Electronic Supplementary Material (ESI) for ChemComm.

First enantioselective total synthesis and configurational assignments of suberosenone and suberosanone as potential antitumor agents

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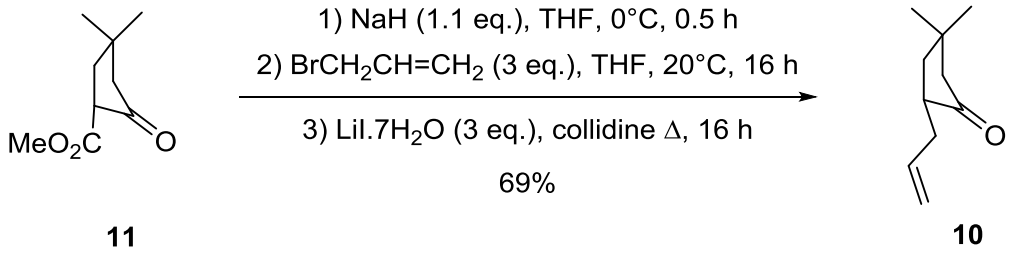
General methods

All operations involving air or moisture sensitive materials were performed under a dry argon atmosphere using syringes, oven-dried glassware, and freshly dried solvents (THF, toluene and CH_2Cl_2 were purified by passage through a solvent drying column and stored under argon over 3Å molecular sieves). Air and moisture-sensitive liquids, reagents and solvents were transferred via syringe using standard techniques. All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Organic solutions were concentrated by rotary evaporation (house vacuum, *ca*. 40 Torr) at 30 °C, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel 60 F254 (0.25 mm thickness) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), and/or submersion in aqueous ceric ammonium molybdate solution (CAM), acidic *p*-anisaldehyde solution (PAA), followed by brief (*ca*. 30 s) heating on a stream of hot air (*ca*. 300 °C). Flash column chromatography was performed as described by Still *et al*.[1] employing silica gel (60 Å pore size, 40-63 mm). IR spectra were recorded as thin films for oils and for solids by the reflexion method on a FT IR spectrometer. NMR spectra were run in $CDCl_3$ at 300 or 400 MHz for ^1H and at 75 or 100 MHz for ^{13}C in $CDCl_3$ using as internal standards the residual $CHCl_3$ signal for ^1H NMR (δ = 7.26) and the deuterated solvent signal for ^{13}C NMR (δ = 77.0). Chemical shifts are expressed in ppm downfield from TMS. Data are reported as follows: chemical shift (multiplicity [s: singlet, d: doublet, t: triplet, q: quartet, Q: quintuplet, m: multiplet, br: broad), coupling constants (*J*) in Hertz, integration]. A combination of 2D COSY, HSQC, HMBC and nOe experiments was used to aid assignment and establish the relative stereochemistry when necessary. Low resolution mass spectra were obtained with an ion trap (ESI source) by the FAB method. High resolution mass spectra were realized either by electronic impact (EI) or by electrospray impact (ESI) and atmospheric pressure chemical ionisation (APCI). Melting points were measured on a digital melting point capillary apparatus and were uncorrected. Specific optical rotations were measured in solution using sodium light (D line 589 nm).

[1] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

Key synthetic procedures[2]

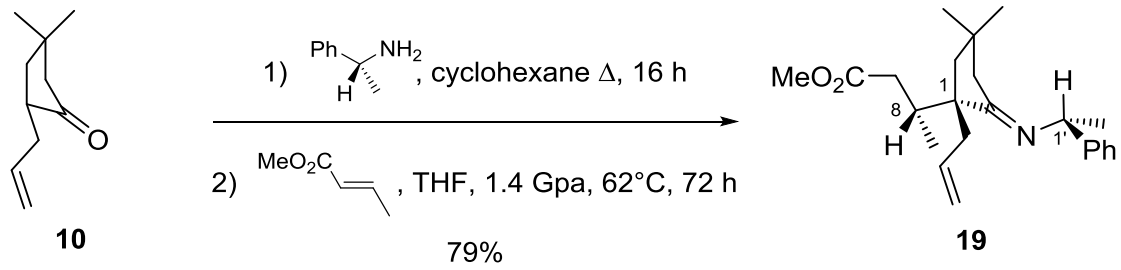
Synthesis of 2-allyl-4,4-dimethylcyclopentanone 10[3]



11 **10**

Scale: keto-ester **11** (21.106 g, 124 mmol). Yield: **10** (13,025 g, 69%) as a colorless oil.

Synthesis of imine 19 and determination of the diastereomeric excess



10 **19**

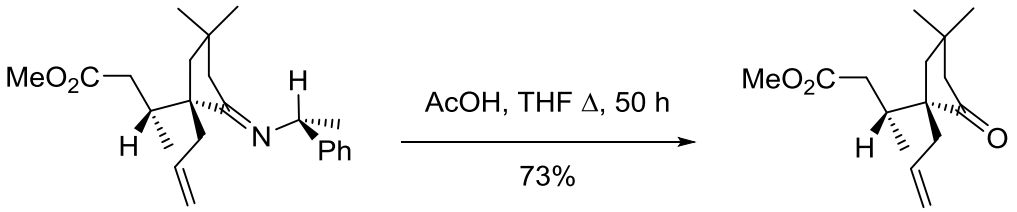
Allyl ketone **10** (16 g, 105,1 mmol), (*R*)-(+)-1-phenylethylamine (15 mL, 116 mmol, 1.1 equiv) and cyclohexane (22 mL) were added in a 100 mL flask equipped with a Dean Stark. The mixture was refluxed for 16 hours and cyclohexane was distilled off via the Dean-Stark trap. The residue obtained was distilled under reduced pressure (Eb 0.005 = 106-108 °C) to give (1'*R*)-*N*-(2-allyl-4,4-dimethylcyclopentylidene)-1-phenylethanamine (22.01 g, 82%) (1:1 mixture of diasteromers) as a colorless oil. This imine (1.78 g, 7 mmol), methyl crotonate (0.76 mL, 7.1 mmol, 1.0 equiv) and dried THF (1 mL) were added into a piston-cylinder teflon cell designed for high pressure. The mixture was compressed under a pressure of 1.4 GPa for 72 hours at 62 °C. After decompression and solvent removal, the imine **19** (2.40 g, 96%) was obtained as a colorless viscous oil. The presence of other potential regio- or diastereomer(s) was not detected on the ^{1}H NMR and ^{13}C spectra, which is in accordance with a de>95% and consequently a high diastererocontrol of the reaction process. The relative stereochemistry of the Michael adduct **19** could not be determined by 2D-NOESY analysis.

[2] Intermediates not appearing in the manuscript are numbered in the Supporting Information beginning with **19**.
[3] A. Padwa, D. J. Austin, S. F. Hornbuckle, M. A. Semones, *J. Am. Chem. Soc.* **1992**, *114*, 1874.

However its elaboration to (-)-suberosenone and the analogy to close addition products[4] made its relative stereochemistry assignment possible as (1'*R*,1*S*,8*R*).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.17 (m, 5H), 5.90-5.74 (m, 1H), 5.01-4.91 (m, 2H), 4.45 (q, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 2.88 (dd, *J* = 14.9, 2.8 Hz, 1H), 2.42-1.91 (m, 6H), 1.69 (d, *J* = 14.0 Hz, 1H),1.58 (d, *J* = 14.0 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 3H), 1.11 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 174.4, 146.4, 136.2, 128.2, 126.6, 126.4, 117.2, 61.7, 53.3, 51.5, 45.7, 44.9, 41.6, 37.3, 36.9, 34.7, 31.4, 31.0, 24.9, 15.5; IR (neat) 3063, 3026, 2953, 2867, 1737, 1668, 1637 cm^{-1}.

Synthesis of keto-ester (-)-9



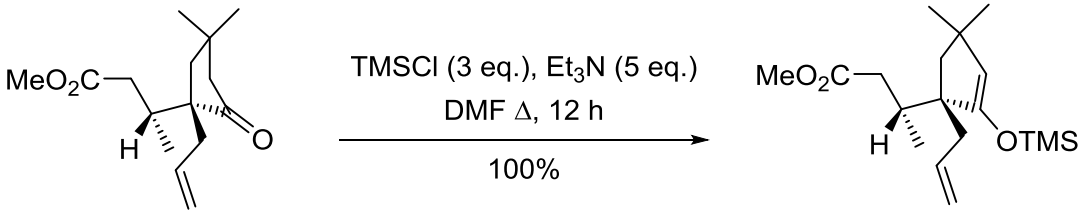
19 **9**

Imine **19** (2.28 g, 6.4 mmol) and acetic acid (20%, 20 mL) were stirred at THF reflux (40 mL) for 50 hours. THF was then evaporated and the residue obtained diluted with ether (50 mL). The resulting organic layer was washed successively with a 10% solution of HCl, a saturated $NaHCO_3$ aqueous solution and finally with brine. The organic layer was dried over $MgSO_4$, filtered through celite, and concentrated. The residue obtained was purified by flash chromatography (AcOEt/cyclohexane = 10/90) to furnish keto-ester **9** (1.19 g, 73%) as a colorless oil. Enantiomeric excess of Michael adduct (-)-**9** is >95% as determined by the diastereomeric excess of its chiral imine progenitor **19**.

$[\alpha]_D^{20}$ = -43 (*c* = 2.6, $EtOH_{abs}$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.5, 10.1, 7.4 Hz, 1H), 5.12-4.99 (m, 2H), 3.65 (s, 3H), 2.61 (dd, *J* = 15.2, 3.4 Hz, 1H), 2.36-2.16 (m, 5H), 1.96 (dd, *J* = 15.1, 10.4 Hz, 1H), 1.85 (d, *J* = 14.1 Hz, 1H), 1.72 (d, *J* = 14.1 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H), 0.90 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.6, 173.5, 134.2, 118.6, 56.0, 54.6, 51.7, 45.3, 39.8, 36.5, 35.4, 32.2, 31.6, 31.2, 15.8; IR (neat) 2954, 2869, 1730, 1639 cm^{-1}; Elemental anal. Calcd (%) for $C_{15}H_{24}O_3$: C 71.39, H 9.59. Found: C 71.77, H 9.44; HRMS (ESI) *m/z* calcd for $C_{15}H_{24}O_3Na$ 275.1623, found 275.1633.

[4] a) A. Chiaroni, C. Riche, F. Dumas, M. Mauduit, C. Miet, *Acta Cryst C*, 1998, **C54**, 401. b) C. Camara, D. Joseph, F. Dumas, J. d'Angelo, A. Chiaroni, *Tetrahedron Lett.*, 2002, **43**, 1445.

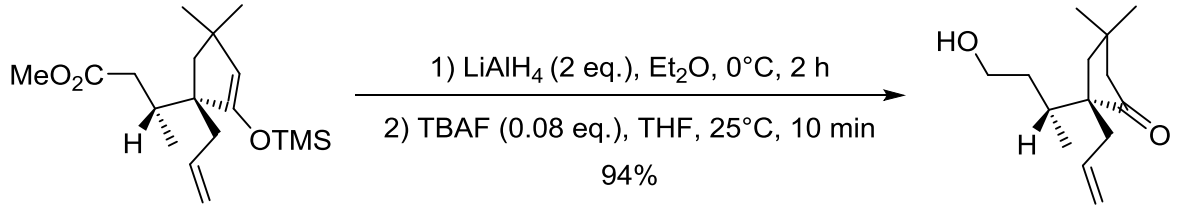
Synthesis of silyl enol ether 20



9 **20**

Scale: keto-ester **9** (5.51 g, 21.83 mmol). Yield: **20** (7.08 g) as a pale yellow-orange oil.

Synthesis of hydroxy ketone 12a

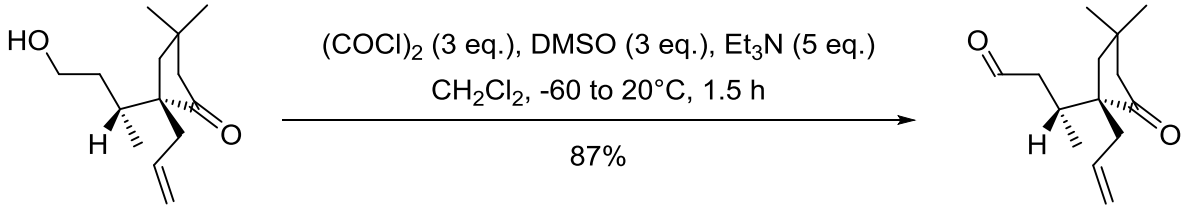


20 **12a**

Scale: **20** (7.08 g, 21.8 mmol). Yield: (1*S*,8*R*) (-)-**12a** (4.59 g, 94%) as a colorless oil.

HRMS(ESI) *m/z* calcd for $C_{14}H_{24}O_2Na$ 247.1674, found 247.1675.

Synthesis of keto-aldehyde 21

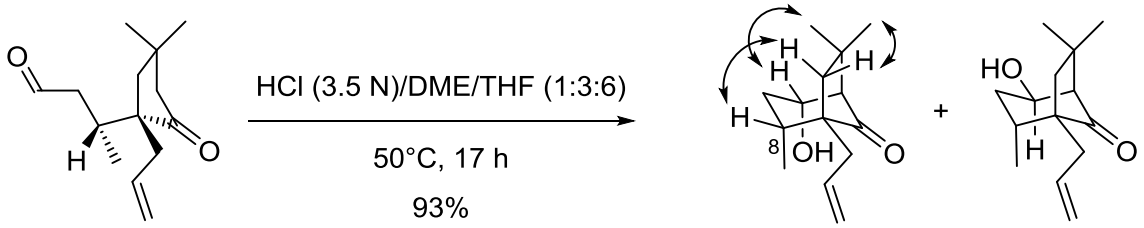


12a **21**

Scale: **12a** (1.86 g, 8.3 mmol). Yield: (1*S*,8*R*) (-)-**21** (1.605 g, 87%) as a pale yellow oil.

HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_2Na$ 245.1517, found 245.1521.

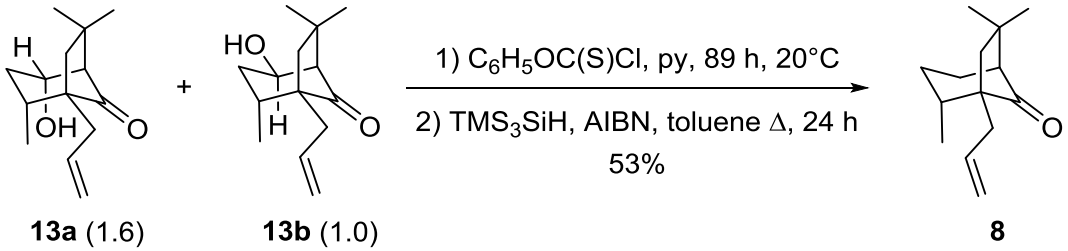
Synthesis of aldols 13a and 13b and confirmation of stereochemistry at C8[5]



Scale: **21** (0.6 g, 2.7 mmol). Yield: (1*S*,8*R*,10*S*,11*R*) **13a** and (1*S*,8*R*,10*R*,11*R*) **13b** (555 mg, 93%) as a mixture of two diastereomers (1.6:1).

13a: $[\alpha]_D^{25}$ = -24.6 (*c* = 0.37, $EtOH_{abs}$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (m, 1H), 5.12-5.04 (m, 2H), 4.44 (sl, 1H), 2.35-2.28 (m, 2H), 2.22-2.17 (m, 2H), 2.01 (d, *J* = 4,1 Hz, 1H), 1.82 (d, *J* = 13,3 Hz, 1H), 1.69 (d, *J* = 13,5 Hz, 1H), 1.59 (d, *J* = 14,5 Hz, 1H), 1.18 (s, 3H), 1.08 (d, *J* = 7,3 Hz, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.0, 134.1, 117.7, 76.8, 64.9, 54.3, 45.0, 44.0, 35.8, 33.7, 32.4, 31.6, 23.6, 16.9; IR (neat): 3437, 2954, 2873, 1735, 1640 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_2Na$ 245.1517, found 245.1517.

Synthesis of (-)-8 from 13



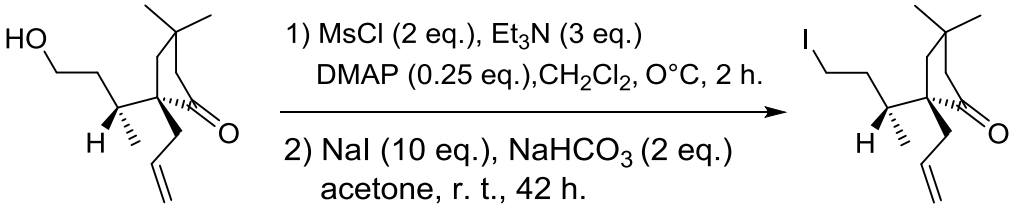
The reaction was carried out in a flame dried flask under argon. Crude aldols **13a** and **13b** (0.715 g, 3.2 mmol) in dry pyridine (3.2 mL) were cooled to 0 °C and phenyl *O*-phenyl chlorothionoformate (0.44 mL, 3.2 mmol) was then added dropwise in 4 portions (0.11 mL each every 30 minutes). The reaction mixture was stirred for 16 hours at room temperature and a second quantity of *O*-phenyl chlorothionoformate (0.6 mL, 1.2 equiv) was added following the same protocol. After stirring 72 hours, the reaction mixture was diluted with ether (30 mL), washed twice with water (2 X 30 mL), 3 times with HCl (10%, 3 X 10 mL), 3 times with a saturated solution of $NaHCO_3$ (3 X 10 ml) and twice with brine (2 X 10 mL). The organic layer was dried over $MgSO_4$, filtered through celite and concentrated. Purification by flash chromatography (AcOEt/cyclohexane = 5/95, 8/92, 10/90

[5] A. B. Smith III, B. A. Wexler, J. Slade, *Tetrahedron Lett.*, 1982, **23**, 1631.

successively) furnished the corresponding phenoxythioformates (0.8 g, 70%) as a 1.6/1 mixture of two diastereomers. Azo-bis-isobutyronitrile (AIBN) (0.246 g, 1.5 mmol, 0.75 equiv) and tris (trimethyl silyl)silane (TMS_3SiH) (1.2 mL, 4 mmol, 2 equiv) diluted with dry toluene (3 mL) were successively added dropwise to this mixture of phenoxythioformates (0.7 g, 2 mmol) diluted with dry toluene (15 mL) and the resulting reaction mixture was stirred under reflux for 24 hours. The reaction mixture was then concentrated and the residue obtained was purified by two successive flash chromatographies (firstly with cyclohexane and secondly with AcOEt/cyclohexane = 5/95, 10/90 successively) to furnish (1*S*,8*R*,11*S*)-(-)-**8** (0.309 g, 53%) as a colorless oil.

$[\alpha]_D^{20}$ = -46.2 (*c* = 0.17, $EtOH_{abs}$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.76-5.60 (m, 1H), 5.18-5.05 (m, 2H), 2.48-2.04 (m, 7H), 1.96 (d, *J* = 12.9 Hz, 1H), 1.95 (sl, 1H), 1.79 (d, *J* = 12.9 Hz, 1H), 1.34 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.8, 134.6, 117.6, 58.0, 54.5, 45.5, 44.2, 36.0, 32.7, 32.2, 28.6, 26.1, 23.2, 15.1; IR (neat) 2951, 2871, 1731, 1638 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}ONa$ 229.1568, found 229.1570.

Synthesis of iodoketone 12c

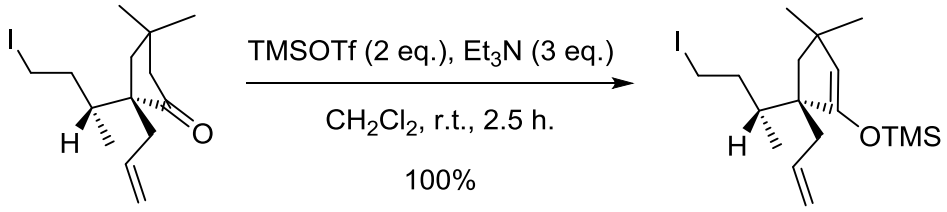


12a **12c**

Scale: **12a** (2 g, 8.9 mmol). Yield: (1*R*,8*S*) (+)-**12c** (2.484 g, 92%) as a colorless oil.

$[\alpha]_D^{20}$ = +7.8 (*c* = 1.0, $EtOH_{abs}$); Elemental anal. Calcd (%) for $C_{14}H_{23}IO$: C 50.31, H 6.94. Found: C 50.39, H 6.8.

Synthesis of 14

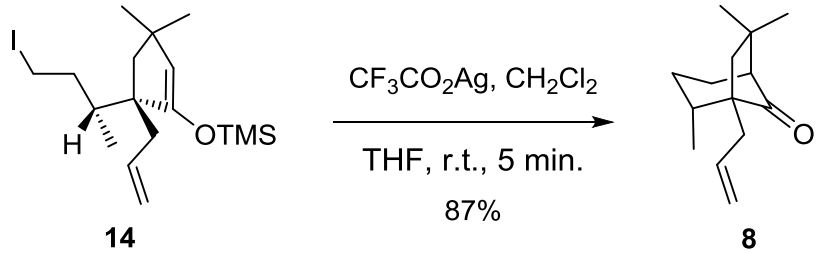


12c **14**

Scale: **12c** (0.334 g, 1 mmol). Yield: **14** (0.406 g, 100%) as a pale yellow-orange oil which was used immediately in the next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85-5.71 (m, 1H), 5.03-4.97 (m, 2H), 4.43 (s, 1H), 3.34 (td, *J* = 9.43, 4.46 Hz, 1H), 3.08(q, *J* = 9.0, 1H), 2.25-2.02 (m, 2H), 1.65-1.22 (m, 5H), 1.02 (s, 6H), 0.83 (d, *J* = 6.6 Hz 3H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 154.00, 136.86, 116.61, 111.97, 54.98, 42.66, 42.38, 39.16, 38.55, 36.38, 31.76, 31.59, 14.70, 6.41, 0.05. IR (neat) 2954, 1638, 1354, 1175 cm^{-1}.

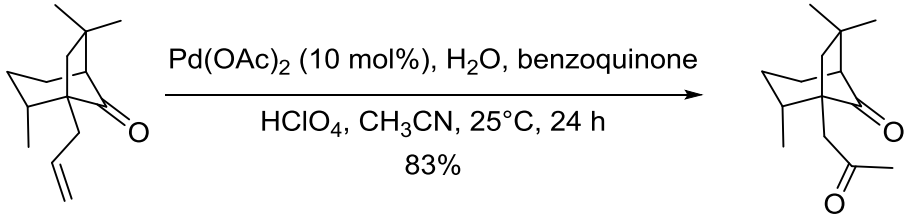
Synthesis of (-)-8 from iodide 14



14 **8**

Silver trifluoroacetate (0.236 g, 1 mmol) in dry dicholromethane (1 mL) was added to a solution of (0.527 g, 1 mmol) of **14** in dry THF (3 mL) under an inert atmosphere (Ar). The reaction mixture was stirred at room temperature for 5 minutes and concentrated. The residue obtained was diluted with EtOAc (20 mL) and washed with water (2 mL). The aqueous layer was extracted with EtOAc (10 mL). The organic layers were mixed, washed with brine (10 mL), dried over $MgSO_4$, filtered through celite and concentrated. Purification by flash chromatography (CH_2Cl_2/cyclohexane = 60/40) furnished (1*S*,8*R*,11*S*)-(-)-**8** (0.188 g, 87%) as a colorless oil.

Synthesis of dione (-)-15



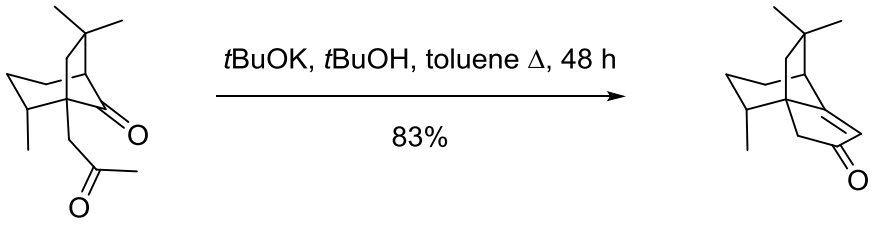
8 **15**

A mixture of $Pd(OAc)_2$ (40 mg, 0.18 mmol), benzoquinone (54 mg, 0.5 mmol, 0.5 equiv), perchloric acid (0.6 mL), water (2.6 mL) and acetonitrile (9 mL) was stirred under nitrogen for 30 minutes at 25 °C. Compound **8** (206 mg, 1 mmol) diluted with acetonitrile (10 mL) was then added and the

resulting mixture stirred for 24 hours. The acetonitrile was evaporated under reduced pressure, and the residue obtained was diluted with ether (20 mL), washed twice with a saturated $NaHCO_3$ solution and with brine (20 mL), dried over $MgSO_4$ and filtered through celite. The organic layer was concentrated and the residue was purified by flash chromatography (cyclohexane/EtOAc = 80/20) to afford (1*S*,8*R*,11*S*) (-)-**15** (184 mg, 83%) as a colorless oil.

$[\alpha]_D^{20}$ = -60.2 (*c* = 1.03, $EtOH_{abs}$);^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (d, *J* = 17.3 Hz, 1H), 2.64 (d, *J* = 17.3 Hz, 1H), 2.57-2.47 (m, 1H), 2.33-2.00 (m, 4H), 2.26 (s, 3H), 1.97-1.93 (m, 1H), 1.84 (d, *J* = 13.3 Hz, 1H), 1.43-1.37 (m, 1H), 1.35 (s, 3H), 1.13 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.8, 206.9, 57.2, 53.2, 46.5, 45.0, 43.7, 32.8, 32.5, 31.5, 28.6, 25.9, 23.3, 15.6; IR (neat) 2945, 1740, 1716 cm^{-1}; Elemental anal. Calcd (%) for $C_{14}H_{22}O_2$: C 75.63, H 9.97. Found: C 75.47, H 10.14; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_2Na$ 245.1517, found 245.1508.

Synthesis of enone (-)-7

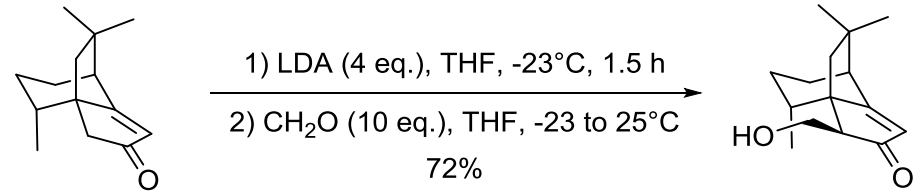


15 **7**

Potassium *tert*-butylate (0.841 g, 7.5 mmol, 10 equiv) was added to a solution of compound **15** (0,160 g, 0.72 mmol) in dry *tert*-butanol (12 mL). The reaction mixture was stirred under reflux for 48 hours, cooled to room temperature and concentrated. The residue obtained was diluted with ether (10 mL), washed with a solution of HCl (10%, 5 mL) and with brine (10 mL). The organic layer was dried over $MgSO_4$, filtered through celite and concentrated. The residue thus obtained was purified by flash chromatography (cyclohexane/EtOAc = 90/10) to afford (1*R*,8*R*,11*S*) (-)-**7** (122 mg, 83%) as a colorless oil.

$[\alpha]_D^{20}$ = -12.3 (*c* = 0.65, $EtOH_{abs}$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 2.52 (d, *J* = 17.5 Hz, 1H), 2.50 (t, *J* = 3.0 Hz, 1H), 2.28-2.09 (m, 2H), 2.22 (d, *J* = 17.5 Hz, 1H), 2.05 (d, *J* = 12.9 Hz, 1H), 1.99-1.90 (m, 2H), 1.53 (d, *J* = 12.9 Hz, 1H), 1.47-1.40 (m, 1H), 1.38 (s, 3H), 1.08 (s, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 191.9, 121.8, 54.2, 50.2, 49.0, 48.8, 40.8, 40.3, 33.3, 25.8, 24.5, 23.3, 14.7; IR (neat) 2933, 2868, 1705, 1643 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{14}H_{20}O$ 204.1514, found 204.1499.

Synthesis of aldol 16[6]

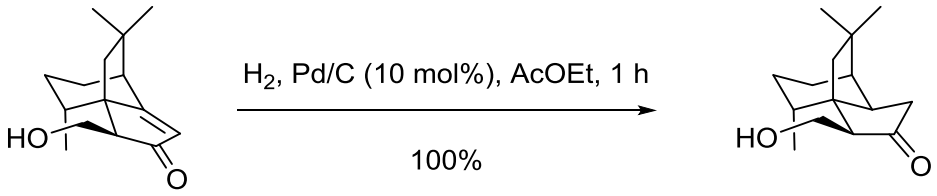


7 **16**

Scale: **7** (200 mg, 0.98 mmol). Yield: (1*S*,8*R*,11*S*,5*R*) (+)-**16** (165 mg, 72%) as a colorless oil.

$[\alpha]_D^{20}$ = +16.7 (*c* = 0.36, $EtOH_{abs}$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (s, 1H), 3.70 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.60 (dd, *J* = 10.5, 8.5 Hz, 1H), 2.75 (bs, 1H), 2.45 (dd, *J* = 8.5; 6.5 Hz, 1H), 2.39 (t, *J* = 3.1 Hz, 1H), 2.19-2.05 (m, 2H), 1.85-1.75 (m, 2H), 1.63 (d, *J* = 13.5 Hz, 1H), 1.51 (d, *J* = 13.5 Hz, 1H), 1.35-1.21 (m, 1H), 1.23 (s, 3H), 0.89 (s, 3H), 0.79 (d, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 193.5, 120.2, 62.5, 56.2, 53.7, 48.9, 42.1, 41.6, 39.3, 32.4, 25.5, 24.4, 22.9, 14.5; IR (neat) 3427, 2929, 2868, 1682, 1636 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NaO_2$ 257.1517, found 257.1516.

Synthesis of compound 17



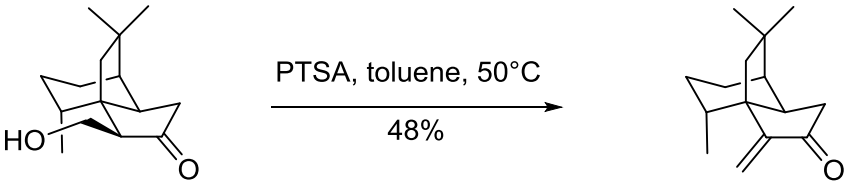
16 **17**

Scale: **15** (18 mg, 0.077 mmol). Yield: (1*R*,2*R*,5*R* 8*R*,11*R*) **17** (18 mg, 100%) as a colorless oil.

HRMS (EI) *m/z* calcd for $C_{15}H_{24}O_2$ 236.1776, found 236.1756.

[6] a) S. Danishefsky, K. Vaughan, R. C. Gadwood, K. Tsuzuki, *J. Am. Chem. Soc.*, 1980, **102**, 4262; b) S. Danishefsky, K. Vaughan, R. C. Gadwood, K. Tsuzuki, *J. Am. Chem. Soc.*, 1981, **103**, 4136.

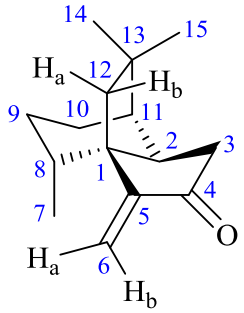
Synthesis of suberosenone (+)-1



17 (+)-**1**

A few crystals of pTsOH were added to a solution of **17** (18 mg, 0.076 mmol) in toluene (5 mL). The reaction mixture was heated at 50 °C for 2 hours. The crude reaction mixture was filtered on celite and concentrated. Purification by flash chromatography (cyclohexane/AcOEt = successively 98/02 and 95/05) furnished (1*R*,2*R*,8*R*,11*R*) (+)-**1** (8 mg, 48%) as a colorless oil.

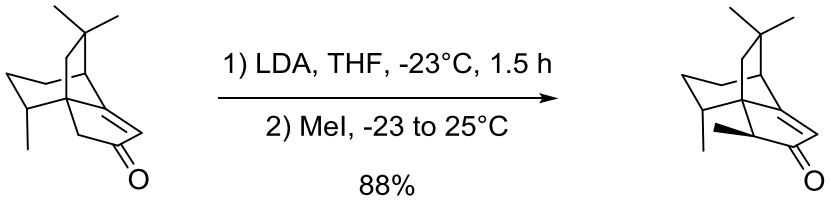
$[\alpha]_D^{20}$ = +66.7 (*c* = 0.31; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.99 (s, 1H), 2.67 (dd, *J* = 19.2, 11.3 Hz, 1H), 2.47 (dd, *J* = 19.2, 9.4 Hz, 1H), 2.32 (dd, *J* = 11.3, 9.4 Hz, 1H); 2.17-2.06 (m, 1H), 2.13 (m, 1H), 1.90 (t, *J* = 3 Hz, 1H), 1.81 (d, *J* = 14.5 Hz, 1H), 1.72-1.69 (m, 1H), 1.70 (d, *J* = 14.5 Hz, 1H), 1.65-1.57 (m, 1H), 1.38 (m, 1H) 1.22 (s, 3H), 1.17 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 151.8, 115.2, 57.8, 54.3, 49.7, 45.2, 41.9, 40.2, 36.4, 34.9, 27.8, 27.0, 26.4, 17.2; IR (neat) 2924, 2866, 1726, 1637 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O$ 218,1671, found 218,1668.



N°	$\delta H_{natural}$ 500 MHz	$\delta H_{synthetic}$ 400 MHz	Δ ppm	$\delta C_{natural}$ 125 MHz	$\delta C_{synthetic}$ 75 MHz	Δ ppm
1				57.8	57.8	0
2	2.30 (ddd, 11.5, 9.5, 0.5)	2.32 (dd, 11.3, 9.4)	0.02	45.1	45.2	0.1
3	α 2.44 (dd, 19.5, 9.5) β 2.64 (dd, 19.5, 12.0)	α 2.47 (dd, 19.2, 9.4) β 2.67 (dd, 19.2, 11.3)	0.03 0.03	41.8	41.9	0.1
4				208.6	208.6	0
5				151.8	151.8	0
6	a 4.97 (d, 0.8) b 5.95 (d, 0.8)	a 4.99 (s) b 5.97 (s)	0.02 0.02	115.2	115.2	0
7	0.88 (d, 7.0)	0.91 (d, 6.7)	0.03	17.2	17.2	0
8	2.12 (m)	2.13 (m)		36.3	36.4	0.1
9	α 1.32 (ddd, 14.0, 6.5, 1.0) β 2.06 (m)	α 1.38 (m) β 2.11 (m)		26.4	26.4	0
10	α 1.59 (m) β 1.67 (m)	α 1.60 (m) β 1.71(m)		27.8	27.8	0
11	1.87 (ddd, 3.5, 3.0, 0.5)	1.90 (t, 3.0)	0.03	49.6	49.7	0.1
12	a 1.69 (d, 14.5) b 1.79 (d, 14.0)	a 1.70 (d, 14.5) b 1.81 (d, 14.5)	0.01 0.02	54.2	54.3	0.1
13				40.2	40.2	0
14	1.15 (s)	1.17 (s)	0.02	26.9	27.0	0.1
15	1.19 (s)	1.22 (s)	0.03	34.9	34.9	0

Table 1: Comparison of the NMR spectroscopic data of natural and synthetic suberosenone

Synthesis of compound (-)-18

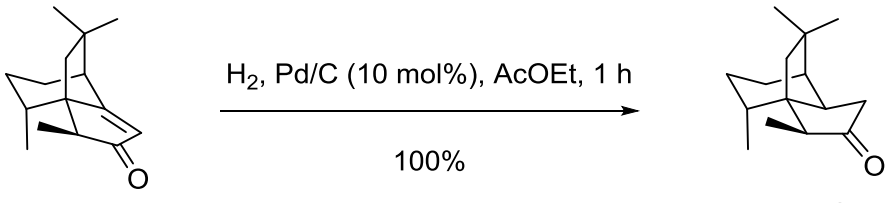


7 **18**

The reaction was carried out in a flame dried flask under argon in a 25 mL flask. A mixture of THF (1 mL), freshly distilled diisopropylamine (0.175 mL, 1.25 mmol, 4 equiv) and butyllithium (2.0 M in hexane, 0.625 mL, 1.25 mmol, 4 equiv) was stirred for 15 minutes at 0 °C. This reaction mixture was then cooled to -23 C° and a solution of compound **7** (43 mg, 0.21 mmol) in THF (1 mL) was added. The reaction mixture was stirred at that temperature for 90 minutes, and MeI (0.08 mL, 1.28 mmol, 5 equiv) was added. The reaction mixture was warmed to room temperature and a saturated solution of NH_4Cl (5 mL) was added. The organic layer was washed several times with of a solution HCl (10%, 5 mL) and with brine (10 mL), dried over $MgSO_4$, filtered through celite and concentrated. Purification by flash chromatography (cyclohexane/AcOEt = 98/2) furnished (1*S*,5*S*,8*R*,11*S*) (-)-**18** (40.5 mg, 88%) as a colorless oil.

$[\alpha]_D^{20}$ = -47.0 (c = 0.62; $EtOH_{abs}$);^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (s, 1H), 2.36 (t, *J* =3.1 Hz, 1H), 2.25 (q, *J* = 7.7 Hz, 1H), 2.13-1.90 (m, 2H), 1.86-1.75 (m, 2H), 1.61 (d, *J* = 13.5 Hz, 1H), 1.52 (d, *J* = 13.5 Hz, 1H), 1.30-1.25 (m, 1H), 1.23 (s, 3H), 0.99 (d, *J* = 7.7 Hz, 3H), 0.88 (s, 3H), 0.76 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 191.0, 119.6, 57.8, 49.3, 47.8, 42.3, 42.0, 39.6, 32.5, 26.2, 24.9, 23.2, 15.8, 14.7; IR (neat) 2961, 2871, 1703, 1644 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{22}O$ 218.1671, found 218.1673.

Synthesis of suberosanone (+)-2

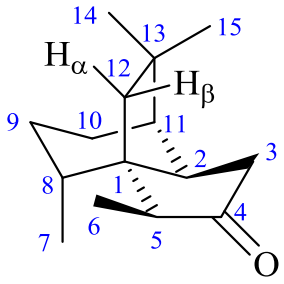


18 (+)-**2**

Pd/C (5 mg, 10%) was added to a solution of **18** (30 mg, 0.137 mmol)) in ethyl acetate (2 mL). The reaction mixture was saturated with hydrogen and allowed to stir for one hour. The crude reaction

mixture was filtered on celite which was washed with ether (5 ml) and concentrated to afford (1*R*,2*R*,5*S*,8*R*,11*R*) (+)-**2** (30 mg, 100%) as a colorless oil.

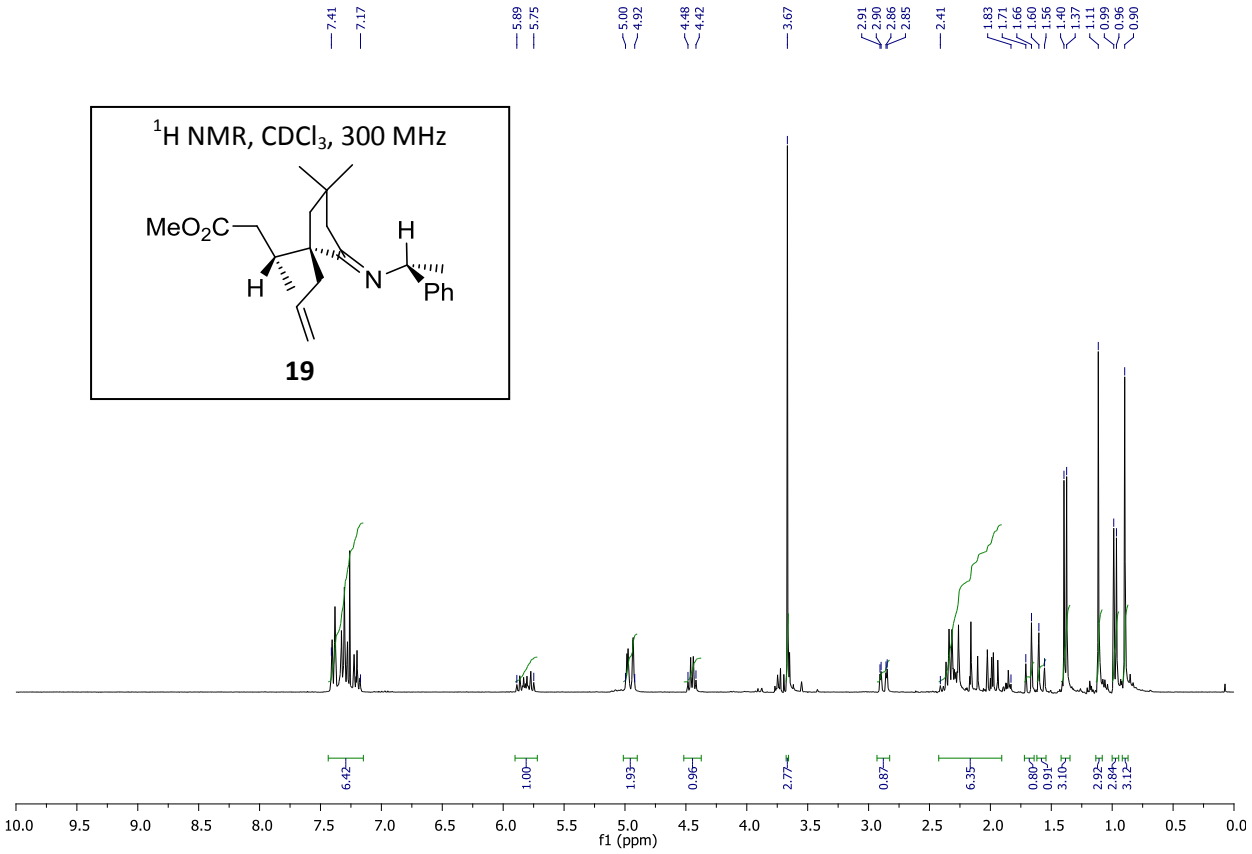
$[\alpha]_D^{19}$ = +53.4 (c = 0.1; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56-2.44 (m, 4H), 2.19 (tt, 1H), 2.03 (quint., *J* = 7,0 Hz, 1H), 1.91 (tl, *J* = 3H, 1H), 1.88-1.69 (m, 2H), 1.57 (d, *J* = 13.9 Hz, 1H), 1.49 (d, *J* = 13.9 Hz, 1H), 1.50-145 (m, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.5, 57.0, 50.1, 49.8, 47.9, 44.0, 40.8, 39.3, 35.8, 34.4, 28.4, 27.1, 27.1, 17.1, 8.2; IR (neat) 2929, 2868, 1737 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{24}O$ 220.1827, found 220.1826.

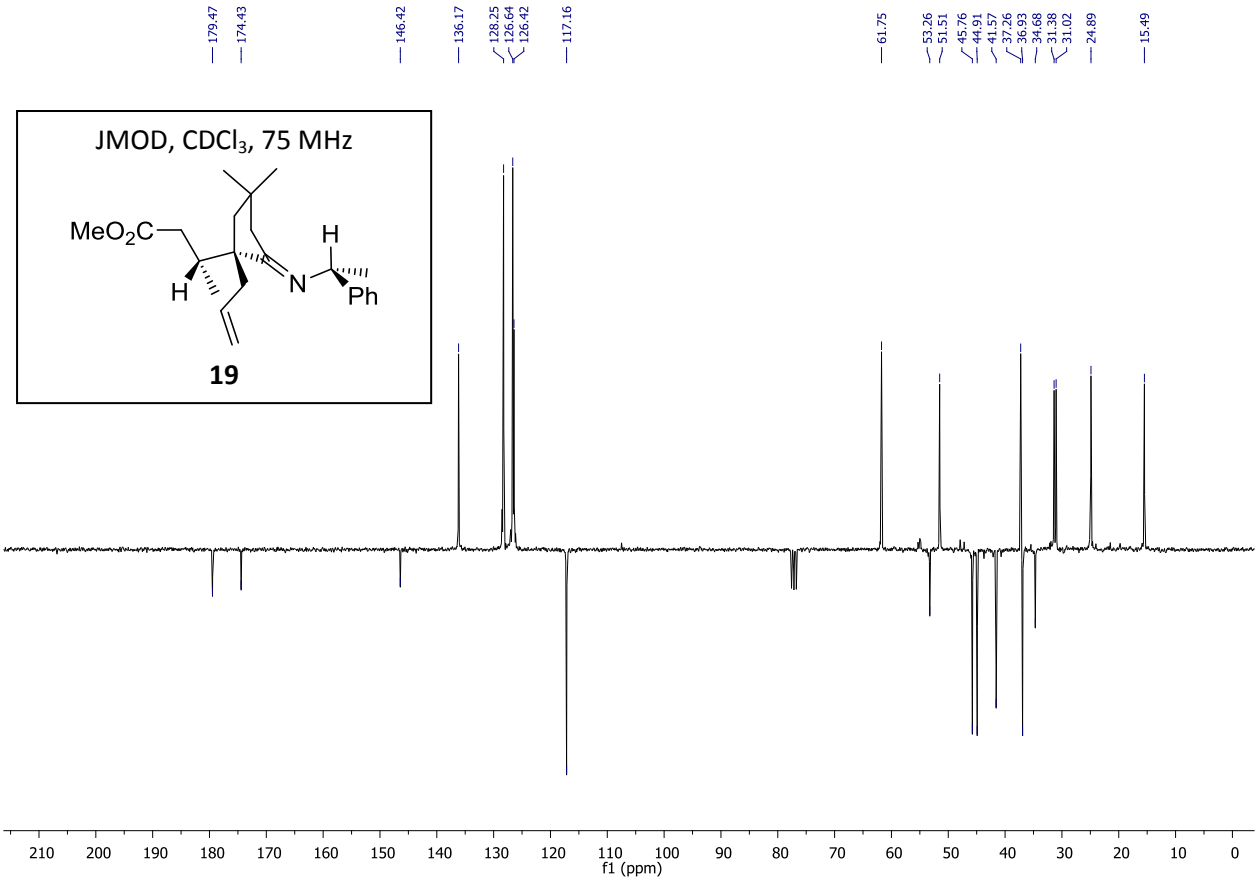


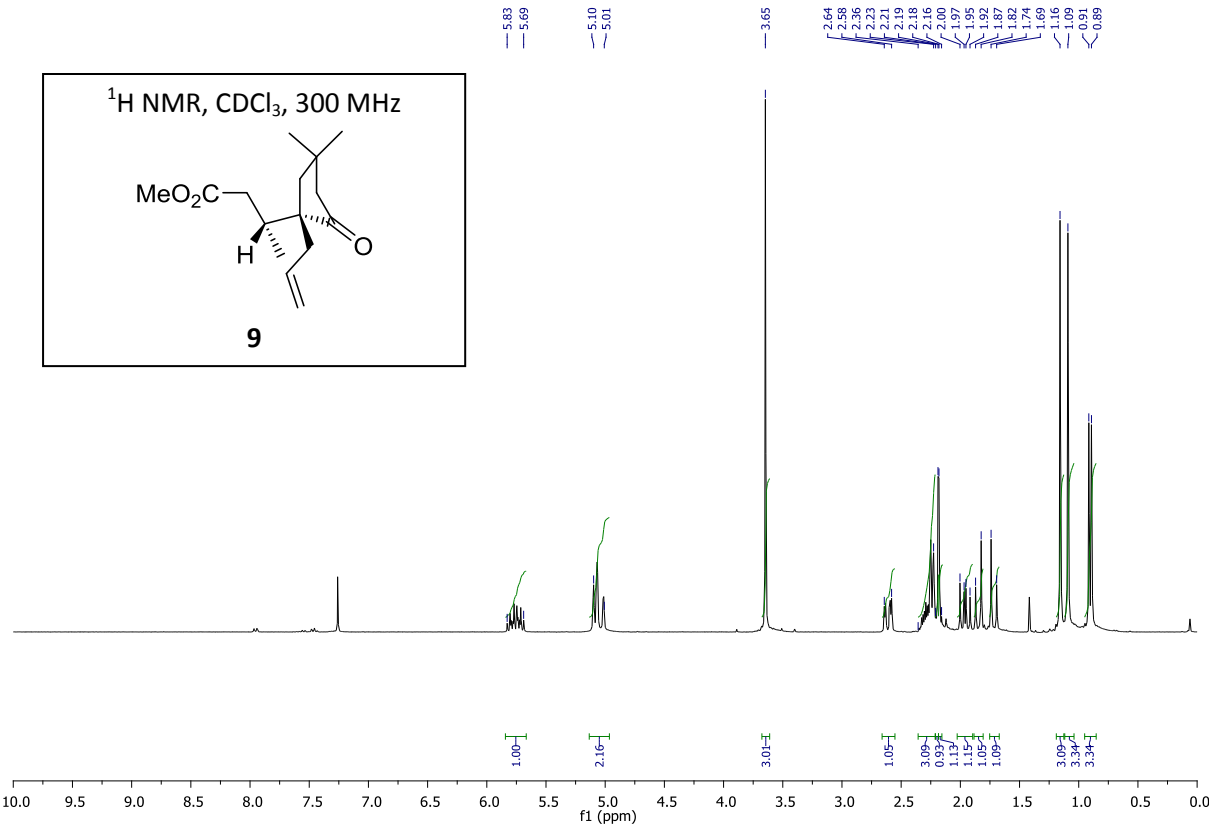
N°	$\delta H_{natural}$ 500 MHz	$\delta H_{synthetic}$ 400 MHz	Δ ppm	$\delta C_{natural}$ 125 MHz	$\delta C_{synthetic}$ 75 MHz	Δ ppm
1			-	56.9	56.9	0.0
2	2.38 (m)	2.36-2.41 (m)		43.8	43.9	0.1
3	α 2.48 (dd, 7.0, 1.5) β 2.35 (dd, 7.0, 3.0)	2.35-2.52 (m)		40.7	40.7	0.0
4			-	220.5	220.3	0.2
5	2.39 (q, 7.0)	2.32-2.37 (m)		50.0	50.0	0.0
6	0.90 (d, 7.0)	0.89 (d, 6.8)	0.01	8.1	8.1	0.0
7	1.04 (d, 7.0)	1.03 (d, 7.1)	0.01	17.0	17.0	0.0
8	1.89 (Q, 7.0)	1.88 (Q, 7.2)	0.01	35.6	35.7	0.1
9	α 1.33 (dd, 7.0, 7.0) β 2.06 (m)	α 1.33 (br d, 13.9) β 2.05 (tt, 13.9, 7)	0.00 0.01	26.9	26.9	0.0
10	α 1.62 (ddd, 13.5, 6.5, 2.5) β 1.68 (m)	α 1.62 (dtd, 13.6, 6, 2.7) β 1.71-1.64 (m)	0	28.3	28.3	0.0
11	1.79 (br t, 3.0)	1.76 (br t, 3.0)	0.03	49.6	49.7	0.1
12	α 1.34 (d, 14.5) β 1.40 (d, 14.5)	α 1.33 (d, 14.5) b 1.40 (d, 14.5)	0.01 0.00	47.7	47.7	0.0
13				39.2	39.1	0.1
14	1.04 (s)	1.13 (s)	0.09	27.0	27.0	0.0
15	1.09 (s)	1.09 (s)	0.00	34.3	34.3	0.0

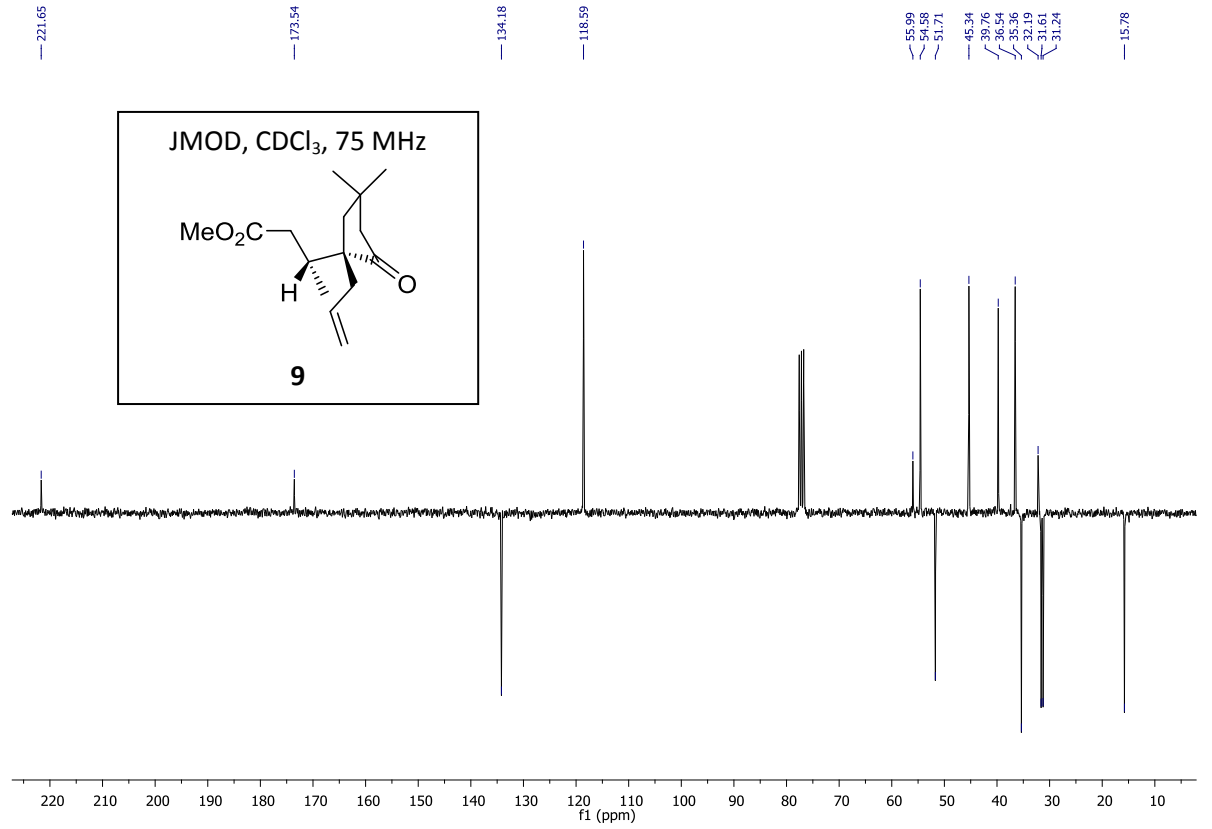
Table 2: Comparison of the NMR spectroscopic data of natural and synthetic suberosanone **2**

NMR spectra.

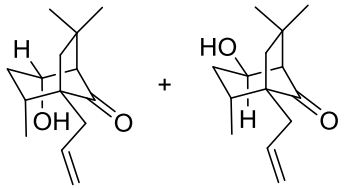

7.41
7.17
5.89
5.75
5.00
4.92
4.48
4.42
3.67
2.91
2.90
2.86
2.85
2.41
1.83
1.71
1.66
1.60
1.56
1.40
1.37
1.11
0.99
0.96
0.90
^{1}H NMR, CDCl$_3$, 300 MHz
MeO$_2$C
H
N
H
Ph
19
6.42
1.00
1.93
0.96
2.77
0.87
6.35
0.80
0.91
3.10
2.92
2.84
3.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


179.47
174.43
146.42
136.17
128.25
126.64
126.42
117.16
61.75
53.26
51.51
45.76
44.91
41.57
37.26
36.93
34.68
31.38
31.02
24.89
15.49
JMOD, CDCl$_3$, 75 MHz
MeO$_2$C
H
N
H
Ph
19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

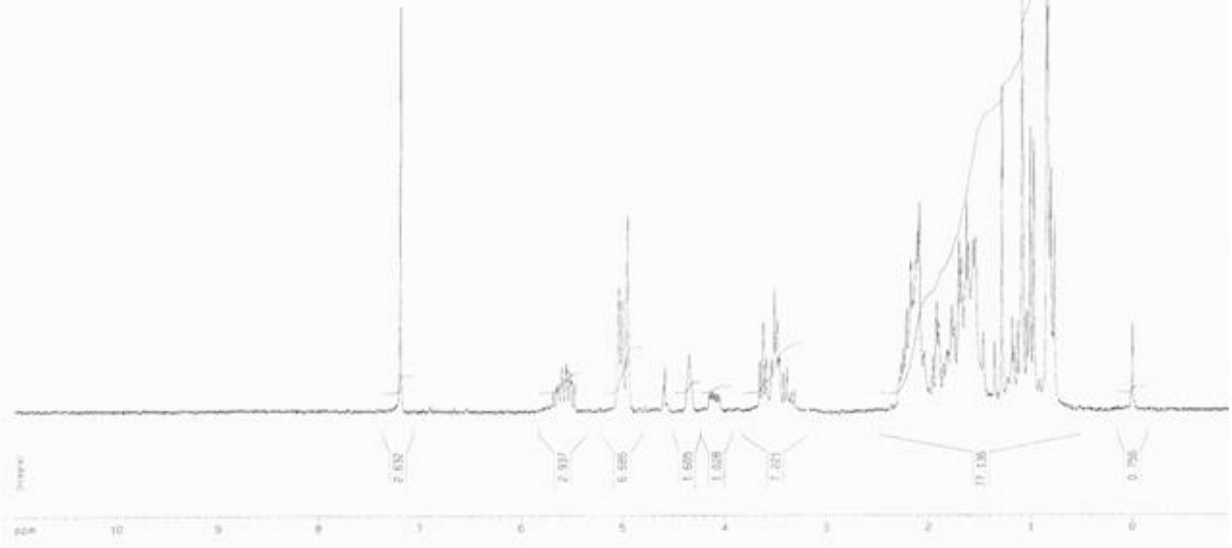

^{1}H NMR, $CDCl_3$, 300 MHz
MeO_2C
H
O
9
f1 (ppm)


JMOD, $CDCl_3$, 75 MHz
MeO_2C
H
O
9
f1 (ppm)

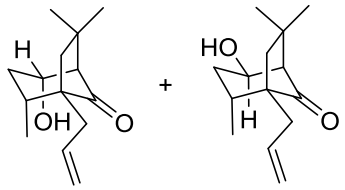
^{1}H NMR, $CDCl_3$, 200 MHz, crude



13a/**13b** = 1.6/1.0

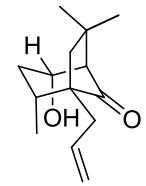


JMOD, $CDCl_3$, 50 MHz, crude



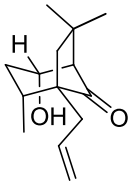
13a/**13b** = 1.6/1.0

^{1}H NMR, $CDCl_3$, 400 MHz



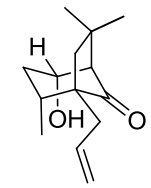
13a

JMOD, $CDCl_3$, 100 MHz



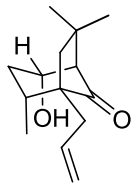
13a

NOESY, $CDCl_3$, 400 MHz

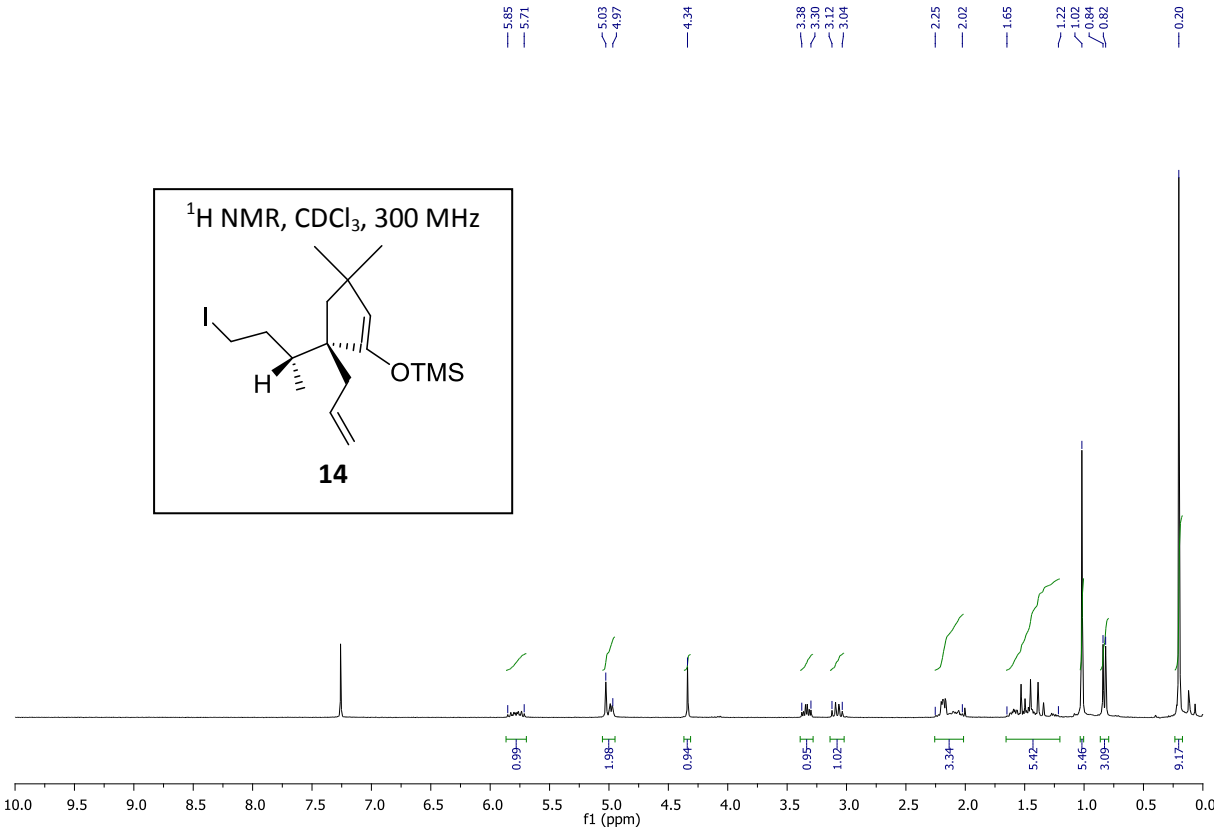


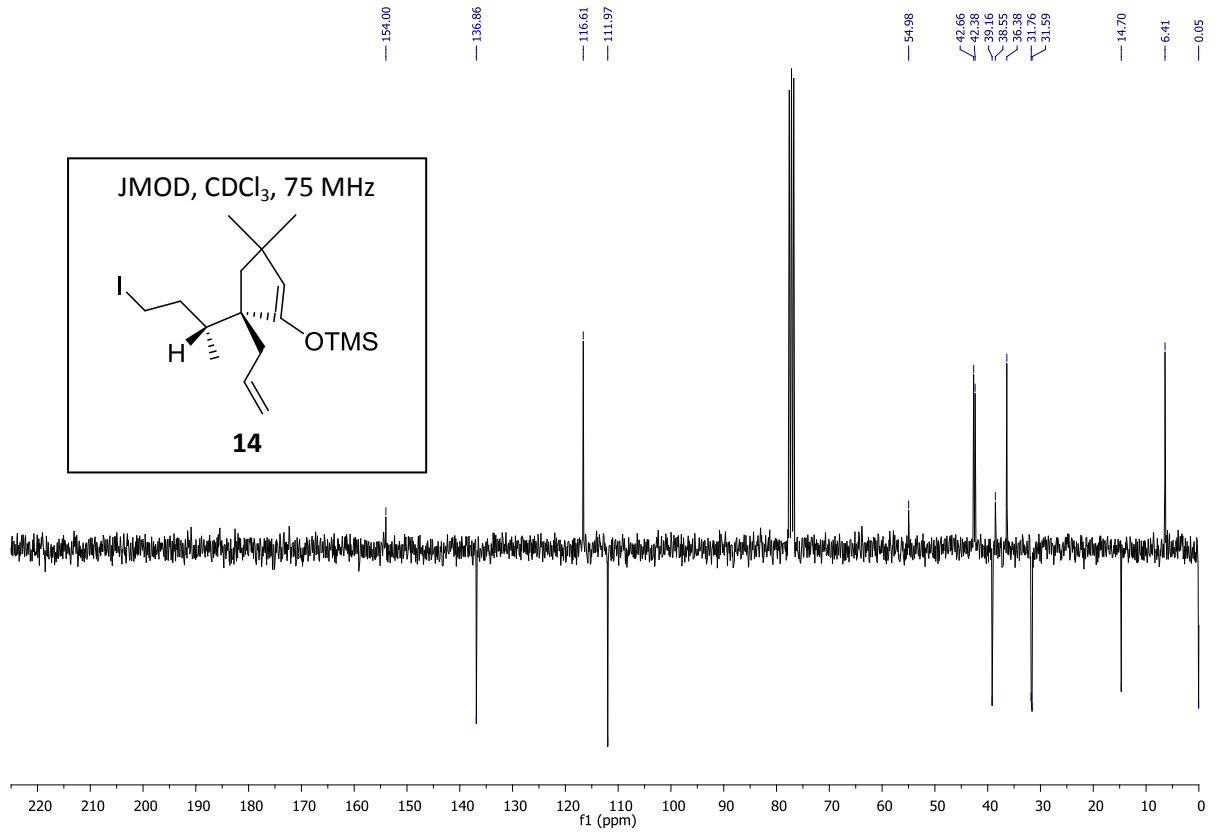
13a

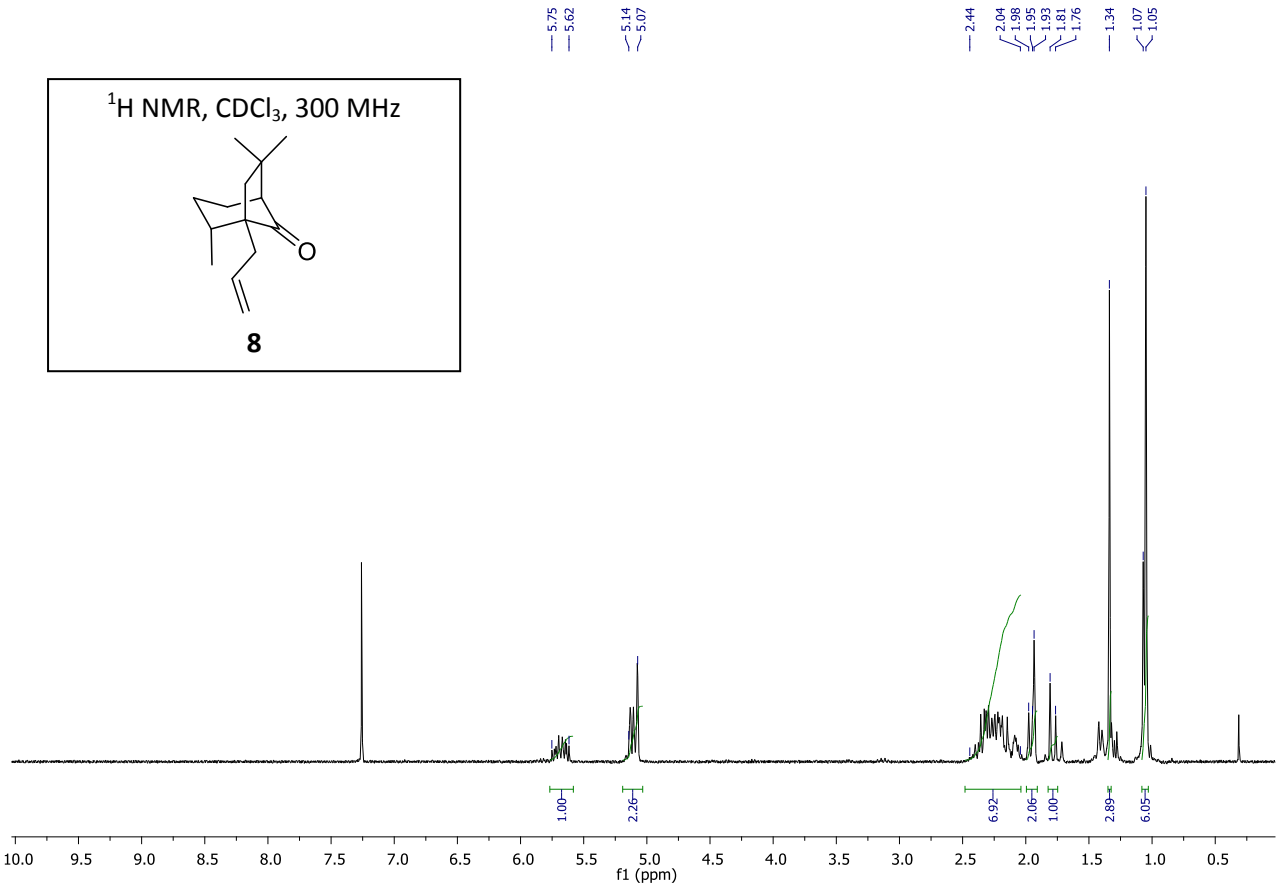
NOESY, $CDCl_3$, 400 MHz



13a

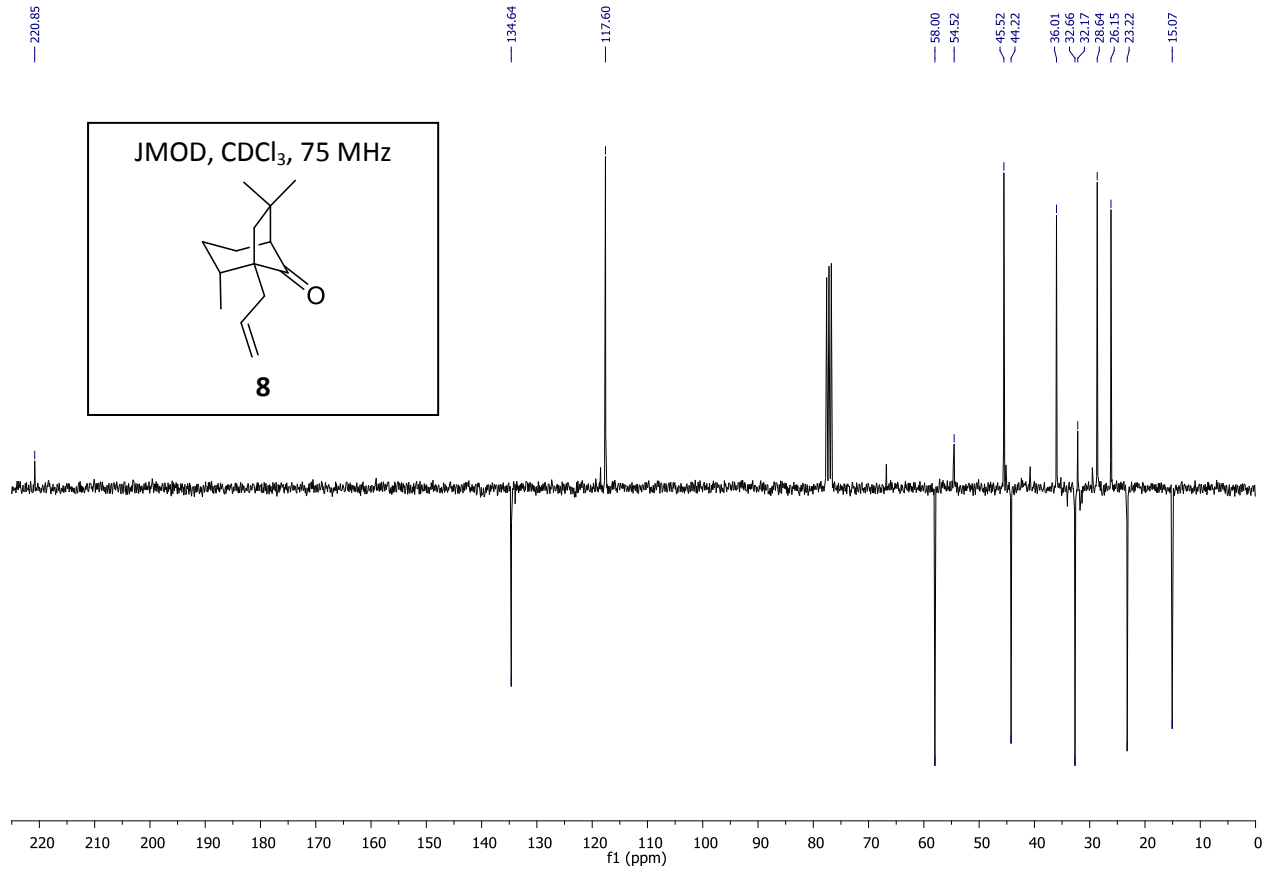

5.85
5.71
5.03
4.97
4.34
3.38
3.30
3.12
3.04
2.25
2.02
1.65
1.22
1.02
0.84
0.82
0.20
^{1}H NMR, $CDCl_3$, 300 MHz
I
H
OTMS
14
0.99
1.98
0.94
0.95
1.02
3.34
5.42
5.46
3.09
9.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


154.00
136.86
116.61
111.97
54.98
42.66
42.38
39.16
38.55
36.38
31.76
31.59
14.70
6.41
0.05
JMOD, $CDCl_3$, 75 MHz
I
H
OTMS
14
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



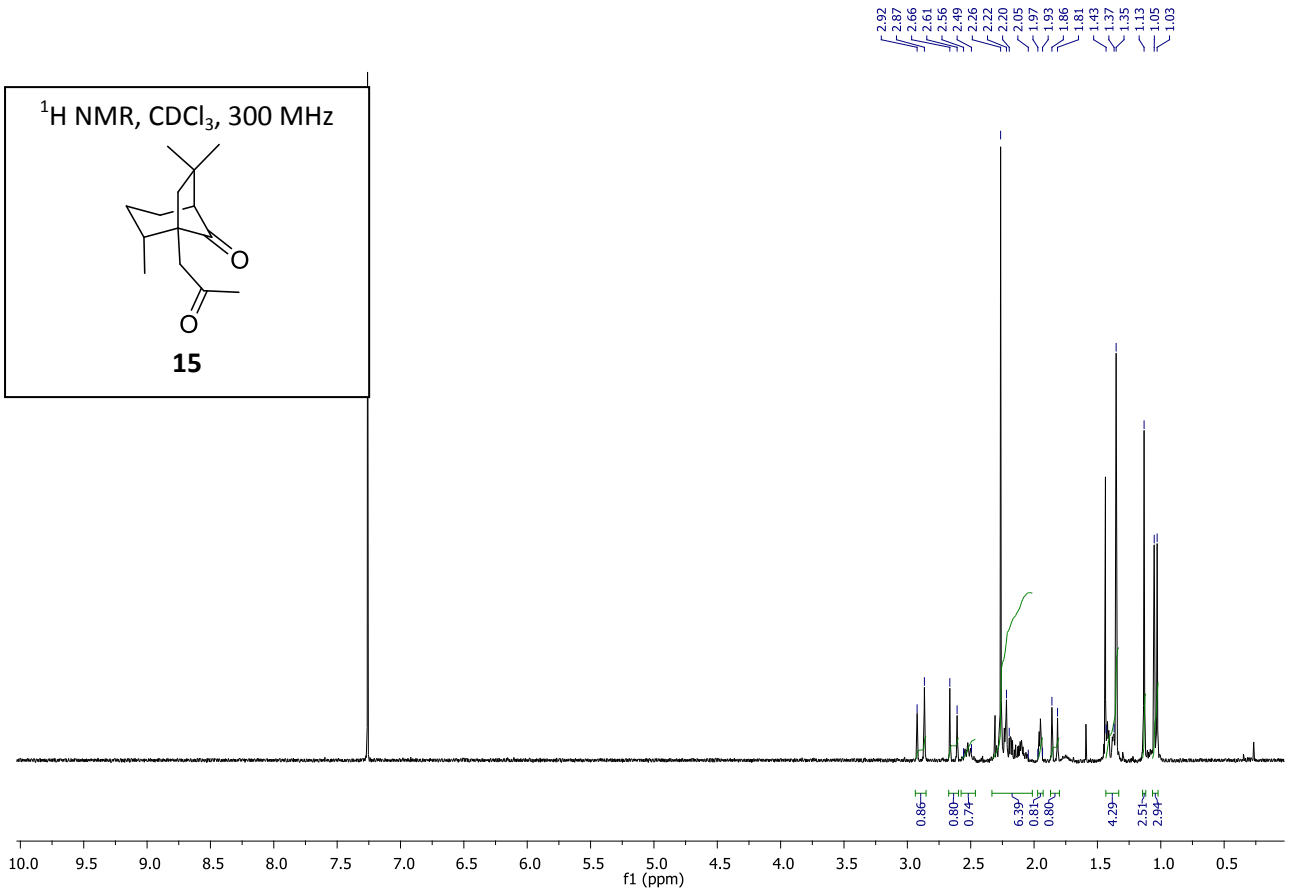
^{1}H NMR, $CDCl_3$, 300 MHz

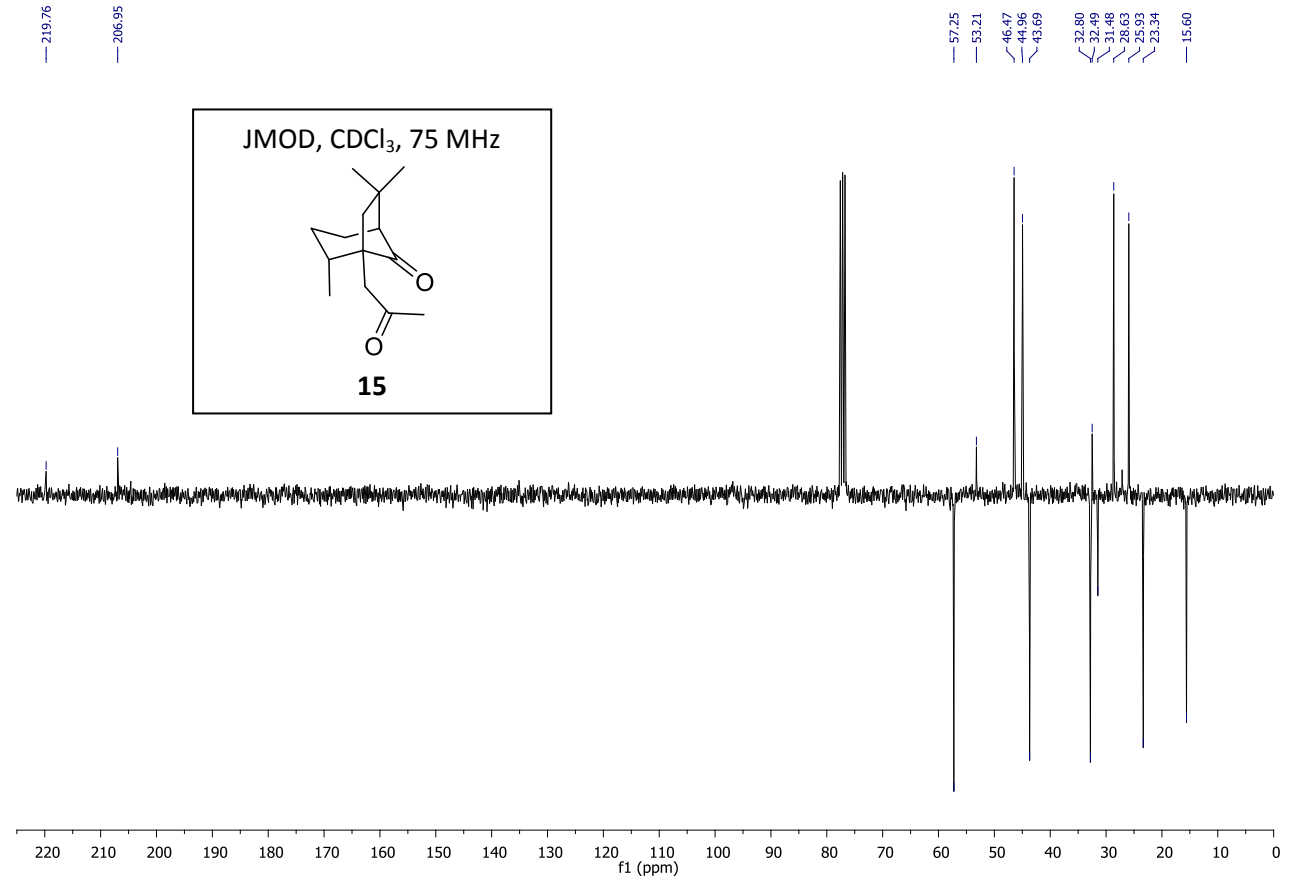
8

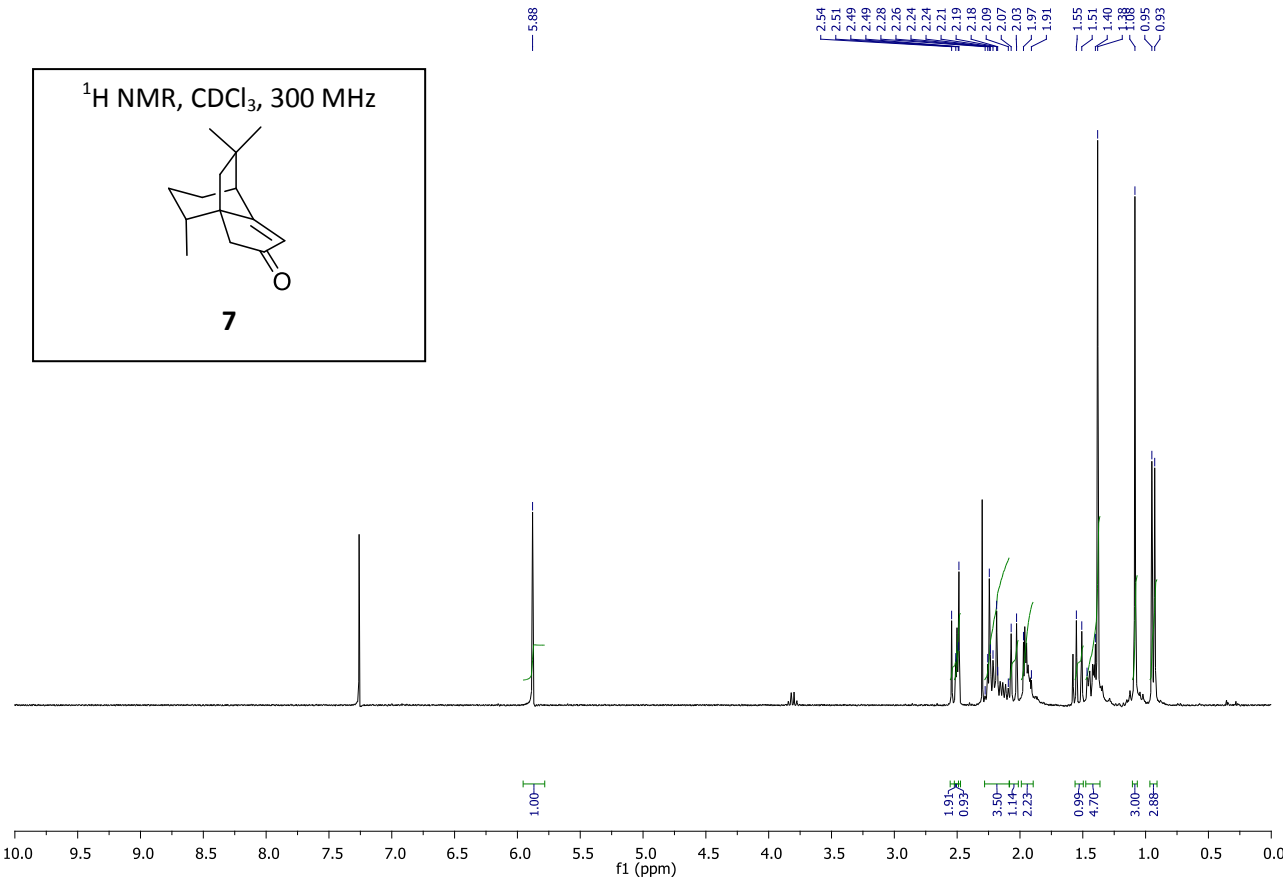


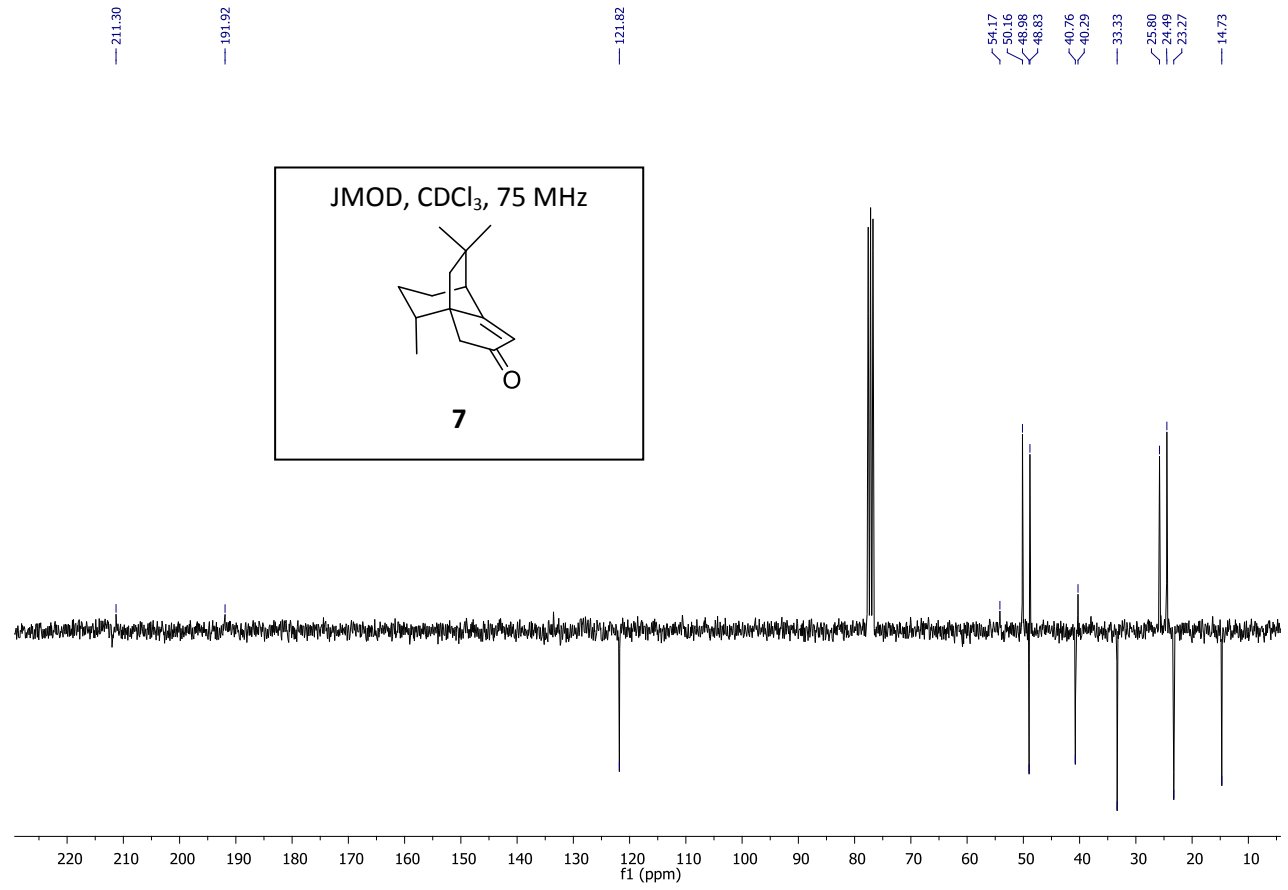
JMOD, $CDCl_3$, 75 MHz

8

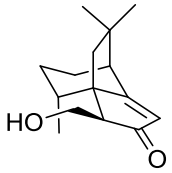

^{1}H NMR, CDCl$_3$, 300 MHz
O
O
15
2.92
2.87
2.66
2.61
2.56
2.49
2.26
2.22
2.20
2.05
1.97
1.93
1.86
1.81
1.43
1.37
1.35
1.13
1.05
1.03
0.86
0.80
0.74
6.39
0.81
0.80
4.29
2.51
2.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


219.76
206.95
57.25
53.21
46.47
44.96
43.69
32.80
32.49
31.48
28.63
25.93
23.34
15.60
JMOD, CDCl$_3$, 75 MHz
O
O
15
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


^{1}H NMR, $CDCl_3$, 300 MHz
7
f1 (ppm)

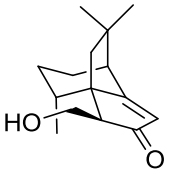

JMOD, $CDCl_3$, 75 MHz
7
f1 (ppm)

^{1}H NMR, $CDCl_3$, 300 MHz



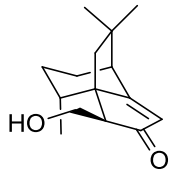
16

^{13}C NMR, $CDCl_3$, 75 MHz

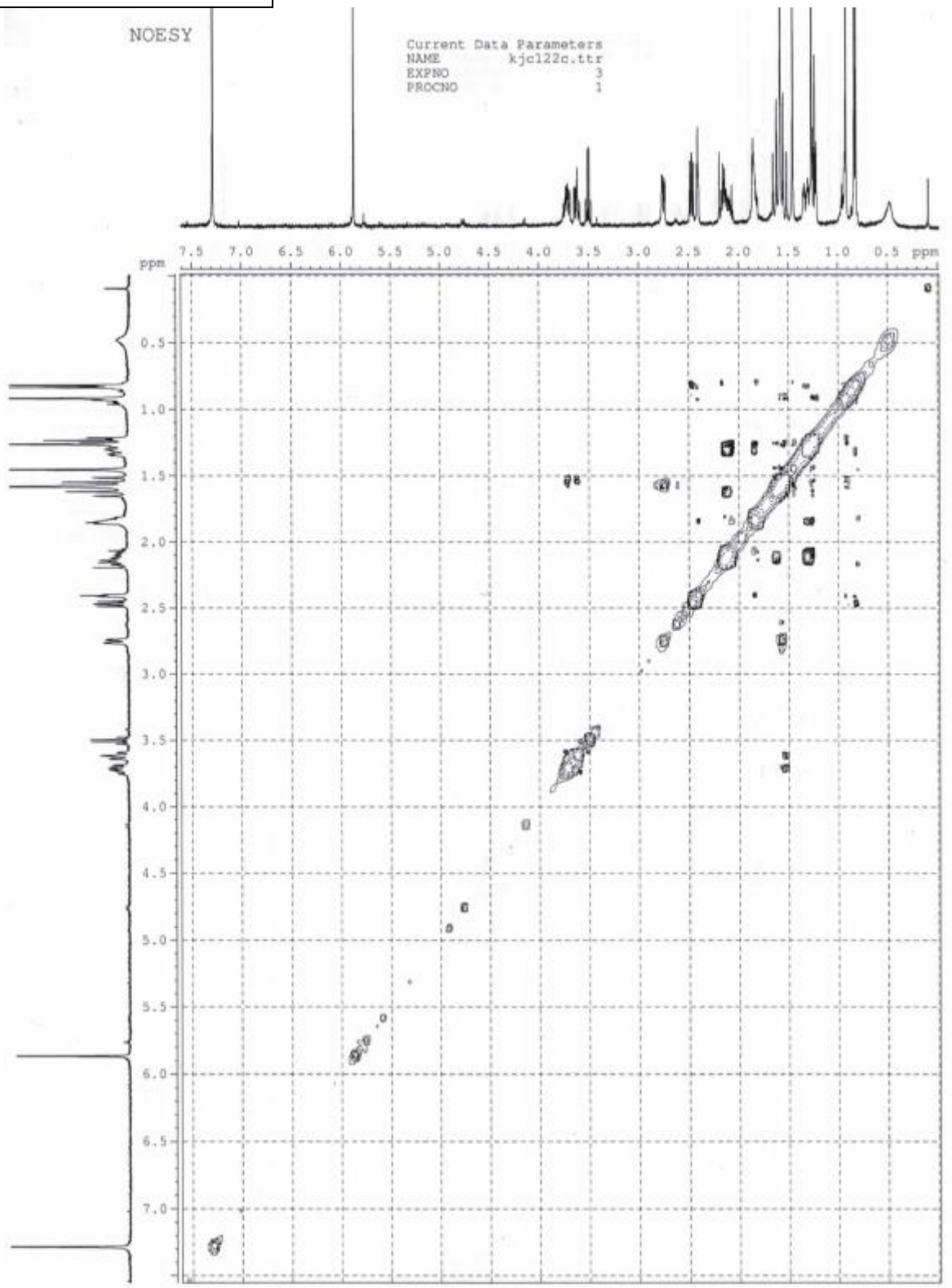


16

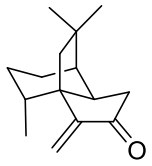
NOESY, $CDCl_3$, 400 MHz



16

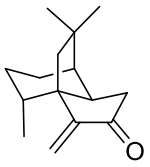


^{1}H NMR, $CDCl_3$, 400 MHz

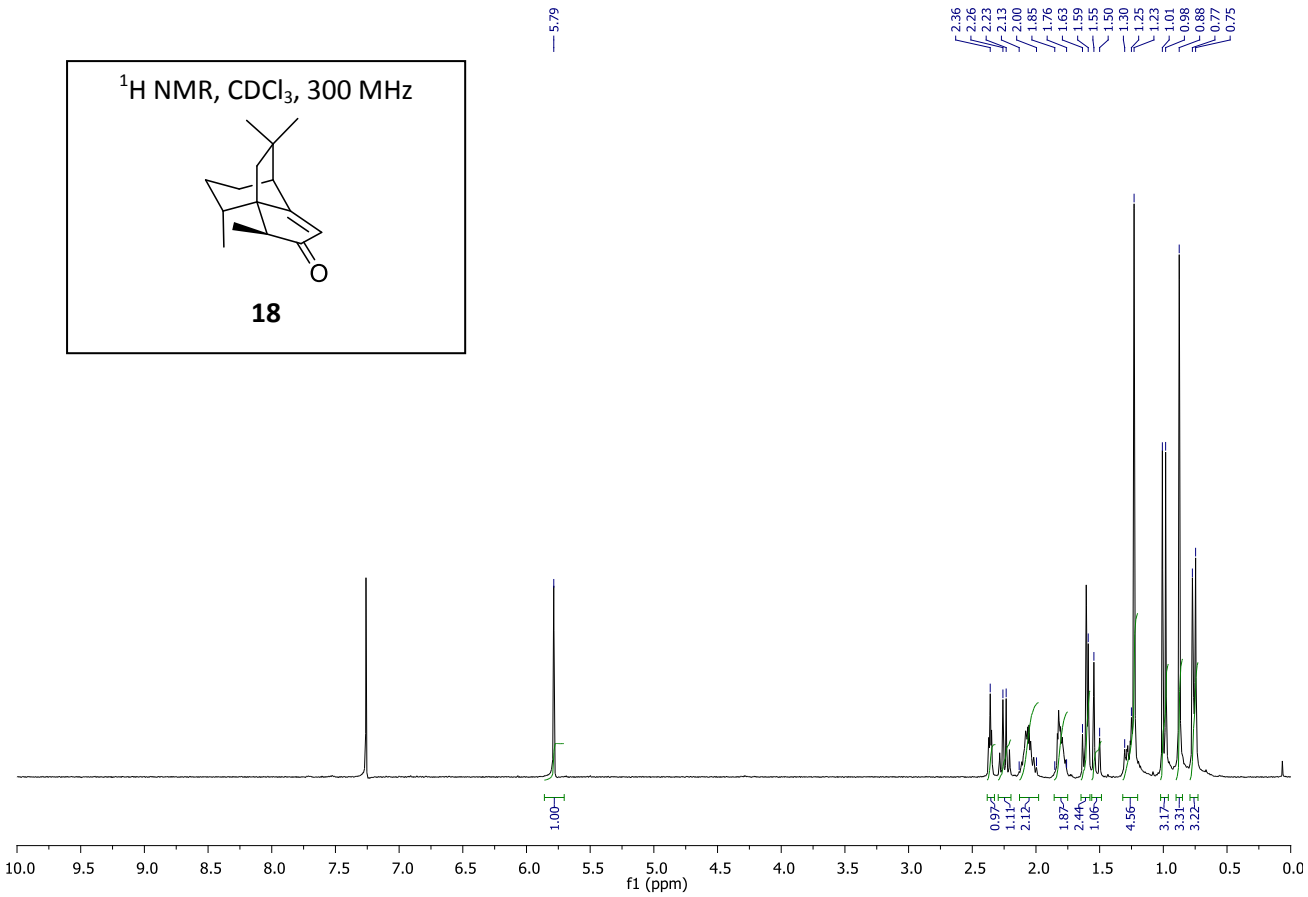


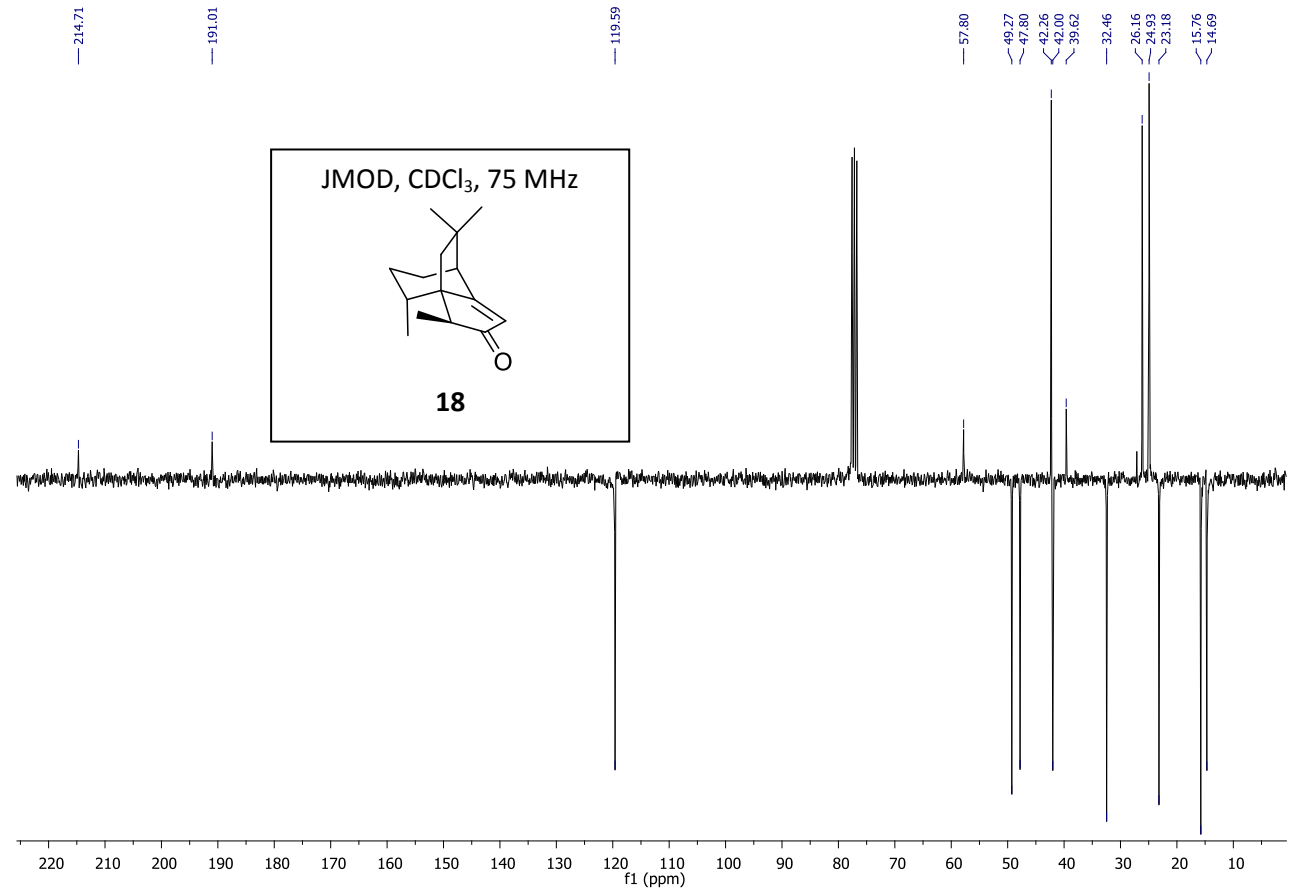
(+)-**1**

JMOD, $CDCl_3$, 75 MHz

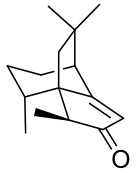


(+)-**1**

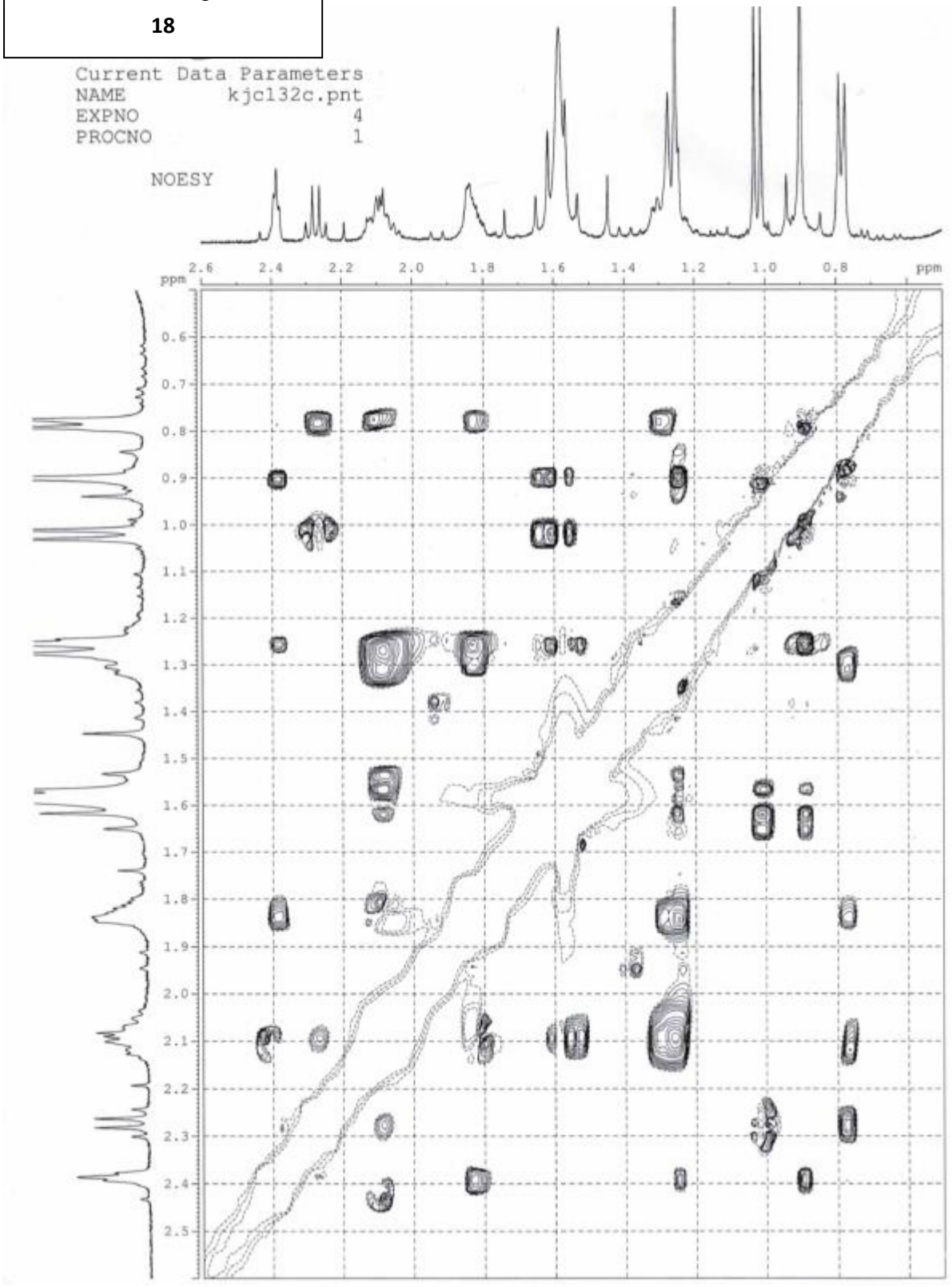

^{1}H NMR, $CDCl_3$, 300 MHz
18
5.79
2.36
2.26
2.23
2.13
2.00
1.85
1.76
1.63
1.59
1.55
1.50
1.30
1.25
1.23
1.01
0.98
0.88
0.77
0.75
1.00
0.97
1.11
2.12
1.87
2.44
1.06
4.56
3.17
3.31
3.22
f1 (ppm)


JMOD, $CDCl_3$, 75 MHz
18
214.71
191.01
119.59
57.80
49.27
47.80
42.26
42.00
39.62
32.46
26.16
24.93
23.18
15.76
14.69
f1 (ppm)

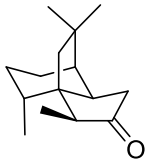
NOESY, $CDCl_3$, 300 MHz



18

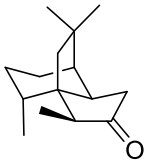


^{1}H NMR, $CDCl_3$, 300 MHz



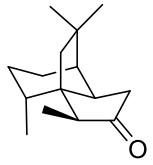
(+)-**2**

JMOD, $CDCl_3$, 75 MHz

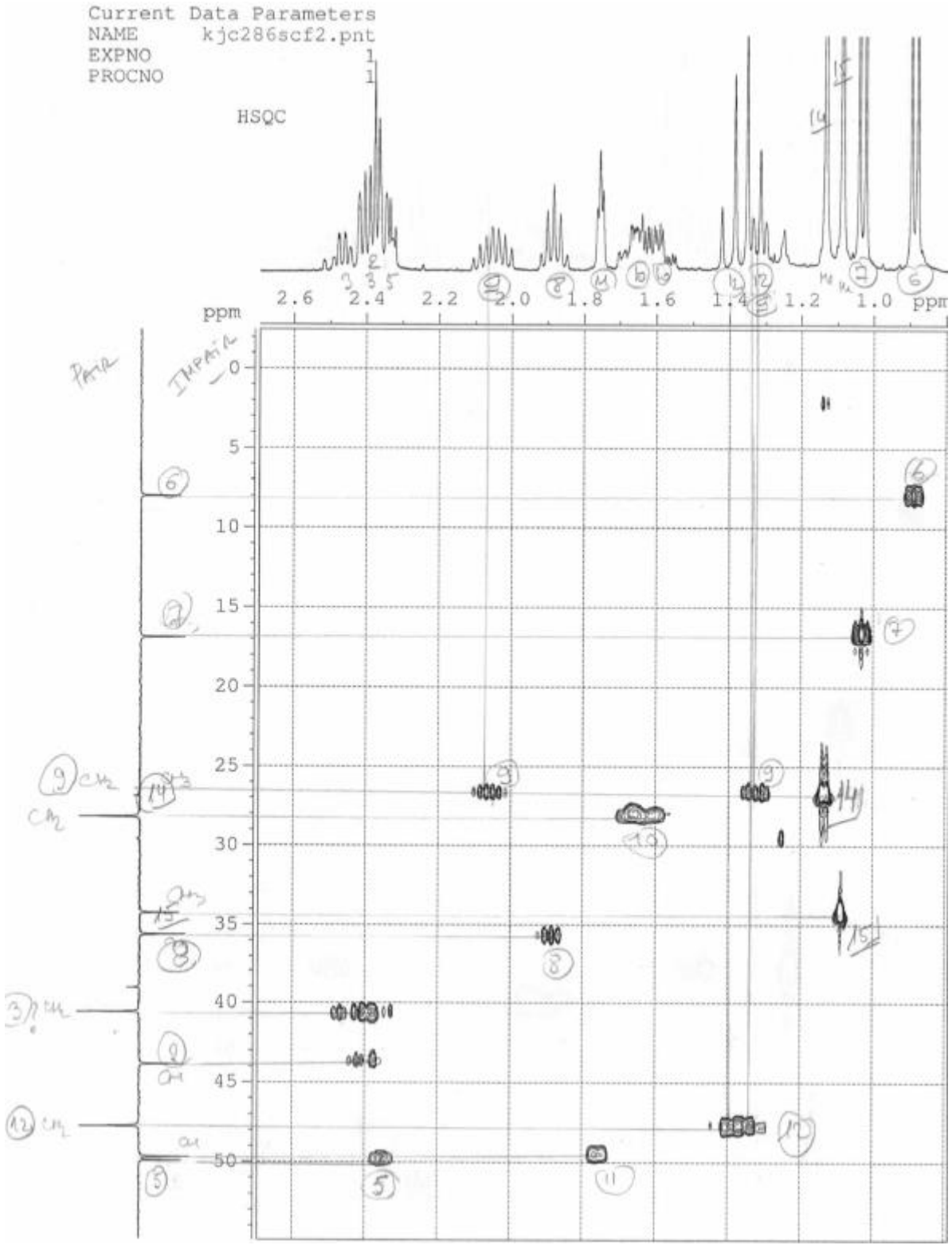


(+)-**2**

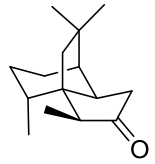
HSQC, $CDCl_3$, 400 MHz



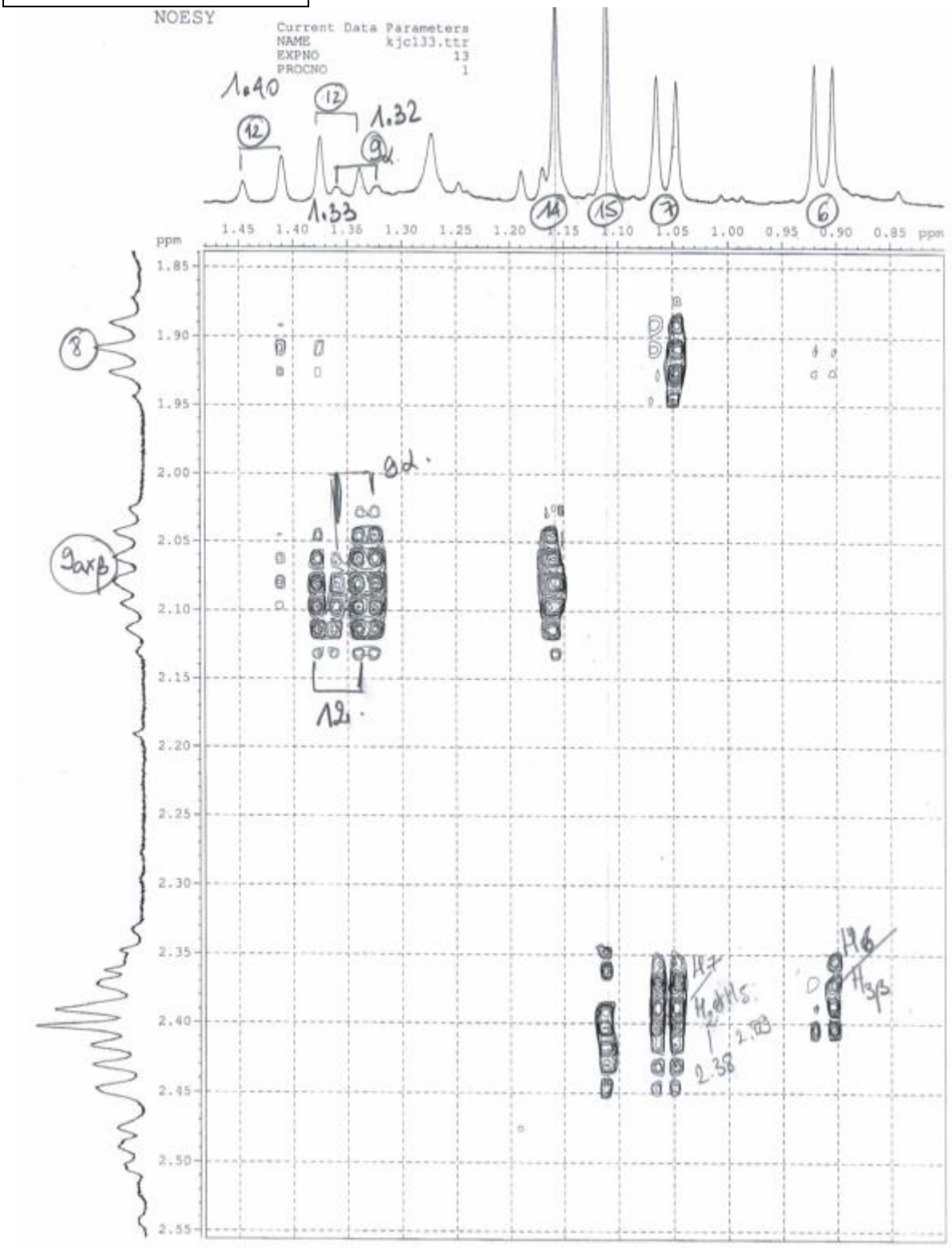
(+)-**2**



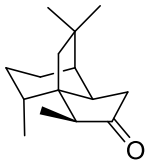
NOESY, $CDCl_3$, 400 MHz



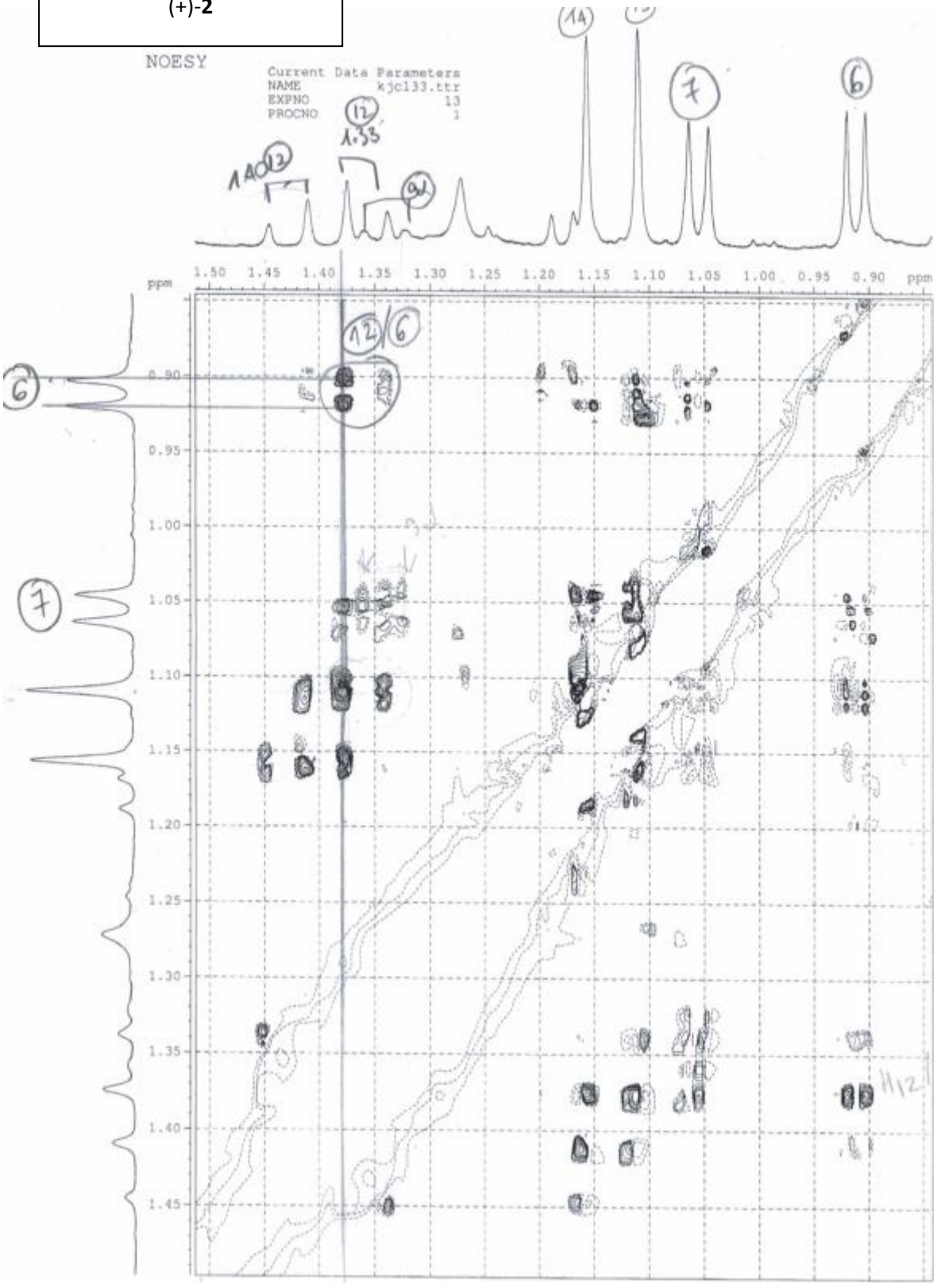
(+)-**2**



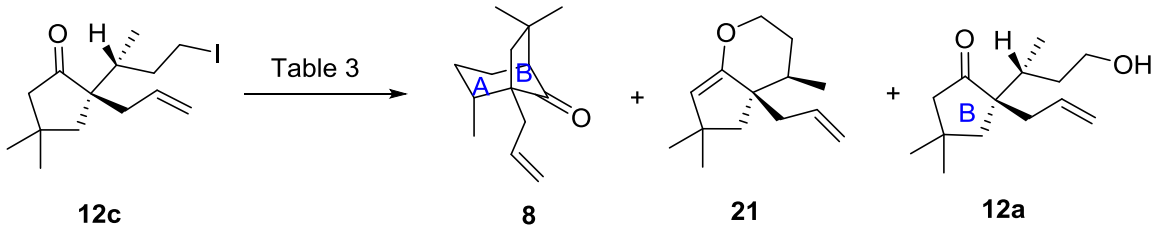
NOESY, $CDCl_3$, 400 MHz



(+)-**2**



Attempted optimization of reaction conditions for the synthesis of 10 from 12c



12c **8** **21** **12a**

Base	Solvent	Temp. (°C)	Time	8 : 21 : 12a (ratio NMR)	8 (%)	Combined yield (%)
tBuOK	tBuOH	Reflux	16 h	29 : 71 : 0	27	93
tBuOK	THF	50	30 min	27 : 73 : 0	13[a]	49[a]
tBuOK (20% in THF)	THF	50	30 min[7]	24 : 76 : 0	13[a]	49[a]
tBuOK (20% in THF)	THF	t.a.	30 min	21 : 79 : 0	13[a]	49[a]
LDA	THF	-78	1 h[8]	24 : 37 : 39	24	62
LiHMDS	THF	-78 to RT.	6 h30	34 : 66 : 0	15[b]	44[b]
tBuONa	DMSO	50	24 h[9]	/	< 10	82
tBuOK (20% in THF)	MeCN	RT	20 min	17 : 83 : 0	12	97

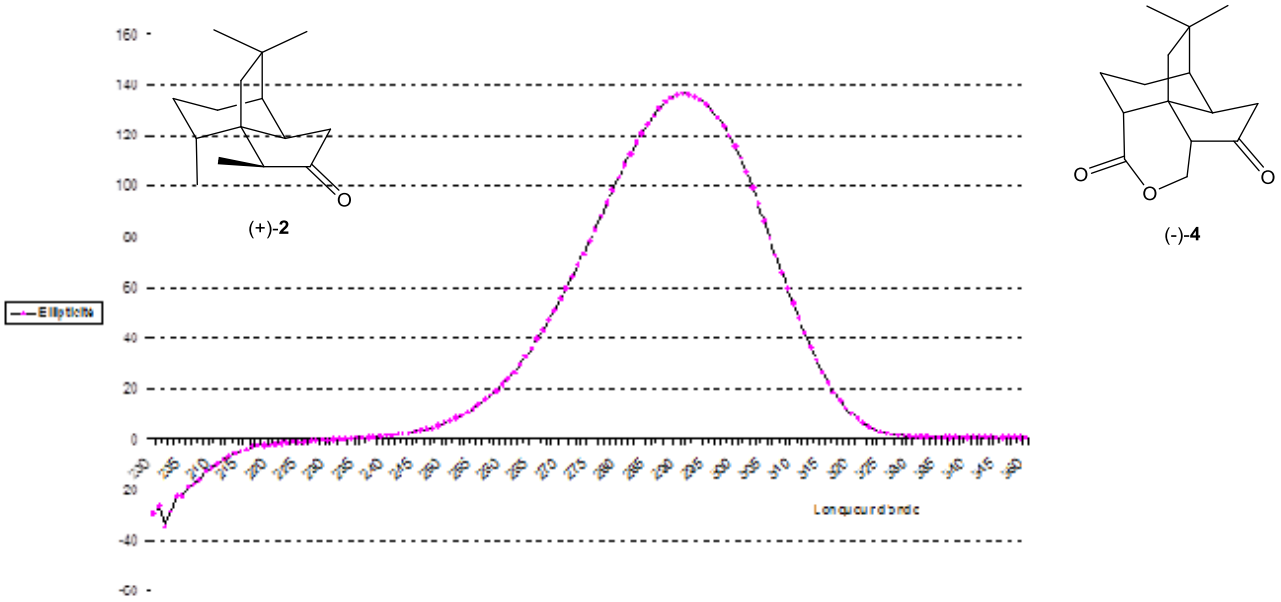
[a] Combined purification of the 3 assays, [b] Calculated from NMR relative to iodide **12c**

Table 3: Optimization of reaction conditions for the synthesis of **8** from **12c**

Enol ether 21: IR (neat, ν cm^{-1}) : 2955, 2862, 1667, 1639; $[\alpha]^{20}_{D}$ = -91° (c = 1.135, $EtOH_{abs}$); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 5.86-5.72 (m, 1H), 5.05-5.00 (m, 2H), 4.74 (s, 1H), 4.18-4.13 (m, 1H), 3.66-3.57 (m, 1H), 2.9 (dd, *J* = 15, 6 Hz, 1H), 1.97-1.79 (m, 2H), 1.73 (d, *J* = 15 Hz, 1H), 1.76-1.68 (m, 1H), 1.51 (d, *J* = 15 Hz, 1H), 1.37-1.32 (m, 1H), 1.05 (s, 3H), 1.04 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm : 158.1 (C), 137.1 (CH), 116.5 (CH_2), 115.7 (CH), 71.4 (CH_2), 49.2 (C), 47.9 (CH_2), 43.1 (CH), 38.1 (CH). 35.7 (CH_2), 33.5 (CH_3), 30.0 (CH_2), 29,8 (CH_3), 16,0 (CH_3).

[7] R. Rodriguez, A-S. Chapelon, C. Ollivier, M. Santelli, *Tetrahedron*, **2009**, 65, 7001-7015
[8] M. Solomon, W. Hoekstra, G. Zima, D. Liotta, *J. Org. Chem.*., **1988,** 53, 5058-5062
[9] Y. Hara, M. Matsuda, *Bul. Chem. Soc. J.*, **1976**, 49(4), 1129-1129

Confirmation of the absolute configuration for (+)-2 by ECD



Experimental CD spectrum of (+)-suberosanone at 25°C in EtOH. $\Delta\varepsilon$ = + 3.19 $L.mol^{-1}cm^{-1}$ (Left) and 1*R*-quadrone (Right).

For comparison, positive Cotton effect and similar $\Delta\varepsilon$ are observed in both cases. Molar circular dichroism value for (-)-(1*R*) quadrone **4** is: $\Delta\varepsilon$ = + 2.68 $Lmol^{-1}cm^{-1}$.[10]

[10] A. B. Smith III, J. P. Konopelski, B. A. Wexler, P. A. Sprengeler, *J. Am. Chem. Soc.* **1991**, *113*, 3533.

Biological studies:

Metastatic breast cancer (MDA231), intestinal (HT29), adenocarcinomic human alveolar basal epithelial (A549), human breast cancer (MCF7), human glioblastoma (SF268) and human diploid embryonic lung (MRC5) cells were seeded into 96-well microplates at 2000 cells per well. The cell lines were incubated for 72 h with different concentrations of drugs. The final volume in each experiment was made up with the media containing 1% DMSO final volume. Docetaxel was used as positive control. The experiments were performed in triplicate. Cell growth inhibition was determined by the MTS assay according to the recommendations of the manufacturer [Promega]. The optical density was measured at 490 nm. The number of viable cells was proportional to the extent of formazan production. The percent cytotoxicity index [(OD490 treated/OD490 control) x100] was calculated from three experiments. Due to these modest cytotoxic activities, IC_{50} were not determined.

	MDA231	HT29	A549	MCF7	SF268	MRC5
10^{-5}M	48±1%	30±1%	32±1%	46±1%	43±1%	55±5%
10^{-6}M	12±1%	12±1%	1±1%	0±15%	13±1%	11±14%

Table 4: *In vitro* cell growth inhibitory effects of (+)-suberosanone at 10^{-5} and 10^{-6} M.