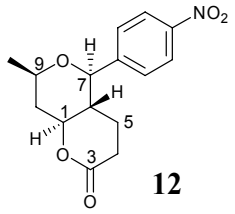




11

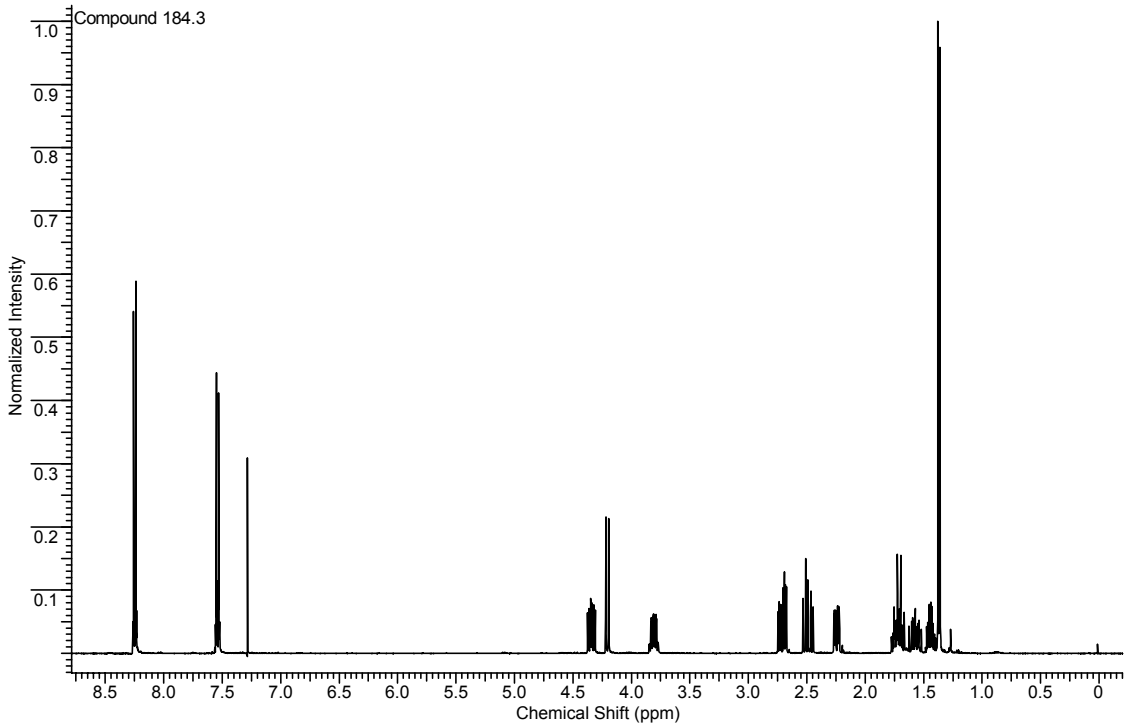
11. Colourless crystalline solid (recrystallised from EtOAc/petrol): silica gel TLC *Rf* 0.29 (40% EtOAc/petrol); mp 124-126 ºC; $[\alpha]_D^{19}$ –26.3 (*c* 1.80, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3061, 3036, 2975, 2935, 2889 and 2871 (CH), 1723 (C=O), 1602 (C=C), 1215 and 1026 (C-O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.1, 9-CH_3), 1.38-1.50 (2H, m, 5-H_2), 1.66 (1H, dt, *J* 12.2, 11.1, 10-H_{ax}), 1.75 (1H, dtd, *J* 16.1, 10.0, 5.9, 6-H), 2.18 (1H, ddd, *J* 12.2, 4.6, 2.0, 10-H_{eq}), 2.45 (1H, dt, *J* 18.1, 8.7, 4-*H*H), 2.65 (1H, dt, *J* 18.1, 7.8, 4-H*H*), 3.75 (1H, dqd, *J* 11.1, 6.1, 2.0, 9-H), 4.05 (1H, d, *J* 10.0, 7-H), 4.29 (1H, ddd, *J* 11.1, 10.0, 4.6, 1-H), 7.29-7.38 (Ar-H); δ_C (100 MHz, $CDCl_3$) 21.4 (C-5), 21.6 (9-CH_3), 29.2 (C-4), 39.4 (C-10), 43.5 (C-6), 71.9 (C-9), 78.0 (C-1), 82.4 (C-7), 127.1, 128.4 and 128.5 (C-Ar) 138.7 (C-Ar_{ipso}), 170.7 (C-3); Found (CI): 247.1326 $[MH]^+$, ($C_{15}H_{19}O_3$ requires 247.1334); *m/z* (CI) 247 ($[MH]^+$, 9%), 229 (5), 203 (4), 169 (15), 141 (100), 123 (17), 107 (11), 89 (25), 61 (36); Found C, 72.71; H, 7.41; $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37.

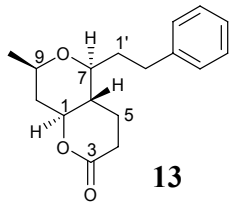




12

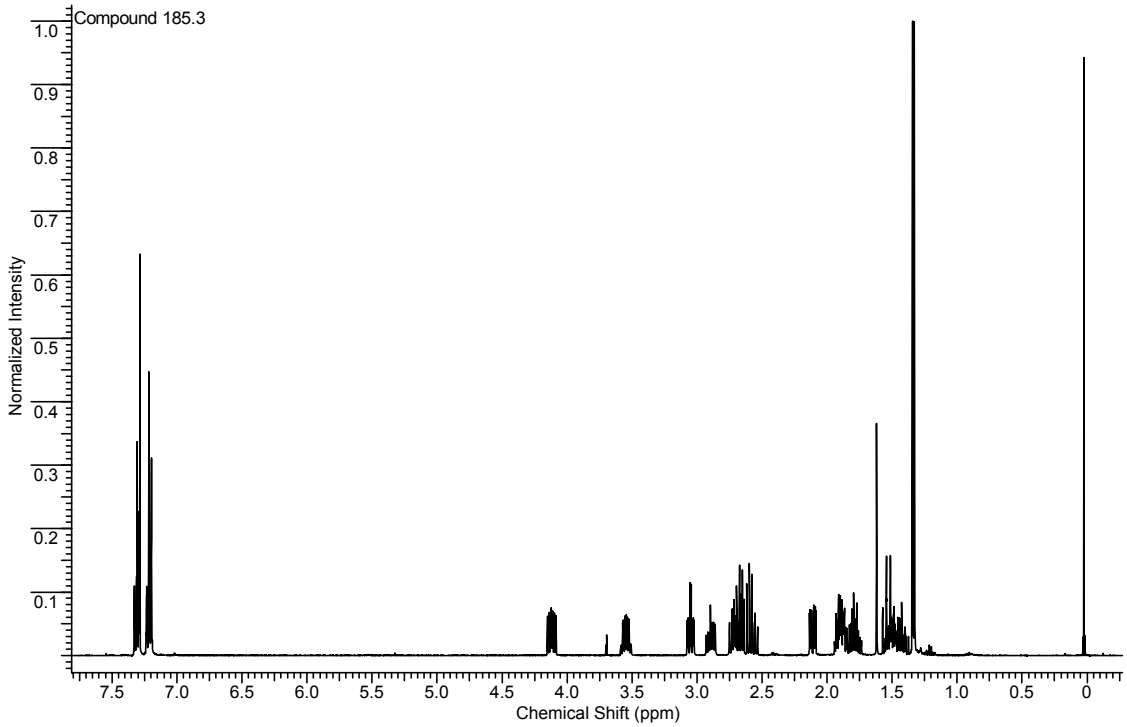
12. Pale yellow crystalline solid (recrystallised from EtOAc/petrol): silica gel TLC *Rf* 0.11 (40% EtOAc/petrol); mp 144-146 ºC; $[\alpha]_D^{19}$ –14.3 (*c* 1.70, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3108, 3079, 2968, 2982, 2903 and 2877 (CH), 1729 (C=O), 1600 (C=C), 1517 and 1348 (NO_2), 1070 and 1039 (C-O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.1, 9-CH_3), 1.43 (1H, m, 5-*H*H), 1.56 (1H, m, 5-H*H*), 1.70 (1H, dt, *J* 12.8, 11.3, 10-H_{ax}), 1.73 (1H, dtd, *J* 11.7, 10.0, 4.9, 6-H), 2.23 (1H, ddd, *J* 12.8, 4.6, 2.0, 10-H_{eq}), 2.47 (1H, dt, *J* 18.1, 8.4, 4-*H*H), 2.69 (1H, ddd, *J* 18.1, 8.1, 3.7, 4-H*H*), 3.80 (1H, dqd, *J* 11.3, 6.1, 2.0, 9-H), 4.19 (1H, d, *J* 10.0, 7-H), 4.33 (1H, ddd, *J* 11.3, 10.0, 4.4, 1-H), 7.53 (2H, d, *J* 8.7, Ar-H_2), 8.24 (2H, d, *J* 8.7, Ar-H_2); δ_C (100 MHz, $CDCl_3$) 21.2 (C-5), 21.4 (9-CH_3), 28.9 (C-4), 39.2 (C-10), 43.4 (C-6), 72.1 (C-9), 79.4 (C-1), 81.2 (C-7), 123.7 and 127.9 (C-Ar), 145.9 and 147.8 (C-Ar_{ipso}), 170.1 (C-3); Found (CI): 292.1184 $[MH]^+$, ($C_{15}H_{18}NO_5$ requires 292.1185); *m/z* (CI) 292 ($[MH]^+$, 96%), 169 (10), 141 (100), 123 (16), 98 (5), 81 (6).

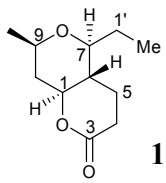




13

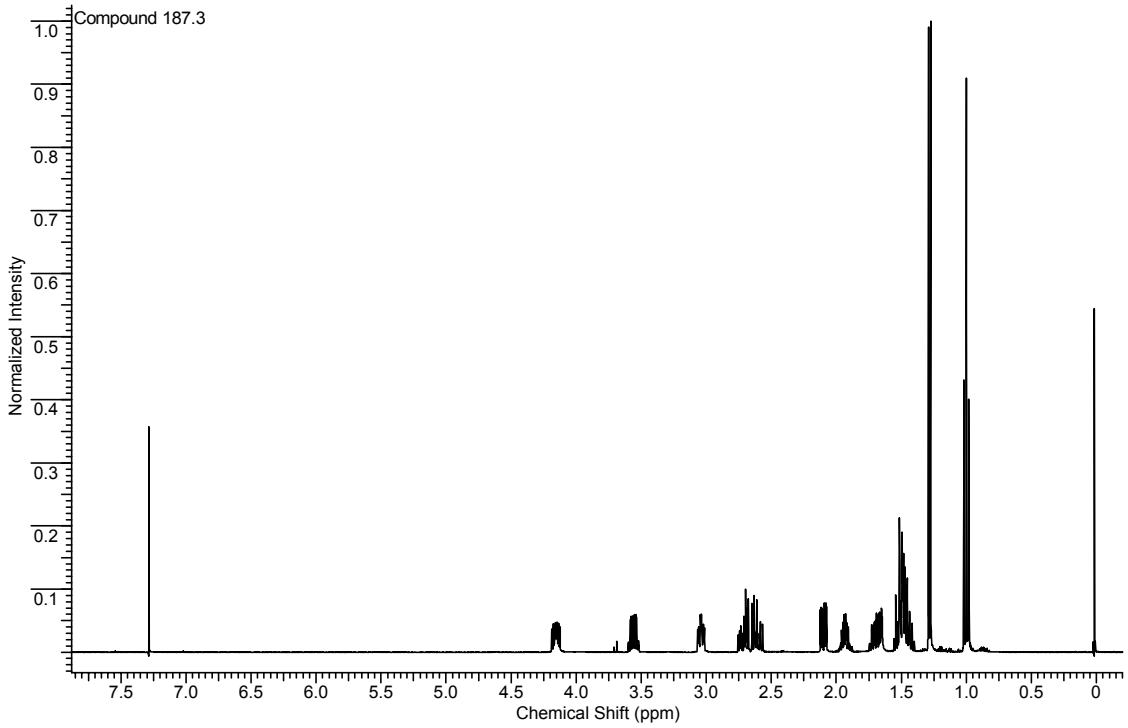
13. Colourless oil: silica gel TLC *Rf* 0.45 (40% EtOAc/petrol); $[\alpha]_D^{21}$ –78.3 (*c* 2.30, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2971 and 2927 (CH), 1735 (C=O), 1603 (C=C), 1032 (C-O); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.1, 9-CH_3), 1.37-1.53 (2H, m, 5-*H*H and 6-H), 1.50 (1H, dt, *J* 12.5, 11.2, 10-H_{ax}), 1.76 (1H, m, 1'-*H*H), 1.82-1.92 (2H, m, 5-H*H* and 1'-H*H*), 2.09 (1H, ddd, *J* 12.5, 4.6, 2.0, 10-H_{eq}), 2.55 (1H, ddd, *J* 17.8, 8.1, 5.6, 4-*H*H), 2.61-2.73 (2H, m, 4-HH and 2'-*H*H), 2.87 (1H, ddd, *J* 13.9, 9.0, 4.9, 2'-H*H*), 3.03 (1H, td, *J* 9.3, 2.7, 7-H), 3.52 (1H, dqd, *J* 11.2, 6.1, 2.0, 9-H), 4.09 (1H, ddd, *J* 11.2, 10.0, 4.6, 1-H), 7.16-7.21 (3H, m, Ar-H), 7.26-7.31 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 20.9 and 21.6 (C-5 and 9-CH_3), 28.9 (C-4), 31.3 (C-2'), 34.1 (C-1'), 39.3 (C-10), 41.9 (C-6), 71.3 (C-9), 77.8 (C-7), 79.7 (C-1), 125.9, 128.4 and 128.5 (C-Ar), 141.8 (C-Ar_{ipso}), 171.1 (C-3); Found (CI): 275.1640 $[MH]^+$, ($C_{17}H_{23}O_3$ requires 275.1647); *m/z* (CI) 275 ($[MH]^+$, 30%), 231 (5), 169 (13), 141 (100), 123 (15), 117 (5), 91 (8).

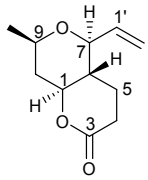




14

14. Colourless oil: silica gel TLC *Rf* 0.34 (40% EtOAc/petrol); $[\alpha]_D^{21}$ −102.1 (*c* 2.90, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2971, 2933 and 2878 (CH), 1735 (C=O), 1041 (C-O); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 7.8, 2'-H_3), 1.27 (3H, d, *J* 6.4, 9-CH_3), 1.38-1.54 (3H, m, 5-*H*H, 6-H and 1'-*H*H), 1.49 (1H, dt, *J* 12.5, 11.5, 10-H_{ax}), 1.68 (1H, ddq, *J* 15.1, 7.8, 3.0, 1'-H*H*), 1.92 (1H, m, 5-H*H*), 2.08 (1H, ddd, *J* 12.5, 4.6, 2.0, 10-H_{eq}), 2.59 (1H, ddd, *J* 17.8, 8.5, 7.3, 4-*H*H), 2.70 (1H, ddd, *J* 17.8, 8.5, 4.6, 4-H*H*), 3.03 (1H, td, *J* 9.0, 3.0, 7-H), 3.54 (1H, dqd, *J* 11.5, 6.4, 2.0, 9-H), 4.14 (1H, ddd, *J* 11.5, 10.0, 4.6, 1-H); δ_C (100 MHz, $CDCl_3$) 9.6 (C-2'), 21.0 (C-5), 21.5 (9-CH_3), 25.3 (C-1'), 29.0 (C-4), 39.3 (C-10), 41.4 (C-6), 71.2 (C-9), 79.9 and 80.0 (C-1 and C-7), 171.1 (C-3); Found (CI): 199.1336 $[MH]^+$, ($C_{11}H_{19}O_3$ requires 199.1334); *m/z* (CI) 199 ($[MH]^+$, 10%), 181 (5), 169 (7), 155 (8), 141 (100), 123 (20), 95 (7), 84 (21), 56 (8).

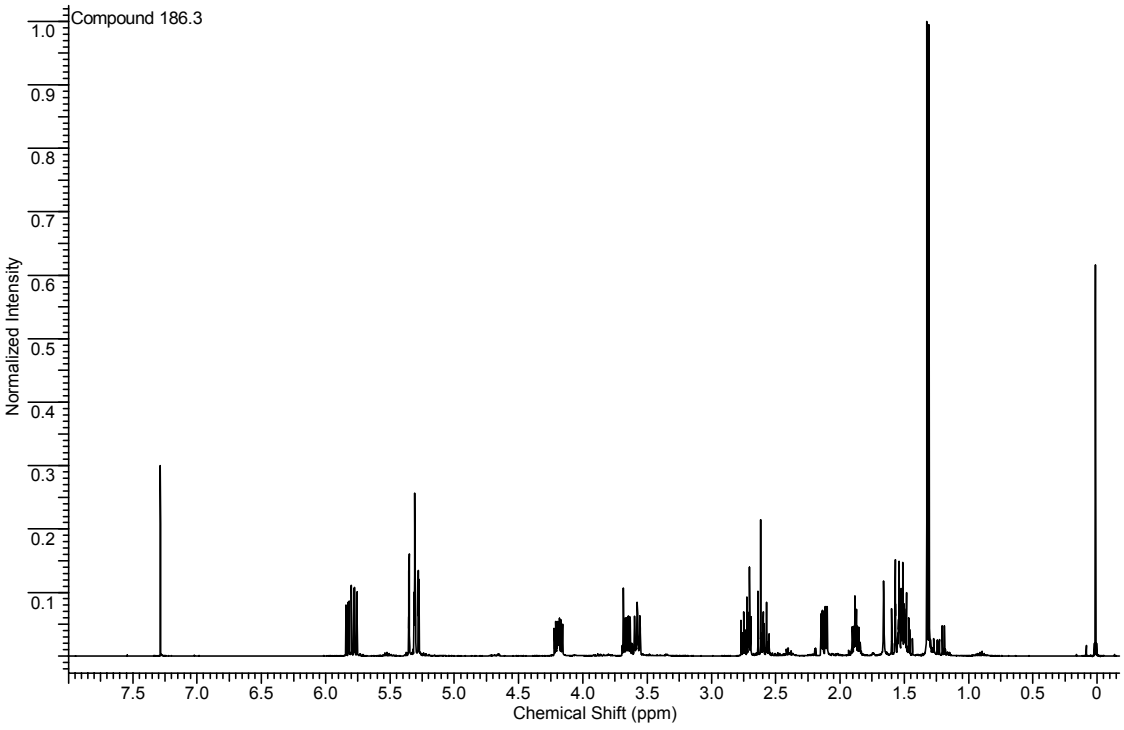


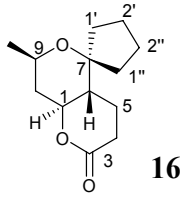


15

15. Pale yellow oil: silica gel TLC *Rf* 0.25 (40% EtOAc/petrol); $[\alpha]_D^{18}$ –56.5 (*c* 1.10, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2973, 2932 and 2876 (CH), 1734 (C=O), 1647 (C=C), 1200 and 1040 (C-O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.3, 9-CH_3), 1.42-1.56 (2H, m, 5-*H*H and 6-H), 1.54 (1H, dt, *J* 12.5, 11.5, 10-H_{ax}), 1.86 (1H, m, 5-H*H*), 2.11 (1H, ddd, *J* 12.5, 4.6, 2.0, 10-H_{eq}), 2.58 (1H, dt, *J* 18.1, 8.3, 4-*H*H), 2.72 (1H, ddd, *J* 18.1, 8.3, 4.4, 4-H*H*), 3.56 (1H, m, 7-H), 3.64 (1H, dqd, *J* 11.5, 6.3, 2.0, 9-H), 4.18 (1H, ddd, *J* 11.5, 10.0, 4.6, 1-H), 5.27 (1H, ddd, *J* 10.3, 1.5, 1.0, 2'-H_{cis}), 5.32 (1H, ddd, *J* 17.2, 1.5, 1.0, 2'-H_{trans}), 5.79 (1H, ddd, *J* 17.2, 10.3, 7.6, 1'-H); δ_C (100 MHz, $CDCl_3$) 21.3 (C-5), 21.5 (9-CH_3), 29.2 (C-4), 39.1 (C-10), 41.6 (C-6), 71.3 (C-9), 79.7 (C-1), 81.1 (C-7), 118.8 (C-2'), 135.3 (C-1'), 170.9 (C-3); Found (CI): 197.1178 $[MH]^+$, ($C_{11}H_{17}O_3$ requires 197.1171);

m/z (CI) 197 ([MH]$^+$, 13%), 179 (2), 169 (3), 153 (6), 141 (100), 123 (19), 95 (7), 84 (11), 56 (11).





16

16. Colourless crystalline solid (recrystallised from EtOAc/petrol): silica gel TLC *Rf* 0.40 (40% EtOAc/petrol); mp 54-56 ºC; $[\alpha]_D^{19}$ –22.6 (*c* 2.70, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2955 and 2869 (CH), 1733 (C=O), 1202 and 1042 (C-O); δ_H (400 MHz, $CDCl_3$) 1.21 (3H d, *J* 6.1, 9-CH_3), 1.43-1.61 (4H, m, 5-*H*H and 3H from 1'-H_2, 1"-H_2, 2'-H_2 and 2"-H_2), 1.44 (1H, dt, *J* 12.2, 11.2, 10-H_{ax}), 1.68-1.83 (5H, m, from 1'-H_2, 1"-H_2, 2'-H_2 and 2"-H_2), 1.78 (1H, td, *J* 11.2, 4.9, 6-H), 1.88 (1H, ddt, *J* 13.1, 7.3, 4.9, 5-H*H*), 2.06 (1H, ddd, *J* 12.2, 4.6, 2.2, 10-H_{eq}), 2.56 (1H, ddd, *J* 17.6, 9.0, 7.3, 4-*H*H), 2.70 (1H, ddd, *J* 17.6, 7.3, 4.9, 4-H*H*), 3.66 (1H dqd, *J* 11.2, 6.1, 2.2, 9-H), 4.23 (1H, td, *J* 11.2, 4.6, 1-H); δ_C (100 MHz, $CDCl_3$) 21.2 (C-5), 21.9 (9-CH_3), 23.4, 25.4 and 28.8 (from C-1', C-1", C-2' and C-2"),

30.1 (C-4), 38.7 (from C-1', C-1", C-2' and C-2"), 40.1 (C-10), 43.8 (C-6), 65.0 (C-9), 78.7 (C-1), 86.3 (C-7), 170.9 (C-3); Found (CI): 225.1488$[MH]^+$, ($C_{13}H_{21}O_3$ requires 225.1491); *m/z* (CI) 225 ($[MH]^+$, 6%), 207 (4), 195 (3), 181 (16), 169 (5), 163 (4), 151 (3), 141 (100), 123 (23), 95 (8), 84 (25), 56 (10); Found C, 69.70; H, 8.98; $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99.