Electronic Supplementary Material (ESI) for Chemical Communications

The first total synthesis of (+)-mucosin

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Supplementary Information

Contents:

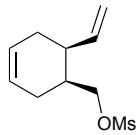
1. General experimental information

All reactions were carried out under an argon atmosphere using standard Schlenk equipment and syringe techniques. All glassware was dried in a hot oven (160 ºC, for at least 12 hours) and cooled in a sealed desiccator over silica gel or assembled while hot and cooled under vacuum. DCM, DMSO and MeCN were freshly distilled from CaH_2. DMF was freshly distilled from $MgSO_4$. Et_2O, THF and toluene were freshly distilled from sodium/benzophenone. *n*-BuLi was used as a 2.5 M solution in hexanes and was stored at 4 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures. Reactions were monitored by GC and/or TLC. GC was performed on a Hewlett Packard HP 6890 series GC system, using a HP-5 (cross-linked 5% PhMe-siloxane) 30 m column, with a film thickness of 0.25 µm and 0.32 mm internal diameter. The carrier gas was helium and the flow rate was 2.7 mL min^{-1}. TLC was performed using Merck silica gel 60 F_{254} plates with detection by UV and/or polyphosphomolybdic acid dip. Silica gel 60A (particle size 35-70 microns) supplied by Fisher Scientific was used for flash chromatography columns. Columns were packed and run under light pressure. Solvent compositions are described as ratios prior to mixing. NMR spectra were recorded on a Bruker DPX400 spectrometer. Chemical shifts for proton and carbon NMR spectra are reported on the δ scale in ppm and were referenced to residual chloroform peaks at 7.27 ppm for ^{1}H spectra and 77.00 ppm (centre peak of triplet) for ^{13}C spectra. The coupling constants (*J*) are measured in Hz (Hertz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), sextet (sxt), multiplet (m), broad (br), or a combination of these. Electron impact ionisation (EI) and chemical ionisation (CI) mass spectra were recorded on a ThermoQuest TraceMS GCMS. Electrospray mass spectra (ESI) were recorded using a VG platform quadrupole spectrometer. Accurate mass spectra were recorded on a VG analytical 70-250-SE double focusing mass spectrometer using EI at 70 eV or a Bruker Apex III using ESI. Infra-red spectra were run as neat films on a Thermo Nicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate attachment. Absorptions are given in wavenumbers (cm^{-1}). Enantioselective ring opening of *cis*-3a,4,7,7a-

tetrahydroisobenzofuran-1,3-dione (**9**) to afford (1*R*,6*S*)-6-(methoxycarbonyl)cyclohex-3-enecarboxylic acid (**10**) was carried out as described by Bolm[1] and enantiomeric excess determined as described in section 5. Reductive ring closure of **10** to give (3a*S*,7a*R*)-3a,4,7,7a-tetrahydroisobenzofuran-1(3H)-one (**11**) was as described by Ferkany,[2] and conversion of **11** into ((1*S*,6*S*)-6-vinylcyclohex-3-en-1-yl)methanol (**12**) as described by Chibale.[3]

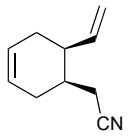
2. Synthesis and characterisation of new compounds.

((1*R*,6*R*)-6-Vinylcyclohex-3-en-1-yl)methyl methanesulfonate



Et_3N (4.3 mL, 31.1 mmol), DMAP (257 mg, 2.1 mmol) and methane sulfonyl chloride (1.9 mL, 25 mmol) were added dropwise sequentially to ((1*S*,6*S*)-6-vinylcyclohex-3-en-1-yl)methanol (**12**) (2.87 g, 20.8 mmol) in dry THF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours, poured into NH_4Cl aq and extracted with ether (3 x 50 mL). The organic extracts were combined, washed with HCl (2 M, 150 mL), $NaHCO_3$ aq (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a yellow liquid (4.14 g). Purification by column chromatography (SiO_2, hexane/Et_2O 2:1) gave the title compound as a colourless liquid (3.95 g, 88%). $[\alpha]_D^{28}$ = −7° (c = 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3026, 2904, 2839, 1170, 941; δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddd, *J* 17.8, 9.7, 8.3 Hz), 5.69 (2H, br. s), 5.14 (1H, m), 5.10 (1H, m), 4.17-4.03 (2H, m), 3.00 (3H, s), 2.61 (1H, sxt, *J* 4.4 Hz), 2.42-2.08 (3H, m), 2.05-1.81 (2H, m); δ_C (101 MHz, $CDCl_3$) 137.6, 125.5, 124.7, 116.5, 71.5, 37.6, 37.2, 36.2, 29.6, 25.1; LRMS (CI): *m*/*z* 234.1 ($[M+NH_4]^+$, 100%); HRMS (ES+) Calculated for $C_{10}H_{16}NaO_3S$ ($M + Na^+$): *m*/*z* 239.0712. Found: *m*/*z* 239.0709.

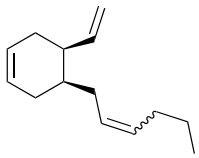
2-((1*S*,6*R*)-6-Vinylcyclohex-3-en-1-yl)acetonitrile (13)



A solution of ((1*R*,6*R*)-6-vinylcyclohex-3-en-1-yl)methyl methanesulfonate (3.91 g, 18.1 mmol) and 18-crown-6 (2.59 g, 9.8 mmol) in dry MeCN (65 mL) was added to KCN (2.36 g, 36.2 mmol) and NaI (195 mg, 1.3 mmol). The mixture was heated to reflux for 60 hours. The mixture was poured into water (200 mL) and extracted with ether (3 x 50 mL). The organic extracts were

combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange liquid (2.80 g). Purification by column chromatography (SiO_2, hexane/Et_2O 5:1) gave the title compound as a colourless liquid (2.25 g, 84%). $[\alpha]_D^{28}$ = −17° (c = 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3028, 2907, 2840, 729; δ_H (400 MHz, $CDCl_3$) 5.76 (1H, ddd, *J* 17.7, 9.8, 8.2 Hz), 5.70-5.61 (2H, m), 5.15 (1H, m), 5.12 (1H, m), 2.55 (1H, m), 2.36-2.13 (5H, m), 2.02-1.87 (2H, m); δ_C (101 MHz, $CDCl_3$) 137.3, 125.2, 124.5, 119.2, 116.8, 39.6, 33.9, 29.0, 28.2, 19.7; LRMS (EI): *m*/*z* 147.0 ($M^{+\cdot}$, 35%), 53.5 (C_4H_6, 100%); HRMS (EI) Calculated for $C_{10}H_{13}N$: *m*/*z* 147.1048. Found: *m*/*z* 147.1049.

(4*R*,5*R*)-4-(Hept-2-en-1-yl)-5-vinylcyclohex-1-ene (6)

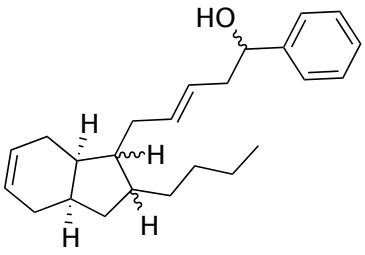


DIBAL-H (31 mL of a 1.0 m solution in toluene, 31 mmol) was added dropwise to a stirred solution of nitrile **13** (2.17 g, 14.7 mmol) in dry THF (45 mL) at –78 °C. The mixture was stirred at –78 °C for 30 minutes and at room temperature for 2 hours. Saturated $NaHCO_3$ solution (100 mL) was added and stirred at RT for 2 hours. The reaction mixture was extracted with ether (3 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the intermediate aldehyde, 2-(6-vinyl-cyclohex-3-enyl)acetaldehyde (**S1**) as a colourless liquid (2.13 g). δ_H (300 MHz, $CDCl_3$) 9.731 (1H, t, J = 1.7 Hz), 5.911 (1H, ddd, J = 17.4, 10.4, 8.4 Hz), 5.1 – 4.9 (2H, m), 2.5 – 2.2 (4H, m), 1.7 – 1.3 (8H, m). δ_C (75 MHz, $CDCl_3$) 202.98, 139.41, 115.81, 46.45, 43.26, 34.28, 29.83, 29.11, 24.23, 22.83 ppm.

n-BuLi (8.4 mL of a 2.5 M solution in hexanes, 21 mmol) was added dropwise to butyltriphenylphosphonium bromide (8.39 g, 21 mmol) in dry THF (60 mL) at 0 °C and left stirring at room temperature for 45 minutes. The reaction mixture was cooled to 0 °C. The intermediate aldehyde **S1** (2.11 g, 14 mmol) was added dropwise to the reaction mixture at 0 °C and the mixture stirred at

room temperature for 45 minutes. The reaction mixture was poured into NH_4Cl solution (300 mL) and extracted with ether (3 x 50 mL). The organic extracts were combined, washed with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* filtered through a plug of silica and the solvent removed *in vacuo* to give the crude product as a pale yellow liquid (4.67 g). Purification by column chromatography (SiO_2, pentane) gave the title compound (4 : 1 *Z* : *E*) as a colourless liquid (1.64 g, 59% over 2 steps). $[\alpha]_D^{28}$ = +4° (c = 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3022, 2958, 2908, 2837; δ_H (400 MHz, $CDCl_3$) 5.87 (1H, m), 5.65 (2H, br. s), 5.48-5.30 (2H, m), 5.11-4.97 (2H, m), 2.45 (1H, m), 2.25 (1H, m), 2.14-1.92 (5H, m), 1.91-1.68 (2H, m), 1.46-1.20 (3H, m), 0.94-0.86 (3H, m); δ_C (101 MHz, $CDCl_3$) (*Z*)-isomer: 139.6, 130.7, 128.6, 126.2, 125.3, 114.8, 40.4, 37.2, 30.1, 29.4, 29.3, 28.7, 22.9, 13.8; (*E*)-isomer, visible in mixture and separately prepared as the major isomer using a Julia olefination: 139.4, 131.6, 129.0, 126.3, 125.3, 114.8, 40.1, 36.9, 35.1, 34.8, 30.3, 28.6, 22.7, 13.7; The *E*/*Z* assignment follows from the high shifts of the 35.1 and 34.8 carbons in the *E* isomer.[5] LRMS (EI): *m*/*z* 190.0 ($M^{+\cdot}$, 7%), 78.9 (100%); HRMS (EI) Calculated for $C_{14}H_{22}$: *m*/*z* 190.1722. Found: *m*/*z* 190.1725.

rac-(*E*)-5-((3a*R*,7a*R*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)-1-phenylpent-3-en-1-ol (16)

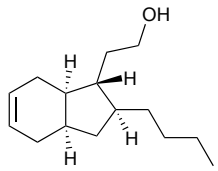


n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (307 mg, 1.05 mmol) in dry THF (5 mL) at −78 °C. Triene **6** (190 mg, 1.0 mmol) in dry THF (3 mL) was added dropwise to the reaction mixture at –78 °C. After stirring at –78 °C for 15 minutes the mixture was warmed to room temperature gradually. To obtain the thermodynamic product **16a** as the major diastereoisomer the reaction

mixture was stirred at 65 °C for 30 minutes (to obtain the kinetic product **16b** as the major diastereoisomer the reaction mixture was instead stirred at room temperature for 75 minutes). The reaction mixture was re-cooled to –78 °C. A solution of allyl chloride (0.1 mL, 1.2 mmol) in dry THF (1 mL) was added followed by dropwise addition of LiTMP [prepared by adding *n*-BuLi (0.48 mL of a 2.5 M solution in hexanes, 1.2 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.2 mmol) in THF (2 mL) at 0 °C and stirring at 0 °C for 20 minutes]. The reaction mixture was allowed to warm to –65 °C over 20 minutes. Benzaldehyde (0.30 mL, 3.0 mmol) in dry THF (3 mL) and $BF_3{\cdot}OEt_2$ (0.36 ml, 3.0 mmol) were added dropwise. The reaction mixture was warmed gradually to –5 °C within 4 h before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The mixture was left stirring at room temperature overnight before being poured into water (100 mL) and extracted with ether (3 x 50 mL). The organic extracts were combined, washed with water (3 × 100 mL), brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a pale yellow oil. Purification by column chromatography (SiO_2, hexane/EA 39:1→9:1) gave the title compound as an inseparable 3.1:1 (**16a**:**16b**) mixture of diastereoisomers, also epimeric at the secondary alcohol centre, as a pale yellow oil (0.026 g, 8%). ν_{max} (neat)/cm^{-1} 3380, 3024, 2956, 2911, 692, 669; δ_H (400 MHz, $CDCl_3$) 7.27-7.16 (5H, m), 5.61-5.47 (3H, m), 5.36-5.28 (1H, m), 4.62-4.58 (1H, m), 2.44-2.32 (2H, m), 2.20-1.96 (5H, m), 1.70-1.59 (2H, m), 1.53-1.39 (3H, m), 1.36-0.96 (9H, m), 0.81 (3H, br t, *J* 7.0 Hz); δ_C (101 MHz, $CDCl_3$) 144.0, 133.6, 128.3, 127.4, 127.3, 127.0, 126.4, 125.8[16b], 125.8[16a], 73.6[16b], 73.5[16a], 52.1[16b], 52.1[16a], 47.1[16b], 47.0[16a], 42.8, 42.3[16b], 42.2[16a], 40.0, 36.9, 36.7, 36.6[16b], 36.5[16a], 32.4, 31.5, 30.7, 22.9, 14.2; LRMS (EI): m/z 320 ([M – H_2O]$^+$, 27%), 130 (100%). LRMS (ES+): *m*/*z* 361.2 (M+Na)$^+$; HRMS (ES+) Calculated for $C_{24}H_{34}NaO$: 361.2502, Found: 361.2502.

Under 'kinetic conditions', after chromatography, the title compound was obtained as a 1:1.5 (**16a**:**16b**) mixture of major isomers still containing 31% **6** (0.20 g, 41% yield of **16**) and smaller amounts of unidentified products, probably isomers of **16**.

2-((1*R*,2*S*,3a*R*,7a*R*)-2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)ethanol (19a)



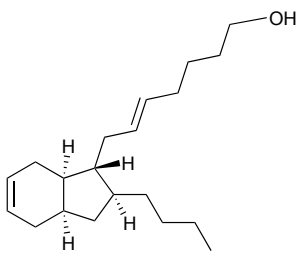
n-BuLi (6.8 mL of a 2.5 M solution in hexanes, 17 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (2.49 g, 8.5 mmol) in dry THF (40 mL) at –78 °C. Triene **6** (1.62 g, 8.5 mmol) in dry THF (25 mL) was added dropwise to the reaction mixture at –78 °C. After stirring at –78 °C for 20 minutes the mixture was warmed to room temperature. After stirring at room temperature for 2 hours the reaction mixture was heated to 65 °C for 30 minutes. The reaction mixture was recooled to –78 °C and (chloromethyl)dimethylphenylsilane (1.5 mL, 8.5 mmol) was added dropwise. LiTMP [prepared by adding *n*-BuLi (3.4 mL of a 2.5 M solution in hexanes, 8.5 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (1.4 mL, 8.5 mmol) in THF (25 mL) at 0 °C and stirring at 0 °C for 30 minutes] was added dropwise at –78 °C. After stirring at –78 °C for 1 hour the reaction mixture was stirred at room temperature for 2 hours. MeOH (40 mL) and a saturated solution of $NaHCO_3$ (40 mL) were added and the reaction mixture stirred at room temperature for 16 hours. The reaction mixture was poured into water (300 mL) and extracted with ether (3 x 50 mL). The organic extracts were combined, washed with water (300 mL), brine (300 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the intermediate silane as a yellow liquid (3.08 g). KH (8.18 g of a 25-35% suspension in mineral oil, 8.5 mmol) was washed with hexane (3 x 20 mL). N-methylpyrrolidinone (NMP) (26 mL) was added and the reaction mixture cooled to 0 °C. *t*-Butylhydroperoxide (9.3 mL, 51 mmol) was added and the reaction mixture warmed to room temperature. The intermediate silane (2.72 g, 7.5 mmol) in NMP (50 mL) was added and the reaction mixture stirred at room temperature for 10 minutes. TBAF (26 mL of a 1.0 M solution in THF, 26 mmol) was added and the reaction mixture heated to 70 °C for 15 hours. $Na_2S_2O_3$ (17.0 g) and water (50 mL) were added and the reaction mixture stirred for 5 minutes. The reaction mixture was extracted with ether (3 x 50

mL). The organic extracts were combined, washed with water (2 x 100 mL), 2M NaOH solution (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a colourless liquid (7.96 g). Purification by column chromatography (SiO_2, DCM) gave a 2.7:1 mixture of diastereoisomeric alcohols **19a** and **19b** as a colourless liquid (1.42 g, 75%). Purification by HPLC (hexane/EA 10:1) allowed isolation of the pure required diastereoisomer **19a**. $[\alpha]_D^{28}$ = +56° (c = 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3323, 3020, 2955, 2920, 2875, 2858; δ_H (400 MHz, $CDCl_3$) 5.74-5.61 (2H, m), 3.71 (2H, t, *J* 7.3 Hz), 2.35-2.15 (2H, m), 1.85-1.47 (7H, m), 1.45-1.06 (9H, m), 0.90 (3H, t, *J* 6.8 Hz); δ_C (101 MHz, $CDCl_3$) 127.3, 126.9, 62.0, 48.9, 48.1, 43.7, 40.1, 38.0, 37.1, 37.0, 32.3, 31.7, 30.8, 22.9, 14.1; LRMS (CI): *m*/*z* 223.2 (MH+, 29%), 221.1 (100%); HRMS (ES+) Calculated for $C_{15}H_{26}NaO$: *m*/*z* 245.1876. Found: *m*/*z* 245.1877.

Purification of 2-((1*R*,2*S*,3a*R*,7a*R*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1H-inden-1-yl)ethanol (19a) by iodoetherification of other diastereoisomers.

Alcohol **19** (1.36 g, 6.1 mmol) and iodine (0.609, 2.4 mmol) were refluxed in benzene (12 mL) for 5 hours. The reaction mixture was poured into a saturated solution of $Na_2S_2O_3$ (300 mL) and extracted with ether (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the crude product as a black liquid (1.81 g). Purification by column chromatography (SiO_2, CH_2Cl_2) gave the title compound as a colourless liquid and single diastereoisomer (533 mg, 39% recovery).

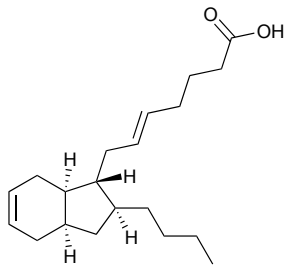
(*E*)-7-((1*R*,2*S*,3a*R*,7a*R*)-2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)hept-5-en-1-ol (23)



DMSO (0.36 mL, 5.1 mmol) in dry DCM (0.60 mL) was added dropwise to oxalyl chloride (0.21 mL, 2.5 mmol) in dry DCM (5.3 mL) at –60 °C. The reaction mixture was stirred at –60 °C for 2 minutes. Alcohol **19a** (0.512 g, 2.3 mmol) in dry DCM (2.3 mL) was added dropwise to the reaction mixture at –60 °C. The reaction mixture was stirred at –60 °C for 15 minutes. Et_3N (1.6 mL, 11.5 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at –60 °C for 15 minutes and then left stirring at room temperature for 1 hour. The reaction mixture was poured into water (25 mL). The aqueous phase was extracted with DCM (3 x 30 mL). The organic extracts were combined, washed with brine (50 mL), 1% HCl solution (50 mL), 5% Na_2CO_3 solution (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give intermediate aldehyde **20** as an orange liquid (0.501 g). Dry DMF (0.48 mL, 6.2 mmol) was added dropwise to $CrCl_2$ (0.762 g, 6.2 mmol) in THF (15 mL) at room temperature. After stirring at room temperature for 45 minutes a solution of intermediate aldehyde **20** (171 mg, 0.77 mmol) and diiodide **21** (0.727 g, 1.6 mmol) in THF (2.5 mL) was added to the reaction mixture. Stirring was continued at room temperature for 3 hours. The reaction mixture was diluted with pentane (15 mL) and poured into water (50 mL). The aqueous phase was further extracted with pentane (3 x 20 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude intermediate silane **22** as a brown liquid (0.976 g). Purification by column chromatography (SiO_2, hexane→hexane/Et_2O 19:1) removed the major impurities to give intermediate silane **22** as a colourless liquid (0.583 g). To a solution of intermediate silane **22** (0.519 g, 0.69 mmol) in THF (3 mL) TBAF (4.8 mL of a 1.0 M solution in THF, 4.8 mmol) was added dropwise. The reaction mixture was left stirring at room temperature for 3 hours. The reaction mixture was poured into water (30 mL) and extracted with ether (3 x 15 mL). The organic extracts were combined, washed with brine (2 x 30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a yellow liquid (0.776 g). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a colourless liquid (162 mg, 81% over 3 steps). $[\alpha]_D^{29}$ = +45° (c = 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3326,

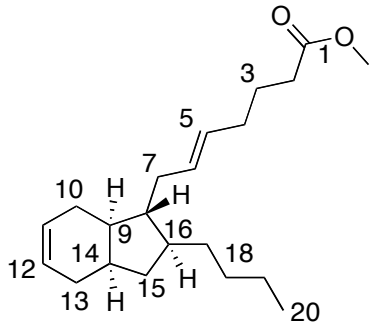
3019, 2917, 2878, 2857, 2833; δ_H (400 MHz, $CDCl_3$) 5.72-5.62 (2H, m), 5.52-5.33 (2H, m), 3.65 (2H, t, *J* 6.5 Hz), 2.35-1.95 (8H, m), 1.81-1.05 (16H, m), 0.89 (3H, t, *J* 6.9 Hz); δ_C (101 MHz, $CDCl_3$) 130.7, 129.5, 127.3, 127.2, 62.9, 52.3, 47.2, 42.3, 40.1, 37.0, 36.7, 36.7, 32.4, 32.3, 31.6, 30.7, 25.6, 22.9, 14.1; LRMS (CI): *m*/*z* 308.2 ($[M+NH_4]^+$, 100%), 291.2 ($[M+H]^+$, 42%), 290.2 ($[M]^{+\bullet}$, 20%), 273.2 ($[M-OH]^+$, 17%), 259.1 ($[M-CH_3O]^+$, 2%), 233.1 ($[M-C_4H_9]^+$, 6%), 231.2 ($[M-C_3H_7O]^+$, 2%), 177.1 ($[M-C_7H_{13}O]^+$, 42%); HRMS (EI) Calculated for $C_{20}H_{34}O$: *m*/*z* 290.2610. Found: *m*/*z* 290.2614.

(+)-Mucosin (1)



Pyridinium dichromate (271 mg, 0.72 mmol) was added to alcohol **23** (32.0 mg, 0.11 mmol) in DMF (1.0 mL) at 0 °C. After stirring at room temperature overnight the reaction mixture was poured into water (30 mL) and extracted with ether (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a colourless liquid (92.3 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as a colourless liquid (28.1 mg, 84%). $[\alpha]_D^{26}$ = +37.1° (c = 0.8, *n*-hexane); ν_{max} (neat)/cm^{-1} 3019, 2954, 2917, 2857, 1706; δ_H (400 MHz, $CDCl_3$) 7.91 (1H, br. s.), 5.85-5.56 (2H, m), 5.53-5.29 (2H, m), 2.35 (2H, t, J 7.5 Hz), 2.31-2.16 (2H, m), 2.15-2.09 (2H, m), 2.06 (2H, q, J 6.9 Hz), 1.81-1.65 (4H, m), 1.65-1.46 (3H, m), 1.46-1.36 (2H, m), 1.36-1.25 (3H, m), 1.24-1.16 (2H, m), 1.15-1.07 (2H, m), 0.89 (3H, t, J 6.8 Hz); δ_C (101 MHz, $CDCl_3$) 179.7, 130.5, 129.6, 127.3, 127.1, 52.2, 47.2, 42.3, 40.1, 37.0, 36.7, 36.7, 33.3, 32.4, 31.8, 31.6, 30.7, 24.5, 22.9, 14.1; LRMS (ES^-): m/z 303.4 $(M-H)^-$; HRMS (ES^+) Calculated for $C_{20}H_{32}NaO_2$: *m*/*z* 327.2295. Found: *m*/*z* 327.2300.

(*E*)-Methyl 7-((1*S*,2*R*,3a*S*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)hept-5-enoate (2)



Diazomethane in dry ether [produced by addition of KOH (99.0 mg, 1.9 mmol) in 96% ethanol (4 mL) to Diazald® (107 mg, 0.5 mmol) in dry ether (14 mL)] was distilled into a flask containing acid **1** (40.0 mg, 0.13 mmol) in ether (1 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 20 minutes followed by stirring at room temperature for 1 hour to remove excess diazomethane. The solvent was removed *in vacuo* to give a pale yellow liquid (112 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 20:1) gave the title compound as a colourless liquid (37.5 mg, 91%). $[\alpha]_D^{26}$ = +38.2° (c = 0.8, *n*-hexane), Lit.[6] for (–)-mucosin methyl ester $[\alpha]_D^{26}$ = = –35.5° (*n*-hexane, c = 0.8); ν_{max} (neat)/cm^{-1} 3019, 2951, 2919, 2857, 1740; δ_H (400 MHz, $CDCl_3$) 5.73-5.60 (2H, m), 5.46 (1H, m), 5.38 (1H, m), 3.67 (3H, s), 2.31 (2H, t, *J* 7.5 Hz), 2.23 (1H, m), 2.17 (1H, m), 2.15-2.08 (2H, m), 2.03 (2H, q, J 7.0 Hz), 1.80-1.65 (4H, m), 1.64-1.48 (3H, m), 1.46-1.33 (2H, m), 1.33-1.23 (3H, m), 1.19-1.13 (2H, m), 1.13-1.08 (2H, m), 0.89 (3H, t, *J* 6.9 Hz); δ_C (101 MHz, $CDCl_3$) 174.2, 130.3, 129.8, 127.3, 127.1, 52.2, 51.4, 47.2, 42.3, 40.1, 37.0, 36.7, 36.7, 33.4, 32.4, 31.9, 31.6, 30.7, 24.7, 22.9, 14.1; LRMS (CI): *m*/*z* 336.3 ($[M+NH_4]^+$, 100%), 319.3 ($[M+H]^+$, 75%), 318.2 ($[M]^{+\bullet}$, 3%), 303.2 ($[M-CH_3]^+$, 5%), 287.2 ($[M-CH_3O]^+$, 1%), 261.2 ($[M-C_4H_9]^+$, 2%); HRMS (EI) Calculated for $C_{21}H_{34}O_2$: *m*/*z* 318.2559. Found: *m*/*z* 318.2560.

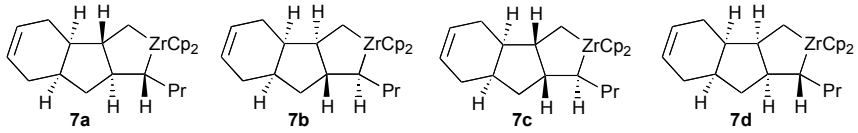
3. Comparison of synthetic and reported NMR data for Mucosin methyl ester

^{1}H NMR ($CDCl_3$)	
Methyl ester of natural sample of (–)-mucosin (500 MHz)[6]	Methyl ester of synthetic sample of (+)-mucosin (400 MHz)
5.67 (2H, m)	5.73-5.60 (2H, m)
5.45 (1H, dt, *J* 15.6, 6.9 Hz)	5.46 (1H, m)
5.39 (1H, dt, *J* 15.6, 7.2 Hz)	5.38 (1H, m)
3.66 (3H, s)	3.67 (3H, s)
2.31 (2H, t, *J* 7.5 Hz)	2.31 (2H, t, *J* 7.5 Hz)
2.25 (1H, m)	2.23 (1H, m)
2.19 (1H, m)	2.17 (1H, m)
2.12 (2H, m)	2.15-2.08 (2H, m)
2.02 (2H, q, J = 7.2 Hz)	2.03 (2H, q, J 7.0 Hz)
1.72 (1H, m)	1.80-1.65 (4H, m)
1.70 (1H, m)	
1.69 (2H, m)	
1.59 (1H ,m)	1.64-1.48 (3H, m)
1.55 (1H ,m)	
1.50 (1H ,m)	
1.40 (2H ,m)	1.46-1.33 (2H, m)
1.33 (1H ,m)	1.33-1.23 (3H, m)
1.28 (2H ,m)	
1.15 (2H ,m)	1.19-1.13 (2H, m)
1.12 (1H ,m)	1.13-1.08 (2H, m)
1.11 (1H ,m)	
0.88 (3H, t, *J* 6.7 Hz)	0.89 (3H, t, *J* 6.9 Hz)

^{13}C NMR ($CDCl_3$)	
Methyl ester of natural sample of (–)-mucosin (125 MHz)[6]	Methyl ester of synthetic sample of (+)-mucosin (100 MHz)
174.2	174.2
130.0	130.3
129.8	129.8
127.0	127.3
127.0	127.1
52.1	52.2
51.4	51.4
47.1	47.2
42.1	42.3
39.9	40.1
36.7	37.0
36.5	36.74
36.4	36.68
33.2	33.4
32.0	32.4
31.7	31.9
31.5	31.6
30.7*	30.7
24.5	24.7
22.6	22.9
13.8	14.1

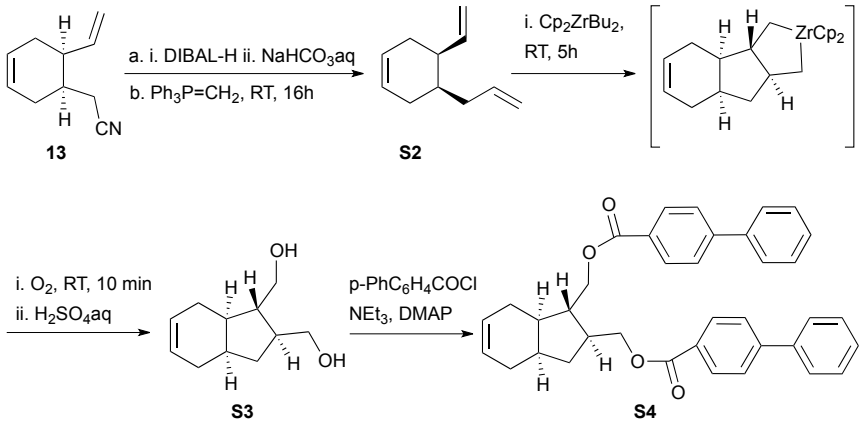
* Note that in the original paper[6] the 30.7 signal was omitted with an additional signal at 36.3. We thank Prof. Casapullo for reacquiring the carbon-13 spectra of natural mucosin to confirm the error.

4. Calculations on relative zirconacycle stability



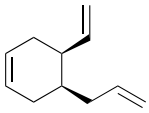
An extensive search for minimum energy conformations of the zirconacycles **7a** -**7d** as well as the epimers at the propyl group were carried out using both molecular mechanics (Merck Molecular Force Field (MMFF) parameter set extended to cope with transition metals and cyclopentadienyl ligands) and the PM3 semi-empirical method as implemented in the Spartan® 08 program from Wavefunction inc. All reasonable conformers obtained were then geometry optimised using the hybrid DFT/HF B3LYP method with the LACVP basis set (6-31G* basis set for light atoms and LANL2DZ effective core basis set for zirconium), as implemented in the Spartan 08 progam.[7] The heats of formation of **7a**-**d** were calculated to be -2574070.9, -2574065.6, -2574064.1 and -2574059.7 kJ/mol (energies relative to **7a**: 0, 5.3, 6.7, 11.2 kJ/mol), whereas for the propyl group epimers they were -2574051.3, -2574049.5, -2574043.6 and -2574040.3 kJ/mol (energies relative to **7a**: 19.6, 21.4, 27.2, 30.5 kJ/mol).

5. Cyclisation of a model system – crystallographic evidence for the relative stereochemistry of Mucosin.



Additional evidence for the relative stereochemistry of the chiral centres present in Mucosin was obtained through zirconocene induced cyclisation of the model substrate **S2** under conditions that gave the thermodynamically more stable zirconacycle (5 h at RT). Work-up with oxygen allowed a single diol **S3** to be isolated in 65% yield. Derivatisation as the bis- biphenylcarbonyl ester gave a crystalline compound **S4**, the structure of which was confirmed by X-ray crystallography.[8]

4-Allyl-5-vinylcyclohexene (S2)

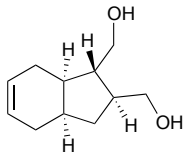


n-Butyllithium (5.9 mL of a 2.5 M solution in hexanes (14.8 mmol) was added to a solution of methyl triphenyl phosphonium bromide (5.28 g, 14.8 mmol) in THF (20 mL) at 0 °C under Ar. After 30 minutes, this red solution was added to a solution of 2-(6-vinyl-cyclohex-3-enyl)acetaldehyde (**S1**) (1.115 g, 7.4 mmol) in THF (20 mL) at –80 °C under Ar until a permanent yellow colour was observed (20 mL, 11.4 mmol of phosphorane solution added). The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into pentane and 2 M HClaq. The aqueous layer was separated and extracted with pentane. The combined organic phases were washed with 2 M HClaq and brine, dried over $MgSO_4$, filtered and

concentrated. The crude compound was purified by column chromatography (SiO_2, pentane) to give the title compound **S2** as a clear, colourless oil (827 mg, 5.6 mmol, 76%).

ν_{max} (neat)/cm^{-1} 3074, 3023, 2908, 2836, 1639, 1436, 994, 911, 658; δ_H (300 MHz, $CDCl_3$) 5.83 (2H, m), 5.66 (2H, m), 5.03 (4H, m), 2.48 (1H, m), 2.28 (1H, m), 2.1-1.7 (6H, m); δ_C (75 MHz, $CDCl_3$) 139.45, 137.93, 126.27, 125.48, 115.74, 115.19, 40.30, 36.53, 36.53, 30.30, 28.66; LRMS (APCI): *m/z* 148 (M^+); HRMS (EI): Calculated for $C_{11}H_{16}$: *m/z* 148.1252. Found: *m/z* 148.1259.

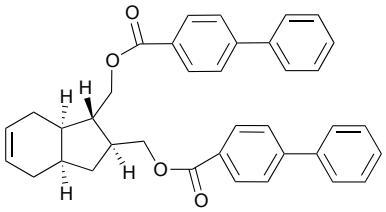
Rac-(2*S*, 3S, 3aR, 7aS)-[2-(Hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenyl] methanol (S3)



To a solution of $ZrCp_2Cl_2$ (234 mg, 0.8 mmol) in THF (5 mL) at –80 °C under Ar was added dropwise n-butyllithium (0.64 mL of a 2.5 M solution in hexanes, 1.6 mmol). After 10 minutes, a solution of 4-allyl-5-vinylcyclohexene **(S2)** (104 mg, 0.7 mmol) in THF (3 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 5 h resulting in a brown solution. Oxygen gas was bubbled through the solution for 10 min, resulting in a slight exotherm and a change of colour to pale yellow. The reaction was quenched by pouring into a 1:1 mixture of 5% H_2SO_4 / saturated sodium sulphate solution (20 mL) and ether (25 mL). The aqueous layer was separated and extracted with ether (6 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was subjected to column chromatography (SiO_2, 70% ether in petrol) providing the title compound **S3** as a viscous pale yellow oil (83 mg, 65%).

ν_{max} (neat)/cm^{-1} 3281, 3022, 2907, 1467, 1433, 1037, 911; δ_H ($CDCl_3$, 300 MHz) 5.67 (2H, m), 4.30 (2H, br s, -OH), 3.76 (2H, ddd, J = 13.2, 10.3, 3.7 Hz), 3.36 (2H, dt, J = 18.0, 9.9 Hz), 1.7 – 2.3 (10H, m); δ_C ($CDCl_3$, 75 MHz) 126.16, 125.78, 67.80, 66.44, 52.15, 47.40, 39.48, 35.15, 34.66, 28.20, 26.87; LRMS (APCI): *m/z* 183 $(M + H)^+$; HRMS (EI) Calculated for $C_{11}H_{16}O$ ($M – H_2O$): *m/z* 164.1201. Found: 164.1204

rac-(2*S*, 3*S*, 3a*R*, 7a*S*)-[2-(Hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenyl] methanol dibiphenoyl ester (S4)



A solution of biphenyl carbonyl chloride (238 mg, 1.1 mmol) in DCM (1 mL) was added dropwise to a solution of [2-(hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenyl]methanol (**S3**) (50 mg, 0.27 mmol), triethylamine (81 mg, 0.8 mmol) and DMAP (5 mg) in DCM (2 mL). After 1 h the reaction mixture was diluted with water and ether. The aqueous layer was extracted with ether and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography of the crude product (SiO_2, 40% ether in petrol) provided the desired product contaminated with biphenyl carbonyl chloride. Further chromatography (SiO_2, 30% - 40% DCM in petrol gradient) provided the desired compound **S4** in pure form as a white solid (67 mg, 46%). Crystallization from methanol provided a crystal suitable for x-ray analysis.

Melting Point: 63 – 65 °C. δ_H (300 MHz, $CDCl_3$) 8.13 (4H, d, J = 8.1 Hz), 7.7 – 7.6 (8H, m), 7.5 – 7.35 (6H, m,), 5.75 (2H, m), 4.5 – 4.4 (2H, m), 2.5 – 2.2 (4H, m), 2.2 – 1.9 (5H, m), 1.50 (1H, dt, J = 12.5, 8.1 Hz); δ_C (75 MHz, $CDCl_3$) 166.73, 145.82, 145.77, 140.13, 130.27, 129.09, 128.31, 127.44, 127.26, 126.12, 125.52, 69.16, 67.39, 47.04, 41.09, 38.87, 35.19, 35.10, 27.48, 27.06.

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Single Crystal X-Ray Diffraction Service
Chemistry - University of Southampton
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Table 1. Crystal data and structure refinement details.

Identification code	**99sot026**	
Empirical formula	$C_{37}H_{34}O_4$	
Formula weight	542.64	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 9.3378(10) Å	α = 80.548(6)°
	b = 10.0810(13) Å	β = 89.178(7)°
	c = 15.368(2) Å	γ = 79.890(7)°
Volume	1404.7(3) Å^3	
Z	2	
Density (calculated)	1.283 Mg / m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	576	
Crystal	Block; Colourless	
Crystal size	0.10 × 0.10 × 0.10 mm^3	
θ range for data collection	2.93 – 24.98°	
Index ranges	$-10 \le h \le 11$, $-11 \le k \le 11$, $-18 \le l \le 18$	
Reflections collected	17252	
Independent reflections	4790 [R_{int} = 0.2069]	
Completeness to θ = 24.98°	97.3 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9918 and 0.9818	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4790 / 276 / 371	
Goodness-of-fit on F^2	0.865	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0661, $wR2$ = 0.1167	
R indices (all data)	$R1$ = 0.2381, $wR2$ = 0.1681	
Extinction coefficient	0.0045(11)	
Largest diff. peak and hole	0.213 and –0.198 e Å^{-3}	

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C101	3866(5)	592(5)	7179(3)	47(1)	1
C102	4216(5)	64(5)	8054(3)	55(1)	1
C103	5051(5)	684(5)	8531(3)	56(1)	1
C104	5566(5)	1827(5)	8131(4)	57(1)	1
C105	5230(5)	2361(5)	7251(3)	46(1)	1
C106	4368(5)	1750(5)	6764(3)	38(1)	1
C107	3962(4)	2359(5)	5835(3)	35(1)	1
C108	3749(4)	3751(5)	5551(3)	40(1)	1
C109	3332(4)	4306(4)	4695(3)	37(1)	1
C110	3130(4)	3491(5)	4087(3)	37(1)	1
C111	3358(4)	2082(4)	4350(3)	38(1)	1
C112	3761(4)	1530(4)	5221(3)	41(1)	1
C113	2686(5)	4166(5)	3167(3)	39(1)	1
C114	2174(5)	3850(4)	1724(3)	42(1)	1
C115	2390(5)	2698(4)	1194(3)	38(1)	1
C116	1464(5)	1578(4)	1507(3)	47(1)	1
C117	646(5)	1410(5)	690(3)	48(1)	1
C118	–895(5)	2248(5)	648(3)	55(1)	1
C119	–1504(6)	2624(5)	–267(4)	60(2)	1
C120	–731(5)	2562(5)	–993(4)	56(2)	1
C121	868(5)	2066(5)	–978(3)	51(1)	1
C122	1581(5)	1928(5)	–80(3)	44(1)	1
C123	1985(5)	3216(4)	213(3)	38(1)	1
C124	3213(5)	3760(4)	–284(3)	43(1)	1
C125	3453(5)	5302(5)	–1615(3)	42(1)	1
C126	2809(5)	5908(4)	–2492(3)	37(1)	1
C127	3484(5)	6837(4)	–3027(3)	44(1)	1
C128	2948(5)	7428(4)	–3857(3)	40(1)	1
C129	1674(5)	7122(4)	–4180(3)	36(1)	1
C130	991(4)	6185(4)	–3640(3)	38(1)	1
C131	1545(4)	5575(4)	–2811(3)	40(1)	1
C132	1110(4)	7770(4)	–5071(3)	39(1)	1
C133	1368(5)	9047(5)	–5452(3)	59(2)	1
C134	869(5)	9653(5)	–6287(3)	67(2)	1
C135	79(5)	8995(5)	–6772(3)	55(1)	1
C136	–237(5)	7751(5)	–6402(3)	48(1)	1
C137	275(4)	7150(5)	–5569(3)	43(1)	1
O101	2411(3)	5379(3)	2935(2)	53(1)	1
O102	2618(3)	3256(3)	2627(2)	40(1)	1
O103	2682(3)	4412(3)	–1166(2)	43(1)	1
O104	4546(3)	5550(3)	–1323(2)	64(1)	1

Table 3. Bond lengths [Å] and angles [°].

C101–C102	1.384(6)	C118–C119	1.489(6)
C101–C106	1.388(6)	C119–C120	1.324(7)
C102–C103	1.368(6)	C120–C121	1.488(6)
C103–C104	1.375(6)	C121–C122	1.516(6)
C104–C105	1.389(6)	C122–C123	1.549(6)
C105–C106	1.390(6)	C123–C124	1.503(6)
C106–C107	1.484(6)	C124–O103	1.458(5)
C107–C108	1.380(5)	C125–O104	1.203(5)
C107–C112	1.395(6)	C125–O103	1.344(5)
C108–C109	1.374(6)	C125–C126	1.475(6)
C109–C110	1.377(5)	C126–C127	1.374(6)
C110–C111	1.390(5)	C126–C131	1.398(5)
C110–C113	1.495(6)	C127–C128	1.377(6)
C111–C112	1.392(6)	C128–C129	1.398(5)
C113–O101	1.200(5)	C129–C130	1.389(5)
C113–O102	1.344(5)	C129–C132	1.478(6)
C114–O102	1.453(5)	C130–C131	1.385(5)
C114–C115	1.509(6)	C132–C133	1.384(6)
C115–C123	1.541(6)	C132–C137	1.389(5)
C115–C116	1.551(6)	C133–C134	1.378(6)
C116–C117	1.527(6)	C134–C135	1.374(6)
C117–C118	1.532(5)	C135–C136	1.369(6)
C117–C122	1.537(6)	C136–C137	1.377(6)

C102–C101–C106	120.7(5)	O102–C113–C110	112.3(4)
C103–C102–C101	120.6(5)	O102–C114–C115	107.1(3)
C102–C103–C104	119.6(5)	C114–C115–C123	111.7(3)
C103–C104–C105	120.4(5)	C114–C115–C116	114.0(4)
C106–C105–C104	120.5(5)	C123–C115–C116	105.9(3)
C105–C106–C101	118.2(4)	C117–C116–C115	106.0(4)
C105–C106–C107	120.2(4)	C116–C117–C118	110.5(4)
C101–C106–C107	121.5(4)	C116–C117–C122	103.7(4)
C108–C107–C112	117.7(4)	C118–C117–C122	112.2(4)
C108–C107–C106	121.9(4)	C119–C118–C117	112.6(4)
C112–C107–C106	120.5(4)	C120–C119–C118	125.0(5)
C109–C108–C107	121.3(4)	C119–C120–C121	122.9(5)
C108–C109–C110	121.2(4)	C120–C121–C122	113.9(4)
C109–C110–C111	118.9(4)	C121–C122–C117	113.6(4)
C109–C110–C113	118.2(4)	C121–C122–C123	118.7(4)
C111–C110–C113	122.9(4)	C117–C122–C123	101.9(4)
C110–C111–C112	119.6(4)	C124–C123–C115	111.5(3)
C111–C112–C107	121.4(4)	C124–C123–C122	114.9(4)
O101–C113–O102	123.6(4)	C115–C123–C122	101.8(3)
O101–C113–C110	124.1(5)	O103–C124–C123	108.4(3)

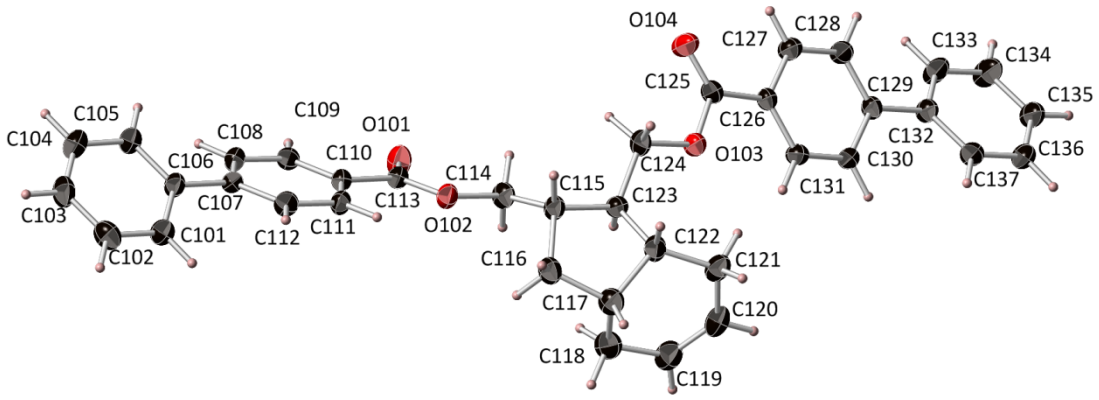
O104–C125–O103	122.7(4)	C130–C131–C126	120.4(4)
O104–C125–C126	124.9(5)	C133–C132–C137	116.0(4)
O103–C125–C126	112.3(4)	C133–C132–C129	121.6(4)
C127–C126–C131	118.2(4)	C137–C132–C129	122.3(4)
C127–C126–C125	118.8(4)	C134–C133–C132	122.2(5)
C131–C126–C125	123.1(4)	C135–C134–C133	120.2(5)
C126–C127–C128	121.6(4)	C136–C135–C134	119.0(5)
C127–C128–C129	120.9(4)	C135–C136–C137	120.3(5)
C130–C129–C128	117.5(4)	C136–C137–C132	122.2(4)
C130–C129–C132	122.3(4)	C113–O102–C114	114.9(3)
C128–C129–C132	120.2(4)	C125–O103–C124	117.0(3)
C131–C130–C129	121.4(4)		

Table 4. Anisotropic displacement parameters [Å²× 10³]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C101	46(3)	51(3)	42(3)	−6(3)	−5(2)	−10(2)
C102	57(3)	56(3)	44(3)	7(3)	3(3)	−8(3)
C103	57(3)	72(4)	34(3)	−8(3)	−7(3)	1(3)
C104	60(3)	67(3)	47(4)	−16(3)	−13(3)	−11(3)
C105	48(3)	54(3)	37(3)	−8(2)	−6(2)	−11(2)
C106	41(3)	42(3)	30(3)	−5(2)	−7(2)	−6(2)
C107	33(2)	40(3)	34(3)	−8(2)	−1(2)	−10(2)
C108	44(3)	46(3)	33(3)	−12(2)	−2(2)	−13(2)
C109	44(3)	34(3)	34(3)	−1(2)	1(2)	−15(2)
C110	39(2)	45(3)	28(3)	−6(2)	0(2)	−14(2)
C111	49(3)	39(3)	31(3)	−10(2)	−1(2)	−15(2)
C112	48(3)	36(3)	40(3)	−2(2)	−3(2)	−11(2)
C113	41(3)	48(3)	31(3)	−6(3)	−1(2)	−16(3)
C114	46(3)	45(3)	30(3)	7(2)	−7(2)	−9(2)
C115	44(3)	41(3)	28(3)	0(2)	−6(2)	−10(2)
C116	55(3)	51(3)	34(3)	−1(2)	0(2)	−12(2)
C117	53(3)	47(3)	43(3)	0(2)	−2(2)	−12(2)
C118	57(3)	55(3)	49(3)	−1(3)	−2(3)	−9(3)
C119	58(3)	67(3)	56(4)	−11(3)	−10(3)	−8(3)
C120	64(3)	57(3)	47(4)	−10(3)	−18(3)	−8(3)
C121	65(3)	45(3)	45(3)	−1(2)	−11(3)	−22(3)
C122	54(3)	48(3)	33(3)	−7(2)	−2(2)	−13(2)
C123	36(2)	45(3)	33(3)	−2(2)	−2(2)	−13(2)
C124	45(3)	54(3)	25(3)	5(2)	−10(2)	−10(2)
C125	43(3)	53(3)	30(3)	1(2)	0(2)	−14(2)
C126	40(2)	46(3)	26(3)	−2(2)	0(2)	−15(2)
C127	42(3)	51(3)	40(3)	−2(2)	−5(2)	−18(2)
C128	45(3)	42(3)	33(3)	7(2)	−5(2)	−19(2)
C129	43(3)	38(3)	28(3)	−1(2)	0(2)	−12(2)
C130	34(2)	47(3)	32(3)	−5(2)	−3(2)	−12(2)
C131	38(3)	47(3)	35(3)	−1(2)	−1(2)	−16(2)
C132	43(3)	42(3)	31(3)	4(2)	−7(2)	−13(2)
C133	79(3)	64(3)	41(3)	9(3)	−21(3)	−43(3)
C134	84(4)	70(3)	48(4)	23(3)	−24(3)	−42(3)
C135	59(3)	70(3)	35(3)	10(3)	−12(3)	−28(3)
C136	46(3)	58(3)	39(3)	−2(3)	−10(2)	−15(3)
C137	46(3)	46(3)	38(3)	−1(2)	−2(2)	−16(2)
O101	79(2)	39(2)	41(2)	−4(2)	−8(2)	−11(2)
O102	49(2)	39(2)	31(2)	−4(2)	−5(2)	−12(2)
O103	46(2)	54(2)	31(2)	2(2)	−4(2)	−20(2)
O104	58(2)	95(3)	42(2)	10(2)	−14(2)	−43(2)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H101	3276	157	6858	56	1
H102	3874	−735	8326	65	1
H103	5273	327	9135	67	1
H104	6156	2254	8458	69	1
H105	5592	3151	6981	55	1
H108	3894	4338	5954	48	1
H109	3180	5269	4521	44	1
H111	3240	1500	3939	46	1
H112	3902	568	5400	50	1
H11A	2772	4542	1485	50	1
H11B	1140	4297	1701	50	1
H115	3440	2263	1236	46	1
H11C	2098	708	1757	56	1
H11D	773	1861	1964	56	1
H117	603	424	697	58	1
H11E	−1540	1714	1019	66	1
H11F	−879	3092	896	66	1
H119	−2524	2930	−335	73	1
H120	−1218	2848	−1548	67	1
H12A	1326	2706	−1405	61	1
H12B	1058	1165	−1175	61	1
H122	2497	1240	−67	53	1
H123	1105	3952	165	45	1
H12C	3561	4432	27	51	1
H12D	4034	3005	−324	51	1
H127	4342	7077	−2819	52	1
H128	3452	8052	−4215	48	1
H130	124	5956	−3843	45	1
H131	1065	4928	−2457	48	1
H133	1908	9521	−5127	71	1
H134	1071	10530	−6529	81	1
H135	−242	9396	−7355	65	1
H136	−813	7300	−6721	57	1
H137	50	6283	−5327	52	1



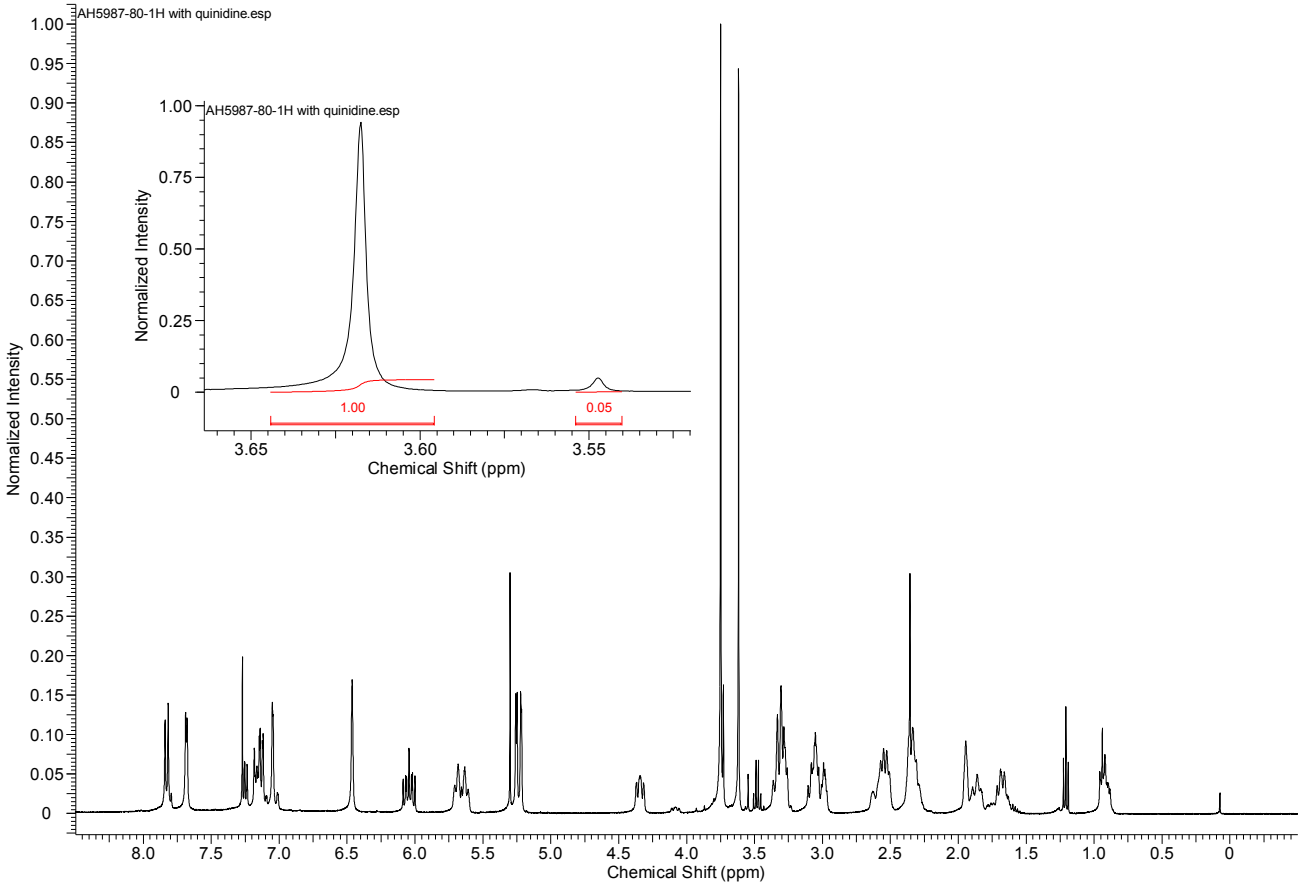
Thermal ellipsoids drawn at the 35% probability level.

6. References

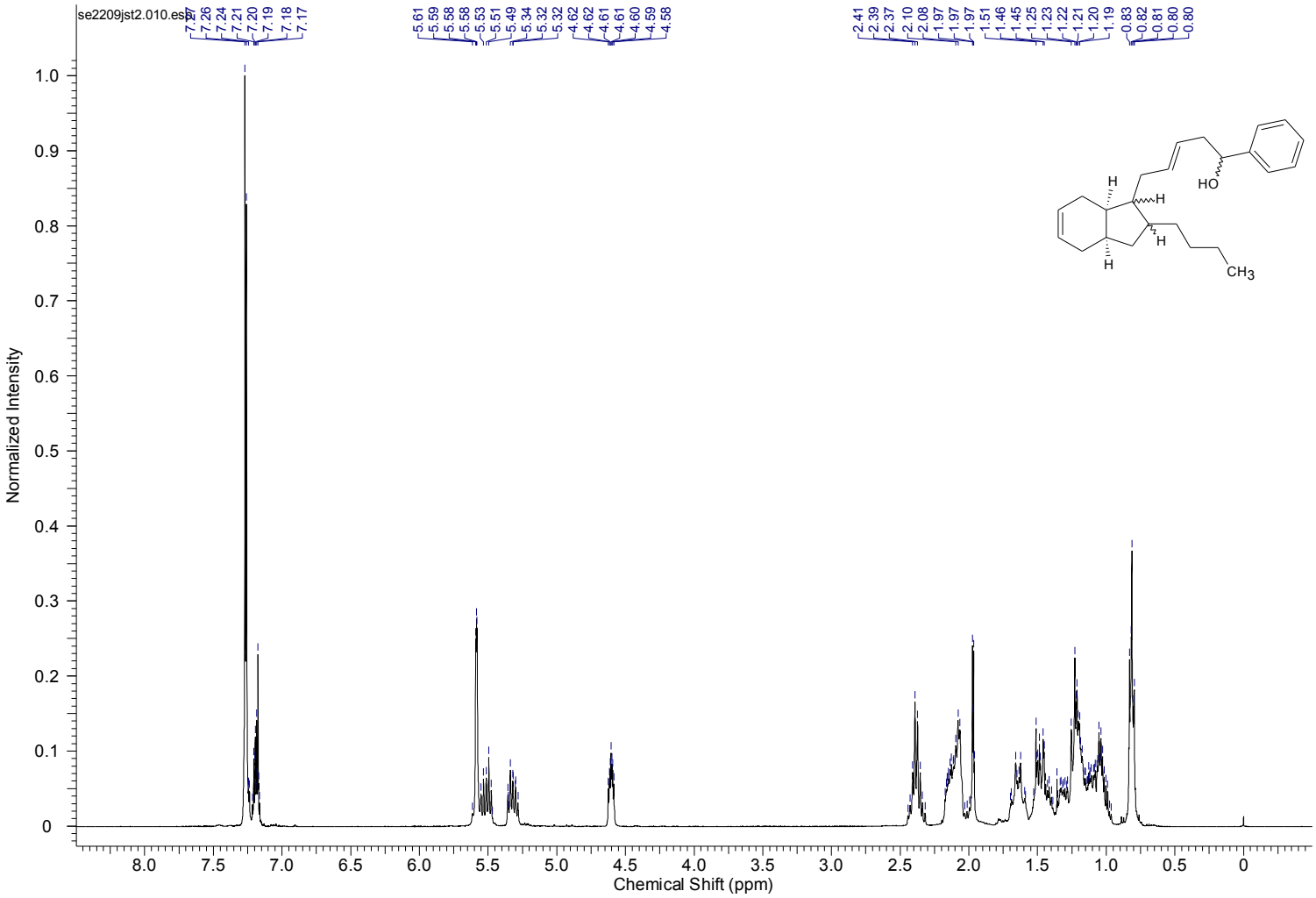
1. C. Bolm, I. Schiffers, C. L. Dinter and A. Gerlach, *J. Org. Chem.*, 2000, **65**, 6984-6991.
2. G. S. Hamilton, Z. W. Huang, X. J. Yang, R. J. Patch, B. A. Narayanan and J. W. Ferkany, *J. Org. Chem.*, 1993, **58**, 7263-7270.
3. A. T. Stevens, J. R. Bull and K. Chibale, *Organic & Biomolecular Chemistry*, 2008, **6**, 586-595.
4. J. K. Whitesell and M. A. Minton, Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy, Chapman and Hall, London, 1987, pp 37 ± 55.
5. Y.-G. Suh, S.-A. Kim, H.-U. Cho and Y.-S. Cho, *Chem. Lett.* 1994, 63.
6. A. Casapullo, G. Scognamiglio and G. Cimino, *Tetrahedron Lett.*, 1997, **38**, 3643-3646.
7. J. Kong, C. A. White, A. I. Krylov, D. Sherrill, R. D. Adamson, T. R. Furlani, M. S. Lee, A. M. Lee, S. R. Gwaltney, T. R. Adams, C. Ochsenfeld, A. T. B. Gilbert, G. S. Kedziora, V. A. Rassolov, D. R. Maurice, N. Nair, Y. H. Shao, N. A. Besley, P. E. Maslen, J. P. Dombroski, H. Daschel, W. M. Zhang, P. P. Korambath, J. Baker, E. F. C. Byrd, T. Van Voorhis, M. Oumi, S. Hirata, C. P. Hsu, N. Ishikawa, J. Florian, A. Warshel, B. G. Johnson, P. M. W. Gill, M. Head-Gordon and J. A. Pople, *J. Comput. Chem.* 2000, **21**, 1532-1548.
8. M. Light, R. Whitby and D Owen (2012) Private communication to the Cambridge Structural Database, deposition number CCDC 864880.

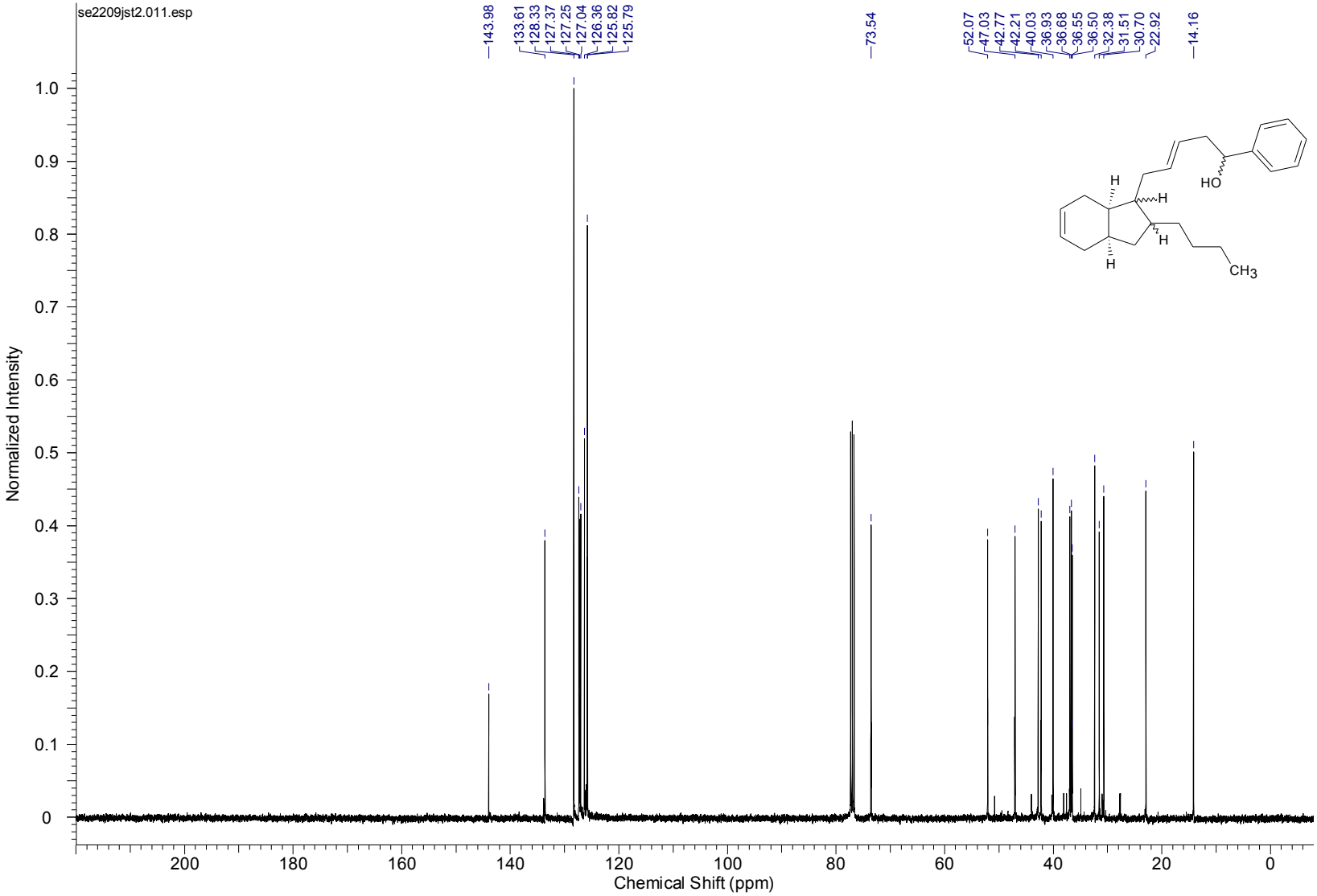
7. Determination of ee of acid ester 10

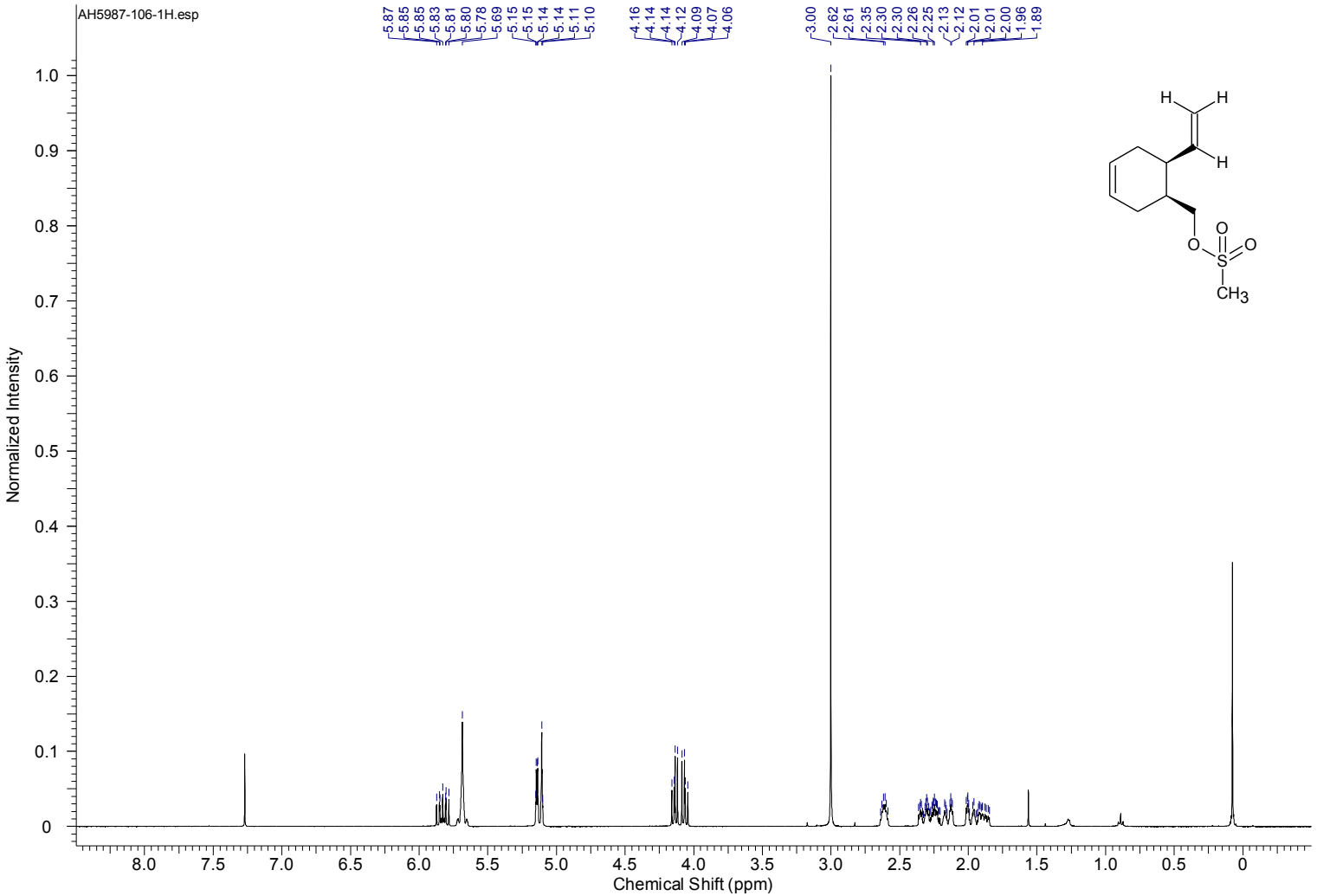
The ee of acid ester **10** was determined using ^{1}H NMR of the adduct formed by addition of quinidine (1.1 eq) to a solution of acid ester **10** in $CDCl_3$. The integrals of the methyl ester singlets in the 3.6 ppm region gave an ee of 90%.

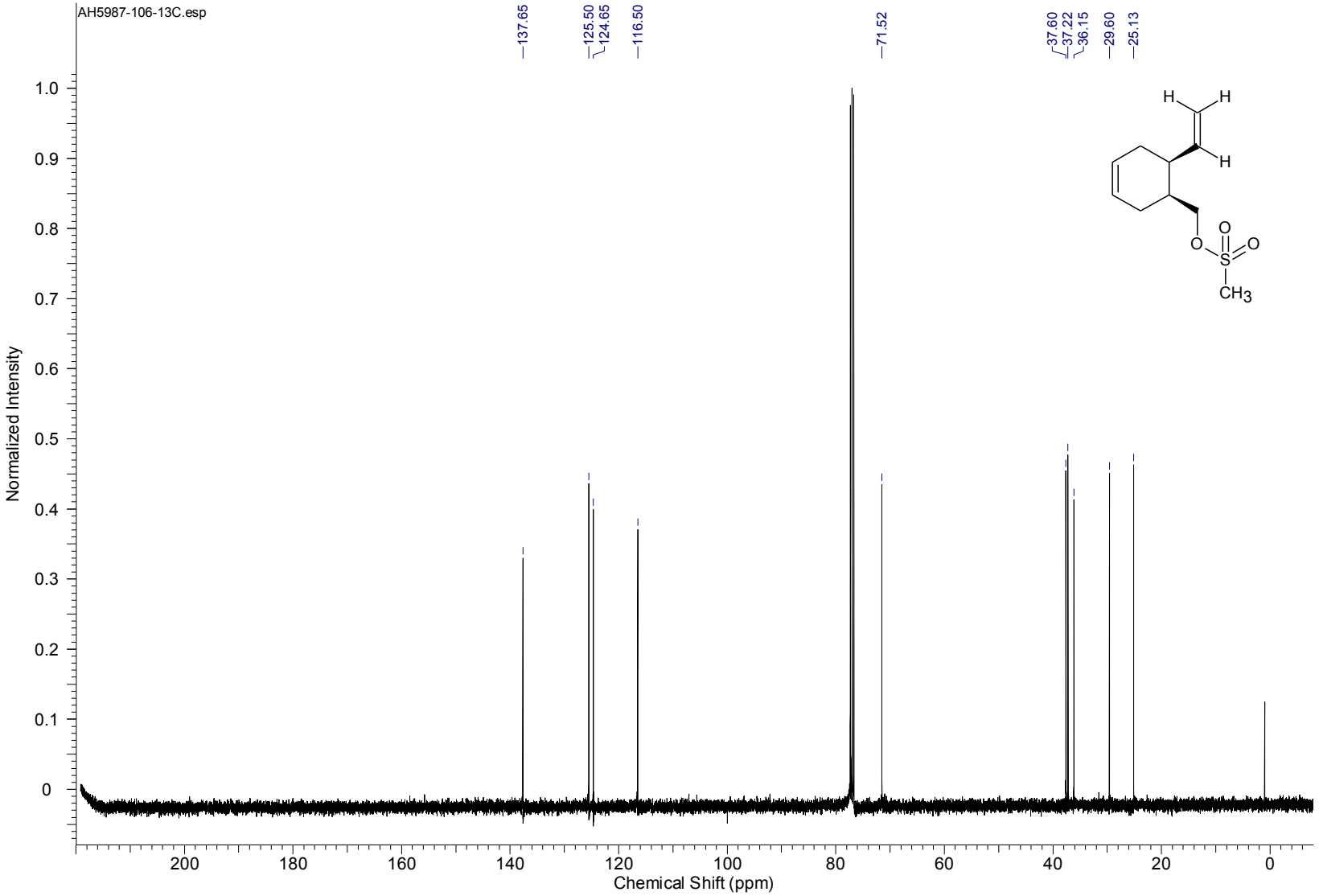


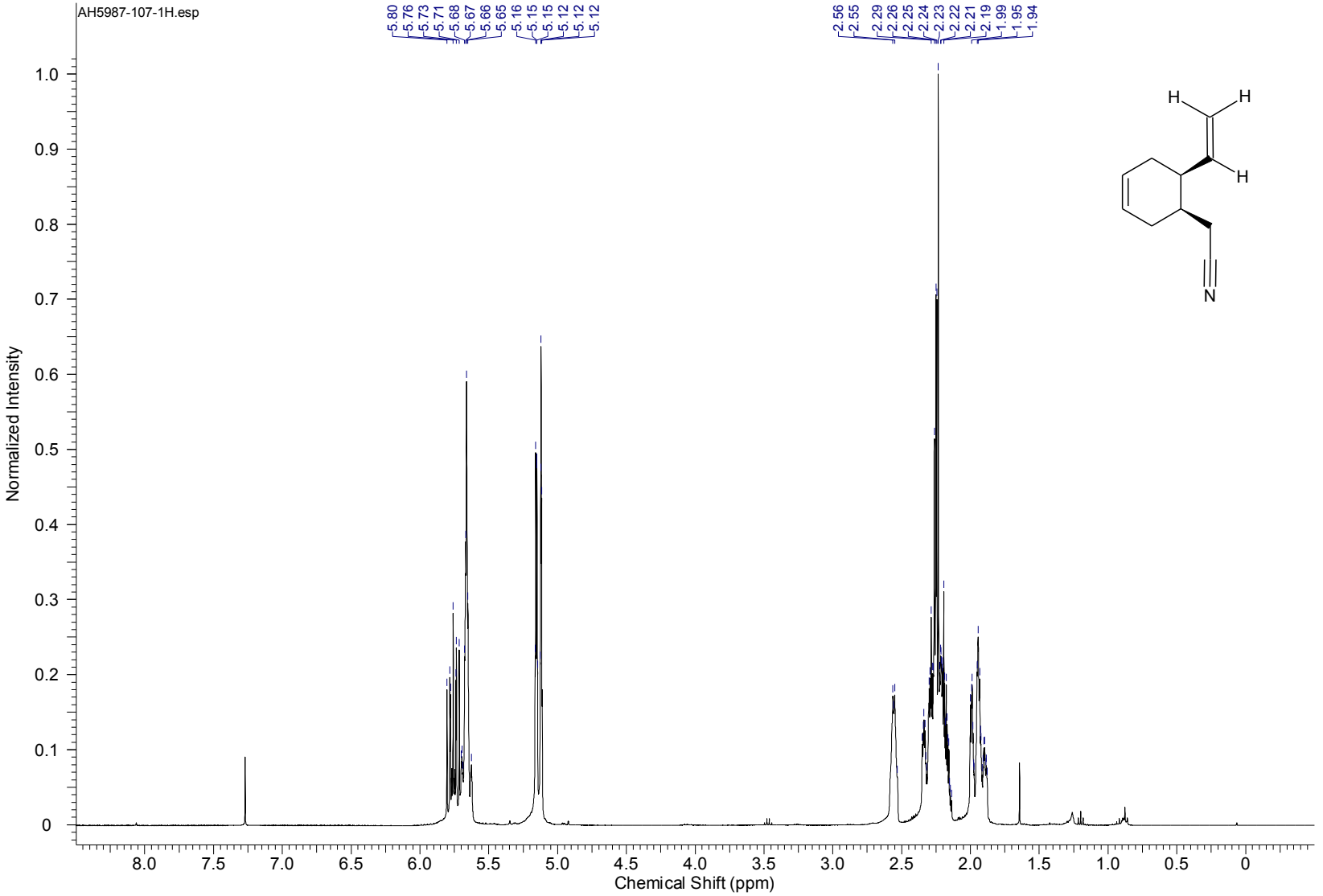
8. NMR spectra

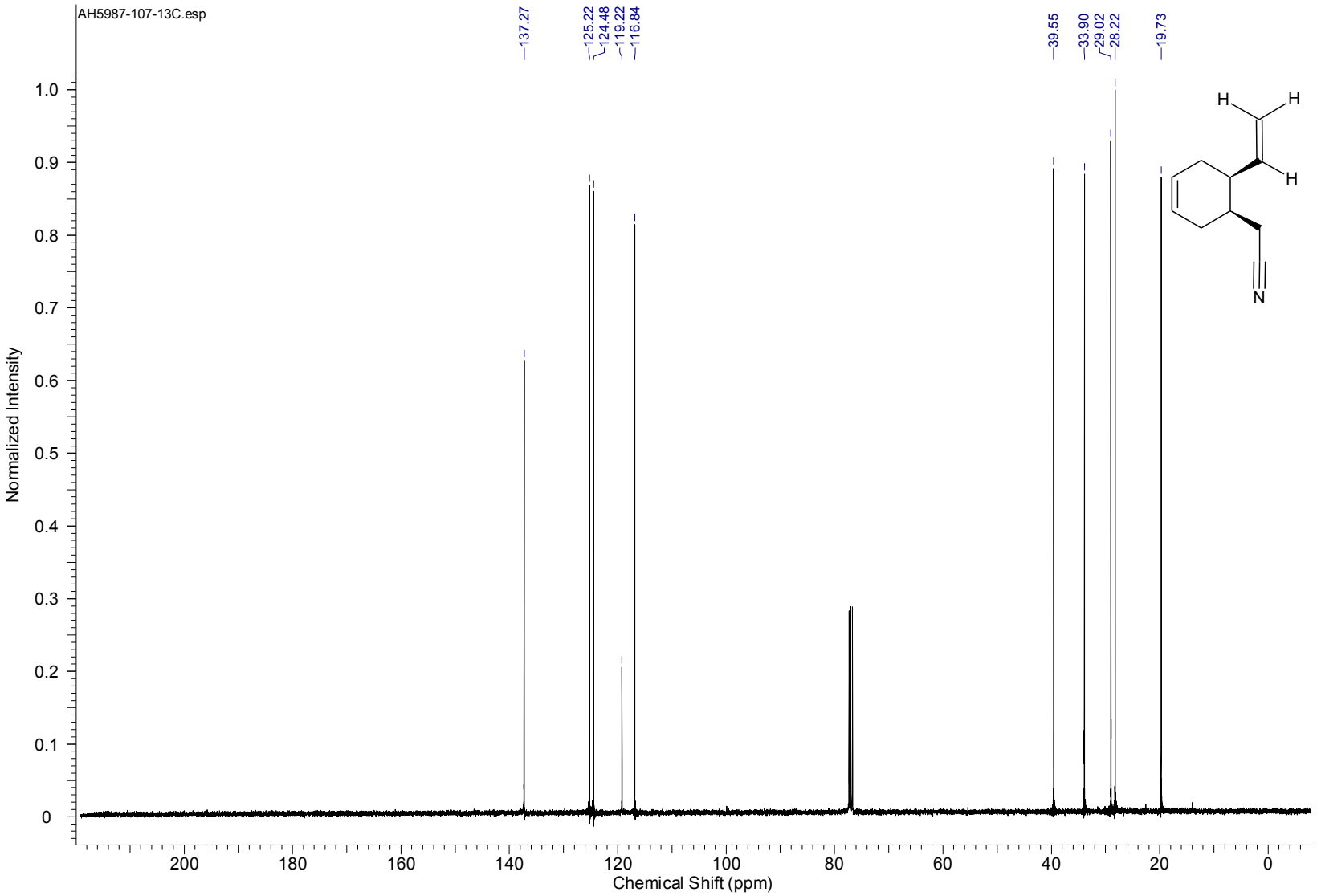


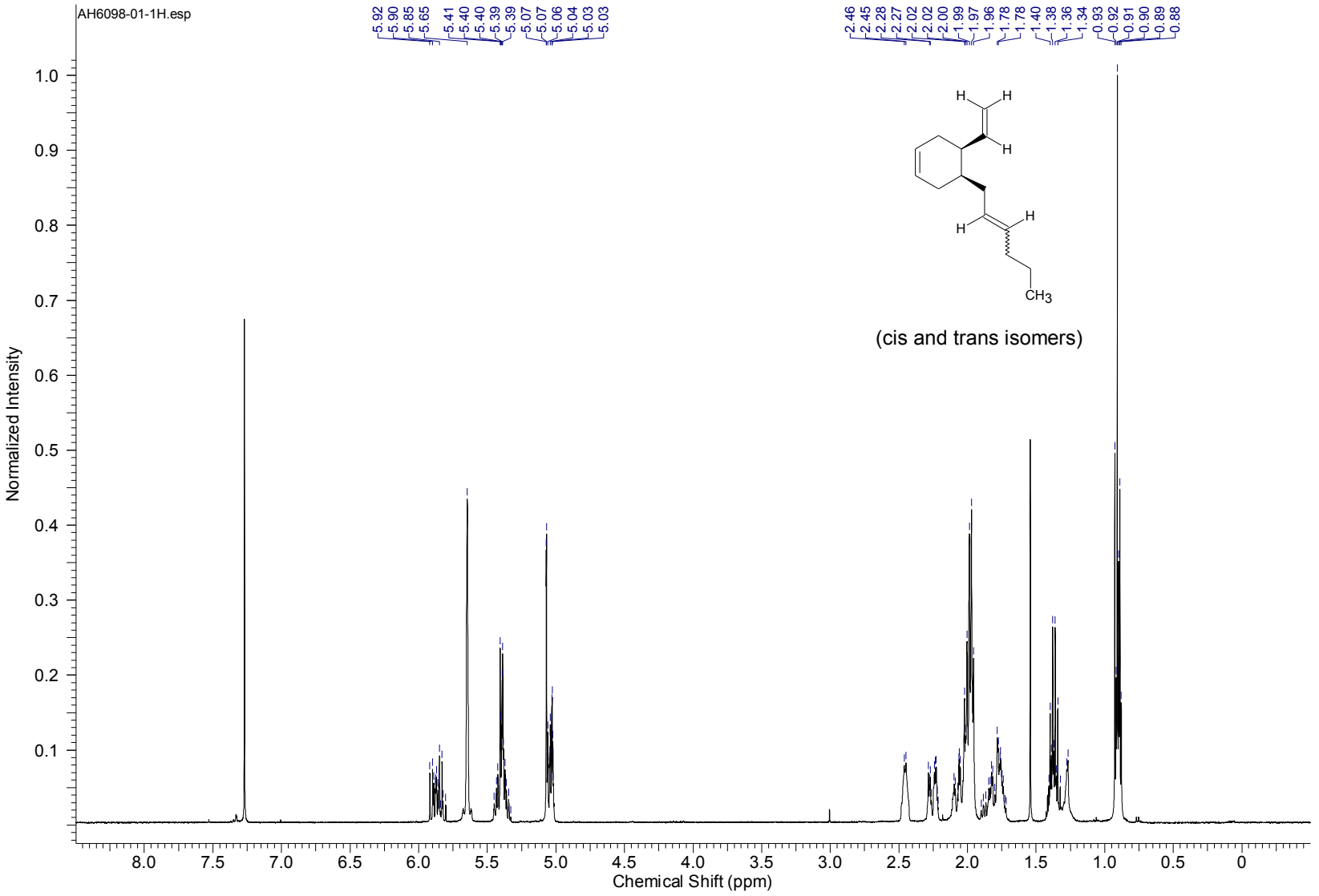


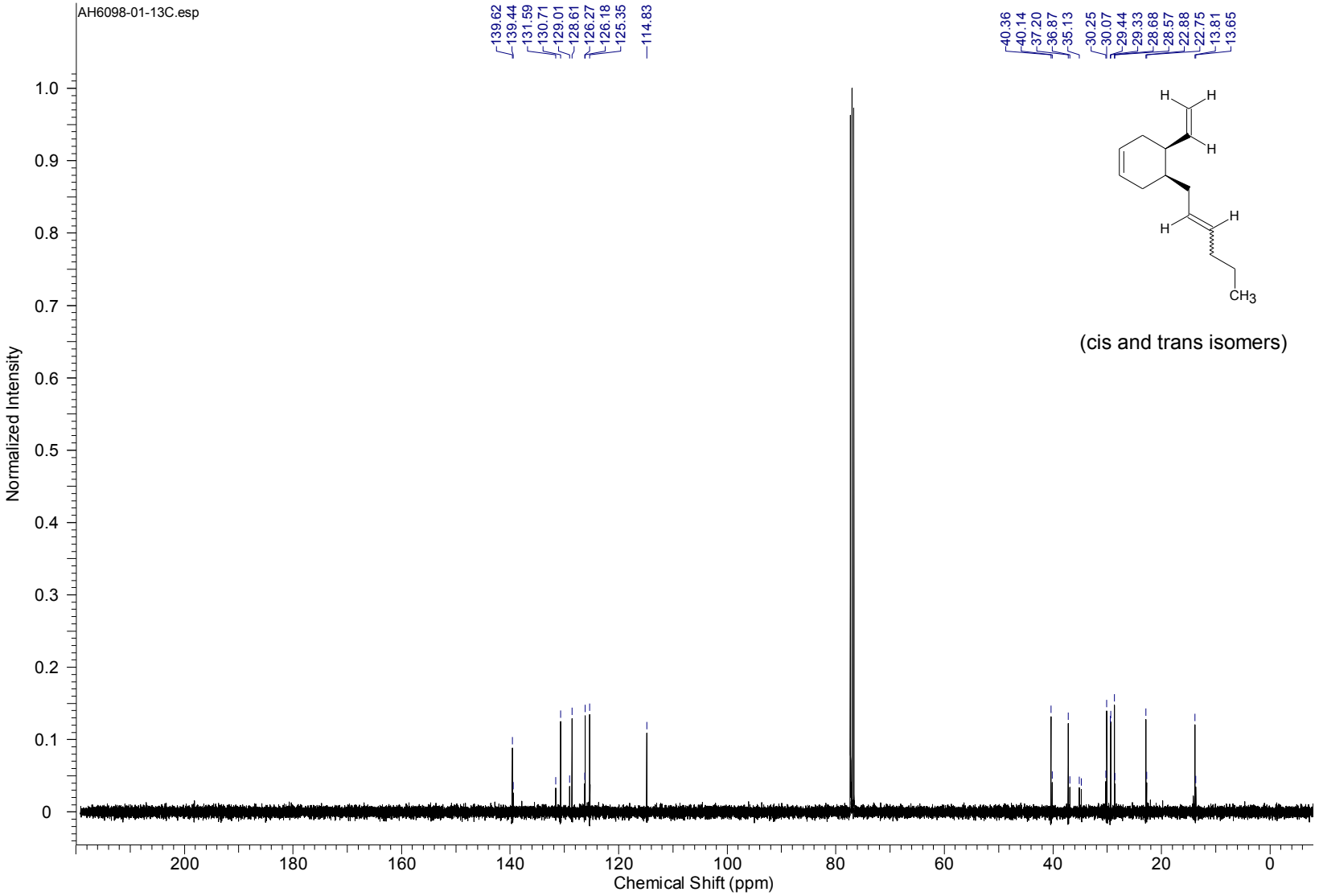












(cis and trans isomers)